

Maternal 25-hydroxyvitamin D level and postpartum depression: A systematic review

Shiva Kazemi¹, Elham Aghaei², Kurosh Djafarian, Sakineh Shab-Bidar^{2*}

¹ Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

² Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

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Background: To evaluate systematically the role of maternal vitamin D levels in postpartum depression (PPD).

Methods: PubMed and EMBASE databases were searched using the search words [vitamin D, cholecalciferol, calcitriol, 1,25 (OH)D] in combination with [postpartum depression, PPD, postnatal depression, PND] in the title, abstract, and keywords. The search was limited to publications in English. Criteria for inclusion in this systematic review were data on maternal 25(OH) D and PPD.

Results: We identified 147 publications at first, from which five observational studies were selected for inclusion in the final review. In one study 25(OH) D was associated with PPD. In another one we found an association but in category with vitamin D lower than 47 nMol/L significant in $p < 0.05$. In two studies the blood samples were obtained after childbirth and observed an increased risk of PPD associated with only serum 25[OH] D levels ≤ 25.46 nmol/L and ≤ 25 nmol/L. In one study no association was observed between vitamin D concentrations and risk of PPD and compared with women 50–79 nmol/L, women with higher 25(OH)D3 concentrations (79 nmol/L) appeared to have significantly increased risks of PPD.

Conclusion: Seemingly, vitamin D plays a role along with other factors that might cause postpartum depression in a specific but unknown cut-off point. Further studies are necessary to explore more on the effect of vitamin D on PPD.

Introduction

Depression is linked with significant weakness, mortality and healthcare costs. It is the third leading cause of disability in high-income countries [1]. Postpartum depression (PPD), also called postnatal depression, is a type of clinical depression which can affect both sexes after childbirth [2]. Changes in mood during the postpartum period are reported by

almost 40% of all new mothers with up to one in every five mothers developing the full phenotype of major depression known as postpartum depression [3]. PPD is associated with the delay in child development and behavior disorders in adult life of the descendants [4]. PPD can cause parenting impairment [5-7] and affecting family health and child behaviors [8], cognitive development [9] and physical health [3]. Although biological, psychological and environmental theories have been considered [10], the basic pathophysiology of depression remains unknown and it is probable that several different mechanisms are involved [11].

Vitamin D is a unique neurosteroid hormone

Corresponding author:

Dr. Sakineh Shab-Bidar

Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Email: s_shabbidar@tums.ac.ir

that may have an important role in the development of depression. Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been involved in the pathophysiology of depression [11]. Vitamin D is involved in numerous brain processes including neuro immunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development [12], making it biologically plausible that this vitamin might be associated with mood disturbance [13].

There is an estimation of one billion people worldwide have vitamin D deficiency or insufficiency [14]. In two decades, vitamin D has become an important focus of current medical research. Recent studies have demonstrated a strong relationship between vitamin D and depression [15,16], whereas others have shown no relationship [16,17]. Some studies have shown that low levels of vitamin D in associate with postpartum depression in pregnant women [18]. However, other studies have proposed that vitamin D deficiency does not increase the risk of PPD [19,20]. The conducted studies findings on the association between vitamin D levels and PPD has been controversial. Moreover, to be noted a single study may have low statistical power due to small sample size, unified ethnicity and other limitations. Therefore, in order to decisively conclude, the present meta-analysis was conducted to overcome the limitations of individual studies, and to resolve these controversial results, as well as to decrease the uncertainty of the effect size of estimated risk. The aim of the meta-analysis was to investigate the relationship between maternal serum 25(OH)D levels and PPD.

Methods

Search strategy and study selection

We conducted a systematic review and meta-analysis of studies based on the PRISMA guidelines. PubMed, Scopus, Google Scholar databases were searched for related articles with an inclusion period until the end 10 March 2016. The following key words were used for studies pertinent to the study objectives: “vitamin D”, “cholecalciferol”, “calcitriol”, “1,25(OH)D” in combination with “postpartum depression”, “postnatal depression”, “PPD”, “PND” in the title, abstract, and keywords. The search was limited to studies published in English. There

was no restriction for publication date. We checked reference lists of published papers also for relevant studies.

Eligibility criteria

Studies were eligible for inclusion if they fulfilled the following criteria:: cross-sectional and cohort studies that investigate the association between maternal serum 25(OH) D levels and PPD. RCTs, cross-over studies and review articles were excluded. Papers checked again with manual search of reference lists of review articles.

