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Review

Vitamin D: Effects on human reproduction, pregnancy, and fetal well-being

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ABSTRACT

Pregnancy places exceptional demands on vitamin D and calcium availability; thus, their deficiencies during pregnancy threaten the woman and her fetus. Globally, vitamin D and other micronutrient deficiencies are common during pregnancy, especially in developing countries where pregnant women have less access to nutritional supplements. Vitamin D deficiency has been reported to be as high as 40% among pregnant women. As a pregnancy progresses, the requirements for vitamin D increase and thus, can worsen preexisting hypovitaminosis D. Consequently, hypovitaminosis D is increasingly associated with a higher incidence of fetal miscarriage, preeclampsia, gestational diabetes, bacterial vaginosis, and impaired fetal and childhood growth and development. This review explores the recent advances in the understanding of vitamin D and the pivotal role it plays in human reproduction, with an emphasis on pregnancy and its outcomes. Given the seriousness of the issue, there is a pressing need for clinicians to become aware of the risks associated with not identifying and correcting vitamin D deficiency. Identifying and correcting vitamin D deficiency, including safe exposure to sunlight, is particularly relevant for those who seek assistance with fertility issues or prenatal counseling, and those in the beginning of their pregnancy. The data point to a significant protective effects of vitamin D during pregnancy when the 25(OH)D serum level exceeds 30 ng/mL before pregnancy and during the first trimester and, sufficient levels are maintained throughout the pregnancy.

1. Introduction

Successful human reproduction depends in part on a hormone created by exposure to UVB radiation, namely vitamin D. Vitamin D adequacy is crucial for optimal maternal and fetal outcomes [1]. Even before a pregnancy begins, vitamin D initiates and/or sustains actions to facilitate fertilization and implantation [2–6]. In the female, having hypovitaminosis D is known to lead to subfertility, infertility, and pathological alteration of critical reproductive tissues, such as the endometrium [7,8].

In both female and male genders, presence of vitamin D deficiency lessens the chance for reproductive success [9,10]. With respect to male fertility, vitamin D influences semen quality, sperm count, and morphology and motility, and plays a role in maintaining DNA integrity in spermatozoa and increasing their viability [7,8]. With respect to female reproduction, the impact of vitamin D deficiency has wider implications; it predisposes to a variety of abnormalities not just for the pregnant women but also for their offspring. Maternal vitamin D deficiency is a global problem. For example, a high proportion of infants

and their mothers in New England (U.S.A.) were reported to have vitamin D deficiency despite the use of prenatal vitamin supplements [11]. Thus, the routine use of prenatal vitamins may not be sufficient (i.e., many multi-vitamins may not contain enough vitamin D) to ensure vitamin D adequacy at the time of delivery.

After a pregnancy is initiated, the persistence of vitamin D deficiency is a recognized threat to the woman and her fetus. Identification and correction of the deficiency during pregnancy is regarded as essential because continuation of the deficiency can inflict permanent damage to the developing fetus [12]. For example, girls who experience infantile rickets because of severe maternal vitamin D deficiency are likely to have a narrow pelvis that creates a physical obstacle to delivering babies and is a known cause of maternal mortality [13].

Even a lesser degree of maternal vitamin D deficiency can be harmful to the woman and fetus. Optimal levels of maternal 25(OH)D [e.g., 40 ng/mL (100 nmol/L)] lead to increased production of 1,25(OH)₂D during pregnancy, which is associated with a marked reduction in the risk of preeclampsia and negative fetal outcomes [14–16]. Meanwhile, serum levels of vitamin D are not affected by

Abbreviations: 25(OH)D, 25 hydroxyvitamin D; 1,25(OH)₂D, 1,25 dihydroxy vitamin D; CYP, cytochrome P450 family; VDR, vitamin D receptor; IU, international units; IOM, institute of medicine; ng/mL, nanograms/milliliter; nmol/L, nanomoles/liter; UVB, ultraviolet B

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molecular polymorphism of its D-binding protein (DBP). However, maternal DBP levels increase with fetal age to the 35th week of gestation [17].

1.1. Vitamin D metabolism

In humans, vitamin D is created by UVB penetration within the epidermis and dermis, where it effects a conformational change in a 7-dehydrocholesterol molecule to become 9,10-secosterol, known as pre-vitamin D₃ [18]. Subsequently, pre-vitamin D enters the circulation bound to vitamin D-binding protein (VDBP) and is transported to the liver, where it undergoes 25-hydroxylation in parenchymal cells to become 25(OH)D [9,19,20]. The final modification into its active form occurs in the kidney tubular cells, generating 1,25(OH)₂D, the hormonal form of vitamin D. This transformation occurs enzymatically in mitochondria of renal tubular cells, by CYP27A1, CYP27B1, and CYP24A1 [19]. In addition, a variety of other cells, such as macrophages possess the ability to transform 25(OH)D into its active, hormonal form outside the kidney [i.e., extrarenal production of 1,25(OH)₂D] [9,20].

Food sources also can provide bioavailable vitamin D, commonly D₂ (e.g., sun-exposed mushrooms) but also as D₃ from fish. D₃ is of animal origin, whereas D₂ is of plant or fungi origin; in circulation, the former has a circulatory half-life twice as long as the latter [10,21,22]. Although both D₃ and D₂ can support physiological needs and maintain a healthy 25(OH)D level, D₂ is less effective in this respect than is D₃ [17]. Furthermore, it has been determined that regular daily dosing of vitamin D—either D₃ or D₂—is considerably more effective in maintaining 25(OH)D levels than is intermittent dosing.

This brings into question the practice of oral-dosing with large boluses, especially D₂, on the order of 50,000–100,000 IU. Recent evidence suggests that D₂ is cleared from the circulation within a week [23]. Nevertheless, both D₂ and D₃ are metabolically transformed into active forms, 1,25(OH)₂D₂ and 1,25(OH)₂D₃ respectively—with both active forms demonstrating comparable affinity to the vitamin D receptor (VDR), whereas the duration of biological activities seems to be different because of the different half-lives [19].

