Published in final edited form as:

Expert Rev Clin Immunol. 2015 ; 11(9): 1055–1063. doi:10.1586/1744666X.2015.1056780.

Immunomodulatory Role of Vitamin D in the Pathogenesis of Preeclampsia

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Summary

Worldwide, preeclampsia is a significant health risk to both pregnant women and their unborn children. Despite scientific advances, the exact pathogenesis of preeclampsia is not yet fully understood. Meanwhile, the incidence of preeclampsia is expected to increase. A series of potential etiologies for preeclampsia have been identified, including endothelial dysfunction, immunological dysregulation, and trophoblastic invasion. In this literature review, we have critically reviewed existing literature regarding the research findings that link the role of vitamin D to the pathogenesis and immunoregulation of preeclampsia. The relationship of vitamin D with the suspected etiologies of preeclampsia underscores its clinical potential in the diagnosis and treatment of preeclampsia.

Keywords

Cathelicidin; Endothelial dysfunction; Immunomodulation; Preeclampsia; Vitamin D

Introduction

Hypertension-related disorders of pregnancy are leading causes of morbidity and mortality for pregnant women and their infants worldwide (1). Preeclampsia is defined as new onset hypertension with proteinuria that may be accompanied by end organ dysfunction (1–3). To

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Financial and competing interest's disclosure

The authors were supported by research grants R01 HL106042, R01 HL112597, and R01 HL120659 to DK Agrawal from the Office of the Director of National Institutes of Health and the National Heart Lung and Blood Institute, NIH, USA. The content of this review is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, USA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

be categorized as preeclampsia, these symptoms must occur in a previously healthy pregnant woman after 20 weeks of gestation (1–3).

Preeclampsia is associated with adverse maternal and fetal outcomes including placental abruption, cerebral hemorrhage, hepatic failure, pulmonary edema, renal failure, disseminated intravascular coagulation, low birth weights, blindness, progression to eclampsia, and death (2, 4). In addition to these adverse outcomes, preeclampsia has been associated with the development of maternal heart disease later in life (1). Despite the severity of this disease, its exact etiology is incompletely understood (5), and is currently an area of active research.

Recent investigations have underscored the importance of vitamin D levels as a potential risk factor in the development of preeclampsia (2, 3). In this article, we reviewed and summarized much of the existing literature on the role of vitamin D in preeclampsia. We conducted a literature search via MEDLINE COMPLETE using the terms related to vitamin D, preeclampsia and pregnancy. Search terms included: preeclampsia, vitamin D, vitamin D pregnancy, vitamin D immune regulation, vitamin D preeclampsia, pathogenesis preeclampsia, trophoblastic invasion vitamin D, placenta vitamin D, and placenta vitamin D preeclampsia. Articles published from 2001–2015 were included, with the majority being published after 2010.

Epidemiology of Preeclampsia

Preeclampsia occurs in an estimated 7.5% of pregnancies worldwide (6), and in about 3.4% of pregnancies in the United States (7). Some estimates place the preeclampsia incidence as high as 8% of all pregnancies worldwide (7). There is evidence that increases in preeclampsia risk factors, including obesity, will cause the incidence of preeclampsia to rise (6–8). For example, an article by Jeyabalan et al. (7) observed that, as obesity rates rise, the rates of preeclampsia seem to increase concomitantly.

As a disease, preeclampsia is devastating. For every 100,000 live births there is one maternal death due to preeclampsia (9). For mothers that survive, long-term health risks have been identified (1). Globally, ten-to-fifteen percent of all maternal deaths caused by obstetric-related pathologies can be attributed to preeclampsia-related complications (4). Taken together, these studies underscore the burden that preeclampsia represents to world health.

A graphic summary of major worldwide causes of obstetric morbidity and mortality, including hypertensive-disorders, is provided in Figure 1.

Diagnosis and Treatment of Preeclampsia

Clinical Diagnosis

The American College of Obstetricians and Gynecologists (ACOG) has established specific guidelines for diagnosing preeclampsia, as summarized in Figure 2. The ACOG standards are divided into three broad categories: hypertension, proteinuria, and proteinuria alternatives. To be clinically diagnosed with preeclampsia, a woman must have been pregnant for twenty weeks or more and must meet the following criteria: elevated blood

pressure with proteinuria or elevated blood pressure with a “proteinuria alternative” (1). The specific diagnostic criteria are discussed in the following sections.

Hypertension—In the preeclampsia algorithm, systolic blood pressure greater than 140 mmHg or diastolic greater than 90 mmHg must be observed on at least two occasions with more than four hours between blood pressure measurements (1). Alternatively, the systolic pressure reading above 160 mmHg or diastolic pressure reading above 110 mmHg can meet this requirement, if verified during the same office visit (1). Any woman past twenty weeks gestation who meets these criteria is considered at elevated risk for preeclampsia.

