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## Role of Vitamin D in Women Health

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**Dr. Prasanta Kumar Nath Barbhuiya,** DGO, MD, FICOG
Retd .Consultant Gynaecologist And Obstetrician, Govt of West Bengal.
81, Banerjee Para Rd, New Panchanantala,
Paschim Putiary, Kolkata, West Bengal 700041.

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# Introduction

Vitamin D deficiency is currently an universal topic of discussion. Discovered as a vitamin in the 1900s, scientists now define it as a prohormone (2011). The first evidence documented of vitamin D deficiency was during the industrial revolution when children in urban environments demonstrated growth retardation and skeletal deformities, termed rickets. The association was established between sunlight and improvement in rickets. (Holick 2004)

Vitamin D's pivotal role in calcium absorption was identified next to its influence on skeletal system. (Moyer 2013) Recent research on non-classical functions of vitamin D, include its possible role in prevention and treatment of cancer, autoimmune diseases, heart disease, and infections. (2011, Wimalawansa 2012) In India, the average life expectancy for women has increased (more than double) from 23.96 in 1901 to 62 years in 1999. It is estimated to reach 70 years by 2020. (Husain and Ghosh 2011) Currently, to address the women health concerns, the emphasis is on healthy living, dietary modifications, lifestyle changes, exercise, and use of supplemental nutrients as vitamins, minerals, and antioxidants over and above specific medications for disease comorbidities. This has led to emergence of new concept of Vitamin D deficiency due to sedentary lifestyle, remaining indoor, lack of sun exposure, and inadequate dietary intake. (Kaur, Bala et al. 2017) Focus of this article is the impact of vitamin D on women's health in both classical and non-classical terms.

### Prevalence

By Horlick's definition, almost 1 billion people worldwide have vitamin D deficiency or insufficiency. (Wimalawansa 2012) India is a large country covering several latitudes, ethnicities, cultures, traditions, and attitudes. Hence the current data on vitamin D status is insufficient and classified in different ways unrepresentative of whole nation. Poor vitamin D status is having serum 25 hydroxyl vitamin D levels < 20 ng/ml. It is universally reported across all age groups neonates (95.7 %), adults (75 %) and pregnant women (67 %). (Trilok Kumar, Chugh et al. 2015) It is more severe (Vitamin D <20 ng/ml) in women of reproductive age (88%). (Sofi, Jain et al. 2017)

### Risk factors

Several factors lead to vitamin D deficiency. Hindrance in natural synthesis is a major factor in its deficiency. Reduced skin synthesis is related to sunscreen use, darker skin pigmentation, aging, winter months, early or late time of day exposure, residing at a latitude >35 degrees, and skin grafts for burns. Natural production is also disrupted by liver and kidney diseases.

Decreased bioavailability of vitamin D is secondary to malabsorption due to gastrointestinal diseases or procedures (e.g., celiac disease, Crohn's disease, gastric bypass surgery). Obesity creates relative insufficiency, as fat-soluble vitamin D gets sequestered in the fat cells. Increased catabolism breaks it down to its inactive forms. It also jeopardizes those who are on anticonvulsants, glucocorticoids, HIV, and anti-graft rejection medications. Insufficient vitamin D content in a mother's milk leaves breast-fed infants vulnerable to the need of supplementation. (Holick 2004).

# Physiological role of vitamin D3

Approximately 80% of an individual's vitamin D comes from ultraviolet B rays exposure to skin and 20% from their diet. (Wimalawansa 2012) Sunlight transforms 7-dehydrocholesterol into pre-vitamin $D_3$, which is then isomerized to vitamin $D_3$ in the skin. It is taken to liver where it is transformed into 25-hydroxyvitamin D (25[OH] D or calcidiol), which is a major circulating metabolite. Calcidiol reaches the kidneys to be converted into 1, 25-dihydroxyvitamin D (1,

25[OH]$_{2D}$ or calcitriol), which is the active form of vitamin D. (Holick 2007, Angeline, Gee et al. 2013) This renal conversion is regulated by serum parathyroid hormone, calcium and phosphorus levels. (Holick 2007)

The inactive metabolite 25(OH) D is currently preferred to obtain more accurate indication of vitamin D status than 1, 25(OH) D. (Holick 2004) Vitamin D is deficient at 21 to 29 ng/mL, while intoxication can occur with serum level of more than 150 ng/mL. (Holick 2007).

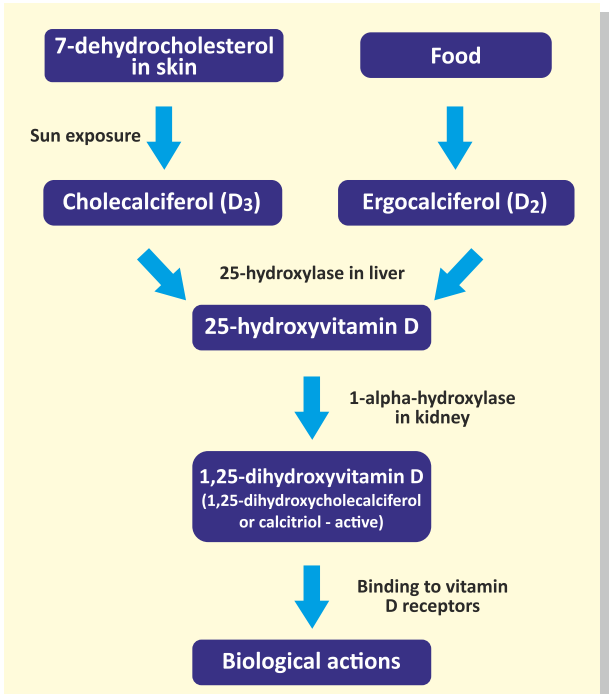


**Figure 1:** Metabolism of vitamin D

***Effect on musculoskeletal system***

Low bone mineral density (BMD) is labeled as osteoporosis. It is common in middle aged post-menopausal women; almost four times more prevalent as compared to men. It is well known fact that Indians have lower BMD compared to the Western population. Relatively younger age of menopause in Indians 46.5 years compared to Western counterparts, results in early onset of bone loss. (Daswani, Desai et al. 2016)

Manifestations of osteoporosis are fragility fractures and associated morbidity, mortality and decrease in quality of life. (Vaishya, Agarwal et al. 2017) Worldwide incidences of hip fractures have increased from 1.7 to 6.3 million and this is expected to increase significantly due to increased life expectancy. (Yadav, Tewari et al. 2016). About 47% of women and 22% of men ≥ 50 years old experience an osteoporotic fracture in their lifetime. (Holick 2007) During the first 3 months following a hip fracture, the mortality risk increases 2.8 to 4 times. (Moyer 2013)

Thus medical interventions vitamin D supplementation is critical. Vitamin D is known to affect bone physiology with its impact on calcium and phosphorus levels. Only 15% of dietary calcium and about 60% of phosphorus can be absorbed without vitamin D. (Holick 2007) Vitamin D even decreases parathyroid hormone levels and secondarily affects bone turnover. (Wimalawansa 2012)

Several studies have been done evaluating the effect of vitamin D on fractures, falls, and muscle strength and to further investigate these supplements' effects on low-energy fractures. These results indicate that vitamin D alone in low doses (400 IU–800 IU) does not prevent fractures, but giving vitamin D and calcium together can reduce total fractures.

