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VITAMIN D IN

PCOS, ENDOMETRIOSIS, GESTATIONAL DIABETES, LOW BACK PAIN, AND PELVIC FLOOR DISORDERS

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CONTENTS

TOG 13th CONCLAVE

PRESIDENTS MESSAGE

Dr S. Shantha Kumari
MD, DNB, FICOG, FRCPI (Ireland),
FRCOG (UK)
Professor Obgyn
President FOGSI 2021-2022
Treasurer FIGO 2021-2023

Today women's health in India is a major concern. Wellbeing and Immunity are vital for overall health, one of the major indicators for this concern is added by vitamin D deficiency, which is extremely common and usually non symptom specific. Common symptoms of the deficiency are pain in the bones and muscles. Additionally, there are other signs like unexplained fatigue, generalized weakness, body aches, muscle and bone pain, low backache, and low immunity.

The first thing, when levels go low people do not usually develop symptoms. In many cases people come for other check-ups and we find low vitamin D levels. However, the three main symptoms of vitamin D deficiency are persistent fatigue where they get tired very easily and also feel tired all the time, bone, joint and muscle pains, and last but not least, recurrent infections due to low immunity. In fact COVID infection is seen more often in patients with vitamin D deficiency.

Incidentally, some studies in the past decade reported a prevalence of 50% to 94% across age groups. Hugh prevalence of vitamin D deficiency was seen throughout the country.

Some of the causes that contribute to vitamin D deficiency could be increased indoor lifestyle, lesser exposure to sun in Urban lifestyle, unspaced and unplanned pregnancies in Women with dietary deficits leading to worsening status of vitamin D in both mother and child.

Educational programs are a must to create awareness along with testing facilities. Multiple analysis revealed hypertension as a significant predictor of vitamin D deficiency and the risk of vitamin D deficiency was double among the elderly with hypertension.

People who do not eat enough vitamin D-rich foods, including fortified dairy products and cereals, may have low levels of vitamin D.

In India, vitamin D deficiency is wide spread, but currently the diagnosed numbers are only tip of the iceberg.

FOGSI with educational grant from PULSE Pharmaceuticals has taken the novel initiative to create awareness on vitamin D sufficiency levels across various indications in Women's Health. This is being done through generation of scientific practice points around the therapy.

We want to create awareness not only in patients but also amongst the doctor fraternity to address the deficiency issue of vitamin D. This is being set through Scientific discussions across indications through the Times of Gynaecology platform.

Vitamin D in women's health

An overview on importance of vitamin D

Nutrition is important for health and development. Good nutrition is associated with improved infant, child and maternal health, better immune systems, safer pregnancy and childbirth, lower risk of non-communicable diseases (such as diabetes and cardiovascular disease), and longevity.[1] Vitamins and minerals are considered essential nutrients–because they perform hundreds of roles in the body including reinforcing bones, healing wounds, and bolstering the immune system. They also convert food into energy and repair cellular damage.[2] Several studies have suggested that vitamin D status is inversely associated with the incidence of several diseases, e.g., cancers, cardio-vascular diseases, and neurodegenerative diseases.[3]

Prevalence of vitamin D deficiency

Figure 1. Prevalence of vitamin D deficiency

Global prevalence

- Approximately 1 billion people worldwide are affected with vitamin-D deficiency and around 50% of the global population have vitamin D insufficiency.[4]

Prevalence in India

- The prevalence of vitamin D deficiency ranged from 40% to 99%, with most of the studies reporting a prevalence of 80%–90%.[5]

Factors for high prevalence of vitamin D deficiency in India are:[5]

Factors in urban population	Factors in rural population
• Skin complexion • Poor exposure to sunlight • Use of sunscreen creams • Food habits and lower intake of vitamin D fortified foods	• High phytate and low calcium in the diet • Phytate rich diet reduces the intestinal absorption of calcium hence there is low dietary calcium which increases the catabolism of 25(OH)D ultimately causing reduced 25(OH)D concentrations.

Since India lacks food fortification, the only means of treatment of vitamin D deficiency is supplementation with pharmaceutical preparations.[5]

Various forms of vitamin D and cholecalciferol

01 Vitamin D3 (alfacalcidiol, cholecalciferol and calcitriol)

02 Vitamin D2 (ergocalciferol)

Majority of preparations available in the Indian market contain vitamin D3 (99.9%).

- Most of the preparations contain calcitriol (46.5%) or alfacalcidol (43.02%).
- Calcitriol is not the preferred agent for treatment of nutritional deficiency since it is associated with a high incidence of hypercalcemia and requires serum calcium monitoring.
- Alfacalcidiol has a rapid onset of action with a half-life of 2–3 weeks and is most useful in patients with liver disease.

Evidence suggests that cholecalciferol is superior to ergocalciferol in terms of potency, elevating and sustaining 25(OH)D concentrations and maintaining the storage form of vitamin D.[5]

Approximately 10% of vitamin D3 preparations are available as cholecalciferol, the inactive, unhydroxylated form of vitamin D3, synthesized in skin from 7 dehydrocholesterol. It has a half-life of 12–30 days and is the preferred form for the prophylaxis or treatment of vitamin D deficient states.[5]

Clinical recommendations on vitamin D supplementation in these women are summarized in Table 2.[6]

Table 2. Vitamin D recommendation

IOM recommendations[21]		Dr. Holick's recommendations for patients at risk for Vitamin D deficiency[21]	
Life Stage Group	**Estimated Average Requirement**	**Daily Allowance (IU/d)**	**UL (IU)**
Females			
9–13 y	400 IU (10 µg)	1,500 – 2,000	4,000
14–18 y	400 IU (10 µg)	1,500 – 2,000	4,000
19–30 y	400 IU (10 µg)	1,500 – 2,000	10,000
31–50 y	400 IU (10 µg)	1,500 – 2,000	10,000
51–70 y	400 IU (10 µg)	1,500 – 2,000	10,000
> 70 y	400 IU (10 µg)	1,500 – 2,000	10,000
Pregnancy			
14–18 y	400 IU (10 µg)	1,500 – 2,000	10,000
19–30 y	400 IU (10 µg)	1,500 – 2,000	10,000
31–50 y	400 IU (10 µg)	1,500 – 2,000	10,000
Lactation*			
14–18 y	400 IU (10 µg)	1,500 – 2,000	10,000
19–30 y	400 IU (10 µg)	1,500 – 2,000	10,000
31–50 y	400 IU (10 µg)	1,500 – 2,000	10,000

Recommended Adequate Intakes (AI), Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA) and Tolerable Upper Limit (UL) by the Institute of Medicine (IOM) and Dr. Holick's recommendation for Daily Allowance and safe Upper Limit (UL) for vitamin D for children and adults who are not obtaining adequate vitamin D from sun exposure and who are at risk for vitamin D deficiency

To sustain an adequate serum 25(OH)D concentrations, vitamin D can be administered daily, weekly, monthly, or every 4 months.

- If there is **extreme vitamin D deficiency**, a high bolus dose of vitamin D (up to 300,000 IU) can be used initially.
- **Maintaining stead-state**: Repeated boluses of high-dose vitamin D at 6- to 12-month intervals have been used, but a steady-state serum 25(OH)D concentration is likely to be maintained by more frequent, lower doses of vitamin D.
- **Prevention of recurrence**: Administration of 600 to 1000 IU/day is effective. Most market preparations in India are available as 60,000 IU and are usually recommended for 6 to 8 weeks for obtaining adequate serum 25(OH)D concentrations.[5]

An effective strategy to treat vitamin D deficient is to administer 60,000 IU of vitamin D3 once a week for 6-8 weeks respectively.

Vitamin D and inflammation

Vitamin D promotes monocyte differentiation to macrophages, preventing them from releasing inflammatory cytokines and reducing their ability to present antigens to lymphocytes.[7]

Vitamin D also suppresses the proliferation and stimulatory abilities of T cells and monocytes, and downregulates proinflammatory cytokines, including C reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin (IL) 6, IL-1 and IL-8, while upregulating anti-inflammatory cytokines such as IL-10.[7]

Vitamin D is important in modulating inflammatory processes, and this seems to be supported by various experimental and observational studies.[7]

Vitamin D in gynecological conditions

Vitamin D status significantly influences female reproductive and pregnancy outcomes. Evidence suggest that low vitamin D status is associated with impaired fertility, polycystic ovary syndrome, endometriosis, gestational diabetes, low back pain, and pelvic floor disorders. Clinical studies have demonstrated that women with low vitamin D levels had higher rates of preeclampsia, preterm birth, and bacterial vaginosis.[8]

Vitamin D deficiency plays a substantial role in regulating women's health. Recent studies are shifting the ideas about the optimal vitamin D status and the role of vitamin D in in relation to modern chronic diseases affecting women.[16]

Vitamin D in gynecological conditions	
PCOS	Low vitamin D in PCOS has been linked to insulin resistance, infertility, menstrual cycle irregularity, and hirsutism. Additionally, vitamin D is also involved in immune regulation, mood, and energy, regulating insulin and glucose metabolism, estrogen and progesterone synthesis, and ovarian follicular development. Restoring a normal vitamin D level improves insulin sensitivity and restore menstrual cycles.[9-10]
Endometriosis	Vitamin D effectively modulates the immune system, suppresses lymphocyte proliferation, immunoglobulin synthesis, and inhibits the action of proinflammatory transcription factors and the production of cytokines. These immunologic properties along with expression of VDR in reproductive tissues, including the uterus, ovary, and placenta, have led to the hypothesis of a possible association between endometriosis and the vitamin D system.[11]
Gestational diabetes	Vitamin D deficiency increases inflammation and decreases insulin action, which could contribute to increased risk of adverse pregnancy outcomes including gestational diabetes mellitus (GDM), preeclampsia, and preterm birth.[12] Active vitamin D (1,25[OH]$_2$D3) has potent anti-inflammatory properties, and directly activates transcription of the insulin receptor gene.
Low back pain	Insufficiency of vitamin D is associated with lower backache. In vitamin D deficiency, the neuromuscular disorders can occur due to hypersensitivity and sensorial hyper-innervations in the muscles.[13] Vitamin D is also involved in regulation of anti- and pro-inflammatory cytokines that control pain and inflammation. Vitamin D can facilitate the uptake of calcium, and lead to bone mineralization, where age and hormonal-related bone density loss can increase the risk of osteoporosis, potentially resulting in pain.[14]
Pelvic floor dysfunction	Vitamin D receptors (VDRs) are found in the bladder neck, urothelium, and muscular layers of the bladder wall. Vitamin D deficiency may contribute to pelvic floor dysfunction by affecting pelvic floor muscle strength. Vitamin D deficiency causes abnormal detrusor contractility leading to hypercontractile or irritable state. Also, vitamin D deficiency is associated with increased inflammatory cytokine production from the urothelium, leading to inflammation of the bladder wall.[15] Pelvic floor dysfunction

Optimal vitamin D levels

The determination of optimal vitamin D levels for its numerous actions throughout a woman's life and the amount of vitamin D supplementation required to achieve those levels would have important public health implications.[8]

Based on the 25(OH)D levels as measured in serum, the following definitions for vitamin D levels are derived:[17-18]

Vitamin D deficiency: 25(OH)D levels of <20 ng/mL

Vitamin D insufficiency: 25(OH)D levels between 20 to <30 ng/mL

Vitamin D normal: 25(OH)D between 30–100 ng/mL (preferred range of 30–60 ng/mL)

Vitamin D toxicity

A serum 25(OH)D concentration of up to 100 ng/mL (250 nmol/L) is generally considered safe for children and adults. The Endocrine Society guidelines concluded that vitamin D toxicity is not only extremely rare, but 25(OH)D concentration of at least 150 ng/mL (375 nmol/L) is required before there would be evidence of vitamin D toxicity. There are numerous studies demonstrating that vitamin D is probably one of the least toxic fat-soluble vitamins.[19] A retrospective investigation of elevated 25(OH)D levels during a 16-year period was performed in patients with serum/plasma 25(OH)D concentrations higher than 120 ng/mL.The study showed that symptomatic vitamin D toxicity is uncommon, and elevated levels of 25(OH)D did not strongly correlate with clinical symptoms or total serum/plasma calcium levels.[20]

Current studies suggest that we may need more vitamin D than presently recommended to prevent chronic disease.[21] A recent study demonstrated that cholecalciferol supplementation of 60,000 IU daily (420,000 IU in the first week) that is higher than existing recommendations but helps in achieving 25(OH)D >50 ng/mL in 75% of participants by day-14 and found to be safe and effective.[22]

Symptomatic vitamin D toxicity is uncommon, and elevated levels of 25(OH)D do not strongly correlate with clinical symptoms or total serum/plasma calcium levels.

Monitoring

All patients receiving pharmacological doses of vitamin D should have the plasma-calcium concentration checked at intervals (initially weekly) and whenever nausea or vomiting are present.[23]

- The National Osteoporosis Society (2018) recommends checking adjusted serum calcium 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked.
- Vitamin D levels do not need to be checked routinely and can take 3-6 months to reach a steady state after treatment has started.
  - » Vitamin D levels should be rechecked 6 months after a loading regimen of vitamin D has been given. If levels are still sub-optimal, compliance with medication should be discussed. Alternatively, consider referral to an appropriate specialist.

Cholecalciferol supplementation of 60,000 IU daily (420,000 IU in the first week) that is higher than existing recommendations but helps in achieving 25(OH)D>50 ng/mL.

