Chapter

Vitamin D Deficiency in Pregnant Women and Newborn

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Abstract

Vitamin-D is not only an essential element in bone health, but it is also a pro-hormone. Deficiency of vitamin D is the most common cause of rickets and is also known to increase the risk of respiratory distress syndrome, lower respiratory infections, food sensitivities, asthma, type I diabetes, autism and schizophrenia. Vitamin D deficiency limits the effective absorption of dietary calcium and phosphorus. Vitamin D status in newborns is entirely dependent on maternal supply during pregnancy. Low maternal vitamin D status during pregnancy is a major risk factor for rickets in infants. Rickets in children is caused by severe, chronic vitamin D deficiency with apparent skeletal abnormalities, but neonates with vitamin D insufficiency have no overt skeletal or calcium metabolism defects. Rickets was a global disease in the early twentieth century. It has nearly disappeared in developed countries after its causal pathway was understood and fortification of milk with the hormone vitamin D was introduced at the population level. Surprisingly, rickets is re-emerging per recent evidence. Vitamin D deficiency is prevalent in both developed and developing countries. The chapter will review the prevalence of vitamin D deficiency in pregnant women and newborn population and its adverse effects on pregnancy and infant's health. The chapter also describes evidence-based recommendations to prevent vitamin D deficiency in these vulnerable population.

Keywords: Vitamin D, deficiency, newborn, preterm, rickets, pregnancy

1. Introduction

Vitamin D is a fat-soluble secosteroid. It is a prohormone that can be ingested or derived from body sterols by the photolytic activity of ultraviolet rays on human skin. Vitamin-D is not only an essential element in bone health, but it is also a pro-hormone that plays a well-recognized role in other organs of body. Vitamin D deficiency is a worldwide health issue that affects more than one billion children and adults globally [1]. Vitamin-D deficiency in neonates has been linked to higher risk of respiratory distress syndrome, lower respiratory infections, food sensitivities, asthma, type I diabetes, autism and schizophrenia [2–9]. Serum 25-hydroxycholecalciferol (25[OH]D) is the main circulating metabolite of vitamin D with a reported half-life of approximately three weeks [10]. It is the best estimator of human body vitamin D stores. During pregnancy it crosses the placenta through passive or facilitated transport according to a concentration gradient [11, 12]. Vitamin-D status in the fetus and newborn infant is largely determined by maternal vitamin-D status [11]. The main risk factor for vitamin-D deficiency in neonates

is maternal vitamin-D deficiency [13]. Rickets was a global problem in the early 20th century. It virtually disappeared in developed countries after its causal pathway was identified and fortification of milk with vitamin-D was implemented at population level [14]. Recent reports have suggested that rickets is re-emerging [15, 16] and vitamin-D deficiency is widespread in developed and developing countries [15, 17–21]. Globally, vitamin-D deficiency at birth is prevalent and in general reflects deficient maternal vitamin-D status [10, 22–24].

2. Vitamin D metabolism and biological functions

Vitamin D is unique among vitamins because it can be made in the skin from sunlight exposure. Vitamin D has two forms: Ergocalciferol (D_2) and Cholecalciferol (D_3). D_2 is produced from ultraviolet irradiation of the yeast sterol ergosterol and is naturally found in sun-exposed mushrooms. D3 is synthesized in the skin from the cholesterol precursor 7-dehydrocholesterol which is naturally present in the skin or obtained from lanolin [25]. Vitamin D (in the form of D_2, or D_3, or both) that is ingested is assimilated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood. Vitamin D that comes from the skin or diet is biologically inert and needs its first hydroxylation in the liver by the vitamin D-25-hydroxylase to 25[OH]D [25, 26]. 25[OH]D undergoes a second hydroxylation in the kidneys by the 25[OH]D-1α-hydroxylase to form the biologically active form of vitamin D 1,25$[OH]_2$D (3, 8). 1,25$[OH]_2$D interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues [25, 26].

1,25$[OH]_2$D plays a main physiological role in bone hemostasis. It stimulates intestinal calcium absorption [27]. Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40% and 80%, respectively [25, 28]. 1,25$[OH]_2$D interacts with its vitamin D receptor in the osteoblast to stimulate the expression of receptor activator of nuclear factor κB ligand; this, in turn, interacts with receptor activator of nuclear factor κB to induce immature monocytes to become mature osteoclasts, which dissolve the matrix and mobilize calcium and other minerals from the skeleton. In the kidney, 1,25$[OH]_2$D stimulates calcium reabsorption from the glomerular filtrate [25, 29].

