



A review of the literature on the association between vitamin D status and the risk of preeclampsia

Ameneh Movahedian (MD)*, Nayereh Ghomian (MD), Samaneh Soltani (MD), Nushin Chalakinia (MD)

Department of Gynecology, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Complications related to pregnancy and childbirth are the leading causes of disability and death among women of reproductive age in developing countries, constituting at least 18% of the global burden of disease in this age-group. Preeclampsia is a serious, pregnancy-specific disorder that affects up to 8% of pregnant women. Preeclampsia may lead to maternal and offspring mortality and it increases the risk of premature birth and fetal growth restriction. Vitamin D is a potent immunomodulatory agent. There is an evidence pointing toward an association between the vitamin D status and preeclampsia risk.

The purpose of the present study is to review the available literature investigating the role of serum levels of vitamin D in preeclampsia.

The study findings further highlight the possibility that vitamin D deficiency is a strong, independent risk factor for preeclampsia and vitamin D supplementation may be a simple step to reduce the risk of adverse pregnancy outcomes providing lifelong benefits both to the mother and her developing child.

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Introduction

Today, complications related to pregnancy and childbirth are the main cause of disability and mortality among women of reproductive age. They consist around 18% of the global burden of disease in this age-group (1). Similarly, vitamin D deficiency, poor maternal health during pregnancy, lack of care during delivery and afterwards play an important role in this event. Almost 8 million stillbirths and early neonatal deaths occur worldwide each year (2).

Preeclampsia is a serious, pregnancy-specific disorder that affects up to 8% of pregnant women (3). Preeclampsia may lead to maternal and offspring mortality and it increases the risk of premature birth and fetal growth restriction

(4). The incidence of preeclampsia is known to be higher in women with certain autoimmune diseases such as type 1 diabetes and rheumatoid arthritis, an association that has suggested the possibility of an immunogenetic link between these disorders (3). It has been suggested that preeclampsia results from a breakdown of tolerance to the developing fetus after maternal immune maladaptation (5). Vitamin D is a potent immunomodulatory agent. There is an evidence pointing toward an association between the vitamin D status and preeclampsia risk (3,6).

Vitamin D has direct effects on molecular pathways which are important in the pathogenesis of preeclampsia such as trophoblastic invasion and

***Corresponding author:** Ameneh Movahedian.

Department of Gynecology, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

E-mail: MovahedianA891@mums.ac.ir

Tel: 051-38012477

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immunomodulation as well as blood pressure control and proteinuria (7). Yet the correlation between vitamin D and preeclampsia has not been fully investigated.

Vitamin D deficiency is a common finding during pregnancy in many regions worldwide. Regarding the high rate of vitamin D deficiency and the possible consequences, the ideal amount of vitamin required to maintain adequate levels in pregnant women is not very well established (1).

Recently, there has been an extensive growth in the studies on vitamin D deficiency in pregnancy; many investigating this condition in different ethnic minority groups.

The purpose of the present study was to summarize the major findings of the available literature investigating the role of serum level of vitamin D (25-OHD) in preeclampsia.

Literature review

Marya et al (1987)

They studied the effect of vitamin D and calcium supplementation on the occurrence of pregnancy toxemia. 200 pregnant women received calcium (375 mg/day) and vitamin D (1,200 IU/day) supplements at 20-24 weeks of pregnancy onwards and were compared with another 200 pregnant women as controls. The study group showed significantly lower systolic and diastolic blood pressures at 32 and 36 weeks of pregnancy. However, no meaningful difference was observed in the incidence of toxemia between two groups (6% vs 9%) (8).

Olsen et al (1990)

In this case-control study, fish oil beside a dietary supplement of vitamins, minerals and halibut liver oil, given from week 20, was studied in pregnant women. The control group received no supplement. 20.4% ($P=0.00083$) and 31.5% ($P=0.0047$) reductions were observed in the possibility of delivering before 40 weeks of gestation and preeclampsia, respectively (9).

Cruikshank et al (1993)

Magnesium sulfate was studied in preeclamptic women and their fetuses. The preeclamptic cases had lower baseline maternal levels of 25-hydroxyvitamin D and parathyroid hormone than controls. Therefore, magnesium sulfate infusion was proposed to decrease calcium levels in both mother and fetus. However, in such cases the mother and fetus respond with increased 1,25-dihydroxyvitamin D and parathyroid hormone levels. This maybe a protective mechanism against more severe maternal, fetal and neonatal hypocalcemia (10).

Magnu et al (2001)

Study of seasonal patterns in preeclampsia showed the lowest incidence in summer, when there was plenty of sunlight with serum 25(OH) D concentrations at their peak. This was exactly vice versa during winter and the pattern was independent of parity, maternal age, year and place of living (11).

Bodnar et al (2007)

They assessed the effect of maternal 25-hydroxyvitamin D concentration on the risk of preeclampsia and the vitamin D status of newborns of preeclamptic mothers. In those mothers subsequently developing preeclampsia, the adjusted serum 25(OH)D concentrations were lower in early pregnancy compared to controls. They reported that maternal vitamin D insufficiency in early pregnancy maybe an independent risk factor for preeclampsia (12).

Haugen et al (2009)

By studying 23,423 nulliparous women, they found that vitamin D intake of 15-20Mg/day, relative to <5 mg/day, was associated with a 27% reduction in the risk of preeclampsia. The investigators suggested a relationship between vitamin D insufficiency and the development of preeclampsia (13).

Algert et al (2010)

They examined seasonality of pregnancy hypertension rates and their relation to levels of sunlight around conception in 24,732 singleton pregnancies in Australia. The level of sunlight before delivery was associated with lower hypertension rates. They concluded that for sunlight or ambient temperature to explain seasonal variation, the plausible exposure window was the period before delivery; however, this may not be true for early-onset preeclampsia (14).

