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The Impact of Maternal Vitamin D Levels on Infant Health: A Review Article

Dr. Sahar Mushtaha[1*], Dr. Karman Bahnam Faraj Katay[2]

[1]BDS Dentistry, M.Sc. Ped Dent, JB Ped Dent, Specialist Peadodontist, PHCC- Qatar
[2]MBChB Medicine, Jordanian Board Family Medicine, Specialist Family Medicine, PHCC -Qatar

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***Corresponding author:** Dr. Sahar Mushtaha
BDS Dentistry, M.Sc. Ped Dent, JB Ped Dent, Specialist Peadodontist, PHCC- Qatar

Abstract **Review Article**

Pregnancy is a unique and demanding time in terms of calcium and phosphate metabolism. Studies have shown that prevalence of vitamin D deficiency among pregnant women varies, as being 33% in US, 24% in Canada and 20-77% in Europe. Low maternal levels of vitamin D during pregnancy are associated with many neonatal outcomes, including small for gestational age (SGA), preterm birth, detrimental effect on offspring teeth and bone development in addition to the susceptibility to infectious diseases. ***Background:*** Pregnancy is a unique and demanding time in terms of calcium and phosphate metabolism. Vitamin D is one important for the developmental process and plays a crucial role for mineral balance, with rapidly growing bone susceptible to mineralization defects such as rickets [1]. Vitamin D deficiency has become a global public health issue, especially for pregnant women [2]. Several studies conducted on a large population have evaluated the effect of vitamin D deficiency during pregnancy and relate it to many adverse outcomes for both the mother and the child [3].

Keywords: metabolism, Pregnancy, vitamin D deficiency, small for gestational age (SGA), preterm birth.

INTRODUCTION

Vitamin D is a fat-soluble vitamin and a steroid hormone recognized for its essential but not limited role in calcium metabolism and bone health [4]. Vitamin D is important for other extra-skeletal targets in the body, such as immune system, cardiovascular system, and the muscles [5, 6].

Maternal hypovitaminosis D is considered when maternal 25-hydroxyvitamin D [25(OH)D] levels is <20 ng/ml or <50 nmol/l. Low maternal levels of vitamin D during pregnancy is associated with many neonatal outcomes, including small for gestational age (SGA), preterm birth, detrimental effect on offspring teeth and bone development in addition to the susceptibility to infectious diseases [7]. Conflicting results of different studies have been found; as many observational studies have linked the low vitamin D levels to the increased risk of placental implantation disorders, impaired glucose tolerance, pre-eclampsia and fetal growth retardation and other randomized controlled trials didn't show any association [10-12].

Studies have shown that prevalence of vitamin D deficiency among pregnant women varies, as being 33% in US, 24% in Canada and 20-77% in Europe [8, 9].

A cohort study has been conducted recently in North West England, and it showed that 27% of mothers has insufficient 25(OH) D levels (< 50 nmol/l), and 7% had deficient levels (<25 nmol/l) during pregnancy. Those levels have been dropped in 48% and 11% of the cases, respectively, 4 months after delivery [13].

Vitamin D Plasma Concentrations

The major plasma level form of vitamin D is the one synthetized in the skin as cholecalciferol (vitamin D3) with very limited food resources containing either ergocalciferol (vitamin D2) or cholecalciferol [14]. Exposing skin to ultraviolet B (UVB) light (290-315 nm wavelengths) is required for endogenous synthesis. Genetic factors play a role in vitamin D metabolism, reflected in inter-individual differences in vitamin D/calcium absorption and transport, or genetic polymorphisms of vitamin D receptor [15].

Table 1 Summarize environmental and dietary contributions of vitamin D in humans [16].

Both vitamin D3 and D2 are biologically inactive. They need further enzymatic conversion to their active forms, in which the kidneys play a role in the process, driven by the parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone. The most active form, which is formed by hydroxylation, is the 1.25(OH) 2D (calcitriol) with a half-life of 4-6 hours [17, 18].

Table 1: **Environmental and dietary contributions of vitamin D in humans**

Table 1 Risk factors for low 25OHD concentrations
Risk factors that limit skin exposure to UVB rays
Latitudes above 40° north
Winter season
Exposure in early morning and evening (before 10 AM, after 4 PM)
Cloud cover and atmospheric pollution
Limited time spent outdoors
Customary dress that conceals large portions of the body
Sunscreen use
Dark skin pigmentation
Older age
Risk factors that limit dietary exposure to vitamin D
Low dietary intake of oily fish and egg yolks
Vegetarian diets
Low/no dietary intake of vitamin D fortified foods
Exclusive breastfeeding in infants
No intake of vitamin D supplements
Other risk factors that alter vitamin D supply or metabolism
Vitamin D status of infant depends on vitamin D status of mother during pregnancy
Low dietary calcium intake
Obesity
Genetic factors that affect vitamin D physiology and requirements
Poor renal function
Liver disease and cholestasis
Chronic disease
Malabsorption (coeliac, inflammatory bowel disease, cystic fibrosis, etc.)