Data extraction and quality assessment

Two independent researchers reviewed all identified studies for titles and abstracts of articles for relevance to the topic, and then retrieved the full-text articles for those that were potentially relevant. A screening form was used to select eligible articles. The quality control of the articles was performed independently by two authors (SK and EA) and any disagreement solved by discussion or help of third author (SS-b). The following information was extracted: first author, publication year and country, study design, sample size, number of cases and controls (if available) and serum 25(OH)D. The quality of all articles was assessed by using the Newcastle-Ottawa Scale.

Results

Study characteristics

Of 147 papers identified, 28 were duplicates. Of the remaining 119 studies, 109 were excluded after screening by title and/or abstract for eligibility based on the selected PICOS inclusion criteria. Of the resulting nine papers, eight were available in full-text and screened by 2 reviewers, and the reference lists of these eight papers were screened for additional relevant citations, but none was identified. Two papers were excluded after full-text assessment, leaving five observational studies on maternal 25(OH)D levels and postpartum depression symptoms in humans [18-21].

Gur et al [18] assessed the association between PPD and serum level of 25-hydroxy vitamin D₃. Serum 25(OH) D of 179 Caucasian pregnant women with mean age 28.5 years and mean BMI 26.5 kg/m² in 24-28 gestational weeks. Serum vitamin D defined as 25(OH)D₃ ≤ 50 nmol/L (mild deficiency) and ≤ 25 nmol/L (severe deficiency). They excluded women who carried the extra PPD risk factors, such as

Table 1. Included studies

First author	Publish year	country	Study design	Sample size	Diagnosis of PPD	PPD assessment time	PPD cut points	Vit D assessment time	categories of vitD (nmol/L)	Cases nationality
F. Gould	2015	Australia	Multi-site RCT Prospective	1040	EPDS	6 weeks & 6 months after delivery	EPDS>12	At delivery	D <25 nmol/L D: 25–50 nmol/L D >50 nmol/L	-
Bahar Gur	2014	Turkey	Cross-sectional study	179	EPDS	1 week, 6 weeks & 6 months after delivery	EPDS≥12	Week 24-28 gestation	D≤50 mild deficiency D≤25 severe deficiency	Caucasian
Monique Robinson	2014	Western Australia	Prospective Study (cohort)	706	EPDS	3 days after delivery	EPDS≥6	Week 18 pregnancy	D <47 nmol/L (quartile 1) D: 47–58 nmol/L (quartile 2) D: 59–70 nmol/L (quartile 3) D >70 nmol/L (quartile 4)	Caucasian
C-W Fu	2014	China	Cohort	213	EPDS	3 months after delivery	EPDS≥12	24-48 hours after delivery	D < 50 deficient D: 50-75 insufficient	Chinese
Nina O. Nielsen	2013	Denmark	Nested case-control retrospective	605 PPD 875 control	-	-	-	10-12 & 25 weeks of pregnancy	D <15 nmol/L, D: 15–24 nmol/L, D: 25– 49 nmol/L, (R)D: 50–79 nmol/L, D: 80–99 nmol/L, D: ≥100 nmol/L	Danish

intrauterine fetal death, having a newborn with an anomaly, having a newborn taken to the intensive care unit, having a difficult delivery, postpartum bleeding and hysterectomy, to reduce possible confounders. PPD with EPDS (Edinburgh Postnatal Depression Scale) were evaluated in one week, 6 weeks and 6 months after delivery and EPDS scores ≥ 12 was considered as depression. The mean 25(OH) D3 level was significantly different between women with and without PPD through three time periods. Furthermore, the mean EPDS score (mean ranks) were significantly different between women with normal and low levels of vitamin D in each of the three time periods. They found that lower maternal 25(OH)D3 levels in the second trimester of pregnancy were associated with higher levels of postpartum depressive symptoms at one week, 6 weeks, and 6 months postpartum and there was a significant negative correlation between vitamin D levels and EDPS at each of the three time points ($r = -0.2, -0.2, -0.3$, respectively).

