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Review Article

# Effect of Vitamin D supplementation during pregnancy on maternal and perinatal outcomes

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## Abstract

Vitamin D deficiency is common globally with a higher prevalence in women, especially during pregnancy. Among the pregnant women, Vitamin D deficiency was reported up to 80% in the Asian group. Vitamin D deficiency was related to a higher risk of maternal complications including preeclampsia, impaired glucose tolerance, and cesarean section rate, and neonatal complications including low birthweight, neonatal hypocalcemia seizure, and impaired skeletal, lung and immune development. There were no data supporting Vitamin D deficiency screening routinely in pregnancy regarding cost-effectiveness or health benefits. The measurement of Vitamin D in the high-risk group of women is necessary. Subsequent supplement with Vitamin D with and without calcium supplement during pregnancy had been statistically significantly reported to decrease the risk of preeclampsia, preterm birth, and low birth body weight. However, due to a lack of studies, the strategies of dietary and nutritional supplement for fetal growth restriction prevention are not statistically effective and are not yet recommended. The present review is to provide an overview of the clinical and the experimental evidence of Vitamin D deficiency-related complication and review of available options for the prevention and management of these complications.

**Keywords:** *Intrauterine growth restriction, Nutrition, Pregnancy, Vitamin D*

## Introduction

In nonpregnant women, after skin or diet synthesized Vitamin D, Vitamin D will bind to Vitamin D-binding protein and transfer to the liver. In the liver, Vitamin D will be converted to active 25-hydroxyvitamin D (25[OH]D). The half-life of 25(OH)D is 2–3 weeks and can be reflected as the body vitamin status. The 25(OH)D is then went into the kidney, after the action of 1α-hydroxylase, 1,25(OH)2D will be formed which half-life is 8 h.

In pregnant women, 25(OH)D can cross the placenta and $1,25(OH)_2D$ cross only at the low concentration. Nevertheless, in the placenta and decidua, the elevation of 1α-hydroxylase activity caused increasing production of $1,25(OH)_2D$ to supply to the mother and fetus [1]. In pregnancy, maintain adequate Vitamin D concentration is pivotal. However, the optimal concentration of serum 25(OH)D is still debated. Now, the optimal concentration of Vitamin D is based on the level of the general population [2].

Vitamin D deficiency is usual globally with a higher prevalence in women, especially during pregnancy. The 78.18% of Asian women was associated with Vitamin D deficiency [3], which was related to a higher risk of both maternal and neonatal complications. Maternal Vitamin D deficiency increased the risk of impaired glucose tolerance, preeclampsia, and cesarean section rate, neonatal low birthweight, neonatal hypocalcemia seizure, and impaired skeletal, lung and immune development. Prenatal examination of Vitamin D deficiency pregnant women may present as fetal growth restriction (FGR).

The etiologies of FGR could be categorized into maternal, fetal, and placental, which have the common final pathway of suboptimal uterine-placental perfusion and fetal nutrition [4]. Since maternal 25(OH)D can cross the placenta during pregnancy, it is postulated maternal Vitamin D concentration might affect through calcium metabolism, bone growth, or altered placental function.

The aim of the present review is to provide an overview of the clinical and the experimental evidence of maternal and

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perinatal complications associated with Vitamin D deficiency and review of available options for the prevention and management of these complications.

## Fetal growth restriction

### Etiology of fetal growth restriction

The etiologies of FGR could be categorized into maternal, fetal, and placental, which have the common pathway of insufficient uterine-placental circulation and fetal nutrition [4]. Maternal conditions that cause FGR include gestational hypertension (preeclampsia), gestational DM;. Placental factors that cause FGR include abnormal placentation reduced blood flow; Fetal factors that cause FGR include genetic disorders, viral or bacterial infection.

However, unknown etiology is identified in 40% of infants with FGR. Moreover in the 60% of remainders where an underlying cause is identified, FGR is caused by extrinsic factors including maternal condition and placental factors in approximately 50% of infants and is related to the intrinsic factors indicating as a fetal condition in the remaining 10% [5]. Table 1 presents an overview. In addition, maternal genes and paternal genes both contribute to infant birthweight, and the former demonstrating a stronger effect [6].