POINTS TO PONDER

- **Target Vitamin D levels:** Maintaining serum concentrations consistently >30 ng/mL is essential.[17-18]
- An effective strategy to treat vitamin D deficient is to administer 50,000 IU of vitamin D3 once a week for 6-8 weeks respectively.[5]
- Doses of 60, 000 IU (> 50,000 IU) per day raise levels of 25(OH)D to >150 ng/mL and are associated with hypercalcemia and hyper-phosphatemia. Doses of 10,000 IU of vitamin D3 per day for up to 5 months, however, do not cause toxicity.[24]
- Evidence has shown that serum 25(OH)D levels >150 ng/mL are considered as toxic. Therefore, supplementation is safer till this level.[25]

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Vitamin D in polycystic ovary syndrome

From left to right: Dr. Shobha, Dr. Silambuchelvi, Dr. Ketan Mehta, Dr. Pratap Kumar, Dr. Jaydeep Tank, Dr. Suvarna Khadilkar, Dr. Rishma Pai and Dr. Rohan Palshetkar

Introduction: PCOS

- Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is characterized by polycystic ovaries, oligo-amenorrhea, and hyperandrogenism. PCOS is commonly related to features of metabolic syndrome, including obesity, impaired glucose metabolism, and insulin resistance (IR) and is one of the main causes of anovulatory infertility.[1]
- Globally, more than 105 million women aged 15–49 years have been diagnosed with PCOS.[2]
- Insulin resistance (IR) has emerged as being central to the pathophysiology of PCOS, with resulting hyperinsulinemia as a mechanism contributory to both the ovulatory dysfunction and hyperandrogenism.[3]
- PCOS also has psychological implications, further, the physical, emotional and social effects of the disorder have negative impact on health-related quality-of-life, with most affected being infertility and weight concerns.[4]
- PCOS patients are at an enhanced lifetime risk for a spectrum of morbidities including poor reproductive outcomes, type 2 diabetes mellitus (DM), cardiovascular disease (CVD), mood disorders including depression and anxiety, as well as endometrial cancer.[3]

Importance of nutrition in PCOS

- Maintaining adequate nutritional status and proper diet is important in prevention and recovery of patients with PCOS.[5]
- Focus of nutritional management should be on weight loss, and improving insulin sensitivity in PCOS patients. Special attention should be given to deficiencies

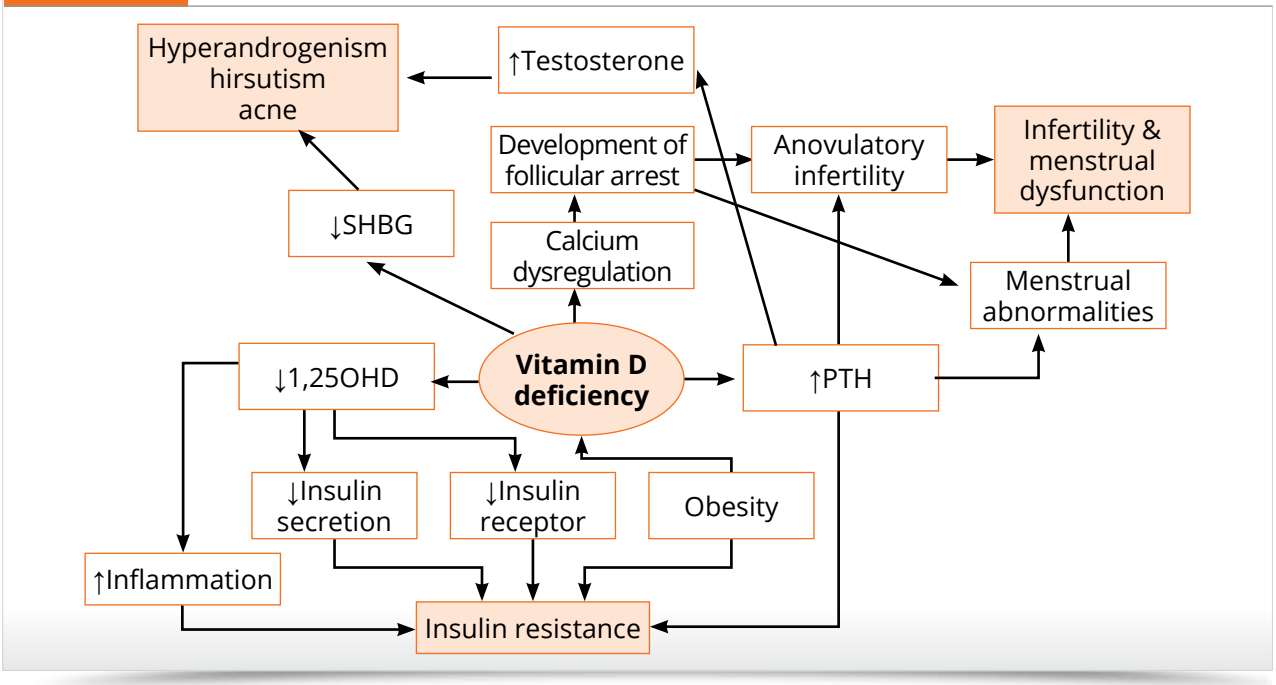
such as vitamin D, chromium, and omega-3 in PCOS women.[6]

- Since vitamin D plays a crucial role in various metabolic pathways including insulin metabolism, its deficiency in PCOS patients may cause insulin resistance and other complications.[6]

Role of vitamin D deficiency in the pathology of PCOS

- About 67%–85% of women with PCOS were reported to have vitamin D deficiency (defined as serum 25-hydroxy vitamin D [25{OH}D] <20 ng/mL).[7]
- Figure 1 elaborates the impact of vitamin D deficiency in causing insulin resistance,

Figure 1. Role of vitamin D deficiency in the pathology of PCOS[3]



Co-relation of vitamin D in the pathology of PCOS:

- ***Abnormal vitamin D metabolism and action is linked to the pathogenesis of PCOS. The targets of vitamin D signaling are the genes that are critical for glucose and lipid metabolism.***
- ***Vitamin D deficiency causes calcium dysregulation and follicular arrest, thereby leads to anovulation and menstrual dysfunction or infertility.***
- ***Vitamin D deficiency also increases the testosterone levels which further leads to hyperandrogenism, hirsutism, and acne.***
- ***Decreased serum vitamin D levels reduces insulin secretion and insulin receptors thereby causing insulin resistance, and increased risk of diabetes.***
- ***Association of obesity with PCOS causes lipopolysaccharide tolerance and indicates a more profound inflammatory state, and hyperandrogenism may potentiate it to cause insulin resistance.***

infertility and menstrual dysfunction as well as hyperandrogenism, acne, and hirsutism is given in Figure 1.[3]

- The recognized targets of vitamin D signaling are the genes that are critical for glucose and lipid metabolism. Abnormalities in vitamin D metabolism and action could be linked to the pathogenesis of PCOS, as this condition is a state of follicular developmental arrest.[3]

Impact of low vitamin D levels in PCOS women

Relationship between low vitamin D status, metabolic disturbance, and PCOS

- Evidence has shown lower serum levels of $25OHD_3$ in obese PCOS patients (31.9 ± 9.4 nmol/L) than in their non-obese counterparts (73.1 ± 20.2 nmol/L).[8]
- Reports have shown that the serum 25(OH)D concentration was significantly lower in PCOS women with obesity or IR than in women without obesity or IR ($p<0.05$). Increased BMI and WHR, high levels of fasting insulin, HOMA-IR, total cholesterol, LDL-C and hs-CRP were regarded as risk factors, but high level of HDL-C was considered to be protective factor of vitamin D deficiency in PCOS women.[9]

In PCOS, lipid-induced cytokine hypersecretion from mononuclear cells is independent of obesity. However, when obesity accompanies PCOS, the lipopolysaccharide tolerance observed indicates a more profound inflammatory state, and hyperandrogenism may potentiate it to limit insulin resistance.[10]

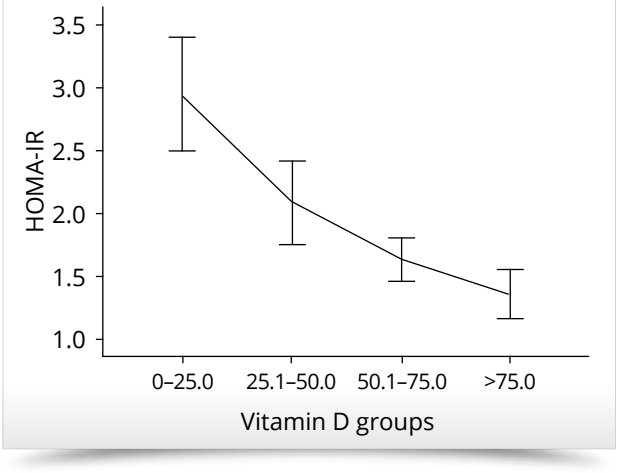
- A compromised vitamin D status in PCOS women is associated with a higher HOMA-IR and an unfavorable lipid profile.[7]
  - » It was observed that in women with lower serum 25(OH)D (<10 ng/mL), a more disturbed metabolic profile existed with a worse lipid profile and higher levels of insulin resistance, which supported the recommendation from the Endocrine Society to achieve a serum 25(OH)D concentration of >75 nmol/L (>30 ng/mL).[7,11]
  - » Low HDL-cholesterol is one of the central features of metabolic syndrome. An additional therapeutic target in women suffering from PCOS is dyslipidemia, therefore vitamin D can be useful in the complex treatment of these women.[7]

PCOS and metabolic syndrome

- ***Vitamin D deficiency in PCOS women leads to a disturbed metabolic profile, a worse lipid profile and higher levels of insulin resistance.***
- ***This may occur due to increased vascularity and deposition of collagen in ovarian stroma and theca (characteristics of TGF-β hyperactivity) in the ovaries of PCOS women. The dysregulation of TGF-β contributes to the metabolic disturbances in these women.***

- In the women with the lowest vitamin D level (0-25 nmol/L or <10 ng/mL), HOMA-IR was on average 24% higher compared to the women with the highest (>75 nmol/L or >30 ng/mL) vitamin D level ($\beta = 0.76$; 95% CI: 0.63–0.91; $p<0.01$) as shown in Figure 2.[7]

Figure 2. Association between serum 25(OH)D (nmol/L) groups and homeostatic model assessment of insulin resistance (HOMA-IR)[7]



- Transforming growth factor-β (TGF-β) dysregulation is associated with the allele 8 variant of fibrillin-3 gene, which may contribute to the metabolic disturbances in women with PCOS. The ovaries of women with PCOS are marked with increased vascularity and increased deposition of collagen in ovarian stroma and theca, which are characteristics of TGF-β hyperactivity.[12]

Link between low vitamin D levels and impact on psychological well-being in PCOS women

- PCOS women carry a substantial psychological burden. Altered physical appearance (obesity, acne, alopecia, hirsutism), menstrual irregularity, and difficulties in conceiving are potential contributors to depression, anxiety disorders, body image dissatisfaction, and sexual dysfunction in women with PCOS.[3]
- Vitamin D deficiency is identified as a risk factor for depressive symptoms in women with PCOS.[13]
  - » Patients with serum 25OHD < 20ng/mL were almost 4 times more likely to meet criteria for depression (Patient Health Questionnaire score [PHQ]>4, OR 3.47, 95% CI 0.78-16.19, p=0.056).
  - » Women with 25OHD<20 ng/mL were 6 times more likely to score >4 (OR 6.51, 95% CI 1.29- 32.91, p=0.023) and 18 times more likely to score >10 (OR 18.28 1.03-325.19, p=0.048).
- Insulin resistance too is positively associated with depressed mood in PCOS.[14]

PCOS and infertility

- A vicious circle of androgen excess is responsible for PCOS, which further facilitates androgen secretion by the ovaries and adrenal glands. This cyclical pathogenetic interaction between IR, hyperinsulinemia, and hyperandrogenism, in combination with hypothalamic-pituitary dysfunction, causes further ovarian dysfunction and results in anovulation and infertility.[15]
- Ovulation disorders are the cause of infertility in around 25% of couples, and PCOS is the major cause of anovulatory infertility, accounting for ~70% of all cases.[15,16]

Various mechanisms explaining the role of vitamin D in female reproduction

1. Vitamin D modulates reproductive processes in women in addition to sex-steroid hormones; its nuclear receptor has been identified in the uterus, oviduct, ovary, placenta, and fetal membranes.[8]
2. There is a direct stimulatory effect of 1,25 dihydroxy vitamin D_3 ($1,25[OH]_2D_3$) on the aromatase gene expression in reproductive tissues.[8]

3. HOXA10 expression is important for the development of the uterus and essential for endometrial development, allowing uterine receptivity to implantation. HOXA10 expression is up-regulated by 1,25$(OH)_2D_3$ in human endometrial stroma cells which indicates that altered vitamin D signaling may have an impact on HOXA10 expression and fertility. Aberrant HOXA10 expression in patients with infertility confirms its function in human implantation.[8]
4. Vitamin D is the key regulating hormone in calcium homeostasis. It has been shown that calcium plays a role in oocyte activation and maturation resulting in the progression of follicular development. Thus, vitamin D and calcium repletion may normalize menstrual cycles and restore ovulation in PCOS women.[8]
5. The physiologic role of vitamin D on female reproductive tissues is elaborated in the Figure 3.[17]

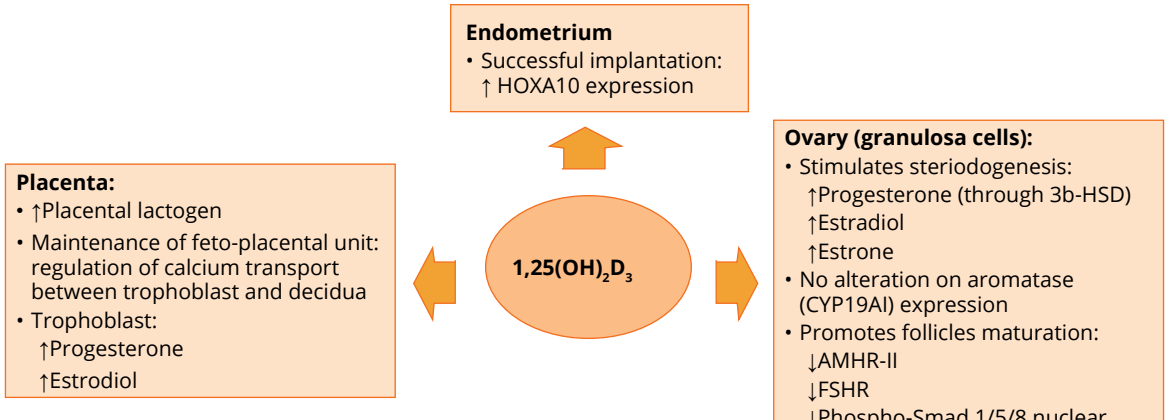
Vitamin D deficiency in infertile PCOS patients

- Evidences have shown that women with infertility and vitamin D deficiency have diminished chance of conceiving a pregnancy in response to treatment compared with those who are vitamin D replete.[18]
- Researchers in a prospective cohort study of 91 anovulatory infertile women with PCOS, showed that BMI and 25(OH)D deficiency were significant predictive parameters. Above all, they noticed that 25(OH)D levels