1.2. Vitamin D actions

The active form, 1,25(OH)₂D, initiates both genomic and nongenomic effects via the VDR [3]. Accordingly, the VDRs are located at strategic locations within the cell nucleus and in various locations within cell membranes and can be found in nearly every tissue and a variety of cells [8,19]. Thus, one would expect vitamin D to have pleiotropic effects in all bodily systems.

The nongenomic effects of vitamin D occur rapidly; examples include protein kinase activation, modulation of the electrical state of the cell, and activation of ion channels [19,24]. In contrast, the genomic effects occur over a longer period of time and are mediated by 1,25(OH)₂D via the nuclear VDR, initiating and modulating gene expression [14], which is the engine that drives fetal development. Therefore, vitamin D deficiency places fetal development in jeopardy [1,10].

Abnormalities in the VDR and inadequate availability of 1,25(OH)₂D lead to the signs and symptoms of vitamin D deficiency [20]. However, with respect to pregnancy, overt signs or symptoms of vitamin D deficiency may not be perceived or recognized by the individual, yet may present as a miscarriage or other complication of pregnancy, such as preeclampsia, gestational diabetes, or preterm birth [25–27]. It is important to note that in addition to sun exposure and dietary intake, serum vitamin D levels can be modulated by maternal diseases, affecting maternal and fetal vitamin D levels. For example, women with maternal depression have been shown to have lower serum 25(OH)D levels and deliver lower-birth-weight babies, especially during winter months, than do non-depressed women [28].

1.3. Vitamin D sufficiency vs. insufficiency and deficiency

For all practical purposes, vitamin D insufficiency should be regarded as vitamin D deficiency, especially during pregnancy, because both represent levels of vitamin D insufficient for adequately supporting vital physiological processes; this separation is artificial and not based on science [29,30]. Current evidence supports the concept that to achieve physiological needs, circulating 25(OH)D should be between 40 and 60 ng/mL (100–150 nmol/mL) during pregnancy; to attain such levels in the blood, a daily intake of 4,000 IU vitamin D₃ is needed [9,26,31].

Historically, until the 1990s, medical community equated vitamin D sufficiency with the absence of rickets or osteomalacia, with little or no consideration of vitamin D requirements during pregnancy and various diseases [32,33]. In 1997, the Institute of Medicine (IOM) stated that 200 IU per day of vitamin D is sufficient to satisfy daily needs, with no increase in vitamin D supplementation recommended during pregnancy or lactation [1].

In retrospect, the 1997 IOM efforts were in effect harmful—allowing many pregnancies to proceed under the cloud of hypovitaminosis D. Moreover, it prevented initiation of vitamin D clinical trials using higher doses of vitamin D; all of this was done out of an unfounded fear (in the absence of data) that vitamin D toxicity would result [32,34]. Thirteen years later, another IOM committee was commissioned to weigh in on the issues, but little changed [35]. Common causes contributing to maternal vitamin D deficiencies are illustrated in Table 1.

1.4. Confusing current recommendations

The 2010 IOM committee defined vitamin D insufficiency as values lower than 20 ng/mL; vitamin D deficiency as any value between 10 and 19 ng/mL; and severe vitamin D deficiency as any value below 10 ng/mL [36]. It should be noted that the IOM cutoff value of below 20 ng/mL for insufficiency and deficiency is validated only for North Americans and based on requirements for bone health, and not for

Table 1

Common risk factors for developing maternal vitamin D deficiency.

Source: Adapted from Wimalawansa [9].

-
- Lifestyle issues:
 - Sun avoidance
 - Sunscreen use, skin cover with garments
 - Night shift work/ day sleeping
 - Vegan and vegetarianism
 - Clothing minimizing UVB exposure
 - Personal, social, and cultural factors
 - Dietetic habits: vegetarianism and non-fish diets
 - Environmental:
 - Atmospheric pollution
 - Living in northern or southern latitudes, and high-altitude
 - Season of the year; prolonged winter
 - Genetic:
 - Having darker skin
 - Enzymatic deficiencies
 - Medications altering vitamin D metabolism:
 - Anti-epileptics, glucocorticoids
 - Immunosuppressants
 - Anti-retroviral drugs
 - Pregnancy:
 - Twins or greater-in-number pregnancy
 - Malabsorption syndromes:
 - Celiac disease
 - Crohn's disease
 - Altered microbiota
 - Eating disorders
 - Inflammatory diseases
 - Obesity and over-weightiness
 - Liver or renal impairment (chronic liver or renal failure)
 - Impaired ability to activate vitamin D
-

reproductive health or any other extra-skeletal health issue [1,32,37,38]. Thus, this value cannot be considered or used for conditions and diseases other than skeletal diseases among Caucasians in north America. Shortly after the current IOM recommendations [35], the Endocrine Society rectified some of the issues created in the IOM guidelines [39]; the issues were further clarified by other guidelines [40–46].

In 2011, the Endocrine Society published recommendation that defined values below 20 ng/mL as vitamin D deficiency and values between 20 and 29 ng/mL as vitamin D insufficiency [36,37,39], which is now accepted globally by most [26,39,45]. Although the Endocrine Society's contributions certainly represent an advancement, they do not reflect the physiological level of vitamin D (i.e., sufficiency) required for any special population, including those who are pregnant. The gap of this lack of knowledge is filled by this review.

In concert with others (the majority), the authors believe that a value of at least 30 ng/mL, if not closer to 40 ng/mL, is necessary during pregnancy to ensure maximum benefit to the woman and her fetus [16]. This level of sufficiency would be expected to minimize the chance of a seasonal drop in vitamin D levels into the insufficiency or deficiency ranges; such a drop customarily occurs during the winter months. Therefore, the higher level of 40 ng/mL would better serve the needs of the pregnant woman and developing fetus and be a safer approach.

