# Maternal vitamin D deficiency and adverse pregnancy outcomes

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## ABSTRACT

**Background and purpose:** Vitamin D is a fat-soluble vitamin, mainly synthesized cutaneously during solar exposure. Vitamin D deficiency is prevalent worldwide and investigation of its health consequences, both classical (skeletal) and non-classical (non-skeletal), is ongoing. The aim of this review is to summarize the evidence regarding vitamin D deficiency and maternal outcomes during pregnancy and provide suggestions for vitamin D supplementation.

**Methods:** We conducted a thorough literature search in the electronic databases of PubMed, Medline, Scopus, and The Cochrane Database of Systematic Reviews for literature available until March 2019.

**Results:** Available data suggest an association between vitamin D deficiency and pre-eclampsia, gestational diabetes mellitus, preterm birth, small for gestational age, delivery mode and bacterial vaginosis. Evidence for causative links, however, is still inconclusive.

**Conclusions:** According to experts' recommendations standard prenatal vitamin D supplementation should be prescribed during pregnancy.

## KEYWORDS

Pregnancy, vitamin D deficiency, pre-eclampsia, gestational diabetes, preterm birth, small for gestational age, cesarean section, bacterial vaginosis.

## Introduction

Vitamin D is a fat-soluble vitamin and its main natural source is cutaneous synthesis during exposure to solar ultraviolet (UV) rays. Dietary sources of vitamin D include cod liver oils and fatty fish, as well as fortified foods [1]. There are two forms of vitamin D: vitamin D3 (cholecalciferol), derived from exposure to sunlight, and vitamin D2 (ergocalciferol) which can be produced in the skin or ingested in the diet. The two forms have minor differences in bioactivity [2].

In order to become bioactive, vitamin D undergoes a first hydroxylation in the liver, into 25-hydroxyvitamin D [25(OH)D] or calcidiol, and a second one in the kidneys and other tissues, into 1,25-dihydroxyvitamin D or calcitriol. The main circulating form of vitamin D is 25(OH)D and its levels are the best laboratory indicator for vitamin D sufficiency. The optimal serum level of 25(OH)D is still debated among experts. The Institute of Medicine suggests that serum 25(OH)D levels of 20 ng/mL (50 nmol/L) are sufficient for most individuals [3], whereas the European Menopause and Andropause Society and the Endocrine Society define vitamin D insufficiency as 25(OH)D concentrations between 20 and 29.99 ng/mL (50 and 74.99 nmol/L), and vitamin D deficiency as concentrations below 20 ng/mL [4,5].

Despite the debate, vitamin D deficiency is a global problem, affecting countries with different latitudes and different availability of fortified products [6]. It is estimated that 40% of the population is vitamin D deficient in the USA [7], whereas among pregnant women, the prevalence fluctuates between 7 and 53.4%, depending on the country of residence [8-12]. The main causes of vitamin D deficiency are poor sunlight exposure, skin hyperpigmentation, obesity, cognitive impairment, institutionalization, reduced dietary intake, malabsorption and specific medications, such as anticonvulsants [13].

Lack of vitamin D results in poor intestinal absorption of calcium and phosphorus, with hypophosphatemia being an earlier electrolytic abnormality than hypocalcemia. Persistent vitamin D deficiency leads to secondary hyperparathyroidism, phosphaturia and bone demineralization causing rickets in children and osteomalacia in adults [14].

The association between reduced exposure to sunlight and rickets in children was first described by Sniadecki in 1822 [15]. Since then, vitamin D deficiency has been associated with increased cancer risk, type 2 diabetes mellitus, adverse cardiovascular outcomes, and autoimmune diseases such as multiple sclerosis, type 1 diabetes mellitus and inflammatory bowel disease [16-22].

Considering the high prevalence of vitamin D deficiency and its unfavorable outcomes, the aim of this article is to provide an updated review on the effects of maternal vitamin D deficiency on the placento-fetal unit and the mother during pregnancy, and recommendations regarding supplementation.

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## Methods

We conducted a thorough literature search in the electronic databases of PubMed, Medline, Scopus, and The Cochrane Database of Systematic Reviews for literature available until March 2019. The following MeSH headings were used: "pregnancy" and "vitamin D deficiency", in combination with "pre-eclampsia" or "gestational diabetes" or "preterm birth" or "small for gestational age" or "cesarean section" or "bacterial vaginosis". Non-English studies and case reports were excluded. Moreover, in an effort to provide an updated perspective, we only focused on recent studies, published after 2007. The reference lists of retrieved studies were also scanned for other relevant ones. After applying exclusion criteria, 40 studies were deemed eligible and are discussed in this review.

## Vitamin D deficiency and pregnancy outcomes

### Pre-eclampsia (Table 1)

Pre-eclampsia, defined as new-onset of hypertension and proteinuria in previously normotensive women after 20 weeks of gestation, affects 4.6% of pregnancies worldwide [23].

A meta-analysis, which included 9 studies, showed that pre-eclampsia was significantly related to decreased vitamin D levels, with a pooled OR of 1.79 (95% CI: 1.25 to 2.58) [24], whereas in another meta-analysis, including 8 studies with 2273 participants, 25(OH)D levels were reported to be -3.86 lower in preeclamptic women than in controls (95% CI: -5.13 to -2.59) [25]. In line with these findings are several case-control studies, with varying sample sizes, which concluded that vitamin D deficiency is associated with pre-eclampsia in pregnancy – OR=3.24; 95% CI: 1.37 to 7.69, OR=2.23; 95% CI: 1.29 to 3.83, OR=2.18; 95% CI: 1.80 to 2.64 – and may increase the odds of pre-eclampsia up to 5 times [26-29]. Neonates born to preeclamptic mothers had 2 times higher odds of vitamin D deficiency compared with neonates born to mothers without preeclampsia [27,30].