The strong correlation between maternal and infant 25[OH]D levels offers further evidence that newborn 25[OH]D levels are dependent on maternal plasma 25[OH]D levels [12, 30, 31]. There is no clear consensus on the cut off levels of serum 25[OH]D levels to define vitamin deficiency. The US Endocrine Society has categorized vitamin D deficiency as 25[OH]D < 20 ng/mL, vitamin D insufficiency as levels 21–30 ng/mL, sufficiency as levels greater than 30 ng/mL, and toxicity as vitamin D levels more than 150 ng/mL [32]. The American Academy of Pediatrics (AAP) and Institute of Medicine define vitamin D deficiency as serum 25[OH] D < 15 ng/mL, mild to moderate deficiency as 5–15 ng/mL, severe deficiency as levels less than 5 ng/mL, and insufficiency as 16–20 ng/mL. They define sufficiency as levels between 21 and 100 ng/mL, excess as 101–149 ng/mL, and intoxication as levels more than 150 ng/mL [33]. The Kidney Disease Outcome Quality Initiative supports the AAP in defining vitamin D deficiency as levels <15 ng/mL. However, it defines insufficiency as levels between 16 and 30 ng/mL and sufficiency as levels of more than 30 ng/mL. An expert committee of the US Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that people are at risk of vitamin D deficiency at serum 25[OH]D concentrations less than 12 ng/mL. The same cutoffs were used for both pregnant

women and neonates, because experts contend that there is no reason to think the definition of vitamin-D sufficiency varies by age [16].

3. Prevalence of vitamin D deficiency in pregnant women

3.1 Developed countries

An US survey from National Health and Nutrition Examination Survey (NHANES) 2011–2014 on serum 25[OH]D levels found that 5.7% women had vitamin D deficiency (<12 ng/ml) and 17.8% women had vitamin D insufficiency (12–20 ng/mL). Rates of deficiency and insufficiency were 7.6% and 23.8% respectively in adults aged 20–39 years. Rates of deficiency varied by race and ethnicity: 17.5% of non-Hispanic Blacks, 7.6% of non-Hispanic Asians, 5.9% of Hispanics, and 2.1% of non-Hispanic White people were at risk of vitamin D deficiency respectively. Vitamin D status in the United States remained stable in the decade between 2003 and 2004 and 2011–2014 [34].

Boston's cross-sectional study from 2005 to 2007 reported vitamin-D deficiency (25[OH]D < 20 ng/mL) in 35.8% of the mothers and 58% of the neonates, severe deficiency (25[OH]D < 15 ng/mL) in 23.1% of the mothers and 38.0% of the neonates. Risk factors for neonatal vitamin-D deficiency included maternal deficiency (adjusted odds ratio [aOR]: 5.28 [95% CI: 2.90–9.62]), winter birth (aOR: 3.86 [95% CI: 1.74–8.55]), African-American (AA) race (aOR: 3.36 [95% CI: 1.37–8.25]), and maternal body mass index of 35 (aOR: 2.78 [95% CI: 1.18–6.55]) [31].

A Canadian study found a prevalence of 25% vitamin D insufficiency (defined as serum 25-[OH]D < 40 nmol/L) in women aged 18–35 years during the winter season [17]. Vitamin D deficiency is also common in Europe and the Middle East. Vitamin D deficiency defined as serum 25[OH]D < 50 nmol/L or 20 ng/mL, occurs in 6–33% of the population in Northern Europe, in 30–60% in Western, Southern and Eastern Europe and 30–90% in the Middle East countries. Severe deficiency (serum 25(OH)D < 30 nmol/L or 12 ng/mL) is found in >10% of Europeans [35]. Vitamin D deficiency is usually is more prevalent in immigrants from non-Western countries, compared with native European people [36]. This is even worse in pregnant non-Western immigrants, who displayed mean serum 25(OH)D levels around 25 nmol/L [37].

3.2 Developing countries

The major proportion of vitamin D is produced endogenously with skin exposure of the skin to sunlight. In tropical areas like India, Africa and middle east, where there is abundant overhead sun for most or all of the year, deficiency of vitamin D is unexpected. However, despite stable and sufficient sun exposure in countries across equator, high prevalence of vitamin D deficiency in pregnancy ranging 26–95% in such areas was reported [38]. In Africa, Asia and the Middle East, women have been always regarded as "high risk" for vitamin D deficiency [39, 40]. In 2009, the International Osteoporosis Foundation reported that vitamin D deficiency was seen in 84% of pregnant women and 96% of infants in Asia [41]. In India, 50–90% of the population suffers from vitamin D deficiency due to inadequate exposure to sunlight and a lower dietary intake [42–44]. A recent study from northern India reported the prevalence of vitamin D deficiency in 85.5% of mothers and 74% of infants [45]. Vitamin D deficiency, defined as <50 nmol/L of 25[OH]D and severe vitamin D deficiency defined as <30 nmol/L of 25[OH]D was reported in 34% and 18% of the population respectively in African countries [46].