Another study by Robinson et al [19] has evaluated this hypothesis that low levels of 25(OH)-vitamin D in maternal serum during pregnancy will be associated with a higher incidence of postpartum depressive symptoms. They prospectively measured serum 25(OH)D in a sample of 796 Caucasian pregnant women (1989-1992) in 18 gestational weeks, The serum

25(OH)-vitamin D was categorized as quartiles based on the cut points vitamin D <47 nmol/L (quartile 1), 47–58 nmol/L (quartile 2), 59–70 nmol/L (quartile 3) and >70 nmol/L (quartile 4). PPD was assessed in 3 days after delivery and EPDS scores ≥ 6 was considered as depression. Results were adjusted for a number of potentially confounders such as maternal body mass index (BMI), cigarette smoking and alcohol use, maternal age, education and total family income (measured at 18 weeks gestation), hypertensive diseases of pregnancy, gender of child, admission to the Special Care Nursery (SCN) and proportion of optimal birthweight (a measure of the appropriateness of intrauterine growth for gestational age) and season of birth. To show the association of maternal serum 25(OH) D levels with risk for postnatal depression symptoms adjusted general linear model was used. In comparison with women in the 4th quartile for 25(OH) D levels, those who were in the lowest quartile had greater endorsement of postnatal depression symptoms. This inverse association between 25(OH) D and depression symptoms was significant for women in the lowest quartile for vitamin D status ($b = 0.93, 95\% \text{ CI} = 0.27, 1.58$). In fully adjusted binary logistic regression model, Women in the lowest quartile for 25(OH) D status were significantly more likely to report six or more depressive symptoms in the first days after birth

(odds ratio (OR)= 2.19, 95 % CI=1.26, 3.78) compared with women in the highest quartile for vitamin D. Multinomial logistic regression model was used to evaluate the impact of vitamin D levels on a greater frequency of depressive symptoms. Women in the lowest 25(OH) D quartile were significantly more likely to have showed six or more depressive symptoms in compare with women in the highest quartile (OR=2.72, 95 % CI=1.42, 5.22). Finally, they reported an inverse association between 25(OH) D levels and risk for postpartum depression with each quartile lower than quartile 4, although for quartiles 2 and 3, these effect sizes were not significant at $p < 0.05$.

The relationship between 25(OH)D at delivery and the risk of PPD at six weeks and six months postpartum in 1040 Australian women was investigated by Gould et al [20], to investigate, This study involved a cohort of women enrolled in the DOMInO trial; a multi-site RCT that aimed to determine the effect of maternal supplementation with the omega-3 fatty acid DHA during the last half of pregnancy on maternal PPD and cognitive development in early childhood. Neither the fish oil nor the placebo capsules contained vitamin D.

Samples of umbilical cord blood collected at delivery were used in this study to determine serum 25(OH)D concentration using a liquid chromatography–tandem mass spectroscopy method. , Vitamin D status was categorized as < 25 , $25\text{--}50$ and > 50 nmol/L; PPD was evaluated with EPDS in 6 weeks and 6 months after delivery and EPDS scores > 12 was considered as depression. After controlling for potential confounders, in control group no association was found between cord blood 25(OH)D concentration and PPD at six weeks (adjusted risk ratio (RR) 0.92 95% CI 0.84– 1.02, $p = 0.11$) or six months after delivery (adjusted RR 0.96 95% CI 0.88–1.05, $p = 0.41$). These findings was same in treatment group (adjusted $P = 0.11$ at six weeks and $P = 0.58$ at six months postpartum), but in control group, at six weeks postpartum, cord blood 25(OH)D < 25 nmol/L was associated with an increased risk of PPD. Finally, authors have suggested that the DHA intervention may have changed the association between vitamin D and PPD at six weeks postpartum.

In a study by Fu et al [21] the association between serum levels of 25hydroxyvitamin D was evaluated in a Chinese cohort sample of 213 women. Samples were collected 24 hours after delivery and postpartum depression was assessed

using EPDS 3 months after delivery and the scores ≥ 12 were considered as depression. After adjusting for all probable confounders such as age, breast feeding, stressful life events, maternal education, family income, partner support, planned or unplanned pregnancy, mode of delivery and previous psychiatric contact, serum 25(OH)D remained as an independent predictor of PPD with an adjusted OR of 0.81 (95%CI 0.70–0.92; $p < 0.0001$). Further, they found an increased risk of PPD associated with 25(OH) D levels ≤ 10.2 ng/ml (unadjusted OR 16.38, 95%CI 5.37–49.38). This relationship was confirmed in the dose–response model. In multivariate analysis, observed an increased risk of PPD associated with serum 25(OH)D levels ≤ 10.2 ng/ml (25.46 nmol/L) (OR 7.17, 95%CI 3.81–12.94; $p < 0.0001$) after adjusting possible confounders.