## Physiology of Vitamin D

Vitamin D has two main forms: Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol). Vitamin D2 is found naturally in sun-exposed mushrooms and yeast and commonly adds to foods, whereas Vitamin D3 is synthesized from the conversion of 7-dehydrocholesterol in the human skin or consumed in the diet through the intake of oil-rich fish [7]. The 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$), biologically

**Table 1: Overview of etiologies of fetal growth restriction [5]**

| Etiology | Potential mechanism |
|---|---|
| Unknown etiology (40%) | Unknown |
| Known etiologies (60%) | |
| Extrinsic (50%) | Diminished uteroplacental-fetal |
| Maternal conditions | blood flow +/− oxygen delivery |
| Medical conditions | |
| Gestational hypertension, preeclampsia | |
| Chronic kidney disease | |
| Pregestational diabetes mellitus | |
| Autoimmune disease (SLE, Antiphospholipid syndrome) | |
| Cyanotic heart disease | |
| Chronic pulmonary disease | |
| Chronic anemia | |
| Environmental factors | |
| Smoking | |
| Alcohol | |
| Drugs (antimetabolites, anticoagulants, anticonvulsants) | |
| Narcotics | |
| High altitude | |
| Others | |
| Multiple gestations | |
| Low prepregnancy weight | |
| Poor gestational weight gain | |
| Malabsorption | |
| Poor nutritional status | |
| Placental factors | |
| Chromosomal mosaicism | |
| Infarcts, focal lesions | |
| Abnormal placentation (placenta previa) | |
| Reduced placental blood flow | |
| Intrinsic (fetal conditions) (10%) | |
| Genetic | Genetic disorder |
| Chromosomal abnormalities | |
| Autosomal trisomies, monosomies, deletions | |
| Infection | Cytolysis and loss of cell function |
| Viral, TORCH | in various organ system in the fetus |
| Bacterial, syphilis | |
| Protozoal (malaria, toxoplasma) | |
| Malformations (CV, GI, GU defects) | |

SLE: Systemic Lupus Erythematosus, TORCH: Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections, CV: Cardiovascular, GI: Gastrointestinal, GU: Genitourinary

active form, is metabolized from Vitamin D in a multistep process. Through the ultraviolet (UV) irradiation, Vitamin D3 was initially formed in the skin. Vitamin D3 is hydroxylated to 25-hydroxycholecalciferol 25(OH)D in the liver by the mitochondrial and microsomal 25-hydroxylases. 25(OH)D is low biologically active but a major form of circulating Vitamin D. The resultant 25(OH)D is further 1α-hydroxylated in the kidney by mitochondrial 1α-hydroxylase, this yields the hormonally active secosteroid $1,25(OH)_2$ D eventually [8]. Dietary intake is a minor source of Vitamin D3 because dairy products only contain a small amount of Vitamin D3 [9]. Besides, decreased sun exposure reduces Vitamin D synthesis. Melanin also absorbs UVB from sunlight and diminishes Vitamin D3 production by at least 90% [10].

## Vitamin D in pregnancy

The nonclassic actions of Vitamin D during pregnancy were including promoting insulin secretion and innate immunity but adaptive immunity to the contrary, oxidative stress, placental implantation, endothelial function, angiogenesis, and inflammatory response [11].

## Correlation between Vitamin D and various etiology of fetal growth restriction

### Vitamin D deficiency in pregnant women

Vitamin D deficiency is common worldwide with a higher prevalence in women, including antepartum, pregnancy, and lactating populations. Vitamin D requirements are probably greater in pregnancy. Physiologically elevation of $1,25(OH)_2D$ level has been observed in the second and third trimesters [12]. While $1,25(OH)_2D$ levels do not rely directly on $25(OH)D_3$ levels, the physiological ascend in the active metabolite, the enhanced intestinal calcium absorption, and fetal requirement of calcium all direct to the importance of Vitamin D metabolism in pregnancy [13]. There are several reasons resulting in Vitamin D deficiency, including factors that restrict skin exposure to UVB light (e.g., high-latitude resident, dark skin pigmentation), decrease dietary intake of Vitamin D (e.g., low dietary intake of vegetarian diets or fish and egg yolks), or change Vitamin D intake or metabolism (e.g., malabsorption, poor liver or renal function, and obesity) [14].