Vitamin D deficiency is even worse in mainland China with deficiency seen in 72% and severe deficiency seen in 37% of pregnant women [47].

4. Effects of vitamin D deficiency on pregnancy

Despite the wide intake of prenatal vitamins, Vitamin D deficiency in pregnancy is still common worldwide. The adverse outcomes of pregnancy secondary to vitamin D deficiency include miscarriages, preeclampsia, intrauterine growth restriction (IUGR), increased risk for gestational diabetes, preterm birth and low birth weight infants [48–50]. Vitamin D deficiency in pregnant women may affect fetal growth, tooth enamel formation and bone ossification [13]. Decreased vitamin D levels in general is associated with increased mortality and vitamin D supplementation reduces mortality [51]. The reasons behind increased mortality include diabetes mellitus, cardiovascular disease and cancer [52]. Vitamin D deficiency has been associated with several autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Hashimoto Thyroiditis (HT), and multiple sclerosis (MS). Autoimmune diseases are more commonly seen in females than males. Pregnant women with these autoimmune disorders are at increased risk for poor pregnancy outcomes [48, 53].

Animal studies showed that vitamin D deficiency causes placental inflammation which leads to placental insufficiency and potentially fetal IUGR [53]. In both pregnancy and lactation it is important to have adequate vitamin D levels to avoid disturbances in bone and mineral metabolism [54]. The fetal and neonatal status of vitamin D is entirely dependent on the mother's vitamin D levels. This confirms the correlation of mother and cord blood 25[OH]D concentrations. While 25[OH]D crosses the placenta, 1,25[OH]2D is produced by the fetal kidneys [54]. Research regarding the exact physiological role of vitamin D in pregnancy and lactation is ongoing. There is convincing data that vitamin D is important for the immunomodulation of the maternal-fetal interface [54–58]. Vitamin D is also crucial for the prevention of pre-eclampsia by stabilizing the endothelium through non-genomic mechanisms [54]. Other functions of vitamin D may include stimulation of sex hormone secretion, implantation/placentation and respiratory epithelium maturation. Vitamin D may also induce epigenetic changes in expressing vitamin D receptors and enzymes involved in vit D metabolism throughout the male and female reproductive tracts [54–58].

5. Etiology of vitamin D deficiency in pregnant women

Vitamin D deficiency is prevalent worldwide in pregnant women and infants. In pregnancy, maternal vitamin D physiology is altered to facilitate the transfer of calcium to the fetus. In pregnancy there is a significant increase in 1,25[OH]2 D concentrations with a two-fold increase in the first trimester followed by a 2–3-fold increase during the second and third trimesters of pregnancy. Then there is a rapid decrease after delivery. PTH-related peptide may also regulate serum 1,25[OH]2D concentrations in pregnancy. 1,25[OH]2D synthesis is dependent up the levels of 25[OH]D. There is a positive correlation between serum 1,25[OH]2D and 25[OH]D concentrations and it is stronger in pregnant women compared to non-pregnant women [54].

Eating foods fortified with vitamin D as well as adequate exposure to sunlight are needed for upholding a normal vitamin D status. The most common reasons for vitamin D deficiency are low sun exposure, decreased vitamin D intake, obesity,

and low socio-economic conditions. Various factors influence vitamin D synthesis from sunlight, such as latitude, pigmentation, and area of skin exposed. Many prevalent social and cultural practices in Asia and middle east that prevent the adequate exposure of young women and adolescent girls to sunlight contribute to vitamin D deficiency [59]. Increasing urbanization resulting in greater pollution and decreased time spent outdoors coupled with greater skin pigmentation contribute to vitamin D deficiency [60]. When women in these circumstances become pregnant with already low serum 25 [OH]D levels, this contributes to vitamin D deficiency or insufficiency in their offspring. These children at increased risk for developing rickets [49]. Furthermore, vitamin D supplementation is not part of antenatal care programs in developing countries like India [59].