In the absence of laboratory testing of 25(OH)D levels, the vitamin D status of a pregnant woman will be unknown, so appropriate intervention will be less likely to occur. For women in developing countries and vulnerable groups in whom the prevalence of vitamin D deficiency is high, routine supplementation of 4,000 IU per day is recommended even in the absence of measuring 25(OH)D (which is an expensive and an unaffordable test for most people); this dose is safe and will not cause any adverse effects in pregnant women.

1.5. Prevalence of vitamin D deficiency

Insufficient UVB exposure is the main cause of vitamin D deficiency [47]. Changes in lifestyles and increased exposure to sunlight are difficult to achieve. Apart from supplementation, diet may provide only 10% of the vitamin D needs of an average person [48,49]. Although nonvegetarian (especially fish-based) diets supply some vitamin D₃—yielding a level of 25(OH)D that is 8 ng/mL higher than that of vegetarians and vegans—diet is not effective in achieving vitamin D sufficiency [50]. All things considered, vitamin D deficiency has become a worldwide disease of epidemic proportions [5,51–53].

Diet plus casual sun exposure has proven to be ineffective in preventing the epidemic of vitamin D deficiency in most vulnerable people. This is particularly true when recommended sun-avoidance measures, such as the use of sunscreen, and near-complete or complete skin coverage by clothing, when followed, because such measures compound the problem by creating further deficiencies [47].

In addition, in the late fall through mid-spring, it is nearly impossible to generate vitamin D through the skin by sunlight exposure because the zenith angle of the earth changes more obliquely with respect to the sun, deflecting UVB radiation and thus, preventing atmospheric UVB penetration [18,54]. During this season, supplementation, diet, and the mobilization of vitamin D from storage sites, such as liver and adipose tissue, become the only sources of vitamin D.

1.6. Prevalence of vitamin D during pregnancy

With respect to women of reproductive age and those who are pregnant, the incidence of vitamin D deficiency is surprisingly high [9,26,27,54]. The incidence of vitamin D deficiency is estimated to be as high as 40% in pregnant women [36]. However, this may be an underestimation because one source placed the incidence of suboptimal maternal vitamin D levels on the order of two of every three pregnancies in the United States, with a greater percentage represented by

African Americans and Mexican Americans [55]. Regarding African Americans in the United States, it is estimated that vitamin D deficiency is six times more prevalent than in whites [9,20,53].

A darker skin tone is universally recognized to increase the risk of developing and maintaining vitamin D deficiency; this is due to the UVB-blocking effects of increased melanin content in the dermal skin [18,56]. Depending on the darkness, a darker skinned individual may need 5–10 times longer UVB exposure than does a white-skinned individual to synthesize the same amount of vitamin D [57]. Smoking during pregnancy further reduces serum 25(OH)D levels and negatively affects other calcium-regulating hormones. The latter leads to relative secondary hyperparathyroidism in the mother and her fetus [58]. The situation may be worse in those who are taking anti-epileptic, anti-retroviral, and anti-psychotic medications [59].

2. Reproductive consequences of vitamin D deficiency

The efficiency of the vitamin D hormonal system is almost entirely dependent on substrate availability, with the substrate being any form of vitamin D that can be transformed progressively into the active hormonal form, 1,25(OH)₂D form [56,57]. With few exceptions, the binding to VDR is specific and responds only to 1,25(OH)₂D, but 25(OH)D also can compete for VDR binding at concentrations greater than 10^{x4} [60–62]. One exception is the ability for the VDR to respond to the secondary bile acid lithocholic acid, acting as a sensor to signal to effect downstream responses [63].

The increase from 50% to 100% of maternal blood 1,25(OH)₂D levels from pre-pregnancy to during pregnancy clearly reflects the greater need for vitamin D during this phase of life [64–66]. To achieve this, women need to increase their intake of vitamin D and/or safe sun exposure throughout pregnancy and during lactation periods [64]. 1,25(OH)₂D does not readily cross the placenta, while its precursor 25(OH)D does—placing the fetus in control of generating his or her own “active” vitamin D from available substrate in a controlled manner [51,53]. Accordingly, maternal 1,25(OH)₂D levels do not reflect substrate availability for the developing fetus, but maternal 25(OH)D levels serve as an accurate reflection of vitamin D availability for the fetus [67,68]. In general, fetal blood vitamin D levels are about 70% of that of the mother [1,65].

2.1. Vitamin D deficiency during pregnancy

Often, the consequences of vitamin D deficiency represent a restriction in the ability to synthesize adequate amounts of 1,25(OH)₂D to facilitate essential biological activities. For example, vitamin D deficiency limits the production of the antimicrobial peptide cathelicidin [5,53]. For those who are pregnant, this results in a decreased ability to defend against bacterial infections, including within the reproductive tract [5]. Consequently, bacterial overgrowth can threaten and even end a pregnancy; cathelicidin counteracts this threat [5,53].

In addition to cathelicidin production within the reproductive structures, the trophoblast generates this antimicrobial peptide to protect the fertilized ovum against bacteria assault [69]. The consequences of reduced substrate availability are amply demonstrated by the consequences of vitamin D deficiency and insufficiency during pregnancy [64]. The results of vitamin D deficiency extend beyond birth and can negatively affect both mother and child. Fig. 1 demonstrates various disease and symptomatic ailments that are associated with maternal hypovitaminosis D.