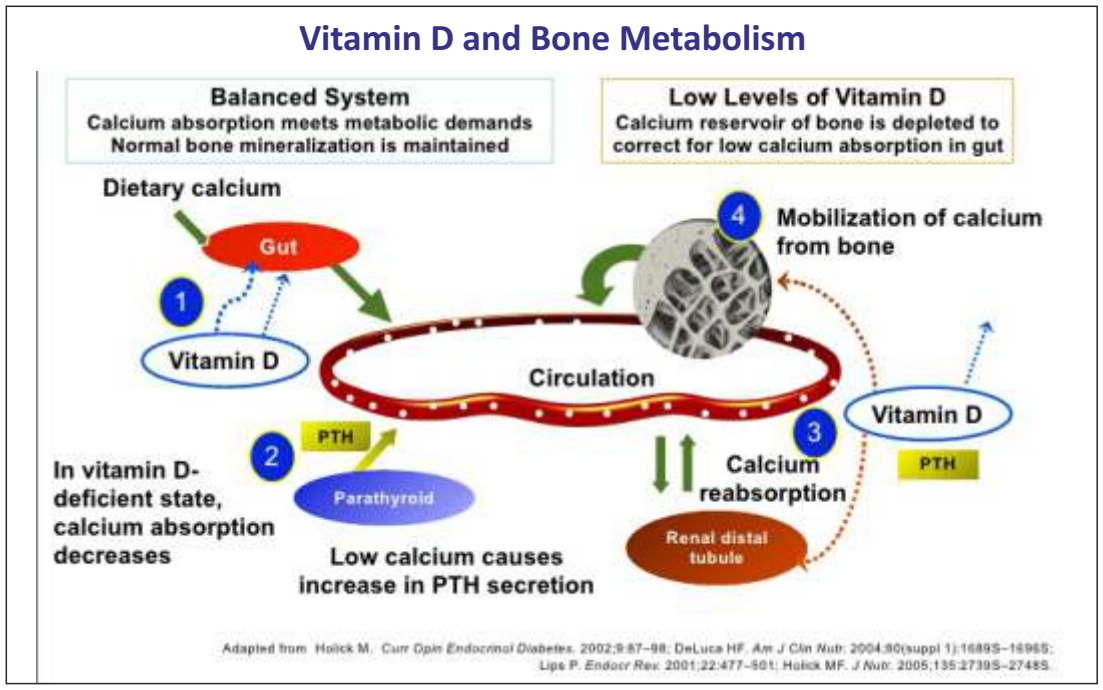


**Figure 2:** Vitamin D and bone metabolism

## Emerging roles of vitamin D3

Traditionally, vitamin D was known for its role in musculoskeletal functions. It has effect also on non-classical sites, (2011) such as the brain, prostate, breast, and colon. (Holick 2007) Disease processes such as cancer, autoimmune disease, cardiovascular disease, infections, endocrine/reproductive diseases, and others have been linked to its low levels. (Holick 2007), (Rosen 2011)

Inhibiting tumor angiogenesis is postulated as the mechanism by which vitamin D (>30 ng/mL) reduces incidence of cancer. (Garland, Garland et al. 2006) (Holick 2007), (Melamed, Michos et al. 2008) In addition to a possible anticarcinogenic effect, autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, and Crohn's disease may be linked to vitamin D, as those living at higher latitudes are once again at increased risk. (Holick 2007) A case control study has demonstrated positive association between low levels of serum vitamin D levels < 20ng/ml and calcium levels < 10.5mg/dl had higher odds of having breast cancer. (Sofi, Jain et al. 2018) Garland et al looked at 30 studies with vitamin D and colon cancer, finding 20 with a statistically significant benefit of vitamin D, its metabolites, or sunlight exposure. (Garland, Garland et al. 2006) This review also examined 13 studies of breast cancer, with 9 showing a favorable association of vitamin D markers or sunlight with decreased cancer risk. Five of the evaluated 7 studies of ovarian cancer showed higher mortality with lower vitamin D intake or lower sun exposure. (Garland, Garland et al. 2006)

Vitamin D has also been a point of discussion in reproductive and endocrine fields. Hypovitaminosis D is very common in polycystic ovarian syndrome (PCOS) patients and exacerbates the metabolic abnormalities. It is essential to screen all the PCOS patients for 25OH D deficiency. (Kumar, Barki et al. 2017) Some cross-sectional studies show a possible association between low levels of vitamin and signs and symptoms of PCOS like menstrual dysfunction, infertility, hirsutism, obesity, and insulin resistance. (Thomson, Spedding et al. 2012)

Association between low vitamin D and adverse pregnancy outcomes has been established. Specifically a higher rate of preeclampsia, preterm birth, and small of gestational age infants, bacterial vaginosis, and gestational diabetes has been observed. (Aghajafari, Nagulesapillai et al. 2013), (Wei, Qi et al. 2013) Currently, the American College of Obstetrics and Gynecology has the same recommendations as the Institute of Medicine of 600 IU of vitamin D daily for pregnant women.

Even without sufficient evidence to screening all pregnant women, most experts agree that 1000 to 2000 IU per day supplementation is safe. (2011)

Metabolic syndrome (MS) and vitamin D deficiency are prevalent among postmenopausal women (PMW) in India. (Srimani, Saha et al. 2017) Women who ingested >400 IU of vitamin D per day showed a decreased risk of developing multiple sclerosis. In terms of cardiovascular disease, living at higher latitudes increases the risk of hypertension and heart disease. Other medical issues linked to its deficiency include infections such as tuberculosis, depression, and schizophrenia. (Holick 2007) The Leicestershire MRC Incontinence Study Group (a longitudinal cohort study) reported that higher intake was significantly associated with reduced risk of overactive bladder onset. (Dallosso, McGrother et al. 2004) Parker-Autry et al. in their study found that women with fecal incontinence had lower Vitamin D levels. (Parker-Autry, Burgio et al. 2012) It is important for normal immune cell function, as well as regression of (Female Genital Tuberculosis FGTB) disease. Its deficiency and BMI alters expression of antimicrobial peptide there by leading to progression and persistence of TB infection. Thus regulating serum vitamin D level concentration can help to Control FGTB. (Gautam, Jain et al. 2017)

## Role of Vitamin D in pregnancy

The commonly used threshold used to define vitamin D deficiency is 25(OH)D concentrations < (<20 ng/ml. Worldwide, 54% of pregnant women and 75% of newborns are below this limit. (Holick, Binkley et al. 2011) Indians have a high prevalence of hypovitaminosis D among pregnant women. (Sharma, Kumar et al. 2016) Vitamin D deficiency (<20 ng/ml) was present in 88% of women. Women from middle socioeconomic class had the lowest mean serum 25(OH) D levels (9.6 ± 6 ng/ml) as compared to women from upper middle (11.4 ± 8 ng/ml), lower (11.2 ± 8 ng/ml), and upper (10 ± 8.6 ng/ml) socioeconomic class. (Sofi, Jain et al. 2017) These women are at higher risk of development of osteoporosis and pregnancy-related complications in future life.

The Institute of Medicine (IOM), the UK Scientific Advisory Committee on Nutrition (SACN) and the International Consensus on Prevention of Nutritional Rickets identified individuals with 25(OH) D concentrations < 10–12 ng/ml as vitamin D deficient due to a concomitant increase in the risk of metabolic bone disease. (Munns, Shaw et al. 2016), (Kiely, Hemmingway et al. 2017) Although there were many limitations to the data available to Saraf and colleagues, notably inconsistent reporting of unstandardized 25(OH)D. They reported 18% of pregnant women and 29% of newborns with 25(OH) D < 10 ng/ml after assessing data from underdeveloped countries. Mostly 11% and 17% of women at 15 weeks' gestation and 35% and 46% of umbilical cord sera were < 10 and 12 ng/ml, respectively, in developed countries. (Saraf, Morton et al. 2016) This evidence of endemic vitamin D deficiency among mothers and infants, particularly in low-resource countries, has serious implications for maternal and child health.

