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Review Article

The association between Vitamin D levels and postpartum depression: a review

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Abstract

According to WHO, Postpartum Depression (PPD) occurs in 10–15% of women after giving birth. Several studies assumed that vitamin D deficiency might worsen PPD symptoms. However, the association between vitamin D levels and PPD is still conflicting. This article summarizes the association between vitamin D levels and PPD. A literature search about Vitamin D levels and PPD from Scopus and PubMed databases was performed in June 2022. Eleven studies were obtained out of 30 studies. Nine out of 11 studies showed that vitamin D levels were significantly associated with PPD. However, the two others showed no significant association. The difference in the blood sample taken and how to assess depression contributes to a different result. The association is related to the role of vitamin D in mood regulation, synthesis of neurotransmitters, stimulating brain receptors, and intercellular neuronal signaling systems.

Keywords

Postpartum depression, Vitamin D, Pregnancy, Deficiency

Introduction

Postpartum depression (PPD) occurs in women after giving birth with characteristics such as weakness, feelings of guilt, unable to sleep, decreased cognitive function, and feelings of suicide. Generally, postpartum depression symptoms appear 3–6 months after birth (CDC 2014). Based on statistical data from the WHO, it is estimated that around 10–15% of women worldwide experience postpartum depression. The clinical manifestations of PPD are losing interest in activities, depression for two weeks, reduced concentration, feeling guilty, and sleep disturbance(Accortt et al. 2016). PPD affects the mother and impacts the growth and development of her family, especially the baby in close contact with the mother (WHO 2012). The etiology of this disease is still not well understood. However, previous studies revealed that the role of micronutrients like vitamin D affected PPD.

Vitamin D is a fat-soluble vitamin usually found naturally in food, sunlight, and supplements. Sources of vitamin D come from food, such as fish oil, red meat, liver, egg yolks, and cow's milk (NHS Choices 2017). One-fifth of vitamin D is obtained through dietary sources, while the remaining 80% is synthesized in the skin by ultraviolet rays from 7-dehydrocholesterol (Akpınar and Karadağ 2022). The serum form of the vitamin, calcidiol, is then hydroxylated in the liver by the enzyme 25-hydroxylase (CYP2R1), and calcidiol is re-hydroxylated in the kidney and brain by the enzyme 1-hydroxylase (CYP27B1), yielding 1,25 (OH)2 cholecalciferol, also known as calcitriol (Akpınar and Karadağ 2022).

This vitamin plays a role in many diseases, such as cancer, osteoporosis, cardiovascular, psychiatric, and diabetes (Fu et al. 2015). Vitamin D shows in low concentration, usually during pregnancy. Even with supplementation, only a few women are vitamin D sufficient (Fu et al. 2015).

The association between vitamin D levels and PPD is still conflicting. Several studies assumed that vitamin D deficiency might worsen PPD symptoms (Robinson et al. 2014; Abedi et al. 2018; Rouhi et al. 2018; Pillai et al. 2021; Amini et al. 2022). A systematic review in 2019, including seven articles, reported that findings from six cohort studies suggest that vitamin D deficiency is associated with the incidence of PPD. However, one study showed no association (Amini et al. 2019). In addition, the studies were between the years 2010 and 2016. Therefore, this article summarizes and updates studies on the association between vitamin D levels and PPD.

Methods

Data search

In June 2022, a literature search was conducted using the PUBMED and SCOPUS databases. "Vitamin D" and "postpartum depression" were the keywords used. The flow diagram's literature search report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Study selection

Original research articles in English published between 2012 and 2022 are eligible for inclusion. Articles that did not discuss the relationship between vitamin D and PPD were not considered.

Article extraction

The author's name, type of study, country, number of participants, age, depression test, methods for measuring the vitamin D levels, study objective, type of sample, time for taking the samples, time for depression assessment, levels of vitamin D, depression scale score, and conclusion were extracted from the obtained articles.

Result and discussion

Fig. 1 depicts the PRISMA flow diagram of the article selection process. The initial search yielded 30 articles: five from PUBMED and twenty-five from the SCOPUS database. Following the selection process, duplicate and inaccessible files were removed until 29 articles were obtained. Following that, 18 articles were eliminated in the second round of selection. As a result, the associations between vitamin D levels and PPD were obtained from 11 studies.