### Maternal complications caused fetal growth restriction related to Vitamin D deficiency

#### *Preeclampsia*

Whether Vitamin D insufficiency in pregnancy is associated with preeclampsia and hypertension is remained controversial. There are several possible mechanisms reported. Low circulating levels of insulin-like growth factor-1 (IGF-1) and $1,25(OH)_2D$ were associated with preeclampsia. *In vitro*, IGF-1 enhances $1,25(OH)_2D$ production by placenta-derived primary human syncytiotrophoblasts from normal pregnancies but not from preeclamptic pregnancies. The other hypothesis is an abnormal expression of 1α-hydroxylase (a Vitamin D – activating enzyme in preeclamptic pregnancies), revealing a latent role as a regulator of placentation for $1,25(OH)2D_3$ [12]. Vitamin D is also hypothesized as an immune modulator [15]. 1,25(OH)2D could suppress T-cell receptor-induced T-cell proliferation, change cytokine expression, and decreasing γ-interferon and interleukin-2 production, which may be related to the occurrence of preeclampsia [16]. Vitamin D also influences blood pressure regulation. The relationship between plasma renin and 1,25(OH)2D activity was opposite [17]. Vitamin D also involved calcium homeostasis could regulate pregnancy-induced hypertension [18]. Calcium supplementation could lower the risk of preeclampsia (relative risk: 0.45, 95% confidence interval [CI]: 0.31–0.65) [18].

In a multicenter case–control study which enrolled women with ($n$ = 1013) or without ($n$ = 1015) preeclampsia, the concentration of 25(OH)D was significantly lower in the preeclampsia (mean 29.99 ng/mL; 95% CI: 29.40–30.58 ng/mL) group compared to the comparison group (mean 33.7 ng/mL; 95% CI: 33.20–34.30 ng/mL). An increased chance of having preeclampsia (odds ratio = 2.18; 95% CI, 1.80–2.64) among women with Vitamin D deficiency was noted after adjusting for covariates [19]. Vitamin D insufficiency associated with preeclampsia and small for gestational age (SGA) infants was also demonstrated in a meta-analysis of 31 studies [20].

#### *Impaired glucose tolerance*

The onset of impaired glucose tolerance is associated with an increased level of both intracellular $Ca^{2+}$ and ROS. Vitamin D is known to promote insulin secretion by increasing expression of antioxidants that reduce levels of ROS, and it maintains low $Ca^{2+}$ levels by increasing expression of the plasma membrane $Ca^{2+}$-ATPase, which could extrude $Ca^{2+}$ [21]. The relationship between insufficient Vitamin D and gestational diabetes mellitus (GDM) is conflicting because not all studies support these findings. However, there is one meta-analysis of 31 studies showed that gestational diabetes was found to be associated with Vitamin D deficiency compared with the control group (odds ratio = 1.98, 95% CI: 1.23–3.23) [20].

### Fetal complications caused fetal growth restriction related to Vitamin D deficiency

Vitamin D insufficiency could potentially be related to fetal growth through the metabolism of calcium, the growth of bone, or change placental function.

#### *Skeletal development and growth*

Hypovitaminosis D associated with impaired fetal bone growth and development is well established [20,22]. Lowe maternal Vitamin D concentration may lead to suboptimal bone size and density after birth and increased risk of osteoporotic fracture in later life [23]. One cohort study revealed in mother had decreased circulating 25(OH)D concentration, their babies' distal femoral metaphyseal cross-sectional area to femur length ratio measured at 19 and 34 weeks were increased, may associate with postnatal rickets [24]. Vitamin D supplementation postnatally can only partly eliminate the differences in bone variables induced by maternal Vitamin D status, which means that prenatal Vitamin D concentration plays a vital role on skeletal development and growth of the fetus.