Diets low in vitamin D are more common in people who have milk allergy or lactose intolerance and those who consume an ovo-vegetarian or vegan diet. Women who are homebound, have occupations that limit sun exposure, or who wear long dresses, robes, or head coverings for religious reasons are at risk for vitamin D deficiency due to limited exposure to sunlight [61]. The use of sunscreen also limits vitamin D synthesis from sunlight. Obese women have lower vitamin D levels than nonobese individuals. The skin's capacity to produce vitamin D is not affected by obesity. In fact, thick subcutaneous fat sequesters more of vitamin D [62, 63]. Serum levels transiently increase following weight loss possibly due to the release of vitamin D in the circulation. This was noted in obese patients after roux-en-y gastric bypass surgery as well as patients with non-surgical weight loss. However, 1 year after a Roux-en-y gastric bypass surgery, vitamin D levels returned to baseline values [64]. Finally, since vitamin D is fat soluble, its absorption is poor in individuals with fat malabsorption disorders like celiac disease, cystic fibrosis, ulcerative colitis and Crohn's disease [65].

6. Prevalence of vitamin D deficiency in newborn

Due to the bone deposition that mostly occurs in the latter half of the pregnancy, vitamin D requirements for the fetus are higher at this time frame [66]. In early pregnancy the plasma levels of 1,25(OH)2D increase and peak in the third trimester. It is estimated that the fetus accumulates 2–3 mg/day of calcium in the skeleton in the first trimester. This calcium accumulation doubles in the third trimester [67]. When infants are born prematurely, the time required for this transfer of Vitamin D and calcium is truncated [68].

Saraf and et al. conducted a global summary and systematic review of maternal and newborn vitamin D status by looking at studies published between 1959 and 2014. They found that 75% of newborns had vitamin D deficiency (defined as 25[OH]D level < 50 nmol/L) and that severe vitamin D deficiency (defined as 25[OH]D level < 25 nmol/L) occurred in 29% of newborns. In this summary, the average newborn 25[OH]D levels in nmol/L by region is as follows: 35–77 (Americans), 20–50 (European), 5–50 (Mediterranean), 20–22 (South-East Asia), 32–67 (Western Pacific) and 27–35 (African). They also found wide variability in 25[OH]D levels within in each defined region [24]. Both this study and another systemic review by Hilger and colleagues found that the average 25[OH]D levels in the general populations in North America were higher compared to Europe and the Middle East [69]. Furthermore, two other reviews found that vitamin D deficiency and severe vitamin D deficiency were more common in South-East Asia and the Eastern Mediterranean regions for newborns [41, 70]. Racial disparity in serum 25[OH]D levels has been well documented in several studies. AA preterm infants and their mothers have lower serum 25[OH]D levels compared to white infants [71–73].

Seto and colleagues measured cord blood 25 [OH]D levels in 276 AA term infants and 162 term white infants and found that AA infants had a 3.6 greater adjusted odds of vitamin D deficiency [74].

Currently, there continues to be emerging information on the distribution of 25[OH]D levels in preterm neonates. A few studies have documented 25[OH]D levels from neonates at birth with sample sizes ranging from 8 to 278 neonates [2, 75–80] with mean 25[OH]D levels ranging from ~6.5 ng/mL among preterm neonates in the United Arab Emirates [78] to 26.8 ng/mL preterm neonates in Canada [10]. A recent study on 596 preterm infants from Ohio, USA reported median 25[OH]D level of 18.5 ng/mL for infants born at 34–36 weeks and 18.6 ng/mL for infants born <32 weeks [81].

The levels of 25[OH]D between the mother and the fetus are positively correlated [68, 81, 82]. Kassai et al. found that mothers who gave birth to preterm neonates had significantly lower mean 25[OH]D blood levels compared to those mothers who gave birth at term. Also, preterm neonates had significantly lower 25[OH]D levels compared to term neonates [83]. A study by Burris et al. measured umbilical cord plasma levels of 25[OH]D in 471 infants born at <37 weeks. They found that babies born at <32 weeks are at increased risk for vitamin D deficiency (25[OH]D levels <20 ng/dL) compared to infants born between 32 and 37 weeks [79]. Monagni et al. studied 120 mother infant dyads at three children's hospitals in Ohio where neonates were delivered at <32 weeks. They not only found that low serum concentrations of 25[OH]D (defined as <50 nmol/L) was common in preterm neonates at admission (64%), but they also found that maternal 25[OH]D levels were lower in infants born at <28 weeks compared to those that were born between 28 and 32 weeks' gestation. Serum 25[OH]D concentrations in preterm infants directly correlated with maternal vitamin D status at the time of delivery. Low 25[OH]D levels were noted at either 36 weeks post-menstrual age (PMA) or at discharge in 40% of infants <28 weeks and 30% of infants between 28 and 32 weeks PMA. Even though infants received vitamin D supplementation from various sources and intake progressively increased during their hospitalization, only 60% received 400 IU vitamin D daily by 36 weeks PMA or discharge [68].