Vitamin D in female reproduction

- ***Vitamin D has direct stimulatory effect on the aromatase gene expression in reproductive tissues.***
- ***Vitamin D upregulates HOXA10 expression (allows uterine receptivity to implantation) in human endometrial stroma cells.***
- ***Vitamin D regulates calcium homeostasis, thus plays a role in oocyte activation and maturation.***
- ***Vitamin D and calcium repletion normalizes menstrual cycles and restores ovulation in PCOS women.***

Figure 3. Physiologic role of vitamin D on female reproductive tissues[17]

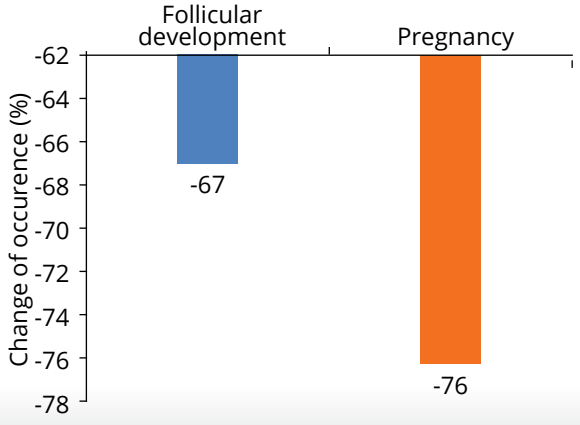


HSD: hydroxysteroiddehydrogenase; CYP: cytochrome; AMH: anti-Mullerian hormone; AMHR-II: AMH-type II receptor; FSHR: follicle-stimulating hormone receptor

of <10 ng/mL reduced the chance of follicle development by 67% and reduced the possibility of becoming pregnant by 76% as shown in Figure 4.[19]

- Vitamin D deficiency was an important modifiable contributor to diminished treatment success in women with either PCOS or unexplained infertility undergoing ovarian stimulation. PCOS women who underwent ovarian stimulation for the treatment of infertility were associated with significantly reduced rates of ovulation, of pregnancy, and ultimately a reduced chance of live birth.[18]

Figure 4. Probability of events in PCOS patients with 25(OH)D levels of <10 ng/mL



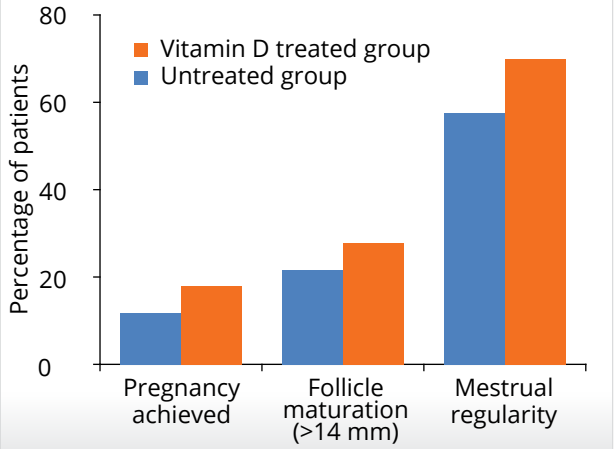
  - » PCOS women with vitamin D deficiency [25(OH)D < 20 ng/mL] who underwent ovarian stimulation for the treatment of infertility were less likely to ovulate (adjusted odds ratio [OR], 0.82; 95% confidence interval [CI], 0.68 to 0.99; p = 0.04) and experienced a 40% lower chance of live birth (adjusted OR, 0.63; 95% CI, 0.41 to 0.98; p = 0.04) than those not deficient.

- Women with a sufficient vitamin D level undergoing in vitro fertilization (IVF) are more likely to achieve clinical pregnancy than women with low vitamin D levels.[8]

Effect of vitamin D supplementation in PCOS women

- Vitamin D supplementation in vitamin D-deficient PCOS women with a history of infertility significantly decreases the bio-availability of TGF-β1, which correlates with an improvement in some abnormal clinical parameters associated with PCOS. This is a novel mechanism that could explain the beneficial effects of vitamin D supplementation in women with PCOS.[12]
- Positive effects of calcium & vitamin D supplementation was observed on weight loss, follicle maturation, menstrual regularity, and improvement of hyperandrogenism, in infertile women with PCOS. After 6 months of treatment, the level of serum 25(OH)D increased from 13.21±6.63 ng/mL to 24.82±6.54 ng/mL in infertile PCOS women.[20]
- Vitamin D 100000 IU/month as an adjuvant therapy for 6 months led to a better improvement in regulating menstrual abnormalities (menstrual regularity in 70% vs. 58% patients, p: 0.211), follicle maturation (>14 mm observed in 28% vs. 22% patients, p: 0.698), and infertility (pregnancy occurred in 18% vs. 12% patients, p: 0.401) in infertile PCOS women vs. untreated counterparts as shown in Figure 5.[20]

Figure 5. Effect of vitamin D supplementation in infertile PCOS women[20]



- Vitamin D supplementation improves insulin resistance and lipid metabolism, reduces testosterone levels, inflammatory indicators and serum anti-mullerian hormone (AMH) levels, and regulates the menstrual cycle in women with PCOS.[21]
- A single dose of 300 000 IU vitamin D supplementation 2 months prior to ovarian stimulation significantly increases the endometrium thickness in PCOS women who undergo intrauterine insemination.[21] Vitamin D supplementation can help return serum vitamin D levels in infertile women with PCOS and IR to normal levels leading to an improvement in the quality of embryos and a significantly higher clinical pregnancy rate. Maintaining a normal serum vitamin D level in PCOS women is very important in achieving a successful clinical pregnancy following in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).[22]
- A study conducted in Indian women showed that vitamin D supplementation of 60,000 IU weekly for 12 weeks in PCOS women decreased insulin resistance and increased in insulin sensitivity. Therefore, there is beneficial effect of vitamin D supplementation on ovulatory dysfunctions and insulin resistance.[23]
- High-doses of vitamin D daily (4000 IU), compared with low-dose (1000 IU), and placebo, showed beneficial effects on total testosterone, sex hormone-binding globulin (SHBG) and free androgen index (FAI). Vitamin D supplementation at high doses for a period of at least 12 weeks, may

PRACTICE POINTS

- **Optimal serum levels of ≥30 ng/mL is suggested to be achieved for desirable benefits.**
- **Based on varied research conducted, the currently widely accepted range for sufficient levels of serum vitamin D levels lie between 30 and 50 ng/mL which can be regarded as adequately and physiologically sufficient. (Level V-A)** [26]
- **The desirable optimal serum vitamin D levels should be maintained in the range of 50–70 ng/mL. (Level V-A)** [26]
- **PCOS women who were given vitamin D 4,000 IU daily for 12 weeks had significantly reduced total testosterone (TT), free androgen index (FAI), and increased SHBG. (Level I-B)**
- **Vitamin D sufficiency is also essential for successful in fertility enhancement.**
- **The European guidelines recommended the use of vitamin D supplements to obtain and maintain the 25(OH)D concentration in a range of 30–50 ng/mL (75-125 nmol/L). (Level IV-A)** [27]

lead to improvement in terms of glucose level, insulin sensitivity, hyperlipidemia, and hormonal functionality in PCOS women.[24]

- High-dose vitamin D supplementation (4000 IU/day) for 12 weeks to insulin-resistant women with PCOS had beneficial effects in total testosterone, SHBG, FAI, hs-CRP and TAC values compared with low-dose vitamin D (1000 IU/day) and placebo groups, but unchanged DHEAS, NO, GSH and MDA values.[25]

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Vitamin D in endometriosis

From left to right: Dr. Shobha, Dr. Silambuchelvi, Dr. Ketan Mehta, Dr. Pratap Kumar, Dr. Jaydeep Tank, Dr. Suvarna Khadilkar, Dr. Rishma Pai and Dr. Rohan Palshetkar

Introduction: Endometriosis

- Endometriosis is an inflammatory condition associated with the presence of endometrial-like tissue outside the uterine cavity. It mainly affects women of reproductive age, and is associated with wide range of symptoms, such as chronic pelvic pain, dysmenorrhea, infertility, dyspareunia, dysuria, dyschezia, and fatigue.[1]
- The etiology of endometriosis is multifactorial, and the following have been reported to be implicated in its pathogenesis:[2]
  - » Genetics
  - » Environmental factors such as:
    - – Exposure of pregnant women to toxins can increase the risk of endometriosis in their daughters, which includes in-utero exposure to dioxins and polychlorinated biphenyls.[3]
    - – Alcohol intake and exposure to endocrine-disrupting chemicals.[4]
  - » Alteration in immune system: Altered immune-cell recruitment, cell-adhesion, and upregulated inflammatory processes facilitates the implantation and survival of endometriotic lesions.[5]
- Chronic inflammation too plays an important role in the pathogenesis of endometriosis. Many studies have reported increased inflammatory cytokines, neutrophils, macrophages, and tumor necrosis factor-α in peritoneal fluid of patients with endometriosis.[2]

- Therefore, immunomodulatory agents can be beneficial in suppressing and overcoming endometriosis-associated symptoms.

Importance of nutrition in endometriosis

- Nutrition has been reported to influence some of the physiological and pathological processes associated with endometriosis, such as oestrogen activity, menstrual cyclicity, inflammation, organochlorine burden, and prostaglandin metabolism.[6]
- Researchers have suggested that addition of nutrients with anti-inflammatory, anti-oestrogen activities, such as antioxidants and omega-3 fatty acids, or both led to a reduction in endometriosis-related pain.[7]
- Vitamin D is an effective modulator of the immune system and an antioxidant. Dietary vitamin D intake and plasma hydroxyvitamin D concentration has shown to influence the risk of endometriosis. Various studies have suggested that vitamin D and expression of vitamin D receptor (VDR) in reproductive tissues may be involved in the pathogenesis of endometriosis. [2,8]

Role of vitamin D deficiency in the pathology of endometriosis

VDR in endometrium

- The classic genomic response of vitamin D is mediated through the VDR, which after binding with the active form of vitamin D interacts with regions of the DNA, called vitamin D response elements (VDRE), and regulates target gene transcription.[9]
- **Various cell types involved in immunologic reactions (monocytes, Langerhans cells, and T and B lymphocytes) express VDR. These immunologic properties attributed to vitamin D, along with VDR expression in reproductive tissues, including the uterus, ovary, and placenta, have led to the hypothesis of a possible association between endometriosis and the vitamin D system.[2]**
- 1, 25-dihydroxyvitamin D acts on the endometrium through regulation of specific genes and via immunomodulation. The endometrium in endometriosis expresses dysregulation of some vitamin D enzymes and receptors. If vitamin D and its metabolites are implicated in endometriosis-associated infertility, it is likely through interference with HOXA10 gene expression. [8]
- The genomic actions exerted by vitamin D through the VDR include antiproliferative and antineoplastic activities, such as activation of apoptosis, induction of cell cycle arrest and differentiation, inhibition of invasion and motility and inhibition of angiogenesis.[9]
- A dysregulation of the vitamin D pathway in the eutopic endometrium of women affected by endometriosis has been shown in a study, wherein VDR mRNA levels in epithelial and endometrial cells in women with laparoscopy-documented endometriosis were greater than in healthy women. [8]

Expression of VDR in endometriosis

- ***Cell types involved in immunologic reactions express VDR. The immunologic properties of vitamin D and expression of VRD in reproductive tissues has linked endometriosis with vitamin D.***
- ***Vitamin D acts on the endometrium through immunomodulation and regulation of specific genes. Interference with HOXA10 gene expression indicates implication of vitamin D on endometriosis-associated infertility.***
- ***Genomic actions of vitamin D include antiproliferative and antineoplastic effects.***
- ***VDR mRNA levels were greater in the endometrial cells in women with endometriosis, which indicated dysregulation of the vitamin D pathway in the endometrium of these women.***

Role of vitamin D binding protein in endometriosis

- Vitamin D binding protein (DBP) may play an important role in the progression of endometriosis.[10]
- DBP is known as a chemotactic factor that recruits neutrophils, monocytes, and fibroblasts, as it plays an important role in the immune system and at sites of inflammation.[10]
- The sequential contact of DBP with B and T cells is able to convert DBP into a potent macrophage-activating factor (Gc-MAF). The MAF stimulates macrophage activity at sites of inflammation or induces cell death in activated macrophages. This explains the relationship between vitamin D and endometriosis.[9]
- In a study, DBP was confirmed to be significantly increased in the ectopic endometrial tissue compared with that in the normal endometrial tissue ($p<0.05$).[10]

DBP and endometriosis

- ***Vitamin D binding protein (DBP) recruits' neutrophils, monocytes and fibroblasts, and plays an important role in the immune system and at sites of inflammation.***
- ***DBP is converted into a potent macrophage-activating factor on contact with B and T cells, which induces cell death in activated macrophages.***
- ***In women with untreated endometriosis, the expression of DBPE in the PF was significantly lower, which indicates relevance of vitamin D in the pathogenesis of endometriosis.***

- A study was conducted to examine the presence and expression of DBP in the peritoneal fluid (PF) and plasma of women with endometriosis. The expression of one DBP isoform (DBPE) in the PF of patients with untreated endometriosis was significantly lower than in the control group (patients with infertility, tubal sterilization or pelvic pain; $p<0.05$). The decreased level of DBPE in the PF but not in plasma of women with untreated endometriosis suggests that this molecule is relevant in the pathogenesis of disease.[11]

Association between vitamin D deficiency and risk of endometriosis

- Vitamin D modulates inflammation and proliferation in endometriotic cells, and a lower vitamin D status is associated with endometriosis.[12]
- A recent study has shown that women with serum levels of 25(OH)D <20 ng/mL had a 2.7 times higher risk of endometriosis than people with 25(OH)D serum levels >20 ng/mL (non-deficient) (OR=2.7). Therefore, people with vitamin D deficiency are at higher risk of endometriosis.[13]

Association of vitamin D with pelvic pain in endometriosis

- Endometriosis is the most common cause of chronic pelvic pain in women of child-bearing age, resulting in significant physical and social debility.[14]
- Vitamin D has been inconsistently implicated in chronic pain conditions, such as musculoskeletal pain, pain perception in elderly, premenstrual syndrome, fibromyalgia, and dysmenorrhea.[14]

Mechanism of vitamin D in combating pain

- $1,25(OH)_2D$ acts on the endometrium and decreases prostaglandin synthesis as well as increases prostaglandin inactivation by suppression of cyclo-oxygenase 2 and up-regulation of 15-hydroxyprostaglandin dehydrogenase, therefore reducing pain.[8]
- $1,25(OH)_2D$ may have a role in endometriosis-related pain as it plays a role as a reducer of angiogenesis *in vivo*, and the neuroangiogenesis, which is generally a leading cause of secondary dysmenorrhea.

