



Current Topic

Vitamin D effects on pregnancy and the placenta

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ABSTRACT

Vitamin D is a pleiotropic secosteroid hormone important for health and disease prevention. The actions of vitamin D are mediated by the vitamin D receptor that binds the active form of vitamin D [1,25(OH)₂D] to induce both transcriptional and non-genomic responses. Vitamin D has well known classical functions in calcium uptake and bone metabolism, but more recent work highlights the importance of the nonclassical actions of vitamin D in a variety of cell types. These actions include modulation of the innate and adaptive immune systems and regulation of cell proliferation. Adequate vitamin D intake is essential for maternal and fetal health during pregnancy, and epidemiological data indicate that many pregnant women have sub-optimal vitamin D levels. Notably, vitamin D deficiency correlates with preeclampsia, gestational diabetes mellitus, and bacterial vaginosis, and an increased risk for C-section delivery. Recent work emphasizes the importance of nonclassical roles of vitamin D in pregnancy and the placenta. The placenta produces and responds to vitamin D where vitamin D functions as a modulator of implantation, cytokine production and the immune response to infection. We describe vitamin D metabolism and the cellular responses to vitamin D, and then summarize the role of vitamin D in placental trophoblast, pregnancy and the fetus.

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1. Introduction

The vitamin D endocrine system is pivotal for calcium homeostasis, bone mineralization, immune function, cell proliferation, and disease prevention [1]. Vitamin D is not a true vitamin because there are sources other than diet. Instead, this key nutrient is a pro-hormone, which can be synthesized from a steroid precursor if not obtained from diet. Vitamin D was discovered as a preventive treatment for rickets, a disease of children that yields bone softening, fractures, and deformity [2]. The classical actions of this hormone were first described in kidney and bone. We now know that vitamin D is also involved in many nonclassical processes [3]. Vitamin D itself is devoid of biological activity, but enzymatic conversion to 1 α , 25-dihydroxyvitamin D [1,25(OH)₂D] generates the hormonal form with diverse biological activities [4]. The actions of 1,25(OH)₂D are mediated through specific, high affinity binding to the vitamin D receptor (VDR), which is present in multiple tissues [5,6]. Target organs for the nonclassical actions of the vitamin D endocrine system include the adaptive and innate immune systems, pancreatic β -cells, the heart and cardiovascular system, and the brain [6]. Tissue responses include effects on hormone secretion, modulation of immune responses, and control

of cellular proliferation and differentiation [3]. Vitamin D analogs may prove useful to prevent some human diseases and to treat autoimmune diseases and cancer [7,8].

Recent work suggests important roles for the VDR and VDR signaling pathways in the placenta. Human placental trophoblasts express the VDR, and the P450 cytochromes encoded by the *CYP27B1* and *CYP24A1* genes. Trophoblasts both produce and respond to 1,25(OH)₂D. 1,25(OH)₂D regulates synthesis of hormones involved in pregnancy and influences the trophoblast anti-inflammatory and anti-microbial responses [9–13]. In early pregnancy, 1,25(OH)₂D induces decidualization, which is key to implantation [14,15]. Moreover, *CYP27B1* modulates immune function during early gestation [16] and vitamin D deficiency associates with bacterial vaginosis, impaired calcium metabolism and fetal growth, preeclampsia, insulin resistance, gestational diabetes mellitus and primary cesarean section [17–21]. This review summarizes vitamin D metabolism and action, with a focus on the function of vitamin D during human pregnancy and on human placental villi and cultures of placental trophoblasts.

2. Biochemistry of vitamin D and the vitamin D receptor

2.1. Metabolism and transport of vitamin D

Vitamin D is a general term for a chemically related family of secosteroid hormones. Vitamin D₂ is produced in plants and

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vitamin D₃ is produced in mammals (Fig. 1). In humans, vitamin D₂, also called ergocholecalciferol, is one-third as potent as vitamin D₃, which is also called cholecalciferol [22].

Vitamin D can be obtained from dietary sources but can also be synthesized. Ultraviolet B light induces cleavage of the B-ring of 7-dehydrocholesterol in skin to yield the secosteroid vitamin D₃ [1,23] (Fig. 2). Hereafter, “vitamin D” is used to represent either vitamin D₂ or vitamin D₃.