### Physiology in pregnancy

#### *Vitamin D metabolism during gestation*

Vitamin D metabolism during pregnancy is a subject of deep research interest. The physiologic adaptations of pregnancy alter maternal vitamin D metabolism, thereby influencing fetal availability. This elucidates pronounced effect on vitamin D requirements during pregnancy. Commencing late in the first trimester and continuing until after delivery, circulating levels of both vitamin D binding protein (DBP) and serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] increase. (Zhang, Lucey et al. 2014), (Papapetrou 2010) DBP levels begin to rise as early as 8–10 weeks' gestation, preceding the steady increase in later. The mechanisms controlling elevation are indeterminate; however oestrogen regulation has been suggested. (Brannon and Picciano 2011) At term, expectant mothers have approximately twice Vitamin D concentration as nonpregnant women. It is generated by increases in renal synthesis plus placental or decidual

tissue production. (Brannon and Picciano 2011), (Zehnder, Evans et al. 2002) A surge in 1a-hydroxylase (CYP27B1) expression, the enzyme that catalyzes conversion of 25(OH)D to 1,25$(OH)_2$D, is accompanied by decreased expression of the catabolic enzyme, 24-hydroxylase (CYP24A1). (Zehnder, Evans et al. 2002) Though the purpose is not clear, this catabolic inactivation potentiates placental/decidual tissues contribution. Metabolic adaptations to pregnancy facilitate fetal calcium accretion as outlined in the following section. Some investigators have proposed an immunomodulatory function for vitamin D within the placenta and maternal decidua. This paracrine production depends on maternal 25(OH) D thresholds and vitamin D requirements. (Tamblyn, Hewison et al. 2015)

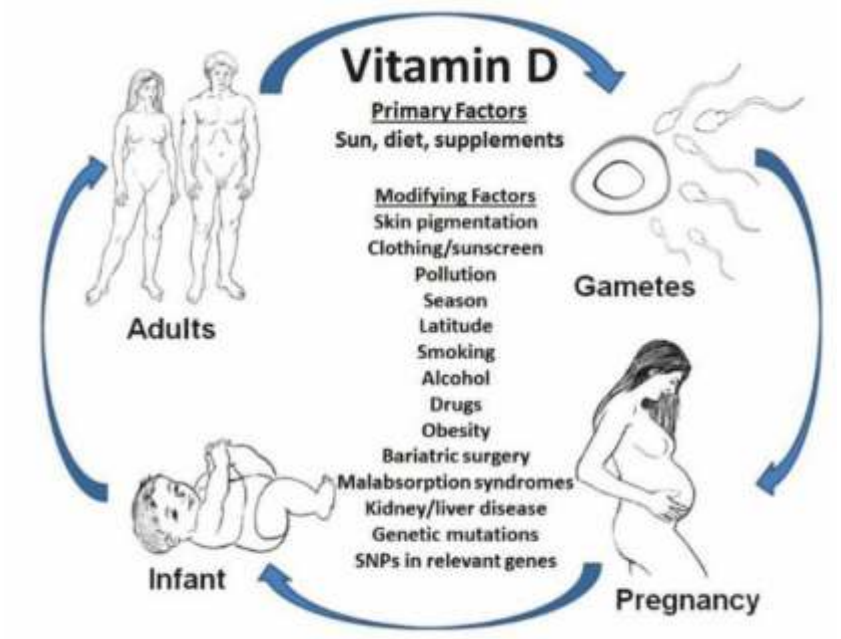


**Figure 3:** Modifying factors that can affect vitamin D status throughout the life cycle

### *Calcium metabolism during pregnancy and the parathyroid hormone axis*

Calcium metabolic stress results from a low calcium containing diet or low serum Vitamin D. This leads to secondary hyperparathyroidism in pregnancy, increasing the risk of preeclampsia (PE) as well as other adverse perinatal outcomes such as small for gestational age infants (SGA). (Scholl, Chen et al. 2013) Pregnancy related adaptations to vitamin D metabolism parallel alterations in the broader calcium homeostatic system, invoked to meet the demands of the developing fetus. The maternal increases in Vitamin D, occur independently of the classical parathyroid hormone (PTH)–vitamin D endocrine system. This leads to increase in calcium absorption and reduction of calcium excretion. (Kirby, Ma et al. 2013) PTH levels fall early in pregnancy and remain low, before rising late in gestation to reach pre-pregnancy levels postpartum. A decrease in serum calcium likely reflects the hemodilution associated with pregnancy. While majority of fetal calcium accumulate in the final trimester, maternal calcium absorptive capacity increases markedly early in pregnancy and remains high throughout. To facilitate fetal mineral demands mother increases her own bone resorption and formation, leading to a transitory reduction in bone mass density (BMD). (Sanz-Salvador, Garcia-Perez et al. 2015) Reflecting on all these facts special consideration should be given to pregnancy in adolescence. These young mothers balance a period of personal active bone accretion with maternal skeletal adaptation. (Kiely, Hemmingway et al. 2017)

In the face of several adaptations in the vitamin D/calcium metabolic system during pregnancy, the inverse 25(OH) D/PTH relationship is retained. (Haddow, Neveux et al. 2011) Elevated PTH reveals stress in the calcium metabolic system, which may be caused by either inadequate calcium consumption or low 25(OH) D status (secondary hyperparathyroidism).

In pregnant women, PTH was negatively correlated with crown-heel length and birth weight, neither of which were related to 25(OH)D. (Brunvand, Quigstad et al. 1996) This, in along with a positive relationship between serum ionized calcium and crown-heel length, suggest that any effect of maternal vitamin D deficiency was indirect, through alteration of maternal calcium homeostasis. Thus, investigation of PTH concentrations in pregnancy as a proxy for maternal calcium stress may help clarify the roles of vitamin D and calcium in maternal and fetal health.

Any disruption to homeostasis in the calcium metabolic system may have nonskeletal effects. Scholl and colleagues found a two- to threefold increase in SGA risk, along with lower birth weight, birth length and head circumference, in women who exhibited dysregulation of maternal calcium homeostasis. (Scholl, Chen et al. 2014) PTH, but not 25(OH) D, was associated with β-cell dysfunction and dysglycemia in pregnancy. Incident gestational diabetes progressively increases across the tertiles of PTH. Secondary hyperparathyroidism [defined by elevated PTH in conjunction with low 25(OH) D] increased the risk of PE threefold. Those with low 25(OH) D or elevated PTH only had no risk. (Scholl, Chen et al. 2014)

## Optimum range and recommendation

In general, there is a profound lack of evidence on which to set recommendations for pregnancy specifically. Most agencies have proposed the same adequacy thresholds for 25(OH) D and dietary recommendations for vitamin D for pregnant and lactating women as nonpregnant adults. Currently in the USA and Canada, serum 25(OH) D < 12 ng/ml is the threshold to label vitamin D deficiency. Concentrations of at least 20 ng/ml, are sufficient on the basis of skeletal health outcomes. On this basis, estimated average requirement (EAR) of the vitamin is 10 μg/day and recommended dietary allowance (RDA) is 15 μg/day. In 2012, the Nordic Nutrition Recommendations for vitamin D, which were also based on skeletal health outcomes, recommended an intake of 10 μg/day with a view to achieving an individual 25(OH)D target of 20 ng/ml. (Saraf, Morton et al. 2016)

**Table 1. The** Summary of current dietary recommendations for vitamin D in pregnant women.

| **Agency** | **Countries** | **25(OH)D threshold (ng/ml)** | | | | | |
|---|---|---|---|---|---|---|---|
| | | ***Deficiency*** | ***Population average*** | ***Individual target*** | ***EAR*** | ***RI*** | ***AI*** |
| IOM | USA/Canada | <20 | 16 | ≥20 | 10 | 15 | – |
| NORDEN | Nordic | <20 | – | ≥20 | 7.5 | 10 | – |
| SACN | UK | <12 | – | ≥10 | – | 10 | – |
| EFSA | EU | – | – | ≥20 | Adjust table column | – | 15 |

25(OH)D, 25-hydroxyvitamin D; AI, adequate intake; EAR, estimated average requirement; EFSA, European Food Safety Authority; IOM, Institute of Medicine; NORDEN, Nordic Council of Ministers; RI, recommended (individual) intake; SACN, Scientific Advisory Committee on Nutrition.