Vitamin D in combating pain

- ***Vitamin D** reduces pain by suppression of cyclo-oxygenase 2 enzyme and decreasing prostaglandin **synthesis.***
- ***Vitamin D** plays a role as a reducer of angiogenesis in vivo, and the neuroangiogenesis, which is a leading cause of secondary dysmenorrhea **in endometriosis-related pain.***

Vitamin D supplementation in women with endometriosis-related pain

- In women with primary dysmenorrhea, a single oral dose of cholecalciferol (300,000 IU/mL) 5 days before their expected menses led to a 41% reduction in the mean pain score in the vitamin D treated group, over the 60-day study period ($p<0.01$) vs. placebo group. The greatest reduction of pain scores ($r=-0.76$; $p<0.01$) was noted in women with severe pain at baseline. [8]
- Use of cholecalciferol in patients with low plasmatic levels of 25(OH)D also allows limiting the use of non-steroidal anti-inflammatory drugs. [8]
- In young women with endometriosis, supplementation with vitamin D 2000 IU daily for 6 months led to significant changes in pelvic pain.[15]

Endometriosis associated infertility and role of vitamin D

- Around 25%–50% of infertile women have endometriosis, and 30%–50% of women with endometriosis are infertile. Various biological mechanisms such as distorted pelvic anatomy, altered peritoneal function, ovulatory abnormalities and impaired

implantation may be responsible for linking endometriosis and infertility.[8]

- The monthly fecundity rate of women with endometriosis has been reported to be 2%–10%, which is lower than the rate of 15%–20% reported for healthy women; greater the severity of the disease, lower the fecundity.[16]
- A large cohort study of women under 35 years of age showed that women with endometriosis were twice as likely to experience infertility as women without endometriosis.[17]
- With no intervention, about 50% of women with mild endometriosis can conceive; of those with moderate endometriosis, only 25% can conceive, and only a few with severe disease can conceive.[18]

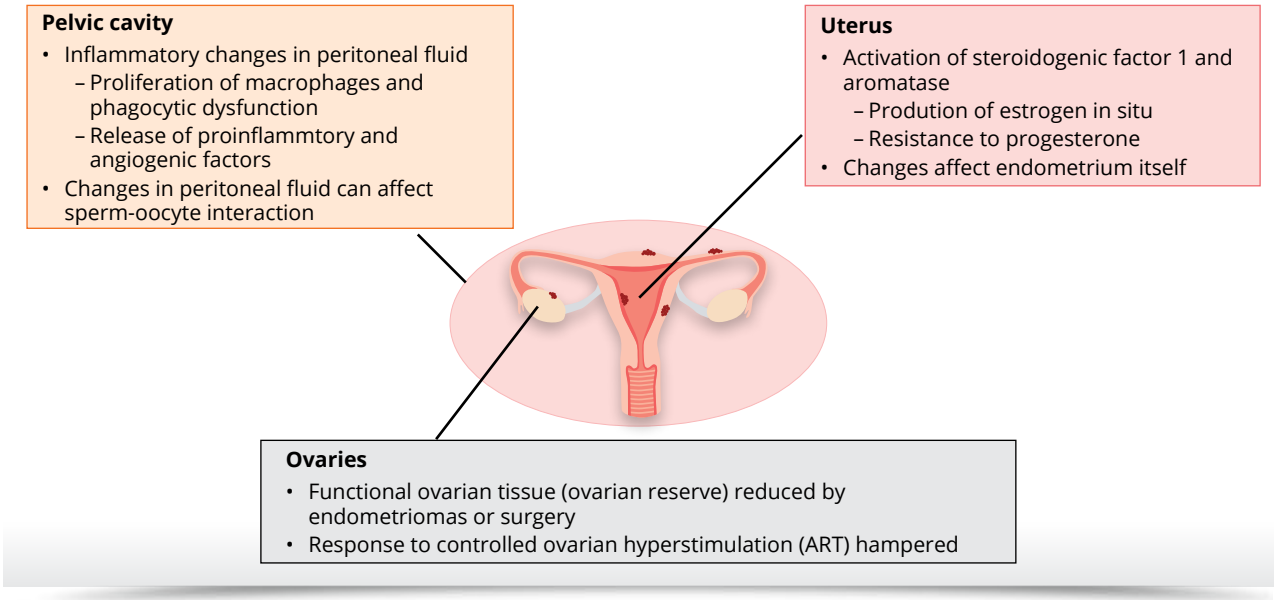
Possible mechanisms that link endometriosis with infertility

- The possible mechanisms by which endometriosis could affect fertility, the processes are described in Figure 1, according to whether they take place in the pelvic cavity, ovaries, or uterus.[16]
- Half of women with endometriosis have low αvβ3 expression which is also a reason for high failure rate of assisted reproductive technologies, as eutopic endometrium has shown to have reduced expression of biological markers of endometrial receptivity such as αvβ3 integrin, glycodelin A, osteopontin, and HOXA10.[8]

Treatment for infertile women with endometriosis[18]

- An inadequate endometrium can be considered as a main hindrance to fertility. Thin endometrium is associated with implantation failure and low implantation rates, therefore leads to infertility, and thus requires intervention.[19]
- Surgical treatment and subsequent intrauterine insemination with ovarian stimulation should be considered in women with minimal to mild endometriosis with infertility.[18]

Figure 1. Possible mechanisms by which endometriosis could affect fertility[16]



- In women with moderate to severe endometriosis, surgical treatment can reduce ovarian reserve and adversely affect subsequent IVF outcomes. [18]
- Clinicians are advised to assess ovarian reserve prior to deciding whether to surgically remove endometriotic lesions. [18]
- It is recommended to measure the AMH level at least 3 months postoperatively to decide on an optimal treatment plan. [18]

Role of Vitamin D in infertile women with endometriosis

- ***Vitamin D plays a role in implantation via HOXA10 gene and is a potent stimulator of the αvβ3 (biomarker of the implantation window).***
- ***Stromal endometrial cells express VDR and the active form of 1α-hydroxylase gene and protein. Endometrium is also a site of target of 1,25(OH)$_2$D actions through gene regulation and immunomodulation.***
- ***Vitamin D improves the thickness of endometrium, and therefore increases rates of pregnancy.***
- ***Vitamin D replete individuals are more likely to achieve a live birth through their IVF treatment vs. the insufficient or deficient counterparts.***

- Individualized care provided with this in mind to women with endometriomas prior to IVF may help optimize their pregnancy outcomes. [18]

Mechanism of action of vitamin D in infertile women with endometriosis

- 1,25(OH)$_2$D plays a role in implantation which involves direct transcriptional activation of HOXA10 gene, and is a potent stimulator of the αvβ3, which is a known biomarker of the window of implantation. [8]
- Further, stromal endometrial cells are shown to express VDR and the active form of 1α-hydroxylase gene and protein, independently of the menstrual cycle phase. The endometrium is also a site of 1,25(OH)$_2$D extra renal synthesis and a target of 1,25(OH)$_2$D actions through gene regulation and immunomodulation. [8]
- The intake of vitamin D has been shown to improve the thickness of endometrium.[20] Various reports have shown an increased pregnancy rate in patients with greater endometrial thickness (pregnancy rates ranged from 28.6% among patients with an endometrial thickness of ≤6 mm to 67.7% among patients with an endometrial thickness of >16 mm) during IVF-ET cycles. Implantation rates were also observed to increase with an increasing endometrial thickness.[21] Therefore, vitamin D can be postulated to have a role in the same.

PRACTICE POINTS

- Optimal serum levels of ≥30 ng/mL is suggested to be achieved for desirable benefits.
- As per the past consensus, serum vitamin D levels is suggested to be maintained at ≥50 ng/mL to achieve optimal clinical benefits in women with endometriosis.
- Vitamin D supplementation can be beneficial in improving pelvic pain, total-/HDL-cholesterol ratio, high-sensitivity C-reactive protein and total antioxidant capacity levels in patients with endometriosis. (Level I-B)
- Supplementation with vitamin D 2000 IU daily for 6 months can help in the management of endometriosis-related pain. (Level I-B)
- Supplementation of vitamin D_3 at moderate doses achieving 25(OH)D_3 serum concentrations of 30–80 ng/mL could be beneficial for reducing the risk of developing ovarian cancer. (Level V-B)[25]
- As per the international consensus guidelines, as vitamin D supplementation plays a beneficial role in human reproduction, maintaining the desirable effects of vitamin D is very crucial; therefore, the serum concentration of vitamin D should not fall <50 ng/mL. (Level V-B)[26]

- Research has also shown that women who are vitamin D replete are more likely to achieve a live birth through their IVF treatment than those who are vitamin D deficient or insufficient. Compared to women with deficient or insufficient vitamin D status, women with replete vitamin D status had more live births (odds ratio (OR): 1.33; 95% confidence interval (CI): 1.08 to 1.65), more positive pregnancy tests (OR: 1.34; 95% CI: 1.04 to 1.73) and more clinical pregnancies (OR: 1.46; 95% CI: 1.05 to 2.02).[22]

Effect of vitamin D supplementation in women with endometriosis

- As vitamin D may prevent disease progression of endometriosis, and that lower vitamin D status was associated with endometriosis; therefore, vitamin D supplementation can be a novel therapeutic strategy for managing the disease.[12]
- An inverse correlation exists between vitamin D levels and the occurrence of endometriosis. Women with high vitamin D plasma levels had a 24% lower risk of endometriosis than women with low plasma levels (rate ratio = 0.76, 95% CI 0.60–0.97; p trend=0.004).[23]
- Vitamin D supplementation in patients with endometriosis resulted in a significant improvement of pelvic pain, total-/HDL-cholesterol ratio, high-sensitivity C-reactive protein, and total antioxidant capacity levels.[24]

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Vitamin D in the management of gestational diabetes

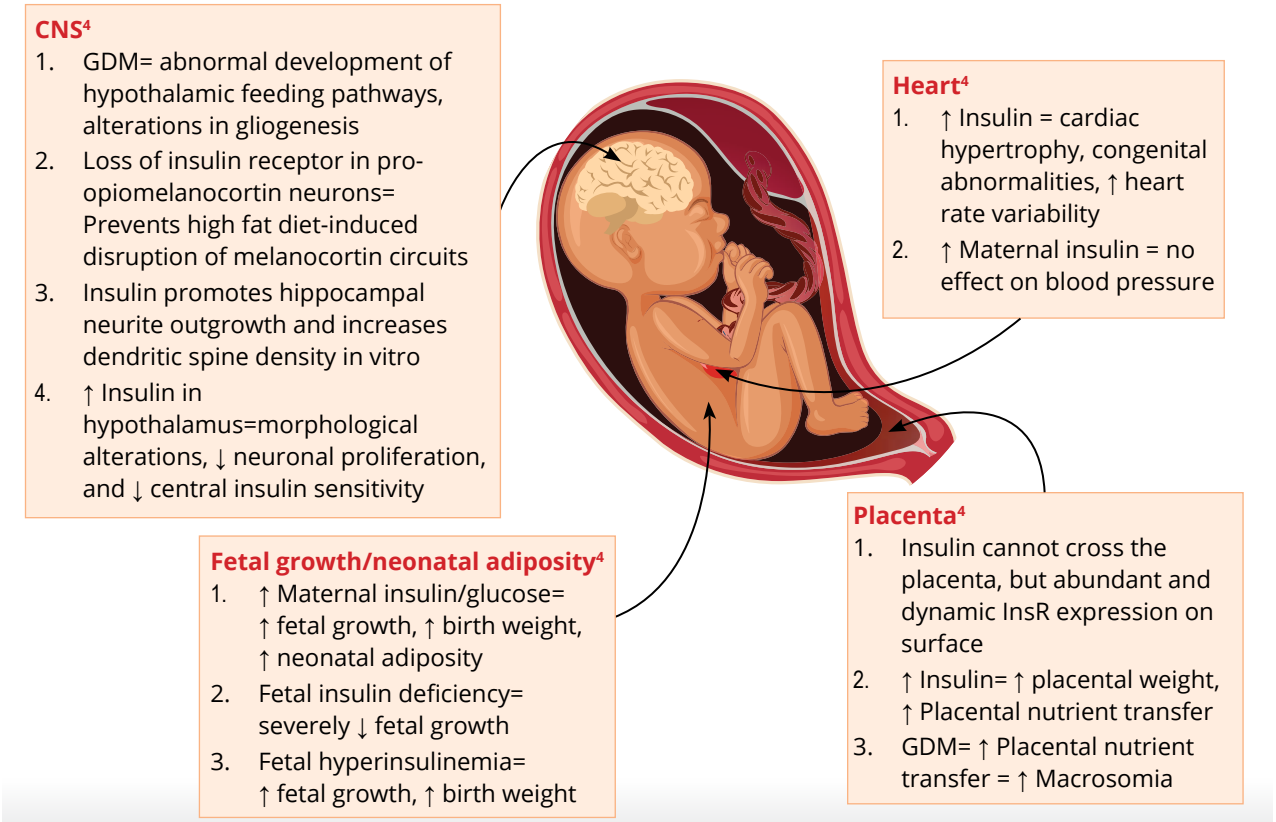
From left to right: Dr. Priyankur Roy, Dr. Ameya Purandare, Dr. Anita Singh, Dr. Nozer Sheriar, Dr. Parag Biniwale, Dr. R K Marwaha, Dr. Aruna Suman and Dr. Sukanta Misra

Introduction: GDM

- As per the American Diabetes Association (ADA), gestational diabetes mellitus (GDM) is usually diagnosed in the second or third trimester of pregnancy, and its prevalence has been increasing worldwide.[1]
- GDM is considered as an early marker of glucose intolerance, associated with both insulin resistance and impaired insulin secretion, and an increased risk of maternal and fetal complications during pregnancy. [2]
- Infants of mothers with GDM may have complications at birth such as macrosomia, birth trauma, respiratory distress syndrome, jaundice, and hypoglycemia, an increased rate of primary cesarean section, preterm labor, fetal growth retardation, and neonatal hypocalcemia as shown in Figure 1.[2]
- Clinicians should focus on preventing postpartum diabetes as well as preventing GDM development, since women with previous GDM have a more than seven-fold higher risk of developing postpartum diabetes than do those without GDM.[3]

Normal pregnancy[4]	GDM/obese pregnancy[4]
60% ↓ insulin sensitivity, maintain glucose-stimulated insulin release and hepatic insulin sensitivity	Heightened ↓ insulin sensitivity, loss of hepatic insulin sensitivity (greater postprandial increases in free fatty acids and increased hepatic glucose production because the liver does not maintain insulin sensitivity in pregnancies complicated by GDM or obesity).
Euglycemia	**Maternal and fetal hyperglycemia; fetal hyperinsulinemia**

Figure 1. Maternal and neonatal complications of GDM[4]



Importance of nutrition in GDM[5]

- Optimal fetal development can be ensured with an adequate dietary intake and nutrient status during pregnancy.
- Nutrient deficiencies are common during pregnancy due to consumption of diets with low nutrient densities. Research has shown that pregnant women are particularly at risk of inadequate intake of iron, folate, and vitamin D.
- Micronutrients are involved in various processes such as formation of new cells and tissues, enzyme activity, signal transduction and transcription pathways, and combating oxidative stress, and therefore its deficiency can adversely affect both maternal and fetal metabolic processes.
- Low vitamin D intake has been associated with a higher risk of GDM

Role of vitamin D deficiency in the pathology of GDM

There are a number of proposed mechanisms for the association between low vitamin D concentrations and the risk of GDM. [2]

Actions of vitamin D on pancreatic β-cell function and insulin sensitivity[2]

1. Vitamin D is thought to modulate pancreatic β-cell function and secretion by binding to its circulating active form of vitamin D with β-cell vitamin D receptor and regulating the balance between the extracellular and intracellular β-cell calcium pools.
2. It has also been proposed that vitamin D can promote insulin sensitivity by stimulating the expression of insulin receptors and

enhancing insulin responsiveness for glucose transport.

