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Chapter

Maternal Vitamin D Status among Different Ethnic Groups and Its Potential Contribution to Adverse Pregnancy and Child Outcomes

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Abstract

Maternal vitamin D deficiency in pregnancy is a widespread public health concern. Race and ethnicity as biological and cultural factors, respectively, can affect vitamin D status through differences in skin color, sunlight exposure, and dietary intake. Low maternal vitamin D status in pregnancy may affect both mother and fetus adversely. Vitamin D deficiency and insufficiency are linked to a wide variety of adverse pregnancy outcomes such as gestational diabetes, preeclampsia, and preterm delivery. Furthermore, maternal vitamin D deficiency has been linked to several adverse health outcomes in infants and children. The examples include, but not limited to, impaired growth, skeletal problems, and autoimmune diseases such as type 1 diabetes and asthma. This chapter reviews the vitamin D status during pregnancy across different ethnic groups, looking into the adverse pregnancy and child outcomes, followed by a discussion on the association between maternal and child vitamin D status and successful interventions. Strong evidence exists about the association between vitamin D and some health outcomes during pregnancy, while more studies are needed to confirm the other claim. The existing body of evidence justifies the need for well-designed policies and systematic interventions to ensure optimal vitamin D status of pregnant women and their offspring across different ethnic and racial groups.

Keywords: vitamin D, pregnancy, ethnicity, child, deficiency

1. Introduction

The calciotropic role of vitamin D is well known from the early twentieth century. The recent advances in research opened a new perspective about vitamin D as prohormone with receptors in most tissues of the human body [1, 2]. This indicates additional non-calciotropic effects of vitamin D, such as its role in autoimmunity, chronic disease, infectious diseases, mental health issues, etc. [2]. However, the current dietary recommendations are based on only calciotropic effects of vitamin D although recent studies suggest that higher intakes are required to achieve the optimal vitamin in D status for both calciotropic and non-calciotropic benefits of vitamin D [2].

Pregnancy is a unique stage of life for women when the normal physiology of mother is changing in order to provide the nutritional needs for the growing fetus [3]. Those changes influence the vitamin D hemostasis and availability for the mother and the fetus. In this chapter, we provide an overview of the evidence about vitamin D metabolism during pregnancy, the association between maternal vitamin D status and pregnancy, fetal and postnatal outcomes. Further, we provide insight into the current recommendation for vitamin D intake to achieve optimal vitamin D status and the associated factors, particularly race and ethnicity. Finally, we review the existing policies and practices to assure optimal vitamin status in pregnant women and their offsprings.

2. Vitamin D metabolism during pregnancy

Vitamin D homeostasis is altered during pregnancy in order to provide a successful delivery and optimal environment for the growth of the fetus. This section focuses on adaptive changes of vitamin D during pregnancy as a background for developing pregnancy and fetal related disorders.

Major vitamin D adaptations in pregnancy include: (1) maternal increase of calcitriol; (2) availability of maternal 25(OH)D for optimal neonatal 25(OH)D; (3) increased concentration of maternal vitamin D-binding protein (VDBP) and placental vitamin D receptor (VDR); and (4) increased activity of renal and placental 25(OH)D-1-α-hydroxylase (CYP27B1) [4, 5]. The first change is started in the first trimester, increasing the level of calcitriol in systemic circulation and placenta to 100–200% by the end of the third trimester [6]. It is originated mostly from the kidneys for the purpose of increased intestinal calcium absorption during pregnancy [7]. In fact, the activity of 1α hydroxylase increases while catabolism of calcitriol decreases leading to more intestinal calcium absorption and immune adaptation [8]. The additional contributors of increased maternal and placental calcitriol are prolactin, calcitonin, PTH-related peptide (PTH-rP), estradiol, placental lactogen [9], IGF-1 [10], and FGF23 [11]. Any dysregulation causing activation decrease and catabolism increase of 25(OH)D may lead to preeclamptic mothers, which will be discussed in this chapter [12].

The second adaptation is likely that the levels of 25(OH)D in cord blood are reduced on average 25% in comparison with maternal 25(OH)D [13]. Maternal 25(OH)D concentration remains constant during pregnancy, meaning that the increased level of calcitriol is not related to its precursor synthesis. Maternal 25(OH)D crosses the placenta barrier as the main source of vitamin D in the fetus [14]. Therefore, vitamin D insufficiency in pregnant mothers could affect the fetus. Other factors, including lifestyle, place of living, skin pigmentation, sunshine exposure, and obesity, contribute significantly to maternal vitamin D status during pregnancy [4]. Consequently, a low level of maternal vitamin D leads to impaired fetal 25(OH)D at birth.

The third adaptation is a 40–50% increase in the concentration of VDBP in both systemic circulation and placenta level compared to the non-pregnant woman reaching to a maximum level at the beginning of the third trimester, before starting to decrease by the end of gestation. This leads to a consistent decrease of free 25(OH)D from 15 to 36 weeks, since there is an inverse relationship between free 25(OH)D and VDBP concentration [15]. The mechanism has not fully understood, although studies suggested the high turnover rate of trophoblasts that are in contact with maternal blood directly leads to the increased expression of VDBP on the cell-surface of human placental trophoblasts during normal human pregnancy [16]. Studies conducted by Ma et al. and Liong et al. indicated that VDBP impairment,

either increase or decrease of its concentration, can contribute to the pathogenesis of preeclampsia (PET) and preterm birth [16, 17].

The placenta is an important organ playing a pivotal role in the optimal embryonic improvement and healthy pregnancy. Placenta regulates vitamin D metabolism by its own mechanism [18]. In fact, 1-α-hydroxylase, 24-hydroxylase, VDBP, and VDR have all been detected in trophoblast cultures and in placenta tissue, resulting in local synthesis of $1,25(OH)_2D$ in the maternal-fetal interface as extrarenal calcitriol. Moreover, in the placenta, VDR gene expression is higher within the first and second trimester compared to term placentas [19] and positively associated with transferring of calcium from mother-to-fetal. This indicates that VDR-dependent mechanisms in the placenta can affect fetal skeletal growth [20]. Vitamin D2 is metabolized in the placenta as well [21]. Thus, the placenta has its own mechanism in the regulation of vitamin D metabolism.

Increased 1, 25(OH)D is attributed to the higher activity of CYP27B1 in maternal, kidney, placental trophoblasts, and decidua during pregnancy [22]. The mechanism by which CYP27B1 activity increases in pregnancy remains unclear. However, it has been suggested that PTH analog PTH-related peptide (PTH-rP), synthesized by fetal parathyroid and placenta, could be a potential regulatory factor for CYP27B1 and augments during pregnancy [23].

Vitamin D metabolism manifests significant changes in pregnant women compared to the non-pregnant state. In an optimal ongoing pregnancy, there are three striking alternation within a gestation; two-fold increase of calcitriol in the first trimester, versus about 25% reduction in the levels of 25(OH)D in cord blood as it crosses the placenta barrier and increase the expression of vitamin D receptor and regulatory metabolic enzymes in the placenta. Also, maternal increase of serum calcitriol and VDBP without changes in 25(OH)D and calcium concentration of mother indicates that neonatal vitamin D stores are dependent on maternal vitamin D status.

3. Current vitamin D intake recommendation guideline during pregnancy

The role of vitamin D intake in pregnancy and its consequences for fetal growth is the focus of current attention. The previous Dietary Reference Intake (DRI) review of vitamin D and Institute of Medicine (IOM) workshop on DRI research needs requested for research to evaluate the intake requirements for vitamin D as related to optimal circulating 25(OH)D concentrations across different life cycles and among different ethnic groups of Canadian and US populations [1]. **Table 1** summarizes different recommendations from various agencies which represents in population and individual level.