Proteinuria—In the preeclampsia algorithm, proteinuria is diagnosed by the protein level of greater than or equal to 300 mg in the 24-hour urine (1), a protein-to-creatinine ratio greater than or equal to 0.3 (1), or a urine dipstick reading of 1+ (1). Although proteinuria is often present in women with preeclampsia, it is not required to reach a clinical diagnosis.

Proteinuria Alternatives—If a woman past twenty weeks gestation has new onset of hypertension without proteinuria, she can still be diagnosed with preeclampsia if she experiences new onset of any of the following: thrombocytopenia (platelet count less than 100,000 per μ L), serum creatinine greater than 1.1 mg/dL, doubling of serum creatinine concentration (with no history of renal disease), or liver transaminases at twice the reference range (1).

Treatment

Currently the only curative treatment for preeclampsia is delivery (10). However, early delivery can harm the fetus. Fortunately, both preventative and symptomatic treatment modalities are available to preeclamptic women. The goal of these therapies is to manage the severity of maternal symptoms so that the fetus has more time to develop *in utero*. Research endorsed by ACOG has concluded that small daily doses of aspirin (60–80 mg) have a slight preventative effect (1). Accordingly, ACOG recommends low dose aspirin regimens to women who are at high risk of developing preeclampsia after 12 weeks gestation (1). Contrary to what has been done historically, bed rest and salt restriction have not been shown to provide measurable benefit to women with preeclampsia (1).

The treatment of intrapartum preeclampsia depends on the severity of maternal symptoms. The Task Force on Hypertension in Pregnancy has established a series of recommendations regarding the management of women with preeclampsia. These guidelines are evidenced based and each recommendation is supported by available scholarly evidence. The treatments focus on monitoring proteinuria and hypertension, controlling hypertension, relaxing uterine smooth muscle, and, in extreme cases, relieving severe symptoms by delivering the fetus (1). The following paragraphs summarize the specific suggestions of the Task Force on Hypertension in Pregnancy.

Preeclamptic women at 34 weeks gestation or more—Women with unstable symptoms that have reached 34 weeks gestation should receive medical stabilization and labor induction (1). Women who have reached 34 weeks gestation that have controlled preeclampsia should receive doses of corticosteroids to stimulate fetal lung development (1).

Steroid doses are precautionary and antenatal steroid treatment prepares fetal lungs and increases the chance of survival in case emergency induction of labor becomes necessary.

Preeclamptic women before 34 weeks gestation—Women with stable symptoms of preeclampsia who have not yet reached 34 weeks gestation should be monitored closely in an inpatient setting (1).. If these women present with a blood pressure over 160 mmHg systolic or 110 mmHg diastolic, they should receive immediate antihypertensive therapy (labetalol or hydralazine being common agents) to correct blood pressure abnormalities,(1). Magnesium sulfate is recommended in women with preeclampsia as a means of preventing progression to eclampsia (1). Magnesium is also indicated in women with eclampsia to slow the progression of disease and to manage disease severity (1).

As per Task Force recommendations, if a woman continues to have severe symptoms of preeclampsia after the administration of treatment, the fetus should be delivered (1). Severe symptoms of preeclampsia include: refractory hypertension, HELLP syndrome characterized by hemolysis, elevated liver enzymes and low platelet count, eclampsia, placental abruption, pulmonary edema, disseminated intravascular coagulation, evidence of fetal stress, or death of the fetus (1).

Pathophysiology of preeclampsia

Although the exact cause of preeclampsia is unknown, recent research has identified a few potential causes. These causes include endothelial cell dysfunction, immune dysregulation, and dysfunctional trophoblastic invasion (2, 5, 11–14). Evidence in the literature links vitamin D deficiency to each of these potential causes of preeclampsia (2, 5, 11, 12). This review explores each of these putative causes of preeclampsia, followed by the discussion on the role of vitamin D deficiency in their respective pathogenesis.

Endothelial Dysfunction

Preeclampsia is a hypertensive disorder of pregnancy characterized by widespread endothelial cell dysfunction (10). Recent studies have suggested that endothelial cell dysfunction may be a major driving cause of preeclampsia (5). This hypothesis is supported by the presence of increased levels of maternal anti-angiogenic cytokines, including soluble fms-like tyrosine kinase 1 (sFlt-1), which is secreted by the placenta (5, 10, 11). For example, Maynard et al. (10) found high concentrations of sFlt-1 weeks before the onset of preeclampsia. The sFlt-1 competitively binds to placental growth factor and vascular endothelial growth factor, inhibiting their ability to promote vascular invasion and endothelial proliferation (5). The process by which sFlt-1 is thought to affect vascular cells is summarized in Figure 3. Research by Wei et al. (5) has shown that although sFlt-1 is produced by the placenta in normal pregnancies, it is produced in significantly higher quantities in preeclampsia. Wei hypothesized that increased levels of sFlt-1 may lead to widespread vascular endothelial dysfunction (5). Manifestations of vascular endothelial dysfunction include hypertension and proteinuria (two hallmarks of preeclampsia). These studies support the claim that endothelial cell dysfunction contributes to the etiology of preeclampsia (10).

