



## HOW DOES VITAMIN D SUPPLEMENTATION CHANGE THE OUTCOME FOR MOTHER AND CHILD?

Nikolai Lazarov, Faisal Saghir,  
*Department of Obstetrics and Gynecology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria.*

### ABSTRACT

**Introduction:** Pregnancy represents a period in which rapid bodily changes occur, which include a wide range of physiological interactions occurring in both the mother and the developing foetus. The role of vitamin D3 metabolism within pregnancy is an over-shadowed but very important aspect for the normal and healthy musculoskeletal development of the foetus and for the various alternative functions associated with vitamin D3 for the pregnant female.

**The purpose:** To provide a detailed understanding of the current status of vitamin D3 and the role it has within pregnancy and to identify the efficacy and the wide range of effects that vitamin D3 has for both the mother and foetus.

**Materials and methods:** We conducted a review of the available literature at PubMed, Google Scholar, and Science Direct, which included observational studies, prospective and controlled trials, reports and guidelines for appropriate dosages of vitamin D3 to be used within pregnant females.

**Results and Discussion:** Our review of the scientific literature showed evidence of the benefits of vitamin D3 within pregnant women and the effect, if any, on the numerous physiological processes taking place within both the mother and the foetus. We found data indicating that vitamin D3 can prove to be very important in preventing preeclampsia, gestational diabetes and congenital malformations of the foetus.

**Conclusion:** The administration of vitamin D3 may be a potential technique to prevent complications to the mother and the developing foetus both during and after pregnancy, either solely or as a combined therapy.

**Keywords:** Cholecalciferol, Osteoporosis, Deficiency, Supplement, Dosage

### INTRODUCTION

The physiological process of pregnancy represents a time of bodily change, which are demonstrated in both physiological and physical proportions. Together with this, there comes a significant change in the requirement of vitamin D and in vitamin D metabolism. The requirement for vitamin D varies depending on the mother's reproductive stage; in pregnant women, vitamin D intake is believed to be of immunomodulatory significance rather than calcium-based regulating factor. Parker's hypothesis states that there are certain adult-onset diseases which may have been due to nutritional insufficiency both in the perinatal period in utero or early in infancy when nutritional requirements are high. These include denoting a connection between neonatal growth restriction and small gestational age status with the risk of heart disease later in adulthood. Vitamin D deficiency has a well-established link to bone mineralization and the development of rickets early in neonatal life, however, another link has been established between vitamin D deficiency and immune function. [1, 2] The purpose of this review is to shed light on the potential impact of dietary vitamin D during the prenatal and perinatal periods as a contributor to maternal complications and, thus, both investigating at a genetic and phenotypic level the effects of vitamin D deficiency. Although Vitamin D deficiency can have implications for both the mother and the neonate, more notably on a widely unknown basis, the function of vitamin D during pregnancy for both the mother and the foetus is not yet identified. [3] What is known is the fact that Vitamin D does have a part to play in skeletal homeostasis during pregnancy, as noted that severe vitamin D deficiency will lead to neonatal seizures due to profound hypocalcaemia. The function of vitamin D during this critical period may also have other side effects such as immune, pancreatic, musculoskeletal, cardiovascular function, as well as including neural development. The treatment of rickets is given in the form of vitamin D supplementation as 400 IU or 10 micrograms daily for infants. Serum 25-hydroxyvitamin D is accepted as the best marker of vitamin D status, although it may serve more of a clinical importance in revealing information surrounding the first exposure rather than the clinical outcomes. The neonatal levels of 25-hydroxyvitamin D reflects a range of in-utero factors, the most significant of these being the

maternal vitamin D status, and even though calcium and phosphorous are transported trans-placentally without vitamin D, the effect of low vitamin D in utero or short after delivery has taken the place the effects are uncertain. Neonates who suffer from vitamin D deficiency rickets have secondary hyperparathyroidism and demineralization of the growing skeleton, as well as impairment of bone elongation. The purpose of this review is to provide an insight into the current research surrounding vitamin D deficiency and whether or not, based on the current data if there are adverse effects and complications arising for both mother and neonate due to this deficiency. [4, 5]