Health Canada [28] and IOM [1] have recommended dietary allowance of 600 IU/day and tolerable upper intake level of 4000 IU/day for pregnant women in the US and Canada would meet the daily need in 97.5% of the population. There is no consensus on the cut-off point for vitamin D insufficiency. To prevent rickets and osteomalacia, IOM recommended >50 nmol/L concentration of 25(OH)D. While, the Endocrine Society and Osteoporosis Canada suggested a target serum concentration >75 nmol/L based on the available evidence with the daily intake of 1500–2000 IU in order to achieve optimal benefits for skeletal and non-skeletal health [29, 30]. Accordingly, the Canadian Pediatric Society suggested 75 nmol/L as "sufficient" for pregnant and lactating women [31]. Moreover, several pilot studies have recommended that daily intake of 2000 [32], 4000 [33], or even 6400 IU [34] vitamin D would reduce vitamin D inadequacy without any toxicity sign in

Agency	Countries	25(OH)D threshold (nmol/L)			Vitamin D intake (μg/d)		
		Deficiency	Population average	Individual target	EAR	RI	AI
IOM [1]	USA/Canada	<30	40	≥50	10	15	—
NORDEN [24]	Nordic	<30	—	≥50	7.5	10	—
SACN [25]	UK	<25	—	≥25	—	10	—
EFSA [26]	EU	—	—	≥50	—	—	15

25(OH)D, 25-hydroxyvitamin D; EAR, estimated average requirement; RI, recommended (individual) intake; AI, adequate intake; IOM, Institute of Medicine; NORDEN, Nordic Council of Ministers; SACN, Scientific Advisory Committee on Nutrition; EFSA, European Food Safety Authority. Table adapted from Kiely et al. [27].

Table 1.
Summary of the current dietary recommendations for vitamin D in pregnant women.

pregnant women and their infants. The discrepancies in some factors, including different measurement tools of vitamin D levels, various patient populations and different sample sizes that were used in studies, might explain the differences in the recommendations. Because of conflicting evidences, identifying sufficient and upper-limit amount of vitamin D for pregnant women requires further research to be performed.

4. Maternal vitamin D status and adverse pregnancy outcomes

Numerous studies have reported pleiotropic role of vitamin D in pregnancy. Maternal Hypovitaminosis D during pregnancy is related to pregnancy related disorders. Complications caused by low serum measurement of 25(OH)D include gestational hypertension (GHT), PET, gestational diabetes mellitus (GDM), timing and mode of delivery, postpartum depression or anxiety, bacterial vaginosis, and other outcomes such as anemia and lipid disorders, which are discussed in this section.

It should be noted that, there is not enough evidence to support a recommendation for screening all pregnant women for vitamin D deficiency but must be at least 20 ng/ml (50 nmol/L) for bone health [35]. Although some experts suggest vitamin D serum level of at least 32 ng/ml (80 nmol/L) for optimal state in pregnancy [36], some adverse effects have been reported at levels exceeding 70 nmol/L [37]. Consequently, due to the lack of standardized measurement procedures, there is no consensus on the optimal vitamin D status during pregnancy.

4.1 Gestational hypertension and preeclampsia

Elevated blood pressure that appears after 20 weeks without proteinuria or other findings is called gestational hypertension (GHT). This problem is confirmed by systolic blood pressure (SBP) ≥160 or diastolic blood pressure (DBP) ≥110 mmHg for anyone (confirmed over a few minutes) or SBP ≥140 or DBP ≥90 mmHg after 20 weeks (confirmed over 4 hours) observing for the first time [38]. At least 25% of women with GHT is predisposed to PET [38]. PET is diagnosed by high blood pressure (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg) after 20 weeks of gestation along with proteinuria (>300 mg/day) and other organ dysfunction including liver involvement, hematological disturbance, neurological

or renal complications [39]. The pathogenesis of PET involves releasing the angiogenic factors to the maternal circulation which causes insufficient remodeling and trophoblastic invasion of spiral arteries. It leads to shallow implantation and hypoxia, and even release of inflammatory mediators [40]. PET is a multifactorial outcome that has not been fully understood yet; however, maternal calcium status is suggested to be an important factor. Therefore, vitamin D due to its role in calcium hemostasis might have an impact on PET [41]. In addition, vitamin D can be protective of placental vasoconstriction and consequently, PET because of its immunomodulatory effect. Also, vitamin D is a regulator of endothelial and vascular smooth muscle cell proliferation through which regulates blood pressure via Renin-Angiotensin-Aldosterone system (RAAS) [42].

Systematic reviews and meta-analysis, including cross-sectional, longitudinal, cohort, ecological, and observational studies, indicate inconsistent results regarding the association between vitamin D deficiency and PET. Some studies reported an increased risk of PET women with vitamin D deficiency in pregnancy in contrast with others [43–45]. This contradiction of finding can be explained by different vitamin D assessment methods, criteria applied to define vitamin D deficiency, different season and trimester in studies [44]. Therefore, associations are inconclusive, often contradictory, confounded, and lack causality. In addition, supplementation helps to raise the level of maternal vitamin D; however, there is no significant reduction of PET risk with a higher level of vitamin D status [22, 46]. In this regard, more observational and interventional studies with different designs are needed.

4.2 Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) is glucose intolerance developed or first diagnosed during pregnancy. Criteria for recognition GDM are controversial [47]; according to World Health Organization (WHO), fasting blood glucose above 92–125 mg/dl and/or 2-h glucose greater than 153–199 mg/dl after glucose intake of 75 g are considered as diabetes mellitus in pregnancy as is a random plasma value of above 200 mg/dl with diabetes symptoms [48, 49]. Vitamin D plays a crucial role in glucose homeostasis through several mechanisms. The first is regulating calcium, which is a regulator for the production and secretion of insulin by the endocrine pancreas. Its second role involves enhancing insulin sensitivity of the target cells in adipose tissues, liver, and skeletal muscles. Moreover, the immune cell regulation role of vitamin D protects β-cells from damaging and improves its function [50, 51]. Although vitamin D deficiency can be associated with the pathogenesis of diabetes mellitus type 1 and type 2, its role in GDM is not conclusive [43]. Conflicting results have been found in case-control, prospective cohort studies, and reviews looking into the risk of GDM with vitamin D status [46]. Some review studies indicate that pregnant women with significant lower 25(OH)D had a higher risk of GDM by 40–60% [45, 52], while in systematic and critical reviews, most studies failed to support the association between vitamin D status and GDM prevention [43, 44]. Thus, more large-scale prospective studies are needed to evaluate this association.

4.3 Postpartum depression (PPD) or anxiety

Depression after delivery is a common psychiatric condition which is called postpartum depression (PPD) [53]. Vitamin D as a neurosteroid suggested having a role in various brain functions and depression by several potential mechanisms. Firstly, Vitamin D plays as a neurotransmitter, neuro-immunomodulation, and neuroprotection in the brain [54]. Secondly, vitamin D has a role in synthesizing norepinephrine and dopamine, which are involved in mood disorders.

Furthermore, vitamin D protects the brain from oxidative stress by preserving the antioxidant glutathione in the brain [55, 56]. Most studies suggested there is an inverse association between vitamin D serum in different stages of gestation and postpartum depression [57–59]. In contrast, some studies indicate no association [60, 61], and even increased risk of PPD with sufficient vitamin D concentrations (≥50 nmol/L) [62]. However, in a systematic review study, a few studies reported the role of vitamin D in this pregnancy outcome [44]. Thus, although postpartum depression might be associated with vitamin D deficiency, inconsistent results need for more extensive studies in this regard.