Vitamin D in Endothelial Dysfunction

Although vitamin D has not been shown to directly change the sFlt-1-induced vascular dysfunction pathway, recent in vitro studies have suggested that vitamin D may improve angiogenesis (5). Evidence suggest that the opposite is also true. Wei et al, (5) for example, found that gravid women with decreased vitamin D levels (below 50 nmol/L serum 25(OH)D level) had corresponding decreases in placental growth factor concentrations. This study suggests that vitamin D insufficiency may underlie the endothelial dysfunction associated with preeclampsia. Vitamin D appears to be important in maintaining vascular endothelial stability and normal angiogenesis.

Immune Dysfunction

There have been several studies that suggest that immune dysfunction is involved in the pathogenesis of preeclampsia. Supporting evidence for this hypothesis include the fact that women with autoimmune diseases have higher rates of preeclampsia (15), and women with preeclampsia have higher levels of pro-inflammatory cytokines such as TNF- α and IL-6, as well as lower levels of the anti-inflammatory cytokine IL-10 (14, 16). Several studies have used animal models to demonstrate the potential role of these cytokines in the development of preeclampsia. A study conducted by Sunderland et al. (17) found that pregnant baboons given a 2-week infusion of low dose TNF- α developed increased blood pressure and proteinuria. In a separate study, Orshal and Khalil (18) demonstrated that a two-fold increase of IL-6 in pregnant rats lead to the development of hypertension. The authors hypothesized that this finding is due to IL-6 inhibition of vascular relaxation and thus enhanced vascular contraction (18). In a research study conducted by Lai et al. (19) it was found that an IL-10 knockout mouse exposed to a hypoxic environment developed preeclampsia. These studies suggest that immune dysfunction, specifically with increased levels of IL-6 or the deficiency of IL-10, plays a significant role in the pathogenesis of preeclampsia.

Dysfunctional Trophoblastic Invasion

Trophoblastic invasion and the formation of the placenta play a critical role in the pathogenesis of preeclampsia (14). Insufficient or reduced trophoblastic invasion can cause placental hypoxia, which leads to increased production and release of pro-inflammatory cytokines, anti-angiogenic factors, and a decrease in IL-10. This cascade of immune dysfunction and changes in angiogenesis contribute to endothelial cell dysfunction, which then leads to the clinical manifestations of preeclampsia (14). Studies have shown that women with higher circulating IL-10 levels have lower blood pressure during pregnancy (14). One study even demonstrated that the administration of an anti-IL-10 antibody to pregnant baboons increased their blood pressure (14). One mechanism by which IL-10 is thought to lower maternal blood pressure is by inhibiting the pro-inflammatory Th1 cytokines, including TNF- α (14), which have been shown to raise maternal blood pressure, a hallmark of preeclampsia.

Vitamin D as an Immune Regulator

Vitamin D receptors are found on nearly every tissue type in the human body (20). In addition, vitamin D receptors are broadly present on nearly all immune cells, including T-

lymphocytes (Th1, Th2, Tregs), B-lymphocytes, dendritic cells, Th17 cells, monocytes, and macrophages (21–23). The 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$), the hormonally active form of vitamin D, modulates the expression of cytokines (21–23). When bound to its receptor, $1,25(\text{OH})_2\text{D}_3$ has been shown to significantly affect transcriptional activity within cells (23). Figure 4 illustrates some of the pathways by which vitamin D either inhibits or up-regulates the expression of cytokines in dendritic cells, Th1 cells, Th2 cells, CD8+ cells, T-regulatory cells, B-cells, monocytes, and macrophages (22, 23).

The $1,25(\text{OH})_2\text{D}_3$ decreases the activity of Th1 cells by decreasing the production of IFN- γ , IL-2, IL-12 and TNF- α (21–23). This effect comes with a complementary increase in the activity of Th2 cells, particularly because of an increase in IL-10, and a decrease in IL-2 secretion (21–23). $1,25(\text{OH})_2\text{D}_3$ has also been found to have an inhibitory effect on Th-17 cells (22). This effect is most likely tied to its inhibitory effect on IL-6 and IL-23 production (22). Similarly, Akbar et al. (21) found $1,25(\text{OH})_2\text{D}_3$ to be inhibitory to the maturation of dendritic cells. This inhibitory action leads to a population of immature dendritic cells, contributing to the inhibition of certain markers (including CD40, CD80, and CD86, and MHC II) (21). The $1,25(\text{OH})_2\text{D}_3$ also causes a down-regulation in the dendritic cell production of IL-12 and an increased production of IL-10 (21).