Recently, SACN proposed a ‘population protective’ level of 10 ng/ml for all individuals, to protect musculoskeletal health. In line with the other agencies, SACN defined intake recommendation target by conducting mathematical modeling of dose–response studies conducted in wintertime at high latitude to minimize potential contributions from UVB exposure. These models provided an estimate of 10 μg/day of vitamin D for almost all individuals aged 11 years and over, including pregnant women. (Saraf, Morton et al. 2016) To avoid confusion, the RDA, recommended intake (RI) and RNI are presented in Table 1 as individual targets.

The European Food Safety Authority (EFSA) reference values for vitamin D, although based on a similar assessment to the other agencies, are substantially different. Citing inadequate data availability as the basis for their decision, the EFSA panel did not publish average requirements or individual intake recommendations. They instead opted for an adequate intake (AI) for vitamin D of 15 µg/day to achieve a 25(OH) D concentration of 20 ng/ml. This intake value applies to all persons over 1 year of age, including pregnant women, for maintenance of skeletal health. The option of setting an AI value is typically reserved for nutrients for which there is much uncertainty in the data when it is not possible to recommend an EAR or a RI. The process of setting dietary recommendations is an iterative one based on the evidence available at that time.

Implementation of the IOM, SACN and Nordic Council of Ministers recommendations may protect pregnant women from vitamin D deficiency if certain outstanding assumptions, for example that pregnancy does not increase the metabolic demand for vitamin D, are met. A recent dose–response trial in Canada (March, Chen et al. 2015)showed that circulating 25(OH) D did not decline to < 12 ng/ml in pregnant and postpartum women taking 10 µg/day (400 IU) vitamin $D_3$. However, a critical additional consideration is protection of fetal vitamin D availability during pregnancy. Cord blood concentrations, while reflective of circulating maternal 25(OH) D, are usually 60–80% of maternal values collected at delivery. Thus, the lower cutoff of 12 ng/ml will not ensure fetal protection. Despite the uncertainties around fetal and neonatal requirements, if requirements were established on the basis of prevention of neonatal deficiency, a higher maternal 25(OH) D concentration would be required. A longitudinal study of maternal–infant, with maternal and cord samples measured at delivery, showed that infants born to women with 20 ng/ml did not have serum 25(OH) D < 12 ng/ml (Vieth Streym, Kristine Moller et al. 2013) Achievement of at least 20 ng/ml required at least 25 µg/day in both the Canadian study and a dose–response trial in pregnant women from New Zealand. (Grant, Stewart et al. 2014, Bountouvi, Douros et al. 2017)

A pharmacokinetic study was conducted to assess the biochemical dose-response and tolerability of high-dose prenatal vitamin D3 supplementation. Pregnant women at 27-30 weeks gestation (n = 28) were randomized to 70,000 IU once + 35,000 IU/week vitamin D3 (group PH: pregnant, higher dose) or 14,000 IU/week vitamin D3 (PL: pregnant, lower dose) until delivery. A group of non-pregnant women (n = 16) was similarly administered 70,000 IU once + 35,000 IU/week for 10 weeks (NH: non-pregnant, higher-dose). It was found that a regimen of an initial dose of 70,000 IU and 35,000 IU/week vitamin D3 in the third trimester of pregnancy was non-hypercalcemic and attained [25(OH)D] ≥ 12.8 32 in virtually all mothers and newborns (Figure 2). (Roth, 2013)

An Indian study revealed that Vitamin D supplementation with 2000 IU/day or 60,000 IU/month is very effective and safe in achieving Vitamin D sufficiency in pregnant women. Although monthly bolus dose proved to be better than daily dose, the difference was insignificant. (Mir, Masoodi et al. 2016) and may be related to better compliance. Delvin *et al*. reported that a daily dose of 1000 IU Vitamin $D_3$ administered to 15 French women during the third trimester modestly raised mean maternal serum (25[OH]D) from 22 ng/ml to 26 ng/ml. (Delvin, Salle et al. 1986) The clinical evidence supports the appropriateness of administering monthly doses of 30,000 IU or 60,000 IU instead of daily administration 1000 IU or 2000 IU.

In yet another study involving pregnant women received supplementation with 60,000 IU vitamin D every two weeks for eight doses or till delivery, whichever was earlier. Subjects had sufficient levels of 25(OH) D in cord blood at birth in maximum cases and neonates had higher birth weights and increased crown heel length. (Nandal, Chhabra et al. 2016)

Oral vitamin D2 supplementation with 2000 IU/d or 60,000 IU/month for 3 months was proved safe, and effective. This suggests that, when sunlight exposure is limited, higher doses of vitamin D may be needed. Monthly dosing appears to be a safe and effective alternative to

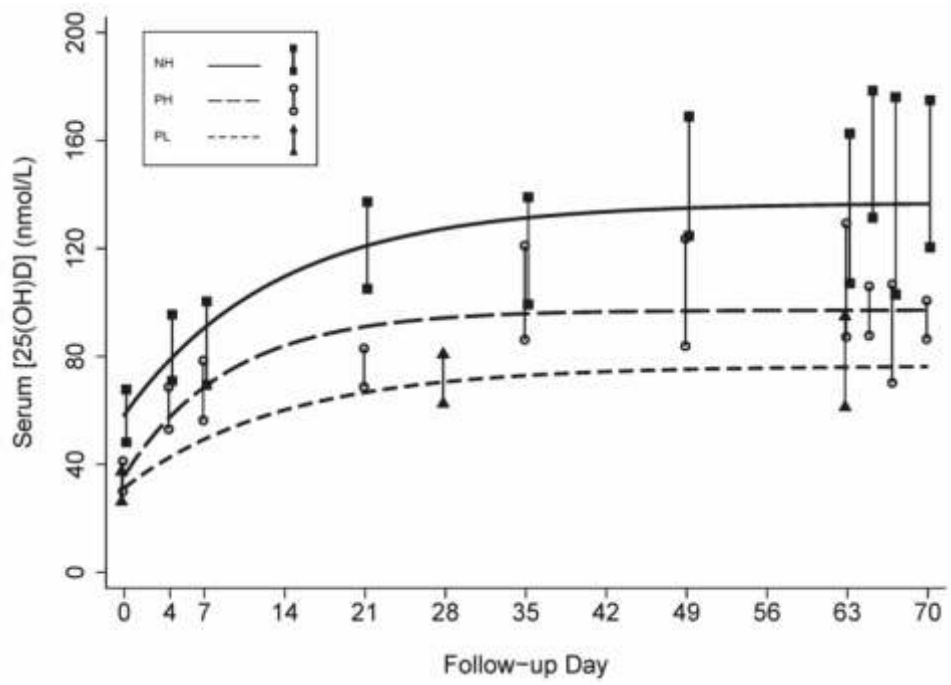


**Figure 4:** Negative exponential models predicting serum 25-hydroxyvitamin D concentrations in response to D3 supplementation

daily dosing. (Saadi, Dawodu et al. 2007)

# Maternal effects

## *Hypertensive disorders of pregnancy*

Each day, 830 women die from preventable pregnancy-related causes. Low- and middle-income countries bear the greatest burden of disease. Hypertensive disorders of pregnancy, including gestational hypertension, pre-eclampsia (PE), and eclampsia, are among the major complications that account for approximately 14% of maternal mortality. (Purswani, Gala et al. 2017)

Pregnancy induced hypertension is defined as blood pressure greater than 140/90 mmHg on two consecutive occasions ≥6 hours apart occurring after 20 weeks of pregnancy. Complicating around 5 to 10% of pregnancies, (Steegers, von Dadelszen et al. 2010) preeclampsia (PE) is responsible for over 70,000 maternal and over 500,000 infant deaths annually on a global basis. (Duley 2003) After 20 weeks of gestation but before the onset of labor, or postpartum, it presents with proteinuria or any multisystem complication in a previously normotensive woman.

