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KEY PRACTICE POINTS
DEFICIENCY TO SUFFICIENCY
WITH VITAMIN D

CLINICAL RECOMMENDATIONS: VITAMIN D IN PREGNANCY, LACTATION, PCOS, INFERTILITY, BONE HEALTH, AND MENOPAUSE

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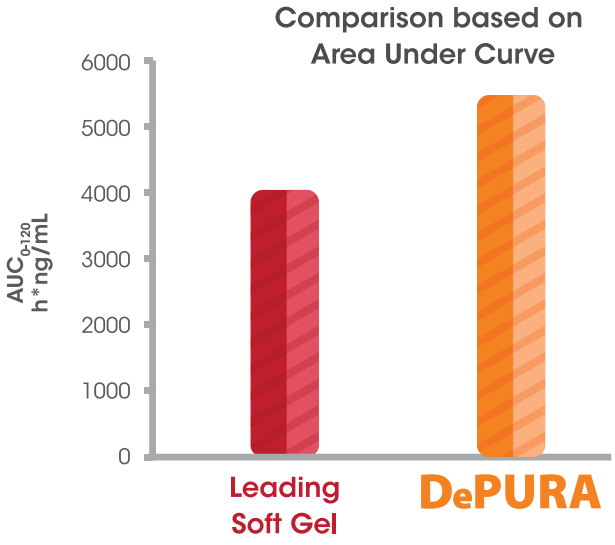

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60,000 IU/week for 8 weeks[1]	3 months-18 years 60,000 IU/week for 6 weeks[1]	60,000 IU/month[1]

References:

*Trademark initiated by Sanofi India Ltd. | #Clinical Study Report - CHOLEL07832 | $Flavoured sugar-free base | AUC - Area Under Curve

1. Mithal A et al. Endocrine society of India expert group. Vitamin D deficiency in India recommendation for treatment Elsevier India 2015

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Dear FOGSIANs,

Best wishes!

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MD, FCPS, FICOG
President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

VITAMIN D SUPPLEMENTATION DURING PREGNANCY, LACTATION, BONE HEALTH AND MENOPAUSE:
CLINICAL RECOMMENDATIONS

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. Ashwini Bhalerao, Dr. Ameya Purandare, Dr. Neelam Aggarwal

Panelists : Dr. Reeti Mehra, Dr. Rajendra Nagarkatti, Dr. Anita Singh, Dr. Ram Prabhoo, Dr. Anahita Chauhan, Dr. Iravati Purandare, Dr. Sandhya Saharan

From left to right: ***Standing*** – Dr. Rohan Palshetkar, Dr. Anita Singh, Dr. Ashwini Kale, Dr. Sandhya Saharan, Subramanian, Anuja, Ramya Mandapaka, Ms. Sneha Shah, Dr.Manish Verma, Dr. Rakesh Sonawane, Bharat Dedhia, Dr. Ram Prabhoo, Dr. Rajendra Nagarkatti and Dr. Dibyendu Banerjee
Sitting - Dr. Ashwini Bhalerao, Dr. Neelam Aggarwal, Dr. Reeti Mehra, Dr. Pratik Tambe, Dr. Nandita Palshetkar, Dr. Ameya Purandare, Dr. R. K Marwaha, Dr. Anahita Chauhan and Dr. Neelam Bhise

KEY PRACTICE POINTS
DEFICIENCY TO SUFFICIENCY WITH VITAMIN D

An astonishingly high prevalence of vitamin D deficiency in Indian pregnant and lactating women

Vitamin D deficiency during pregnancy is reported to be associated with an increased risk of preeclampsia, altered immune response and risk of preterm birth. Moreover, vitamin D deficiency in infants is likely to be associated with lung dysfunction, disordered immune response, and suboptimal growth.Research has shown that babies born to vitamin D deficient mothers are also vitamin D deficient with prevalence ranging from 28% to 90%. Therefore, it is essential to establish the need for optimization of vitamin D levels during pregnancy and lactation.[1] During pregnancy, serum level of 1,25-hydroxyvitamin D [1,25(OH)D] increase up to two-fold starting at 10–12 weeks of gestation and reaching a maximum in the third-trimester.[2]

- Based on few study reports, the prevalence of hypovitaminosis D ranged from 42% to 74% among pregnant women, 44.3% to 66.7% among infants, and 70% to 81.1% among lactating mothers. Overall, a high prevalence of vitamin D deficiency (>65%) was reported among infants, pregnant and lactating mothers.[3]
- Another recent study from 2019 showed that the prevalence of vitamin D deficiency and insufficiency in pregnancy was 96.62%.[2] It is therefore important for pregnant women to have adequate levels of vitamin D as undernutrition in pregnant women has been linked with multiple adverse effects.[3]
- An updated review of global vitamin D status was conducted which showed that vitamin D deficiency is a major public health problem worldwide in all age groups. The review demonstrated that, in India around 96% of the pregnant or lactating women and about 99% of the infants had vitamin D levels <20ng/ml.[4]

Recent reports have revealed an astonishingly high prevalence of up to 96% of vitamin D deficiency in pregnant and lactating women, and up to 99% of the infants in India.

Vitamin D requirements during pregnancy and lactation

Vitamin D deficiency during pregnancy and lactation has a detrimental impact on maternal and foetal health. Stages of vitamin D deficiency and adverse effects in pregnancy and during lactation is mentioned in Table 1.[5]

Recommended daily doses of vitamin D during pregnancy and lactation

The only source for vitamin D is sun exposure. Therefore, to meet the increased requirements during pregnancy, vitamin D supplementation is important. The recommended daily dose of vitamin D during pregnancy and lactation is given below:

- The recommended daily dose as per Institute of Medicine (IOM) of vitamin D during pregnancy and lactation is given in Table 2.[6] This recommendation is based on the amount of intake necessary to sustain blood levels of 25(OH)D above 50 nmol/L for populations with minimal sunlight exposure.[7]
- Studies have also reported that, by second-trimester, daily supplementation of up to 4000 IU/day is safe and effective in achieving the minimal level of 25(OH)D for optimal 1,25-dihydroxyvitamin D [1,25(OH)D] production.[8]

Table 1. Stages of vitamin D deficiency and adverse effects[5]

Stage	Serum 25(OH)D	Maternal adverse effects	Newborn infant adverse effects
Severe deficiency	<10 ng/mL	Increased risk of preeclampsia, calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels	Small for gestational age, neonatal hypocalcemia, hypocalcemic seizures, infantile heart failure, enamel defects, large fontanelle, congenital rickets, rickets of infancy if breastfed
Insufficiency	11–32 ng/mL	Bone loss, subclinical myopathy	Neonatal hypocalcemia, reduced bone mineral density, rickets of infancy if breastfed
Adequacy	32–100 ng/mL	Adequate calcium balance, parathyroid hormone levels	None, unless exclusively breastfed
Toxicity	>100 ng/mL	Hypercalcemia, increased urine calcium loss	Infantile idiopathic hypercalcemia

Serum 25(OH)D: Serum 25 hydroxyvitamin D

- The IOM has also defined adequate vitamin D status as having serum 25(OH)D concentrations greater than 50 nmol/L (or 20 ng/mL) in all women.[9]

Table 2. Institute of Medicine recommendation for daily allowance of vitamin D in pregnancy and lactation[6]

Life stage group	AI	EAR	RDA
Infants			
0–6 months	400IU		
6–12 months	400IU		
Pregnancy		400 IU	600IU
Lactation		400 IU	600IU

AI: Adequate intake, EAR: Estimated average requirement, RDA: Recommended daily allowance

Vitamin D metabolism during pregnancy

A key role of vitamin D is the regulation of calcium homeostasis. The synthesis, metabolism and actions of vitamin D are important for bone mineralization, immune functions and disease prevention.[10]

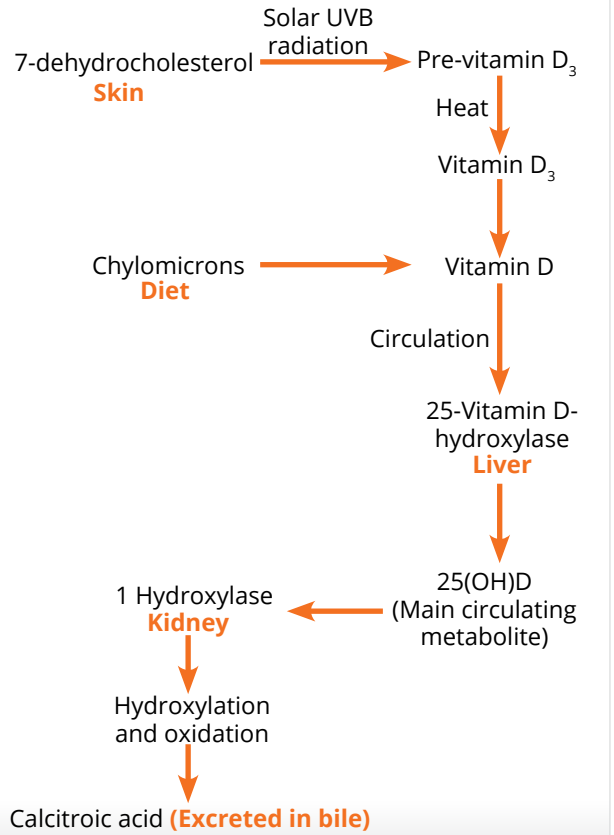
Serum 25(OH)D levels: An indicator of vitamin D status

The source for vitamin D includes sun exposure, intake by natural foods, supplement intake and vitamin D-fortified foods. After vitamin D intake, in liver, vitamin D [isoforms: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol)] is metabolized to 25(OH)D by different 25-hydroxylase enzymes. The half-life of serum 25(OH)D is around 2 to 3 weeks and it is the best metabolite which reflects vitamin D supply from all different sources. Therefore, it is used for the classification of vitamin D status. The kidney and other tissues then metabolize 25(OH)D to $1,25(OH)_2D$, the active vitamin D hormone or calcitriol. The biological effects of calcitriol are mediated by binding to vitamin D receptor (VDR). After several hydroxylation and oxidation steps, the vitamin D metabolites are then degraded to calcitroic acid, which is excreted in the bile and urine (Figure 1).[11,12]

Placenta plays a key role in the transportation of vitamin D to the foetus

A major change in the vitamin D metabolism during pregnancy, as compared to non-pregnant women, is a significant increase in $1,25(OH)_2D$ concentrations which rapidly declines after delivery. But despite of the increased

Figure 1. Synthesis and metabolism of vitamin D[12]



concentration of $1,25(OH)_2D$, there is no change in total serum 25(OH)D concentrations.[11]

Placenta plays a key role in the transportation of vitamin D to the fetus that is totally dependent on the mother's vitamin D status. Practically, $1,25(OH)_2D$ does not cross the placenta, while, 25(OH)D, the inactive precursor of vitamin D readily crosses the tissue of the foetal compartment.[13]

1. Placenta potentially activates 25(OH)D via 1-α-hydroxylase enzyme and produces $1,25(OH)_2D$ (Figure 2).
2. In addition, the placenta also inactivates 25(OH)D to $24,25(OH)_2D$ by 24-hydroxylation, suggesting that it has a paracrine control of vitamin D metabolism.

This dual role of placenta helps in the local regulation of vitamin D levels within its tissues and in turn affects the pregnancy development and/or perinatal outcomes.[13]

CLINICAL RECOMMENDATIONS

- **Higher maternal levels of $1,25(OH)_2D$ are essential to increase intestinal calcium absorption during pregnancy and to support calcium for maternal and fetal metabolism.**
- **Higher maternal levels of $1,25(OH)_2D$ are also essential for regulating the immune system during pregnancy.**

Figure 2. Materno-fetal vitamin D transfer

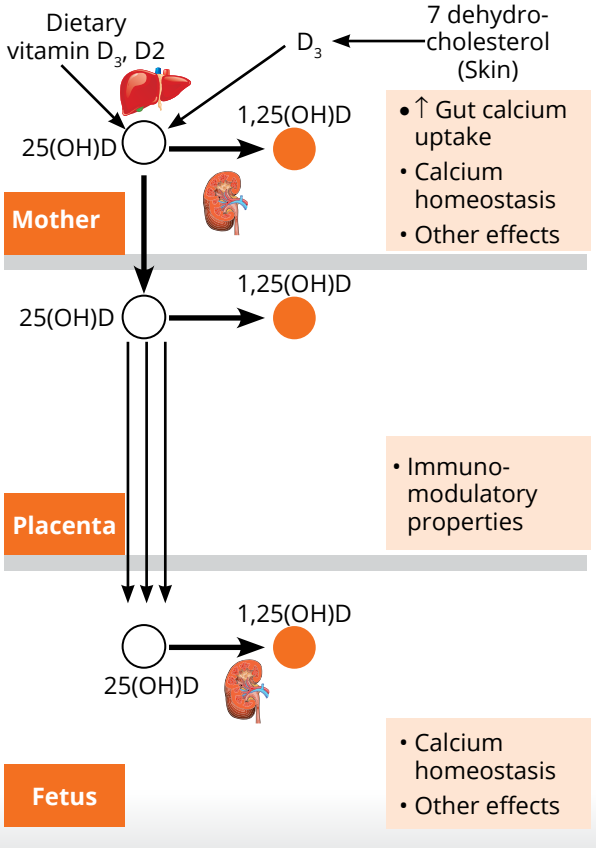
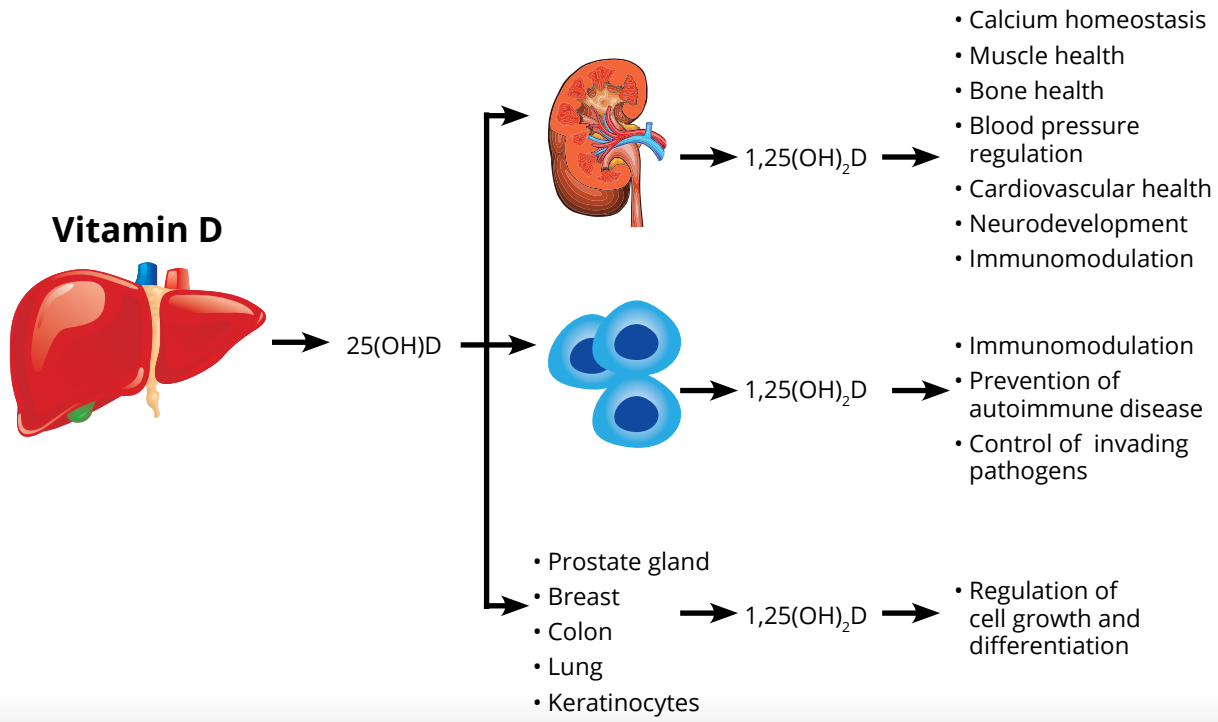