Table 1 shows eleven association studies between vitamin D levels and PPD. The studies were conducted in South India, Iran, Denmark, Australia, the USA, China, and Turkey, with 4,893 participants. One of the eleven studies was cross-sectional, two were case-control studies, three were randomized controlled trials, and four were cohort studies. Different methods for measuring vitamin D levels were found, such as ELISA, LCMS/MS, a competitive chemiluminescence immunoassay, reverse-phase HPLC, E601 modular analyzer, and enzyme immunoassay. The depression test was measured by Edinburgh Depression Scale (EPDS), Beck Depression Scale (BDS), The Center for Epidemiological Studies Depression (CES-D), and Beck Depression Inventory (BDI).

Table 1. Studies of the relationship between Vitamin D and post-partum depression.

No.	Authors	Type of Study	Country	Number of Participants	Age	Depression test	Vit D measurement methods
1	Pillai, R. R., et al	Cross-sectional study	South India	660	18–40	EPDS	ELISA
2	Abedi, P., et al	Case-control	Iran	120	18–35	BDS	ELISA
3	Nielsen, N. O, et al	Case-control	Denmark	Case = 605 Control = 875	18–34+	Taking anti-depressant within one year after delivery	LCMS/ MS
4	Gould J. F, et al	Randomized controlled trial	Australia	1040	24–35	EPDS	LCMS/ MS
5	Amini S, et al	Randomized controlled trial	Iran	81	18–45	EPDS	ELISA
6	Rouhi, M., et al	Randomized controlled trial	Iran	80	Mean: 24.7	EPDS	-
7	Accortt, E. E, et al (2015)	Cohort study	USA	91	18–44	CES-D and EPDS	A competitive chemiluminescence immunoassay
8	Accortt, E. E, et al (2020)	Cohort study	USA	89	average 27.80	BDI and CES-D	Reverse-phase liquid chromatography
9	Fu, C. et al	Cohort study	China	248	Median: 31 (29–32)	EPDS	E601 modular analyzer
10	Gur, EB, et al	Cohort study	Turkey	208	18–40	EPDS	ELISA
11	Robinson, M., et al	Cohort study	Australia	796	<20–>30	EPDS	Enzyme immunoassay
				Total = 4,893			

Abbreviation: EPDS = The Edinburgh Postnatal Depression Scale; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; ELISA = The enzyme-linked immunosorbent assay; LCMS/MS = Liquid chromatography-mass spectrometry.