Gestational- or pregnancy-induced hypertension is the *de novo* development of high blood pressure after 20 weeks of gestation, without any of the abnormalities that define PE. However up to 25% of these cases go on to develop PE. (Tranquilli, Dekker et al. 2014) Risk factors for PE include a previous history, multiple pregnancy, primiparity, underlying metabolic disorders such as pre-existing diabetes, family history, African American race, advanced maternal age and obesity. Undefined etiology and the existence of several subtypes of the disorder challenges the development of clinical prediction models.

In the longer term, hypertensive disorders during pregnancy (as well as gestational diabetes) predispose mothers to cardiovascular and metabolic disorders in later life. Whether increased risk of cardiovascular disease follows PE or the metabolic stress of pregnancy aggravates a pre-existing metabolic dysfunction is unclear. A quarter of the babies born to mothers with PE are growth restricted and a third is preterm. It accounts for up to 20% of neonatal intensive

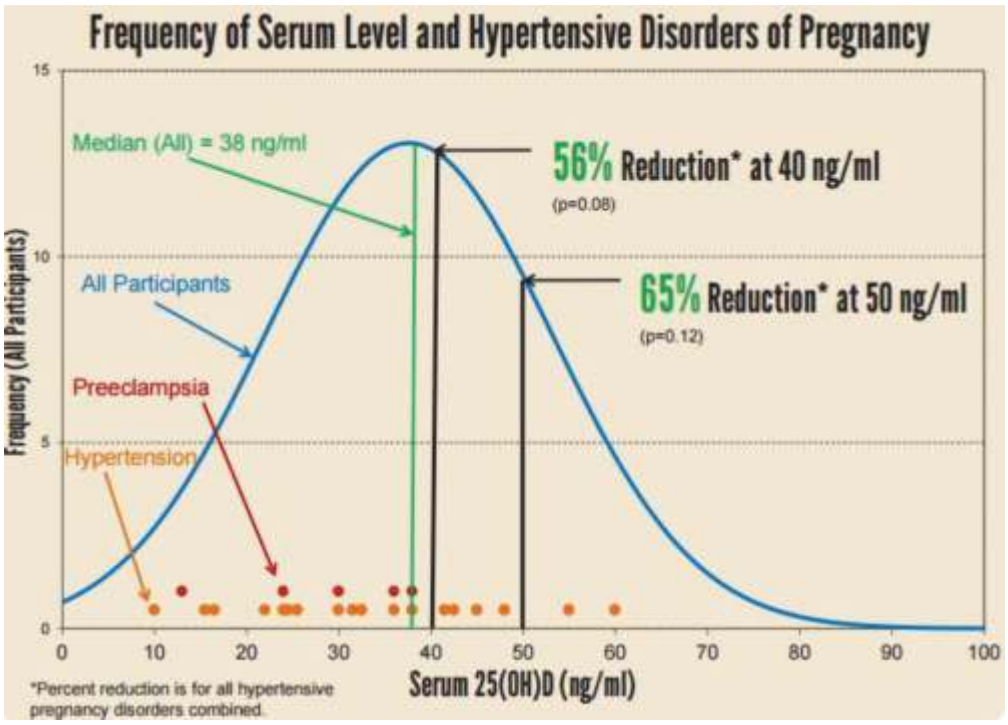


**Figure 5:** Frequency of vitamin D3 and hypertensive disorders of pregnancy

care unit admissions. Gestational hypertension, with or without PE, itself predisposes to fetal growth restriction (FGR) and small for gestational age (SGA) birth, with immediate and potentially life-long consequences. (Valdes, Quezada et al. 2009)

The question is, whether maternal and infant health outcomes can be improved by optimizing vitamin D status? An intense interest on this topic may address the persistent uncertainties around 25(OH) D concentrations that meet the criteria for 'optimal status'. In the updated Cochrane review of vitamin D supplementation and maternal and infant health outcomes, De-Regil and colleagues included 15 trials, assessing a total of 2833 women. (De-Regil, Palacios et al. 2016) Nine trials compared the effects of vitamin D *versus* no supplementation or a placebo and six trials compared the effects of vitamin D and calcium with no supplementation. Data from two trials involving 219 women, both of which were of low quality, suggest that women who received vitamin D supplements may have a lower risk of PE than those receiving no intervention or placebo.

A systematic review and meta-analysis of 31 observational studies of 25(OH) D and pregnancy outcomes by Aghajafari and colleagues, nine focused on PE. (Aghajafari, Nagulesapillai et al. 2013) Heterogeneity in the studies was a limiting factor, but there was a substantial difference in serum 25(OH) D concentrations between women who subsequently developed PE and those who did not. The mechanistic underpinning and biological plausibility of associations, plus the relative consistency indicated that low 25(OH) D preceded the adverse outcome. The authors were persuaded that, intervention studies with defined outcomes were warranted.

A recently conducted economic analysis of the burden of vitamin D deficiency in pregnant women in the UK concluded that despite uncertainties in the data, there was enough evidence to propose that addressing vitamin D adequacy in pregnant women in England and Wales would reduce PE cases by a margin sufficient to have a positive impact on the national health budget. (Kamudoni, Poole et al. 2016)

The occurrence of hypertensive disorders of pregnancy were calculated according to achieved 25(OH) D concentration using data from two supplementation trials. Women with achieved 25(OH) D concentrations ≥40 ng/ml had a 56% lower risk of hypertensive pregnancy disorders than women with concentrations. There was a trend of lower rates of hypertensive

disorders of pregnancy and bacterial vaginosis with increasing dose, with the lowest rates noted with 4000 IU. (Wagner, 2013)

Although gestational hypertension is clinically managed in high resource settings and perceived as a 'softer' outcome than PE, is a meaningful indicator of an unhealthy pregnancy. Low 25(OH) D concentrations at the first prenatal visit were associated with increased risk of GDM and might be useful in identifying women at risk of GDM for performing early prevention strategies.

Pregnancy and lactation-associated osteoporosis (PLO) is very rare, but it can cause severe vertebral compression fractures with disabling back pain. Though rare, PLO must be kept in mind in the differential diagnosis in patients presenting with low back pain during or after pregnancy. (Zhang, Chen et al. 2017)

## Foetal effects

### *Small for gestational age*

From the perspective of infant health, Aghajafari and colleagues identified a significant association between maternal 25(OH) D levels and risk of SGA birth. (Aghajafari, Nagulesapillai et al. 2013) More recently a 36% lower risk of combined PE and SGA birth at 25(OH) D concentrations greater than 30 ng/ml among a large cohort of well characterized, low-risk nulliparous women was reported. (Kiely, Hemmingway et al. 2017) A low birth weight, in conjunction with asymmetric growth and a reduced amniotic fluid index, distinguishes FGR from SGA. FGR is coupled with an increased risk of preterm birth, (Gardosi, Mul et al. 1998) which was ranked seventh in the leading causes of global years of life lost.