2.2. Fertilization and immune regulation

The act of fertilization is also influenced by 1,25(OH)₂D—VDR mediated nongenomic activity. By increasing intracellular concentrations of calcium, active vitamin D improves sperm–egg binding and increases the activity of acrosine, the enzyme responsible digesting the

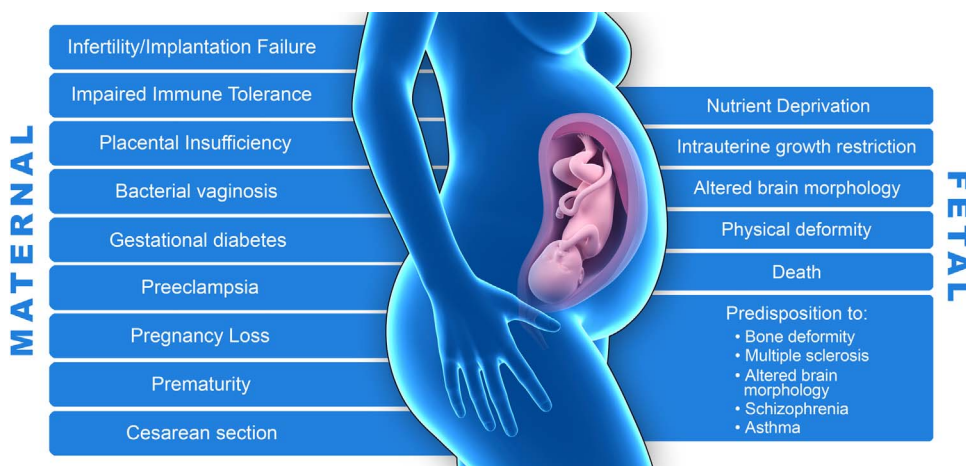


Fig. 1. Maternal and fetal components that are affected or influenced by the presence of vitamin D as well as the vulnerabilities secondary to hypovitaminosis D, are illustrated.

outer wall (i.e., zona pellucida) of the ovum to allow the sperm to penetrate and the complete the fertilization process [2,3]. In women, infertility issues are more complex and beyond the scope of this review.

In the event of fertilization, the female immune system must be influenced to tolerate foreign tissue, as the fertilized ovum transforms into a collection of foreign tissue and cells within the maternal reproductive tract. In this regard, vitamin D in its active form stimulates T_{reg} cell activity to induce immune tolerance and favor implantation, a protective mechanism that has developed during evolution [70].

In a further effort to induce immune tolerance and prevent rejection of the implanted embryo, $1,25(OH)_2D$ inhibits the release of what may be considered pro-rejection Th1 cytokines while favoring the release of tolerance-promoting Th2 cytokines [5]. Vitamin D orchestrates immune tolerance from the beginnings of conception and continues to do so during pregnancy [5]. In addition to the critical roles vitamin D plays in human reproduction, D deficiency has also been shown to associated with failed implantation [54].

In both genders, vitamin D deficiency can compromise fertility. However, not always do the defects lie with the female. Studies have indicated that in infertile couples between 30% and 40% of the infertility responsibility (i.e., the problem) lies with the male partner [55]. Vitamin D has been shown to directly influence sperm motility and viability [71] and the biosynthesis of estrogen and testosterone, the levels of which exert a positive influence on male fertility [72].

2.3. Infertility

With respect to male infertility, a strong association appears to exist between reproductive success and vitamin D status [2,7]. Studies in rodents provide valuable insights [55]. One study on rats found the reproductive success rate was 44% lower in male rats who were made vitamin D deficient compared with rats who were vitamin D replete [73]. VDR knockout mice with vitamin D deficiency have significantly impaired fertility, reduced sperm counts, and fewer mobile spermatozoa [74]. These effects also seem to be present in humans [74].

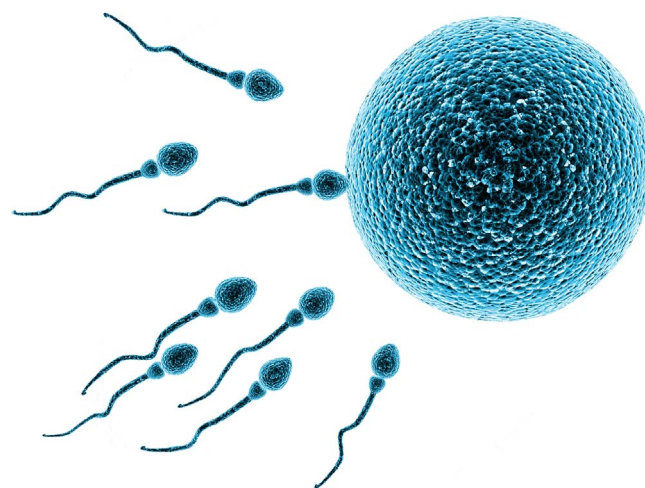
Sperm mobility is affected by a nongenomic elevation of intracellular calcium [3]. The readily available extracellular calcium is present in fluid from the prostate and seminal vesicles [3] and in the fluids in the female reproductive tract [6] and serves to facilitate sperm motility and activity. Importantly, it has been determined that sperm mobility is more relevant to male fertility than is abnormal sperm morphology, highlighting the importance of the nongenomic role of $1,25(OH)_2D$ in sperm mobility and fertilization, notwithstanding indirect evidence [3].

Blomberg et al found that men with a vitamin D level of < 10 ng/mL had a lower number of morphological normal sperm and reduced sperm mobility compared with men with a vitamin D level of > 30 ng/

mL [55,74]. The men in the study were selected from the general population, of which 44% were found to be vitamin D insufficient. In addition, men with testicular dysfunction have low CYP21R expression, thus, low serum and tissue $25(OH)D$ levels and prone to develop osteoporosis, despite normal testosterone levels [55]. Fig. 2 demonstrates physiological functions that are associated with having sufficient levels of material serum $25(OH)D$ levels.

