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Review

Role of vitamin D in pregnancy and Toll-like receptor pathway

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ABSTRACT

There is a growing concern about the impacts of hypovitaminosis D on the health of pregnant woman, fetal development, childhood, and adult life. Variations in maternal nutrition during gestation and/or lactation play a critical role in the physiological and metabolic development of the fetus and neonate, which can induce phenotypic changes and trigger important consequences throughout life, such as type 2 diabetes, cardiovascular disease, obesity, and hypertension. Vitamin D plays a role in regulating cell proliferation and differentiation and in modulating the innate and adaptive immune response. Also, vitamin D correlates with changes in cytokines, anti and proinflammatory, as well as prevents inflammation induced by changes in myometrial cells mediated by the nuclear factor kappa B pathway. Further investigation is required regarding these relationship.

1. Introduction

The inadequacy of vitamin D status has been recognized as a worldwide problem, observed in countries with temperate and equatorial climates, reaching all age groups and leading to many health consequences [1–4]. It is estimated that one billion people worldwide have vitamin D deficiency or insufficiency [5]. In pregnancy, 18%–84% of inadequate 25-hydroxyvitamin D levels has been reported in several populations inhabiting different latitudes, depending on the country, ethnicity, and dietary intake [6].

A review of the sunny Mediterranean region concluded that the prevalence of deficient maternal vitamin D status (25-hydroxyvitamin D (25(OH)D) < 20 ng/mL) is quite common, ranging from 23% to 90%, and the prevalence of insufficient maternal vitamin D status (25(OH)D levels between 20 and 30 ng/mL), ranging from 9% to 41% [7]. In northern European countries, up to 96% of vitamin D insufficiency has been reported in pregnant with 12 and 20 weeks gestation [8].

In the pregnancy, the risk of hypovitaminosis D is high due to increased maternal and fetal demands [9]. Mir et al. [10] reported that the maternal 25(OH)D crosses the placenta and fetus is entirely dependent on the mother for its supply, emphasizing the importance of maternal vitamin D status in this period [11]. Deficient vitamin D status during pregnancy is often associated with adverse outcomes in mothers and their neonates [7]. Thus, there is a growing concern about the impacts of hypovitaminosis D on the health of pregnant, fetal development, childhood, and adult life [12].

In addition to the role of vitamin D in bone homeostasis, recent clinical and experimental studies have shown an association between inadequate 25(OH)D levels and gestational complications as well as neonatal adverse outcomes [13–16].

Vitamin D plays a role in regulating cell proliferation and differentiation and in modulating the innate and adaptive immune response due to the wide tissue distribution of the vitamin D receptor (VDR) in several cell types, such as macrophages, dendritic cells, and lymphocytes [17,18]. Liao et al. [14] mentioned that vitamin D status correlates with changes in cytokines, such as interleukins (IL)-4, IL-5, IL-6, IL-10, IL-13, and interferon-gamma (IFN-γ), as well as prevents inflammation induced by changes in myometrial cells mediated by the nuclear factor kappa B (NF-κB) pathway, observed by *in vitro* studies.

Although there are controversial results regarding the relationship of maternal vitamin D status and its effects in metabolic programming, there is strong evidence that circulating levels below 20 ng/mL during pregnancy will result in bone and non-bone adverse outcomes to the mother and her descendents. The aim of this review is to identify how

Abbreviations: NF-κB, nuclear factor kappa B; TLR, Toll-like receptors; 25(OH)D, 25-hydroxyvitamin D; VDR, vitamin D receptor; DBP, vitamin D-binding protein; 1,25(OH)2D, 1,25-dihydroxyvitamin D; SGA, small for gestational age; IL, interleukine; IFN-γ, interferon-gamma; PTH, parathyroid hormone; FGF 23, fibroblast growth factor 23; APC, antigen-presenting cells; NK, natural killer; TGF-β, transforming growth factor beta; LPS, lipopolysaccharides; PAMPs, molecular patterns associated with pathogens; MyD88, myeloid differentiation primary response gene 88; IRAK, interleukin-1 receptor-associated kinase; TAK, TGF-β-activated kinase; IKK, IκB kinase; IkB, inhibitor of kappa B; RXR-α, retinoid receptor-alpha cofactor.