Vitamin D and metabolites are hydrophobic, and >99% are transported in the blood bound to vitamin D binding protein (DBP, also known as Gc-globulin) which binds with high affinity in the order 25OHD = 24,25(OH)₂D > 1,25(OH)₂D > vitamin D₂ or D₃. A small fraction (<1%) of these metabolites are also carried by albumin and lipoprotein [2,24]. DBP-bound vitamin D₂ and D₃ are internalized in the liver and hydroxylated by a mitochondrial P450 enzyme generates 25OHD, which is the predominant vitamin D compound in the circulation. In the renal proximal tubules of the kidney, DBP-25OHD binds to and is internalized by megalin/cubilin, a heterodimeric endocytic receptor pair [25,26]. The 25OHD is released and is hydroxylated by 25-hydroxyvitamin D₃ 1 α -hydroxylase, the product of the *CYP27B1* gene, to yield 1,25(OH)₂D. This kidney generated 1,25(OH)₂D is key in mediating the classical functions of vitamin D in calcium homeostasis and bone mineralization [4,27,28]. The production of 1,25(OH)₂D in the kidney is stimulated by parathyroid hormone and inhibited by fibroblast growth factor 23 and by elevated calcium and phosphate concentrations [29]. Extra-renal expression of *CYP27B1* and 1,25(OH)₂D production from 25OHD occurs in immune cells, the skin, the placenta and other tissues [1,13,30] and may contribute to health in both non-pregnant and pregnant women [13,31,32].

Importantly, both 1,25(OH)₂D and 25OHD are inactivated by *CYP24A1*, a 24-hydroxylase mitochondrial cytochrome p450 enzyme. This hydroxylase converts both substrates into inactive end products, including 1,24,25-trihydroxyvitamin D and 24,25-dihydroxyvitamin D [27,33]. As *CYP24A1* transcription is induced by 1,25(OH)₂D [34], 1,25(OH)₂D provides a negative feedback control on 1,25(OH)₂D levels.

The mechanisms of 25OHD and 1,25(OH)₂D import into most non-kidney tissues are poorly understood. DBP-bound vitamin D compounds have limited effect on most target cells and biological activity often correlates with the free hormone concentration [2,35,36]. This is in agreement with the “free hormone hypothesis” which postulates the active form for most target cells is unbound

1,25(OH)₂D that diffuses across the plasma membrane and binds the VDR to effect either non-genomic, transcriptional, or both, responses [37]. However, megalin/cubilin mediates the import of DBP-bound 25OHD into mammary cells, which express *CYP27B1* and can therefore produce 1,25(OH)₂D intracellularly [38]. Megalin/cubilin-mediated endocytosis may be involved in import of DBP-25OHD into other *CYP27B1*-expressing target cells [39]. One such candidate is the placenta, which expresses megalin and cubilin [40–45]. What has not been studied is whether or not vitamin D compounds enter placental cells by endocytosis of DBP-25OHD, by diffusion of free hormone, or by both mechanisms. Polymorphisms and allelic variants of the vitamin D system have been correlated with disease. Notably, polymorphisms in the *VDR* and *DBP* genes associate with several forms of cancer, multiple sclerosis and chronic obstructive pulmonary disease and polymorphisms in the *VDR*, *CYP27B1* and cubilin genes are associated with type I diabetes [46–50]. Some of these polymorphisms yield altered levels of circulating 25OHD, while others may affect the vitamin D pathway at other levels [46].

2.2. Vitamin D receptor and response pathways

The biological activity of vitamin D occurs via two pathways, a slow genomic response and a rapid, non-genomic response [6] (Fig. 3). Both involve binding of 1,25(OH)₂D with the VDR, a member of the super family of nuclear receptors for steroid hormones [51–53]. In the genomic response pathway, ligand-bound VDR then binds a partner receptor, typically the retinoid X receptor (RXR), and the heterodimer regulates the transcription of vitamin D target genes by binding with high affinity to vitamin D response elements (VDREs) in the promoter region of the gene [2,52]. The VDR contains two globular domains, a DNA-binding domain (DBD) and a ligand-binding domain (LBD) [52,53]. The DBD has two zinc-finger motifs responsible for recognition and binding to the VDREs. The LBD binds to 1,25(OH)₂D with high affinity and is involved in dimerization and transcriptional activation. Coactivators and corepressors also affect VDR molecular action [3,54,55]. The steroid receptor coactivator complex (SRC) 1-3 and vitamin D receptor interacting complex (DRIP) act as coactivators to enhance gene transcription. Corepressors, such as those encoded by the hairless gene, bind to VDR in the absence of ligand and block VDR-mediated transcription but the corepressors rapidly detach from the VDR in the presence of 1,25(OH)₂D. In the non-genomic