Robinson et al (2010)

Regarding the link between vitamin D deficiency and adverse pregnancy outcomes, this study aimed to assess the levels of total 25-hydroxyvitamin D (25-OH-D) at diagnosis of early-onset severe preeclampsia (EOSPE). EOSPE subjects had reduced total 25-OH-D levels in comparison to healthy controls ($P<001$) (4).

Nassar et al (2011)

In this systematic review aimed at assessing normal levels of vitamin D in early pregnancy and its relation to subsequent pregnancy outcomes, no clear definition of vitamin D deficiency in pregnancy was obtained. They found insufficient evidence to suggest an association between low

levels of vitamin D in early pregnancy and adverse pregnancy outcomes (15).

Bomba-Opon et al (2013)

In this study, maternal serum concentration of vitamin D did not seem to be related to markers of preeclampsia in the first trimester (16).

Aghajafari et al (2009)

In a systematic review and meta-analysis on 31 eligible studies, the effect of 25-hydroxy vitamin D (25-OHD) levels on pregnancy outcomes and birth indices were studied.

A higher rate of gestational diabetes, preeclampsia, and small for gestational age (SGA) infants was observed in vitamin D deficient mothers. Moreover, an increased risk of bacterial vaginosis and lower birth weight infants were obtained with no difference in delivery by caesarean section (17).

Bener et al (2013)

In a cohort study in Doha, 1,873 Arab pregnant women over 24 weeks of gestation with any maternal complication were enrolled. They found a significant association between vitamin D deficiency in pregnancy and the elevated risk for preeclampsia, GDM and anemia (2).

Tabesh et al (2013)

This systematic review and meta-analysis of eight published observational studies also revealed a significant relationship between vitamin D deficiency and increased risk of preeclampsia (18).

Gernand et al (2014)

Serum samples of 792 high-risk women at 12-26 weeks of gestation were assayed for 25-hydroxyvitamin D in a multicenter clinical trial of low-dose aspirin for the prevention of preeclampsia. They drew a conclusion that maternal vitamin D levels in the second pregnancy trimester correlated with the risk of SGA among all women and in the subgroups of white and nonobese women (19).

Bodnar et al (2014)

They determined the association between maternal vitamin D status at ≤ 26 weeks of gestation and the risk of preeclampsia by clinical subtype. In a case-cohort study, serum collected from 717 women who later developed preeclampsia and from 2986 mothers without preeclampsia were measured for 25-hydroxyvitamin D. The conclusion was that maternal vitamin D deficiency might be a risk factor for severe preeclampsia but not for its mild subtypes (20).

Hyppönen et al (2014)

Finally, a recent systematic review and meta-analysis including novel data from 2 large-scale epidemiological studies investigated vitamin D supplementation or status with a subsequent risk of preeclampsia. They concluded that low maternal serum 25(OH)D levels lead to an increased risk of preeclampsia whereas vitamin D supplementation lowered this risk (21).

Discussion

Despite the disappearance of rickets with the discovery of vitamin D hormone, vitamin D deficiency is still a widespread disorder even in industrialized countries (22). This condition was first introduced in 2005 by 25(OH)D concentration less than 75 nmol/L (or 30 ng/mL). Today, a rise in the incidence of low vitamin D status has taken place in both the developing world and other developed nations. Therefore, vitamin D deficiency during pregnancy is an ongoing epidemic (23).

Although it seems that vitamin D deficiency is related to preclampsia and gestational diabetes, recent data in the literature are contradictory and the administration of vitamin D supplementation during pregnancy is still controversial (24).

Transplacental transfer of 25(OH)D from mother to fetus in early pregnancy is the main step for initiation of vitamin D storage in the infant. It is clear that in order to prevent hypovitaminosis D in the fetus and vitamin D deficiency in early infancy, it is essential to maintain optimum vitamin D levels during pregnancy (25).

Literature review revealed a higher risk of vitamin D deficiency among pregnant women under 30 years of age (43.2%), housewives (65.3%), the educated (41.1%) and those with low income (49.2%). When considering lifestyle habits, this disorder was more common in women with the history of inadequate sun exposure (63.4%) and less daily physical activity (64.4%). Accordingly, women of low socioeconomic status and inadequate sun exposure were more prone to have lower 25(OH)D concentrations. In most nations, no monitoring of serum 25(OH)D3 levels for vitamin D deficiency is available during pregnancy (1). Vitamin D intake during pregnancy is even considered unnecessary by some societies whereas others recommend up to 2000 IU/d. Altogether, no case of teratogenicity has been reported regarding linkage with vitamin D intake in such cases so far (24).

In a case-control study conducted in Ahwaz, Iran on 59 preeclamptic women and 59 healthy pregnant controls, vitamin D deficiency demonstrated a statistically significant relationship with

preeclampsia. Nevertheless, serum vitamin D levels seemed to be low among Iranian women due to their special lifestyle. Therefore, more than 400IU/day vitamin D supplement may be required during pregnancy (26).

Eventually, this review of the available literatures suggests low levels of 25(OH)D as a modifiable risk factor in pregnancy. Furthermore, vitamin D supplementation in early pregnancy can be recommended as a safe and beneficial treatment for preventing preeclampsia and promoting neonatal well-being. Therefore, healthcare providers should be encouraging pregnant women to take vitamin D.

Conclusion

Vitamin D deficiency is a strong, independent risk factor for preeclampsia and vitamin D supplementation during pregnancy may be a simple step to reduce the risk of undesired pregnancy outcomes and provides lifelong benefits both to the mother and to her developing child.

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Conflict of Interest

The authors declare no conflict of interest.

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