While largely inhibitory effects, $1,25(\text{OH})_2\text{D}_3$ has also been found to serve a stimulatory function in certain pathways. For example, vitamin D contributes to the activation of T-regulatory cells (2, 23). In the setting of pregnancy, increased T-regulatory cell activity is essential for the development of a maternal environment in which there is no immune response against the fetus (2). Vitamin D mediates its stimulatory effect on T-regulatory cells by upregulating forkhead box protein 3 (FOXP3), a factor that supports the differentiation and expansion of T-regulatory cells (22). This role is of significant clinical significance in the setting of organ transplants, inflammatory diseases, autoimmune diseases, and others. $1,25(\text{OH})_2\text{D}_3$ has also been found to increase the production of IL-1 (a pyrogen) and cathelicidin (a bactericidal peptide) (22).

Epigenetic Effects of Vitamin D

A recent review article published by Hossein-Nazhad et al. (24) suggests that vitamin D has effects on placental development, fetal development, and epigenetic expression of the developing fetus (24). They conclude that vitamin D plays a role in placental implantation by regulating implantation-associated genes, such as Homeobox A10. Hossein-Nazhad et al (24) also found vitamin D to have potent immunosuppressive effects that play a role in placental development. Neonatal rats, for example, who were exposed to low levels of maternal vitamin D in utero had slowed cardiac development and decreased heart weight (24). In humans it has been found that 2-year-olds with dilated cardiomyopathy and hypovitaminosis D experienced improvement in cardiac function after vitamin D supplementation (24). This study also suggested that vitamin D deficiency during pregnancy impairs both maternal skeletal health and fetal skeletal formation. Moreover, vitamin D deficiency increases the risk that a fetus will develop chronic asthma, type 1 diabetes, food allergy, type 2 diabetes, cardiovascular disease, osteoporosis, and cancer (24). This research

underscores both immediate and long-term consequences of vitamin D deficiencies to both mother and fetus.

Role of Vitamin D in Preeclampsia

A number of investigators have recognized the potential role of vitamin D in preeclampsia (11, 13, 23–32). For example, Xu et al. (11) conducted a retrospective study investigating both maternal IL-6 levels and vitamin D levels in the third trimester. The study concluded that women with maternal vitamin D deficiency are five-times more likely to develop preeclampsia than their vitamin D competent counterparts (11). Xu and colleagues hypothesized that since vitamin D influences the inflammatory response outside of pregnancy, vitamin D deficiency may be associated with the increased inflammation seen in preeclampsia (11). Xu et al. confirmed that there is an association between elevated IL-6 levels and the incidence of preeclampsia (11), and added that preeclamptic women have on an average 14% less vitamin D than healthy controls (11). Despite these associations, their assertion that low maternal vitamin D levels lead to elevated IL-6 levels was not supported (11). Xu et al. (11) concluded that, while the relationship between elevated IL-6, hypovitaminosis D, and preeclampsia is not clear, there is in vitro evidence suggesting that low vitamin D levels in non-pregnant patients are associated with increased inflammation (11).

A study by Reslan et al. (13) similarly linked preeclampsia to low serum vitamin D levels, and proposed an alternative explanation for the link between vitamin D deficiency and preeclampsia. Rather than emphasizing the immune modulatory capabilities of vitamin D, Reslan and colleagues hypothesized that preeclamptic changes are tied to decreased calcium absorption in vitamin D deficient subjects (13). This study concluded that, as a major cofactor in calcium absorption, decreased plasma calcium is associated with increased blood pressure and increased urine protein output (13). Reslan et al. used two animal models to support this hypothesis. First, pregnant ewes have been shown to have decreased plasma calcium that corresponds to preeclampsia-like effects (13). Similarly, in rats, decreased plasma calcium increases the ability of angiotensin II to cause vascular smooth muscle contraction (13). The authors concluded by proposing that decreased vitamin D led to decreased calcium absorption, causing the systemic effects of preeclampsia.

A study by Diaz et al. (8) investigated the ability of placenta to synthesize $1,25(\text{OH})_2\text{D}_3$ and the level of vitamin D receptor expression within placental cells. They proposed that increased serum $1,25(\text{OH})_2\text{D}_3$ is one mechanism through which expectant mothers are able to increase calcium absorption during pregnancy (8). They found that human placental tissue synthesizes $1,25(\text{OH})_2\text{D}_3$ through cytochrome P450 1α -hydroxylase (8). They suggest that, since low levels of $1,25(\text{OH})_2\text{D}_3$ are associated with preeclampsia, there is a possibility that preeclampsia and chronic hypertension during pregnancy may be due to deficient production of $1,25(\text{OH})_2\text{D}_3$ by the placenta (8). Further, they found that syncytiotrophoblasts from preeclamptic placentas had a reduced ability to synthesize $1,25(\text{OH})_2\text{D}_3$ when compared to syncytiotrophoblasts from normotensive placentas (8). Preeclamptic placentas also expressed less 1α -hydroxylase mRNA at all stages of pregnancy compared to normotensive placental tissue (8). Diaz et al. (8) proposed that deficiencies in circulating $1,25(\text{OH})_2\text{D}_3$

levels in preeclampsia may be caused by deficient 1α -hydroxylase expression at the level of the placenta.