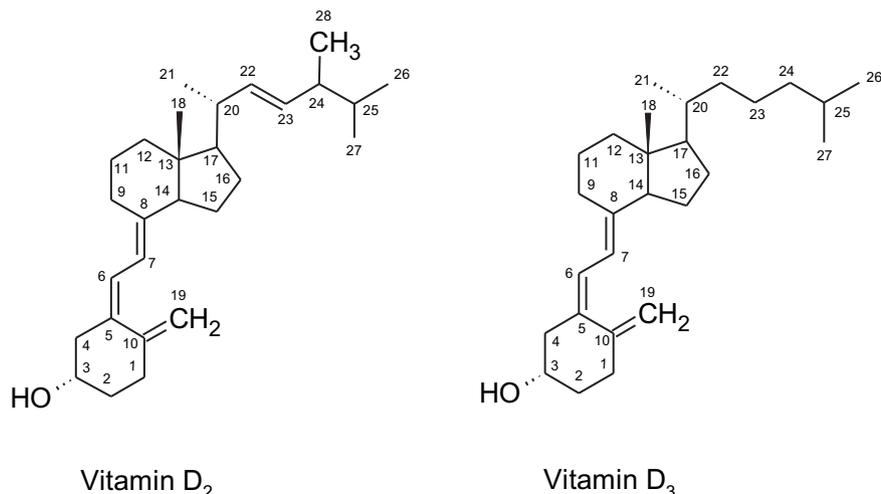


Fig. 1. Chemical structures of vitamins D₂ and D₃.

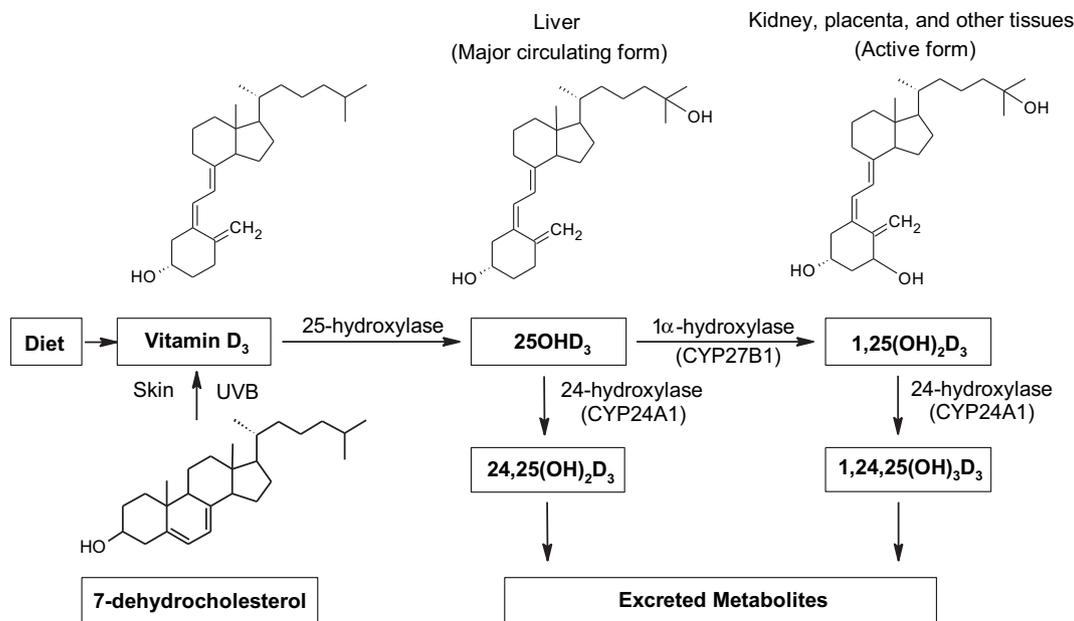


Fig. 2. Synthesis and metabolism of vitamin D. Vitamin D₂ and D₃ can be obtained by diet. Vitamin D₂ is metabolized similarly to vitamin D₃, but with only one-third of the biological activity (see text). Vitamin D₃ is synthesized photochemically in the skin from 7-dehydrocholesterol by ultraviolet B exposure and converted to 25OH D₃ by a 25-hydroxylase in the liver. The major circulating form of vitamin D, 25OH D₃, is hydroxylated in the kidney, placenta, and other tissues by the enzyme, 1α-hydroxylase (encoded by the *CYP27B1* gene), to the bioactive form, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]. The enzyme, 24-hydroxylase (encoded by the *CYP24A1* gene), catabolizes both 25OH D₃ and 1,25(OH)₂D₃ to inactive metabolites 24,25(OH)₂D₃ and 1,24,25(OH)₃D₃, respectively, which are then excreted.

response pathway, 1,25(OH)₂D binds to VDR associated with caveolae of the plasma membrane and the ligand-bound VDR then activates one or more signaling cascades, including protein kinase C, mitogen-activated protein kinases, phospholipase A₂, and phospholipase C [6,56].