However, a few studies failed to show a correlation between vitamin D and pre-eclampsia [31,32]. When vitamin D was measured in the first trimester, the development of pre-eclampsia was not significantly associated with low serum levels [33], although an increased trend was identified (OR=1.35 95% CI: 0.40-4.5) [34]. Two prospective studies, which did not find any correlation either, attributed the lack of association to the late gestational age at sampling, the small sample size, and the small number of women with pre-eclampsia [35,36].

Despite the inconsistent evidence among case-control and prospective studies, the underlying mechanism of hypovitaminosis D leading to pre-eclampsia has started to be elucidated. It is suggested that antiangiogenic factors, such as soluble FMS-like tyrosine kinase 1 (sFlt-1) and vascular endothelial growth factor (VEGF), are down-regulated by placental gene modification in in pregnant women with normal vitamin D levels [37]. Both factors, sFlt-1 and VEGF, have been associated with the development of pre-eclampsia in laboratory and clinical studies [38-41].

### Gestational diabetes (Table 2)

Vitamin D deficiency in the general population is associated with diabetes mellitus [18,21]. Aghajafari *et al*. confirmed this finding among pregnant women in a meta-analysis of 9 studies without evidence of heterogeneity (P=0.58; I2=0.0%). 25(OH) D deficiency was associated with increased risk of developing gestational diabetes mellitus (GDM), with an OR of 1.49 (95% CI: 1.18 to 1.88), which increased further to 1.98 (95% CI: 1.23-3.23) when only studies with adjustment for critical covariates were considered [24].

In agreement with the aforementioned study are most meta-analyses, which have reported OR values of 1.38 (95% CI: 1.12-1.70), 1.53 (95% CI: 1.33-1.75), 1.57 (95% CI 1.04-2.37), and 1.85 (95% CI: 1.47-2.33), whilst the association may differ in subgroup analyses based on countries, study design, assessment of vitamin D levels, sample size, age at baseline, adjusted models, study quality, and smoking status [25,42-45]. In line with these findings, a Chinese cohort study showed that maternal vitamin D levels <20 ng/mL increased the risk of GDM, with an OR of 1.08 (95% CI: 1.04-1.1) [46]. On the contrary, there are observational studies that were not able to find any correlation between vitamin D status and GDM [47-49]. However, it is suggested that HMW-adiponectin may be one of the mediators between vitamin D levels and adverse pregnancy outcomes, such as GDM [50].

### Preterm birth (Table 3)

The evidence regarding hypovitaminosis D and preterm birth is less conclusive. Wei *et al*., in a meta-analysis of 5 studies, showed that vitamin D <50 nmol/L and preterm delivery were significantly correlated with an OR of 1.58 (95% CI: 1.08–2.31), without heterogeneity across the studies.25 A prospective study among 7,098 mothers in the Netherlands found that women in the lowest quartile of vitamin D levels, defined as 1.5 to 24.1 nmol/L, had an OR of 1.72 (95% CI: 1.14 to 2.60) for preterm birth, defined as <37 weeks of gestational age [51]. Vitamin D concentrations ≥40 ng/mL seem to lower preterm birth risk by 60% among general obstetric patients [52]. Interestingly, two studies showed greater association between vitamin D deficiency and preterm births among non-white/ethnic minority women than among white women [53,54].

Both twin pregnancy and HIV infection are factors known to contribute to preterm delivery. Vitamin D-deficient women carrying twins had 60% increased risk of preterm delivery (<35 weeks) compared with women sufficient in vitamin D who also carried twins [55].

The association between vitamin D status and preterm birth was found to be even higher among HIV-infected women, with an OR of 4.7 (95% CI: 1.3 to 16.8) [56]. On the contrary, other observational studies reported a lack of association between vitamin D status and preterm birth [31,32,49,57,58].

### Small for gestational age (SGA, Table 4)

Less consistent is the evidence regarding maternal 25(OH) D deficiency and birthweight. A recent meta-analysis, which assessed 13 cohort studies with 28,285 individuals from seven countries, demonstrated an OR of 1.588 (95% CI: 1.138 to 2.216; p<0.01) for SGA infants among women with vitamin D