4.4 Bacterial vaginosis (BV)

Bacterial vaginosis (BV) is a common vaginal infection in women in reproductive ages caused by the replacement of normal vaginal flora for mixed anaerobic bacteria [63]. Women diagnosed with BV are more likely to have preterm delivery [64]. Evidence indicates that vitamin D deficiency is an independent risk factor for bacterial vaginosis in pregnancy [65], and in several systematic reviews and meta-analysis articles, this association has been reported [5, 52, 55, 66]. The risk of BV increases from 3- to 5-fold for serum 25(OH)D values <75 to <30 nmol/L, respectively [67–69]. Therefore, several cross-sectional and observational studies consistently stated the plausible inverse association between vitamin D status and BV during pregnancy. A possible mechanism is related to immune responses regulated by calcitriol. In fact, as mentioned above, vitamin D activates potent antimicrobial peptide hCTD, an active peptide with broad-spectrum antimicrobial activity, in the placenta, macrophages and dendritic cells, inducing the innate immune responses [70]. These findings indicate that adequate vitamin D levels are crucial to enhance immunity, especially in pregnancy.

4.5 Preterm delivery

Preterm delivery is defined as birth completed before 37 weeks gestation [71]. Infection is the most common factor in preterm delivery [72]. Vitamin D plays as an anti-inflammatory and immunomodulatory factor, enabling to reduce the risk of preterm delivery in several plausible ways. One mechanism involves response reduction to microbial pathogens via cancelation of IL-1, IL-6, and TNF-alpha production by macrophages [73]. Uterine immune cells, such as dendritic cells, macrophages, and natural killer cells are modulated by vitamin D [74], and vitamin D receptors are expressed in the ovary, endometrium, and myometrium to maintain reproductive health [75].

There are conflicting findings regarding the effect of Vitamin D on preterm delivery. Some articles including critical and narrative reviews, reported no association between vitamin D deficiency and preterm delivery [43, 46, 76, 77], while single studies, systematic review, and meta-analysis showed significant relationship between them [45, 78–81]. Inconsistent findings can be explained by different designs of each study including the timing of 25(OH)D assessment, and different definition of preterm delivery. For instance, in two studies, ≤35 weeks gestation for preterm delivery was considered [78, 82], while in another study it was <37 weeks gestation [77].

Ethnicity appears to be an important factor regarding preterm birth. Bodnar et al. reported that the risk of preterm delivery increased only in non-white mothers compared to white women [82]. In a cohort study by Wagner et al., Hispanic women with serum 25(OH)D > 40 ng/ml had 79% reduced risk of preterm birth in comparison with those with serum 25(OH)D ≤ 20 ng/ml, while the reduced risk was

45% among black women [83]. Also, an increased risk of preterm birth associated with Vitamin D insufficiency in ethnic minority women in Canada [84] suggests the stratification of women based on their ethnicity in further studies. Another important thing should be considered in study design is the association of vitamin D status in different gestational age with pregnancy outcome. For instance, one study suggested that maternal vitamin D status closest to delivery time was the best indicator for preterm birth because of the more significant reduced risk in the third semester compared to serum concentrations of vitamin D in the first and second semesters [85]. Thus, vitamin D deficiency is likely to be associated with preterm birth, nevertheless, to investigate the explicit relationship between vitamin D status and preterm delivery several factors should be noted including the timing of 25(OH)D assessment (first, second, or third trimester), ethnicity, precise definition of preterm birth, different study design such as human interventional and cohort studies.

4.6 Cesarean delivery

Uterine muscle and skeletal muscle cells have VDR, which is a regulator of the contractile proteins of uterine myometrial cells [86]. Therefore, the strength of the contractile muscles is decreased with vitamin D deficiency as well as malformation of the pelvis, which are indications for C-section [87]. The indication of C-section can be related to vitamin D deficiency, but there is a mixture of results regarding this association. For example, prospective cohort studies suggested there was an inverse association with having a cesarean section and serum 25(OH)D levels [88–90], whereas others did not support this relationship [76, 87, 91]. Regarding ethnicity, in a cohort multi-ethnic Asian study, vitamin D deficiency was related to a higher risk of C-sections in Chinese and Indian women compared to Malay women [86]. Factors such as the different definition of C-section in terms of indication, primary or secondary, emergency or elective might be the reason of inconclusive findings [91]. Although observational studies mentioned above investigated a possible relationship between vitamin D and cesarean delivery, more studies are needed to verify this association along with biological and geographical factors.

4.7 Recurrent pregnancy losses (RPL)

Recurrent pregnancy losses (RPL) and repeated implantation failures (RIF) are two auto- and cellular immune abnormalities, and vitamin D deficiency is prevalent in women with RPL and RIF. Vitamin D plays a pivotal role in the regulation of auto- and cellular immune disorders [92]. Studies reported that 45% of RPL patients had vitamin D deficiency in one study, and increased risk of first-trimester miscarriage and recurrent pregnancy losses (RPL) was found with vitamin D insufficiency [93, 94]. Even this association has been found in early spontaneous pregnancy loss [95]. Studies show an inverse association between vitamin D deficiency and RPL; however, no conclusion can be drawn based on the findings of a few studies and more observational and interventional studies are necessary to confirm such association [43].

4.8 Other related outcomes

Other outcomes including spontaneous abortion [77, 96, 97] and stillbirth [77, 96], short gestational length [98], and low Apgar score [76, 96, 98] were not associated with vitamin D insufficiency, according to a systematic review and meta-analysis of longitudinal studies [99]. However, more studies with different designs such as clinical trials are necessary. Anemia, lipid disorders, periodontal disease,

and HIV-related mortality are other pregnancy implications related to vitamin D deficiency. There is a mixture of results with regard to the vitamin D deficiency and anemia in pregnancy. Some studies indicated this relationship [100], while other studies failed to support it [76, 101]. The findings show a positive correlation between serum vitamin D and atherogenic factors such as total cholesterol and triglycerides [102, 103]. As vitamin D has immunomodulatory effects, it may have a protective role against mother-to-child transmission (MTCT) of the human immunodeficiency virus (HIV). A study on HIV-infected pregnant women conducted in Tanzania found that low maternal vitamin D level (<32 ng/mL) at 12–27 weeks gestation was associated with a 50% higher risk of MTCT of HIV [104]. Moreover, vitamin D insufficiency (serum 25[OH]D < 75 nmol/l) was associated with maternal periodontal disease during pregnancy, as reported by Boggess et al. [105].

Almost all the pregnancy complications related to vitamin D deficiency were discussed in this section. However, the results were contradictory due to small study samples in some studies, cross-sectional design, lack of adjustment for seasonal variation, race and ethnicity, various study design in terms of the trimester (first, second, or third trimester), different definition of some outcomes and even cut points to categorize vitamin D status. These inconsistencies justify the need for more large-scale prospective studies and interventional studies to evaluate these associations comprehensively.

5. Maternal vitamin D status across different ethnic groups

Vitamin D deficiency has been reported among pregnant women globally, particularly among ethnic minorities and white women residents at high latitude [106]. Ethnic variety in vitamin D status of pregnant women can be relevant to large disparities in skin color, vitamin D intake, religion, culture, sun exposure (seasonal variation), and geographical location [107]. In ethnic minorities, the prevention of vitamin D deficiency on a population basis is challenging due to the shortage of clarity surrounding the metabolism and transport of vitamin D [108]. Due to lack of enough evidence regarding the nutritional requirements for vitamin D during pregnancy, there is no pregnancy-specific dietary recommendation for vitamin D. In addition, the question of specific dietary reference setting specifically for each ethnicity (for pregnant women) has not been addressed to date [109].