Robinson and co-investigators (3) suggested an association between low maternal 25-hydroxyvitamin D (25(OH)D) and early onset severe preeclampsia (EOSPE). EOSPE is associated with an increased risk of pre-term birth and an increased risk for vascular pathologies later in life (3). Not only did Robinson et al. (3) find that women with EOSPE had lower serum levels of 25(OH)D, they found that an increase of only 10 ng/ml in serum 25(OH)D level was enough to reduce the risk of developing preeclampsia (3). This research suggests that vitamin D could potentially serve as both a marker for predicting preeclampsia and a treatment to mitigate the risk of developing EOSPE (3).

In a different study, Robinson et al. (27) investigated vitamin D levels in women who had both EOSPE and gave birth to an infant that was small for gestational age (SGA). The study found mothers of SGA infants to have low serum levels of 25(OH)D relative to the mothers of children with normal gestational sizes (27). Robinson suggested that vitamin D affects the placenta and fetal growth by changing gene expression (27). Robinson et al. further observed that $1,25(\text{OH})_2\text{D}_3$ also acts on endothelial cells, increasing the transcription of vascular endothelial growth factor (VEGF), leading to vasculogenesis (27).

Bodnar et al. (28) found that serum 25(OH)D concentrations in early pregnancy were 15% lower in women who ultimately developed preeclampsia than healthy controls. They also observed, similar to Xu et al. (11), that vitamin D deficiencies in early pregnancy increase the odds of developing preeclampsia by five times (compared to healthy controls) (11, 28). Bodnar et al. (28) concluded that there was a strong inverse relationship between serum vitamin D levels before 22 weeks gestation and the risk of developing preeclampsia.

As stated above, Royle et al. (14) suggest that defective trophoblastic invasion leads to the development of preeclampsia is through an increase in $\text{TNF-}\alpha$, and a decrease in IL-10. Similarly, vitamin D acts as an immune modulator by increasing the expression of IL-10 and decreasing the expression of Th1 mediated pro-inflammatory cytokines such as $\text{IFN-}\gamma$, IL-2, and $\text{TNF-}\alpha$ (Figure 4). A deficiency in vitamin D causes a cascade of changes in cytokine expression that closely mirrors the cytokine changes caused by incorrect trophoblastic invasion. This observation gives one possible explanation as to how a vitamin D deficiency leads to the development of preeclampsia.

Collectively, these findings suggest that the immunomodulatory capabilities of vitamin D underlie its role in the pathogenesis of preeclampsia.

Inconclusive or No Association

Shand et al. (26) conducted a prospective cohort study of 221 women by measuring serum 25-hydroxyvitamin D at 10 and 20 weeks gestation. According to their article, they found 78% of women were vitamin D insufficient (serum 25-hydroxyvitamin D <75 nmol/l) and 53% were vitamin D deficient (serum 25-hydroxyvitamin D <50 nmol/l). Despite the findings of widespread deficiency and insufficiency of serum 25-hydroxyvitamin D, they found no difference in the rates of pre-eclampsia, gestational hypertension, or adverse

pregnancy outcomes. Despite this finding, they do acknowledge that low maternal vitamin D is associated with poor fetal bone mineralization, and a greater chance of the fetus developing asthma and type 1 diabetes later in life (26). They further acknowledge that more research is needed at different gestational ages to further investigate the association of vitamin D in preeclampsia (26).

Expert commentary & five-year view

While the exact etiology of preeclampsia remains unknown, several potential causative factors have been proposed. Specifically, the research emphasizes endothelial damage as a result of oxidative processes, immune dysfunction, and trophoblastic invasion (2, 5, 11–14). Given the indispensable role of vitamin D in the regulation of cytokines and immune processes, vitamin D insufficiency is a likely contributor to the processes that damage endothelial cells in preeclamptic women (5, 14, 16).

Despite many research findings showing an association between low maternal vitamin D and preeclampsia (23–44), one prospective study we found disputed these findings and found no association between the development of the disease and maternal vitamin D levels at 10 and 20 week gestation in women at high risk for developing preeclampsia (26). Research by Christensen and co-investigators (33) evaluated these studies and noted that many studies that find no relationship between vitamin D and preeclampsia have small sample sizes. More research needs to be done to determine both the pathogenesis of preeclampsia, and what role vitamin D plays in the development, progression, and outcomes of this disease.