#### *Low birthweight*

Maternal Vitamin D concentration has been revealed to correlate with birthweight centile positively [25]. One

meta-analysis of 31 studies revealed a significant association between 25-(OH)D deficiency and SGA infants compared with the comparison group (odds ratio = 1.85, 95% CI: 1.52–2.26) [20].

### Other complications related to Vitamin D deficiency

#### *Fetal development of lung and immune disorder*

Maternal Vitamin D deficiency at 18 weeks, related to fetal lung development, was associated with a decreased lung function in children at the age of 6-year-old [26]. Some studies combined with *ex vivo* studies revealed Vitamin D involving in the maturation of fetal alveolar type II cells and epithelial-mesenchymal interactions, implied that Vitamin D is implicating in early lung growth [26]. In addition, Vitamin D plays an important role in the homeostasis of the immune system [27]. Vitamin D has been shown to modulate innate immunity. Macrophages, epithelial cells, granulocytes, and monocytes can produce antimicrobial peptides, such as defensin and cathelicidin [28]. Antimicrobial peptides are in charge of rapid protection against pathogens in epithelial tissues such as the mucosa, epidermis, lungs, and bladder. Moreover, Vitamin D is shown to decrease interferon and chemokine release in epithelial cells infected by the virus while not affecting viral replication. The aforementioned explains in humans with superior Vitamin D status decreased inflammatory response and disease severity. Th1 was selectively suppressed by Vitamin D, but not Th2 or CD8+ cell activity. Therefore, Vitamin D can interfere with cytokine production of monocytes and lymphocytes, including IgE-mediated allergy development, acts as an immunoregulatory hormone on the maturation of the immune system [27]. Based on the pathophysiology mentioned above, maternal Vitamin D deficiency at 18 weeks was found correlated with current wheezing in 6-year-old children (both sex) and an elevated risk of asthma in boys [26]. Several studies report that low concentrations of cord blood plasma 25-(OH) D were associated with the respiratory syncytial virus caused bronchiolitis and respiratory infections in babies within 1-year-old [29,30].

#### *Primary cesarean section rate*

1$\alpha$,25(OH)$_2$D increases the function of skeletal muscle by the initiation of myogenesis, cell proliferation, differentiation, and apoptosis [31]. On the contrary, Vitamin D deficiency would cause proximal muscle weakness and reduced lower extremity muscle function might be increased the risk for cesarean section [32]. A prospective study revealed that Vitamin D deficiency (<37.5 nmol/l) was associated with an elevated risk of primary cesarean section (adjusted odds ratio = 3.84, 95% CI = 1.71–8.62) [33].

#### *Neonatal hypocalcemic seizure*

Maternal Vitamin D deficiency may cause Vitamin D deficiency in neonates, which is the major cause of hypocalcemic seizures in neonates and infants [34,35]. Neonatal seizures may occur in the first 2 weeks of life with the incidence of 0.5% in live births. The cause of neonatal seizures is immature neurons cannot sustain repetitive stimulation for a long time and to be multifocal or focal [36]. High prevalence of Vitamin D deficiency was observed in the mothers whose infants had hypocalcemic seizures (85%), and their infants (90%) [35]. On the other hand, excessive calcium ingestion could be harmful. One case report showed one newborn had hypocalcemic seizures. It may cause by excessive maternal calcium ingestion (3–6 g of calcium carbonate daily) during the past 4 months of pregnancy, which led to transient neonatal hypoparathyroidism and hypocalcemia [37].

## Screening

### Screening for Vitamin D deficiency during pregnancy

Routine screening for Vitamin D deficiency in pregnancy was not evident regarding cost-effectiveness or health benefits. However, measurement of Vitamin D in the high-risk group women, including with bone pain, malabsorption, alcohol abuse, or a previous child with rickets is necessary [38].