The best indicator of vitamin D status is the serum 25(OH)D concentration, because it is not regulated, and reflects both dietary intake and synthesis form of vitamin D [110]. However, there is no absolute agreement on normal range of vitamin D, although most authors have consensus that serum 25(OH)D concentration should be ≥50 nmol/L [110–112]. Ethnic differences in vitamin D status are in accordance with the ethnic differences in circulating vitamin D, where a mean value of 57 nmol/L has been reported for Caucasian pregnant women in Canada [113], a median value of 53 nmol/L has been reported for Belgian women [114], 57 nmol/L has been reported for pregnant women in Australia [115]. A cohort study in 2011 indicated that the mean 25(OH)D level in African-Americans was 38.75 nmol/L, Hispanics was 60.25 nmol/L, and Caucasians was 72.5 nmol/L [116]. African-American pregnant women had the lowest serum 25(OH)D in this study. However, in Southern Europe, Morales et al. demonstrated a median plasma value of 25(OH)D in pregnancy of 73.88 nmol/L [117]. Furthermore, a recent systematic review reported that mean 25(OH)D levels in the general populations were higher in America (North America) (75 nmol/L) than in the Middle East (50 nmol /L) or Europe (52 nmol/L) [118].

The absence of race- and pregnancy-specific dietary recommendations places pregnant women of the ethnic minority among the most vulnerable and

under-investigated population groups concerning vitamin D [106]. A review study indicated that pregnant women in Latin America, Asia, the Middle East, and Africa are at the danger of vitamin D deficiency and these are known as the topmost universally locations for occurrence of vitamin D deficiency and reported that incidence of vitamin D deficiency varied from 51.3 to 100% [119]. Recent studies in the United States, Canada, Australia, Iran, Sweden, and Pakistan reported that the range of vitamin D deficiency and insufficiency were 24–95.8% and 54–100% among pregnant women [116, 120–125]. The evidence for racial differences in vitamin D deficiency (**Table 2**) indicated that the global prevalence of 25(OH)D concentrations <50 nmol/L is 54% among pregnant women and 75% among newborns [106]. In other words, one in five pregnant women (18%) and one in three newborns (20%) had serum vitamin D concentration <25 nmol/L, which is a public health concern [106]. Vitamin D status is poorly defined in the South-East Asian, African, and Eastern Mediterranean regions and the non-European population in the Western Pacific region (**Table 2**) [106].

Maternal vitamin D deficiency is also investigated for each trimester across different regions and ethnicities. For instance, in Thai pregnant women, high prevalence of vitamin D deficiency and inadequacy were reported in the first trimester: 26.7% (<50 nmol/l) and 56.7% (<75 nmol/l), respectively. Then, vitamin D inadequacy decreased to 30.9% (1.8% deficiency) in the second trimester and 27.4% (2.8% deficiency) in the third trimester [120]. Pregnant women were studied in the first trimester of pregnancy (gestational week 11–14) living in Mediterranean seacoast at latitude 36°N, therefore at a high sun exposure area, were classified as Spanish Caucasians and Arab immigrants [121]. The median serum 25(OH)D concentration for the whole sample was 68.39 nmol/L. Only 35.9% of the participants had adequate serum 25(OH)D concentrations (75 nmol/L), while these concentrations were found to be inadequate (50–75 nmol/L) in 41.4% and deficient (<50 nmol/L) in 22.7% of respondents. Vitamin D status was lower in Arab women in comparison to Caucasian women [121]. Another study reported that in second trimester 40.7% (<50 nmol/L) of Chinese pregnant women who lived at their urban locations had vitamin D deficiency [122]. According to a cross-sectional study in China, 74.9% of Chinese pregnant women had vitamin D shortage (25-hydroxyvitamin D < 50 nmol/L) [123]. In one of the National Health and Nutrition Examination Survey (NHANES) studies reported that among different factors, the largest magnitude of association was observed between race and 25(OH)D status. Those who were non-Hispanic whites in third trimester had a higher vitamin D levels (93 nmol/L) than non-Hispanic black (45 nmol/L) or Hispanic (69 nmol/L).

WHO regions	Percentage of 25-hydroxyvitamin D deficiency	
	% < 25* (nmol/L)	% <50** (nmol/L)
Americas	64	9
European	57	23
Eastern Mediterranean	46	79
South-East Asian	87	N/A***
Western pacific	83	13

Adopted by Saraf et al. [106].
**Vitamin D deficiency.*
***Severe vitamin D deficiency.*
****Not available.*

Table 2.
Prevalence of maternal vitamin D deficiency classified by WHO region.

Vitamin D insufficiency in this study was 13%, 54% among whites, 80%, 95% among blacks, and 45%, 83% among Hispanics for 25(OH)D concentrations <50 and <75 nmol/L, respectively [124]. A recent cohort study reported that 44% of non-European pregnant women in the Netherland had vitamin D deficiency compared to European ones either with maternal serum or cord blood [125]. While from one of the Persian Gulf countries (United Arab Emirates (UAE)), 69% of vitamin D deficiency was reported among pregnant women [126].

Generally, previous recommendations have indicated that winter, higher latitude, dark pigmentation, season, limited sun exposure, and dressing style as risk factors for vitamin D deficiency. It can be difficult to describe the prevalence of pregnant women at risk to vitamin D deficiency because vitamin D status varies according to how deficiency is defined, as well as aforementioned risk factors [127–129]. These studies indicated that despite the geographical location of each region, vitamin D deficiency is highly prevalent among pregnant women because of the lifestyle and nutrition status of mothers. Future studies are required to investigate vitamin D deficiency of pregnant women among different ethnic groups based on similar cut-off values for vitamin D deficiency.

As we discussed in Section 4, vitamin D deficiency has a key role in the development of PET and GDM. In this section, we elaborate on the differences that the occurrence of these two diseases might have among different ethnic groups.

5.1 PET and GDM among ethnic disparities

Pregnant minorities have been the least studied in vitamin D-related diseases such as PET and GDM. According to a meta-analysis, the occurrence of PET is seen at lower vitamin D levels due to the immunomodulation properties of vitamin D [52]. A recent study examined the evidence linking vitamin D deficiency in pregnancy to PET among different ethnic groups. Although prevalence of vitamin D deficiency differed significantly among African-Americans (72.3%), Hispanics (10.6%), and Caucasians (2.1%), there were no direct associations between low 25(OH)D levels and risk for PET among different ethnic groups [130]. While another recent study in UK indicated a greater prevalence of white British women developed GHT (12.0%) and PET (3.4%), compared to Pakistani women (the proportion of GHT and PET were 5.4 and 1.7%, respectively) [131]. The heterogeneity that exists among studies in terms of sun exposure (naturally occurring vitamin D synthesized from), geographical locations, considering different ethnic groups with divergent cultures, may lead to the differences in results.

It has been shown that maternal vitamin D concentration has inversely been linked to impaired glucose metabolism in pregnancy [132]. A few studies considered the effect of ethnicity on this relationship in pregnancy such as Clifton et al. study in Australia, which examined the association between serum 25(OH)D with GDM among five different ethnic groups including European (European Australian, English, German, Spanish), South-East Asian (Chinese, Japanese, Korean, Indonesian, Thai, Malaysian), Asian (Indian, Pakistani, Bangladeshi, Sri Lankan), Middle Eastern (Iranian, Iraqi, Lebanese, Syrian), and Other (Aboriginal Australian, Samoan, Papua New Guinean). They found no significant association between 25(OH)D and GDM in any ethnic group [132]. Generally, ethnicity was not an independent predictor of insulin resistance.

Overall, well-designed prospective cohort studies are needed to inform and update our knowledge regarding vitamin D deficiency and its association with PET and GDM among different ethnic minorities.