References

Reference annotations

* Of interest

** Of considerable interest

- 1*. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013; 122:1122–1131. The American College of Obstetricians and Gynecologists outlined a definition of preeclampsia, and offered diagnostic criteria for the disease.
2. Baker A, Haeri S, Camargo C, et al. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *J Clin Endocr Metab.* 2010; 95:5105–5109. [PubMed: 20719829]
3. Robinson C, Wagner C, Hollis B, et al. Association of maternal vitamin D and placenta growth factor with the diagnosis of early onset severe preeclampsia. *Am J Perinat.* 2013; 30:167–172.
4. Duley L. The global impact of Preeclampsia and eclampsia. *Semin Perinatol.* 2009; 33:130–137. [PubMed: 19464502]
- 5**. Wei S, Audibert F, Fraser W, et al. Maternal plasma 25-hydroxyvitamin D levels, angiogenic factors, and preeclampsia. *Am J Obstet Gynecol.* 2013; 208:390. This was a prospective cohort study in which maternal plasma 25(OH)D levels were measured at 12–18 weeks and again at 24–26 weeks. Maternal levels of sFlt-1, PIGF, ICAM-1, and VCAM-1 were also measured at 24–26 weeks. The study suggested that low maternal plasma 25(OH)D levels were associated with low PIGF levels and increased risk of preeclampsia. It is concluded that low vitamin D may

contribute to the development of preeclampsia through endothelial cell dysfunction. [PubMed: 23618499]

6. Ananth CV, Keyes KM, Wapner J. Preeclampsia rates in the United States, 1980–2010: age-period-cohort analysis. *BMJ*. 2013; 347:f6564. [PubMed: 24201165]
7. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. *Nutr Rev*. 2013; 71:S18–S25. [PubMed: 24147919]
8. Díaz L, Arranz C, Avila E, et al. Expression and activity of 25-hydroxyvitamin D-1 alpha-hydroxylase are restricted in cultures of human syncytiotrophoblast cells from preeclamptic pregnancies. *J Clin Endocr Metab*. 2002; 87:3876–3882. [PubMed: 12161526]
9. MacKay P, Berg J, Atrash K. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol*. 2001; 97:533–538. [PubMed: 11275024]
10. Maynard S, Karumanchi S. Angiogenic factors and preeclampsia. *Semin Nephrol*. 2011; 31:33–46. [PubMed: 21266263]
- 11*. Xu L, Lee M, Jeyabalan A, et al. The relationship of hypovitaminosis D and IL-6 in preeclampsia. *Am J Obstet Gynecol*. 2014; 210:149, e1–7. This cohort study compared plasma samples of 100 preeclamptic and 100 normotensive pregnant women. They found that both increased IL-6 and decreased plasma vitamin D levels were associated with preeclampsia. However, there was no association between low vitamin D and increased IL-6 levels. [PubMed: 24080305]
12. Wei S, Qi H, Luo Z, et al. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2013; 26:889–899. [PubMed: 23311886]
13. Reslan O, Khalil R. Molecular and vascular targets in the pathogenesis and management of the hypertension associated with preeclampsia. *Cardiovasc Hematol Agents Med Chem*. 2010; 8:204–226. [PubMed: 20923405]
- 14**. Royle C, Lim S, Xu B, et al. Effect of hypoxia and exogenous IL-10 on the pro-inflammatory cytokine TNF- α and the anti-angiogenic molecule soluble Flt-1 in placental villous explants. *Cytokine*. 2009; 47:56–60. This study investigated changes in the levels of IL-10, TNF- α , and sFlt-1 in placenta under various oxygen contents. They found that under hypoxic conditions the release of placental IL-10 was significantly reduced, however expression of TNF- α and sFlt-1 was not significantly different. They report, however, that under in vitro conditions IL-10 inhibits the release of in vitro TNF- α . [PubMed: 19501525]
15. Trostad L, Magnus P, Stoltenberg C. Pre-eclampsia: Risk factors and causal models. *Best Pract Res Clin Ob*. 2011; 25:329–342.
16. Pennington KA, Schlitt JM, Jackson DL, et al. Preeclampsia: multiple approaches for a multifactorial disease. *Dis Model Mech*. 2012; 5:9–18. [PubMed: 22228789]
17. Sunderland NS, Thomson SE, Heffernan SJ, et al. Tumor necrosis factor alpha induces a model of preeclampsia in pregnant baboons (*Papio hamadryas*). *Cytokine*. 2011; 56:192–199. [PubMed: 21737300]
- 18**. Orshal JM, Khalil RA. Interleukin-6 impairs endothelium-dependent NO-cGMP-mediated relaxation and enhances contraction in systemic vessels of pregnant rats. *Am J Physiol-Reg I*. 2004; 286:R1013–R1023. IL-6 is elevated in the plasma of preeclamptic women. This research showed that IL-6 is also elevated in pregnant rats with hypertension. A mechanism is proposed for how elevated levels of IL-6 contribute to the development hypertension in pregnant rats.
19. Lai Z, Kalkunte S, Sharma S. A critical role of interleukin-10 in modulating hypoxia-induced preeclampsia-like disease in mice. *Hypertension*. 2011; 57:505–514. [PubMed: 21263114]
20. Bozzetto S, Carraro S, Giordano G, et al. Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy*. 2012; 67:10–17. [PubMed: 21933195]
- 21***. Akbar N, Zacharek M. Vitamin D: immunomodulation of asthma, allergic rhinitis, and chronic rhinosinusitis. *Curr Opin Otolaryngo*. 2011; 19:224–228. This review combined input from several sources to outline the role of vitamin D as an immune modulator. Their research suggests that vitamin D affects the regulation of many cytokines including, but not limited to, IL-6, IL-10, IL-12, and TNF- α .
22. Mora JR, Iwata M, Von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*. 2008; 8:685–698. [PubMed: 19172691]