Figure 3. Biological functions of vitamin D[14]



Implication of vitamin D status on maternal and fetal health

Maternal vitamin D nutrition and vitamin D nutrition *in utero* and in breastfeeding infants is interlinked Figure 3.[14] In the foetus and infant at birth, vitamin D stores,as measured by serum 25(OH)D concentrations in cord blood depends on maternal vitamin D status. Clinical studies suggest that the umbilical cord blood 25(OH)D level is maintained at 60%–85% of the maternal value. Therefore, maternal vitamin D deficiency may expose fetus to hypovitaminosis D and leading to vitamin D deficiency in infants at birth.[14]

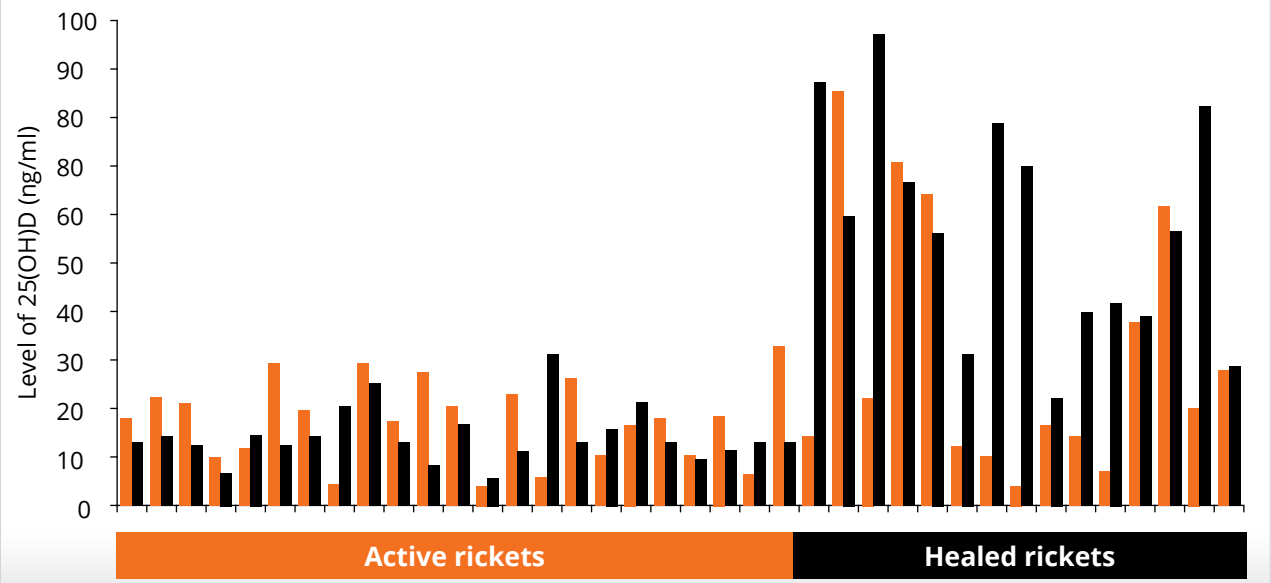
Therefore, inadequate dietary intake of vitamin D during pregnancy may have a detrimental impact on maternal and foetal health. The complications include preeclampsia, and preterm delivery or long-term morbidities, such as excessive bone loss, effect on infants neurodevelopment and the increasing the risk of asthma.[13,15]

Maternal and fetal bone health

During pregnancy, vitamin D plays an important role for maintaining maternal calcium homeostasis. A low vitamin D levels are associated with bone resorption. Maternal serum 25(OH)D levels below 30 ng/mL is associated with maternal periodontal disease. In addition to this, increase in parity is reported to be associated with an increased tooth loss.[13]

In a study, at 19 weeks gestation, lower maternal vitamin D levels were related to greater femoral metaphyseal cross-sectional area (r = –0.16, 95% CI –0.25 to –0.06). While at 34 weeks gestation, it was associated with femoral splaying index (r = –0.17, 95% CI –0.26 to –0.01). A low maternal vitamin D level increases the geometric mean femoral splaying indices.[13]

Figure 4. Paired 25(OH)D levels in active and healed rickets in infants their mothers[16]



Maternal deficiency of vitamin D is also a major factor in development of rickets in her breastfeeding infants. In a study, among mother-breastfeed infant pair (n=38), the mean level of 25(OH)D in infants with active rickets was 10.5 ng/ml and their mothers 12.1 ng/ml. While in the infants with healed rickets the mean level of 25(OH)D was 53.6 ng/ml and in their mothers was 19 ng/ml (p=0.0393 between the active rickets group and healed rickets group) (Figure 4).[1]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency during early pregnancy may lead to a lower bone mineral content (BMC) and bone mineral density (BMD) in offspring in later life, and is associated with the development of rickets in infants.**
- **Assessment of vitamin D status in early pregnancy or in woman at pre-conception maybe considered.**

In another study, maternal vitamin D deficiency at 18 weeks gestation was associated with 2.7% lower total body bone mineral content (BMC) (mean ± SE) (2846 ± 20 vs. 2924 ± 16 g, p=0.004) and 1.7% lower total body bone mineral density (BMD) (1053 ± 7 vs. 1071 ± 5 mg/cm^2, p=0.043) in the offspring at 20 years of age.[17]

Perinatal outcomes

Preeclampsia

In a prospective case control study, 83.3% of pregnant women with preeclampsia/eclampsia had severe deficiency [25(OH)D levels <10 ng/ml] vs. 68% uncomplicated pregnant women. The mean serum 25(OH)D levels were significantly less in pregnant women with preeclampsia/eclampsia (6.7236 ng/ml) vs. uncomplicated pregnant women (9.8862 ng/ml, p=0.004).[18]

In another study, a significantly lower incidence of preeclampsia was observed in women who had sufficient vitamin D levels (at least 30 ng/mL) in both early and late pregnancy vs. those who had an insufficient level at these time points (2.25 vs. 11.92%; RR 0.20; 95% CI, 0.06–0.66; p<0.008).[13]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency during pregnancy increases the risk of preeclampsia.**

Preterm delivery

Vitamin D deficiency is also associated with an increased risk of preterm birth. In a meta-analysis of prospective cohort studies (13 cohort studies), for women with vitamin D deficiency the pooled overall OR for babies born small for gestational age (SGA) was 1.588 (95% CI 1.138 to 2.216; p<0.01). This suggests that vitamin D deficiency is associated with an increased risk of SGA.[19]

In a cross-sectional study, the mean maternal vitamin D level of low birth weight neonates was low compared to mothers of neonates with a birth weight of >2500 gm (25.05 vs. 38.13, p=0.001). Vitamin D deficiency was also observed in all mothers of neonates with head circumference ≤ 33 cm (p=0.0007).[20]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency during pregnancy increases the risk of preterm birth and low birth weight neonates.**
- **Modifying maternal vitamin D levels could be beneficial for positive pregnancy outcomes.**

Prenatal vitamin D and neurodevelopment

In human brain, the presence of 1-hydroxylase, which converts inactive form of vitamin D to the active form suggests the paracrine properties of vitamin D.[13]

Neurocognitive development

In a birth cohort study, a significant association was observed between maternal vitamin D deficiency at 18 weeks' gestation and language impairment at ages 5 and 10. As compared to women within the highest quartile of the 25(OH)D distribution (>70 nmol/L), risk of having a child with clinically significant language difficulties was increased close to two-fold in pregnant women who had 25(OH)D levels within the lowest quartile of the distribution (≤46 nmol/L).[21]

In a study (7,065 mother-child pairs), as compared to children of vitamin D-sufficient mothers (≥50·0 nmol/l), children of vitamin D-deficient mothers (<50·0 nmol/l) were more likely to have scores in the lowest quartile for gross-motor development at 30 months (OR: 1·20; 95 % CI: 1·03–1·40), fine-motor development at 30 months (OR: 1·23; 95% CI: 1·05–1·44) and social development at 42 months (OR: 1·20; 95% CI: 1·01–1·41).[22]

Attention deficit hyperactivity disorder (ADHD)

In pre-schoolers, aged 4–5 years, 10 ng/mL increment of maternal 25(OH)D_3 at 13 weeks of gestation decreased ADHD-like symptoms by 11%. In another study, in early pregnancy (13 weeks), higher maternal levels of vitamin D (> 50.7 nmol/L) was found to be associated with reduced hyperactivity-impulsivity symptoms and total ADHD-like symptoms in offspring at age 4.[13]

Autism spectrum disorder

A positive association is observed between prenatal vitamin D status with autistic traits or autism spectrum disorder (ASD). In a study, both mid-gestational and neonatal vitamin D deficiency [25(OH)D levels < 25 nmol/L] was found to be associated with autism-related traits at 6 years of age. In addition to this, mid-

gestation vitamin D deficiency was associated with a higher risk of being diagnosed with clinical ASD.[13]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency during early pregnancy impacts the neuropsychological development of children (language impairment, low quartile gross-motor development and fine motor development, attention deficit hyperactivity disorder like symptoms and autism-related traits) in later life.**

Prenatal vitamin D status and risk of asthma

A high dietary vitamin D intake during pregnancy is associated with a reduced risk of wheeze in the offspring. A recent meta-analysis has reported an inverse association between prenatal intake of vitamin D and the risk of developing recurrent wheeze in the offspring (RR 0.812; 95% CI: 0.67–0.98).

In another study, by the ages of 5 years, multivariable-adjusted logistic regression models showed a significant inverse association between cord serum 25(OH)D levels and risk of transient early wheezing and atopic dermatitis.[23]

CLINICAL RECOMMENDATIONS

- **Clinical evidence supports a preventive role of vitamin D during pregnancy on offspring wheeze and/or respiratory tract infections.**

Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth

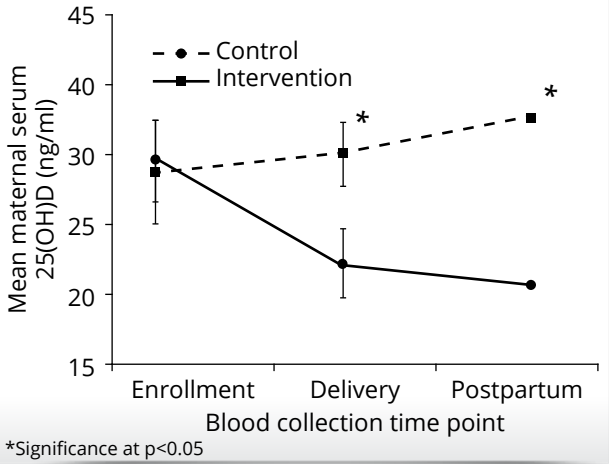
Breastfed infants of vitamin D–sufficient mothers are protected from rickets during the first few months of life,due to the 25(OH)D levels which cross the placenta and lead to neonatal concentration of approximately two-thirds that of maternal vitamin D concentrations. Moreover, recommendation to exclusively breastfeed infants to 6 months of age has led to the introduction of vitamin D supplementation of breastfed infants. However, supplementing the lactating mother has been considered as an alternative to supplementing the infant. Hence, supplementing the mother with high-dose vitamin D during lactation results in an increase in the total vitamin D concentration of breast milk thereby increasing both, the maternal and infant serum 25(OH)D concentrations.[24]

Vitamin D_3 supplementation during pregnancy and lactation improves vitamin D status of the mother–infant dyad

A double-blind randomized study was initiated to establish the combined effects of prenatal and postnatal vitamin D_3 supplementation on the vitamin D status of pregnant and lactating women and their exclusively breastfed infants. The intervention group (pregnant women planning to exclusively breastfeed) was given vitamin D_3 at a dosage of 3800 IU daily and the control group was administered 400 IU vitamin D_3 at 24-28 weeks gestation through 4–6 weeks post-partum. Vitamin D status was determined by evaluating serum 25(OH)D levels compared with control group, significantly higher maternal vitamin D levels were observed in the active intervention group

at time of birth (p=0.044) and at 4–6 weeks post-partum (p=0.002) as shown in Figure 5. Infants in the interventional group had significantly higher vitamin D levels at birth (p=0.021) with clinically relevant but non-significant increase at 4–6 weeks of age. The authors concluded that prenatal to postpartum vitamin D_3 supplementationis an efficacious and safe intervention in rectifying maternal and infant vitamin D deficiency, and helps in promoting optimal vitamin D status in new-borns and exclusively breastfed infants.[1]

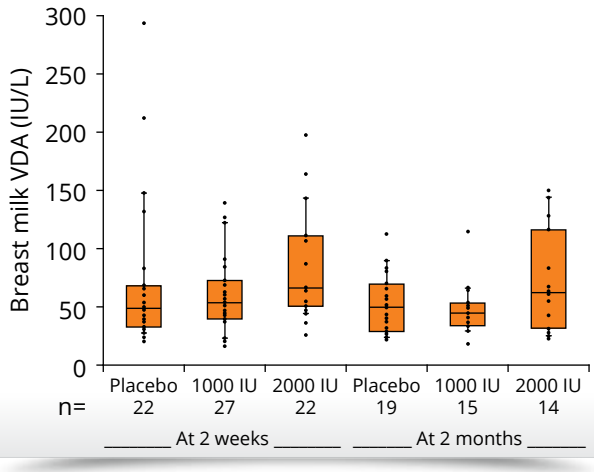
Figure 5. Mean maternal 25 hydroxy vitamin D [25(OH)D] level in the control and intervention groups.