### *Preterm birth*

Several investigators have described an association of preterm birth with low maternal vitamin D status. The series of events that initiate preterm birth, including induced uterine contractions, membrane rupture and subsequent dilation and effacement of the cervix, are potentially accompanied by systemic inflammation, which is associated with low 25(OH) D status. (Urrutia and Thorp 2012) It is likely that 25(OH) D concentrations measured at time-points closest to delivery, reflecting maternal vitamin D status at that time, are better predictors of preterm birth than those taken in early gestation. (Wagner, Baggerly et al. 2015)

### *Impaired growth and development*

Longer-term child health outcomes have been examined in several prospective birth cohort studies. Evidence for an inverse association between impaired skeletal development in children and maternal 25(OH) D concentrations throughout gestation have been extended to offspring skeletal health in young adulthood. (Zhu, Whitehouse et al. 2014) Maternal vitamin D supplementation during pregnancy significantly reduces the risk of infantile rickets and hypocalcaemia. (Ward, Gaboury et al. 2007)

### *Cardiomyopathy*

Hypocalcaemia is a rare, yet reversible cause of dilated cardiomyopathy in infants born to vitamin D deficient mothers. Supplementation during pregnancy in order to prevent the cardiac complication of maternal vitamin D deficiency in the infants should be considered. (Moges, Shiferaw et al. 2017)

### *Respiratory distress syndrome*

Vitamin D deficiency might be associated with increased risk of Respiratory distress syndrome (RDS) in preterm infants. Reasonable vitamin D supplementation during pregnancy might reduce the incidence. (Yu, Chen et al. 2017)

### *Asthma*

Vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring. Especially among women with 25(OH) D level ≥ 30 ng/ml at randomization, the risk was almost halved. Future studies should examine the possibility of achieving this early in pregnancy or using higher doses. (Wolsk, Chawes et al. 2017)

## Vitamin D3 deficiency, insulin resistance and infertility

The traditionally recognized calcium-phosphorus homeostasis and regulation of bone metabolism are the calcemic effects of vitamin D. Recently a lot of in vitro and in vivo studies recognized several “noncalcemic” effects of its metabolites. A key role of its metabolic pathways in developing insulin resistance and infertility is evident. Vitamin D receptor-mediated signaling pathways and vitamin D levels seem to affect the risk of several gynecological diseases, such as polycystic ovary syndrome (PCOS), and endometriosis factors responsible for infertility. Since the maternal-fetal unit is under the influence of vitamin D, a breakdown in its homeostasis may underlie infertility and gestational diabetes mellitus (GDM). (Heyden and Wimalawansa 2017)

## Vitamin D and Gestational Diabetes Mellitus

Gestational Diabetes Mellitus is a condition of abnormal maternal glucose tolerance that occurs, or is detected for the first time, during pregnancy. In 2013, about 6 million women in India had some form of hyperglycemia in pregnancy, of which 90 % were GDM. (2004) Vitamin D deficiency during early pregnancy significantly increases the risk for gestational DM (GDM) in later pregnancy. (Zuhur, Erol et al. 2013) It is well-known fact that vitamin D deficiency is prevalent among pregnant Indian women. (Sachan, Gupta et al. 2005), (Harinarayan, Ramalakshmi et al. 2007)

Increasing prevalence of obesity leading to insulin resistance and better screening protocols, have unveiled GDM in Indian women greater than ever. Any degree of glucose intolerance is a risk factor for adverse maternal and fetal outcomes in pregnancy. Adverse maternal outcomes include pregnancy-induced hypertension and a heightened risk for subsequent development of Type 2 DM (T2DM). It contributes to prematurity, macrosomia, congenital anomalies, and neonatal hypoglycemia. It is also a trigger to obesity and DM in the later life of offspring. Vitamin D replenishment in Type 2 diabetics with established deficiency has restored insulin secretion and sensitivity. This points toward role for Vit D. (Cade and Norman 1987)

Mothers experience physiological insulin resistance during pregnancy to facilitate the fetus absorb more nutrients. Maternal postprandial hyperglycemia is the reason why the fetus can take in more carbohydrates and amino acids via the placenta. Carrier passage (typically facilitated transport) facilitates gradient difference. Mothers unable to compensate with an increase of pancreatic $\beta$-cell insulin secretion, present with GDM. (Catalano, Tyzbir et al. 1993), (Catalano, Huston et al. 1999) Women affected by GDM generally maintain high levels of insulin resistance, even in the puerperium, and/or later in life. The role of $\beta$-cell dysfunction, suggests that GDM is a transient manifestation of longstanding metabolic impairment. It has a predisposition to reappear in the future. (Corrado, D'Anna et al. 2014) Strong correlation exists between glucose metabolism and vitamin D pathways. This vitamin and PTH play a key role in the extracellular homeostasis of calcium. Hyperparathyroidism cases develop type 2 diabetes mellitus more frequently with respect to the general population. (Danescu, Levy et al. 2009) Vitamin D induce insulin secretion, decrease insulin resistance, so its low levels lead to GDM.

A cross-sectional study was conducted by Maghbooli et al on 741 pregnant women. Prevalence of severe vitamin D deficiency (<5 ng/mL) was higher in GDM as compared to normoglycaemic pregnancies. Homeostatic model assessment, HOMA index is a method to

quantify insulin resistance and beta-cell function. Index had strong correlation with serum levels of vitamin D. (Maghbooli, Hossein-Nezhad et al. 2008) Zhang et al. confirmed these findings; 33% of GDM cases in their study had prespecified hypovitaminosis (<20 ng/mL). (Zhang, Qiu et al. 2008) Moreover, each 5 ng/mL decrease in 25(OH) D concentrations was related to a 1.29-fold increase in GDM risk. Correlation between low levels of vitamin D and risk of GDM presented even after adjusting for well-established risk factors (maternal age, race, family history of diabetes, and pre-pregnancy BMI). (Zuhur, Erol et al. 2013) Even with all supportive data and results; further larger population based studies can provide crystal clear evidence about firm correlation between vitamin D and glucose metabolisms,.(Makgoba, Nelson et al. 2011)

## Vitamin D, Polycystic Ovary Syndrome, and Insulin Resistance

Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive-aged women in the general population. (Keen, Shah et al. 2017) Indian prevalence of 3-10% is associated with increased chances for the development of metabolic syndrome (MS). (Shabir, Ganie et al. 2014) It is a multigenic endocrine disorder characterized by increased ovarian and adrenal androgen secretion. It presents with hyperandrogenic symptoms such as hirsutism, acne, and/or alopecia; menstrual irregularity; and polycystic ovaries. (Pizzo, Lagana et al. 2014), (Asuncion, Calvo et al. 2000) In addition, insulin resistance (IR) and an increased risk of type 2 diabetes is frequent associated finding. (Ehrmann 2005) Increasing evidence is available correlating PCOS, IR and MS. (Hahn, Haselhorst et al. 2006)

Vitamin D' regulation of about 3% of the human genome, include genes crucial for glucose and lipid metabolism. Obesity, hypertension, and menstrual dysfunction findings are supported by this fact. Polymorphisms in the VDR gene are associated with vitamin D deficiency in PCOS and its metabolic and endocrine disturbances. The VDR Cdx2 "AA" genotype is reported as an associated marker of fasting insulin. Homeostatic model assessment-IR and the ApaI "CC" genotype was associated with an increased risk for PCOS. The VDR gene BsmI A/G ApaI A/C TaqI T/C and haplotype may constitute an inheritable risk factor for PCOS in South Indian women. (Siddamalla, Reddy et al. 2017)