## MATERIALS AND METHODS

We undertook a review of the available scientific literature from Google Scholar and Science Direct, which included prospective controlled trials, randomized research studies, reports and various guidelines on the efficacy and role of vitamin D in the post-partum outcome of both mother and neonate. In the scientific articles, we found various different achievements related to vitamin D uses, vitamin D pathophysiology, Vitamin D relationship with calcium and phosphorous, vitamin D functions and uses, vitamin D role and effect within the bodily system, vitamin D complications and vitamin D current role in pregnancy and the effect on the outcome for both the neonate and the mother during and after pregnancy. We also took an insight into the future and prospective role of vitamin D within the field of obstetrics and gynaecology and whether a better understanding of the role of vitamin D will translate into more positive and beneficial outcomes before and after delivery.

## RESULTS AND DISCUSSION

Vitamin D, although within the general medical specialities, is referred to as a vitamin, it is, in fact, a steroid hormone that acts on almost all bodily tissues. Vitamin D is naturally synthesized via natural phenomena within the skin upon exposure to ultraviolet B radiation from the sun. The lighter the skin of the individual, the less time is needed before the levels of vitamin D reach an adequate level. When vitamin D is synthesized in the skin or ingested in the supplementation form, it binds with the vitamin D binding protein and travels to distant sites in the blood stream. Once in the circulatory system, vitamin D is converted in the liver to 25-OH-Cholecalciferol, which is the major circulating form of vitamin D and is regarded as the evaluating marker for the levels of vitamin D within the circulation. Then, in order for it to be biologically active, the 25-OH-Cholecalciferol is further converted to one 25 dihydroxycholecalciferol. This final conversion step is catalyzed by the enzyme 1-alpha-hydroxylase, which is actively known to be in large quantities within the kidney; however, it has now been noted to also be distributed within the breast, placental and immune system tissues and cells. The active 1, 25, dihydroxycholecalciferol binds with nuclear receptor sites on DNA to actively induce protein synthesis and regulation. [6]

Vitamin D has been understood to regulate calcium homeostasis; it acts within the intestine to increase calcium

absorption. As the levels of vitamin D drop, absorption of calcium and phosphorous from the intestine is, in the same way, reduced. Consequently, the lower levels of calcium and phosphorous in the bloodstream lead to a stimulated increase in the levels of parathyroid hormone, which maintains sufficient quantities of calcium within the blood via the action of bone reabsorption within the biochemical indices a norm level of calcium within the blood is said to be between 9.0 and 10.5 milligrams per decilitre. The negative loop feedback system ensures that the serum calcium is readily available, and if chronic activation does occur, it can lead to various bone diseases such as osteoporosis osteomalacia. Within the neonate and infants, the depletion of vitamin D levels is the primary aetiological factor in the onset of rickets, a clinical bone-deforming condition characterized by a bowing curvature of the lower limbs due to decreased bone density and cortical bone mineral mass with increased prone susceptibility to fractures and a waddling gait. [7]