Vitamin D deficiency also may negatively affect female fertility by disrupting ovarian physiology and dysregulating follicular recruitment and selection [4]. For example, the endometrium may become less receptive for implantation in women with hypovitaminosis D [2]. To set the stage for implantation, active vitamin D serves as a potent regulator of growth factors and cytokine expression creating a favorable local environment for implantation, which play critical roles in endometrial receptivity and trophoblastic invasion and placentation [6].

Once fertilization takes place in the fallopian tube, the fertilized ovum passively embarks on a 3- to 5-day journey to the endometrium [75]. This is an assisted journey involving propulsion by a carpet of cilia that line the lumen of the fallopian tube and forward peristalsis by the fallopian tube [75]. Future studies may reveal an important role of vitamin D in these pre-implantation events.



- Reduced sperm counts
- Altered sperm morphology
- Altered sperm motility
- Impaired egg binding and acrosome activation

Fig. 2. The physiological effects of vitamin D on enhancing the efficacy of sperm in fertilization.

2.4. Placental insufficiency

The roles played by vitamin D in implantation and placentation are well established, with placental VDR expression regarded as a critical regulator of the growth of the placenta and fetus [76]. Vitamin D also is considered to play major roles in regulating genes involved in early placental development [77]. In addition, 1,25(OH)₂D increases the availability of vascular endothelial growth factor [78]. Reportedly, pregnant women with 25(OH)D levels below 20 ng/mL have low levels of placental growth factor, which in turn could lead to preeclampsia and fetal growth failure [70,79].

Dysregulation of placental growth leads to placental vascular insufficiency and inflammation; the combination predisposes pregnant mothers to preeclampsia and associated adverse effects [80]. With respect to placental inflammation, vitamin D has been recognized to play a pivotal role in its suppression [69,80]. The classical calcitropic effects of vitamin D and the less well established immunological functions of vitamin D, both are known to influence pregnancy outcome, including physiological functions of the placenta [27].

Placental insufficiency threatens the growth of the fetus by depriving the fetus of adequate oxygen and nutrients. The inflammatory state of the placenta is a product of nitric oxide and cytokine dysregulation, perpetuated in part by vitamin D deficiency, and poses a serious threat to the pregnancy and possibly to the life of mother and fetus [80]. In addition, local generation and release of nitric oxide and calcitonin gene-related peptide (CGRP) is known to subdue development of placental insufficiency and preeclampsia (REFs. [81,82,83]). Clearly, placental insufficiency should be recognized as vascular insufficiency and an insufficiency regarding restraining cytokine aggression and other proinflammatory responses that threaten the pregnancy [65].

2.5. Preeclampsia

Preeclampsia is a hypertensive disorder of pregnancy that can lead to serious consequences if not handled properly. It complicates and threatens the lives of mothers and fetuses, affecting as many as 8% of pregnancies that extend beyond 20 weeks' gestation [84,85]. A great deal of published data support an association between vitamin D deficiency and an increased risk of preeclampsia [86]. Indeed, cross-sectional studies report a significant association between vitamin D deficiency and the risk of preeclampsia and associated complications [87–89].

Vitamin D deficiency is a predisposing factor for the development of preeclampsia [90]. Maternal physiological levels of 25(OH)D are known to modify placental gene transcriptions, including reduction of antiangiogenic factors (e.g., FMS-like tyrosine kinase-1 and vascular endothelial growth factor gene expressions) that may reduce the risks to vascular complication during pregnancy [12]. Evidence supports an immunological etiology and possible toxicity in preeclampsia associated with autoimmunity. These findings emphasize the importance of having vitamin D sufficiency during pregnancy to minimize the risk of preeclampsia.

Vitamin D deficiency increases not only the risks of preeclampsia but also negatively affects the growth and development of the child in later life [91–93]. The incidence of preeclampsia inversely correlates with the serum 25(OH)D levels. One study found a five-fold increase in preeclampsia in pregnant women with a vitamin D level below 15 ng/mL as compared with pregnant women with normal levels of vitamin D [94]. Another study reported a 27% reduction in preeclampsia risk in women taking vitamin D supplements as opposed to those who were not taking supplemental vitamin D [53,86].

Another study reported a strong association between hypovitaminosis D and preeclampsia, demonstrating a reduction in the odds of severe preeclampsia by 38% for every 10 nmol/mL (4 ng/mL) increase in the serum 25(OH)D level [95]. In addition, a baby born to a

preeclamptic mother is five times more likely die during first month than are control subjects [96]—underscoring the extreme seriousness of vitamin D deficiency during pregnancy [86,87].

The timing of effective vitamin D supplementation/availability appears to be an important factor in the prevention of preeclampsia, favorably influencing implantation, placentation, and extra-villous trophoblast invasion [84]. Inadequacies of these physiologic events in early pregnancy enhance the risk of preeclampsia [84,85]. In support of the importance of vitamin D sufficiency in mitigating the risk of preeclampsia, one study found that women who had 25(OH)D levels of at least 30 ng/mL in early as well as late pregnancy had a 2.25% incidence of preeclampsia, compared with an 11.92% incidence of preeclampsia in women who were vitamin D insufficient during early and late pregnancy [84]. Therefore, vitamin D adequacy is an important factor that can be cost-effectively mitigated to prevent the development of preeclampsia in pregnancy.

2.6. Bacterial vaginosis

This relatively common genital infection occurs in as many as 15%–20% of pregnant women. Vitamin D deficiency is associated with an increased risk of bacterial vaginosis [5,53]. Although this may not interfere with the ability to conceive, it causes discomfort to the woman and poses a threat to the viability of a pregnancy [97–100]. Bacterial vaginosis is also associated with reproductive failure, fetal loss, premature rupture of membranes, and premature birth [97,98].