The exact mechanisms underlying this association of vitamin D are not fully understood. First is stimulation of insulin receptor and glucose transport by enhancing insulin responsiveness. (Pittas, Lau et al. 2007) The responsibility of vitamin D to promote human insulin gene and its transcription is activated by 1,25(OH)D2. (Maestro, Davila et al. 2003), (Maestro, Molero et al. 2002) Secondly, vitamin D regulates extracellular and intracellular calcium. Through this mechanism insulin-responsive tissues such as skeletal muscle and adipose tissue are regulated. (Pittas, Lau et al. 2007) Insulin secretion being a calcium dependent process, can be adversely affected by calcium flux. Modulating effect of hypovitaminosis D on the immune system, might induce a higher inflammatory response, is linked to IR. (Shoelson, Herrero et al. 2007)

Recent review of 29 eligible trials by Krul-Poel et al had inconsistent results. These conflicting findings might be due to small sample sizes, lack of adjustments for confounders, different definitions for PCOS, amounts of vitamin D supplementation in intervention trials and assays for serum 25(OH) D measurement, duration of intervention, , and lack of an optimal serum 25(OH)D level in the general population. (Krul-Poel, Snackey et al. 2013) Univariate regression analyses of the weighted means revealed vitamin D to be a significant and independent predictor of IR in both PCOS and control women.

A randomized, placebo-controlled clinical trial involving 44 PCOS women aged 20-38 years with plasma 25OHD < 20 ng/mL with intervention or placebo groups were followed for 8 weeks. Participants received either 50,000 IU of oral vitamin D3 once weekly or placebo. Intervention, improved the fasting plasma glucose (FPG), HOMA-B (assessment of β-cell activity), Adiponectin, and serum vitamin D level. (Seyyed Abootorabi, Ayremlou et al. 2017)

In a dose finding study the effects of vitamin D supplementation on the metabolic profiles of insulin-resistant subjects with polycystic ovary syndrome (PCOS) were determined. Ninety participants were randomly assigned to three groups (n = 30) to intake either 4000 IU of vitamin D or 1000 IU of vitamin D or placebo daily for 12 weeks. High-dose vitamin D had beneficial effects on total testosterone, sex hormone binding globulin (SHBG), free androgen index (FAI), serum high-sensitivity C-reactive protein (hs-CRP) and plasma total antioxidant capacity (TAC) levels compared with low-dose vitamin D and placebo groups. (Jamilian, Foroozanfard et al. 2017) In another study androgen profile did not change with vitamin D supplementation when combined with low-calorie diet, but menstrual frequency significantly improved. (Jafari-Sfidvajani, Ahangari et al. 2017)

An Indian randomized controlled study revealed beneficial effect of vitamin D 60,000 IU weekly for 12 weeks on ovulatory dysfunctions and blood pressure. Post-supplementation, there were decrease in insulin resistance and increase in insulin sensitivity. Decreased serum fasting insulin level and fasting blood sugar after vitamin D supplementation suggest underlying role of vitamin D in glucose homeostasis. (Gupta, Rawat et al. 2017)

Still, it remains unclear whether vitamin D and IR are causally interrelated or whether they constitute two independent characteristics in women with PCOS. The causal relationship between vitamin D status and metabolic disturbances in PCOS remains to be determined in well-designed placebo-controlled randomized clinical trials. Until then, screening women who are at risk and supplementation with vitamin D could be considered.

## Vitamin D, Infertility, and In Vitro Fertilization (IVF)

Accumulating evidence strongly indicates a potential role of vitamin D in human reproduction. Vitamin D receptors are present and differentially expressed in murine endometrium and ovary throughout the estrous cycle. (Zarnani, Shahbazi et al. 2010) Vitamin D receptor knock-out mice (null mice) experience uterine hypoplasia and impaired folliculogenesis. (Yoshizawa, Handa et al. 1997) Cell cultures have confirmed the expression of vitamin D receptors in human endometrial cells. The expression of 1-alpha-hydroxylase is upregulated. This enzyme catalyzes the hydroxylation of calcidiol to calcitriol in the human endometrial stromal cells of early pregnancy. (Vigano, Lattuada et al. 2006) However, in vivo data supporting a role for vitamin D in female fertility in general and embryo implantation in particular are not robust. Finally, a recent retrospective study postulated endometrium mediated vitamin deficiency may negatively affect pregnancy rates. Ovarian stimulation characteristics of or with markers of embryo quality was observed. (Rudick, Ingles et al. 2012)

An innovative study to evaluate the influence of vitamin D deficiency on pregnancy rates among women undergoing IVF/ICSI (Intra Cytoplasmic Sperm Injection) and Day 5 (blastocyst stage) single embryo transfer (SET) was recently carried out by Polyzos et al. Significant hypovitaminosis and lower clinical pregnancy rates were documented in this setting of women. 368 consecutive infertile women treated over a period of 15 months were included. Future prospective confirmatory studies are needed to validate these results and examine the exact underlying mechanism.(Polyzos, Anckaert et al. 2014)

Yet another study witnessed significantly higher rates of clinical pregnancy per IVF cycle started (52.5%) in women with sufficient levels of vitamin D. Implantation rates were also higher, but DeLuca 2011) Crescioli et al proved from prostatic stromal cell cultures both in vitro and in vivo that calcitriol (1, 25(OH) D2) and other analogs of vitamin D (BXL-253, BXL-628) modulated cell proliferation and apoptosis. (Crescioli, Maggie et al. 2000), (Crescioli, Morelli et al. 2005)