23. Shin J, Choi M, Longtine M, Nelson D. Vitamin D effects on pregnancy and the placenta. *Placenta*. 2010; 31:1027–1034. [PubMed: 20863562]
24. Hossein-Nazhad A, Holick MF. Vitamin D for Health: A Global Perspective. *Mayo Clin Proc*. 2013; 88:720–755. [PubMed: 23790560]
25. Lapillonne A. Vitamin D deficiency during pregnancy may impair maternal and fetal outcomes. *Med Hypotheses*. 2010; 74:71–75. [PubMed: 19692182]
26. Shand A, Nassar N, Von Dadelszen P, et al. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for Preeclampsia. *BJOG-Int J Obstet Gy*. 2010; 117:1593–1598.
27. Robinson C, Wagner C, Hollis B, et al. Maternal vitamin D and fetal growth in early-onset severe preeclampsia. *Am J Obstet Gynecol*. 2011; 204:556, e1–4. [PubMed: 21507371]
28. Bodnar L, Catov J, Simhan H, et al. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocr Metab*. 2007; 92:3517–3522. [PubMed: 17535985]
29. Tabesh M, Salehi-Abargouei A, Tabesh M, et al. Maternal vitamin D status and risk of Preeclampsia: a systematic review and meta-analysis. *J Clin Endocr Metab*. 2013; 98:3165–3173. [PubMed: 23783101]
30. Lechtermann C, Hauffa B, Grasmann C, et al. Maternal vitamin d status in preeclampsia: seasonal changes are not influenced by placental gene expression of vitamin d metabolizing enzymes. *PLOS One*. 2014; 9:e105558. [PubMed: 25148115]
31. Robinson C, Alanis M, Wagner C, et al. Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. *Am J Obstet Gynecol*. 2010; 4:366, e1–6. [PubMed: 20692641]
32. Azar M, Basu A, Lyons T, et al. Serum carotenoids and fat-soluble vitamins in women with type 1 diabetes and preeclampsia: a longitudinal study. *Diabetes Care*. 2011; 6:1258–1264. [PubMed: 21498785]
33. Christesen H, Falkenberg T, Lamont R, et al. The impact of vitamin D on pregnancy: a systematic review. *Acta Obstet Gyn Scan*. 2012; 12:1357–1367.
34. Barrett H, McElduff A. Vitamin D and pregnancy: An old problem revisited. *Best Pract Res Clin En*. 2010; 24:527–539.
35. Lewis S, Lucas R, Halliday J, et al. Vitamin D deficiency and pregnancy: from preconception to birth. *Mol Nutr Food Res*. 2010; 54:1092–1102. [PubMed: 20440696]
36. Ullah M, Koch C, Tamanna S, et al. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. *Horm Metab Res*. 2013; 45:682–687. [PubMed: 23733167]
37. Shand A, Nassar N, Von Dadelszen P, et al. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for Preeclampsia. *BJOG-Int J Obstet Gyn*. 2010; 117:1593–1598.
38. Bennett SE, McPeake J, McCance DR, et al. Maternal vitamin D status in type 1 diabetic pregnancy: impact on neonatal vitamin D status and association with maternal glycaemic control. *PLOS One*. 2013; 8:e74068. [PubMed: 24019947]
39. Bowyer L, Catling-Paull C, Diamond T, et al. Vitamin D, PTH and calcium levels in pregnant women and their neonates. *Clin Endocrinol*. 2009; 70:372–377.
40. Scholl T, Chen X, Stein T. Vitamin D, secondary hyperparathyroidism, and preeclampsia. *Am J Clin Nutr*. 2013; 98:787–793. [PubMed: 23885046]
41. Yu C, Ertl R, Skyfta E, et al. Maternal serum vitamin D levels at 11–13 weeks of gestation in preeclampsia. *J Hum Hypertens*. 2013; 27:115–118. [PubMed: 22336906]
42. Shand A, Nassar N, Von Dadelszen P, et al. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for Preeclampsia. *BJOG-Int J Obstet Gyn*. 2010; 117:1593–1598.
43. Wallis AB, Saftlas AF, Hsia J, et al. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. *Am J Hypertens*. 2008; 2:521–526. [PubMed: 18437143]
44. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet*. 2014; 2:e323–e333. [PubMed: 25103301]