Metabolism of Vitamin D in Pregnancy

It is essential to allow the accretion of calcium within the fetal skeleton, particularly in the third trimester, and vitamin D plays an important role in this. An Increase in 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] levels has been reported during early stages of pregnancy, to be doubled by the few weeks before delivery, in order to meet the increased demand of calcium for adequate bone mineral accrual. This process has been suggested to be connected normal immunological adaptations for successful maintenance of pregnancy [19]. In order for a mother to provide the 30 g of calcium required for adequate fetal bone development, maternal intestinal calcium absorption and calcium resorption from bones are increased [20].

Figure 1 schematic summery shows a review of the maternal physiological mechanisms that occur during pregnancy to optimize fetal skeletal development [16].

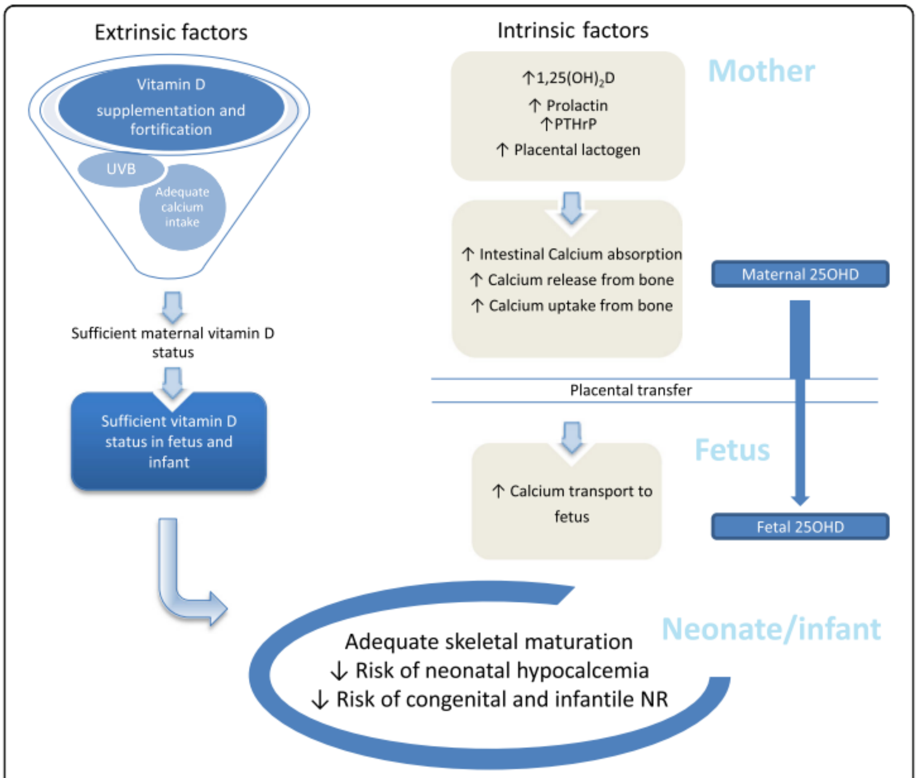

Fig. 2 Schematic representation of some maternal factors and physiological changes during pregnancy that optimize bone health in offspring. Increased calcium transport to fetus and sufficient maternal vitamin D status result in adequate skeletal maturation, decreased risk of neonatal hypocalcemia, and decreased risk of congenital and infantile NR. Maternal 25OHD likely crosses the placenta resulting in fetal levels that approximate maternal levels. $1,25(OH)_2D$, on the contrary, is not thought to cross the placenta. $1,25(OH)_2D$ 1,25-dihydroxycholecalciferol, UVB ultraviolet B, NR nutritional rickets

Figure 1

Vitamin D Deficiency during Pregnancy and Infant outcomes

Many infant related outcomes have been recently studied in relation to maternal vitamin D deficiency during pregnancy, making a daily supplement of 600 IU supplement of Vitamin D in pregnancy essential to ensure sufficient maternal 25(OH)D levels to avoid any complications in infants [21, 22].

Admission to Neonatal Intensive Care Unit (NICU)

Meng Ni *et al.*, (2021) cohort study revealed a strong association between the incidence of newborns admission to NICU and the maternal vitamin D status in the first trimester of pregnancy [23]. Newborns admitted to the NICU were premature or suffering from severe complications such as septicemia, hypoxic-ischemic encephalopathy (HIE), or necrotizing enterocolitis [24].