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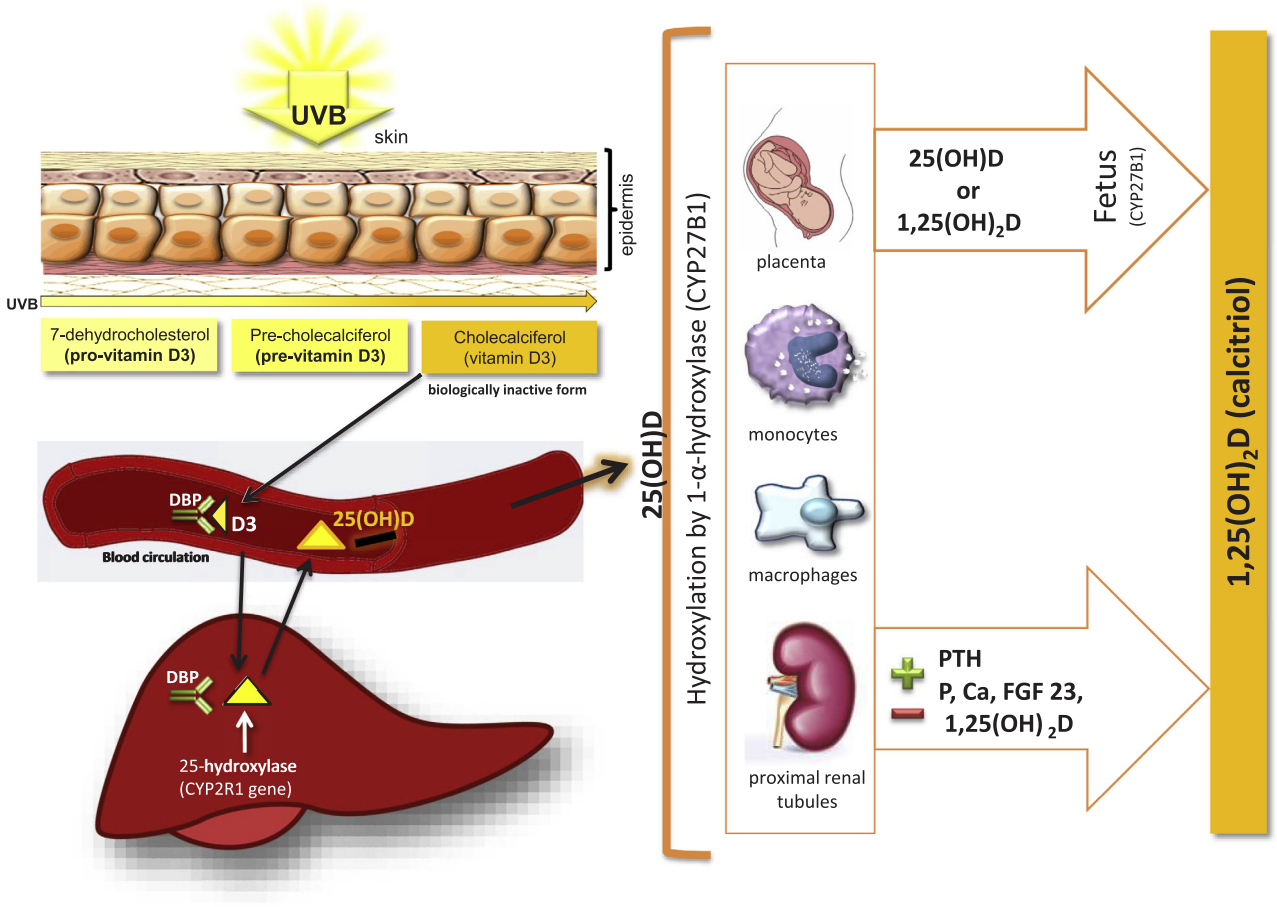

Fig. 1. Schematic representation of vitamin D synthesis and metabolism in pregnant and non-pregnant women. DBP: Vitamin D-binding protein; FGF 23: Fibroblast growth factor 23; 25(OH)D: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D.

vitamin D participates in gestational period in order to evaluate its role in modulation of Toll-like receptors (TLR) pathway and in fetal programming.

2. Vitamin D metabolism and pregnancy

Vitamin D represents a group of lipid soluble substances, including vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol) and its metabolites. Most of the body's vitamin D is formed endogenously by exposing the skin to ultraviolet radiation, resulting in the conversion of 7-dehydrocholesterol (provitamin D3) into precholecalciferol (previtamin D3) and, subsequently, in vitamin D3 in the basal epidermal layers (Fig. 1) [19].

Vitamin D must be converted to its active form to play its role in bone mineral homeostasis and in the immune system [20]. Both vitamin D2 and D3 are hydrophobic and transported in the blood circulation bound to a specific α-globulin, vitamin D-binding protein (DBP), to the liver, and hydroxylated at C-25 position by 25-hydroxylase, encoded by the CYP2R1 gene, which converts vitamin D to the major circulating form 25(OH)D (Fig. 1) [20,21].

In the proximal renal tubules and other tissues (placenta) and cells (monocytes and macrophages), 25(OH)D is hydroxylated at 1-α position by 1-α-hydroxylase, encoded by the CYP27B1 gene, and converted into a biologically active steroid hormone, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The renal synthesis of $1,25(OH)_2D$ is stimulated by the parathyroid hormone (PTH) and suppressed by the calcium, phosphorus, Fibroblast growth factor 23 (FGF 23) and active vitamin D itself (Fig. 1) [22]. In contrast, the placental enzymes 1-α-hydroxylase and 24-hydroxylase are stimulated by cytokines and are not regulated by the same negative feedback that occurs in the kidney [23]. Degradation of 25(OH)D and $1,25(OH)_2D$ to 24,25(OH)D and $1,24,25(OH)_3D$, respectively, occurs by 24-hydroxylase, encoded by the CYP24A1 gene [24].

According to the Institute of Medicine (IOM), the vitamin D Recommended Dietary Allowance for adults aged up to 70 years, including pregnant, is 600 IU daily. However, since this recommendation is not sufficient to maintain a 25(OH)D serum level above 20 ng/mL during pregnancy, the risk of developing hypovitaminosis D in this population is high [20]. However, a study conducted by Wagner et al. [25] demonstrated that levels of 25(OH)D ≥ 40 ng/mL significantly decreased the risk of preterm birth. This finding suggests the importance of reaching 40 ng/mL during pregnancy, aiming reduce the risk of gestational and neonatal complications. Some randomized controlled trials investigated the supplementation of vitamin D to pregnant population. The main finding of these studies was that a 4000 IU daily dose of vitamin D3 safely elevates circulating 25(OH)D to a level that normalizes vitamin D metabolism and calcium homeostasis in pregnant [26–28].

There is a profound change in vitamin D metabolism during pregnancy compared to non-gestational and non-fetal states. At 12 weeks of gestation, serum concentrations of $1,25(OH)_2D$ are greater than double that of a non-pregnant and continue to increase by two to three times,