**Table 1** Studies evaluating the association between vitamin D deficiency and pre-eclampsia.

| | STUDY DESIGN | SAMPLE SIZE | GESTATIONAL AGE AT TIME OF SAMPLING | 25-OHD CONCENTRATION CUT-OFF | 25-OHD QUANTIFICATION METHOD | RESULTS | CONCLUSIONS |
|---|---|---|---|---|---|---|---|
| Aghajafari et al., 2013 [24] | Systematic review and meta-analysis of 7 studies | 3,191 | <16 wks in 5 studies >16 wks in 2 studies | <50 nmol/L in 2 studies <75 nmol/L in 5 studies | 3 studies HPLC-MS, 4 studies RIA | OR=1.79 (95% CI: 1.25 to 2.58) | Vitamin D insufficiency is associated with an increased risk of pre-eclampsia. |
| Wei et al., 2013 [25] | Systematic review and meta-analysis of 8 studies | 2,273 | Varying between the studies | Variable cut-offs | 5 studies HPLC-MS, 3 studies RIA | OR=2.09 (95% CI: 1.50to2.90) | Low maternal vitamin D levels in pregnancy may be associated with an increased risk of preeclampsia. |
| Weietal., 2012 [26] | Prospective cohort | 697 | 12-18 and 24-26 wks | <50 nmol/L | CLIA | 12-18 wks: no association, 24-26 wks: OR 3.24, (95% CI 1.37 to 7.69) | Lower maternal 25(OH)D levels at late mid-trimester were associated with an increased risk of pre-eclampsia. |
| Achkar et al., 2015 [27] | Nestedcase-control | 2,144 | <20 wks | <30 nmol/L | CLIA | OR=2.23 (95% CI: 1.29 to 3.83) | Maternal vitamin D deficiency early in pregnancy may be an independent risk factor for pre-eclampsia. |
| Serranoetal., 2018 [28] | Case-control | 2,028 | N/A | <30 ng/mL | HPLC-MS | OR=2.18 (95% CI: 1.80 to 2.64) | Although the results suggest that low maternal concentrations of 25(OH) D increase pre-eclampsia risk, this evidence may not be indicative of a causal association. |
| Ullah et al., 2013 [29] | Case-control | 188 | ≥ 20 wks | <30 ng/mL | ECLIA | OR=3.9 (95% CI:1.18 to 12.87) | The odds of developing preeclampsia and eclampsia may increase up to 5-fold in women with vitamin D insufficiency. |
| Bodnaretal., 2007 [30] | Nested case-control | 274 | <22 wks | <37.5 nmol/L | ELISA and HPLC | OR= 2.2 (95% CI: 1.2 to 4.1) | Maternal vitamin D deficiency may be an independent risk factor for preeclampsia. |
| Wetta et al., 2014 [31] | Nested case-controlstudy | 266 | 15-21 wks | insufficiency: <30 ng/mL, deficiency: <15 ng/mL | LC-MS | No association in either of the groups: OR=1.1, (95% CI: 0.6 to 2.0), OR=1.4 (95% CI: 0.7 to 3.0) | Midtrimester maternal vitamin D was not significantly associated with preeclampsia. |
| Boyle et al., 2016 [32] | Prospective cohortstudy | 1,710 | 15 wks | <25, <50 and <75 nmol/l | LC-MS | OR=0.9 (95% CI: 0.3 to 2.9), OR=0.95 (95% CI: 0.53 to 1.73) and OR=1.15 (95% CI: 0.69 to 1.91) | Hydroxyvitamin D concentration at 15 weeks was not associated with development of pre-eclampsia. |
| Gidlöf et al., 2015 [33] | Nested case-control | 157 | mean of 12 wks | <50 nmol/L | CLIA | Vitamin D concentration among women who developed pre-eclampsia (52.2 ± 20.5 nmol/L) and the controls (48.6 ± 20.5 nmol/L, p = 0.3) | The data do not support the hypothesis that vitamin D deficiency in early pregnancy is associated with preeclampsia, but we cannot rule out a relationship later in gestation. |
| Poweetal., 2010 [34] | Nested case-control | 170 | 1st trimester | <15 ng/mL | LC-MS/MS | OR=1.35 (95% CI 0.40 to 4.5) | These data suggest that first trimester total and free 25(OH)D levels are not independently associated with first trimester blood pressure or subsequent preeclampsia. |
| Gbadegesin et al., 2017 [35] | Prospective study | 461 | 10-28 wks | 0-20 ng/mL deficiency, 21-30 ng/mL insufficiency | HPLC | p >0.05 | There were no differences between the groups regarding complications during pregnancy, including preeclampsia. |
| Shandetal., 2010 [36] | Prospective study | 221 | 10-20 wks | 3 cut-offs of <37.5, <50 and <75 nmol/l | RIA | p >0.05 | Vitamin D deficiency and insufficiency were common in a group of women at high risk of pre-eclampsia; however, it was not associated with subsequent risk of an adverse pregnancy outcome. |

wks=weeks; HPLC=high-performance liquid chromatography; MS=mass spectrometry; LC-MS=liquid chromatography–mass spectrometry; RIA=radioimmunoassay; CLIA=chemiluminescent immunoassay; ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay

**Table 2** Studies evaluating the association between vitamin D deficiency and gestational diabetes mellitus.

| | STUDY DESIGN | SAMPLE SIZE | GESTATIONAL AGE AT TIME OF SAMPLING | 25-OHD CONCENTRATION CUT-OFF | 25-OHD QUANTIFICATION METHOD | RESULTS | CONCLUSIONS |
|---|---|---|---|---|---|---|---|
| Aghajafari et al., 2013 [24] | Systematic review and meta-analysis of 10 studies | 4,112 | <16 wks in 5 studies >16 wks in 5 studies | <50 nmol/L in 7 studies <75 nmol/L in 3 studies | 4 studies HPLC-MS, 6 studies RIA | OR=1.49(95% CI: 1.18 to 1.88) | Vitamin D insufficiency is associated with an increased risk of GDM. |
| Wei et al., 2013 [25] | Systematic review and meta-analysis of 12 studies | 5,615 | Varying between the studies | Variable cut-offs | Variable methods | 1.38 (95% CI: 1.12-1.70) | Low maternal vitamin D levels in pregnancy may be associated with an increased risk of preeclampsia. |
| Zhang et al., 2015 [42] | Meta-analysis of 20 studies | 9,209 | Varying between the studies | Variable cut-offs | 5 studies HPLC-MS, 4 studies RIA, 4 studies ELISA, 3 studies ECLIA, 4 studies CLIA | OR=1.53 (95% CI: 1.33to1.75) | The evidence from this meta-analysis indicates a consistent association between vitamin D deficiency and an increased risk of GDM. |
| Zhang et al., 2018 [43] | Systematic review of 87 observational studies and 25 randomized controlled trials | 55,859 and 2,445 | Varying between the studies | Variable cut-offs | Variable methods | OR=1.85 (95% CI: 1.47to2.32) | Low blood vitamin D level could increase the risk of GDM. |
| Luetal., 2016 [44] | Meta-analysis of 20 observational studies | 16,515 | Varying between the studies | <50 nmol/L in 15 studies <75 nmol/L in 5 studies | 10 studies HPLC-MS, 10 studies RIA | RR=1.45 (95% CI: 1.15 to 1.83) | This meta-analysis revealed that maternal vitamin D insufficiency is associated with increased risk of GDM. |
| Dodds et al., 2016 [45] | Nested case-control | 2,320 | <20 wks | <30 nmol/L | CLIA | Smokers with vitamin D deficiency OR=3.73 (95% CI: 1.95 to 7.14) compared with controls | The study supports the inverse association of vitamin D status with GDv risk, particularly among women who smoke during pregnancy. |
| Wang et al., 2018 [46] | Prospective cohort study | 1,978 | Not reported | <20 ng/mL | ECLIA | OR=1.08 (95% CI: 1.04to1.1) | Maternal vitamin D deficiency independently increased the risk of GDM |
| Hauta-Alus et al., 2017 [47] | Cross-sectional study | 723 | on average at 11 wks | <50 nmol/L | CLIA | p > 0.53 | Maternal vitamin D concentration was similar in mothers with and without GDM in a mostly vitamin D sufficient population. |
| Eggemoen et al., 2018 [48] | Longitudinal study | 745 | 15 and 28 wks | <50 nmol/L | RIA | OR=1.1 (95% CI: 0.69t o 1.6) | Vitamin D deficiency was not associated with GDM after adjustments for confounding factors |
| Rodriguez et al., 2015 [49] | Prospective cohort study | 2,382 | mean of 13.5 wks | <20 ng/mL (deficiency, reference), 20–29.99 ng/mL (insufficiency), and >30 ng/mL (sufficiency) | HPLC | OR=0.53 (95% CI: 0.29 to 0.97), OR=0.92 (95% CI: 0.55 to 1.55) | This study did not find any evidence of an association between vitamin D status in pregnancy and GDM. |