Maternal low vitamin D level has been associated with increased risk of respiratory tract infections (RTIs) for neonates [7]. It was proposed that vitamin D reduces the risk of RTIs of viral or bacterial origin by modulating the immune response; with a decreased chemokine production, inhibition of dendritic cell activation, and alteration of T-cell mediation [25]. One study conducted in Turkey, on 13 preterm infants diagnosed with respiratory distress syndrome, a total of 31 infants developed bronchopulmonary dysplasia (BPD), all of them had a vitamin D level < 25 nmol/l, with a univariate regression analysis OR of 0.76 for maternal 25(OH)D level [26].

Upala S. *et al.*, (2015) systematic review and meta-analysis showed that vitamin D deficiency is an important risk Factor for sepsis, with a pooled or OF 1-78 (95% ci 1.55-2.03) [27]. Cetinkaya M. *et al.*, (2015) investigated the correlation between maternal and neonatal vitamin D levels and the risk of neonatal sepsis. For the entire group of 50 infants with early onset neonatal sepsis (EONS), the postpartum maternal and neonatal 25(OH) D levels were 56 nmol/l (SD = 17 nmol/l), compared with 91 nmol/l (SD = 5 nmol/l) and 45 nmol/l (SD = 12 nmol/l) respectively for the controls [28]. This was consistent with other study involved 40 infants diagnosed with EONS and 43 controls, which found out that core blood 25(OH)D levels were 32 nmol/l (8-197 nmol/l) for EONS group and 53 nmol/l (13-295 nmol/l) for controls ($P = 0.04$) [29].

Preterm Birth

The incidence of preterm birth is increasing in many counties however, the survival rate for preterm infants has improved dramatically especially in the developed countries [30]. Preterm birth represents a significant cause of death and can lead to serious harm to survivors all around the word [31]. De-Regil L. *et al.*, (2016) meta-analysis confirmed the result of previously conducted RCTs of moderate quality, which reported that vitamin D supplementation during pregnancy compared to those receiving placebo decrease the risk of preterm birth, with an average RR of 0.36 (95% CI 0.14-0.93) [32-35]. Same result was shown in a combined *post hoc* analysis done by Wagner C. *et al.*, (2015) of two studies, in which maternal 25(OH) D levels below 50 nmol/l is associated with increased risk of preterm birth [36]. This association was stronger near the delivery date, indicating optimization of maternal vitamin D levels in the third trimester might be beneficial [36].

Controversial result was shown by Meng Ni *et al.*, (2021), in which no correlation was found between maternal vitamin D status and preterm birth [23]. Same was concluded in the meta-analysis of RCTs examining both vitamin D AND calcium supplementation in pregnant woman, however, these results could be explained by the small sample size of these RCTs [32].

Prematurity also would increase the probability of vitamin D deficiency in infants. Preterm birth amputates the time for adequate transplacental transfer of vitamin D leading to vitamin D deficiency in infants [37]. Preterm infants are born during a phase of rapid growth including rapid bone mineral accretion, as most of the fetal skeletal phosphorus and calcium deposition is accomplished in the third trimester, and so premature infants have low mineral stores [20]. However, multiple observational and interventional studies was reviewed by an international panel of bone experts and found it to be inconclusive [21].

Low Birth Weight / Small for Gestational Age (SGA)

Small of Gestational Age (SGA) is given for infants born smaller in size than normal for the gestational age, most stipulated by a weight less than 10% percentile for the corresponding gestational age [38, 39]. Infants born SGA have much higher neonatal morbidity and mortality [40].

Meta-analysis of observational studies and clinical trials has suggested that vitamin D may have a beneficial effect on fetal growth [41, 42]. Although numerous studies have focused on the association between maternal vitamin D and SGA, the results of these studies remain controversial. A prospective cohort study conducted in Netherlands concluded that infants born to mothers with vitamin D deficiency had an increased risk of being SGA [43]. Consistent result was reported by other study which reported that if the maternal vitamin D level was less than 15ng/mL infants had a significantly higher risk of SGA [44]. Wang H. *et al.*, (2018) indicated that for each 1ng/ml decrease of maternal 25(OH) D, an increase by 19% of risk of SGA is expected [45]. Chen Y. *et al.*, (2017) meta-analysis of prospective cohort studies revealed that maternal vitamin D deficiency during pregnancy was significantly associated with increased risk of infants who are SGA (pooled OR = 1.588; 95% CI 1.138 to 2.216; $P<0.01$) [46].