Key Issues

- Further Randomized controlled trials using vitamin D supplementation pregnant women is needed to establish a link between preeclampsia and vitamin D.
- Preeclampsia continues to be a major cause of maternal and fetal morbidity and mortality worldwide.
- Although the precise pathophysiology of preeclampsia has not been established, is thought to occur due to a combination of endothelial cell dysfunction, immune dysfunction, and insufficient or reduced trophoblastic invasion.
- Vitamin D has been shown to improve angiogenesis and some research suggests that low serum vitamin D may contribute to endothelial cell dysfunction.
- Vitamin D has been shown to act as an immune modulator, and there are vitamin D receptors found on almost all immune cells.
- Vitamin D increases IL-10 production and decreases IL-6 production. Increased levels of IL-6 have been associated with preeclampsia, and decreased levels of IL-10 have also been associated with the disease.
- A deficiency in vitamin D causes a decrease in the expression of IL-10 and an increased expression of Th1-mediated pro-inflammatory cytokines such as IFN- γ , IL-2, and TNF- α . This closely resembles the cytokine changes that take place due to insufficient or reduced trophoblastic invasion. This observation gives one possible explanation as to how a vitamin D deficiency leads to the development of preeclampsia.
- Vitamin D's role in changing calcium absorption may also play a role in the pathogenesis of preeclampsia.

Figure 1.

A summary of preeclampsia epidemiology. Worldwide up to 8% of all pregnancies are complicated by preeclampsia. In the United States 3.5% of pregnancies are complicated by preeclampsia. In 2014 the World Health Organization (WHO) published a paper entitled: Global causes of maternal death: a WHO systematic analysis, and some of their findings are summarized here. This figure summarizes the most common causes of maternal death. Preeclampsia is included in the “hypertension” category.

Figure 2.

A proposed algorithm for diagnosing preeclampsia based on the 2013 American College of Obstetricians and Gynecologists Task Force on Hypertension Pregnancy.

Figure 3.

Soluble Fms-like Tyrosine Kinase 1 (sFlt-1)-mediated Vascular Endothelial Dysfunction: Preeclampsia is a hypertensive disorder of pregnancy characterized by widespread endothelial cell dysfunction. Preeclamptic mothers have an increased level of circulating anti-angiogenic cytokines such as sFlt-1. sFlt-1 acts by competitively binding to placental growth factor and vascular endothelial growth factor, inhibiting their ability to promote vascular invasion and endothelial proliferation. This dysfunction results in hypertension and proteinuria, both of which are hallmarks of preeclampsia.

Figure 4.

Cellular effects of the active form of vitamin D (1,25(OH)₂D₃) acts as an immune modulator. The 1,25(OH)₂D₃ modulates immune cells including: dendritic cells, CD4+ T-cells, CD8+ T-cells, T-regulatory cells (T-Regs), TH-17 cells, monocytes and macrophages. In dendritic cells 1,25(OH)₂D₃ inhibits differentiation, maturation, and immunostimulatory effects. The 1,25(OH)₂D₃ also decreases dendritic cell expression of MHC class II, CD40, CD80, CD86. The activation of vitamin D receptors (VDR) also causes dendritic cells to decrease synthesis of IL-12 and increases IL-10 production, which acts to stimulate TH2 expression and inhibit TH1 expression. In both CD4+ and CD8+ T-lymphocytes, 1,25(OH)₂D₃ binding to the VDR causes a five-fold increase in VDR expression. In vitro, 1,25(OH)₂D₃ inhibits the expression of IL-2, IFN-γ, and TNF-α. A decrease in the expression of these cytokines decreases TH1 cell proliferation and skews immunity to a Th2 mediated response. The 1,25(OH)₂D₃ also increases IL-4 production by TH2 cell, further inducing TH2 cell proliferation. In addition, 1,25(OH)₂D₃ has a stimulatory effect on FOXP3⁺ T-regulatory cells (T-Regs), causing differentiation and expansion. The 1,25(OH)₂D₃ has also been shown to inhibit Th17-cells by inhibiting IL-6 and IL-23 cytokine production. The 1,25(OH)₂D₃ decreases the activity of both antigen presenting cells (APC) and T-cells, leading to decreased B-cell proliferation, plasma-cell differentiation, and immunoglobulin secretion. Although most of the effects of 1,25(OH)₂D₃ on the immune system are inhibitory, it stimulates the activity of the innate immune system. The 1,25(OH)₂D₃ has been shown to stimulate monocyte proliferation in vitro, and it caused an increase in the production of IL-1 and cathelicidin (a bactericidal peptide) by monocytes and macrophages.