3. Nonclassical actions of vitamin D

The classical functions of vitamin D are in the kidney, liver and intestine to regulate calcium and phosphate absorption and bone synthesis and metabolism. Recent data indicate vitamin D functions in nonclassical ways as well. Over 30 human tissues express the vitamin D receptor and are thus equipped to respond to 1,25(OH)₂D [6]. Vitamin D and the VDR play a role in immune function, cell proliferation, cellular differentiation and hormone secretion.

3.1. Regulation of immune function

Vitamin D affects the function of both the adaptive and innate immune systems. In general, 1,25(OH)₂D reduces the activity of the adaptive immune system and enhances the activity of the innate immune system [3,57,58].

In the adaptive immune system, 1,25(OH)₂D inhibits IgG production, proliferation and differentiation of B lymphocytes and inhibits proliferation of T lymphocytes [58–61]. 1,25(OH)₂D also inhibits proliferation of T helper 1 (Th1) cells and thus limits the cytokines produced by these cells. Conversely, 1,25(OH)₂D induces the cytokines of T helper 2 (Th2) and regulatory T cells (Treg) [58,62]. Th1 cells produce interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α) and Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 [63]. Perhaps because of its ability to inhibit the adaptive immune response and inflammation, vitamin D and vitamin D agonists are effective in suppression of autoimmune disorders in several animal models. Among these disorders are rheumatoid arthritis, type 1 diabetes, experimental allergic encephalitis, inflammatory bowel disease,

and systemic lupus erythematosus [7]. Vitamin D analogs are currently being investigated for treatment of autoimmune diseases in humans [64,65]. Recommendations for treatment however must await clinical studies of safety as suppression of the adaptive immune system may compromise resistance to infection.

The innate immune system acts immediately when confronted with microbial infection. This process involves vitamin D and myeloid and epithelial cells that express Toll-like receptors (TLRs), CYP27B1, and the VDR [66–68]. There are ten TLRs in humans and they are activated by binding ligands of microbial origin. Antimicrobial peptides, including α- and β-defensins and cathelicidins, kill organisms in the macrophage and are secreted by epithelial cells [69]. A typical anti-microbial secreted by epithelium is cathelicidin anti-microbial peptide (CAMP), which is also called LL-37/FALL-39 in the cleaved, active form [67,70,71]. TLR activation induces LL-37 secretion in multiple epithelial lined tissues exposed to microbial agents, from salivary glands to reproductive tissues [70]. TLR activation also increases *CYP27B1* transcription, 1,25(OH)₂D levels, and *CAMP* transcription [66,67,70,71]. *CAMP* activation and the response capability is limited if VDR is blocked, *CYP24A1* is inhibited, or 25OHD is deficient. These data show that vitamin D clearly affects multiple arms of the body's immune response.

3.2. Regulation of cell proliferation and differentiation

1,25(OH)₂D can regulate cell cycle progression, cell differentiation and induce apoptosis [8,72–76]. Over the last several decades, 1,25(OH)₂D has been shown to have anti-proliferative and pro-differentiation activity in a variety of cell types, including keratinocytes, osteoblasts, mesenchymal, neural, vascular endothelial, chondrocytes and immune cells. The proliferation effects are mediated, at least in part, by the induction of cell cycle inhibitors that prevent the transition from the G1 to the S phase of the cell cycle, and the differentiation effects by changes in the expression of growth factors and cytokines. 1,25(OH)₂D does not always inhibit