5.2 Latitude

Sun exposure decreases dramatically, with increasing latitude [129]. It seems logical that higher latitudes would report a higher proportion of vitamin D deficiency like Northern European countries, in comparison to the European South. In addition, almost all European Mediterranean countries are located at a high latitude (37–38°N), and previtamin D3 photosynthesis is lower during winter. Similar or even smaller proportion of vitamin D deficiency among pregnant women was reported from countries with higher latitudes in Western and Central Europe (latitudes 46–81°N) [133]; Slovenia with 46.5°N latitude, showed a high prevalence of severe vitamin D deficiency (23.6% with the threshold of <25 nmol/l) among pregnant women [134]. Even if in lower latitudes, the prevalence of maternal vitamin D deficiency is still high such as a study in China demonstrated that over 90% of pregnant women in urban northern China (39.9°N), had vitamin D deficiency (<50 nmol/l) and none had normal 25(OH)D concentrations (≥75 nmol/L) [135]. Although the Goulburn Valley in Northern Victoria (Australia) experiences abundant sunshine and located at 36° South of the equator, a place where vitamin D synthesis is possible during the year, 49.4% of pregnant women (<75 nmol/l) had vitamin D inadequacy and 12.2% (25–50 nmol/L) of pregnant women had a mild deficiency and 3.2% (<25 nmol/l) suffered a moderate/severe deficiency in summer [136]. A recent study from Bangkok, Thailand also revealed that 23.3% of Thai pregnant women had vitamin D deficiency in fall and 44.6% in winter (<50 nmol/L), despite the fact that this city is located at 13.45 N latitude and benefits sunlight throughout the year [137].

Over the past few decades, several studies have reported a high prevalence of maternal vitamin D deficiency in countries where women wear concealing clothing such as India (31%) [138], Saudi Arabia (14.2%) [139], and Iran (5.7%) [140] and countries in northern latitudes such as the United Kingdom (21.2%) [141] and Norway (33% deficiency and 18% severe deficiency across three ethnic groups) [142]. Due to less sunlight exposure, these pregnant women are at high risk of vitamin D deficiency. The duration of sun exposure is directly associated with the concentration of 25(OH)D [135, 138]. Mothers with less than 0.5 h/day of sun exposure had a higher prevalence of vitamin D deficiency (38.4%) in China, which would worsen the situation in winter that the tendency toward outdoor physical activity decrease among pregnant women [135]. However, in sunny regions like Turkey, vitamin D deficiency among pregnant women is still a serious problem with the prevalence of 90% [143]. In addition, the prevalence of vitamin D deficiency (48%) was noted among pregnant women in South Carolina at latitude 32°N, where women lived in a sun-rich climate for most of the year [144]. Despite the longer duration of sunlight in UAE (ranges from 9 to 11 h), 69% of pregnant women suffer from vitamin D deficiency. It can be due to the decrease in time spent on outdoor activities and to the dressing style, which limits the surface area exposed to the sun [126].

Overall, latitude is an important factor but the other factors such as culture, belief, indoor lifestyle, etc., would play key roles in vitamin D deficiency in sun-rich countries.

5.3 Skin pigmentation

Skin pigmentation is the main determinant of ultraviolet B-rays (UV-B) absorption in humans [129]. The absorption of UV-B would be more when the skin is pale compared with the darker skin. In other words, the probability of vitamin D deficiency would be higher when skin pigmentation increases in critical periods

like pregnancy [126]. Pregnant women who live in southern Europe have more pigmented skin, probably with less efficient vitamin D synthesis [145]. In Italy, vitamin D deficiency of pregnant women (with different ethnic groups) was examined based on their skin color (fair, black, light brown). It was found that 22% had severe vitamin D deficiency (<25 nmol/L) in total and fair-skinned mothers had higher 25(OH)D concentrations [146]. Another study in Netherland observed several ethnic backgrounds who reside in The Hague in the Netherlands (52°N), that vitamin D deficiency is more common among most non-Western participants (dark-skinned) (59–84%) compare to western women (fair-skinned) (8%) [147]. In southwestern Sweden, vitamin D deficiency was examined among pregnant women from different backgrounds with various skin colors. The prevalence of vitamin D deficiency was 10% overall, and 2% among mothers born in north Europe, while vitamin D deficiency among women born in Africa was 50% (<30 nmol/L) and deficiency was common among Asian mothers as well [148]. A recent US study reported in the multi-ethnic population of pregnant women in the southeastern USA, non-Hispanic black pregnant women are most at risk for vitamin D insufficiency (91%) compare to non-Hispanic white women (47%) and Hispanic women (75%) [149]. The concentration of melanin in the skin determines vitamin D production. Melanin, which absorbs UV-B in the 290–320 nm range, functions as a light filter and therefore regulates the proportion of the vitamin D production [150]. Thus, skin pigmentation is a dominant variable controlling the production of vitamin D under circumstances of low levels of sun exposures because melanin absorbs UV photons in competition with 7-dehydrocholesterol [151, 152]. Overall, darker-skinned pregnant women need a greater duration of sun exposure (4–5 times) (they are more at risk in higher latitudes) in comparison to light-skinned ones to provide a comparable amount of vitamin D [153].

6. Maternal vitamin D status and fetal and postnatal outcomes

A growing body of evidence suggests that maternal vitamin D deficiency is associated with not only pregnancy outcomes, but also later physical and mental health of the offspring. In this section, we aim to review the existing literature investigating the impact of maternal vitamin D status during pregnancy on a range of fetal and postnatal outcomes.

6.1 Fetal skeletal development

During pregnancy, the fetus relies on maternal supply and placental delivery of vitamin D and calcium for optimal development and function, particularly of the skeletal system [154]. Maternal vitamin D deficiency during pregnancy predisposes breast-fed infants to neonatal hypocalcemia and infantile rickets [155, 156]. It has been reported that maternal UV-B exposure in pregnancy is related to bone mineral content (BMC) and bone mineral density (BMD) at age 9.9 years independently of height and lean mass [157]. Further, winter newborns in Korea were found to have 6% lower total body BMC, lower cord serum 25(OH)D and 1,25-dihydroxyvitamin D than summer newborns [158]. These results suggest that low maternal vitamin D concentrations due to limited UV-B exposure may exert direct effects on offspring bone mineral accrual.

The influence of maternal vitamin D status on bone outcomes has been investigated in several observational studies at fetal [159–161], postnatal [162–164], and adult stages [115, 165–167]. Using data from a prospective longitudinal study, Mahon et al. observed that lower maternal 25(OH)D concentration was associated with the

greater femoral metaphyseal cross-sectional area at 19 weeks gestation and 34 weeks gestation. However, lower maternal 25(OH)D concentration was not related to fetal femur length [159]. In another prospective longitudinal study, Young et al. found a significant positive association between maternal 25(OH)D levels and fetal femur and humerus z-scores only when maternal calcium intake was <1050 mg/d [160]. It has also been reported that maternal serum 25(OH)D concentration, together with maternal height and adiposity, was significant predictors of femoral size [161]. In a cross-sectional study with a longitudinal follow-up, tibia BMC was 0.047 g/cm higher, and cross-sectional area was 12.3 mm^2 larger in newborns with the first trimester and cord serum 25(OH)D above the median (42.6 nmol/L) compared with below median newborns [162]. In another study, Morley et al. found smaller knee-heel length in infants of mothers with low 25(OH)D levels (<28 nmol/L) in late pregnancy (28–32 weeks of gestation) compared to babies whose mothers had higher concentrations [163]. Dror et al. reported no association between feto-maternal vitamin D status and early infant whole-body BMC. However, a large percentage of mothers in their study had adequate vitamin D status, which may have affected the results [164]. These observations suggest that maternal vitamin D status during pregnancy can influence fetal bone growth as early as the second trimester of pregnancy.