*Significance at p<0.05

Another study determined the effect of vitamin D supplementation (2000 IU in 2 divided doses daily) during pregnancy on breast-milk vitamin D activity in the first 2 months of lactation compared with those supplemented with low doses of vitamin D (1000 IU daily). It was observed that the vitamin D activity in the higher-dose–vitamin D group was greater than that in the lower-dose–vitamin D group (39% difference; 95% CI: 4%, 87% difference; p=0.04; Figure 6). Therefore, maternal vitamin D supplementation during pregnancy of 2000 IU/d (compared with 1000 IU/d and with a placebo) results in a higher vitamin D activity of breast milk ≥2 months postpartum.[24]

Figure 6. Median [IQR (box)] breast-milk vitamin D activity (VDA) at infant age of 2 week and 2 months in lactating mothers[24]



CLINICAL RECOMMENDATIONS

- **Prenatal to postpartum vitamin D_3 supplementation is an efficacious and safe intervention in rectifying maternal and infant vitamin D deficiency.**
- **Vitamin D supplementation should be considered to promote optimal vitamin D status in new-borns and exclusively breastfed infants**

Positive effects of Vitamin D supplementation on pregnancy outcomes

Protection of extra skeletal health outcomes in pregnancy

Hypovitaminosis D in pregnancy may decrease birth-weight and increase the risk of HIV mother-to-childtransmission, respiratory infections, wheezing, rhinitis,eczema, type 1 diabetes and schizophrenia in the off-spring. Severe hypovitaminosis during pregnancy may also cause fetal death, infant hypocalcemictetany and life-threatening cardiomyopathy. The

potential extraskeletal effects on the offspring of hypovitaminosis D during pregnancy have gathered much interest in recent years, as have the effects of hypovitaminosis D occurring later in childhood andin non-pregnant adults.[25]

A systematic review of 6 randomized controlled trials and 24 observational studies was conducted to evaluate the impact of vitamin D in pregnancy on extraskeletal health in children. Higher vitamin D intake, or higher 25(OH)D, was associated with increased birthweight, and lower risk of HIV mother-to-child transmission, rhinitis symptoms and eczema.[25]

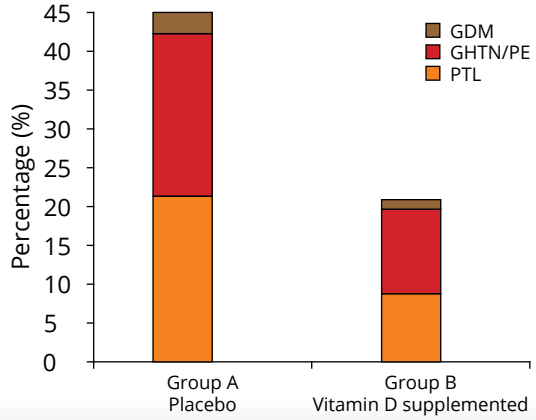
Another recent systematic review and meta-analysis of randomized clinical trials (RCTs) showed that maternal vitamin D supplementation reduced the risk of low birth weight (3 RCTs; RR = 0.40, 95% CI: 0.22–0.74) and small for gestational age (5 RCTS; RR = 0.69, 95% CI: 0.51–0.92).[26]

An RCT has demonstrated that vitamin D supplementation in deficient pregnant women reduces the risk of pre-eclampsia and intrauterine growth restriction (IUGR) in a dose dependant manner. Patients with vitamin D_3 deficiency (serum levels <25 nmol/L) were included in the study and randomized for vitamin D_3 supplementation 400 IU (Group 1) versus 4000 IU (Group 2), and were compared for the prevalence of pre-eclampsia and dose effect on vitamin D level.[27]

- In comparison to Group 1, the Group 2 reported fewer pre-eclampsia events during the study period (8.6% versus 1.2%; p<0.05). The total number of IUGRs was lesser in the Group 2 (9.6%) versus Group 1 (22.2%); p=0.027. However, other obstetric outcomes were comparable between both groups.[27]

Another study showed that vitamin D supplementation reduces risk of maternal comorbidities and helps improve neonatal outcomes. The development of preterm labour/ pre-eclampsia/gestational diabetes was lesser in the vitamin D supplemented group vs. non-supplemented group (Figure 7). Newborns of mothers in non-supplemented group had lower cord blood levels of 25(OH)-D levels and lower birth weight as compared to supplemented group.[28]

Figure 7. Effect of vitamin D supplementation starting at 20 weeks of pregnancy with respect to the development of complications of pregnancy[28]



PTL: preterm labor; GHTN: gestational hypertension; PE: preeclampsia; GDM: gestational diabetes mellitus.

Preterm labor (PTL), gestational hypertension (GHTN)/preeclampsia (PE) or gestational diabetes mellitus (GDM) were observed in 44% women taking placebo compared to 20.4% women being supplemented with vitamin D. Significance between groups was p<0.02.[28]

A systematic review and dose-response meta-analysis demonstrated an inverse relationship to exist between vitamin D intake during pregnancy and wheezing or asthma in offspring (pooled OR: 0.68, 95% CI: 0.55-0.83, I^2: 24%, Z statistic=3.64, p<0.01). A nonlinear U-shaped association was observed between vitamin D supplementation during pregnancy and

asthma or wheezing in offspring, with the lowest risk at approximately 800 IU/d.[29]

CLINICAL RECOMMENDATIONS

- **Vitamin D supplementation during pregnancy reduces the risk of low birth weight infants and small for gestational age, risk of pre-eclampsia, preterm labour, gestational diabetes and asthma or wheezing in offspring, therefore, is beneficial.**

Vitamin D supplementation in lactating mothers

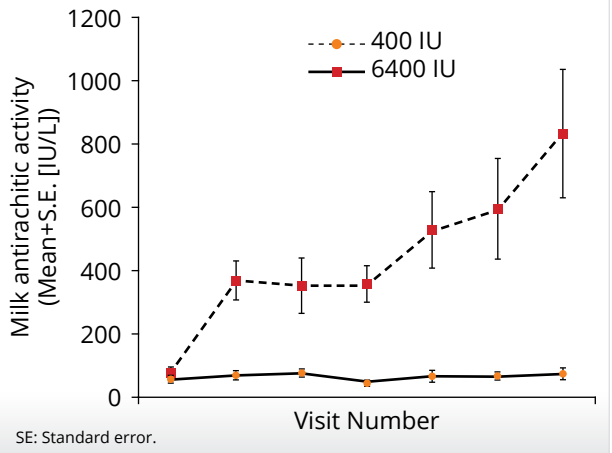
Research has shown that the vitamin D content of human milk is directly related to maternal serum vitamin D levels, and therefore, may potentially be adequate if the mother's vitamin D levels are sufficient. Estimates have revealed that 90.4% of breastfed infants are vitamin D deficient vs. 15.4% of formula fed infants.[30]

Literature has suggested that high-dose vitamin D supplementation in the lactating mother corrects the mother's vitamin D deficiency and is as effective at maintaining infant vitamin D levels as direct infant supplementation. A review was conducted to evaluate the impact of high-dose maternal vitamin D (ranging from 4000 IU to 6000 IU/day) during lactation on human milk content and infant vitamin D status. Monthly supplementation at levels of 150,000 IU was observed to correct both maternal and infant deficiency but not lower levels of 50,000 IU and 100,000 IU. Therefore, maternal supplementation of vitamin D may be an effective method of improving breastfed infants' vitamin D status.[30]

The Tolerable Upper Limit is set at 4000 IU during lactation is considered as the minimum dose necessary to meet the nursing infant's vitamin D needs.[30]

Another study showed that the milk antirachitic concentration (which is the vitamin D content of the breast milk) was significantly higher in women supplemented with 6000 IU compared with the 400 IU group without evidence of toxicity (Figure 8). Additionally it was also observed that, the infants of mothers in the 6000 IU arm had circulating 25(OH)D levels comparable to those infants who were administered 300 IU vitamin D/day.[31]

Figure 8. Milk antirachitic activity as a function of maternal vitamin D_3 dose: 400 versus 6400 IU/day.[31]



The recommendations set forth by the American Academy of Pediatrics and the IOM are for the mother to take a prenatal vitamin and for her recipient infant to be given 400 IU vitamin D/day unless her infant receives at least a liter of infant formula/day.[8]

Improves early development and later health of infants

Vitamin D, through its effects on calcium absorption, parathyroid hormone (PTH) expression, phosphate metabolism, growth plate function, and possible regulation of the insulin-like growth factor axis may influence fetal and postnatal growth.[32]

A study showed that maternal vitamin D_3 supplementation (35 000 IU/wk) during the third trimester of pregnancy enhanced early postnatal linear growth. Mean change in length-for-age z-score from birth to 1 month was significantly greater in vitamin D (0.53 per month) vs placebo (0.19 per month; p=0.004). Stunting was less common in vitamin D (17% of infants were ever stunted) vs. placebo (31%; p=0.049).[33]

CLINICAL RECOMMENDATIONS

- **Vitamin D supplementation in the lactating mother can correct the mother's vitamin D deficiency and can maintain the infants' vitamin D levels just as direct infant supplementation.**
- **A dose of 4000 IU vitamin D is considered to be effective and safe and can maintain the maternal and nursing infant's vitamin D needs.**
- **Maternal vitamin D supplementation aids in fetal and early postnatal growth of infants**

Vitamin D supplementation and maternal and fetal bone health

Maternal vitamin D and calcium levels are modified during pregnancy to support fetal calcium homeostasis. Maternal parathyroid hormone levels increase when vitamin D levels are insufficient affecting bone resorption to keep proper maternal serum calcium levels. The negative correlation between serum 25(OH) D and cross-linked C-terminal telopeptide of type 1 collagen in pregnant women with serum 25(OH)D <20 ng/mL also strengthened the relationship of bone resorption and low vitamin D levels in pregnancy, especially in the 2nd and 3rd trimesters.[13]

It is widely known that that severe vitamin D deficiency (VDD) can result in rickets, osteomalacia and neonatal hypocalcemia. Clinically, neonatal hypocalcemia can result in seizures, and has been associated with softening and thinning of the skull (craniotabes) and rarely, dilated cardiomyopathy.[34]

Evidence for bone loss during pregnancy and lactation

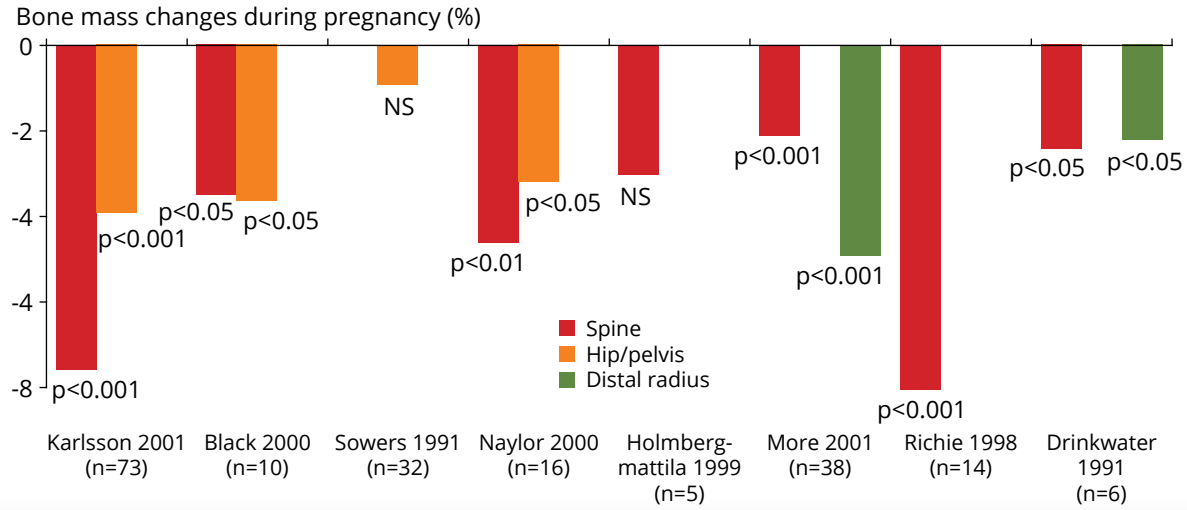
Reduced physical activity, as well as the increase in maternal weight and fat content during pregnancy increases the mechanical load on the skeleton, and generate high levels of estrogens, which all together influences the BMD. Few published studies have reported of around 5% loss of maternal BMD during pregnancy. Lactation is also associated with hormonal fluctuations which affect the BMD.[35]

Clinical evidences suggesting the bone loss during pregnancy and lactation are presented in Figures 9 and 10, respectively: [35]

CLINICAL RECOMMENDATIONS

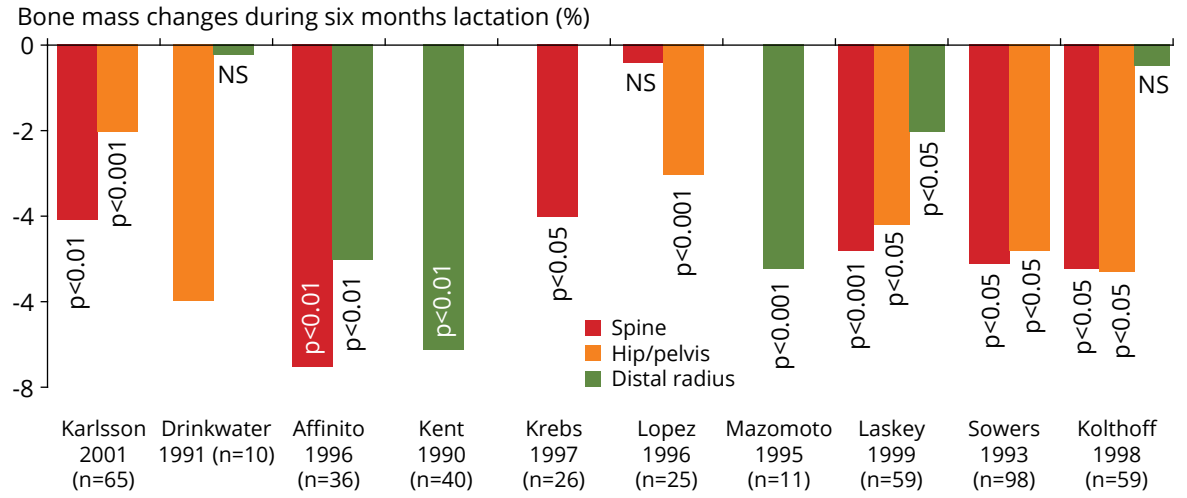
- **Pregnancy and lactation affects maternal BMD, by increasing the mechanical load on the skeleton, high levels of estrogens, and hormonal fluctuations**
- **Severe vitamin D deficiency can result in neonatal hypocalcemia rickets which can increase the risk of seizures, osteomalacia, softening and thinning of the skull (craniotabes) and, dilated cardiomyopathy.**

Figure 9. Relative changes in bone mass during a pregnancy evaluated in several original studies



The data are presented with level of significance for the comparison between the pre-pregnancy and the post-pregnancy values.

Figure 10. Relative changes in bone mass during 6 months of lactation evaluated in several original studies



The data are presented with level of significance for the comparison of values found directly after delivery and 6 months post-pregnancy.

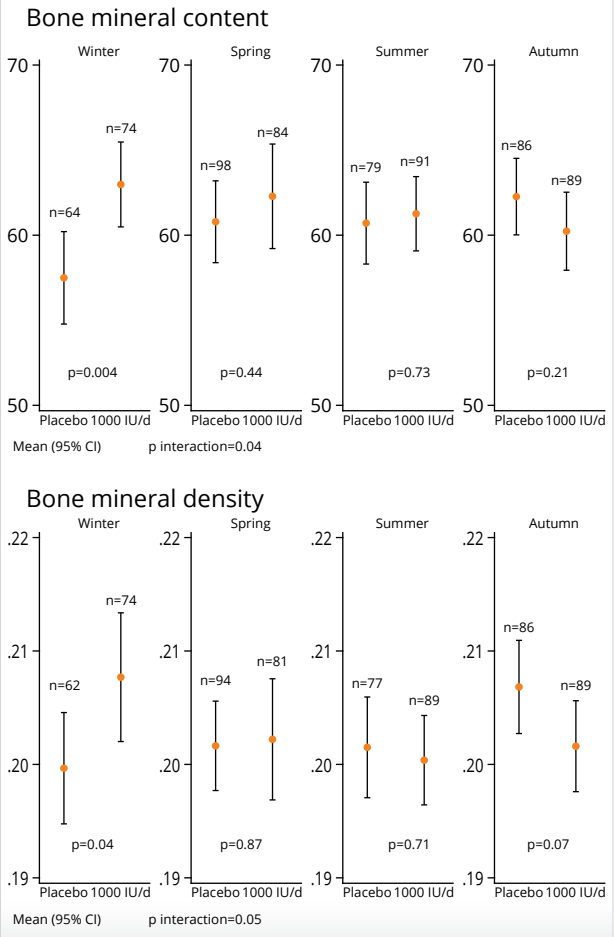
Effects of vitamin D supplementation during pregnancy and lactation on bone heath

The maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS) study was conducted to assess whether neonates born to mothers supplemented with vitamin D during pregnancy had greater whole-body BMC at birth than those of mothers who were not supplemented.[36]

Pregnant women (n=1134) with a baseline 25(OH)D between 25 and 100 nmol/l were randomized to 1000 IU/day cholecalciferol or placebo from 14 weeks of gestation until delivery; 965 remained in the study until delivery, and 736 infants underwent Dual-energy X-ray absorptiometry (DXA) of the whole body and/or LS.[36]

Although there were no differences in whole body or LS BMC, bone area or a BMD between the two groups overall, a significant interaction was observed between season of birth and maternal randomization group, as shown in (p for interaction for BMC 0.04). There was a statistically significant effect of treatment on neonatal BA, BMC, and BMD for births in the winter months, between December and February (Figure 11).[36]

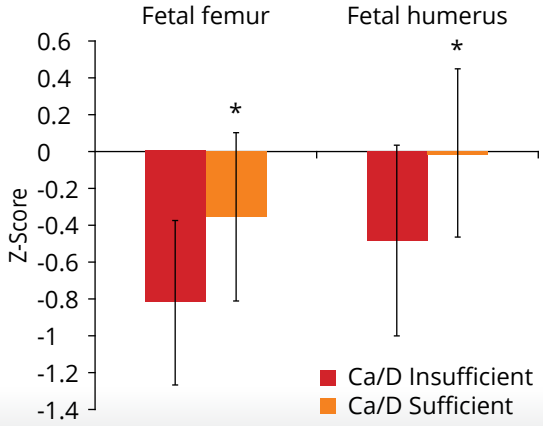
Figure 11. Neonatal whole body bone mineral content and bone mineral density by intervention group and season of birth[36]



[Winter = December to February]. Data shown are mean and 95%CI.