In contrast to the above studies, a Canadian study and an US study did not show any significant difference in vitamin-D status between term and preterm neonates [10, 81]. A study of 3731 term infants in Jordan revealed that 94% had vitamin D deficiency defined as 25[OH]D level < 50 nmol/L. Shahraki et al. found that 25[OH]D levels in preterm neonates were not significantly lower than term neonates. Over 50% of both the term and preterm infants in this study had vitamin D insufficiency and about 25% had vitamin D deficiency [82]. In a cohort born in Cleveland area in US (latitude 41^0N), Kanike et al. reported a remarkably high proportion of vitamin-D deficiency and insufficiency among neonates at birth, 31% and 49% respectively. Notably, they noted low stores of vitamin D despite 75% of women reporting regular multivitamin intake during pregnancy. Vitamin D deficiency was found to be more common in AA neonates (63%) than Caucasian (27%) neonates [81]. Bodnar et.al studied 400 mother–infant pairs in Pittsburgh. They showed that nearly 50% of AA neonates and 10% of white neonates, had serum 25[OH]D levels at birth less than 15 ng/mL despite adequate compliance with a 400 IU daily vitamin-D intake by 90% of their mothers [22]. A prolonged winter season with limited sun exposure in Cleveland might be a contributing factor to the vitamin-D deficiency found in this population. There has been no significant improvement in the vitamin-D status among neonates born to AA women in the last 3 decades in Cleveland area [12].

7. Consequences of vitamin D deficiency in children

Vitamin-D deficiency is the most common cause of rickets and also increases the risk of respiratory distress syndrome, lower respiratory infections, food sensitivities, asthma, type I diabetes, autism and schizophrenia [2, 3, 6, 8, 15]. Vitamin D deficiency in pregnancy impairs fetal lung development partially through suppressing type II pneumocyte differentiation increasing the risk of respiratory distress syndrome in the newborn period [84]. Furthermore, studies have shown that early onset sepsis and late onset sepsis occurs more frequently in term infants with vitamin D deficiency [85–87]. To highlight, one study by Singh and Chaudari found that vitamin D deficiency was more common in neonates with early onset sepsis and was associated with increased severity of sepsis and mortality [87].

Vitamin D deficiency prevents effective absorption of dietary calcium and phosphorus. Vitamin D stores in newborn are completely dependent on vitamin D supply from the mother [12]. Not surprisingly, poor maternal vitamin D status during pregnancy is a major risk factor for infant rickets [13, 88, 89]. Severe chronic vitamin D deficiency leads to overt skeletal abnormalities in children like rickets [90, 91]. However, neonates who are vitamin-D insufficient have no apparent skeletal or calcium metabolism abnormalities [16]. In developing countries rickets has been ranked among the five most prevalent diseases in children [92]. Poorer outcomes during pregnancy, at birth and during infancy are associated with lower serum 25[OH]D levels [24, 93]. Reduced bone mass at 9 years of age was seen in children born with low serum 25[OH]D concentrations [94].

There is conflicting data about role of vitamin D and neurodevelopmental outcomes. A meta-analysis by Tous and colleauges found that infants born to mothers with vitamin D insufficiency had lower scores in both mental and language development [95]. In contrast, Wang et al. found that vitamin D deficiency was not associated with neurodevelopment in infancy [84]. A prospective cohort study by McCarthy et al. found no association between antenatal 25[OH]D levels and neurodevelopmental outcomes at 5 years. Tous et al. found that maternal vitamin D deficiency is associated with lower birth weights, smaller head circumference, increased risk for small for gestational age (SGA) status, and preterm birth. Maternal vitamin D insufficiency was associated with increased risk for infants with SGA status and preterm birth [95]. Seto and colleagues found that black infants with vitamin D deficiency had 2.4 greater adjusted odds for SGA status at birth. The association between SGA and vitamin D deficiency was not demonstrated in white infants [74]. Furthermore, a systematic review by Pligt et al. found the maternal vitamin D deficiency was associated with low birth weight, SGA status at birth, stunting of growth immediately after delivery, and preterm birth [96].