wks=weeks; HPLC=high-performance liquid chromatography; MS=mass spectrometry; LC-MS=liquid chromatography–mass spectrometry; RIA=radioimmunoassay; CLIA=chemiluminescent immunoassay; ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay; GDM=gestational diabetes mellitus

deficiency [59]. This inverse relationship between vitamin D status and birthweight was also found in two older meta-analyses; the first showed an OR=1.52 of SGA infants (95% CI: 1.08 to 2.15) for women with 25(OH)D levels <50 nmol/L [25], and the second an OR=1.85 (95% CI: 1.52 to 2.26) for women with vitamin D levels <75 nmol/L [24].

Observational studies reported similar results for birthweight, namely OR=2.07 (95% CI: 1.33 to 3.22) when vitamin D levels were in the lowest quartile (1.5 to 24.1 nmol/L) [51], and RR=6.47 (95% CI: 4.30 to 9.75) [60] for vitamin D deficiency. Recent observational studies among Chinese women found that 25(OH)D <20 ng/ml increased significantly the risk of SGA infants, with OR values of 1.17 (95% CI: 1.03 to 1.32) and 3.05 (95% CI: 2.24 to 4.40) respectively. [46,61].

Racial disparity has also been reported in the association between vitamin D status and birthweight, but the findings were contradictory; Seto *et al*. reported an association of vitamin D deficiency and SGA infants only among black women [62]. On the contrary, other studies showed no association between vitamin D status and the risk of having a SGA baby [32,49,57,58,63].

**Table 3** Studies evaluating the association between vitamin D deficiency and preterm birth.

| | STUDY DESIGN | SAMPLE SIZE | GESTATIONAL AGE AT TIME OF SAMPLING | 25-OHD CONCENTRATION CUT-OFF | 25-OHD QUANTIFICATION METHOD | RESULTS | CONCLUSIONS |
|---|---|---|---|---|---|---|---|
| Wei et al., 2013 [25] | Systematic review and meta-analysis of 5 studies | 1,271 | Varying between the studies | Variable cut-offs | LC-MS, ELISA, RIA, CLIA, ECLIA | OR=1.58 (95% CI: 1.08 to 2.31) | Low maternal vitamin D levels in pregnancy may be associated with an increased risk of preterm birth. |
| Miliku et al., 2016 [51] | Prospective cohort study | 7,098 | median of 20.3 wks | Lowest quartile (1.5 to 24.1 nmol/L) | LC-MS/MS | OR=1.72 (95% CI: 1.14 to 2.60) | Low maternal 25(OH)D concentrations are associated with an increased risk of preterm birth. |
| McDonnell et al., 2017 [52] | Prospective cohortstudy | 1,064 | First prenatal visit | <20 ng/mL (reference) >40 ng/mL | LC-MS | OR=0.38 (95% CI: 0.23 to 0.63) | Those with serum 25(OH)D concentrations ≥40 ng/mL had a 62% lower risk of PTB compared to those with concentrations <20 ng/mL. |
| Tabatabaei et al., 2017 [53] | Case-control study | 480 | 8-14 wks | <50, 50–75, and >75 nmol/L | LC-MS | OR=2.01 (95% CI: 1.20 to 3.38) | Vitamin D insufficiency is associated with an increased risk of preterm birth in ethnic minority women in Canada. |
| Bodnaretal., 2014 [54] | Case-cohort study | 3,468 | <26 wks | <30 nmol/L | LC-MS | Reductions of 1.0–1.6 cases of spontaneous preterm birth per 100 when vitamin D>30 nmol/L | Association between vitamin D deficiency and spontaneous preterm birth found only in non-white mothers. |
| Bodnar et al., 2013 [55] | Randomized controlled trial | 211 | 24-28 wks | <75 nmol/L | LC-MS | In twin gestation, vitamin D>75 nmol/L decreased by 60% the risk of preterm birth | Late second trimester maternal 25-hydroxyvitamin D < 75 nmol/L is associated with an increase in the risk of preterm birth in this cohort of twin pregnancies. |
| Jao et al., 2017 [56] | Prospective cohort study | 715 | 12-34 wks | Severe deficiency <10 ng/mL | LC-MS | OR=4.7 (95% CI: 1.3 to 16.8) | Severe maternal vitamin D deficiency is associated with PTB in HIV-infected Latin American pregnant women. |
| Wetta et al., 2014 [31] | Nested case-control study | 267 | 15-21 wks | insufficiency: <30 ng/mL, deficiency: <15 ng/mL | LC-MS | No association in either of the groups: OR=0.8, (95% CI: 0.4 to 1.4), OR=1.3 (95% CI: 0.6 to 3.0) | Midtrimester maternal vitamin D was not significantly associated with spontaneous preterm birth. |
| Boyle et al., 2016 [32] | Prospective cohort study | 1710 | 15 wks | <25, <50 and <75 nmol/l | LC-MS | OR=1.7 (95% CI: 0.5 to 5.5), OR=1.46 (95% CI: 0.82 to 2.58) and OR=0.92 (95% CI: 0.57 to 1.49) | Hydroxyvitamin D concentration at 15 weeks was not associated with development of spontaneous preterm birth. |
| Rodriguez et al., 2015 [49] | Prospective cohort study | 2382 | mean of 13.5 wks | <20 ng/mL (deficiency, reference), 20–29.99 ng/mL (insufficiency), and >30 ng/mL (sufficiency) | HPLC | OR=0.98 (95% CI: 0.52 to 1.85), OR=1.08 (95% CI: 0.75 to 1.67) | This study did not find any evidence of an association between vitamin D status in pregnancy and preterm delivery. |
| Ong et al., 2016 [57] | Prospective cohort study | 1120 | 26-28 wks | deficiency: <50 nmol/L, insufficient: 50-75 nmol/L | LC-MS/MS | OR=1.16 (95% CI: 0.64 to 2.11), OR=1.06 (95% CI: 0.48 to 2.38) | Maternal vitamin D status in pregnancy did not influence infant birth outcomes. |
| Morgan et al., 2016 [58] | Nested case-control study | 1,328 | Cord blood | deficiency: <50 nmol/L, insufficiency: 50-75 nmol/L | CLIA | OR=0.81 (95% CI: 0.53 to 1.22), OR=0.74 (95% CI: 0.52 to 1.05) | No significant associations were observed between [25(OH)D] and preterm birth. |