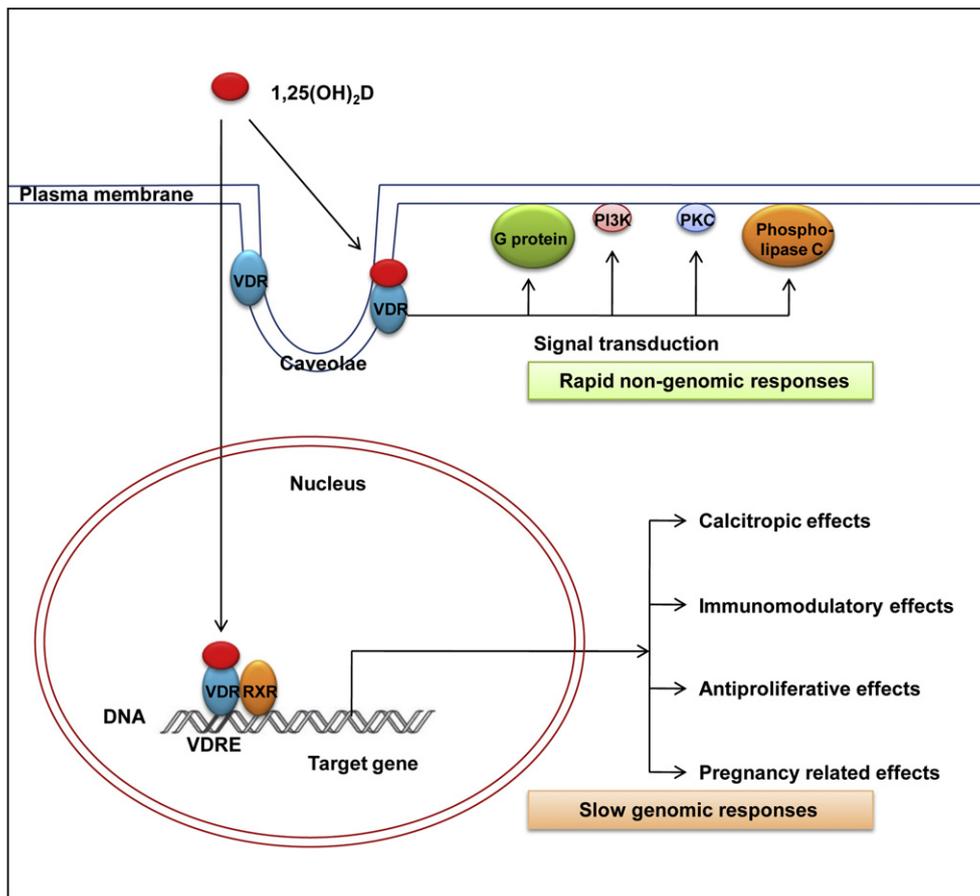


Fig. 3. Genomic and non-genomic responses of vitamin D receptor binding to $1,25(\text{OH})_2\text{D}$. In the genomic response, $1,25(\text{OH})_2\text{D}$ binds to the nuclear vitamin D receptor (VDR). Heterodimerization of the VDR with the retinoid X receptor (RXR) and binding to vitamin D response elements (VDREs) in the promoters of target genes affects transcription, usually by increasing transcription, and generating downstream biological responses. In the non-genomic response pathway, binding of $1,25(\text{OH})_2\text{D}$ to VDR associated with caveolae of the plasma membrane activates one or more second messenger systems to elicit rapid responses. PI3K, phosphatidylinositol-3-kinase; PKC, protein kinase C.

proliferation and promote differentiation: in dendritic cells $1,25(\text{OH})_2\text{D}$ promotes a persistent state of immaturity [77]. Thus, the effects of vitamin D on cell proliferation and differentiation are complex and vary between cell types.

Vitamin D and its analogs have clinical importance in the treatment of psoriasis, a skin condition characterized by keratinocyte hyperproliferation, abnormal differentiation, and immune cell infiltration into the epidermis and dermis [74]. Topical administration of calcipotriene, a vitamin D analog, and corticosteroids are an effective treatment [78]. The anti-psoriatic activity of calcipotriene and other vitamin D analogs likely involves increased differentiation and decreased proliferation of keratinocytes, and reduced expression of proinflammatory cytokines and of several genes, including keratin 16 which is abnormally expressed in psoriatic epidermal cells [74,78].

The anti-proliferative and pro-differentiation effects of vitamin D have recently suggested a role for this hormone in cancer evolution and in the suppression of tumor growth. *Vdr*^{-/-} mutant mice display hyperproliferation of cells in the kidney and mammary gland and develop cancer at elevated rates when challenged with carcinogens [79]. Parathyroid hyperplasia is a serious secondary complication in patients with kidney failure, and recent studies indicate vitamin D or its analogs may have clinical relevance. In a uremic rat model of kidney disease, parathyroid hyperplasia is associated with an increase in expression of transforming growth factor- α (TGF- α) and its receptor (epidermal growth factor receptor, EGFR), are increased [80]. Treatment with

$1,25(\text{OH})_2\text{D}$ diminished TGF- α expression and increased expression of p21^{WAF} with a concomitant reduction in parathyroid cell proliferation [81]. In a recent clinical trial with dialysis patients, intravenous treatment with $1,25(\text{OH})_2\text{D}$ reduced the progression of parathyroid enlargement [82].