Emerging evidence suggests that the relationships between maternal vitamin D status and bone outcomes persist into childhood and beyond [115, 165, 166]. In a longitudinal study by Javaid et al., it was found that reduced concentration of maternal 25(OH)D during late pregnancy was associated with reduced whole-body and lumbar-spine BMC in children at age 9 years. Besides, childhood bone mass was predicted by maternal use of vitamin D supplements and the estimated exposure to UV-B radiation during late pregnancy [165]. Zhu et al., in a study of 341 mother and offspring pairs, found a positive association between maternal 25(OH)D concentration and total body BMC and BMD in offspring at 20 years of age [115]. These results were confirmed in another study where maternal vitamin D deficiency (25(OH)D < 50 nmol/L) during pregnancy was associated with lower peak bone mass at 20 years [166]. In contrast to these studies, Lawlor and colleagues observed no relevant association between vitamin D deficiency in pregnant women and offspring's BMC in late childhood [167]. In another study, compared to children born to mothers with high vitamin D status, tibial BMC was lower at birth in children with low maternal vitamin D status, while BMC gain was greater, resulting in similar BMC at 14 months [168]. The evidence derived from observational studies, although conflicting, tends to suggest an association between vitamin D deficiency in pregnant women and reduced bone mineral accrual in the offspring, which may increase fracture risk in later life.

6.2 Birth anthropometry, small-for-gestational-age (SGA), and childhood growth

There is controversy regarding the relationship between maternal vitamin D status and neonatal birth weight, with some studies reporting an association between reduced maternal vitamin D levels and lower neonatal birth weight [169–174], and others showing no association [175–178]. While some studies found no association between maternal vitamin D levels and other anthropometric birth outcomes such as length and head circumference [176–179], others suggested a nonlinear relation between 25(OH)D levels and head circumference [171, 174].

Inconsistencies in the literature have led several researchers to conduct meta-analyses to further clarify the association between maternal vitamin D concentrations and anthropometric outcomes in offspring. Four meta-analyses of observational studies have been published in recent years [45, 52, 180, 181]. In

the first study, Wei et al. carried out a meta-analysis on six studies and found that pregnant women with circulating 25(OH)D levels less than 50 nmol/L experienced an about 1.5-fold increased risk of SGA [45]. These results were confirmed in another meta-analysis of 13 prospective cohort studies, in which a significant positive association was found between maternal vitamin D deficiency and risk of SGA infants (pooled odds ratio 1.58; 95% CI 1.14–2.22) in the random effects model [180]. Similar results were obtained in subgroup analyses by study quality (high vs. low), gestational week for blood sampling (first trimester vs. second trimester vs. mixed), cut-off vitamin D levels (<10 ng/mL vs. <15 ng/mL vs. <20 ng/mL), sample size (N > 1000 vs. N < 1000), adjustment for critical confounders (Yes vs. No), and method for measuring vitamin D (liquid chromatography with tandem mass spectrometry vs. others) [180]. There results suggest that maternal vitamin D deficiency may be associated with an increased risk of SGA infants.

A meta-analysis conducted in 2013 showed that insufficient serum levels of 25(OH)D in pregnant women was associated with increased risk of having SGA infants (pooled odds ratio 1.85; 95% CI 1.52–2.26) [52]. In terms of birth weight, the authors used data from four observational studies and found infants of mothers with low 25(OH)D concentrations during pregnancy (<37.5 nmol/L) had lower birth weight (random weighted mean difference −130.9 g). However, no significant difference was observed between maternal vitamin D status and other anthropometric outcomes such as birth length and head circumference [52]. The most recent meta-analysis conducted by Tous et al. included 54 eligible studies and reported that vitamin D-deficient mothers (<30 nmol/L) had offspring with lower birth-weight (mean difference −87.82 g), head circumference (mean difference −0.19 cm), and a higher risk of SGA infants (odds ratio 1.59; 95% CI 1.24–2.03) compared to mothers with concentrations ≥30 nmol/L. However, no difference was observed in terms of infants' length [181]. The results also revealed a significant association between vitamin D insufficiency (<50 nmol/L) and increased risk of SGA (odds ratio 1.43; 95% CI 1.08–1.91). The authors found no significant differences in birth-weight and SGA between offspring born to mothers with 25(OH)D concentrations <75 nmol/L and those born to mothers with 25(OH)D concentrations ≥75 nmol/L [181]. Further, a meta-analysis of 13 interventional studies revealed that vitamin D supplementation during pregnancy was associated with significantly higher circulating 25(OH)D levels (mean difference: 66.5 nmol/L), birth weight (mean difference: 107.6 g), and birth length (mean difference: 0.3 cm), when compared to the control group [182]. Neonates exposed to low levels of vitamin D *in utero* (<30 nmol/L) showed accelerated growth in length and weight during the first year of life to compensate for their small initial size [183, 184]. There results suggest that maternal vitamin D deficiency is associated not only with increased risk of SGA infants but also with lower birth-weight. However, more studies are required to draw a firm conclusion on the relationship between maternal vitamin D status and other anthropometric outcomes.

6.3 Offspring soft tissue body composition

A growing body of evidence suggests that maternal vitamin D status in pregnancy may play a part in the offspring adipogenesis [185–189]; however, not all studies are in agreement [190, 191]. Tint et al. conducted a study to examine the association between maternal 25(OH)D status at mid-gestation and neonatal abdominal adipose tissue (AT) compartments. The findings indicated an inverse liner correlation between maternal 25(OH)D and both superficial and deep subcutaneous AT compartments measured by magnetic resonance imaging (MRI). In addition, compared to neonates born to mothers with 25(OH)D sufficiency

(>75.0 nmol/L), neonates with maternal 25(OH)D inadequacy had higher superficial and deep subcutaneous AT volumes, despite similar birth weight [185]. However, in a prospective observational study, Godang et al. reported a positive association between neonatal total body fat mass (FM) and umbilical cord plasma, but not maternal, 25(OH)D [190]. This was confirmed in another study where a positive correlation between cord blood 25(OH)D levels and neonatal percentage body fat was observed [192]. Using data from the Southampton Women's Survey, Crozier et al. found that lower maternal vitamin D status at 34-week gestation was associated with lower FM in the offspring at birth but with greater FM at ages 4 and 6 years [186]. Similarly, a prospective pregnancy cohort conducted by Daraki et al. showed that offspring of mothers in the low 25(OH)D tertile (<37.7 nmol/L) had higher BMI and waist circumference at preschool age, compared with the offspring of women with higher 25(OH)D concentrations, and this relationship persisted at age 6 years [187]. Results from a recent prospective cohort conducted in 476 mother/infant dyads also demonstrated that reduced maternal 25(OH)D (first quartile compared to the fourth quartile) was associated with lower birth weight for gestational age z-scores (−0.43 units) but higher 1-year weight-for-length (0.78 units) and 3-year BMI z-scores (0.83 units) in offspring [188]. In another study, maternal deficit of 25(OH)D (<50 nmol/L) was reported to be associated with increased risk of fetal overweight defined as abdominal circumference ≥90th percentile or either as the estimated fetal weight ≥90th percentile. Moreover, a significant association was found between deficit of 25(OH)D in pregnancy and increased risk of overweight in offspring at age 1 year. However, this association was attenuated at age 4 years [189]. In contrast to these studies, Ong and colleagues, in a mother-offspring cohort in Singapore, observed no significant associations between maternal vitamin D status and any of the adiposity outcomes (i.e., BMI and skinfold thickness) at birth or postnatally. This was partly explained by the low prevalence of severe maternal vitamin D deficiency in the studied population (mean maternal vitamin D concentration of 81.3 nmol/L) [191]. These findings suggest that intrauterine exposure to low 25(OH)D concentrations may be linked to lower FM at birth but greater FM during childhood. A higher FM may also contribute to decreased 25(OH)D levels in obese individuals, partly due to the sequestration of vitamin D by AT [193].