Optimal calcium intake and adequate maternal vitamin D status are both needed to maximize fetal bone growth. Maternal 25(OH)D > 50 nmol/L was significantly positively associated with fetal femur and humerus Z scores (p<0.01). Calcium intake was associated with fetal femur Z scores and birth length only when maternal 25(OH)D was ≤50 nmol/L (p<0.05). Similarly, maternal 25(OH)D was associated with fetal femur and humerus Z scores only when maternal calcium intake was <1050 mg/d (p<0.03).[37]

Figure 12. Adolescents consuming calcium intakes <1100 mg/d who also had a 25(OH)D concentration ≤50 nmol/L (Ca/D insufficient) were compared with adolescents with a calcium intake ≥1100 mg/d and/or a 25(OH)D concentration >50 nmol/L (Ca/D sufficient)[37]



- Adolescents within the calcium/vitamin D sufficient category (n=94 and 93, respectively) had higher fetal femur and humerus Z scores (*p=0.002 and p=0.003, respectively) than did those in the calcium/vitamin D insufficient category.[37]

Another study was conducted to assess the BMC, BMD, and body composition in offspring of women supplemented with vitamin D during pregnancy. Pregnant women were randomized and administered oral cholecalciferol 60,000 units 4 weekly (group 1), 8 weekly (group 2), or placebo (group 3). All received 1 g calcium daily (groups 1 and 2 without, and group 3 with 400 units vitamin D). Babies in group 3 had higher whole-body BMC (250.8 ± 42.5 gm) and BMD (0.335 ± 0.033 gm/cm^2) compared to group 1 (213.1 ± 46.2 gm and 0.295 ± 0.041 gm/cm^2) and group 2 (202.9 ± 29.9 gm and 0.287 ± 0.023 gm/cm^2) (p=0.006 and 0.001, respectively).

CLINICAL RECOMMENDATIONS

- **Vitamin D along with calcium supplementation during pregnancy may have a positive effect on fetal skeletal development and can maximize fetal bone growth.**
- **Treatment with vitamin D during pregnancy can help in improving neonatal bone area, bone mineral content and bone mineral density.**

Therefore, vitamin D supplementation to pregnant women with severe deficiency in doses that improved cord blood 25(OH)D did not result in improved bone health or body composition in offspring at 12-16 months, compared to a dose too small to improve 25(OH)D levels.[38]

Recommendations from National and International guidelines

National and International guidelines recommend vitamin D supplementation during pregnancy or offer guidance on defining deficiency and sufficiency as shown in the Table below.[34]

Guideline	Countries covered by recommen-dation	Deficiency (nmol/l)	Insufficiency (nmol/l)	Sufficiency (nmol/l)	Dietary recommendation for vitamin D intake in pregnancy (IU)*- RI +
Scientific Advisory Committee on Nutrition (SACN) and UK Department for Health	UK	<25		≥25	400
Institute of Medicine (IOM)	USA and Canada	< 30	30-50	≥ 50	600
Endocrine Society Practice Guidelines	Worldwide	< 50	50-75	≥ 75	600
British Paediatric and Adolescent Bone Group	UK	< 25	25-50	≥ 50	Refers to SACN, 400
Global Consensus Recommendations on Prevention and Management of Nutritional Rickets	Worldwide	< 30	30-50	≥ 50	600
National Osteoporosis Society (UK)	UK	< 30	30-50	≥ 50	No recommendation
Canadian Paediatric Society	Canada	< 25	25-75	75-225	No recommendation
Working group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia	Australia and New Zealand	< 50		≥ 50 At the end of winter (level may need to be 10-20 nmol/l higher at the end of summer)	No recommendation
NORDEN Nordic Nutrition Recommendations	Nordic countries	<30		≥ 50	400
European Food Safety Authority	EU countries	< 50		≥ 50	600

Impact of type of vitamin D formulation on absorption of vitamin D

Vitamin D_3 has been reported to have greater efficacy in raising 25(OH)D concentrations, which has increased awareness about vitamin D deficiency in treating physicians and led to increased prescriptions of vitamin D. This increase in demand forced pharmaceutical companies to market many oral vitamin D preparations in the form of sachet, tablets, softgel capsule, syrup, and drops, etc.[39]

An Indian study was conducted to assess cholecalciferol content of commonly available vitamin D formulations. A very high variability was reported in cholecalciferol content between the printed strength and actual level in the preparations as measured by HPLC. Only 28.5% of the formulations tested were within the acceptable range(–90 to +125%) as defined by Indian Pharmacopeia while 5 (35.7%) had higher and 5 (35.7%) had lower than the acceptable range. The percentage variation as observed from the printed ranged widely from –91% to +65%.[39]

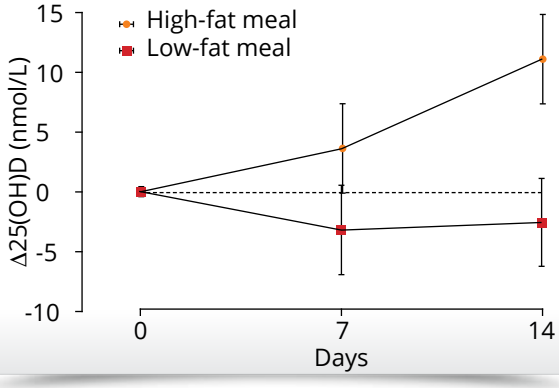
Such variability in cholecalciferol content has also beenreported by several other investigators from other parts of the world. Another analysis of 12 cholecalciferol formulations available in New Zealand market was carried out, and it was reported that 50% of these formulations were out of the acceptable range.[40]

Another study from United Arab Emirates reported that only 39% of vitamin D fortified milk and milk products were within the acceptable range with 31% were under-fortified and 30% over-fortified.[41]

Challenges in current conventional formulation of vitamin D_3[42]

- Absorption of vitamin D_3 from conventional formulation is highly dependent on high-fat meal (Figure 13).

Figure 13. Absorption of conventional formulation of vitamin D from low- and high-fat meal



- Bioavailability of vitamin D_3 is dependent on bile secretions, micelle formation, and diffusion through the unstirred-water layer
- Compliance/convenience becomes a challenge, as most vitamin D_3 preparations are to be administered along with milk or clarified butter

CLINICAL RECOMMENDATIONS

- **Very high variability in cholecalciferol content is reported between the printed strength and actual level in the formulations sold in India as well as globally.**
- **Challenge in administering the conventional vitamin D formulation:**
  - **Absorption is dependent on high-fat meal**
  - **Bioavailability is dependent on bile secretions, micelle formation, and diffusion through the unstirred-water layer**
  - **Compliance/convenience has to be administered along with milk or clarified butter**

Efficacy of micellized vs. fat-soluble vitamin D_3 supplementation

Micellization is a new delivery system for fat-soluble nutrients that disperses fatty substances into microscopic, water-soluble and micellar spheres enabling them to reach the absorptive surface of the intestinal tract, facilitating maximum absorption.

A study showed that micellized form of vitamin D_3 is more efficacious in achieving higher levels of serum 25(OH)D than that observed with a similar dose of fat-soluble vitamin D_3 following supplementation. Significantly higher number of subjects administered 60,000 IU water-miscible vitamin D_3 (78.4%) achieved more than >30 ng/mL as against 48.2% in those administered 60,000 IU of fat-soluble vitamin D_3/ month with milk. This is suggestive of better absorption of micellized form of vitamin D_3.[43]

CLINICAL RECOMMENDATIONS

- **Micellized form of vitamin D_3 is more efficacious in achieving higher levels of serum 25(OH)D vs. similar dose of fat-soluble vitamin D_3.**

Increased absorption with nanoparticulate form of vitamin D vs. soft gelatin capsules

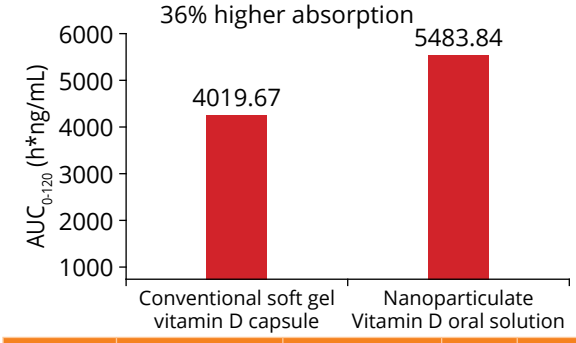
Another randomized, balanced, open label, 2-sequence, 2-treatment, 2-period, crossover, study was conducted to evaluate the relative bioavailability of test product liquid of vitamin D (nanoparticulate formulation) with a reference product, vitamin D soft gelatin capsules in healthy adult male and female subjects under fasting condition. The absorption of liquid was 36% higher than soft gelatin capsules (Figures 14 and 15).[44]

CLINICAL RECOMMENDATIONS

- **A dose of 60,000 IU nanoparticulate vitamin D oral solution has greater rate and extent of absorption vs. conventional soft gel vitamin D capsuleunder fasting conditions.**

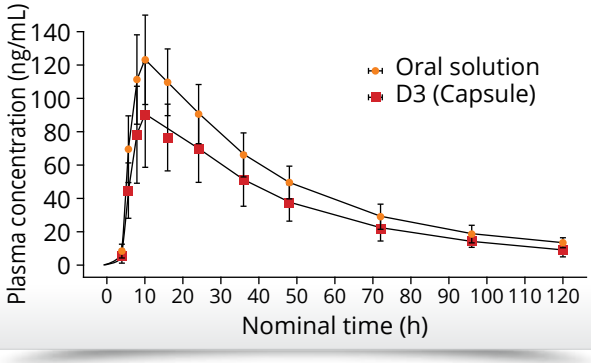
Therefore, based on the point estimate for AUC_{0-120} and C_{max}, **Vitamin D** oral solution (nanoparticulate formulation) was observed to have a **greater rate and extent of absorption** when compared to the **Vitamin D soft gel capsule (conventional formulation)** following a dose of 60,000 IU under fasting conditions.[44]

Figure 14. Absorption of vitaimin D oral nonoparticulate solution vs conventional soft gel capsule



Parameter	Nanoparticulate oral solution	Conventional soft gel capsule	Ratio	p value
AUC_{0-120} (h* ng/ml)	5483.84	4019.67	136.43	0.0001

Figure 15. Time taken to achieve plasma concentration of vitamin D for oral solution and soft gel capsule



Facts about absorption of nanoparticles[45]

Absorption of nanoparticles takes place via 3 pathways:

1. Paracellular: Nanoparticles pass through the narrow gaps between the neighboring epithelial cells
2. Transcellular: Nanoparticles get absorbed directly through the epithelial cell membranes by either passive or active transport mechanisms
3. Persorption: Nanoparticles get absorbed through the gaps formed in the layer of epithelium cells lining the gastrointestinal tract due to shedding and replacing of cells

Hence, their absorption is not fat-dependent and is unaffected by fed fast variations.

Convenience of using nanoparticulate formulations[45]

- Since nanoparticles get absorbed paracellularly, transcellularly, and by persorption, their absorption is independent of the amount of fat in the gut
- Compliance of taking nanoparticle formulation is high, as it does not require milk or clarified butter for absorption
- The formulation is highly palatable and in the form of ready to drink shot
- The results are assured in fed as well as fasting state

CLINICAL RECOMMENDATIONS

- **Advantages of nanoparticulate vitamin D formulation:**
  - **The absorption of nanoparticles is not fat-dependent and is unaffected by fed fast variations.**
  - **High compliance as nanoparticle formulation does not require milk or clarified butter for absorption**
  - **Highly palatable and in the form of ready to drink shot**
  - **Assured results in fed as well as fasting state**

Efficacy of nanotechnology-based miscellized vitamin D_3 vs. conventional vitamin D_3

Micellized or conventional vitamin D_3 at a monthly dose of 60,000 IU (1500 µg) for 6 months was administered in 180 healthy adults.

- A significant increase in their serum 25(OH)D levels following supplementation was observed:
  - Micellized: 21.5 (SD 10.9) to 76.7 (SD 18.8) nmol/l ($p \leq 0.001$)
  - Conventional: 22.8 (sd 10.4) to 57.8 (SD 16.0) nmol/l ($p \leq 0.001$))
- An additional increase of 20.2 nmol/l in serum 25(OH)D levels was observed in those administered micellized vitamin D
- Micellized vitamin D_3 was observed to be more efficacious in achieving higher levels of serum 25(OH)D

CLINICAL RECOMMENDATIONS

- **Micellized vitamin D_3 was more efficacious in achieving higher levels of serum 25(OH)D vs. conventional vitamin D.**

Indian Endocrine Society Recommendations[46]

- The Endocrine Society of India defines 25(OH)D levels between 20 ng/mL and 40 ng/mL as adequate for most of the population.
- The serum 25(OH)D >30 ng/mL may provide additional health benefits than a cut-off above 20 ng/mL for individuals presenting with conditions such as osteoporosis, obesity, pregnancy, lactation, elderly, malabsorption syndromes, renal or liver insufficiency, and medications interfering with the Vitamin D metabolism.
- Cholecalciferol (vitamin D_3) is the preparation of choice. The doses vary according to the degree of deficiency, the patient's age, and the presence of risk factors.
- Vitamin D_3 supplementation is a safe procedure with doses up to 10,000 IU daily for 5 months not inducing signs of toxicity.

SUMMARY OF RECOMMENDATIONS

- Recent reports have revealed an astonishingly high prevalence of vitamin D deficiency, with 96% pregnant and lactating women, and 99% of the infants in India being deficient.
- Higher maternal levels of $1,25(OH)_2D$ are essential to increase the intestinal calcium absorption during pregnancy and to support calcium for maternal and fetal metabolism.
- Higher maternal levels of $1,25(OH)_2D$ are also essential for regulating the immune system during pregnancy.
- Vitamin D deficiency during early pregnancy may lead to a lower BMC and BMD in offspring in later life, and is associated with the development of rickets in infants.
- Assessment of vitamin D status in early pregnancy or in woman at pre-conception should be considered.
- Vitamin D deficiency during pregnancy increases the risk of preeclampsia.
- Vitamin D deficiency during pregnancy increases the risk of preterm birth and low birth weight neonates.
- Modifying maternal vitamin D levels could be beneficial for positive pregnancy outcomes.
- Vitamin D deficiency during early pregnancy impacts the neuropsychological development of children (language impairment, low quartile gross-motor development and fine motor development, attention deficit hyperactivity disorder like symptoms and autism-related traits) in later life.
- Clinical evidence indicates a role of vitamin D in preventing wheeze and/or respiratory tract infections in offsprings of mothers who received vitamin D supplementation during pregnancy.
- Prenatal to postpartum vitamin D_3 supplementation is an efficacious and safe intervention in rectifying maternal and infant vitamin D deficiency.