wks=weeks; HPLC=high-performance liquid chromatography; MS=mass spectrometry; LC-MS=liquid chromatography–mass spectrometry; RIA=radioimmunoassay; CLIA=chemiluminescent immunoassay; ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay

**Table 4** Studies evaluating the association between vitamin D deficiency and the delivery of small for gestational age infants.

| | STUDY DESIGN | SAMPLE SIZE | GESTATIONAL AGE AT TIME OF SAMPLING | 25-OHD CONCENTRATION CUT-OFF | 25-OHD QUANTIFICATION METHOD | RESULTS | CONCLUSIONS |
|---|---|---|---|---|---|---|---|
| Chen et al., 2017 [59] | Meta-analysis of 13 prospective cohort studies | 28,285 | Varying between the studies | Variable cut-offs | Variable methods | OR=1.588 (95% CI: 1.138 to 2.216; p<0.01) | This meta-analysis suggests that vitamin D deficiency is associated with an increased risk of SGA. |
| Aghajafari et al., 2013 [24] | Systematic review and meta-analysis of 6 studies | N/A | <16 wks in 4 studies >16 wks in 2 studies | <37.5 nmol/L in 3 studies <80 nmol/L in 3 studies | Variable methods | OR=1.85 (95% CI: 1.52 to 2.26) | Vitamin D insufficiency is associated with an increased risk of SGA infants. |
| Miliku et al., 2016 [51] | Prospective cohort study | 7,098 | median of 20.3 wks | Lowest quartile (1.5 to 24.1 nmol/L) | LC-MS/MS | OR=2.07, 95% CI: 1.33to 3.22) | Low maternal 25(OH)D concentrations are associated with an increased risk of SGA at birth. |
| Chenetal., 2015 [60] | Prospective cohort study | 3,658 | Serum samples from any stage of pregnancy | <20 ng/mL (50 nmol/L) | RIA | RR=6.47 (95% CI: 4.30 to 9.75) | Maternal vitamin D deficiency during pregnancy elevates the risk of SGA infants in a Chinese population. |
| Wang et al., 2018 [46] | Prospective cohort study | 1,978 | Not reported | <20 ng/mL | ECLIA | OR=1.17(95% CI: 1.03 to 1.32) | maternal vitamin D deficiency significantly increased the risk of SGA. |
| Wangetal., 2018 [61] | Prospective cohort study | 747 | First prenatal visit | Deficiency: <20 ng/mL | ECLIA | OR=3.05 (95% CI: 2.24 to 4.40) | Maternal vitamin D insufficiency is independently associated with high risk of SGA in term infants. |
| Setoetal., 2016 [62] | Retrospective study | 438 | Cord blood | <50 nmol/L | CLIA | OR=1.1 (95% CI: 0.32 to 3.9) for white infants OR=2.4 (95% CI: 1.0 to 5.8) for black ones | Vitamin D deficiency was not significantly associated with SGA in white infants. |
| Gernandetal., 2014 [63] | Observational cohort study | 792 | 12-26 wks | <50 nmol/L (reference), ≥50 nmol/L | LC-MS/MS | RR=0.86 (95% CI: 0.55 to 1.34) in black mothers RR=0.32 (95% CI: 0.17 to 0.63) in white ones | There was no association between 25-hydroxyvitamin D and risk of SGA in black mothers. |
| Boyle et al., 2016 [32] | Prospective cohort study | 1710 | 15 wks | <25, <50 and <75 nmol/l | LC-MS | OR=1.6 (95% CI: 0.8 to 3.3), OR=1.33 (95% CI: 0.91 to 1.96) and OR=0.97 (95% CI: 0.7 to 1.36) | Hydroxyvitamin D concentration at 15 weeks was not associated with development of SGA infants. |
| Rodriguez et al., 2015 [49] | Prospective cohort study | 2382 | mean of 13.5 wks | <20 ng/mL (deficiency, reference), 20–29.99 ng/mL (insufficiency), and >30 ng/mL (sufficiency) | HPLC | OR=1.05 (95% CI: 0.73 to 1.51), OR=0.99 (95% CI: 0.69 to 1.42) | This study did not find any evidence of an association between vitamin D status in pregnancy and SGA. |
| Ong et al., 2016 [57] | Prospective cohort study | 1,120 | 26-28 wks | deficiency: <50 nmol/L, insufficiency: 50-75 nmol/L | LC-MS/MS | No association in either group: OR=1.00 (95% CI: 0.56 to 1.79), OR=1.08 (95% CI: 0.50 to 2.34) | Maternal vitamin D status in pregnancy did not influence infant birth outcomes. |
| Morgan et al., 2016 [58] | Nested case-control study | 1,328 | Cord blood | deficiency: <50 nmol/L, insufficiency: 50-75 nmol/L | CLIA | OR=0.92 (95% CI: 0.64 to 1.33), OR=0.85 (95% CI: 0.62 to 1.16) | No significant associations were observed between [25(OH)D] and SGA. |