A limited number of studies have investigated the influence of maternal vitamin D status on offspring lean mass or muscle strength [194, 195]. Using data from Mysore Parthenon Study, Krishnaveni et al. reported that Indian children born to vitamin D-deficient mothers (serum 25(OH)D < 50 nmol/L) had a smaller arm-muscle area at ages 5 and 9.5 years in comparison with children born to mothers without deficiency. However, no difference in grip strength was observed between the offspring of mothers with and without vitamin D deficiency [194]. In contrast, a study conducted in 678 mother-child pairs showed that maternal serum 25(OH)D concentration in pregnancy was positively associated with height-adjusted hand grip strength but not muscle mass in offspring at 4 years of age [195]. These results suggest that low maternal vitamin D status may be associated with the smaller arm-muscle area and lower muscle strength in the offspring. However, more observations are required to draw a firm conclusion on this matter.

6.4 Respiratory health

In humans, lung development starts *in utero* with the formation of two endodermally derived lung buds and continues through childhood, adolescence, and early adulthood [196]. A growing body of evidence suggests that the origins of respiratory disorders such as asthma can be traced back to the fetal period when the lung is undergoing rapid development [197, 198]. It has been shown that vitamin D

is involved in the process of maturation of the fetal lung including type II alveolar cells maturation and the alveolarization [199]. Currently, there are four meta-analyses published within a 3-year period from 2016 to 2018, which examined the association between maternal 25(OH)D levels during pregnancy and the offspring's respiratory conditions [200–203]. The first meta-analysis included eight studies on the association between maternal vitamin D status and childhood asthma or wheeze. This meta-analysis showed no statistical association between maternal vitamin D during pregnancy and risk of childhood asthma or childhood wheeze [200]. In contrast, the second meta-analysis included 15 prospective studies with 12,758 participants and found a U-shaped relationship between 25(OH)D levels during pregnancy and risk of childhood asthma, with the lowest risk at approximately 70 nmol/L [201]. The third meta-analysis assessed the association of both cord blood and maternal 25(OH)D levels with the risk of offspring's asthma, wheeze, and respiratory tract infections. The results revealed borderline significant inverse associations between *in utero* exposure to vitamin D and risk of asthma and wheeze, but not the risk of respiratory tract infections in offspring [202]. In the final and most recent meta-analysis, Pacheco-González et al. found an inverse association between prenatal exposure to 25(OH)D and the risk of respiratory tract infections. The authors also observed a positive borderline association between maternal or cord blood 25(OH)D levels and lung function at school age. However, no associations were found for asthma and wheeze [203]. The apparently conflicting results of meta-analyses may be partly explained by differences in inclusion criteria, the number of studies, the characteristics of participants and the methodology used. Further, the results of two other meta-analyses revealed that higher maternal intake of vitamin D was associated with lower odds of wheeze during childhood [204, 205]. Taken together, these results suggest the role of maternal vitamin D status as a protective factor for the development of offspring respiratory disorders.

6.5 Immunity and allergies

Some studies are suggesting that low maternal or cord blood 25(OH)D concentrations are associated with an increased risk of developing atopic disorders, including atopic dermatitis or eczema, allergic rhinitis, asthma, and food allergy [206–209]. A study conducted in 270 mother-child pairs showed that a higher cord blood 25(OH)D concentration was associated with reduced risk of eczema in children at 1 and 3 years of age. However, no significant associations were found between cord blood 25(OH)D concentration and the development of allergic rhinitis, allergic sensitization, or asthma [206]. In another study, cord serum 25(OH)D levels were found to be inversely associated with the risk of atopic dermatitis by the age of 5 years, but no association was reported with allergic rhinitis and asthma [207]. Chiu et al. observed a significant association between low cord blood 25(OH)D levels and increased risk of milk sensitization but not eczema, allergic rhinitis, or asthma in early childhood [208]. In another study with the same authors, it was revealed that lower maternal 25(OH)D levels (<20 ng/ml) were associated with a higher prevalence of allergen sensitization before age 2, and higher maternal 25(OH)D levels were associated with lower risk of eczema and asthma at age 4 [209]. Wei et al. conducted a meta-analysis of prospective cohort studies to examine the association between maternal vitamin D status and childhood allergic diseases. They found an inverse association between maternal vitamin D status during pregnancy and risk of childhood eczema but not childhood asthma or wheeze [200]. However, a recent meta-analysis of observational studies reported no significant associations between 25(OH)D levels in cord blood at birth or maternal blood in

pregnancy and the risk of atopic disorders [203]. Taken together, these studies indicate that lower maternal 25(OH)D concentration may be associated with an increased risk of developing atopic disorders.

Here, we discuss the role of intrauterine vitamin D exposure on the risk of two common autoimmune diseases—type 1 diabetes and multiple sclerosis. Type 1 diabetes mellitus is an autoimmune disease characterized by the destruction of the insulin-producing pancreatic β-cells of the Langerhans islets [210]. Staples et al. found an inverse association between annual ambient UV radiation exposure and prevalence of type 1 diabetes in Australia, which was suggested to be due to the role of UV radiation in vitamin D synthesis [211]. In a case-control study conducted in 109 cases and 219 control women, it was observed that lower levels of vitamin D during pregnancy were associated with a higher risk of developing type 1 diabetes in offspring before 15 years of age [212]. In contrast, in another case-control study conducted in Finnish women, Miettinen et al. found no difference between serum 25(OH)D levels during early pregnancy between mothers whose children later on developed type 1 diabetes, and mothers of healthy children [213]. Thorsen and colleagues showed that normal variation in maternal or neonatal 25(OH)D levels has no significant effect on the risk of childhood type 1 diabetes [214]. Jacobsen et al. also failed to find an association between 25(OH)D levels around the time of birth and the risk of developing type 1 diabetes before the age of 18 years [215]. As these studies found inconsistent results, more research is still needed before any conclusions can be drawn on the relationship between maternal vitamin D status and risk of developing type 1 diabetes in offspring.

Multiple sclerosis (MS) is an autoimmune disease, in which the immune system attacks the myelin sheaths surrounding nerve cells [216]. Accumulating evidence suggests an association between the month of birth and risk of MS [217–219], possibly due to variation in UV exposure, which in turn determines maternal vitamin D levels during pregnancy. In support of this hypothesis, Munger et al. reported that maternal vitamin D deficiency (<30.0 nmol/L) during early pregnancy was associated with increased risk of MS (almost 2-fold) in the offspring compared with women with normal 25(OH)D levels [220]. A nested case-control study demonstrated that exposure to high 25(OH)D levels during the years preceding disease onset was associated with decreased risk of MS in the offspring. However, no decrease in risk of MS was observed in the offspring exposed to high levels of 25(OH)D *in utero* (≥75 vs. <75 nmol/L) [221]. Nielsen et al. also carried out a matched case-control study and found an association between lower levels of 25(OH)D in neonates and increased risk of MS [222]. However, in another population-based case-control study conducted in Sweden, Ueda et al. failed to find such as association [223]. These results suggest that exposure to low levels of 25(OH)D prenatal and in early postnatal life may act as a risk factor for developing MS.

6.6 Offspring brain development and function

A growing body of evidence suggests that low maternal 25(OH)D levels during pregnancy are associated with impaired neurodevelopmental and neurocognitive outcomes during infancy and childhood [117, 224–228]; however, not all studies are in agreement [229, 230]. In this regard, several studies have shown a significant association between suboptimal maternal vitamin D status and reduced language developmental outcomes in the offspring [224–226].