SUMMARY OF RECOMMENDATIONS

- Vitamin D supplementation should be considered to promote optimal vitamin D status in new-borns and exclusively breastfed infants.
- Vitamin D supplementation during pregnancy reduces the risk of low birth weight infants and small for gestational age, risk of pre-eclampsia, preterm labour, gestational diabetes and asthma or wheezing in offspring, therefore, it is beneficial.
- High-dose vitamin D supplementation in the lactating mother can correct the mother's vitamin D deficiency and can maintain the infants' vitamin D levels just as direct infant supplementation.
- A dose of 6000 IU vitamin D is considered to be effective and safe and can maintain the maternal and nursing infant's vitamin D needs.
- Maternal vitamin D supplementation aids in fetal and early postnatal growth of infants.
- Severe vitamin D deficiency can result in rickets, osteomalacia and neonatal hypocalcemia, which can increase the risk of seizures, softening and thinning of the skull (craniotabes) and, dilated cardiomyopathy.
- Pregnancy and lactation affects bone mineral density, by increasing the mechanical load on the skeleton, high levels of estrogens, and hormonal fluctuations.
- Vitamin D along with calcium supplementation during pregnancy may have a positive effect on fetal skeletal development and can maximize fetal bone growth.
- Treatment with vitamin D during pregnancy can help in improving neonatal bone area, bone mineral content, and BMI for births in the winter months.
- Long-term follow up of children born to participants is required that can help in determining if the effect of gestational vitamin D supplementation on increased bone mineralization in children born in winter, does persist beyond the neonatal period and whether this can influence peak bone mass obtained.
- Very high variability in cholecalciferol content is reported between the printed strength and actual level in the formulations sold in India as well as globally.
- Challenge in administering the conventional vitamin D formulation:
  - » Absorption is dependent on high-fat meal
  - » Bioavailability is dependent on bile secretions, micelle formation, and diffusion through the unstirred-water layer
  - » Compliance/convenience has to be administered along with milk or clarified butter
- Micellized form of vitamin D_3 is more efficacious in achieving higher levels of serum 25(OH)D vs. similar dose of fat-soluble vitamin D_3.

SUMMARY OF RECOMMENDATIONS

- A dose of 60,000 IU nanoparticulate vitamin D oral solution has greater rate and extent of absorption vs. conventional soft gel vitamin D capsule under fasting conditions.
- Advantages of nanoparticulate vitamin D formulation:
  - » The absorption of nanoparticles is not fat-dependent and is unaffected by fed fast variations.
  - » High compliance as nanoparticle formulation does not require milk or clarified butter for absorption
  - » Highly palatable and in the form of ready to drink shot
  - » Assured results in fed as well as fasting state

Table of vitamin D levels and dosage required during pregnancy and lactation

Vitamin D supplementation	Required levels	Suggested dose for the mother
Pregnancy[@]	To maintain circulating 25(OH)D of at least 40 ng/ml in the mother	4,000 IU daily
Lactation*	To maintain sufficient serum levels (>30 ng/ml) in infants	4,000 IU daily
Breastfed infants supplemented with 400 IU*	To maintain sufficient serum levels (>30 ng/ml) in infants	400 to 2,000 IU daily

[@]Wagner CL et al. Womens Health (Lond Engl). 2012 May; 8(3): 323–340.
*Drugs and Lactation Database (LactMed) [Internet]. Vitamin D. April 1, 2019.

Recommended dietary allowance and treatment of vitamin D deficiency: Indian guidelines

Life stage group	IOM recommendations		Committee recommendations for patients at risk of vitamin D deficiency
	EAR (IU)	RDA (IU)	Daily requirement (IU)
Infants (0–12 mo)	400	600	400–1000
Children (1–8 yr)	400	600	600–1000
Adolescents (9–18 yr)	400	600	600–1000
Adults (19–70 yr)	400	600	1500–2000
Elderly (>70 yr)	400	600	1500–2000
Pregnancy and lactation	400	600	1500–2000

EAR: Estimated Average Requirement; RDA: Recommended Dietary Allowance; IOM: Institute of Medicine
Singh P. Journal of The Association of Physicians of India. 2018; 66: 75-82.

VITAMIN D SUPPLEMENTATION IN POSTMENOPAUSAL WOMEN: CLINICAL RECOMMENDATIONS

Risks encountered in postmenopausal women

Menopause, an age-dependent physiological condition, is associated with natural decrease in estrogen levels.[47] It is associated with vasomotor symptoms, and also affects many other areas of the body such as urogenital, psychogenic, and cardiovascular systems. Menopause also causes a progressive decrease of bone density, muscle mass, and strength.[48]

- Osteoporosis-related fractures are reported to occur in nearly half of the post-menopausal women during their lifetime.[49] Estimates have shown that in women over the age 50, at least 1 in 3 will experience osteoporotic fractures, and may require hospitalization and long-term care.[47]
- The incidence and rates of breast cancer have shown to increase with age. Estimates have shown that around 79% of new cases of breast cancer and 88% of breast cancer deaths occurred in women during the average age of onset of menopause (>50 years).[49]
- Recent statistics have shown that cardiovascular disease (CVD) is the leading cause of morbidity and mortality in postmenopausal women.[49]

CLINICAL RECOMMENDATIONS

- **Postmenopausal women, due to natural decrease in estrogen levels, are prone to various life-threatening health conditions such as osteoporosis-related fractures, breast cancer, cardiovascular disease and metabolic syndrome.**

Prevalence and risks of vitamin D deficiency in postmenopausal women

A gradual reduction in amount of estrogen produced by the ovaries occurs during menopausal stages, which is proposed to promote vitamin D deficiency. Since estrogen increases the activity of 1-α-hydroxylase (expressed in the kidneys) and is responsible for the activation of vitamin D and upregulates the vitamin D receptors (VDR), its reduction decreases the number of VDR.[50]

A recent study has revealed that vitamin D deficiency in postmenopausal women was associated with a higher prevalence of metabolic syndrome (MetS). Women with vitamin D deficiency had a higher risk of MetS, hypertriglyceridemia and low high-density lipoprotein than those with adequate levels. Women with low 25(OH)D levels had higher TC, triglycerides, insulin, and HOMA-IR levels ($p<0.05$). MetS was detected in 57.8% (182/315) of women with hypovitaminosis D (insufficient and deficient) and in 39.8% (59/148) of those with sufficient vitamin D ($p=0.003$).[51]

A study showed high prevalence of vitamin D inadequacy in postmenopausal women.

Hypovitaminosis D was more prevalent among the postmenopausal type 2 diabetes women (63.8% vs. 58.2% premenopausal women). Hypovitaminosis D was also significantly associated with insulin (R2=0.01760, p=0.0008), glycated haemoglobin (R2=0.3709, p≤0.0001), and fasting blood glucose (FBG) (R2=0.3465, p=0.0001) in only the postmenopausal women.[50]

Another recent study showed that overweight postmenopausal women with hypovitaminosis D had a significant risk of reduced muscle mass (OR 5.70; p<0.001), strength (OR 12.05; p<0.001), and performance (OR 5.84; p<0.001) compared to women with normal weight and normal serum 25(OH)D_3.[52]

Research has demonstrated an association to exist between vitamin D insufficiency or deficiency and tumors with worse prognostic features in postmenopausal women with breast cancer. Low vitamin D levels were shown to be a risk factor for estrogen receptor (ER)- negative tumors, with positive axilla and a higher rate of cell proliferation. Patients with insufficient and deficient 25(OH)D levels had a higher proportion of tumors with a high grade and locally advanced and metastatic disease, more positive lymph node, a lower proportion of ER-, progesterone receptor (PR)- positive tumors and higher epithelial proliferative activity (Ki-67) (p<0.05).[53]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency in postmenopausal women occurs due to reduction in amount of estrogen produced by the ovaries during menopausal stages.**
- **Vitamin D deficiency in postmenopausal women is associated with increased risk of metabolic syndrome, diabetes, CVD, reduced muscle mass and strength, osteoporosis and breast cancer.**

Benefits of vitamin D supplementation in postmenopausal women

Supplementation with daily median doses of 2000 IU vitamin D successfully repleted 88% of postmenopausal women with osteoporosis with serum 25(OH)D levels <50 nmol/L within 48 days to a serum vitamin D level of 50 nmol/L.[54]

Another study showed that vitamin D_3 supplementation 1,000 IU/day/orally for 9 months resulted in a lower incidence of falls and improvement in postural balance in postmenopausal women at greater risk for falls.[55]

Calcium 1,000 mg plus 400 IU of vitamin D_3 supplementation, given daily for 7 years, reduced hip fracture and total fracture among postmenopausal women.[49]

A study by Cadeau et al showed that postmenopausal women on menopausal hormone therapy (MHT), vitamin D supplementation was associated with decreased breast cancer risk, across body mass index (BMI) strata. Therefore, vitamin D supplementation may reduce the risk of breast cancer in MHT users.[56]

Another recent study in a cohort of women with elevated risk of breast cancer demonstrated that high serum 25(OH)D levels and regular vitamin D supplement use were associated with lower rates of incident, postmenopausal breast cancer over 5 years of follow-up. The 25(OH)D levels of > 38.0 ng/mL levels were associated

with a 21% lower breast cancer hazard (highest versus lowest quartile: adjusted; CI: 0.63, 0.98).[57]

Research has shown that postmenopausal women with vitamin D deficiency had more cardiovascular risk factors than vitamin D-replete women. Moreover, women with low 25(OH)D levels had a significantly higher BMI and triglycerides, lower high-density lipoprotein and hip-to waist ratio than vitamin D-replete women. Vitamin D promotes formation of large, high-density lipoprotein particles, and affects reverse cholesterol transport, therefore is reported to protect against CVD risks.[49]

CLINICAL RECOMMENDATIONS

- **Vitamin D supplementation in postmenopausal women lowers the incidence of falls and improves postural balance, decreases the risk of fractures, decreases the breast cancer risk, and protects against CVD risks.**

Maintaining vitamin D levels in postmenopausal women[58]

- Healthy postmenopausal women over the age of 65 years should be administered 800–1000 IU/day of vitamin to maintain sufficient serum 25(OH)D levels.
- Postmenopausal women with risk factors for low vitamin status should be screened for serum 25(OH)D status and adequately treated. This marker should be measured at 2-3 months intervals until its level is stabilized in the normal range.
- Women with serum 25(OH)D levels below 20 ng/mL (50 nmol/L) may need treatment with 4000–10,000 IU/day to achieve adequate levels.
- Women with morbid obesity (pre- and post-gastrointestinal bypass surgery), malabsorption syndromes, and hepatic or renal diseases require specific tailored doses of vitamin D supplements.
- Women with vitamin D deficiency related to osteoporosis and/or previous incidental fractures should receive adequate amounts of vitamin (800–1200 IU/day if there are no risk factors for low serum vitamin D) and specific bone conserving therapies

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ROLE OF VITAMIN D – PCOS AND INFERTILITY: CLINICAL RECOMMENDATIONS

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. Pratik Tambe & Dr. Parikshit Tank

Panelists : Dr. Ashwini Kale, Dr. Neelam Bhise, Dr. R. K Marwaha, Dr. Dibyendu Banerjee, Dr. Rohan Palshetkar, Dr. Sarita Bhalerao

From left to right: ***Standing*** – Dr. Rohan Palshetkar, Dr. Anita Singh, Dr. Ashwini Kale, Dr. Sandhya Saharan, Subramanian, Anuja, Ramya Mandapaka, Ms. Sneha Shah, Dr.Manish Verma, Dr. Rakesh Sonawane, Bharat Dedhia, Dr. Ram Prabhoo, Dr. Rajendra Nagarkatti and Dr. Dibyendu Banerjee
Sitting - Dr. Ashwini Bhalerao, Dr. Neelam Aggarwal, Dr. Reeti Mehra, Dr. Pratik Tambe, Dr. Nandita Palshetkar, Dr. Ameya Purandare, Dr. R. K Marwaha, Dr. Anahita Chauhan and Dr. Neelam Bhise

Introduction

Vitamin D plays an important role in human reproduction and its receptors are present throughout the female reproductive tract (uterus, oviduct, and ovary) and are also found in placenta, and fetal membranes. Vitamin D has been shown to modulate reproductive processes in women.

Hence, vitamin D has clinical significance first due to the presence of receptors in reproductive tract and the prevalence of vitamin D insufficiency or deficiency in 45% to 90% of women in their reproductive age.[1]

CLINICAL RECOMMENDATIONS

- **Vitamin D is important for bone mineralization, and is implicated in the pathogenesis and risk amplification of numerous chronic disease processes**

Vitamin D is important for bone mineralization, but it is also implicated in the pathogenesis and risk amplification of numerous chronic diseases. One of the condition is polycystic ovarian syndrome (PCOS), which is a multifactorial endocrine disorder affecting 4%–12% of reproductive age women.[2] It is generally characterized by chronic-oligo or anovulation, menstrual irregularities, polycystic ovaries, and infertility.[3] type 2 diabetes, and CVD, and all of these diseases have been linked with vitamin insufficiency. Several studies reported that low levels of vitamin D are negatively correlated with body mass index, body fat and insulin resistance in women with PCOS. Additionally, vitamin D insufficiency induced altered intracellular calcium causes ovarian dysfunction and reproductive abnormalities in PCOS women. The prevalence of vitamin D deficiency in women with PCOS has been reported to be around 67%–85%.[4] Although, the prevalence of PCOS varied by diagnostic criteria, it is estimated to be as high as 15% to 20%. PCOS has been found to be the most common cause of anovulatory infertility with the prevalence (90% – 95%) and around 40% of PCOS women has been found to be affected by infertility.[5]

CLINICAL RECOMMENDATIONS

- **Prevalence of Vitamin D deficiency is universally high irrespective of age, sex, race, ethnicity, and rural/urban background**
- **Prevalence of vitamin D deficiency is noted to be high in women with PCOS, which is the most common cause of anovulatory infertility**

There have been clinical reports of the beneficial effects of vitamin D on the metabolic disorders, in women with PCOS vitamin D supplementation shows improvement in ovarian dysfunction. Hence, vitamin D supplementation is recommended as a potential therapeutic adjunct for ovulatory dysfunction and metabolic disorders in women with PCOS. In a study conducted by Seyyed Abootorabi et al. vitamin D supplementation at a dosage of 50,000 IU/week for 8 weeks reduced fasting glucose and increased adiponectin levels in women diagnosed with PCOS who were vitamin D deficient.[6]

Vitamin D deficiency

Vitamin D deficiency has become the global health burden due to its high prevalence. Over 1 billion people are estimated to be vitamin D deficient or insufficient, worldwide. In spite of having abundant sunlight, middle-income counties have the highest prevalence of vitamin D deficiency. The prevalence of vitamin D deficiency in the general population of middle-income countries (South Asia and the Middle East) is reported to be around 67%–82%, and 20%–80% respectively.[7] In India the prevalence of vitamin D deficiency is observed in 70%–100% of the general population.[8]

In an Indian study, researchers found that the prevalence of vitamin D level <20 ng/ml was 64.06% and the level of vitamin D <30 ng/ml was 98.75%. Vitamin D deficiency was higher in younger (65.51%), illiterate (89.92%), and homemakers (70%), and its prevalence was higher in women residing in rural areas (69.94%) and also having an income <10,000 (61.96%).