wks=weeks; HPLC=high-performance liquid chromatography; MS=mass spectrometry; LC-MS=liquid chromatography–mass spectrometry; RIA=radioimmunoassay; CLIA=chemiluminescent immunoassay; ECLIA=electrochemiluminescence immunoassay; ELISA=enzyme linked immunosorbent assay

## Other adverse pregnancy outcomes

Data regarding the impact of hypovitaminosis D on the delivery mode are inconclusive. It has been reported that vitamin D deficiency is associated with a fourfold increase in the risk of cesarean section [64]. Less pronounced was the risk estimated by Scholl *et al*., who reported an OR of 1.66 (95% CI: 1.09 to 2.52) [65]. In contrast, other observational studies failed to show any correlation between serum vitamin D levels and delivery mode [35,66-68].

Findings from three observational studies show an association between bacterial vaginosis in pregnancy and vitamin D deficiency. Using National Health and Nutrition Examination Survey data, Hensel *et al*. found that the adjusted OR of bacterial vaginosis was 2.87 (95% CI: 1.13 to 7.28) among gravidas with vitamin D deficiency (<30 ng/mL) [69]. A stronger association with an OR=4.4 was reported when a lower cut-off of 15 ng/mL was used to define vitamin D deficiency among pregnant African American adolescents [70]. It is also concluded that women with normal vaginal flora have higher concentrations of serum 25(OH)D compared with women affected by bacterial vaginosis (geometric mean difference 10.6; p<0.001) [71]. It has been suggested that the increased risk of infection in pregnant women with vitamin D deficiency may be the result of high levels of proinflammatory cytokines, such as IL-6 and TNF-a [72].

## Vitamin D supplementation in pregnancy

A large body of evidence has assessed the need for vitamin D supplementation during pregnancy. In a meta-analysis of 9 studies, each of which used different doses of vitamin D, vitamin D supplementation was compared with no intervention or placebo [73]. It was found that vitamin D supplementation reduced the risk of pre-eclampsia, but the significance was borderline (8.9% vs 15.5%; RR=0.52; 95% CI: 0.25 to 1.05), whereas no protective effect was reported on the development of GDM. Furthermore, vitamin D supplements seem to exert a protective effect against preterm birth (RR=0.36; 95% CI: 0.14 to 0.93) and SGA infants (RR=0.40; 95% CI: 0.24 to 0.67), but no impact was shown on delivery mode.

According to the WHO, vitamin D supplementation is not recommended for pregnant women for maternal and perinatal outcome improvement, and women should simply be given advice regarding a balanced diet and sources of vitamin D. Nonetheless, if vitamin D deficiency is documented, the recommended nutrient intake (RNI) is 200 IU/day [74].

The Royal College of Obstetricians and Gynaecologists recommends that every pregnant and breastfeeding woman should be advised about vitamin D and prescribed 400 IU daily, based on the importance of vitamin D on calcium metabolism and on its non-calcium effects. For high-risk women – namely with skin hyperpigmentation, reduced exposure to sunlight, or those who are socially excluded or obese –, the daily dose should be increased to at least 1000 IU/day. Moreover, 800 IU/day of vitamin D combined with calcium is suggested for women with a high risk of pre-eclampsia. Treatment doses of cholecalciferol 20,000 IU/week or ergocalciferol 10,000 IU twice/week for 4-6 weeks, followed by regular supplementation should be used for vitamin D deficient women [75].

As suggested by the American College of Obstetricians and Gynecologists Committee opinion, a standard prenatal dose of 400 IU of vitamin D daily should be prescribed. However, there is no sufficient evidence supporting vitamin D supplementation for preterm birth or pre-eclampsia prevention. Higher doses of 1,000-2,000 IU/day are recommended for pregnant women with vitamin D deficiency [76].

## Conclusions

Vitamin D deficiency is highly prevalent worldwide, affecting people from different latitudes and regardless of their access to fortified products. Many observational, case-control and cross-sectional studies have demonstrated an association between maternal vitamin D status and adverse pregnancy outcomes, such as pre-eclampsia, gestational diabetes, preterm birth, small for gestational age, delivery mode and bacterial vaginosis; solid evidence, however, is still lacking. Variable cut-offs, different quantification methods, diversity between study groups, and confounding factors may account for the inconsistent results. Both the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists recommend standard prenatal vitamin D supplementation of 400 IU, whereas WHO suggests a balanced diet instead of supplementation for pregnant women without documented vitamin D deficiency.