Normal pregnancy requires efficient, well-coordinated, antimicrobial and anti-inflammatory responses at the fetal–placental unit [53]. The constant exposure and the bacterial threat are magnified by bacterial vaginosis. Chronic bacterial vaginosis should be regarded as a fertility issue, with its resolution favoring pregnancy [99,100]. Vitamin D sufficiency minimizes this common reproductive threat and enhances the antimicrobial responses not only in the genital tract but also in the placenta [53]. For example, in one study of 440 pregnant women, those with serum 25(OH)D levels below 30 ng/mL shown to have a threefold increase in bacterial vaginosis [95].

2.7. Gestational diabetes

Gestational diabetes complicates as many as 14% of pregnancies in the United States and can decrease fetal viability and increase the need for C-section [101]. Gestational diabetes also increases the pregnant woman's risk of experiencing type 2 diabetes later in the life and exposes the fetus to an increased risk for congenital and structural abnormalities such as macrosomia, trauma during birth, and respiratory distress syndrome [101].

Many studies have confirmed an association between vitamin D deficiency and gestational diabetes [102–104]. Other observational studies and clinical trials have reported the beneficial effects of vitamin D supplementation during pregnancy with maternal and neonatal outcomes [105,106], including findings from meta-analyses [103,107]. 25(OH)D is hydroxylated by CYP27B1 to the bioactive 1,25(OH)₂D form, and CYP24A1 catabolizes both 25(OH)D and 1,25(OH)₂D to the inactive metabolites; elevated activity of CYP24A1 in the placenta (e.g., under ischemic status, leading to develop preeclampsia) is likely to play a key role in the development of vitamin D deficiency in gestational diabetes [104].

In addition, vitamin D deficiency has been suggested as a risk factor for glucose intolerance [41,107,108]. This is supported by the finding that high-dose, vitamin D supplementation (50,000 IU every 2 weeks) reduces insulin resistance in pregnant women with gestational diabetes [106]. Studies support that hypovitaminosis D can negatively affect the pregnant woman, among others by inducing gestational diabetes, and therefore can impair fetal growth and abnormal growth effects such as macrosomia [106,109]. However, other studies have failed to find such relationships [109], with one study showing no reverse of glucose

intolerance with aggressive bolus-dose vitamin D₂ supplementation in vitamin D-deficient women at less than 28 weeks' gestation [110].

Vitamin D deficiency is associated with an increased risk of gestational diabetes [104,108,111]. Given the positive effects of 1,25(OH)₂D on increasing insulin sensitivity and insulin production, the association between hypovitaminosis D and gestational diabetes is not surprising [112]. Indeed, another study found that mothers with serum 25(OH)D levels below 20 ng/mL at 16 weeks' gestation had a 3.7-fold increase in gestational diabetes compared with those with a 25(OH)D level greater than 30 ng/mL; a 1.36-fold increase in gestational diabetes was reported for every 5 ng/mL decrease in 25(OH)D concentration [48,113]. However, other studies have not been able to confirm a relationship between hypovitaminosis D and gestational diabetes. This may be related to methodological differences, including study designs and smaller sample sizes [101,104,114].

Conflicting reports exist on the relationship between vitamin D deficiency and gestational diabetes, and the differences may be related to the dosages used and serum 25(OH)D levels achieved. For example, one study found that daily doses of 2,000 IU vitamin D were ineffective in significantly reducing insulin resistance in the study participants, whereas doses of 4,000 IU/daily measurably decreased insulin resistance and fasting insulin levels [112]. The authors of that study concluded that vitamin D supplementation on the order of 4,000 IU/daily is necessary to raise maternal vitamin D levels above the 30 ng/mL range [112]. Based on a variety of data, the current authors strongly support this conclusion.

2.8. Intrauterine growth restriction

Intrauterine growth restriction is essentially a placental vascular disorder and leads to inadequate nutritional support of fetal growth. It prevents the fetus from achieving the genetically predetermined growth potential, reprograms the fetal metabolism, and induces circulatory changes to protect the brain and heart from hypoxia at the expense of growth of other tissues. This creates fetal abnormalities that can persist beyond birth [115]. This condition affects as many as 1 in 12 pregnancies and can lead to fetal demise, perinatal asphyxia, meconium aspiration, impaired cognition, and cerebral palsy [116].

Those who survive intrauterine growth restriction have demonstrated later in life an increased risk for several common diseases, such as metabolic syndrome, type 2 diabetes, hypertension, stroke, and coronary artery disease [116]. Vitamin D deficiency is accepted as an easily correctable contributory factor for intrauterine growth restriction and associated placental insufficiency. Although, intrauterine growth retardation has been commonly attributed to placental insufficiency [116], maternal malnutrition also may play a role.

Vitamin D and CGRP plays an important physiological role in placental development, making its deficiency a threat to normal fetal growth and development [66]. In one study, women whose babies experienced signs of intrauterine growth restriction had on average 33% lower vitamin D levels than did women whose infants exhibited normal intrauterine growth at the time of delivery [117]. In this study, the average 25(OH)D level of the mothers giving birth to growth-restricted babies was 16.8 mg/mL, whereas that of the mothers of babies exhibiting normal growth was 25.3 ng/mL.

Underscoring the importance of vitamin D sufficiency for normal fetal growth, a Cochrane Review reported a greater than 50% reduction in low birthweight infants born to women who supplemented with vitamin D during pregnancy compared with the infants of women who did not supplement [118]. In another study, the risk for small-for-gestational age neonates was 2.4 times higher if the mother's 25(OH)D level was less than 12 ng/mL compared with 20 ng/mL or greater during the first trimester of pregnancy [78,118,119].

2.9. Spontaneous abortions, preterm birth, and cesarean section

The consequence of maternal vitamin D deficiency can be severe. Studies involving *in vitro* fertilization have reported the importance of vitamin D to the maintenance of pregnancy [2]. It is estimated that 31% of pregnancies end in loss, with two-thirds of the losses escaping clinical detection [120]. Studies have revealed that women who had normal pregnancy and normal delivery had significantly higher vitamin D levels than did those who experienced spontaneous abortions [121]. In addition to having the right levels and ratio of estrogen/progesterone, having adequate levels of vitamin D protects against spontaneous abortions [122].