CLINICAL RECOMMENDATIONS

- **Around 70.3% of infertile PCOS women were found to be vitamin D deficient, 20.3% were vitamin D insufficient, and 9.4% had normal vitamin D levels**

The prevalence of vitamin D deficiency is high (67%–85%) in PCOS women.[4] There is a high prevalence of infertility affecting nearly 10%–15 % of married couples in India, nearly 27.5 million couples seek treatment for their problem.[9] Among women suffering infertility PCOS represents 80% of anovulatory infertility cases.[10] Recently, a study was conducted on 256 infertile women with PCOS to evaluate the prevalence of vitamin D deficiency in PCOS women. Around 70.3% of infertile PCOS women were found to be vitamin D deficient, 20.3% were vitamin D insufficient, and 9.4% had normal vitamin D levels. Therefore researchers reported that vitamin D deficiency is a highly prevalent condition among infertile PCOS women.[7]

Role of vitamin D deficiency in the pathogenesis of PCOS and infertility

Women having PCOS may present with menstrual irregularities and signs of hyperandrogenism. Infertility, diabetes, obesity, and metabolic syndrome are also in these patients. PCOS has a complex pathophysiology, one commonly mechanism is excessive pituitary gland secretion of luteinizing hormone that subsequently stimulate ovarian theca cells for overproduction of androgens. PCOS is closely correlated with obesity, insulin resistance, and hyperinsulinemia which may augment the gonadotropin hormonal effect on ovaries.[11]

Vitamin D deficiency is shown to be linked to PCOS pathophysiology through its associations with obesity, insulin resistance, hyperandrogenism, dyslipidemia, inflammation, as well as features of depression and risk for dibetes mellitus and CVD.[12]

CLINICAL RECOMMENDATIONS

- **There is a sufficient evidence to indicate a relevance of vitamin D insufficiency in the pathophysiology of PCOS**

In the recent years, vitamin D deficiency has emerged as a plausible mechanism to explain some of the metabolic and endocrine features

of PCOS (Figure 1). A number of observational as well as randomized controlled trials, have assess the relevance of vitamin D in PCOS.[12] Low 25(OH)D levels may aggravate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, and obesity.

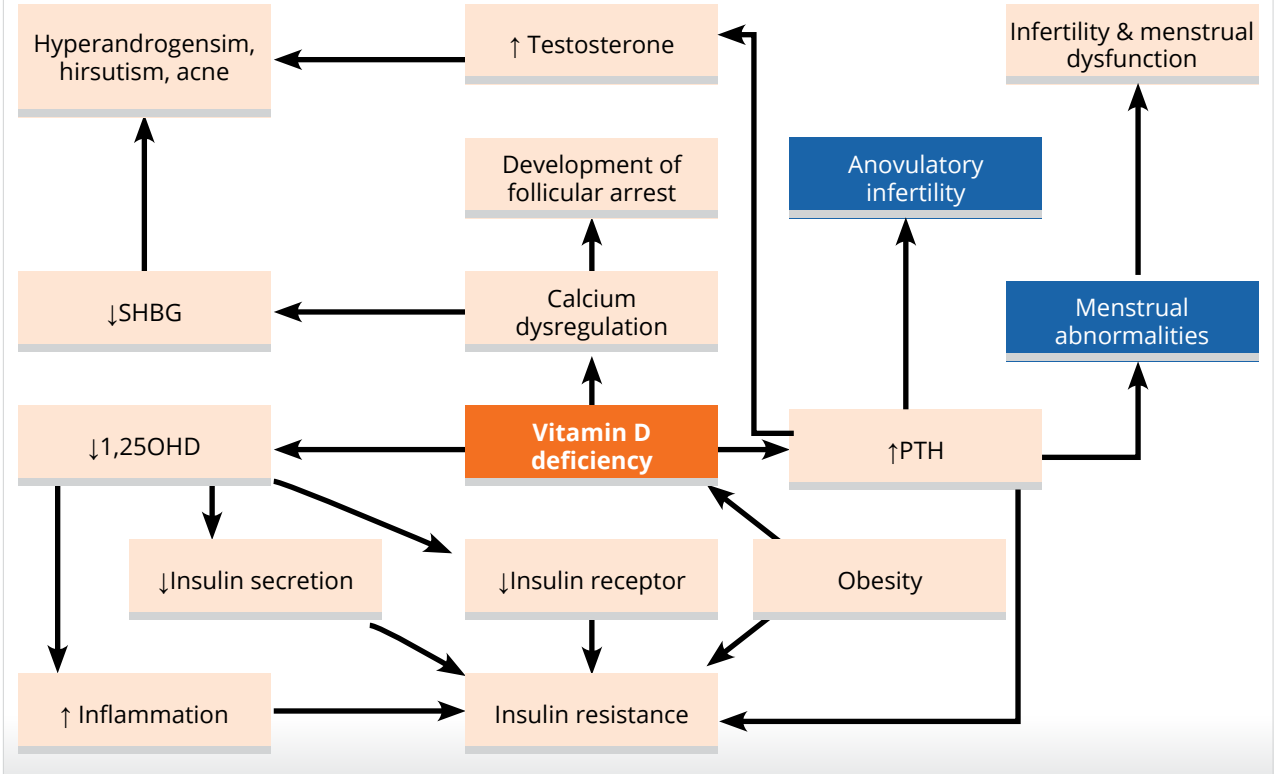
- There is a trend and association between insulin resistance and vitamin D deficiency in women with PCOS. In an observational study of 120 women with PCOS, Hahn et al. observed inverse correlation between serum levels of 25(OH)D and indices of insulin resistance (IR) such as HOMA-IR.[13]
- Serum levels of 25(OH)D are shown to correlate positively with sex hormone-binding globulin (SHBG) levels, which were lower in severely vitamin D-deficient women with PCOS, and negative correlation hairsutism[12]

CLINICAL RECOMMENDATIONS

- **Serum levels of 25(OH)D are associated with low SHBG levels, hirsutism, hyperparathyroidism and hyperandrogenemia in women with PCOS**

- A higher parathyroid hormone (PTH) levels and lower 25(OH)D levels are observed in obese compared to normal-weight women with and without PCOS and there is a significant positive correlation between PTH and total testosterone levels independent.

Figure 1. The role of vitamin D deficiency in the pathology of PCOS[14]



This is suggestive of mechanistic implications of vitamin D deficiency-related secondary hyperparathyroidism for the hyperandrogenemia of PCOS[12]

- Addition of vitamin D and calcium to metformin regimen is more effective in correcting menstrual disorders and follicular growth as compared to either of the therapy given alone.

Vitamin D deficiency is associated with poor reproductive outcomes in PCOS

In infertile women undergoing in vitro fertilization, a significantly higher 25(OH)D levels have been observed in the ovarian follicular fluid, especially those who achieved clinical pregnancy following fresh embryo transfer.[12]

The effect of vitamin D has been recognized in folliculogenesis, spermatogenesis, steroidogenesis, and implantation. Vitamin D deficiency is an important modifiable contributor to diminished treatment success in women with PCOS. Vitamin D deficiency in women with PCOS who underwent ovarian stimulation for the treatment of infertility were found to have significantly diminished rates of ovulation, of pregnancy, and ultimately a reduced chance of live birth. In pregnant women, with or without PCOS, vitamin D deficiency has been shown to be significantly associated with increased risk of early pregnancy loss.[1]

CLINICAL RECOMMENDATIONS

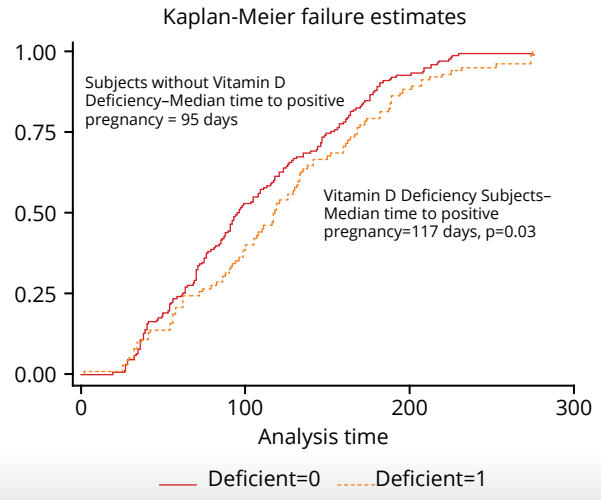
- **Vitamin D deficiency is an important modifiable contributor to diminished treatment success in women with either PCOS**

In a study, Butts S et al determined the relationship between preconception vitamin D status and reproductive outcomes in women with either PCOS or unexplained infertility treated with ovulation induction. Participants from Pregnancy in PCOS II (n=595, PPCOS II) and AMIGOS (n=597) RCT of unexplained fertility were included in this study. Findings of the study revealed that vitamin D deficiency was associated with diminished odds of clinical pregnancy rate (p=0.002), and live birth (p=0.002) in the PPCOS II analysis, whereas no association was reported between vitamin D deficiency and treatment outcome in the AMIGOS analysis, Figure 2. In PCOS subjects, an association was observed between vitamin D deficiency and the risk of pre-eclampsia (p=0.003), intrauterine growth restriction (IUGR, p=0.01) and gestational diabetes (p=0.01), and there was no association reported in the AMIGOS analysis. Therefore, researchers concluded that vitamin D deficiency in women with PCOS is significantly associated with a 40% reduction in odds of live birth and clinical pregnancy rate irrespective of insulin resistance or ovulation induction treatment.[1]

CLINICAL RECOMMENDATIONS

- **Vitamin D is associated with hyperandrogenism which predominates in PCOS**

Figure 2. Time from PPCOS II randomization to pregnancy (d) according to vitamin D status



Vitamin D deficiency is associated with lower success rates of fertility treatment in PCOS

Vitamin D deficiency has been found to be associated with the reduction of treatment success in women with PCOS who have unexplained infertility, and who had undergone ovarian stimulation. The cohort study included participants from pregnancy in PCOS II (n=607) and the assessment of multiple intrauterine gestations from ovarian stimulation (AMIGOS) RCTs of unexplained infertility (n=647) to evaluate the relationship between vitamin D deficiency and reproductive outcomes after ovarian stimulation. Serum 25-hydroxyvitamin D [25(OH) D] levels were measured using the banked sera samples. Researchers observed that women who had low vitamin D levels (< 20 ng/mL or 50 nmol/L) were less likely to ovulate (p=0.04) and had a 40% lower chance of live birth (p=0.04) as compared to women who had normal vitamin D levels. Vitamin D deficiency was also associated with a higher risk of early pregnancy loss (p=0.05) in both studies. Thus, vitamin D deficiency in women with PCOS, who had undergone fertility treatment with ovarian stimulation is significantly associated with reduced rate of ovulation and had a low chance of live birth.[1]

CLINICAL RECOMMENDATIONS

- **Vitamin D deficiency in women with PCOS, who had undergone fertility treatment with ovarian stimulation is significantly associated with reduced rate of ovulation and have a low chance of live birth**

Infertility in PCOS Women

Infertile is common in patients with PCOS.[11] According to the World Health Organization (WHO), one in every four couples in developing countries are affected by infertility. In India, there are 22 to 23 million infertile couples, and the total fertility rate has declined from 3.9 in 1990s to 2.3 in 2013.[15]

To make matter worse, the incidence of PCOS is raising with a global prevalence of PCOS of 5%–10% and prevalence is Indian subcontinent being 4%–25% in various studies. Furthermore, the ovarian reserves Asian women are lower in their reserves compared to Caucasians. Hence, there is reduced fertility at younger ages.[16]

CLINICAL RECOMMENDATIONS

- **Vitamin D is associated with several vital cellular processes, such as: cell differentiation and proliferation, hormonal secretion (such as insulin)**

Role of vitamin D in infertility

Vitamin D is involved in several vital cellular processes, such as: cell differentiation and

proliferation, hormonal secretion (such as insulin). There are reports of an association between vitamin D and hyperandrogenism which predominates in PCOS, an association that recent clinical studies have established a low prevalence of vitamin D with metabolic disorders in PCOS.[17] Evidence demonstrates the beneficial role of vitamin D in a pathological process spectrum including diabetes, CVD, cancer, and immune diseases.

Most studies suggest that vitamin D may be directly or indirectly related to gonadal functions. Vitamin D's effects on reproductive functions may be indirectly related to diseases such as PCOS, uterine leiomyomas, and endometriosis. In case of vitamin D deficiency during infertility treatment, vitamin D supplementation can be recommended especially for women who have PCOS.[18]

CLINICAL RECOMMENDATIONS

- **Vitamin D is associated with several vital cellular processes, such as: cell differentiation and proliferation, hormonal secretion (such as insulin)**
- **Vitamin D is associated with hyper-androgenism which predominates in PCOS**

Relationship between vitamin D and infertility in PCOS women

Vitamin D deficiency has been advocated as a possible cause of infertility in many studies conducted in the past several years.[19] Vitamin D in addition to sex steroid hormones also modulates reproductive process in women. Researchers have shown a direct stimulatory effect of $1,25(OH)_2D_3$ on aromatase gene expression in reproductive tissue.[20] The expression of HOXA10 (critical to the control of early embryonic development) is up-regulated by $1,25(OH)_2D_3$ in human endometrial stroma cells pointing to altered vitamin D signalling that might affect HOXA10 expression and fertility. HOXA10 expression is also important for the development of uterus and essential for endometrial development allowing for uterine receptivity to implantation.[20]

Vitamin D is the key regulating hormone in calcium homeostasis and calcium plays a role in oocyte activation and maturation resulting in the progression of follicular development. In this context, vitamin D and calcium repletion normalizes menstrual cycles and restores ovulation in PCOS women. In women with PCOS, serum 25OHD was an independent predictor of measures of reproductive success after ovulation induction. A decline in circulating 25OHD below the lower reproductive threshold may be contributory to ovulatory dysfunction. The 25OHD levels at and above the upper reproductive threshold may confer improved endometrial receptivity, an effect that has been previously suggested for vitamin D. Also, 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.[21]

- In women with PCOS, vitamin D deficiency has been related to menstrual irregularity, and hyperandrogenemia[12]
- Observational data suggest compromized fertility treatment prognosis in women with evidence of vitamin D deficiency[12]

CLINICAL RECOMMENDATIONS

- **Vitamin D is the key regulating hormone in calcium homeostasis and calcium plays a role in oocyte activation and maturation resulting in the progression of follicular development**
- **Post vitamin D supplementation decreased insulin resistance and increased insulin sensitivity has been observed**

Role of vitamin D supplementation in women with PCOS

Improved vitamin D status through supplementation has the potential for improving ovulation induction treatment related ovulation and live birth rates and for reducing risk of pregnancy loss in women with PCOS who are at an enhanced risk for pregnancy loss.[21]

In a study, researchers found that women with PCOS who were given vitamin D 50,000 IU/week versus placebo had significant change in fasting blood glucose and improvements in the HOMA-B and adiponectin.[6] Also, PCOS women who were given vitamin D 4,000 IU, 1,000 IU, or placebo daily for 12 weeks had significantly reduced total testosterone (TT), free androgen index (FAI), and increased SHBG on high-dose of vitamin D supplementation compared to the low-dose or placebo group.[22] Vitamin D 4,000 IU/day, 1,000 IU/day, or placebo group for 12 weeks of intervention. It was also observed that vitamin D 4,000 IU/day group, there were significant decreases in the fasting plasma glucose, serum insulin concentrations, and HOMA-IR.[23] Researchers have also reported vitamin D supplementation has beneficial effect on ovulatory dysfunctions and blood pressure. Post-supplementation, there were decrease in insulin resistance and increase in insulin sensitivity. In the study, decreased serum fasting insulin level and fasting blood sugar after vitamin D supplementation suggest underlying role of vitamin D in glucose homeostasis.[24]

CLINICAL RECOMMENDATIONS

- **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**

Vitamin D supplementation in infertile PCOS women

Women who are deficient in vitamin D when starting fertility treatments are 40% less likely to achieve a pregnancy. According to International Federation of Gynecology and Obstetrics (FIGO), vitamin D may play a key role in helping some women seeking treatment for PCOS-related infertility to get pregnant.[25] It has been reported that there are beneficial effect of vitamin D supplementation on ovulatory dysfunctions and insulin resistance.[24] Vitamin D sufficiency is also essential for successful in vitro fertilization, and it is probably protective against endometriosis.[11]

CLINICAL RECOMMENDATIONS

- **Vitamin D sufficiency is also essential for successful in vitro fertilization**

A supplementation with vitamin D improves has been shown to improve:[26]

- Insulin sensitivity
- Circulating testosterone
- Parameters of ovarian folliculogenesis and ovulation

Efficacy of vitamin D supplementation

Effect on insulin resistance

Insulin resistance is one of the most common features of PCOS, and studies shown that vitamin D deficiency may have role in insulin resistance.