## References


1. Holick MF. Vitamin D deficiency. New Engl J Med. 2007;357:266-81.
2. Shieh A, Chun RF, Ma C, et al. Effects of High-Dose Vitamin D2 Versus D3 on Total and Free 25-Hydroxyvitamin D and Markers of Calcium Balance. J Clin Endocrinol Metab. 2016;101:3070-8.
3. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011.
4. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30.
5. Pérez-López FR, Brincat M, Erel CT, et al. EMAS position statement: Vitamin D and postmenopausal health. Maturitas. 2012;71:83-8.
6. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144 Pt A:138-45.
7. Parva NR, Tadepalli S, Singh P, et al. Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). Cureus. 2018;10:e2741.
8. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001-2006. NCHS Data Brief. 2011 Mar;(59):1-8.
9. Krieger JP, Cabaset S, Canonica C, et al. Prevalence and determinants of vitamin D deficiency in the third trimester of pregnancy: a multicentre study in Switzerland. Br J Nutr. 2018;119:299-309.
10. Hong-Bi S, Yin X, Xiaowu Y, et al. High prevalence of vitamin D deficiency in pregnant women and its relationship with adverse pregnancy outcomes in Guizhou, China. J Int Med Res. 2018;46:4500-5.
11. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficien-

cy and supplementation during pregnancy. Clin Endocrinol (Oxf). 2009;70:685-90.
12. Emmerson AJB, Dockery KE, Mughal MZ, Roberts SA, Tower CL, Berry JL. Vitamin D status of White pregnant women and infants at birth and 4 months in North West England: A cohort study. Matern Child Nutr. 2018;14(1).
13. Wimalawansa SJ, Razzaque MS, Al-Daghri NM. Calcium and vitamin D in human health: Hype or real? J Steroid Biochem Mol Biol. 2018;180:4-14.
14. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. The Am J Clin Nutr. 2008;87:1080S-6S.
15. Mozołowski W. Jędrzej Sniadecki (1768–1838) on the Cure of Rickets. Nature. 1939;143:121.
16. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586-91.
17. Vaughan-Shaw PG, O'Sullivan F, Farrington SM, et al. The impact of vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: systematic review and meta-analysis Br J Cancer. 2017;116:1092-110.
18. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr. 2013;97:774-81.
19. Apostolakis M, Armeni E, Bakas P, Lambrinoudaki I. Vitamin D and cardiovascular disease. Maturitas. 2018;115:1-22.
20. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296:2832-8.
21. Cooper JD, Smyth DJ, Walker NM, et al. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. Diabetes. 2011;60:1624-31.
22. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2015;21:2708-17.
23. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170:1-7.
24. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169.
25. Wei S-Q, Qi H-P, Luo Z-C, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2013;26:889-99.
26. Wei SQ, Audibert F, Hidiroglou N, et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG. 2012;119:832-9.
27. Achkar M, Dodds L, Giguère Y, et al. Vitamin D status in early pregnancy and risk of preeclampsia. Am J Obstet Gynecol. 2015;212:511.e1-7.
28. Serrano NC, Guio E, Quintero-Lesmes DC, et al. Vitamin D deficiency and pre-eclampsia in Colombia: PREVitD study. Pregnancy Hypertens. 2018;14:240-4.
29. Ullah MI, Koch CA, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. Horm Metab Res. 2013;45:682-7.
30. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab. 2007;92:3517-22.
31. Wetta LA, Biggio JR, Cliver S, Abramovici A, Barnes S, Tita AT. Is midtrimester vitamin D status associated with spontaneous preterm birth and preeclampsia? Am J Perinatol. 2014;31:541-6.
32. Boyle VT, Thorstensen EB, Mourath D, et al. The relationship between 25-hydroxyvitamin D concentration in early pregnancy and pregnancy outcomes in a large, prospective cohort. Br J Nutr. 2016;116:1409-15.
33. Gidlöf S, Silva AT, Gustafsson S, Lindqvist PG. Vitamin D and the risk of preeclampsia--a nested case-control study. Acta Obstet Gynecol Scand. 2015;94:904-8.
34. Powe CE, Seely EW, Rana S, et al. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hypertension. 2010;56:758-63.
35. Gbadegesin A, Sobande A, Adedeji O, et al. Maternal serum vitamin D levels and pregnancy outcomes: from Lagos, Nigeria. J Obstet Gynaecol. 2017;37:25-8.
36. Shand AW, Nassar N, Von Dadelszen P, Innis SM, Green TJ. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. BJOG. 2010;117:1593-8.
37. Schulz EV, Cruze L, Wei W, Gehris J, Wagner CL. Maternal vitamin D sufficiency and reduced placental gene expression in angiogenic biomarkers related to comorbidities of pregnancy. J Steroid Biochem Mol Biol. 2017;173:273-9.
38. Gram A, Hoffmann B, Boos A, Kowalewski MP. Expression and localization of vascular endothelial growth factor A (VEGFA) and its two receptors (VEGFR1/FLT1 and VEGFR2/FLK1/KDR) in the canine corpus luteum and utero-placental compartments during pregnancy and at normal and induced parturition. Gen Comp Endocrinol. 2015;223:54-65.
39. Lu F, Longo M, Tamayo E, et al. The effect of over-expression of sFlt-1 on blood pressure and the occurrence of other manifestations of preeclampsia in unrestrained conscious pregnant mice. Am J Obstet Gynecol. 2007;196:396.e1-7.
40. Makris A, Thornton C, Thompson J, et al. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. Kidney Int. 2007;71:977-84.
41. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012;125:911-9.
42. Zhang MX, Pan GT, Guo JF, Li BY, Qin LQ, Zhang ZL. Vitamin D Deficiency Increases the Risk of Gestational Diabetes Mellitus: A Meta-Analysis of Observational Studies. Nutrients. 2015;7:8366-75.
43. Zhang Y, Gong Y, Xue H, Xiong J, Cheng G. Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. BJOG. 2018 Jun;125:784-93.
44. Lu M, Xu Y, Lv L, Zhang M. Association between vitamin D status and the risk of gestational diabetes mellitus: a meta-analysis. Arch Gynecol Obstet. 2016;293:959-66.
45. Dodds L, Woolcott CG, Weiler H, et al. Vitamin D Status and Gestational Diabetes: Effect of Smoking Status during Pregnancy. Paediatr Perinat Epidemiol. 2016;30:229-37.
46. Wang Y, Li H, Zheng M, et al. Maternal vitamin D deficiency increases the risk of adverse neonatal outcomes in the Chinese population: A prospective cohort study. PLoS One. 2018;13:e0195700.
47. Hauta-Alus HH, Viljakainen HT, Holmlund-Suila EM, et al. Maternal vitamin D status, gestational diabetes and infant birth size. BMC Pregnancy Childbirth. 2017;17:420.
48. Eggemoen AR, Waage CW, Sletner L, Gulseth HL, Birkeland KI, Jenum AK. Vitamin D, Gestational Diabetes, and Measures of Glucose Metabolism in a Population-Based Multiethnic Cohort. J Diabetes Res. 2018;2018:8939235.
49. Rodriguez A, García-Esteban R, Basterretxea M, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG. 2015;122:1695-704.
50. Mousa A, Abell SK, Shorakae S, et al. Relationship between vitamin D and gestational diabetes in overweight or obese pregnant women may be mediated by adiponectin. Mol Nutr Food Res. 2017;61(11).
51. Miliku K, Vinkhuyzen A, Blanken LM, et al. Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. Am J Clin Nutr. 2016;103:1514-22.
52. McDonnell SL, Baggerly KA, Baggerly CA, et al. Maternal 25(OH) D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLoS One. 2017;12:e0180483.
53. Tabatabaei N, Auger N, Herba CM, et al. Maternal Vitamin D Insufficiency Early in Pregnancy Is Associated with Increased Risk of Preterm Birth in Ethnic Minority Women in Canada. J Nutr. 2017; 147:1145-51.
54. Bodnar LM, Klebanoff MA, Gernand AD, et al. Maternal vitamin D