The pathophysiological mechanism behind vitamin D metabolism in both the pregnant and non-pregnant states differs, and a significant discovery has been made in the availability and activity of vitamin D levels within these two physiological states. The conversion of vitamin D to 25-OH-cholecalciferol appears unchanged during pregnancy due to the law of kinetics. On the contrary, the conversion of 25-OH-cholecalciferol into its active form during pregnancy is unique, as it has been shown that the maximum production of the active 1, 25, OH-cholecalciferol is not achieved during pregnancy until circulating 25-OH-cholecalciferol reaches a concentration of 40 nanograms per millilitre. By the end of the first trimester, 1,25 OH-cholecalciferol reaches levels more than twice that of the non-pregnant women, and they continue to rise in concentration to over 700 picomols per litre at which these levels are essential to the normal progression of pregnancy, but in a non-pregnant woman, it would be a toxic condition due to the presence of hypercalcaemia. The high levels of 1-25 OH-cholecalciferol are in nature from two different sites, which can be of either placental origin or from the renal 1-alpha-hydroxylase that would have to be uncoupled from reasons other than maintaining calcium homeostasis. The second reason is women with non-functional renal 1-alpha-hydroxylase and normal placental function fails to increase circulating 1,25, OH-cholecalciferol during pregnancy. The increase in 1,25 OH-cholecalciferol can also be due to the methylation of the catabolic CYP24A1 placental gene, and a possible suggestion is the involvement of calcitonin within this process as it rises during pregnancy and is known to stimulate the renal 1-alpha-hydroxylase gene independent of calcium levels and also serves to protect by opposing hypercalcaemia. To further this, the rise in circulating 1, 25 –OH cholecalciferol levels in the mother/foetus was thought to increase in quantities to ensure adequate delivery of calcium to the maternal skeleton for osteopreservation and fetal skeletal development; however, this is not true as at 12 weeks of gestation there is no increase in demand for calcium by either the mother or the foetus. In contrast, the increased concentration of 1, 25 OH-

cholecalciferol is sustained during pregnancy, but this is not sustained during lactation when the maternal calcium demand is as high as it is during pregnancy. From this, we can say that within the mother and foetus during pregnancy, the rise in one, 25, OH-cholecalciferol is dependent upon substrate availability and is independent of calcium homeostasis. [8]

The condition of idiopathic infantile hypercalcaemia was attributed mainly to hypervitaminosis about vitamin D levels, which is an inaccurate association to be made as it led to a profound misunderstanding and hesitation amongst obstetricians and gynaecologists in the thought that vitamin D administration during pregnancy and infancy was to be avoided. During the 1960's, it was observed that elfies facies was documented in an infant with severe idiopathic infantile hypercalcaemia, which resembled the facies observed in patients with supravalvular aortic stenosis syndrome. Furthermore, a patient was documented suffering from elfin facies, mental retardation, supravalvular aortic stenosis and peripheral pulmonary stenosis; however, during this period of time, there was no quantitative way of assessing the levels of vitamin D in circulation, and it was not even proved whether vitamin D was metabolized within the body. As a result, the theory that maternal vitamin D supplementation during pregnancy caused supravalvular aortic syndrome was conducted on animal models to show that toxic excess levels of vitamin D during pregnancy would result in supravalvular aortic syndrome. In the current period, this theory has been debunked, and the vitamin D causing SAS syndrome is now known as Williams's syndrome, but there is still a misconception relating vitamin D supplementation during pregnancy as the cause of supravalvular aortic syndrome. Beyond the relationship between vitamin D levels and calcium homeostasis, there have been observational studies which unmasked strong relationships between maternal circulating levels of 25-OH-cholecalciferol and preeclampsia, altered placental vascular pathology, glucose tolerance, adverse birth outcomes due to race, infection rates, brain and respiratory function. [9] However, observations that are more recent have pointed to the fact that maternal vitamin D deficiency is a risk factor for abnormal fetal growth patterns, adverse birth outcomes, reproductive failure and a further strengthening of vitamin D levels acting as a contributing agent in the onset and pathogenesis of preeclampsia. A cohort study carried out indicated that an administration of 4000 IU per day dose of Vitamin D3 safely increases the circulating 25-OH-cholecalciferol to a level that, regardless of race, fully normalizes vitamin D metabolism and calcium homeostasis in pregnant women. The dosage of vitamin D3 administered also indicated that an increase in vitamin D supplementation decreased complications of pregnancy and caesarean section deliveries. In addition to this, an increase in vitamin D supplementation during pregnancy greatly decreased complications of birth and gestational diabetes, alloallergen sensitization and markers of regulatory immunity. Vitamin D is interesting in breastfeeding women, as it was thought