In a randomized, placebo-controlled, interventional, double-blind study, researchers determined the effect of vitamin D supplementation on the clinical, hormonal and metabolic profile of the PCOS women. The study participants were supplemented with vitamin D 60,000 IU weekly for 12 weeks (n=25) or placebo (control group; n=25) for the same period. Researchers observed vitamin deficiency (≤ 20 ng/ml) in 68% of PCOS patients of which 29% were severely deficient (< 10 ng/ ml). The difference in mean serum fasting glucose pre- and post-supplementation of vitamin D in study group was found to be statistically significant (p=0.041). There was significant difference in insulin resistance (2.38 ± 4.88–1.00 ± 0.58, p=0.003), serum fasting insulin (10.34 ± 20.00–5.00 ± 3.25, p=0.021), and increase in insulin sensitivity (0.37 ± 0.04–0.394 ± 0.009, p=0.001) after supplementation with vitamin D.

The study concluded that post-supplementation, insulin resistance decreased and insulin sensitivity increased. In the study decreased serum fasting insulin level and fasting blood sugar after vitamin D supplementation suggest underlying role of vitamin D in glucose homeostasis.[24]

CLINICAL RECOMMENDATIONS

- **A supplementation with vitamin D has been shown to improve:**
  - **Insulin sensitivity**
  - **Circulating testosterone**
  - **Parameters of ovarian folliculogenesis and ovulation**
- **Post vitamin D supplementation there is a decreased insulin resistance and increased insulin sensitivity.**

Effect on ovarian function and infertility

Some clinical studies have demonstrated an improvement in fertility status in PCOS women who have better vitamin D status. Among women with PCOS, supplementation with vitamin D has been reported to normalize menstrual cycles and improve ovarian folliculogenesis and ovulation.

A cross-sectional study in 1,102 African American women illustrated that doubling of vitamin D levels from median of 14.7 ng/mL to 29.4 ng/mL was associated with half the odds of having long menstrual cycles. Vitamin D was not associated with the occurrence of short or irregular menstrual cycles.[27]

CLINICAL RECOMMENDATIONS

- **Vitamin D status may influence the menstrual cycle and plays a role in the ovarian function**
- **Vitamin D deficiency can cause reduced ovulation and live birth rate**

The findings of this study suggest that vitamin D status may influenced the menstrual cycle and plays a role in the ovarian function. In a retrospective study, researchers assessed the status of vitamin D in PCOS women and their reproductive outcomes after ovulation induction. It was observed that the live birth rate was 40% reduced in women with vitamin D levels of <30 ng/mL.

Furthermore, improvements in live birth success were noted at thresholds ≥ 38 ng/mL (OR: 1.42) and ≥ 45 ng/mL (OR: 4.46). The status of vitamin D levels was an independent predictor of ovulation and live birth post induction, Figures 3 and 4.[21]

In the obese PCOS women started on weight loss intervention plus 50,000 IU/week vitamin D or weight loss intervention plus placebo for 12 weeks, there were no significant differences found between the groups in fat mass, waist and hip circumference, dehydroepiandrosterone sulfate (DHEAS),, total testosterone, weight, BMI, fat mass, waist and hip circumference, waist-to-hip ratio, DHEA-S, TT, FAI, and SHBG. However, there was a significant improvement in menstrual frequency in women on vitamin D.[28]

Butt et al assessed the impact of vitamin D on the success of ovarian stimulation in women with PCOS or unexplained infertility and found that in the PCOS women group, those with vitamin D deficiency (<20 ng/mL) had lower chance of ovulation and a 40% decrease in the rate of live birth.[1]

In a prospective cohort study, researchers assessed serum 25(OH)D levels in 91 anovulatory women with PCOS undergoing ovulation induction treatment with clomiphene citrate (CC). Serum 25(OH)D levels were positively predictive of likelihood for achieving a dominant follicle in response to CC treatment (p=0.014) and of successful pregnancy (p<0.001).

CLINICAL RECOMMENDATIONS

- **Vitamin D status influences the menstrual cycle and plays a role in the ovarian function**

Figure 3.

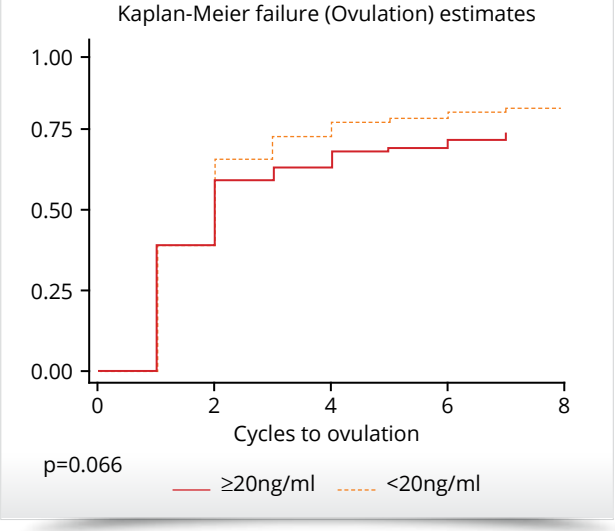
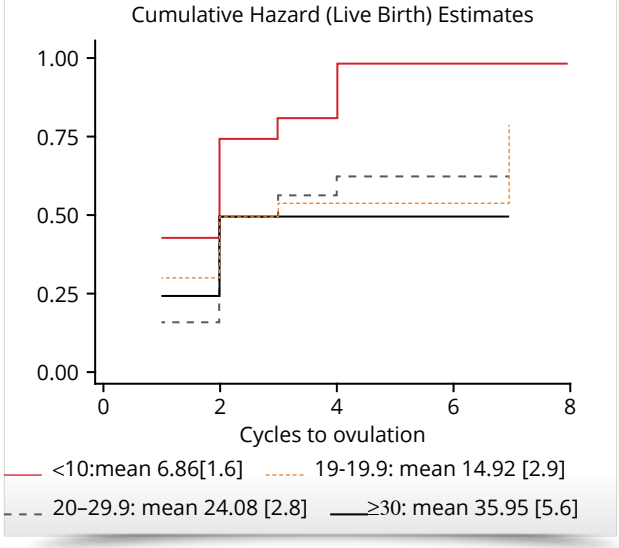


Figure 4.



Conversely, the likelihood for ovarian responsiveness to CC was reduced by 77% (OR: 0.33, 95 % CI: 0.13–0.85) and for CC treatment-related pregnancy was reduced by 76 % (OR: 0.24, 95 % CI 0.07–0.84) in women with evidence of severe vitamin D deficiency (serum 25[OH]D level <25 nmol/L or <10 ng/mL).[29]

Effect on endometrium

In a randomized placebo-controlled trial, PCOS women (n=110) with fertility issues undergoing intrauterine insemination (IUI) were treated with either vitamin D or placebo.

CLINICAL RECOMMENDATIONS

- **Vitamin D supplementation may improve endometrial thickness**

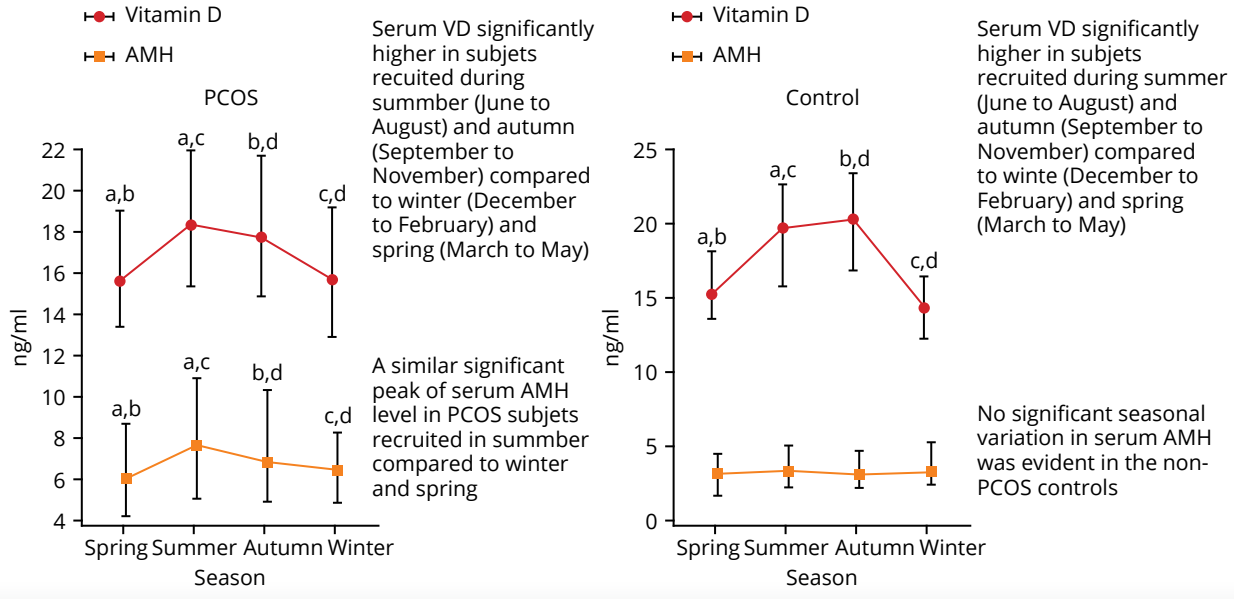
To determine whether administration of vitamin D affects the success rates of intrauterine insemination (IUI) in infertile PCOS women and their endometrial thickness. The infertile PCOS patients undergoing IUI were randomly divided to receive vitamin D or placebo. Researchers determined endometrial thickness, IUI results, number of dominant follicles, duration of IUI cycle, and dose of HMG. The endometrial thickness was significantly different in the group treated with vitamin D versus the placebo group (p=0.003). It seems that administration of vitamin D induces endometrial proliferation in PCOS women during IUI cycle. The women in vitamin D group had significant improvements in their endometrial thickness.[30]

Effect on hormone levels

Wong et al. reported that in women with PCOS, serum anti-mullerian hormone (AMH) levels were positively and independently correlated with the vitamin D levels, Figures, 5 and 6.[31]

A randomized, double-blind, placebo-controlled study reported the effect of vitamin D supplementation and concluded that there are beneficial effects of vitamin D supplementation

Figure 5. Serum vitamin D and anti-mullerian hormone (AMH) levels in PCOS women compared to health control

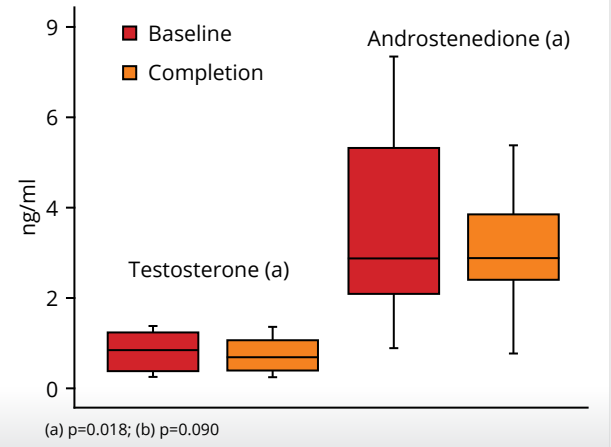


[a,b,c,d]Statistically significant (p<0.05)

on liver markers and modest improvements in insulin sensitivity in vitamin D deficient women with PCOS.[32]

A 3 months supplementation of vitamin D and calcium supplementation undertaken in 12 overweight women with PCOS showed a significant reduction in serum levels of total testosterone and androstenedione levels, Figure 6.[12]

Figure 6. Effects of vitamin D and calcium supplementation on total testosterone (a) and androstenedione (b) levels in overweight women with PCOS (n=12).



Identification of deficiency

- Levels of 25(OH)D < 20 ng/mL indicate deficiency
- Correction should be to maintain levels 20–30 ng/mL
- However, measurement of levels is not routinely recommended to monitor response to therapy

Vitamin D formations and variability in cholecalciferol content of commercial preparations

Absorption of vitamin D

A number of studies have indicated that only 50% of a typical dosage of vitamin D is absorbed from the intestinal lumen owing to complex absorption process.[33] Micellization is a new delivery system for fat-soluble nutrients that disperses fatty substances into microscopic, water-soluble and micellar spheres enabling them to reach the absorptive surface of the intestinal tract, facilitating maximum absorption.[34]

CLINICAL RECOMMENDATIONS

- **Only 50% of a typical dosage of vitamin D is absorbed from the intestinal lumen owing to complex absorption process**
- **Micellization enables vitamin D reach the absorptive surface of the intestinal tract, facilitating maximum absorption**

Variability of vitamin D content in commercial preparation

A high degree of variability is observed that cholecalciferol content may result in variability in clinical response to treatment. Use of cholecalciferol preparations with less content will not result in an increase in serum 25(OH) D level and clinical improvement in patients with vitamin D deficiency. However, treating physician will think that he/she has used adequate doses of cholecalciferol for treatment of vitamin D deficiency, but the subject is still vitamin D deficient.[35] There are several reports of life threatening complications of vitamin D toxicity with severe hypercalcemia and acute renal failure because of errors in the manufacturing and labeling of dietary supplements have recently emerged in the literature.

In a study, researchers assessed the cholecalciferol content of commonly available

Table 1. High degree of variability in cholecalciferol content of commercial preparations available in the Indian pharmaceutical market

Author	Year	Patients number	Type	Conclusive remarks
Fang et al	2017	502	Meta-analysis	Vitamin D supplement significantly improved follicular development in polycystic ovarian syndrome (PCOS)
Sidabutar et al	2016	23 patients 23 controls	Cross-sectional	Vitamin D level is lower in PCOS and lower in obese PCOS
Voulgaris et al	2015	NA	Review article	Vitamin D was associated with fertility Vitamin D ameliorated reproductive dysfunction in females with PCOS.
Lin MW et al	2015	NA	Review article	Polymorphism in VDR gene is associated with PCOS, but the role of Vitamin D is still debatable
Ratnabali Chakravorty DS et al	2015	NA	Review article	Increase Vitamin D deficiency in PCOS Vitamin D deficiency was associated with insulin resistance, fertility problems, and hyperandrogenism signs and symptoms.
Irani et al	2015	68	Prospective, randomized, placebo-controlled trial	Vitamin D supplementation improved vitamin D deficiency and TGF-β1 bioavailability in PCOS, and decreased the interval between menstrual cycles and triglycerides levels.
Kim et al	2014	38 patients 109 controls	Case-control	No difference in Vitamin D levels between PCOS and controls
Lerchbaum et al	2014	NA	Review article	High Vitamin D level is necessary for successful IVF, protective against endometriosis, and decrease metabolic parameters in PCOS
Rainer et al.	2012	53	Retrospective	Increase Vitamin D deficiency among PCOS patients No association between Vitamin D deficiency and time to pregnancy

Fang F, et al. Effect of vitamin D supplementation on polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Complementary Therapies in Clinical Practice. 2017 [cited 2017 Oct 16] Available from: http://www.sciencedirect.com/science/article/pii/ S174438811630 130X Sidabutar E, Halim B, Siregar MFG, et al. Vitamin D Levels in Women with Polycystic Ovary Syndrome. KnE Med. 2016;1(1):125–32. Voulgaris N, et al. Vitamin D and aspects of female fertility. Hormones (Athens, Greece) 2017;16(1):5–21. Lin MW, Wu MH. The role of vitamin D in polycystic ovary syndrome. Indian J Med Res. 2015;142(3):238–40. Ratnabali Chakravorty DS, Chakravorty R (2015):The Relationship between Vitamin D, Insulin Resistance and Infertility in PCOS Women. Gynecol Obstet. OMICS International. Available from: https://www.omicsonline.org/open-access/the-relationship-between-vitamin-d-insulin-resistance-and-infertility-in-pcoswomen-2161-0932-1000294. php?aid=52835 Irani M, et al. Vitamin D supplementation decreases TGF-β1 bioavailability in PCOS: A randomized placebo-controlled trial. The Journal of Clinical Endocrinology and Metabolism. 2015;100(11):4307–14. Kim JJ, Choi YM, Chae SJ, et al. Vitamin D deficiency in women with polycystic ovary syndrome. Clin Exp Reprod Med. Korean Society for Reproductive Medicine. 2014; 41(2):80–5. Lerchbaum E, Rabe T. Vitamin D and female fertility. Curr Opin Obstet Gynecol.,26(3):145–50. Rainer D, Davis E, Peck J, Hansen KR, Craig LB et al. (2012) : Vitamin D Deficiency and Time to Pregnancy in Women With Polycystic Ovary Syndrome. Fertil Steril.,97(3):S22.

vitamin D formulations. Researchers measured assessed cholecalciferol content of 14 commercial preparations available in Indian market. It was observed that of the total 14 samples analysed only 28.57% were found to be within the acceptable ranges from −90% to 125% as defined by Indian Pharmacopia. A total of 35.7% had higher and 35.7% had lower than the acceptable range. The percentage variation in cholecalciferol content as observed from the printed ranged widely from −91% to +65%.