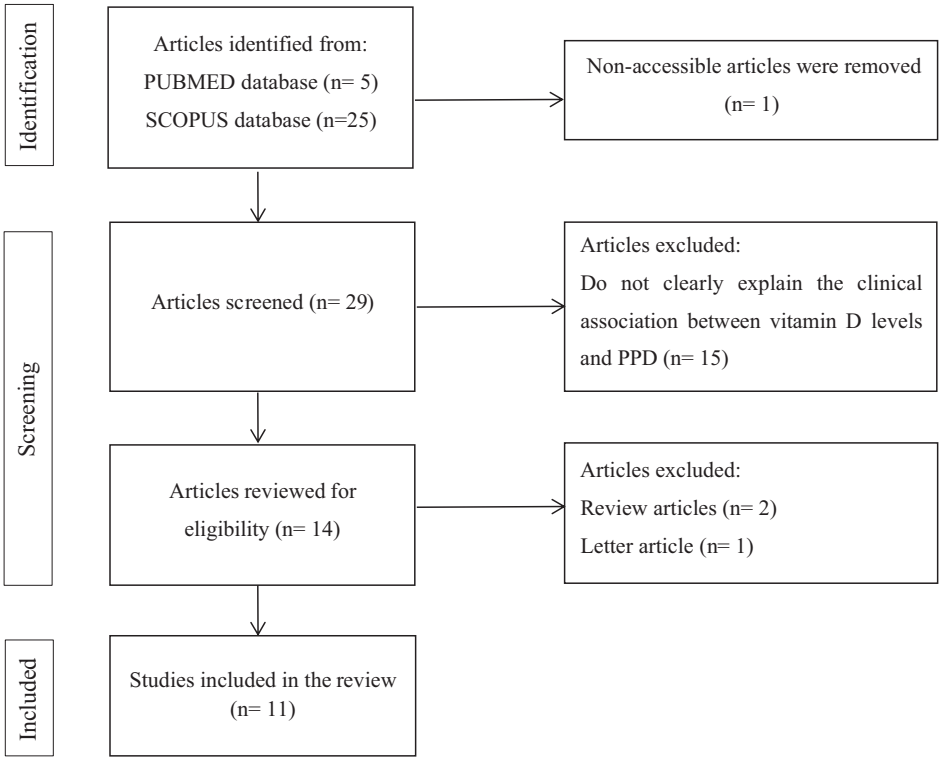

Figure 1. PRISMA flow diagram of the literature search.

Studies with a significant association between vitamin D levels and PPD

Table 2 presents nine studies with a significant association between vitamin D levels and PPD. Most samples measuring vitamin D were venous blood taken during 13–28 weeks of pregnancy, 24–48 hours after birth, and 6–8 weeks after childbirth. A Depression assessment was conducted within 4–12 weeks after delivery.

A cross-sectional study in South India that measured serum 25(OH)D levels in women with and without PPD discovered that low serum 25(OH)D levels are associated with depression in women six weeks after delivery (Pillai et al. 2021). A case-control study of reproductive-aged Iranian women who had a venous blood sample taken 6–8 weeks after childbirth discovered an association between low vitamin D levels and PPD. (Abedi et al. 2018).

Vitamin D supplementation had positive effects on PPD symptoms and serum concentrations of 25[OH]D, according to two randomized controlled trials by Amini et al. (2022) and Rouhi et al. (2018), which examined the effects of vitamin D supplementation in PPD (Amini et al. 2022). Furthermore, in the intervention group, vitamin D reduced depression and fatigue ($P < 0.001$) (Rouhi et al. 2018).

Five cohort studies conducted in the USA, China, Turkey, and Australia revealed that low vitamin D levels during pregnancy and childbirth were associated with PPD. In the United States, Accortt et al. reported that low prenatal 25(OH)D and high prenatal inflammation may predict future postpartum depressive symptomatology in African American women, and Vitamin D deficiency, as measured by the Vitamin D Metabolite Ratio (VMR), is associated with an increased risk of PPD (Accortt et al. 2016, 2021). In addition, Fu et al. in China investigated the possible relationship between serum 25[OH]D (25-hydroxyvitamin D) levels collected 24 hours after delivery and postpartum depression and discovered that lower serum 25[OH]D levels were associated with postpartum depression (Fu et al. 2015). Moreover, according to studies by Gur et al. and Robinson et al., vitamin D levels in mid-pregnancy may be associated with increased depressive symptoms in postpartum women. (Gur et al. 2014; Robinson et al. 2014).

Studies with no significant association between Vitamin D levels and PPD

Table 3 shows two studies in that found no link between vitamin D levels and PPD. In a case-control study from Denmark, Nielsen et al. found no overall association between vitamin D status during pregnancy and PPD risk (Nielsen et al. 2013). However, in this study, no depression scale score was reported. The depression assessment was obtained from women who took anti-depressant within one year after delivery. A study in Australia also found no association between cord blood 25(OH)D concentration at delivery and PPD six weeks or six months later (Gould et al. 2015). The difference in the blood sample taken and how to assess depression contributes to a different result.

Association between Vitamin D levels and PPD

Our study revealed that most studies (9 out of 11) of Vitamin D levels were associated with PPD. A theory suggests

that vitamin D plays an important role in mood regulation. Mood regulation and the incidence of depression are closely related to neurotransmitters. The association of low vitamin D levels with depression is related to hypothalamic function and neurotransmitter production (Ellsworth-Bowers and Corwin 2012). Neurotransmitters involved in the process of depression are mainly dopamine and norepinephrine. The synthesis of dopamine and norepinephrine is influenced by the role of the essential enzyme Tyrosine Hydroxylase in their gene expression, which is influenced by vitamin D (Khan et al. 2022). Vitamin D stimulates receptors in the limbic system, cor-

Table 2. Studies with a significant association between Vitamin D and PPD.