status and spontaneous preterm birth by placental histology in the US Collaborative Perinatal Project. Am J Epidemiol. 2014;179:168-76.
55. Bodnar LM, Rouse DJ, Momirova V, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Maternal 25-hydroxyvitamin d and preterm birth in twin gestations. Obstet Gynecol. 2013;122:91-8.
56. Jao J, Freimanis L, Mussi-Pinhata MM, et al; NISDI LILAC Protocol. Severe Vitamin D Deficiency in Human Immunodeficiency Virus-Infected Pregnant Women is Associated with Preterm Birth. Am J Perinatol. 2017;34:486-92.
57. Ong YL, Quah PL, Tint MT, et al. The association of maternal vitamin D status with infant birth outcomes, postnatal growth and adiposity in the first 2 years of life in a multi-ethnic Asian population: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study. Br J Nutr. 2016;116:621-31.
58. Morgan C, Dodds L, Langille DB, et al. Cord blood vitamin D status and neonatal outcomes in a birth cohort in Quebec, Canada. Arch Gynecol Obstet. 2016;293:731-8.
59. Chen Y, Zhu B, Wu X, Li S, Tao F. Association between maternal vitamin D deficiency and small for gestational age: evidence from a meta-analysis of prospective cohort studies. BMJ Open. 2017; 7:e016404.
60. Chen YH, Fu L, Hao JH, et al. Maternal vitamin D deficiency during pregnancy elevates the risks of small for gestational age and low birth weight infants in Chinese population. J Clin Endocrinol Metab. 2015;100:1912-9.
61. Wang H, Xiao Y, Zhang L, Gao Q. Maternal early pregnancy vitamin D status in relation to low birth weight and small-for-gestational-age offspring. J Steroid Biochem Mol Biol. 2018;175:146-50.
62. Seto TL, Tabangin ME, Langdon G, et al. Racial disparities in cord blood vitamin D levels and its association with small-for-gestational-age infants. J Perinatol. 2016;36:623-8.
63. Gernand AD, Simhan HN, Caritis S, Bodnar LM. Maternal vitamin D status and small-for-gestational-age offspring in women at high risk for preeclampsia. Obstet Gynecol. 2014;123:40-8.
64. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. J Clin Endocrinol Metab. 2009;94:940-5.
65. Scholl TO, Chen X, Stein P. Maternal vitamin D status and delivery by cesarean. Nutrients. 2012;4:319-30.
66. Gernand AD, Klebanoff MA, Simhan HN, Bodnar LM. Maternal vitamin D status, prolonged labor, cesarean delivery and instrumental delivery in an era with a low cesarean rate. J Perinatol. 2015;35:23-8.
67. Savvidou MD, Makgoba M, Castro PT, Akolekar R, Nicolaides KH. First-trimester maternal serum vitamin D and mode of delivery. Br J Nutr. 2012;108:1972-5.
68. Yuan Y, Liu H, Ji C, et al. Association of Maternal Serum 25-hydroxyvitamin D Concentrations in Second Trimester with Delivery Mode in A Chinese Population. Int J Med Sci. 2017;14:1008-14.
69. Hensel KJ, Randis TM, Gelber SE, Ratner AJ. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. Am J Obstet Gynecol. 2011;204:41.e1-9.
70. Davis LM, Chang SC, Mancini J, Nathanson MS, Witter FR, O'Brien KO. Vitamin D insufficiency is prevalent among pregnant African American adolescents. J Pediatr Adolesc Gynecol. 2010;23:45-52.
71. Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. J Nutr. 2009;139:1157-61.
72. Akoh CC, Pressman EK, Cooper E, Queenan RA, Pillittere J, O'Brien KO. Low Vitamin D is Associated With Infections and Proinflammatory Cytokines During Pregnancy. Reprod Sci. 2018;25:414-23.
73. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2016;(1):CD008873.
74. World Health Organization. Vitamin D supplementation during pregnancy. Available at: https://www.who.int/elena/titles/vitamind_supp_pregnancy/en/. Published 2019, February 11. Accessed.
75. Royal College of Obstetricians and Gynaecologists. Vitamin D in pregnancy. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/vitamin_d_sip43_june14.pdf. Published 2014, June. Accessed.
76. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. Obstet Gynecol. 2011;118:197-8.