8. Recommended dietary intake in pregnant women and Newborn at risk for vitamin D deficiency

As per the US federal government's 2020–2025 guidelines, fortified foods and dietary supplements are beneficial when it is impossible to meet needs for one or more nutrients during certain life stages such as pregnancy. Milk, many ready-to-eat cereals, and some brands of yogurt, orange juice and margarines are fortified with vitamin D. Trout, tuna, salmon, and mackerel are fatty fish with a high content of vitamin D. One tablespoon of cod liver oil has 1360 IU of vitamin D. Cheese, beef liver and egg yolks naturally contain small amounts of vitamin D. The United States

and Canada mandates the fortification of infant formula with 1–2.5 mcg/100 kcal (40–100 IU) vitamin D and 1–2 mcg/100 kcal (40–80 IU) respectively.

Global consensus recommendations on prevention and management of nutritional rickets states that pregnant women should receive 600 IU/d of vitamin-D, preferably as a combined preparation with other recommended micronutrients such as iron and folic acid [97]. The Endocrine Society clinical practice guidelines also recommend at least 600 IU/d of vitamin D in pregnant and lactating women. They also recognize that 1500–2000 IU/day of vitamin D may be needed to maintain 25[OH]D levels>30 ng/mL [32]. However, the average prenatal supplements contain only 400 IU of vitamin D [97]. There is also mounting evidence of the importance of vitamin D supplementation to achieve serum 25[OH]D level of ≥40 ng/ml [55].

Rostami et al. evaluated the effectiveness of a prenatal screening study for optimizing vitamin-D status during pregnancy. The outcome of this program was the prevention of complications of pregnancy. They observed a > 25-fold increase in the number of pregnant women who were able to accomplish a 25[OH]D that was >20 ng/mL when they were screened for their vitamin-D status and provided supplementation compared with pregnant women who were not screened and consequently were not counseled to take vitamin-D supplements. They observed an outstanding decrease in adverse outcomes in pregnant women who were screened and received vitamin-D supplementation. They reported 60%, 50%, and 40% decreases in preeclampsia, gestational diabetes, and preterm delivery, respectively [98].

A recent Cochrane review on Vitamin D supplementation in pregnancy included 30 clinical studies on 3700 pregnant women and reported that taking vitamin D supplements in pregnancy probably reduces the risk of pre-eclampsia, gestational diabetes, post-partum hemorrhage and low-birthweight infant, but there was no difference in the risk of preterm birth before 37 weeks. They also reported that taking vitamin D and calcium together in pregnancy may increase the risk of preterm birth. These results warrant further research [99]. Prenatal supplementation with 4400 IU daily decreased the incidence of asthma and recurrent wheezing in these children at age 3 years by 6.1% [100].

In the 2020 WHO guidelines, routine oral supplementation of vitamin D is not recommended for pregnant women to improve maternal and perinatal outcomes. Pregnant women should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet. Pregnant women should be advised that sunlight is the most important source of vitamin D. The amount of time needed in the sun is not known and depends on many variables, such as the amount of skin exposed, the time of day, latitude and season, skin pigmentation and sunscreen use. For pregnant women with suspected vitamin D deficiency, vitamin D supplements may be given at the current recommended nutrient intake of 200 IU per day. This may include women in populations where direct sun exposure is limited.

9. Conclusion

Vitamin D status is more significant during pregnancy, affecting not only the mother but also her growing fetus, and later, her growing child. There are variations in vitamin D status based on gestation at birth, global region of birth, race, and maternal vitamin D status during pregnancy. The current literature suggests that neonates are at high risk of vitamin-D deficiency, even when mothers are compliant with prenatal vitamins. Current prenatal vitamins may not contain enough vitamin-D to prevent deficiency. There has been substantial debate surrounding

the daily requirement of vitamin D and what constitutes sufficiency during pregnancy. Higher-dose supplementation may be needed to improve maternal and neonatal vitamin-D status. Future multicenter studies are needed to determine the minimum dose of vitamin-D requirements during pregnancy to achieve vitamin-D sufficiency. It is time to rethink our approach to ensure vitamin-D sufficiency in pregnant women and their newborn infants.

Conflicts of interest statement

The authors have indicated no financial relationships relevant to this article to disclose. The authors have indicated they have no potential/perceived conflicts of interest to disclose.

Author contributions

N.K and J.C conceptualized and drafted the initial manuscript and reviewed and revised the manuscript. N.KG reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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