3. Since vitamin D is also known to regulate extracellular calcium, low vitamin D levels may lead to inadequate intracellular cytosolic calcium, which is required for the insulin-mediated intracellular processes and glucose regulation.

Association of vitamin D deficiency with deregulation of glucose homeostasis

Mechanisms of glucose homeostasis deregulation related to vitamin D deficiency status is elaborated in Figure 2.[6]

Multiple actions of vitamin D in diabetes patients

Vitamin D exerts multiple actions in patients with diabetes mellitus. It increases insulin responsiveness for glucose transport in the muscles, prevents beta cell damage in the pancreas, decreases inflammation in blood vessels, and improves insulin secretion. Beneficial effects of vitamin D is illustrated in the Figure 3:[7]

Association between low vitamin D levels and risk of GDM and postpartum glucose intolerance

A high prevalence of vitamin D deficiency exists in pregnant Indian women (~90%).[2] Obesity and increased age in the mother are independent risk factors for both vitamin D deficiency and gestational diabetes; which may link vitamin D deficiency and gestational diabetes.[8]

- A higher prevalence of GDM was observed among women with 1st trimester plasma total vitamin D in the lowest quartile (≤23.6 nmol/L) compared to the subjects

Figure 2. Mechanisms of glucose homeostasis deregulation associated with vitamin D deficiency[6]

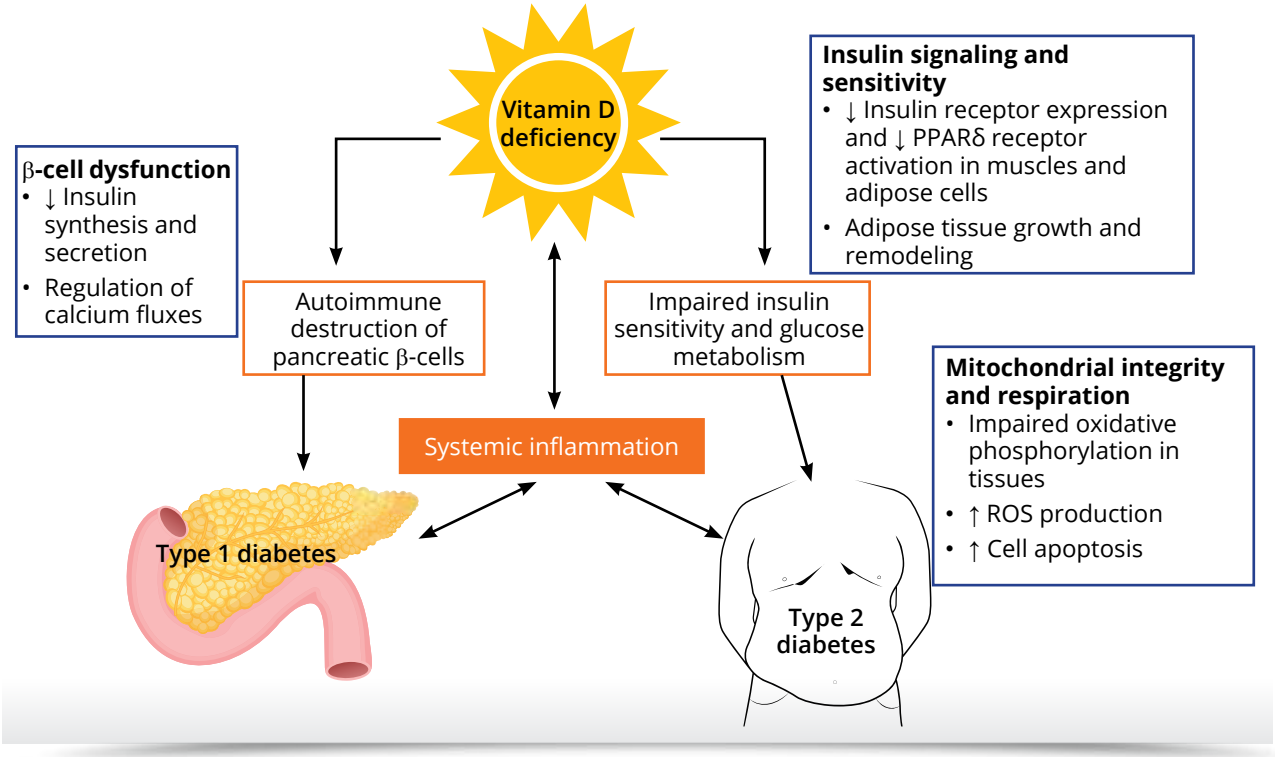
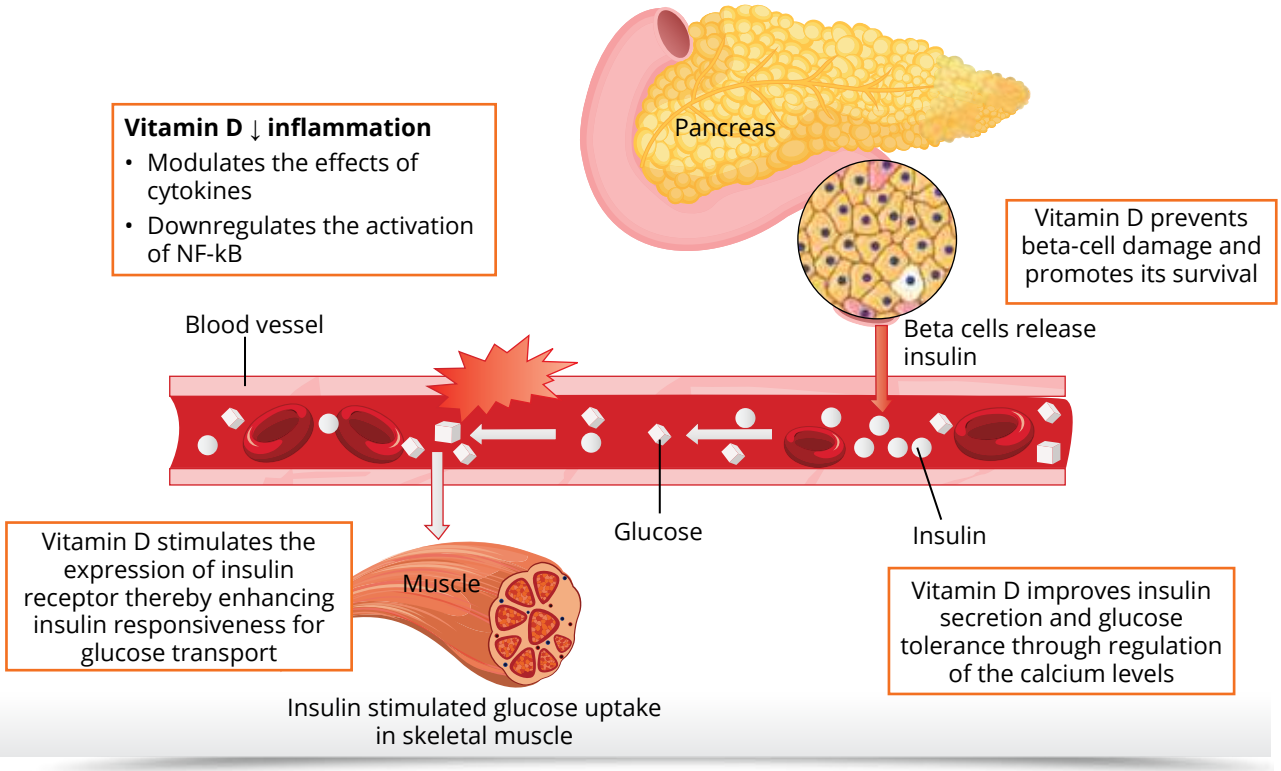


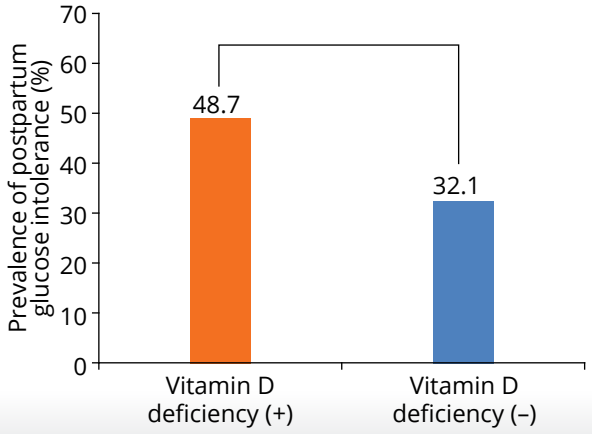
Figure 3. Mechanisms of action of vitamin D in diabetes[7]



in the other three quartiles (16.1 vs. 8.6%, p=0.033).[2] It was observed that 81.5% of the women had plasma vitamin D concentrations that would classify them to be "insufficient" and about 50% of the women diagnosed to have GDM had vitamin D concentrations <30 nmol/L (<12 ng/mL).[2]

- In a study, women with vitamin D deficiency had a higher prevalence of postpartum glucose intolerance than did those without vitamin D deficiency (48.7% vs. 32.1%, p=0.011) as shown in Figure 4.[9]

Figure 4. Prevalence of postpartum glucose intolerance in women with vitamin D deficiency[9]



- The risk of postpartum glucose intolerance was 2.00 times (95% confidence interval, 1.13 to 3.55) higher in women with vitamin D deficiency than in those without vitamin D deficiency (p=0.018). Even after adjustment for the cofounders, the risk of postpartum glucose intolerance was still 2.00 times (95% confidence interval [CI], 1.13 to 3.55) higher in women with vitamin D deficiency than in those without vitamin D deficiency (p=0.018; Table 1). Hence, vitamin D deficiency at mid-pregnancy is associated with an elevated risk of postpartum glucose intolerance in women with GDM.[9]

Table 1. OR for postpartum glucose intolerance according to serum 25(OH)D level in pregnancy

Vitamin D status	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Serum 25(OH)D ≥20 ng/dL	Reference		Reference	
Serum 25(OH)D <20 ng/dL	2.01 (1.19–3.39)	0.009	2.00 (1.13–3.55)	0.018

Adjusted for maternal age, pre-pregnany body mass index, weight gain, family history of diabetes, blood pressure (systolic and diastolic), and season. OR, odds ratio; 25-hydroxyvitamin D; CI: confidence interval

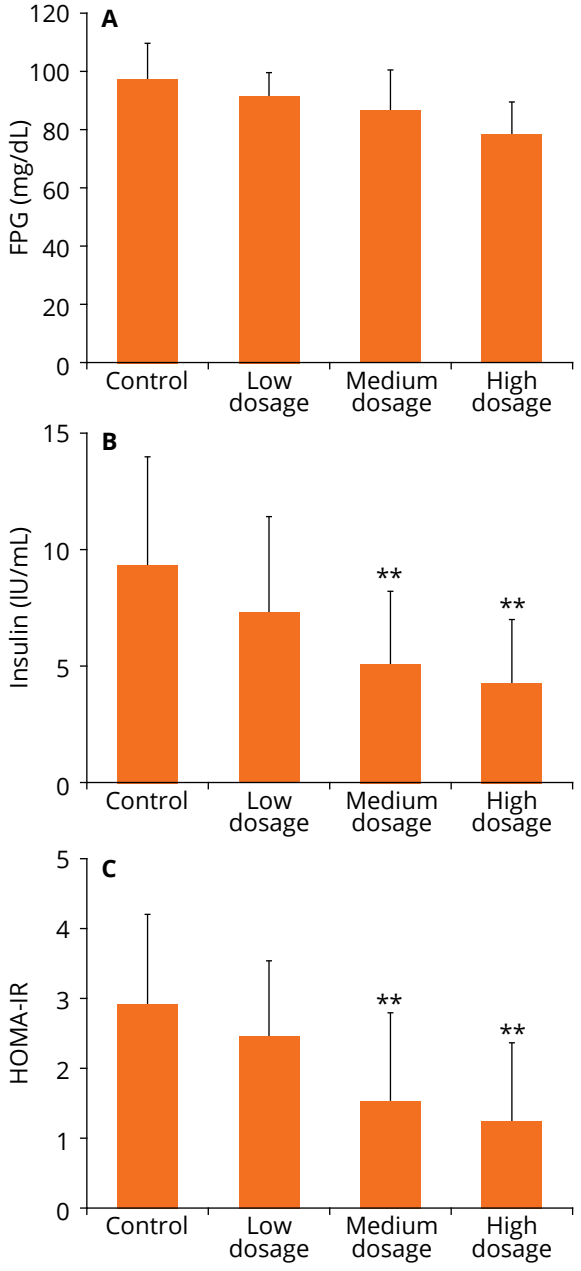
Vitamin D supplementation prevents GDM and postpartum glucose intolerance