Breast, colon, prostate and other cancers are associated with vitamin D deficiency [29,53,83]. Importantly, postmenopausal women who received four years of 1100 IU vitamin D per day and 1500 mg calcium per day had substantially lower risks of many forms of cancer compared to control [84]. Vitamin D and its analogs show promise in the treatment of breast, colon and prostate cancers in animal and cell culture models [8,53,85], likely because of the anti-proliferative, pro-differentiation and pro-apoptotic activities of this hormone. Because the hypercalcemic effects of vitamin D limit its therapeutic application, non-hypercalcemic analogs are more likely to have clinical value. Collectively, these studies show that vitamin D has wide ranging effects on normal and dysregulated cellular growth.

4. Vitamin D effects during pregnancy

4.1. Effects of vitamin D on the placenta and trophoblast cells

The human placenta expresses all components for vitamin D signaling, including the VDR, RXR, CYP27B1 and CYP24A1. Weisman et al. [86] found that human decidual and placental tissues synthesize $1,25(\text{OH})_2\text{D}$ and $24,25(\text{OH})_2\text{D}$. In agreement with these

findings, cultured primary human syncytiotrophoblasts and decidual cells produce $1,25(\text{OH})_2\text{D}$ and secrete the active form into the culture medium [86–89]. Increased levels of $1,25(\text{OH})_2\text{D}$ reduces transcription of *CYP27B1* in primary human cytotrophoblasts and syncytiotrophoblasts [13,34] but transcription of *CYP24A1* increases [34]. Antagonists of VDR can block the $1,25(\text{OH})_2\text{D}$ induced increase in *CYP24A1* levels, suggesting the effect is mediated by ligand-bound VDR [34]. Insulin-like growth factor I (IGF-I), a key regulator of fetal growth, stimulates hydroxylation of 25OHD in a dose-dependent manner in cultured placental cells [90]. In the 3A human trophoblast cell line, unlike in macrophages, *CYP27A1* expression is not increased by TLR2 binding ligand [13,91]. $1,25(\text{OH})_2\text{D}$ inhibits expression of cytokines, such as granulocyte macrophage colony stimulating factor 2 (GM-CSF-2), TNF- α , IL-6, and increases expression of CAMP in primary cultured human decidual cells and cytotrophoblasts [12,13,89]. Importantly, when the 3A trophoblast cell line was exposed to *E. coli*, vitamin D treatment resulted in a lower rate of infection and reduced cell death, likely because of the increased CAMP levels [13]. This finding suggests vitamin D supplementation may reduce infection during pregnancy.

4.2. Vitamin D functions during pregnancy

Important changes occur in the maternal concentration of vitamin D and in calcium metabolism during pregnancy. Calcium is transported from the mother to the fetus through the placenta. In rats, the placenta transports $25(\text{OH})_2\text{D}$ and $24,25(\text{OH})_2\text{D}$ but not $1,25(\text{OH})_2\text{D}$ [92]. Although transplacental transport has not been studied in humans, vitamin D passage from the mother to the fetus would be facilitated by serum concentrations of $1,25(\text{OH})_2\text{D}$ being higher in the maternal compared to the fetal circulations [93]. Synthesis in the kidney of $1,25(\text{OH})_2\text{D}$ increases during pregnancy. In addition, the decidua and placenta generate a large amount of $1,25(\text{OH})_2\text{D}$ by *CYP27B1* enzyme activity [86]. Moreover, specific methylation of the placental *CYP24A1* represses transcription of this gene [94]. Production thus exceeds clearance and $1,25(\text{OH})_2\text{D}$ levels increase, being two-fold higher in serum of women in the third trimester of pregnancy than in non-pregnant or post-partum women [93,95].