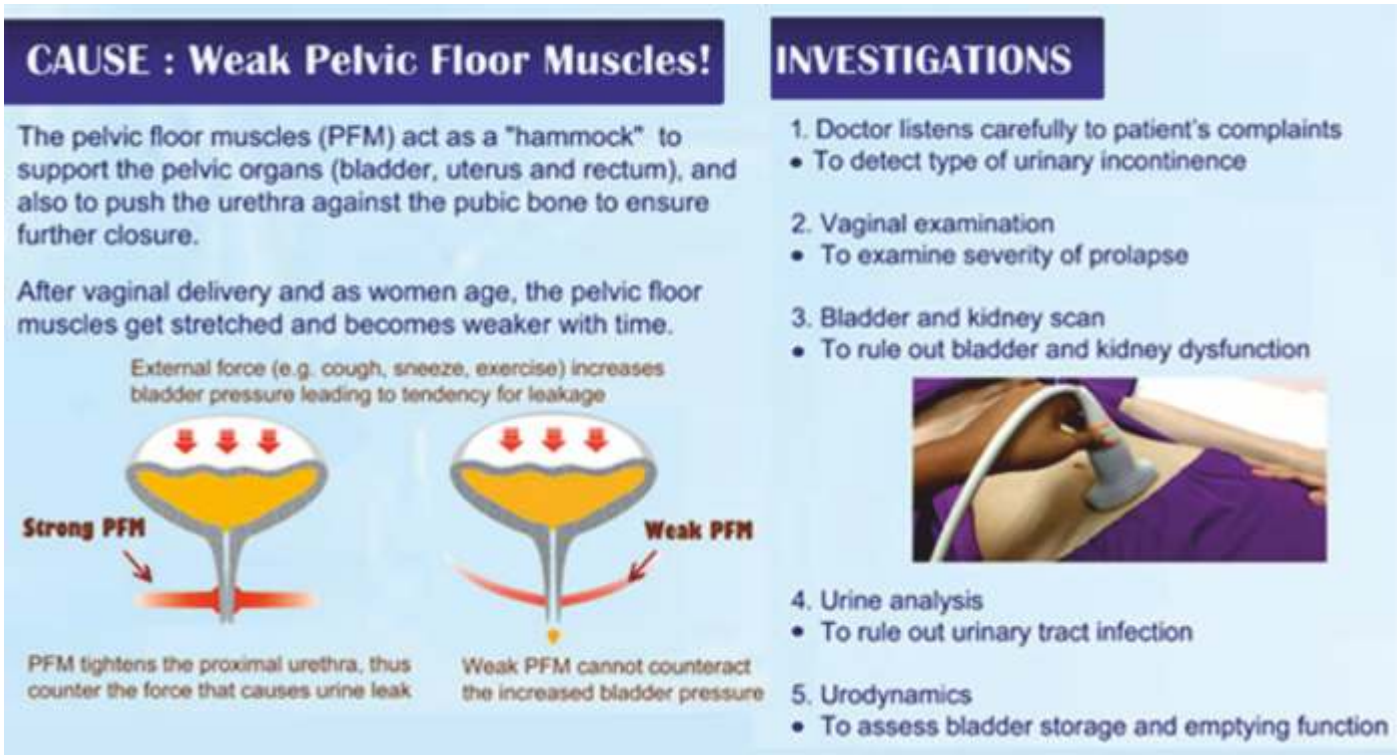


**Figure 6:** Causes and investigations of weak pelvic floor muscles

## Pelvic floor Insufficiency

The female pelvic floor compared to its male counterpart is a complex element. Its overall function relies on musculoskeletal connections to pelvic bones. These delicate entities support abdominal cavity and pelvic viscera. Disorders of the pelvic floor include urinary and fecal incontinence, pelvic organ prolapse, and other problem in the storage and emptying functions of distal part of urinary and gastrointestinal tracts.

Pelvic floor disorders are very common. Its prevalence increases with age. Nygaard et al reported that 24% of US women ≥20 years of age had at least 1 pelvic floor disorder. (Nygaard, Barber et al. 2008) The prevalence of urinary incontinence (UI) varies by definition, but has been reported to range between 13–49%. Women's Health Initiative study reported 41% have pelvic organ prolapse among women aged 50–79 years. (Sung and Hampton 2009), (Hendrix, Clark et al. 2002) The economic burden of pelvic floor disorders is projected to grow exponentially.

Pelvic floor muscle weakness clinically observed in women with pelvic floor disorder (PFD) symptoms is impacted by insufficient serum Vitamin D. The Vitamin D receptor has also been identified in the detrusor wall. Thus its insufficient level may impact bladder function also.

## Role of Vitamin D in Urinary incontinence

Vitamin D may play a role in the efficiency of muscle function that is distinct from the role of calcium in muscle contractility. (Sharma and Aggarwal 2017) Many studies have demonstrated a correlation between skeletal muscle weakness and low vitamin D concentrations. Preliminary clinical study results support an association between vitamin D and incident UI in community-dwelling older adults. (Vaughan, Tangpricha et al. 2016)

Deficient and insufficient 25(OH) D concentrations may also contribute to pelvic floor muscle weakness and predispose women to incontinence. However, few observational studies exist that have investigated the relationship between pelvic floor disorders and 25(OH) D nutritional status.

Urgency urinary incontinence (UI) is a urinary storage symptom as a result of a neurologic abnormality, bladder outlet obstruction, bladder wall inflammation, or may be idiopathic. In vivo studies demonstrated vitamin D receptor in the bladder neck including urothelium and the inner longitudinal, middle circular, and outer longitudinal smooth muscle layers of the bladder wall. (Crescioli, Morelli et al. 2005) Since action is mediated through vitamin D receptor, deficiency or insufficiency result in abnormal calcium homeostasis and detrusor contractility. Weakened detrusor muscles as in hypocalcemic skeletal muscle become hyper-contractile or irritable. Augmented inflammatory cytokine activity of urothelium results in bladder wall inflammation.

The Leicestershire MRC Incontinence Study was conducted on the prevalence and incidence of incontinence and other lower urinary tract symptoms. This was the first ever study to demonstrate an association between vitamin D nutritional status and pelvic floor disorders. It is a cohort study involving community dwelling women. Baseline questionnaires to assess urinary symptoms and vitamin D intake were sent via mail. Questionnaire developed for this study modeled after the International Continence Society's standards for the diagnosis of Over Active Bladder (OAB). Vitamin D intake was evaluated using a food frequency questionnaire. (Crescioli, Morelli et al. 2005)

Badalian and colleagues examined the relationship between pelvic floor disorders and 25(OH) D concentration in 1,881 US women. UI was defined by the Incontinence Severity Index which is a 2 question derivative from the Incontinence Impact Questionnaire (IIQ). A score of greater than three defined the presence of urinary incontinence. (Nygaard, Barber et al. 2008) Fecal incontinence was defined as having at least one episode of leakage in a month. Serum 25(OH) D was measured using the Diasorin's radioimmunoassay method. Vitamin D deficiency and insufficiency were defined as 25(OH) D concentrations <10ng/ml and <30ng/ml, respectively. The prevalence of UI and more than one pelvic floor disorder was significantly higher in women with vitamin D insufficiency. A similar trend was seen for fecal incontinence, but the difference was not statistically significant. (Badalian and Rosenbaum 2010)

Prospective cohort or randomized studies investigating the relationship between vitamin D nutritional status and pelvic floor disorder symptoms are lacking. However, Jen-Tzer Gau reported two case studies of resolution of UI with vitamin D supplementation. (Gau 2010)

Alkhatib et al reported a small case series of 10 patients with fecal incontinence (8 males, 2 females). Patients with known causes of hypovitaminosis D (chronic kidney and liver disease, malabsorption) were excluded. All study subjects had hypovitaminosis D - 60% 25(OH) D <20 ng/ml and 40% 25(OH) D <29 ng/ml. The mean 25(OH)D concentration was 17ng/ml. (Alkhatib and Tuteja 2010) Fecal continence requires normal function and strength of the levator ani muscles (puborectalis), the internal, and external anal sphincter muscles. Weakened or disrupted muscles may significantly compromise the continence mechanism.

High dose vitamin D may benefit lower urinary tract symptoms (LUTS) in postmenopausal women. Randomized controlled study of 297 postmenopausal women with low bone mineral density was completed. The participants were allocated 20 000IU of vitamin D3 capsules twice a week (high dose group) or similar looking placebo (standard dose group). In addition, all the participants received 1g of calcium and 800IU of vitamin D daily. Statistically significant reduction in the severity of urine incontinence in the high dose group was reported. (Oberg, Verelst et al. 2017)

Vitamin D supplementation may prove to be a beneficial adjunctive treatment helping to optimize the response to Pelvic Floor Muscle Training (PFMT) and the quality of life.

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Dear Doctor,

Vitamin D3, popularly called the “sunshine Vitamin,” is a critical nutrient for women’s health. Regardless of its discovery 100 years ago, Vit D has emerged as one of the most debatable nutrients and prohormones of the 21st century. Vast research has been in place on this molecule which gave rise to newer therapies with newer concepts. Research has now shown Vit D’s indisputable role in musculoskeletal disorders and its emerging role both in inherent and adaptive immunity.

It is indeed a pleasure to present to you this QMR issue by Dr. Prasanta Kumar Nath Barbhuiya, renowned Gynaecologist and Obstetrician. In this issue, he is enlightening us on ‘The role of vitamin D deficiency on women’s health”.

I sign off by once again reminding you to continue sending in your comments and suggestion regarding the QMR. Do write to me at balaji.more@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

With best regards,

**Dr. Balaji More**
Vice President - Medical

**Feedback form: October - December 2018.**
**Role of Vitamin D in Women Health**

1. Your comments on this issue of Q.M.R.
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