- Vitamin D co-supplementation with calcium or omega-3 fatty acids in women with GDM had beneficial effects on metabolic parameters such as FPG, HOMA-IR, quantitative insulin sensitivity check index, and lipid profiles. To prevent postpartum glucose intolerance, vitamin D supplementation during the entire pregnancy period may be necessary.[8]
- A systematic review and meta-analysis showed that daily vitamin D supplementation (800–1,000 IU per day) had protective

Benefits of vitamin D supplementation in GDM

- ***Protective effects on maternal health outcomes before and after childbirth and on the newborn.***
- ***Reduces the risk of GDM; more significant effects in obese women.***
- ***Improves insulin resistance in pregnant women with GDM.***
- ***High dose reduces insulin, homeostatic model assessment-insulin resistance, and total cholesterol in GDM.***
- ***Elevates total antioxidant capacity and total glutathione levels.***
- ***Decreases fasting blood glucose, glycated hemoglobin and serum insulin concentration.***

Figure 5. Effect of different doses of vitamin D supplementation on (A) FPG (B) insulin and (C) HOMA-IR in patients with gestational diabetes mellitus[11]

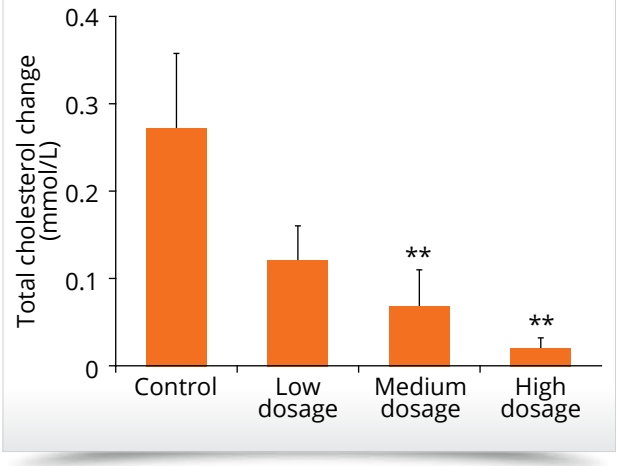


Data are presented as mean ± standard deviation. **p<0.01 vs. control group. FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment-insulin resistance.

effects on maternal health outcomes before and after childbirth and/or on the newborn. Vitamin D supplementation during the gestational period also had a positive effect on glycemic, sensitivity, and insulin resistance as well as metabolic characteristics (decreases total and LDL-cholesterol concentrations, and decreases levels of serum high-sensitivity C-reactive protein).[8]

- The level of vitamin D in pregnancy is significantly related to the outcome of gestational diabetes mellitus. Vitamin D > 20 ng/mL can reduce the risk of GDM, and the protective effect of vitamin D is more significant in obese pregnant women.[10]
- High-dose vitamin D supplementation (every 2 weeks) significantly improved insulin resistance in pregnant women with GDM.[11]
- It was determined that insulin, homeostatic model assessment-insulin resistance and total cholesterol were significantly reduced by high dosage vitamin D supplementation ($p<0.05$) as shown in Figure 5 and Figure 6.[11]

Figure 6. Effect of different doses of vitamin D supplementation on lipid concentrations, including total cholesterol change[11]



- Total antioxidant capacity and total glutathione levels were significantly elevated as a result of high dosage vitamin D supplementation ($p<0.01$).[11]
- **Vitamin D supplementation of 1000–4762 IU/day in pregnant women with GDM was associated with a decrease in fasting blood glucose** by a mean of 0.46 mmol/L (−0.68, −0.25) ($p<0.001$), glycated hemoglobin by a mean of 0.37% (−0.65, −0.08) ($p<0.01$) and serum insulin concentration by mean of 4.10 μIU/mL (−5.50, −2.71) ($p<0.001$) compared to controls. Therefore, has the potential to promote glycemic control in women with GDM.[12]
- The functions of vitamin D at different stages of pregnancy, and its relation to different clinical outcomes, and the appropriate 'critical windows' for measuring and treating deficiency or insufficiency in line with relevant pregnancy outcomes still remains uncertain.[13]

Recommended dosage of vitamin D during pregnancy

- A substantial variation in dosage regimens were observed between studies, few trials used daily or weekly doses ranging between 200 IU to 5000 IU, and the few studies used **biweekly or monthly doses of 50,000 IU, or bolus doses of 50,000, 60,000 or 120,000 IU** at different frequencies and time points during the course of the pregnancy.[13]
- In 2011, guidelines released by the Endocrine Society suggested that all pregnant and lactating women with vitamin D deficiency

receive 1000–2000 IU of vitamin D daily in addition to the 400 IU provided in prenatal vitamins.[13]

- Doses of 2,000 and 4,000 IU have been used in subjects under endemic vitamin deficiency obtaining vitamin levels above the 30 ng/mL and with significant increases in cord blood.[14]

PRACTICE POINTS

- **Vitamin D >20 ng/mL has shown to reduce the risk of GDM; therefore, optimal serum levels of ≥30 ng/mL is suggested to be achieved for desirable benefits.**
- **As per the passed consensus, serum vitamin D levels is suggested to be maintained at ≥50 ng/mL to achieve optimal clinical benefits in women during pregnancy.**
- **The Endocrine Society Guidelines suggest that all women, including pregnant and lactating women with vitamin D deficiency receive 1000–2000 IU of vitamin D daily. (Level IV-A)**
- **It is recommended that the daily dosage of vitamin D would be 1000 IU for maintenance, 2000 IU for deficiency, with a maximum dose per day being 4000 IU. (Level V-C)**
- **Weekly dose of 60,000 IU for 6 to 8 weeks is suggested for women presenting with a deficiency late in pregnancy. (Level V-C)**

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Vitamin D in women with low back pain

From left to right: Dr. Ram Chaddha, Dr. Aditi Tandon, Dr. Kiranmai Devineni, Dr. Vidya Pancholia, Dr. Jayam Kannan, Dr. Madhuri Patel, Dr. Neerja Bhatla, Dr. Niranjan Chavan, Dr. Kawita Bapat and Dr. Archana Verma.

Introduction: LBP

Pregnancy and post-partum[1]

- Low back pain (LBP) is common in pregnant women, has specific characteristics, and is more frequent in the second trimester of pregnancy.[1]
- LBP has shown to affect at least half of the pregnant population. Around 5% to 40% of patients are reported to experience LBP at some point during pregnancy or at 6 months post-delivery.[1]

Menopause and hormonal issues

- LBP is also often caused due to lumbar disc degeneration (LDD), a common musculoskeletal disease, due to dramatic drop in estrogen levels in postmenopausal women.[2]
- Older women are more likely to have severe LDD and LBP than their male counterparts.[2] Women with a higher menopause symptom burden may be the most vulnerable for chronic back pain.[3]
- Estrogen participates in a variety of biological processes through different molecular mechanisms. [3] The cartilage collagen synthesis in joints is reduced with decrease in blood estrogen levels in postmenopausal women. Therefore, women are more prone to suffer from osteoarthritis than men.[4] Hence, collagen wasting is commonly observed in bone and skin in the postmenopausal period due to decreased estrogen levels.[3]

Dysmenorrhea

- LBP during menstruation is reported by 33% to 56% of the women and is the third most common menstrual distress symptom.[5] Lower back pain (61.4%) was reported to

be among the most common complaint in women with premenstrual syndrome.[6]

- Menstrual low back pain (MLBP) is the third most common form of menstrual discomfort; it affects 46% to 56% of the population, and the proportion increases with age. Among young women who experience MLBP, 58% to 90% manage the condition through conservative approaches, such as resting.[7]

Endometriosis[8]

- Endometriosis is a very common condition in fertile woman and professional who treat patients with LBP has to investigate gynecological diseases which often manifest with musculoskeletal disorders, such as LBP.
- A possible hypothesis is that endometrial implants cause a compression on the lumbosacral plexus, sometimes generating disorders at both lumbar spine and lower limbs, even with neurological deficits.
- Inflammation in the bladder or uterus results in vasoconstriction of the connective tissue in the abdomen, lower back, pelvic girdle and thighs. The viscerocutaneous reflex in one example of the phenomenon known as 'viscerosomatic convergence', in which the visceral and somatic afferent nerves converge on the same dorsal horn transmission cell of the spinal cord.

Post-operative LBP[9]

- Gynecological surgery might serve as a clinically silent marker for altered motor control of the lumbopelvic junction, possibly from surgically induced dysfunction of local muscles, leading to LBP later in life. Women with a history of surgery are more prone to demonstrate these changes vs. those without a surgery history.
- Older women treated with hysterectomy reported a significantly higher degree of moderate severity of LBP in later life
- Prior gynecological surgery is reported to compromise the core stability MCS of the lumbopelvic region, requiring greater large-muscle activation for low-load stability, leading to excessive abdominal pressure generation relative to pelvic floor muscle, ligament, and fascia support.

Role of vitamin D deficiency in the pathology of LBP

- Numerous mechanisms provide rationale for the link between vitamin D and the risk of LBP, including:[10]
  - » The regulation of anti- and pro-inflammatory cytokines that control pain and inflammation
  - » The modulation of pain through sensory neuron excitability
- It is well-established that vitamin D can facilitate the uptake of calcium and lead to bone mineralization, which is particularly important for women where age and hormonal-related bone density loss can increase the risk of osteoporosis, potentially resulting in pain. [10]
- An inverse relationship exists between inflammatory markers and serum concentrations of 25-hydroxyvitamin D (25[OH]D), with research showing reductions in inflammatory markers following vitamin D supplementation.[11]

Actions of vitamin D in managing pain in LBP

- ***Vitamin D reduces the levels of inflammatory markers, and regulates anti- and pro-inflammatory cytokines that control pain and inflammation***
- ***Vitamin D modulates pain through sensory neuron excitability***
- ***Vitamin D facilitates the uptake of calcium and leads to bone mineralization***

Vitamin D deficiency and insufficiency in LBP

- The prevalence of vitamin D deficiency is high in the Indo-Pak subcontinent and range from 50 to 90%.[10] Low vitamin D concentration in blood is a significantly associated factor for the development of LBP in adults along with other risk factors.[8] The association of chronic LBP with vitamin D deficiency is more prominent in females of old age as compared to males of the same age.[12]
- Smoking, severe vitamin D deficiency, lack of vitamin D supplementation, high body mass index, and osteoporosis are associated with a higher prevalence of moderate-to-severe pain.[11] Literature has demonstrated that in cases of vitamin D deficiency, the neuromuscular disorders can occur as a consequence of hypersensitivity and sensorial hyper-innervations in the muscles.[13]
- Vitamin D deficiency (serum level < 20 ng/mL) and insufficiency (serum level < 30 ng/mL) have been linked with skeletal health and disorders, such as osteoporosis, osteomalacia, or rickets.[10]
- A serum vitamin D concentration <10 ng/mL is a marker of severe lumbar disc degeneration and LBP. A recent study conducted in postmenopausal women showed that participants with severe vitamin D deficiency (<10 ng/mL) had more severe disc degeneration in the lumbosacral region (L4-S1, L1-S1, $p<0.05$), than those with sufficient levels. The severely deficient group had higher visual analog scale (VAS) scores for LBP ($p=0.002$) and lower bone mineral density T scores ($p=0.004$) than the other groups.[13]
- Patients with LBP are more likely to have vitamin D deficiency (particularly severe deficiency) and lower serum concentrations of 25(OH)D, compared to those without LBP.[11]
- The relationship between vitamin D deficiency and LBP is stronger in women and in those <60 years old. This may highlight the importance of screening for severe vitamin D deficiencies in these populations to potentially reduce the risk of serious disease. This may also provide a rationale for vitamin D supplementation in the management of LBP in this population or considering vitamin D supplementation to reduce the risk of developing LBP.[11]

Effect of vitamin D supplementation in LBP

- Vitamin D supplementation increases plasma levels of 25(OH)D_3 potentially correcting the effects of vitamin-D deficiency. Evidence has shown that two- thirds of patients with chronic LBP achieved normalization of vitamin D levels after **supplementation with 60,000 IU of oral vitamin D3 given every week for 8 weeks.**[14]

» An improvement in vitamin D levels from a mean baseline level of 12.8 ng/mL to 36.07 ng/mL post-supplementation was observed.

» A significant reduction in pain score and improvement in functional ability with the vitamin D supplementation was also observed in patients with chronic LBP.

- Another study showed that patients aged 20–65 years with chronic LBP for ≥3 months not responding to medications and physical therapies, having serum **vitamin-D level <5 ng/mL were given 60,000 IU daily orally for the initial 5 days and then 60,000 IU every week for the next 8 weeks.** An improvement was observed in the Mcgill Pain Questionnaire (MPQ) which was used to measure the state of pain, and other scores use for evaluating pain-related functional capacity and the flexibility of trunk flexion.[15]

Recommendations for dose and serum vitamin D levels by several societies

Table 1. Recommendations for treatment of vitamin D deficiency or insufficiency[16] (Level IV-A)

Serum 25(OH) D level (ng/mL) (adults [19–70 years] and elderly [>70 years])	Vitamin D3 supplementation dose (IU)	Frequency of vitamin D supplementation
< 30	10,000	Daily
	60,000	Weekly for 8 weeks, and then once a month for long term
To maintain serum concentrations consistently >30	1500–2000 IU	Daily

NOTE. These doses are in addition to what the patient is ingesting at baseline. Patients receiving more than the equivalent of 2,000 IU of vitamin D3 daily in supplements should have 25(OH)D levels monitored approximately every 12 weeks.