The synthesis, metabolism and function of vitamin D compounds during pregnancy are complex. The human endometrial decidua makes $1,25(\text{OH})_2\text{D}$ and $24,25(\text{OH})_2\text{D}$ and the placenta synthesizes $24,25(\text{OH})_2\text{D}$ [86]. Notably, the $24,25(\text{OH})_2\text{D}$ synthesized by the placenta accumulates in bone [92] and may be involved in ossification of the fetal skeleton [86]. Although the sheep fetus can synthesize $24,25(\text{OH})_2\text{D}$ from 25OH and the 24-hydroxylase enzyme is expressed in the fetal kidney [96] the sheep fetus cannot produce $1,25(\text{OH})_2\text{D}$, as renal 1-hydroxylase activity is suppressed in this relatively hypercalcemic and hyperphosphatemic environment. $24,25(\text{OH})_2\text{D}$ is the major form of vitamin D in the fetal lamb [96] and this metabolite, instead of $1,25(\text{OH})_2\text{D}$, may promote calcium absorption by the placenta and enhance skeletal ossification, without increasing fetal blood calcium concentrations or urinary excretion of calcium. If the sheep placenta produces $1,25(\text{OH})_2\text{D}$, as does the human placenta, increased calcium absorption by the maternal gut may be enhanced to meet the increasing demands of the fetus for calcium through gestation.

$1,25(\text{OH})_2\text{D}$ and *CYP27B1* play a role in the autocrine and paracrine immunomodulatory networks prominent during gestation [16]. $1,25(\text{OH})_2\text{D}$ affects decidual dendritic cells and macrophages, which in turn interact in the maternal–fetal interface to stimulate T-regulatory cells [97,98]. $1,25(\text{OH})_2\text{D}$ also inhibits the release of Th1 cytokines and increases release of Th2 cytokines, as

discussed in Section 3.1, and Th2 cytokines thus dominate at implantation [16,63]. This modulation of the immune system may prevent rejection of the implanted embryo. $1,25(\text{OH})_2\text{D}$ also aids in the transformation of endometrial cells into decidual cells [14,97] and increases expression of *HOXA10* [15] a gene important for embryo implantation and myeloid differentiation in early pregnancy [14,15,97].

Established as the chorioallantoic placenta at the end of the first trimester, villous tissues secrete multiple hormones that maintain pregnancy and regulate placental physiology. In human syncytiotrophoblasts, the VDR, *CYP27B1*, *CYP24A1* and $1,25(\text{OH})_2\text{D}$, in an autocrine manner, combine to regulate the expression of human chorionic gonadotropin (hCG), human placental lactogen (hPL), estradiol and progesterone [9–11]. Collectively, the data suggest that $1,25(\text{OH})_2\text{D}$ aids implantation and maintains normal pregnancy, supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines.

4.3. Vitamin D effects on the mother and child

Vitamin D intake is essential for maternal health and prevention of adverse outcomes. Circulating 25OHD concentrations reflect vitamin D status, and the normal range is between ~ 32 ng/mL and ~ 80 ng/mL, with values below ~ 32 ng/mL defined as deficient [29,99] (Table 1). Pregnancy does not exacerbate hypocalcaemia and secondary hyperparathyroidism in people with pre-existing vitamin D deficiency [100]. However, vitamin D deficiency during pregnancy is associated with the nonclassical actions of this hormone, being linked with preeclampsia, insulin resistance, and gestational diabetes mellitus [18,32,98,101,102]. Notably, vitamin D deficiency during pregnancy is of epidemic proportions, present in ~ 20 –85% of women, depending on country of residence and other factors [99,103].

Preeclampsia, as identified by new onset hypertension and proteinuria during pregnancy, is a serious disorder affecting 5–8% of pregnancies, and is alleviated only by delivery of the placenta. Preeclampsia rates are elevated during winter months, when sunlight-dependent 25OHD production is reduced [104], and vitamin D deficiency increases the risk of preeclampsia [18,102]. Vitamin D supplementation reduces preeclampsia risk, compared to unsupplemented controls [101]. Preeclampsia is associated with low circulating levels of IGF-I and $1,25(\text{OH})_2\text{D}$ [102] and, in vitro, IGF-1 increases $1,25(\text{OH})_2\text{D}$ production by primary human syncytiotrophoblasts from placentas from normal pregnancies [90] but not from preeclamptic pregnancies [105]. Furthermore, trophoblasts isolated from the placentas of preeclamptic women have only one-tenth the *CYP27B1* enzyme activity of trophoblasts from uncomplicated pregnancies [68]. Although the role of vitamin D in preeclampsia is unclear [32,102,106], one hypothesis is that low vitamin D levels impair the normal Th1 to Th2 cytokine balance,

Table 1
Risks of vitamin D deficiency (serum 25OHD < 32 ng/mL) during pregnancy to mothers and offspring.