Accumulating evidence also suggests a link between maternal vitamin D levels and the risk of developing neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD) [231, 232], autism spectrum disorder (ASD) [233–236], and schizophrenia [237]. Results from a prospective pregnancy cohort

conducted in 487 mother-child pairs revealed that children born to mothers in the high 25(OH)D tertile (>50.7 nmol/l) had decreased risk of developing ADHD-like symptoms at 4 years of age, compared to children of women in the low 25(OH)D tertile (<38.4 nmol/l) [231]. In another prospective study conducted in 1650 mother-child pairs, Morales et al. found an inverse association between maternal circulating levels of 25(OH)D in pregnancy and risk of developing ADHD-like at ages 4–5 years [232]. Using a case-control design study, Chen and colleagues reported that low maternal first-trimester serum levels of 25(OH)D was associated with increased odds of ASD diagnosis at age 3–7 years in the offspring [233]. Another study also found an increased risk of ASD in children who were born to mothers with vitamin D deficiency at mid-gestation [234]. In a large population-based cohort of mothers and their children, gestational vitamin D deficiency was associated with a continuous measure of autism-related traits at 6 years [235]. Magnusson et al. also observed a relationship between maternal vitamin D deficiency and risk of ASD with, but not without, intellectual disability [236]. Further, it has been demonstrated that low maternal vitamin D levels are associated with increased risk of schizophrenia within the subgroup of black but not white individuals [237]. Although more robust studies needed, these results highlight the importance of maternal vitamin D status in offspring brain development and function.

7. The association of maternal vitamin D status and child vitamin D status

Several lines of evidence suggest that there is a strong association between maternal 25(OH)D levels during pregnancy and newborn 25(OH)D concentrations at birth or in the early neonatal period [238–242]. Novakovic et al. reported that maternal circulating 25(OH)D levels were the most significant regulator of neonatal circulating vitamin D concentrations, even over the impact of genetic factors [243]. In another study, maternal characteristics explained 12.2%, and maternal 25(OH)D concentrations explained 32.1% of the neonatal vitamin D variance [13]. These results were confirmed in a systematic review reporting the range of correlation coefficients between maternal and newborn 25(OH)D concentrations, by region: European 0.42–0.95, America 0.68–0.97, Western Pacific 0.19–0.85, South-East Asian 0.78–0.81, and Mediterranean 0.03–0.88 [106]. Therefore, since maternal vitamin D status in pregnancy is an important determinant of neonatal 25(OH)D concentrations, attention should be given not only to vitamin D-deficient pregnant women, but also to their newborns, especially if they are exclusively breast-fed [244].

8. Policy and best practices (supplementation/education)

Vitamin D deficiency is very prevalent across the globe among pregnant women [245]. The range of recommended vitamin D from during pregnancy varies from 200 to 4000 IU/d worldwide. The American Pregnancy Association stated that pregnant women are recommended to have (100 μg/d) of vitamin D intake to reduce the risk of premature birth and infections which is a considerably higher amount of vitamin D compared to the recommended intake of 10 μg/d for women [246]. A daily intake of 600 IU is suggested during pregnancy in China to have healthy and balanced fetal growth [247]. In the United Kingdom, it is advised to have a maternal vitamin D intake of 400 IU/d. Switzerland follows the IOM dietary recommended nutrient intake. For pregnant/lactating women who are at risk of vitamin D deficiency, the advised vitamin D is 1500–2000 IU/d, and for women,

without deficiency, the recommended intake is 600 IU [248]. The ministry of health of New Zealand recommended 200 IU/d dietary intake of vitamin D [249]. Vitamin D requirements are higher among pregnant women (average 400 IU/d), and it is very important to maintain optimum serum level of vitamin D during maternity and for the fetus growth.

WHO encourages receiving vitamin D from a healthy and balanced diet [250]. Some recent studies suggest vitamin D food fortification can work as a means to improve vitamin D status among the overall population, which can benefit pregnant women as well [251]. Currently, Canada, United States, India, and Finland had a vitamin D food fortification policy. In North America, the foods that are naturally enriched by vitamin D, such as fatty fish, are quite expensive and are not readily available to the general population. A majority of vitamin D intake comes from fortified food in North America. The United States has a voluntary fortification policy, and Canada has both voluntary and mandatory fortification policies for specific foods. In the United States, milk including fluid, acidified, cultured, skimmed powder, evaporated milk (1.05 μg/100 g), soy-based beverages (1.25 μg/100 g), soy products (2.23 μg/100 g), margarine (8.3 μg/100 g), butter alternatives spread (8.25 μg/100 g), cheese alternatives spread (6.25 μg/100 g), yogurt (2.22 μg/100 g), fortified fruit juice (2.5 μg/240 mL), meal replacement products (2.5 μg/40 g), cheese products (2.02 μg/30 g), and enriched ready to eat cereal (8.75 μg/100 g), rice, cornmeal, noodle, macaroni (2.25 μg/100 g), farina (8.75 μg/100 g), and instant formula (1–25 μg/100 kcal) are vitamin D fortified [252]. Mandatory fortified products in Canada are margarine (1.5 μg/10 g), infant formulas (10 μg /L), milk (powder, sterilized, flavored, skim, evaporated) (2.5 μg/250 mL), meal replacements (5% of DV/55 g), soy beverages, and soy beverage products (1.5–3 μg/250 mL) [253]. Some recent studies have shown a high prevalence of vitamin D inadequacies despite the mandatory fortification. The Department of Health, the Government of Canada, recently announced that vitamin D fortification levels need to be increased to alleviate the risk of rickets in children and osteomalacia in adults. It proposed that by the end of December 2022, vitamin D level in cow's milk, and goat's milk will be increased to 2 μg/100 ml (current range 0.9–1.2 μg/100 ml) and in margarine, it will be increased 26 μg/100 g (current range 13.3–17.5 μg/100 g) [254]. Fluid milk (2.5 μg/250 mL) and margarine (2 μg/10 g) are also fortified in Finland that had helped the general Finish population to improve vitamin D status. Similar to the United States, Canada fortification policy, edible oil, margarine (0.55 μg/10 g), cow's milk (1.25 μg/250 mL), and ready to eat cereals (5 μg/1/2-¾ cups) are fortified in Australia [255]. Similar approaches can be adopted by other countries to improve vitamin D inadequacy among pregnant women as well as the general population.

Supplement intake can also play an important role in improving vitamin D status among pregnant and lactating women. A recent study assessing maternal vitamin D inadequacies showed that vitamin D supplementation of ≤2000 IU/d minimizes the chance of neonatal mortality [256]. Taking a vitamin D supplement may also reduce the risk of PET, GDM, and low birth weight during pregnancy [257]. The current WHO guideline recommends 200 IU/d of vitamin D supplement intake among pregnant women with vitamin D deficiency to reduce the risk of PET, low birth weight, and preterm birth [258]. In Turkey, free supplementation of vitamin D (1200 IU/d) is provided to all women from early pregnancy to 6 months after delivery [259]. In Canada, pregnant women are suggested to take a vitamin D supplement of 400–600 IU/d [260]. A similar vitamin D supplementation intake approach (400 IU/d) is followed in New Zealand as well during pregnancy The United Kingdom Health Department provides free vitamin D supplementation to pregnant women and newborn children and recommends taking 10 μg (400 IU) of

vitamin D supplements during pregnancy and lactation [261]. Taking vitamin D enriched food and supplement can be advised to maintain optimum serum levels during pregnancy.

9. Conclusion

The existing evidence reveals the importance of adequate vitamin D status during pregnancy for the mother, fetus, and child, although more studies are needed to clarify the exact mechanisms. In a situation where optimal vitamin D status cannot be achieved through diet and sun exposure, food fortification and supplementation seem to be proper approaches. Policies for vitamin D fortification vary across the globe, while more countries are recognizing the importance of vitamin D. The current evidence indicates the need for vitamin D supplementation in pregnant women in a situation that fortification alone cannot address the needs [262]. To our knowledge, only a few countries have free supplementation policies during pregnancy and early life. Effective systematic approaches by relevant agencies and governments are required to synthesize evidence-based recommendations for vitamin D supplementation during pregnancy and customize interventions considering cultural factors to ensure the optimal vitamin D status for pregnant women and their newborns.

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