Study No	Authors	Study objective	Sample	The sample was taken at	Depression assessment	Level of Vit D	Depression scale score	Conclusion
1.	Pillai, R. R., et al	To compare serum 25(OH)D concentrations in women with and without PPD.	5 ml of peripheral venous blood	6 weeks post delivery	at 6 weeks post delivery	Total Vit D With PPD: 23 (18.1–28.6) Without PPD: 26 (18.2–34.9)	With PDD: 13 (11–15) Without PDD: 3 (1–6)	Low 25(OH)D serum levels are associated with depression in women 6 weeks after delivery.
2	Abedi, P., et al	To investigate the association between vitamin D and postpartum depression in Iranian women of reproductive age.	5mL venous blood	at 6–8 weeks after childbirth.	at 6–8 weeks after birth.	With PPD: 16.89±7.05 Without PPD: 21.28±7.13	-	There is an association between low vitamin D levels and postpartum depression in Iranian women of reproductive age.
5.	Amini S, et al	To see how vitamin D and calcium supplementation affected the severity of symptoms and some inflammatory biomarkers in women with PPD.	5 ml of fasting blood samples were collected pre-and post-intervention.	at baseline and the end of the study.	at baseline and the end of the study	Vit D+Ca: Baseline: 36.56 (28.67, 46.72) Post-intervention: 51.39 (39.73, 63.04) *p = 0.003* Vit D+Ca placebo: Baseline: 39.83 (31.94, 47.69) Post-intervention: 58.03 (45.17, 70.91) *p < 0.001* Placebo: Baseline: 36.74 (28.40, 45.05) Post-intervention: 42.90 (33.77, 52.04) *p = 0.025*	Vit D+Ca: Baseline: 17.41 (4.10) Post-intervention: 15.70 (5.15) *p = 0.042* Vit D+Ca placebo: Baseline: 17.50 (3.97) Post-intervention: 13.33 (6.38) *p = 0.004* Placebo: Baseline: 16.43 (3.07) Post-intervention: 16.68 (5.99) *p = 0.586*	Vitamin D supplementation with an oral pill containing 50,000 IU vitamin D3 fortnightly for 8 weeks improved PPD symptoms and serum 25[OH]D concentrations.
6.	Rouhi, M., et al	To assess the effectiveness of vitamin D supplements in treating postnatal depression and fatigue.	Vitamin D deficiency was not assessed by blood samples.	-	at baseline and end of the study (six months after the study)	-	Baseline: Vit D group: 15.1 (1.9) Placebo group: 15.3 (1.8) Post-intervention: Vit D group: 8.6 (4.3) Placebo group: 13.4 (4.7)	Vitamin D reduced depression and fatigue in the intervention group (P < 0.001).
7.	Accortt, E. E, et al	To see if low prenatal vitamin D status predicted PPD symptoms in pregnant African-American women.	a 10–ml blood	the second-trimester research visit (13–28 weeks gestation).	routine postpartum visits, which are usually scheduled 4–6 weeks after delivery	13.2±9.4	Prenatal CES-D:16.1±11 EPDS 5.20±4.95	In African American women, low prenatal 25(OH)D and high prenatal inflammation may predict future postpartum depressive symptoms.
8.	Accortt, EE, et al	To investigate the relationship between the Vitamin D Metabolite Ratio (VMR), a new candidate biomarker during pregnancy, and PPD.	Plasma	in the second trimester (18–20 weeks gestation)	in the third trimester (28–30 weeks gestation) using BDI; at 6–10 weeks postpartum with CESD	Not at PPD risk: 30 (50.8) PPD risk: 17 (56.7)	Prenatal BDI: Not at PPD risk: 12.4 PPD risk: 14.9 Postpartum CES-D Not at PPD risk: 8.7 PPD risk: 22.0	Vitamin D deficiency, as measured by the VMR, is associated to an increased risk of PPD.
9.	Fu, C. W. et al	To investigate the possible association between serum 25[OH] D (25-hydroxyvitamin D) levels collected 24 hours after delivery and postpartum depression in a Chinese cohort sample.	blood	A blood sample was taken between 24 and 48 hours after the birth.	within 3 months after delivery	Serum 25 [OH]D levels were significantly higher in women without PPD than in women with PPD [14.3 (IQR 10.2–18.2) versus 8.3 (IQR 7.5–9.3) ng/ml; P 0.0001.	At three months' follow-up, 26 women (12.2%) were identified with PPD.	lower serum 25[OH]D levels were associated with postpartum depression.
10.	Gur, E.B., et al	To investigate a possible association between PPD and serum levels of 25-hydroxy vitamin D3 (25 (OH)D3) during mid-pregnancy.	blood	Between 24–28 weeks of pregnancy	1 week, 6 week, and 6 month after delivery	Average 22.4 (11.2)	1st week Postpartum: 17.6 6th weeks Postpartum 18.9 6th months Postpartum 16.6	Vitamin D levels during pregnancy may be associated to an increase in depressive symptoms in postpartum women.
11.	Robinson, M., et al	To assess mid-pregnancy women's 25(OH)D levels in relation to PPD	Venous blood	at 18 weeks of pregnancy	3 days after delivery	-	-	A lower level of 25(OH)-vitamin D in serum at 18 week gestation was associated to an increased risk of postnatal depression symptoms three days after birth.