Compared with women with recurrent pregnancy losses and normal vitamin D levels, women with recurrent pregnancy losses and hypovitaminosis D have an increased prevalence of autoimmune and cellular immune abnormalities [122]. Pregnant women with vitamin D intake of less than 400 IU per day were the ones who are most vulnerable to pregnancy losses [123]. Furthermore, the women in this study with a 25(OH)D level of 26.4 ng/mL exhibited a four-fold greater chance of reproductive success compared with women with low 25(OH)D levels [2].

Hollis and associates demonstrated a 50% reduction of preterm birth and a 25% reduction in maternal infection in women who were supplemented with 4,000 IU of vitamin D per day compared with woman receiving lesser amounts vitamin D, on the order of 400 or 2,000 IU per day [16,55]. Maternal vitamin D deficiency also leads to increased number of cesarean delivery. One study reported a nearly fourfold increase in cesarean section in women with a 25(OH)D level below 15.2 ng/mL compared with women with a 25(OH)D level greater than 15.2 ng/mL [124].

2.10. Other implications of vitamin D deficiency during pregnancy

Maternal 1,25(OH)₂D levels gradually rise during pregnancy, increasing the maternal "calcium efficiency" to meet the rising calcium demands of the fetus. At the time of delivery, active vitamin D levels are elevated above normal adult values. However, older data using placental vein concentrations reported that infant blood vitamin D levels were significantly lower than maternal values and had no relation to maternal values [125].

By the time infants reached 24 h of age, their serum 25(OH)D concentrations reached normal adult values, with a reduction of the serum ionized calcium concentration to physiologic levels. The authors of the study suggested that low 1,25(OH)₂D concentrations *in utero* correlate with the lack of need for intestinal calcium absorption in the fetus. The postnatal increase of 1,25(OH)₂D may result from its production as a prerequisite to extrauterine requirements for intestinal absorption of calcium and phosphorus [125].

A parallel increase of the vitamin D-dependent protein osteocalcin in blood and tissues also has been reported after delivery [126]. However, an animal study reported that the plasma vitamin D metabolites [25(OH)D; 24,25(OH)₂D, and 1,25(OH)₂D] showed no significant differences 2 weeks before and 4 days after delivery. However, a rapid change in plasma 1,25-(OH)₂D concentrations was reported during the first 2 days [127], reflecting the need for adjustment immediately after birth.

Maternal hypovitaminosis D complicates and compromises newborn health, and the effects of maternal vitamin D deficiency may extend through infancy and beyond. The newborn may present with hypocalcemia, which in the extreme may manifest as a seizure or tetany [1]. In addition, vitamin D deficiency in an infant at birth is reported to slow the development of neonatal cardiac, motor, and brain development [48,124]. An infant whose 25(OH)D level is less than 10 ng/mL and who remains vitamin D deficient is likely to develop rickets or, in the absence of radiologically demonstrable rickets, inadequate bone mineralization and other skeletal abnormalities, like pelvic deformity [1].

3. Management of maternal vitamin D deficiency

Few researchers and clinicians accept that less than 1,000 IU of vitamin D per day is sufficient for successful pregnancy [48]. Accumulated evidence indicates higher doses of supplementation are needed. In addition, to maintain physiological blood 25(OH)D levels greater than 30 ng/mL during pregnancy, regular, consistent UVB exposure is needed.

In a randomized, controlled trial, Hollis and associates gave groups of pregnant women 400, 600, or 4,000 IU of vitamin D daily starting from the 12th to 16th week of pregnancy and continuing until delivery. Those women who received 4,000 IU/day had the most favorable responses, including neonatal outcomes; none of them had any vitamin D-related adverse events [16]. Data from the study also suggest that a level of 40 ng/mL is optimal during pregnancy.

3.1. Optimal serum 25(OH) D level for pregnancy

Most scientists and physicians and the current authors recommend 4,000 IU of vitamin D supplements per day during pregnancy for women who are not receiving relevant sunlight exposure. We suggest that this level of supplementation be adopted by the medical community worldwide, with the goal of achieving maternal serum 25(OH) D levels of approximately 40 ng/mL. With the inherent variation of blood levels, this mode would allow for more than 98% of pregnant women to have serum 25(OH)D levels greater than 30 ng/mL. Table 2 illustrates the maternal beneficial effects of vitamin at various serum 25(OH)D levels.

It is important to maintain blood 25(OH)D levels through supplementation during pregnancy, with the goal of keeping serum 25(OH)D levels between 30 and 50 ng/mL. When the measurement of serum 25(OH)D levels is freely available at an affordable cost, monitoring 25(OH)D levels before pregnancy and during the third trimester should become the standard of practice for the benefit of the pregnant woman and the fetus.

However, affordable testing may not be available for most women in developing countries and those who do not have appropriate health insurance coverage or governmental assistance. Table 3 illustrates the beneficial effects in fetuses and infants, of having normal maternal serum 25(OH)D levels (above 30 ng/mL).

4. Conclusion

The importance of vitamin D to reproductive health is aptly underscored by the results of one study that reported favorable outcomes

from a 6-week supplementation of calcium and vitamin D in pregnant women with gestational diabetes mellitus. This led to a decrease in the rate of cesarean sections, macrosomia, and hyperbilirubinemia, and reduced length of hospital stay for newborns and mothers [141].

Vitamin D supplementation during pregnancy increases the circulating 25(OH)D levels in women and their fetuses. A daily maternal intake of more than 2,000 IU of vitamin D is associated with increased birth weight and infant height but not with other favorable neonatal outcomes [142]. After birth, the requirement for vitamin D sufficiency persists. Because breast milk has little vitamin D, breast-fed infants require oral vitamin D supplementation as liquid drops and/or safe sun exposure [39]. Alternatively, the mother who is breastfeeding may need to supplement with 4,000–6,000 IU of vitamin D daily to enrich her breastmilk to meet the increasing needs of her baby [1].