Mother	Fetus and newborn	Child
Preeclampsia [18]	Low birth weight [70]	Bone weakening [120,121]
Gestational diabetes [20]	Craniotabes [115]	Type I diabetes [125]
Cesarean section [21]	Acute lower respiratory tract infection [119]	Schizophrenia [124]
Bacterial vaginosis [17]	Hypocalcemic seizure [116] Reduced femur growth in utero [117] Infant heart failure [118]	Asthma [122,123]

with higher Th1 cytokine expression adversely affecting the immunological tolerance of embryo implantation [107].

Insulin resistance, glucose intolerance, and diabetes are correlated with deficits in vitamin D. 1,25(OH)₂D regulates insulin secretion by pancreatic β -cells and thereby affects circulating glucose levels [32,108,109]. As expected, low concentration of 25OHD is a risk factor for glucose intolerance while higher serum concentrations of 25OHD correlate with improved insulin sensitivity [108]. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy [20].

Vitamin D may influence the course of infectious diseases during pregnancy. In limited studies, low vitamin D levels in HIV-positive pregnant women were correlated with increased mortality and mother-to-child HIV transmission [110,111] and a polymorphism in the *VDR* gene is correlated with the frequency of HIV-to-AIDS progression [112]. Low 25OHD levels are correlated with increased bacterial vaginosis in the first trimester [17] and bacterial vaginosis is more prevalent in black women. Indeed, black women typically have lower serum 25OHD concentrations and have a six-fold higher chance of vitamin D deficiency, compared with white women [17,103]. Vitamin D effects on the immune system, cytokines, and antibacterial peptides likely regulate the bacterial flora.

Serum 25OHD levels are inversely related to primary cesarean section in nulliparous women, an unexpected and unexplained maternal outcome recently identified [21]. The risk was four-fold higher in women with serum 25OHD level below 37.5 nM/L (15 ng/mL) controlling for multiple confounding factors. *VDR* and 1,25(OH)₂D normally increase skeletal muscle function. Conversely, vitamin D deficiency results in proximal muscle weakness and decreased lower extremity muscle function [113], perhaps contributing to the risk for cesarean section [21].

Adequate maternal vitamin D levels are also important for fetal and child health (Table 1). Inadequate vitamin D intake during pregnancy is associated with low infant birth weight in populations at risk for adverse outcomes [114]. Maternal vitamin D deficiency also has been associated with craniofacial [115], a softening of skull bones that is one of the earliest signs of vitamin D deficiency, in a case study with neonatal seizures of a hypocalcemic infant [116] and with impaired skeletal development in utero [117]. Recent retrospective studies found a significant and previously undetected association of maternal vitamin D deficiency with rickets-associated infant heart failure [118] and with acute lower respiratory tract infection [119], a serious complication often associated with sepsis without clinical signs of rickets. Interestingly, vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 yrs of age [120,121], asthma [122,123], schizophrenia [124], and type I diabetes [125].

5. Conclusions

We have described the multiple effects of vitamin D in human health. The classical and nonclassical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection, and cancer. The enzymes encoded by the *CYP27B1* and *CYP24A1* genes are local regulators of levels of 1,25(OH)₂D, which binds the *VDR* to induce both the genomic and non-genomic responses. Importantly, vitamin D analogs offer new potentials for treatments of a variety of diseases and disorders. What is clear is that adequate vitamin D intake in pregnancy is optimal for maternal, fetal and child health. However, vitamin D deficiency is prevalent and this potentially has negative consequences for both mother and child. Clearly, further investigation into the effects of vitamin D, of vitamin D supplementation, and of

vitamin D analogs will contribute to an improvement in human health generally and mothers and children specifically.

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Abbreviations

1,25(OH) ₂ D	1 α ,25-dihydroxyvitamin D
25OHD	25-hydroxyvitamin D
CYP24A1	24-hydroxylase
CYP27B1	1 α -hydroxylase
CAMP	cathelicidin anti-microbial peptide
DBD	DNA-binding domain
EGFR	epidermal growth factor receptor
hCG	human chorionic gonadotropin
hPL	human placental lactogen
IFN- γ	interferon-gamma
IGF	insulin-like growth factor
IL	interleukin
LBD	ligand-binding domain
RXR	retinoid X receptor
Th1	T helper 1
Th2	T helper 2
TLR	toll-like receptor
TGF- α	tumor growth factor-alpha
TNF- α	tumor necrosis factor-alpha
Treg	regulatory T cell
DBP	vitamin D binding protein (Gc-globulin)
VDR	vitamin D receptor
VDRE	vitamin D response element

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