that vitamin D was unable to be passed onto the infant via breast feeding and this is untrue, as during lactation, vitamin D supplement in the exogenous form has the same effect on infant 25-OH-cholecalciferol status as direct infant supplementation, but they also may provide additional benefits to the mother and child. [10] With this, vitamin D supplementation during pregnancy has been found to be associated with a reduction in the risk for delivery and birth of small for gestational age babies or babies delivered with a birth weight of less than 2500 grams whilst also observing no increased risk of fetal or neonatal mortality or congenital malformations. During pregnancy, a vitamin D supplement delivered in lower doses, such as lower than or equal to 2000 IU per day, is associated with a reduction in the risk of fetal and neonatal mortality. In conjunction to with an administration of vitamin D during pregnancy was also associated with higher calcium levels, a more proficient and promising APGAR score, which is used as a clinical assessment score to identify the physiological and anatomical integrity of the infant post-birth. Also observed is a greater neonatal skin fold thickness, higher birth weight and a greater height seen in offspring.

An interesting discovery made is the link between vitamin D and childhood asthma. A study was conducted involved giving supplemental vitamin D3 in dosages of 400 or 4400 IU per day to pregnant women across three different major racial/ethnic groups from 16 weeks gestational age until term. [11] The endpoint of this study is the prevention of asthma/wheezing in the infant or child at 1, 2 and 3 years of age post-birth. The general findings included those infants at the age of three experienced significantly lower rates of asthma in the higher dosage group the intake of 4400 IU per day of vitamin D3. The development of neurological based diseases, including multiple sclerosis, has been found to have a positive correlation with vitamin D3 deficiency and this interaction is thought to be found due to the various genetic alterations that 25-OH-cholecalciferol induces are of transcriptome and epigenetic nature via DNA methylation in the gene transmission gen regulates processes such as antigen processing, inflammation, regulation of cell death, cellular proliferation, the transmission of nerve impulses, neurogenesis, neuronal differentiation and sensory organ development. In regards to vitamin D3 deficiency during pregnancy and the manifestation of DNA development of neurological diseases during pregnancy, there is emerging evidence within animal models that there may be adverse neurological consequences during pregnancy if supplementation of vitamin D3 is restricted. Finally, proposals for pregnant women include the intake of and maintaining a circulating 25-OH-cholecalciferol concentration of at least 40 nanograms per millilitre during the earliest time of pregnancy, which will ensure protection for the mother in terms of contributing to the prevention of the development of preeclampsia and for the child the prevention of childhood asthma. To achieve this, an exogenous administration of vitamin D3 has to be in dosages of 4000 IU per day due to the individual discrepancies of

having the ability to convert vitamin D into its final active end product, 1,25-OH-cholecalciferol. The aforementioned supplements have been demonstrated to be safe for use in practice as till yet, no adverse events have been observed with a dosage of 4000 IU being given to pregnant women per day. An interesting question arises in regards to when vitamin D3 should be given to pregnant women. and based on the placental gene expression and individual methylation of genes responsible for a verity of functions, as mentioned in the article, indicates that the onset of disease inflammation occurs early in pregnancy, and so this provides us with information that vitamin D3 supplementation should be administered before placentation. [12, 13]

## CONCLUSION

Pregnancy is a multi-factorial process involving a series of interactions occurring on both physiological as well as dynamic and physical changes for both the mother and the developing foetus. The aspect of vitamin D3 metabolism within various observational studies has indicated an important role of vitamin D3 in the maintenance and healthy bodily functioning of the mother and the foetus, it is still better served to use vitamin D3 as a biomarker of disease severity and future work is needed to truly determine the required vitamin D3 levels within all pregnant women taking into account the sedentary and environmental factors which can influence the outcome of pregnancy.

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### Address for correspondence:

Nikolay Lazarov  
Department of Obstetrics and Gynaecology, Medical Faculty, Trakia University, Stara Zagora;  
11, Armejska Street, Stara Zagora, Bulgaria.  
E-mail: [n.lazaroff@gmail.com](mailto:n.lazaroff@gmail.com)