- The American College of Obstetricians and Gynecologists (ACOG) recommends treatment with 1000-2000 IU of vitamin D daily in pregnant/lactating women with vitamin D deficiency. Most experts agree that 1,000–2,000 IU per day of vitamin D is safe.[17] **(Level IV-A)**
- The IOM recommends an intake of 600 UL of vitamin D to pregnant women with the goal to achieve in serum more than 20 ng/mL 25(OH)D considered by them as a sufficient level.[18] **(Level IV-A)**
- US Endocrine Society suggests that at least 1,500–2,000 IU/of vitamin D may be needed to maintain blood levels of 25(OH)D above 30 ng/dL and that should be considered the sufficient level for pregnant women.[19] **(Level IV-A)**
- The **European guidelines recommended the use of vitamin D supplements to obtain and maintain the 25(OH)D concentration in a range of 30–50 ng/mL**.[20] **(Level IV-A)**

PRACTICE POINTS

- **Optimal serum levels of ≥30 ng/mL is suggested to be achieved for management of LBP associated with gynaecological conditions.**
- **Based on varied research conducted, the currently widely accepted range for sufficient levels of serum vitamin D levels lie between 30 and 50 ng/mL which can be regarded as adequately and physiologically sufficient. (Level V-A)[21]**
- **The expected optimal serum vitamin D levels for desired outcomes should be 50–70 ng/mL.[21] (Level V-A)**

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Vitamin D in pelvic floor disorders

From left to right: Dr. Dr. Jamuna Devi, Dr. Krishna Kumari, Dr. Elizabeth Jacob, Dr. Shyjus Nair, Dr. Basab Mukherjee, Dr. S. Shantha Kumari, Dr. Basab Mukherjee, Dr. Anahita Chauhan, Dr. Manjula Anagani, Dr. Karishma Thariani and Dr. T Vindhya

Introduction: Pelvic floor dysfunction

- The pelvic floor is a group of dome-shaped muscles and fascia surrounding the urethra, vagina, and anus. The pelvic floor maintains the stability of internal organs and participates in continence, micturition, defecation, sexual functions, and childbirth through proper coordination with the nervous system, ligaments, and fascia, as well as proper contraction and relaxation of pelvic floor muscles (PFM).[1]
- PFM can contract voluntarily on demand and involuntarily in response to increased intra-abdominal pressure, such as during physical activity or coughing.[1]
- They can also relax, returning to the initial muscle tone after voluntary contraction. Any disturbance in the functions of PFM causes their dysfunction. Pelvic floor consists of muscles, ligaments, fascia, and the visceral system.[1]
- PFM can be divided into three layers. The first or the most external layer is the urogenital triangle. The middle layer is the urogenital diaphragm and the third or the deep layer is the pelvic diaphragm, which is made up of levator ani and coccygeus.[1]

Weakness of the levator muscle group, which provides essential support to the pelvic floor, is the main factor in pelvic floor dysfunction (PFD).[1]

Pelvic floor dysfunction: Prevalence and impact

- PFD represents a broad collection of symptoms and anatomic changes associated with the abnormal function of the pelvic floor musculature.[2]
- The disordered function results in either increase activity (hypertonicity) or diminished activity (hypotonicity) or inappropriate coordination of the PFM.[2]
- PFD is associated with a significant burden on the healthcare system and a poor quality-of-life for individuals suffering from it.[3]
- Strategies for managing PFD are focused on the course of pregnancy, mode and management of delivery, and pelvic exercise methods.[3]

Prevalence of PFD in women of reproductive age and post-menopausal age

- PFD represents a substantial global health problem affecting hundreds of millions of women throughout the world. The prevalence of PFDs in women is summarized in Figure 1.[4]
- The aging process seems to play a negative role in either the function or structure of the pelvic floor in women.[5]
- Aging contributes to the deterioration of pre-existing PFD during the life span of a woman or interact with other potential predisposing factors (Figure 2).[5]

Figure 1. Prevalence of pelvic floor disorders[2,4]

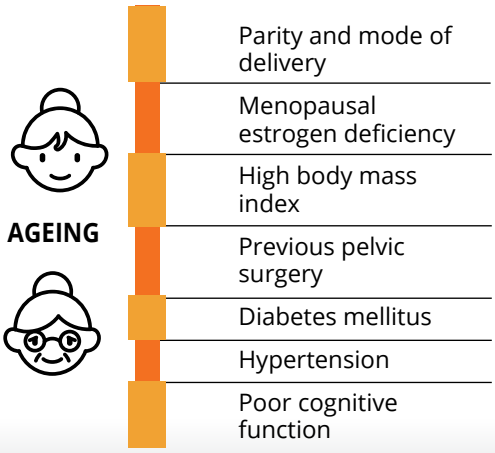
Global prevalence

- The prevalence of at least one form of PFD has been reported to be as high as 46%.
- ~ 10% of women between 20-39 years, compared with 50% of women aged ≥ 80 years, suffer from at least one PFD

Prevalence in India

- A study carried out in India showed a prevalence of 17.33%.
- The prevalence of PFDs increased from 2.91% among 20 to 29 year old participants, to 16.16% among 70 years and older.

Figure 2. Aging and risk factors for pelvic floor disorders[6]



Importance of nutrition on health

- Nutritional status and health are important determinants of whether people can lead an active and healthy life.[7] Consumption of a diverse diet including plant and animal source foods as well as fortified foods is required for an adequate intake for each of these nutrients. Poor nutrition is responsible for many chronic diseases including obesity, heart disease, and some cancers.[7]
- Women of reproductive age worldwide are increasingly becoming vitamin D deficient due to increased rates of obesity, sedentary

lifestyles, and large amounts of time spent indoors, along with sun avoidance behaviours and use of sunscreen due to fear of skin cancer.[8]

- Low vitamin D status is associated with impaired fertility, endometriosis and polycystic ovary syndrome and PFD.[9-10]
- It is important to pay special attention on the medical and social fronts to combat this preventable epidemic of vitamin D deficiency.[11]

Prevalence of vitamin D deficiency in women with PFD

- The deficiency of vitamin D is clinically associated with impaired muscle strength and loss of muscle mass. A low vitamin D status contributes to the development of poor muscle strength, resulting in PFD.[12]
- A cross-sectional study on women presenting to the gynecology outpatient department showed a very high prevalence of vitamin D deficiency in women with symptoms of PFD, with 75% patients showing deficient levels and 17.5% showing insufficient levels.[12]

There was a high prevalence of vitamin D deficiency in women with symptoms of PFD, with 75% patients showing deficient levels and 17.5% showing insufficient levels

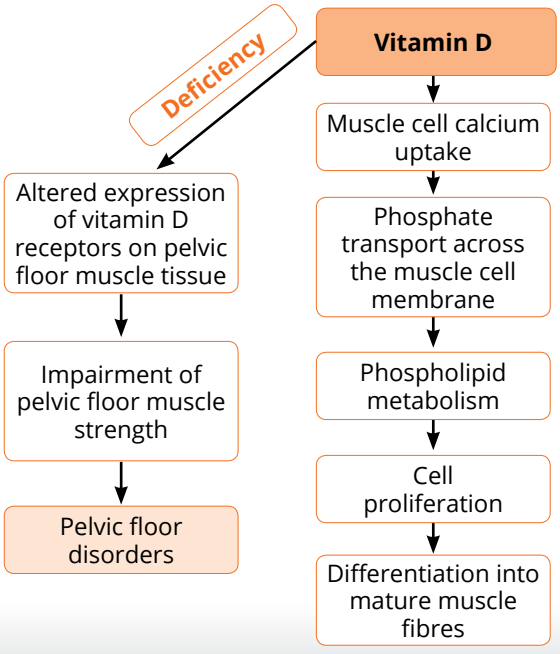
Role of vitamin D in the pathology of PFD

- The direct effect of vitamin D on muscle physiology is biologically plausible since vitamin D receptors are present in human muscle tissue.[12]
- Cell culture studies have identified the specific receptors for the vitamin D active metabolite, $1,25(OH)_2D_3$, on skeletal muscle myoblasts and myotubes.[12]
- A host of cell-signaling pathways are induced by exposure of muscle cells to $1,25(OH)_2D_3$ in vitro.[12]

Deficiency of vitamin D is clinically associated with impaired muscle strength and loss of muscle mass.

- The activation of these pathways may play a role in regulating the force of muscle contraction in a muscle fiber.[12]
- Vitamin D affects several functions including muscle cell calcium uptake, phosphate transport across the muscle cell membrane, phospholipid metabolism and mediate cell proliferation and subsequently differentiation into mature muscle fibres (Figure 3).[13]

Figure 3. Vitamin D and pelvic floor disorders[13-14]



- Vitamin D receptors (VDR) are present in the brain, bone, and muscle tissue. In vitro

studies have suggested that vitamin D exerts a potentially selective effect of vitamin D on type II muscle fibers.[13]

Vitamin D affects PFM strength, and its deficiency can lead to impaired PFM strength and PFD. Women with PFD have an adverse quality-of-life. Supplementing vitamin D in women with PFD may improve PFM strength, symptoms as well as QoL.[13]

- Hence, vitamin D deficiency is implicated in impaired muscle strength, leading to postural instability and increased risk of fall.[13]
- Disorders of the pelvic floor include urinary incontinence (UI), fecal incontinence (FI), pelvic organ prolapse (POP), and other storage and emptying problems of the lower urinary and gastrointestinal tracts.[15]

Vitamin D and muscle pathophysiology

- Since a strong relationship exists between vitamin D and calcium, vitamin D also affects muscle function by affecting calcium homeostasis.[15]
- Furthermore, vitamin D may affect muscle strength by influencing cell proliferation and differentiation and muscle fibre size (Figure 4).[15]
- Vitamin D also protects against muscle degradation by preventing fatty degeneration, insulin resistance, and arachidonic acid mobilization. Hence, the role of vitamin D on the efficiency of muscle function that is distinct from the role of calcium in muscle contractility.[15]

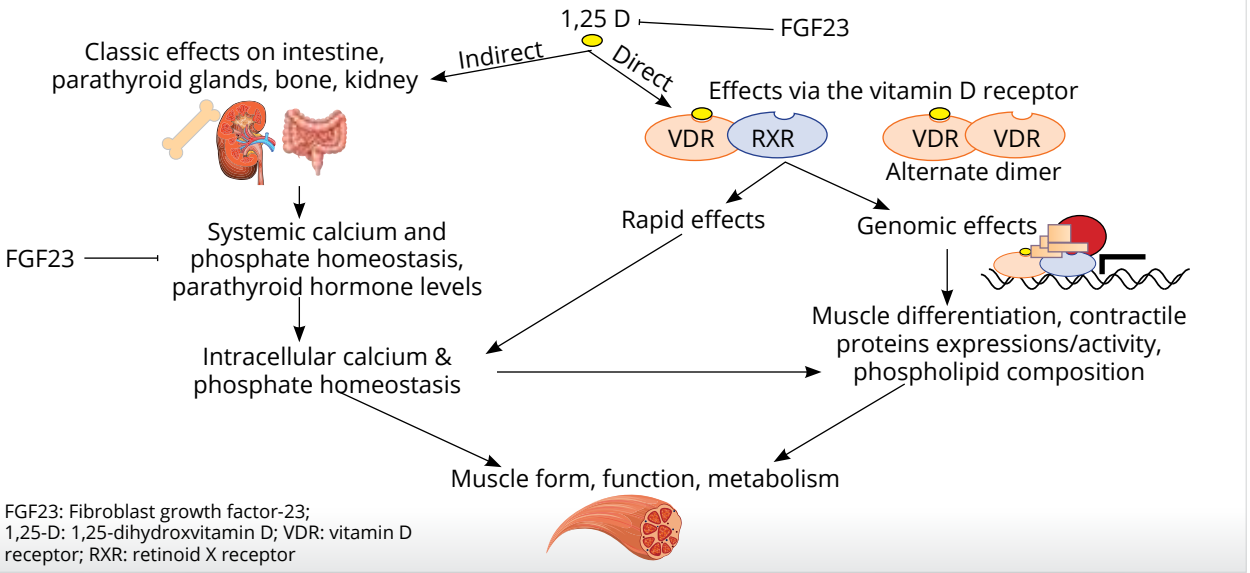
Vitamin D status and bladder function

- VDR are present in the bladder neck comprising the urothelium and the inner longitudinal, middle circular, and outer longitudinal smooth muscle layers of the bladder wall.[15]
- Furthermore, VDR are also distributed throughout the bladder wall.[15]

Correlation between vitamin D and PFD

- ***Exposure of muscle cells to vitamin D3 induces a host of cell-signaling pathways which regulate the force of muscle contraction in a muscle fiber.***
- ***Vitamin D plays a role in muscle cell calcium uptake, phosphate transport across the muscle cell membrane, phospholipid metabolism and mediate cell proliferation and subsequently differentiation into mature muscle fibres. It can thus affect muscle strength.***
- ***Vitamin D protects against muscle degradation by preventing fatty degeneration, insulin resistance, and arachidonic acid mobilization.***
- ***VDR is distributed throughout the bladder wall. Therefore, vitamin D deficiency or insufficiency can result in abnormalities in calcium homeostasis with subsequent abnormal detrusor contractility.***
- ***Further, insufficient serum 25(OH)D may allow for more inflammatory cytokine activity with resultant bladder wall inflammation.***
- ***Deficient and insufficient 25(OH)D concentrations may also contribute to PFM weakness. Thus, all of these factors can predispose women to PFDs.***

Figure 4. Vitamin D and muscle function[16]



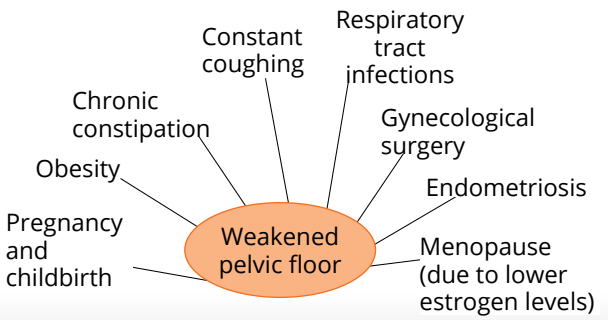
FGF23: Fibroblast growth factor-23; 1,25-D: 1,25-dihydroxvitamin D; VDR: vitamin D receptor; RXR: retinoid X receptor

- Since the active metabolite [1,25(OH)D2] acts through the VDR, vitamin D deficiency or insufficiency may result in abnormalities in calcium homeostasis with subsequent abnormal detrusor contractility.[15]
- Weakened detrusor muscles may also become hyper-contractile.[15]
- Additionally, insufficient serum 25(OH)D may allow for more inflammatory cytokine activity with resultant bladder wall inflammation.[15]