## Management

### Vitamin D supplement and treatment for women during pregnancy

Due to the maternal or fetal complications associated with Vitamin D deficiency which are mentioned above, Vitamin D supplement during pregnancy is an important issue.

#### *Recommendation of Vitamin D supplement in women during pregnancy*

There are two forms of Vitamin D supplement. Vitamin D3 (cholecalciferol) may be more effective than Vitamin D2 (ergocalciferol) for increasing and maintaining higher serum 25(OH) D levels [39]. According to the guideline of Vitamin D in pregnancy by the Royal College of Obstetricians and Gynecologists, regardless of the baseline serum status of Vitamin D, Vitamin D ingestion are suggested [38]. First, for all pregnant women, Vitamin D 10 μg (400 units) daily used is suggested. However, 600 units a day has been shown to maximize bone health and muscle function [40]. Second, at least 800 units a day combined with calcium was suggested for pregnant women with a high risk of preeclampsia. Third, for those of high risk (increased skin pigmentation, reduced sunlight exposure, or obese), 1000 units a day was suggested [38].

#### *Vitamin D treatment in women with known Vitamin D deficiency during pregnancy*

As for the women who have already been diagnosed with Vitamin D deficiency, treatment with either ergocalciferol 10,000 unit twice a week or cholecalciferol 20,000 unit a week for 4–6 weeks, followed by standard dosage, is appropriate [38]. There was also evidence showed that 1500–2000 units/day (37.5–50 mcg/day) may be required to increase 25(OH)D level to consistently >30 ng/mL (75 nmol/L) [40].

#### *Maternal and neonatal outcome after Vitamin D supplement during pregnancy*

According to the Cochrane review on Vitamin D supplementation for pregnant women which included 15 trials assessing a total of 2833 women [41] and updated meta-analyses on maternal outcomes [42], two subgroups were discussed. In the subgroup of Vitamin D alone versus no supplementation or a placebo, fourteen parameters including risk of GDM, preeclampsia, low birthweight (<2500 g), and preterm birth, adverse effects, cesarean section rate, poor birth

activity (Apgar score <7/5'), maternal or neonatal death and stillbirth and level of 25(OH)D, birth length, head circumference, and birthweight were analyzed. There was a statistically significant lower risk of low birthweight (<2500 g), preterm birth, and a higher level of 25(OH)D and head circumference. In the subgroup of Vitamin D and calcium versus placebo or no supplementation, statistically significant lower risk of preeclampsia was noted but with a higher risk of preterm birth.

### *Fetal growth restriction outcome after Vitamin D supplementation*

Previous meta-analysis revealed Vitamin D deficiency is associated with FGR (odds ratio = 1.558, 95% CI = 1.138–2.216) [43]. Therefore, Vitamin D supplement may decrease FGR occurrence. Tao *et al*. reported daily supplement of Vitamin $D_3$ 600 IU daily could increase cord blood and maternal blood 25(OH)D concentration and decrease FGR (odds ratio = 0.53, 95% CI = 0.32–0.87) [44]. Another randomized controlled trial also showed a daily supplement of Vitamin D could decrease blood pressure and increase the newborn's length [45]. However, a newly published article found Vitamin D supplement in midpregnancy until birth or until 6 months postpartum did not improve fetal or neonatal growth [46]. Up till now, whether Vitamin D supplementation could decrease FGR is inconclusive. The answer to this question needs further large-scale prospective study to elucidate.

## Conclusion

Vitamin D deficiency in pregnancy is common and nonclassic actions have given rise to increasing concern in recent one decade, which contribute to both maternal and neonatal complications. It could present a FGR during the prenatal examination. Although Vitamin D with and without calcium supplement during pregnancy had been statistically significantly reported to decrease the risk of preeclampsia, preterm birth, and low birth body weight which were all postpartum maternal complications, there are few studies discussing the peripartum improvement of FGR after supplement and postpartum neonatal long-term prognosis. Therefore, further research focusing on the peripartum improvement of FGR after supplement and consequential clinical outcomes is warranted.

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### Conflicts of interest

There are no conflict of interest.

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