Most clinical studies have reported the beneficial effects of vitamin D on maternal health and fetal development. Likewise, many studies warn of the dangers of maternal vitamin D deficiency on fetal outcomes. Despite these warnings, the epidemic of maternal vitamin D deficiency continues. Policy makers, administrators, and clinicians need to take the necessary steps to eliminate this easily preventable threat to mothers and infants.

As the statistics bear out, mothers typically are not getting enough vitamin D on their own. The health threats caused by vitamin D deficiency can be addressed effectively only by making pregnant women vitamin D sufficient, one individual at a time. Maternal vitamin D deficiency is easy to resolve through policy decisions in each country and by women taking individual responsibility. Guidance regarding safe sunlight exposure and effective vitamin D supplementation is needed. Dealing with the complications and unfavorable outcomes caused by hypovitaminosis D is challenging, heart wrenching, and expensive.

Pregnancy and lactation are unique (calcium-stress) situations, during which a deficiency of vitamin D (and calcium) in the mother creates a vitamin D deficiency in another; the negative consequences can be far reaching. Studies report maternal vitamin D deficiency predisposes infants to many common diseases later in life, autism, asthma during the childhood, type 1 diabetes, multiple sclerosis, and schizophrenia as adults [48,143,144]. It follows that the maternal vitamin D sufficiency will reduce the incidence to these challenging and expensive medical conditions and lessen the impact they have on individuals and our society.

Given the importance of vitamin D to reproductive health, including maternal well-being and fetal outcome, clinicians should take the steps necessary—aside from policy and current practice—to prevent the epidemic of vitamin D deficiency during pregnancy from playing out in the lives of those under their care. The risks are too great to not do so

Table 2
Maternal benefits of optimizing serum 25(OH)D levels.^a

Benefit	Serum 25(OH)D levels (intervention)	Statistical significance	References ^a
Fewer overall pregnancy complications	≥ 30 ng/mL		[16,121,122,128–135]
Fewer cesarean sections (4 times less likely)	≥ 15 ng/mL (37.4 nmol/L)	p = .012	[128]
Less preeclampsia (2 to 4 times less likely)	≥ 20 ng/mL (50 nmol/L)		[70,136,137]
Better outcomes with no adverse effects	4,000 IU/day, effective in achieving sufficiency	Safety	[16,129]
Improved outcomes	Multiple		[138]
Reduced incidence of preterm birth (by 57%)	≥ 40 ng/mL vs. ≤ 20 ng/mL		[139]
Reduced spontaneous abortions	> 20 ng/mL		[121,122]
Less periodontal diseases and dental caries	≥ 30 ng/mL	P < .05	[140]
Less bacterial vaginosis	≥ 25 ng/mL	P = .04	[134]
Reduced gestational diabetes	50,000 IU twice during pregnancy	p = .02	[131,135]
Improved insulin sensitivity in gestational diabetes	Calcium 1,000 mg/day and vitamin D ₃ 50,000 IU twice a month	p = .03	[131]
Improved insulin sensitivity	vitamin D (50,000 IU twice a month), and omega-3 fatty acids (2,000 mg/day)		[130,131]
Lesser incidence of postpartum depression	32 ng/mL	Significant inverse relationship	[132,133]

^a Data presented are from multiple studies, including www.vitamindwiki.com.

Table 3
Offspring benefits of optimizing maternal 25(OH)D levels.

Benefit	Notes	References ^a
Increased bone mineralization/rickets prevention	Skeletal effects have been reported in several studies (one of the first hazards of maternal vitamin D deficiency identified)	[70,79,124,137]
Decreased risk of atopic disorders -Asthma -Eczema -Hay fever	Decreased risks of asthma and eczema have been reported in children of mothers with higher 25(OH)D levels during late pregnancy (> 30 ng/mL vs. < 12 ng/mL) [5,48,49,53,70,79,124]	[5,48,49,53,70, 79,124]
Reduced risk of language difficulties	25(OH)D levels < 18 ng/mL associated with language difficulties at ages 5 and 10 years [70,79,124,138]	[32,33,70,79]
Reduced lower respiratory tract infection	Vitamin D deficiency at birth associated with higher risk of lower respiratory tract infection during the first 3 months of life [25(OH)D levels, 10–30 ng/mL (OR = 1.39); 25(OH)D < 10 ng/mL (OR = 2.16)]	[70,79,124,138]
Reduced risk of maternal transmission of HIV	Children born of vitamin D-deficient mothers in Tanzania (at 12–27 weeks' gestation) had (A) 46% increased risk of HIV infection by 24 months of age [5,48,49,53,70,79,124], and (B) 103% higher risk of HIV transmission through breastfeeding at age 24 months (95% CI 8%–282% [16,129]	[70,124,136,137]
Reduced risk of type 1 diabetes	Incidence is diabetes decreased in those who are vitamin D sufficient	[5,48,49,53,70,79, 124,138]
Reduced risk of multiple sclerosis	Incidence and the severity of diabetes is decreased with vitamin D sufficiency	[5,48,49,53,124]
Reduced risk of schizophrenia	In males [5,48,49,53,70,79,124]	[48,49,124,138]
Reduced risk of autism	Vitamin D deficiency during pregnancy and childhood, both seems to contribute	[5,53]
Reduced risk of diseases, such as ailments associated with metabolic syndrome, in adulthood	Type 2 Diabetes Hypertension Stroke Coronary artery disease	[116]
Fulfilled growth potential		[70,79]

^a Referenced, data presented are from multiple studies.

and may lead to legal vulnerability in years to come.

Conflicts of Interest

The authors have no conflicts of interest.

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