Vitamin D deficiency and pelvic floor weakness

- Several factors can contribute to the weakening of the pelvic floor (Figure 5) which may subsequently cause muscle and or nerve damage.[15]
- Studies have demonstrated an association between low vitamin D skeletal muscle weakness. Deficient and insufficient 25(OH)D concentrations may also contribute to PFM weakness and predispose women to PFDs.[15]

Figure 5. Causes of pelvic floor dysfunction[1]



Deficient and insufficient 25(OH)D concentrations may also contribute to PFM weakness and predispose women to PFDs

Vitamin D deficiency may impair the function of urinary bladder leading to paravaginal defect symptoms

Effect of vitamin D supplementation

- A systematic review and meta-analysis revealed that vitamin D status is significantly compromised among women diagnosed with PFD, compared to healthy women.[17]
- Small case reports and observational studies suggest that there is an association between insufficient vitamin D and PFD symptom severity.[17]

Vitamin D dosage

- Deficiency may be adequately treated with many different therapeutic regimens of either cholecalciferol or ergocalciferol.[18]
- Nevertheless, the current evidence suggests that regular dosing with oral cholecalciferol (60,000 IU weekly) are effective in replenishing vitamin D stores following deficiency.[18]
- For long-term supplementation, smaller regular doses, such as cholecalciferol 1,000 IU daily, or 10,000 IU weekly, are suitable Table 1 elaborates the doses for treating and supplementing adults.[18]

Table 1. Treating and supplementing adults[18]

Dose
Treatment Cholecalciferol 10,000 IU daily x 8–12 weeks Cholecalciferol 60,000 IU weekly x 8–12 weeks Cholecalciferol 600,000 once or 300,000 IU twice (stoss therapy)
Supplementation Cholecalciferol 1,000 –2,000 IU daily Cholecalciferol 10,000 IU weekly Cholecalciferol 300,000 IU once or twice annually

Recommended dosage of vitamin D in women with PFD

Clinical recommendation

- Vitamin D supplementation may prove to be a beneficial adjunctive treatment helping to optimize the treatment response and the quality-of-life of women with PFD.[15]
- In women at least 50 years old, maintaining vitamin D levels of 30 ng/mL or higher (OR, 0.55; 95% CI, 0.34 - 0.91) significantly reduces the likelihood of urinary incontinence.[19]
- Clinical recommendations on vitamin D supplementation in these women are summarized in Table 2.[20]

Table 2. Vitamin D recommendation

IOM recommendations[21]		**Dr. Holick's recommendations for patients at risk for vitamin D deficiency**[21]	
Life stage group	Estimated average requirement	Daily allowance (IU/d)	UL (IU)
Females			
9–13 y	400 IU (10 µg)	1,500 – 2,000	4,000
14–18 y	400 IU (10 µg)	1,500 – 2,000	4,000
19–30 y	400 IU (10 µg)	1,500 – 2,000	10,000
31–50 y	400 IU (10 µg)	1,500 – 2,000	10,000
51–70 y	400 IU (10 µg)	1,500 – 2,000	10,000
> 70 y	400 IU (10 µg)	1,500 – 2,000	10,000

Recommended Adequate Intakes (AI), Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA) and Tolerable Upper Limit (UL) by the Institute of Medicine (IOM) and Dr. Holick's recommendation for Daily Allowance and safe Upper Limit (UL) for vitamin D for children and adults who are not obtaining adequate vitamin D from sun exposure and who are at risk for vitamin D deficiency

Several studies have evaluated association between serum 25(OH)D concentration and the chronic illnesses or mortality. Some of the studies plotted serum 25(OH)D concentrations versus a chronic illness mortality demonstrated, that vitamin D deficiency was associated with an increased risk and that the risk gradually decreased with increasing 25(OH)D

concentrations that reached a nadir plateau being usually between 30-40 ng/mL.[22] **The desirable optimal serum vitamin D levels should be maintained in the range of 50–70 ng/mL.[23]**

25(OH)D concentrations of 30-50 ng/mL (75-125 nmol/L) are beneficial for overall health.

PRACTICE POINTS

- **The desirable optimal serum vitamin D levels should be maintained in the range of 50–70 ng/mL.[23] (Level V-A)**
- **Deficiency of vitamin D is clinically associated with impaired muscle strength and loss of muscle mass, resulting in PFD.[11] (Level II-A)**
- **Supplementing vitamin D in women with PFD may improve pelvic floor muscle strength, symptoms as well as quality-of-life.[12] (Level III-B)**
- **Regular dosing with oral cholecalciferol (60,000 IU weekly) are effective in replenishing vitamin D stores following deficiency.[18] (Level V-A)**

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Functionalized nano particle carrier for delivery of vitamin D

The importance of vitamin D deficiency as a health risk led to the development of new functional foods and therapies using nanotechnologies for Vitamin D incorporation into foods and pharmaceutical formulations without reducing its bioavailability or activity.[1]

Nanoparticles provide protection from external conditions and increase the stability and solubility of the molecule. Also, nanoparticles allow decreasing its toxicity associated with the hypercalcemia phenomena and allowing circumventing the multidrug resistance problem hindering the molecule efflux out of the cells.[1]

A prospective, open label, single arm, non-comparative, dose response post-marketing efficacy study showed that nanoparticle-based formulation of vitamin D3 is effective and safe in correction of vitamin D levels in patients with documented deficiency or insufficiency of vitamin D. Also, the safety and tolerability are well accepted and reported good to excellent by patients and physician.[2]

Challenges of current formulations[3]

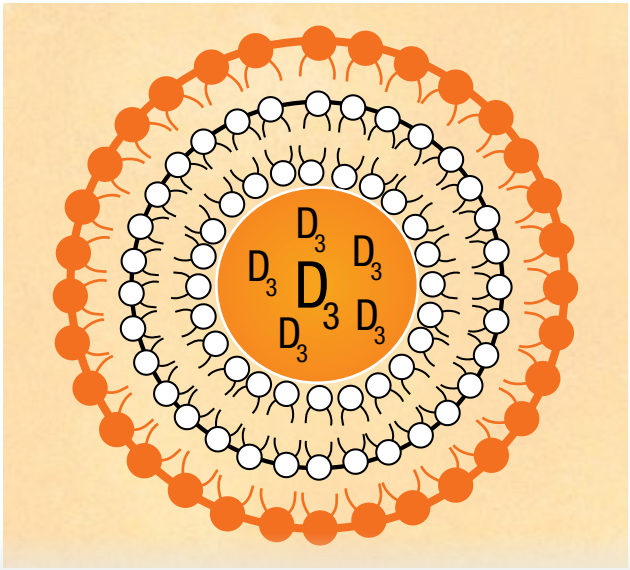
- **Currently available vitamin D3 formulations** largely depend upon the lipid absorption pathway for their absorption thus leading to poor and inconsistent oral bioavailability
- In disease condition where lipid absorption pathway is itself compromized the bioavailability from these formulations is questionable.

Need of better technology for to enhance oral absorption of vitamin D3[3]

- A patented nano-carrier based technology in which lipophilic/ hydrophobic drugs are entrapped within nano-carrier particles, which in-turn are dispersed in a aqueous medium.
- Because of special ligands and polymers covering the surface of nano particles carrying vitamin D3, the nano particles are protected from any degradation due to gastric acid and lipases, and therefore, remain functional. These functionalized nanoparticles are directly absorbed through gastrointestinal mucosa thereby enhancing the bioavailability of vitamin D.

A schematic representation of vitamin D3 entrapped in a nano-carrier

Figure 1. The technology with functionalized nano vitamin D particles



Advantages of vitamin D entrapped in nano-lipid carrier[3]

Vitamin D molecules entrapped in nano-Lipid CARRIER	Each nano-lipid-carrier contains approximately 8000 molecules of vitamin D3
PH-resistant barrier and enzyme-resistant barrier	Protects the nano-lipid-carrier particles in harsh gatrointestinal environment, i.e. effect of varying pH conditions, different enzymes and thus, facilitates nano-entrapped D3 to reach the enterocytic surface (for absorption)
Outer hydrophilic layer	Facilitates transportation of nano particles through unstirred aqueous layer of gatrointestinal tract
Size of nanoparticle is less than 150 nanometer	Space between 2 enterocytes being 150 nm, the nanoparticles perfectly pass through the space between two enterocytes

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3. Data on file.

Summary

CLINICAL PRACTICE POINTS

- Cholecalciferol is the preferred form for prophylaxis or treatment of vitamin D deficient states.
- An effective strategy to treat vitamin D deficient is to administer 50,000 IU of vitamin D3 once a week for 6-8 weeks respectively
- Symptomatic vitamin D toxicity is uncommon, and elevated levels of 25(OH)D do not strongly correlate with clinical symptoms or total serum/plasma calcium levels.
- Optimal serum levels of ≥30 ng/mL is suggested to be achieved for desirable benefits in all indications.
- Based on varied research conducted, the currently widely accepted range for sufficient levels of serum **vitamin D levels lie between 30 and 50 ng/mL which can be regarded as adequately and physiologically sufficient. (Level V-A)**
- **The desirable optimal serum vitamin D levels should be maintained in the range of 50–70 ng/mL. (Level V-A)**
- PCOS women who were given vitamin D 4,000 IU daily for 12 weeks had significantly reduced total testosterone (TT), free androgen index (FAI), and increased SHBG. **(Level I-B)**
- Vitamin D sufficiency is also essential for successful fertility enhancement.
- As per the passed consensus, serum vitamin D levels is suggested to be maintained at ≥50 ng/mL to achieve optimal clinical benefits in women with endometriosis.
- Vitamin D supplementation can be beneficial in improving pelvic pain, total-/HDL-cholesterol ratio, high-sensitivity C-reactive protein and total antioxidant capacity levels in patients with endometriosis. **(Level I-B)**
- Supplementation with vitamin D 2000 IU daily for 6 months can help in the management of endometriosis-related pain. **(Level I-B)**
- Supplementation of vitamin D3 at moderate doses achieving 25(OH)D_3 serum concentrations of 30–80 ng/mL could be beneficial for reducing the risk of developing ovarian cancer. **(Level V-B)** [25]
- As per the international consensus guidelines, as vitamin D supplementation plays a beneficial role in human reproduction, maintaining the desirable effects of vitamin D is very crucial; therefore, the serum concentration of vitamin D should not fall <50 ng/mL. **(Level V-B)** [26]

CLINICAL PRACTICE POINTS

- Vitamin D >20 ng/mL has shown to reduce the risk of GDM; therefore, optimal serum levels of ≥30 ng/mL is suggested to be achieved for desirable benefits.
- The Endocrine Society Guidelines suggest that all women, including pregnant and lactating women with vitamin D deficiency receive 1000–2000 IU of vitamin D daily. **(Level IV-A)**
- It is recommended that the daily dosage of Vitamin D would be 1000 IU for Maintenance, 2000 IU for Deficiency, with a maximum dose per day being 4000 IU. **(Level V-C)**
- Weekly dose of 60,000 IU for 6 to 8 weeks is suggested for women presenting with a deficiency late in pregnancy. **(Level V-C)**
- Optimal serum levels of ≥30 ng/mL is suggested to be achieved for management of LBP associated with gynaecological conditions.
- The American College of Obstetricians and Gynecologists (ACOG) recommends treatment with 1000-2000 IU of vitamin D daily in pregnant/lactating women with vitamin D deficiency. Most experts agree that 1,000–2,000 IU per day of vitamin D is safe.[17] **(Level IV-A)**
- The IOM recommends an intake of 600 UL of vitamin D to pregnant women with the goal to achieve in serum more than 50 nmol/L (20 ng/mL) 25(OH)D considered by them as a sufficient level.[18] **(Level IV-A)**
- US Endocrine Society suggests that at least 1,500–2,000 IU/of vitamin D may be needed to maintain blood levels of 25(OH)D above 75 nmol/L (30 ng/dL) and that should be considered the sufficient level for pregnant women.[19] **(Level IV-A)**
- The **European guidelines recommended the use of vitamin D supplements to obtain and maintain the 25(OH)D concentration in a range of 30–50 ng/mL** (75-125 nmol/L).[20] **(Level IV-A)**
- **The** expected **optimal serum vitamin D levels for desired outcomes should be 50–70 ng/mL.(Level V-A).[21]**
- Deficiency of vitamin D is clinically associated with impaired muscle strength and loss of muscle mass, resulting in pelvic floor disorders.[11] (**Level II-A**)
- Supplementing vitamin D in women with pelvic floor disorders may improve pelvic floor muscle strength, symptoms as well as quality-of-life.[12] **(Level III-B)**
- Regular dosing with oral cholecalciferol (e.g., 60,000 IU weekly) are effective in replenishing vitamin D stores following deficiency.[18] **(Level V-A)**
- The desirable optimal serum vitamin D levels should be maintained in the range of 50–70 ng/mL.[23] **(Level V-A)**

Levels of evidence

Evidence Levels	Description
Level I	• Experimental study, randomized controlled trial (RCT) • Explanatory mixed method design that includesonly a level I quantitative study • Systematic review of RCTs, with or without meta-analysis
Level II	• Quasi-experimental study • Explanatory mixed method design that includes only a level II quaNtitative study • Systematic review of a combination of RCTs and quasi-experimental studies, or quasi-experimental studies only, with or without meta- analysis
Level III	• Nonexperimental study • Systematic review of a combination of RCTs, quasi-experimental and nonexperimental studies, or nonexperimental studies only, with or without meta-analysis • Exploratory, convergent, or multiphasic mixed methods studies • Explanatory mixed method design that includes only a level III quaNtitative study • QuaLitative study Meta-synthesis
Level IV	• Opinion of respected authorities and/or nationally recognized expert committees or consensus panels based on scientific evidence. Includes: » Clinical practice guidelines » Consensus panels/position statements
Level V	• Based on experiential and nonresearch evidence Includes: » Integrative reviews » Literature reviews » Quality improvement, program, or financial evaluation » Case reports » Opinion of nationally recognized expert(s) based on experiential evidence

Quality ratings	Description
A	**High quality**: Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence.
B	**Good quality**: Reasonably consistent results; sufficient sample size for the study design; some control, fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence.
C	**Low quality or major flaws**: Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn.
Quantitative A/B	**High/Good quality:** Single studies and meta-syntheses. Thorough studies with all the data consistent and transparent. Data and knowledge are linked in meaningful ways to relevant literature

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