Although many studies showed the association between maternal vitamin D deficiency and SGA, however, many other studies didn't show consistent results. Roth D. *et al.*, (2018) concluded that maternal vitamin D supplementation from mid-pregnancy till birth or 6 months after birth, in a population with a widespread prenatal vitamin D deficiency, did not improve fetal or infant growth [47]. This result was consistent with earlier high-quality trials [35, 48-50].

Rickets and Hypo-Calcemic Complications

Severe vitamin D deficiency might cause rickets in infants or children. Congenital rickets is defined as the presence of rickets in the first month of life [21]. Nutritional rickets is a pediatric condition where chondrocyte differentiation and bone mineralization at the growth plates are defective and can lead to short stature and skeletal deformities [21, 51]. Consequences of rickets extend beyond bone; as rickets related hypocalcemia can lead to seizures, tetany, generalized weakness, cardiomyopathy, and raised intracranial pressure, all of which can have devasting consequences [16]. Many interventional and observational studies reported an association between low maternal vitamin D status and abnormal infant outcomes such as elevated blood alkaline phosphatase [52], larger fontanelle size at birth [53], and neonatal hypocalcemia [53-56].

Even term infants remain at risk for nutritional rickets and vitamin D deficiency. One liter of breast milk contains a maximum of 25 IU vitamin D [57], well below the intake levels necessary to prevent nutritional rickets. Mothers with additional risk factors, who exclusively breastfeed, are particularly at risk of having an infant with symptomatic vitamin D deficiency [58-60]. Even infants on formula feeding can remain at risk for nutritional rickets if they are born from 25(OH) D deficient mothers and/or consume less than 1 liter of formula per day [1, 61].

Infant Ora Health

Early Childhood caries (ECC) is a multifactorial disease, influenced by environmental factors, such as dietary intake, oral microbiome, and social determinants of health [62, 63]. Prenatal Vitamin D deficiency has been identified as a possible risk factor for ECC. Tooth mineralization process occurs parallel to skeletal mineralization, yet if mineral metabolism is disturbed then failures will occur similarly to those that occur in bone tissue. Cockburn F. *et al.*, (1980) reported that 400 IU daily supplement of vitamin D during pregnancy was significantly associated with a lower prevalence of enamel defects [64]. Schroth R *et al.*, (2014) were the first who demonstrated that infants with ECC have lower prenatal 25(OH) D levels [65]. This was consistent with a recent observational study which identifies that; participants with mothers who has 25(OH) D insufficiency during the third trimester of pregnancy had over three times the rate (IRR 3.55) of dental caries at age 6, compared to children whose mothers has sufficient levels of vitamin D during pregnancy [66].

Adequate Maternal Vitamin D Levels

Hollis *et al.*, (2011) randomized controlled trial showed the effectiveness of vitamin D supplementation during pregnancy starting from week 12 of gestation until delivery. Pregnant women received 400, 2000, or 4000 IU vitamin D, results showed vitamin D levels ≥ 80 nmol/l in 50%, 71%, and 82% nmol/l respectively, and these levels were significantly correlated with neonatal vitamin D levels; and so the authors suggested vitamin D supplements in pregnant women of all race should be raised to 4000 IU in order to stabilize maternal vitamin D level up to 100 nmol/l [50]. Despite these results, it is more appropriate to provide the suitable dose of supplementation based on the local climate for that particular population, keeping in mind that doses up to 4000 IU could be appropriate in profound hypovitaminosis D [67].

The global consensus on nutritional rickets strongly recommended that levels between 40-50 nmol/l were insufficient. In order to prevent nutritional rickets, it is important to maintain 25(OH) D levels beyond 50 nmol/l to counteract the plunge seen with seasonal variations. So it is recommended that all pregnant women should receive 600 IU daily of vitamin D supplement to prevent both neonate and infant biochemical and radiographic signs of nutritional rickets [21]. This coincides with the recommendations from American College of Obstetrics and Gynecologists [68], National Institute for Health and Care Excellence [69], and Institute of Medicine [22] that also recommend vitamin D supplementation during pregnancy.

DISCUSSION

Vitamin D plays an essential role for the development in infants and children. Children and pregnant women are vulnerable for vitamin D deficiency. Many studies revealed how low 25(OH) D levels during pregnancy affects the infant health with a severe outcome in some cases, and so vitamin D supplementation as recommended is a convenient and effective way to reduce the incidence of such unfavorable outcomes.

CONCLUSION

Pregnancy is a unique and demanding time in terms of calcium and phosphate metabolism. Studies have shown that prevalence of vitamin D deficiency among pregnant women varies, as being 33% in US, 24% in Canada and 20-77% in Europe. Low maternal levels of vitamin D during pregnancy are associated with many neonatal outcomes, including small for gestational age (SGA), preterm birth, detrimental effect on offspring teeth and bone development in addition to the susceptibility to infectious diseases.

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