The researchers concluded that there is a high degree of variability in cholecalciferol content of commercial preparations available in the Indian pharmaceutical market, See Table 1. This variation has many clinical implications as it may lead both, under treatment as well as vitamin D toxicity.

The formulation that contained highest cholecalciferol content (600,000 IU/ml) was in the form of injection. A percentage variation in the ranges from 8% ± 2% to 201% ± 29% was observed in the printed strength and the actual strength of the formulation as against the accepted norms of 100% ± 10%. Of the six formulations were not within the acceptable range, three were on the lower side (29 ± 11%, 8 ± 2%, 21 ± 8%) and the remaining three were on the higher side (201 ± 29%, 156 ± 6%, and 133 ± 9%).[35]

CLINICAL RECOMMENDATIONS

- **A high degree of variability in cholecalciferol content of commercial preparations available in the Indian pharmaceutical market**
- **Variation has many clinical implications as it may lead both, under treatment as well as vitamin D toxicity**

Leblanc et al reported a variation of 52–105% in compounded 50,000 IU cholecalciferol tablets and 23%–146% in 1000 IU compounded tablets.[36] Only one-third of pills were within 10% of the expected strength as recommended by US Pharmacopeia (USP) convention standard for compounded pills. Furthermore, when one pill was sampled from each of five bottles of the same lot, the potency variation ranged from

Table 2. Cholecalciferol contents of different preparations available in India

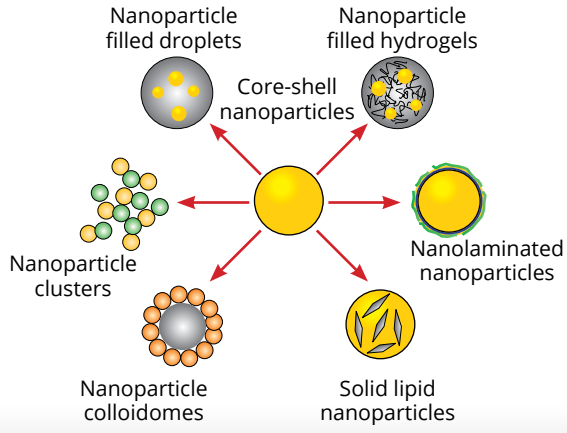
Drug	Preparation	Claimed dose of cholecalciferol as printed	Actual dose of cholecalciferol	Suggested range by Indian Pharmacopeia (−10% to +25%)	Percentage deviation from claimed strength
A	Tablet	60,000	99,106	54,000-75,000	+65
B	Tablet	2,000	2,621	1,800-2,500	+31
C	Sachet	60,000	39,095	54,000-75,000	−34
D	Sachet	60,000	19,223	54,000-75,000	−68
E	Sachet	60,000	16,556	54,000-75,000	−72
F	Sachet	60,000	81,500	54,000-75,000	+36
G	Sachet	60,000	81,361	54,000-75,000	+36
H	Sachet	60,000	64,569	54,000-75,000	+7.6
I	Sachet	60,000	52,872	54,000-75,000	−12
J	Sachet	60,000	90,833	54,000-75,000	+51
K	Sachet	60,000	5,537	54,000-75,000	−91
L	Sachet	60,000	68,026	54,000-75,000	+13
M	Sachet	60,000	63,987	54,000-75,000	+7
N	Sachet	60,000	67,790	54,000-75,000	13

57%–138% of the stated amount. Similar large variation (9%–140%) in the potency of the pills was also observed when pills were analysed from five bottles with different lot numbers. The USP convention standards for over-the counter (OTC) cholecalciferol preparation states that the content of the preparation when analysed should be within 90%–120% of the stated dose; however, the authors reported a percentage variation of 52%–135% of stated dose OTC preparations.

Miscible form of vitamin D_3 appears to be better

Food-grade nanoemulsions are often used in the food industry to encapsulate, protect, and deliver hydrophobic functional components, such as oil-soluble flavors, colors, preservatives, vitamins, and nutraceuticals. These nanoemulsions contain lipid nanoparticles (radius <100 nm) whose physicochemical characteristics (e.g., composition, dimensions, structure, charge, and physical state) can be controlled by selection of appropriate ingredients and fabrication techniques, see Figure 7.

Figure 7. Structures assembled using lipid nanoparticles as building blocks, including nanoparticle filled droplets and hydrogels, nanoparticle clusters, nanoparticle colloidosomes, solid lipid nanoparticles, and nanolaminated nanoparticles.



An open-labeled nonrandomized study that included 180 healthy individual who were divided in two groups and supplemented Group A (n=60) with 60,000 IU of fat-soluble vitamin D_3/month with milk and Group B (n=120) with 60,000 IU/month of water miscible vitamin D_3 under supervision for 6 months. Serum 25(OD)D, PTH, calcium, phosphate, and alkaline phosphatase (ALP) levels were evaluated before and after supplementation in 156 participants (54 in Group A and 102 in Group B) who completed the study. The study researchers reported that there was a significantly greater increase in the serum 25(OH)D levels in group B as compared to group A (31.8 levels of serum 25[OH]D [> 20 ng/mL]) as against 83.3% children in group A. Serum PTH and ALP levels declined considerably in both the groups following supplementation.

Vitamin D supplementation significantly increased the serum 25(OH)D levels in both groups± 9.1 ng/mL vs. 23.7 ± 10.4 ng/mL; p<0.001). All children in group B achieved adequate. Miscible form of vitamin D_3 appears to be better in achieving higher levels of serum 25(OH)D than that observed with a similar dose of fat-soluble vitamin D_3.[37]

CLINICAL RECOMMENDATIONS

- **Miscible form of vitamin D_3 appears to be better in achieving higher levels of serum 25(OH)D than that observed with a similar dose of fat-soluble vitamin D_3**

Absorption of nanoparticles

Absorption of nanoparticles involves three pathways:

- Paracellular: Nanoparticles pass through the narrow gaps between the neighboring epithelial cells

Nanoemulsion formulation of vitamin D_3 has better bioavailability as compared to coarse emulsion product. In a study, researchers compared the efficacy of nanotechnology-based miscellized vitamin D_3 with conventional vitamin D_3. The study included 180 healthy adults who were randomized to receive either micellized (group A, n=89) or conventional vitamin D_3 (Calcirol, group B, n=77) at a monthly dose of 60 000 IU (1500 µg) for 6 months. The outcome parameters were serum 25(OH)D, PTH, calcium, phosphate, alkaline phosphatase and urinary calcium:creatinine ratio.

After supplementation the individuals in both the groups had a significant increase in their serum 25(OH)D levels following supplementation:

- **Group A: 21·5 (SD 10·9) to 76·7 (SD 18·8) nmol/l (p<0·001)**
- **Group B: 22·8 (SD 10·4) to 57·8 (SD 16·0) nmol/l (P<0·001))**

The individuals in micellized vitamin D_3 group had an additional increase of 20·2 nmol/l in serum 25(OH)D levels (p<0·001)

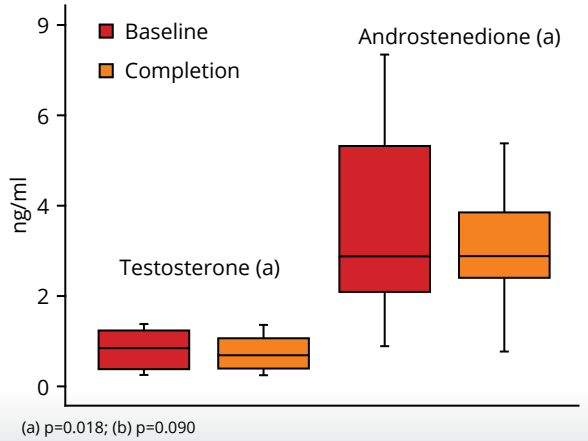
After adjustment for age and sex the difference between the groups was 17·5 (95% CI 11·8, 23·1) nmol/l remained statistically significant (p<0·001). There was a significant decline in mean serum PTH in both the groups. There were no reports of hypercalcemia or hypercalciuria. The study concluded that micellized vitamin D_3 is more efficacious in achieving higher levels of serum 25(OH)D.[38]

- Transcellular: Nanoparticles get absorbed directly through the epithelial cell membranes by either passive or active transport mechanisms
- Persorption: Nanoparticles get absorbed through the gaps formed in the layer of epithelium cells lining the gastrointestinal tract due to shedding and replacing of cells
- Hence, their absorption is not fat-dependent and is unaffected by fed fast variations.

Advantages of using nanoparticulate formulations

Nanoparticles get absorbed paracellularly, transcellularly, and by persorption, their absorption is independent of the amount of fat in the gut. The compliance to receiving nanoparticle formulation is found to be high, as it does not require milk or clarified butter for absorption. Also, formulation is highly palatable and in the form of ready to drink shot, and it can be taken in fasting state as well, Figure 8.[39]

Figure 8. The properties of nanoparticles may occur in a number of different ways as they pass through the GI tract



Nanoparticulate form of vitamin D vs. soft gelatin capsules: Effect on absorption

In the randomized crossover study, researchers evaluated the relative bioavailability of a nanoparticulate formulation and compared it with reference product (vitamin D Soft gelatin capsules) in healthy adult under fasting condition. Researchers observed that the absorption of liquid was 36% higher than Soft gelatin capsules.[40]

Based on the point estimate for AUC_{0-120} and C_{max}, Vitamin D oral solution (nanoparticulate formulation) was observed to have a greater rate and extent of absorption when compared to the vitamin D soft gel capsule (conventional formulation) following a dose of 60,000 IU under fasting conditions.

Correction regimens

- 2000 IU/day OR 60,000 IU once a week for 8 weeks, followed by 60,000 IU once a month lifelong as maintenance therapy
- 4000 IU/day is recommended for patients with fertility issues
- 6,00,000 IU once every 6 months in cases of malabsorption syndromes, and chronic disease
- Hypervitaminosis and toxicity is rare as long as one of these regimens is followed

SUMMARY OF RECOMMENDATIONS

- Vitamin D is important for bone mineralization, and is implicated in pathogenesis and risk amplification of numerous chronic diseases
- Prevalence of vitamin D deficiency is high in women with PCOS, which is also the most common cause of anovulatory infertility
- Around 70.3% of infertile PCOS women were found to be vitamin D deficient, 20.3% were vitamin D insufficient, and 9.4% had normal vitamin D levels
- There is relevance of vitamin D insufficiency in the pathophysiology of PCOS
- Serum levels of 25(OH)D are positively associated with SHBG levels, negatively associated with hirsutism, PTH, hyperandrogenemia in women with PCOS
- Vitamin D deficiency is an important modifiable contributor to diminished treatment success in women with either PCOS
- Vitamin D deficiency in women with PCOS, who had undergone fertility treatment with ovarian stimulation is significantly associated with reduced rate of ovulation and had a low chance of live birth
- In India, there are 22 to 23 million infertile couples, and the total fertility rate has declined from 3.9 in 1990s to 2.3 in 2013
- This is compounded by the rising incidence of PCOS globally and the prevalence is Indian subcontinent is 4% to 25%

SUMMARY OF RECOMMENDATIONS

- Vitamin D is associated with several vital cellular processes, such as: cell differentiation and proliferation, hormonal secretion (such as insulin). Vitamin D is associated with hyperandrogenism which predominates in PCOS
- Vitamin D is the key regulating hormone in calcium homeostasis and calcium plays a role in oocyte activation and maturation resulting in the progression of follicular development
- Vitamin D sufficiency is also essential for successful in vitro fertilization, and it is probably protective against endometriosis
- Only 50% of a typical dosage of vitamin D is absorbed from the intestinal lumen owing to complex absorption process
- PCOS women who were given vitamin D 4,000 IU, 1,000 IU, or placebo daily for 12 weeks had significantly reduced total testosterone (TT), free androgen index (FAI), and increased SHBG
- Post vitamin D supplementation decreased insulin resistance and increased insulin sensitivity
- Vitamin D status may influenced the menstrual cycle and plays a role in the ovarian function, vitamin D deficiency can cause reduced ovulation and live birth rate
- Vitamin D status may influenced the menstrual cycle and plays a role in the ovarian function
- Vitamin D supplementation may improve endometrial thickness

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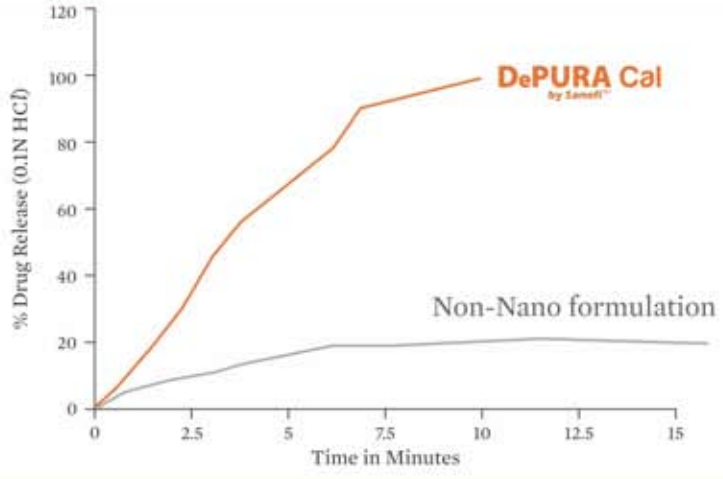

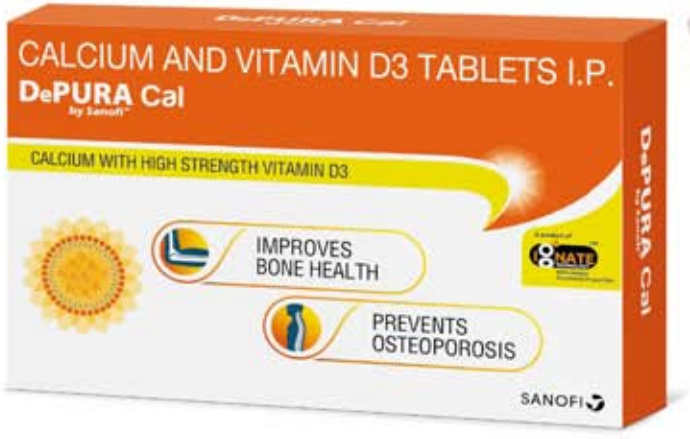

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