The relationship between maternal serum 25(OH) D the risk of PPD was examined in a nested case control in the Danish National Birth Cohort. Nielsen et al [21] measured serum concentrations of 25(OH)D3 in 605 pregnant women with PPD who filled prescriptions for anti-depressive medications within one year after delivery and 875 controls who did not fill prescriptions for anti-depressive medications. Venous blood was collected at weeks 10–12 and 25 of pregnancy and divided to 6 levels (< 15 nmol/L, $15\text{--}24$ nmol/L, $25\text{--}49$ nmol/L, $50\text{--}79$ nmol/L, $80\text{--}99$ nmol/L, ≥ 100 nmol/L). They found no association between vitamin D concentrations and risk of PPD. However, in women with higher 25(OH)D3 concentrations (79 nmol/L) the risk of PPD significantly increased, compared with women with concentrations in the reference category ($50\text{--}79$ nmol/L). This research suggests that the 24-hydroxylase-based degradation mechanism that occurs in response to elevated vitamin D levels may also apply to PPD.

Discussion

This systematic review revealed that there are evidences to show the role of vitamin D deficiency on the risk of PPD but not adequate. Five observational studies identified in this systematic review include one cross-sectional study, two prospective studies, a cohort and a nested case-control study.

In the cross-sectional study [18] observed an association between low vitamin D concentrations and PPD, and found negative correlation between vitamin D levels and EDPS.

In two prospective studies and a cohort reviewed here, found inverse association between 25(OH) D levels and risk for postpartum depression in lowest levels of vitamin D. In this study, PPD was evaluated 3 days after delivery. However, recent studies show that PPD typically begins around two weeks after childbirth [22]. In another study, it was found that the maximum prevalence of depression was after the 2nd month after delivery [23]. Two review studies reported that the serum 25(OH)D was measured at delivery [24] and 24-48 hours after delivery [25] which have little credibility to show the actual levels of vitamin D during pregnancy.

In the nested case-control study women with higher 25(OH)D3 concentrations appeared to have significantly increased risk of PPD, compared with women with concentrations in the reference category. In this study only included women with PPD who used antidepressants and used no objective criteria, such as EPDS scores to show severity of PPD. However, other reviewed studies, included the women who had an EPDS score and did not apply for professional health support, and none of them used antidepressant drugs [26].

Vitamin D plays important roles in many cellular events by virtue of its autocrine and paracrine effects [26]. The biological mechanism linking vitamin D with mood disorders is still unclear.

This mechanism could be related to the location of vitamin D receptors within the brain. VDRs are inadequately filled in the presence of vitamin D deficiency, which may interfere with the proper functioning of hormonal processes that prevent mood disorders [24]. Moreover, it has been shown that vitamin D is involved in the synthesis of norepinephrine and dopamine [25] and vitamin D response elements in the promoter regions of serotonin genes have detected [27]. Active vitamin D enhances glutathione metabolism in neurons, therefore promoting the antioxidant activities that protect them from oxidative degeneration [28]. Because vitamin D regulates calcium homeostasis, membrane permeability and axonal conduction, it is thought to have an indirect role in the regulation of neurotransmission. VDRs and catalytic enzymes are co-localized in areas of the brain involved in complex planning, processing and the formation of new memories [28]. Recent studies have shown that A high concentration of vitamin D receptors can be found in the amygdala, the thalamus, the hypothalamus, the

dorsal raphe nucleus, and in the motor neurons located both cranially and spinally, suggesting effects on the sensory pathways, the endocrine autonomic, and the motor system. Thus, symptoms of depression, such as fatigue, mood regulation, motor function, and pain may be related to effects of vitamin D deficiency [29].

Recently a systematic review and meta-analysis conducted to investigate the relationship between vitamin D deficiency and depression in adults and estimates of all analyses suggest a relationship between vitamin D and depression, and all but one were close to being statistically significant [30]. One of the strengths of this study is that, this is the first systematic review that has investigated the relationship between maternal vitamin D concentrations and PPD.

There are several limitations to our systematic review that there was no RCT of vitamin D for PPD. Our review was restricted to observational and cohort studies, which usually have lower-quality evidence than RCTs.

Three studies collected serum 25(OH) D in pregnancy period and two studies collected it after childbirth, there were high heterogeneity among included studies to compare and to conclude.

Conclusion

It seems that vitamin D plays a role along with other factors that might cause postpartum depression, in a specific but unknown cut off. Further studies are necessary to identify the exact role of vitamin D on PPD.

Conflict of interest

The authors declared no potential conflicts of interest.

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