Table 3. Studies with no significant relationship between Vitamin D and PPD.

Study No	Authors	Study objective	Sample	The sample was taken at	Depression assessment	Level of Vit D	Depression scale score	Conclusion
3.	Nielsen, N. O, et al	To determine if low vitamin D levels during pregnancy are associated with a higher risk of PPD.	Venous blood on routine visits	Weeks 25 pregnancy	Taking anti-depressant within one year after delivery	With PPD: 55.62 nmol/L Without PPD: 55.60 nmol/L	-	There was no overall relationship between vitamin D status during pregnancy and PPD risk.
4.	Gould J. F, et al	To investigate the relationship between 25(OH)D at birth and the risk of PPD six weeks and six months later in a large cohort of Australian women.	Cord blood sample	at delivery	six weeks and six months after birth	Over half of the women (58%, n = 598) had cord blood 25(OH)D > 50 nmol/L, 34% (n = 358) had 25(OH)D 25–50 nmol/L, and 8% (n = 84) had 25(OH)D 25 nmol/L.	-	There was no association found between cord blood 25(OH)D concentration at delivery and PPD six weeks or six months later.

tex, and cerebellum, which are associated with emotion and behavior regulation. Vitamin D also promotes the release of neurotrophins, which play an important role in neuronal development regulation (Khan et al. 2022). Vitamin D can prevent depression associated with dysfunction of the intracellular neuronal signaling system. A hypothesis explained that increased neuronal Ca^{2+} levels significantly determine the onset of depression. Vitamin D works to maintain Ca^{2+} homeostasis. As a result, the increase in Ca^{2+} caused by vitamin D deficiency influences the onset of depression (Berridge 2017).

Vitamin D deficiency has been proposed to contribute to brain development and function in humans based on animal studies (Pet and Brouwer-Brolsma 2016). Increased expression of region-specific vitamin D receptors (VDR) in brain regions known to play an important role in mood regulation (such as the prefrontal and cingulate cortices) is thought to be effective in slowing the progression of depression (Berridge 2017; Menon et al. 2020). It has been established that people with abnormalities in this hippocampus structure experience chronic depression because it regulates memory, emotional processes in other brain regions, and limbic structure atrophy. Following the identification of VDR in the hippocampus, the activity of vitamin D in this structure was investigated, and it was discovered that vitamin D is a powerful modulator of the expression of neurotrophic agents such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3. Vitamin D can boost the expression of neurotrophic factors, which are required for the viability, development, and migration of neurons that demonstrate their biological roles by interacting with cognate tropomyosin-related kinase (Trk) receptors (Akpınar and Karadağ 2022). It is underlined that neurogenesis and neurons that release neurotransmitters play crucial roles in depression and that vitamin D is crucial for supporting the health of neurons (Geng et al. 2019).

Conclusion

Most studies found a significant association between vitamin D levels and PPD. The association is related to the role of vitamin D in mood regulation, influencing the synthesis of neurotransmitters, stimulating receptors in the brain, and being involved in the intercellular neuronal signaling system.

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Disclosure

The authors have declared no conflicts of interest in this work.

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