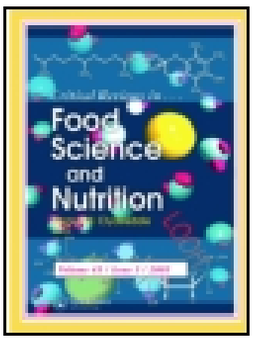

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Postpartum depression and vitamin D: A systematic review

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ABSTRACT

Postpartum depression (PPD) is a prevalent mood disorder estimated to affect 20%–40% of women worldwide after childbirth. In recent studies, the effect of vitamin D on prevention of mood disorders and depression has been investigated, but it is still unclear how vitamin D may affect PPD. The evidence on the relevance between vitamin D deficiency and PPD is inconsistent, and assessment of the recent literature has not previously been carried out. Moreover, there are few clinical studies on PPD and vitamin D supplementation. Five studies have so far assessed the relationship between the levels of vitamin D and PPD. Findings from cohort studies suggest that vitamin-D deficiency is related to the incidence of PPD and vitamin D may play a significant role in the recovery of women with PPD, but it is uncertain whether these actions are the effect of vitamin D on the function of hypothalamic-pituitary-adrenal (HPA) axis, the levels of estradiol, serotonin, pro-inflammatory cytokines, and/or of other mechanisms involved in PPD.

KEYWORDS

Depression; Pregnancy; Postpartum Period; Vitamin D; Review

Introduction

Post-partum depression (PPD) is a prevalent mood disorder estimated to affect 20%–40% of women worldwide after childbirth (Nielsen et al. 2013). The prevalence of PPD is closely related to cultural and social factors, and therefore, it varies among countries and has been estimated as 100-150 per 1000 births (Upadhyay et al. 2017). Epidemiological data estimated that approximately 8.5% in Canada, 5 to 13.4% in Denmark, 13.4 to 36% in Brazil and Chile are affected by PPD, in post-delivery period (Lanes et al. 2011). In Asian countries the highest prevalence of PPD is 63% in Pakistan and lowest is 3.5% in Malaysia (Field et al. 2010).

According to the DSM-V, PPD is referred to diagnosis of major depression with an onset in pregnancy or within 4 weeks of delivery (American Psychiatric Association 2013). PPD is identified by tearfulness, emotional liability, sleep disorder, loss of appetite, irritability, disinterest in life events, poor memory, fatigue, sense of blame, feelings of inability, and inadequacy to take care of the child (Beck 2008).

PPD can have destructive effects on the infant-mother relationship during the 12-month period after childbirth and may affect the child's emotional and cognitive growth. Among the risk factors associated with PPD, history of previous depression, insufficient economic and social support, maternal age, recent psychological stress, unwanted pregnancy or a difficult birth experience can be mentioned (Rasmussen et al. 2017; Baron et al. 2016; Ellsworth-Bowers and Corwin 2012; Bottino et al. 2012; Villegas et al. 2011) (Figure 1).

The etiology of PPD is obscure; however, there is some documentation that appears to propose a psychoneuroimmune relevance. Three hypotheses have focused on this area (Ellsworth-Bowers and Corwin 2012) (Figure 2).

First, PPD has been related with a reduction in the action of monoamine neurotransmitters in the brain. Of these monoamines, serotonin has been studied in more details (Hendrick et al. 1998). Estriol and estradiol are two biological forms of estrogen that are generated by the placenta and rise during pregnancy. Animal studies have shown that estradiol elevates serotonin function through its reduced breakdown and its increased synthesis (Hendrick et al. 1998; Obradovic et al. 2006), which is strongly involved in mood disorders. Estrogen has a major effect on the functioning of the portions of the brain. It acts on monoamine rich regions such as the raphe and the locus coereleus, known to be involved in the control of mood. Estradiol levels rise greatly during pregnancy, and show a sharp drop immediately after delivery. Firstly, this sudden decrease in estradiol levels may contribute to PPD (Hendrick et al. 1998). Secondly, PPD has been linked to the impact of stress on psychological functioning. In stressful situations, the hypothalamus releases corticotrophin-releasing hormone (CRH) that stimulates the pituitary to release corticotropins, which in turn, stimulate the adrenals to release cortisol (Obradovic et al. 2006). A disorder in hypothalamic-pituitary-adrenal (HPA) axis

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Authorship and Originality: Shirin Amini: contributed significantly to the work's conception, data interpretation and analysis; Sima Jafarirad: participated in the writing and critical revision of the article in a manner sufficient to establish ownership of the intellectual content; Reza Amani: contributed to the work's conception, read and approved the version of the manuscript being submitted.

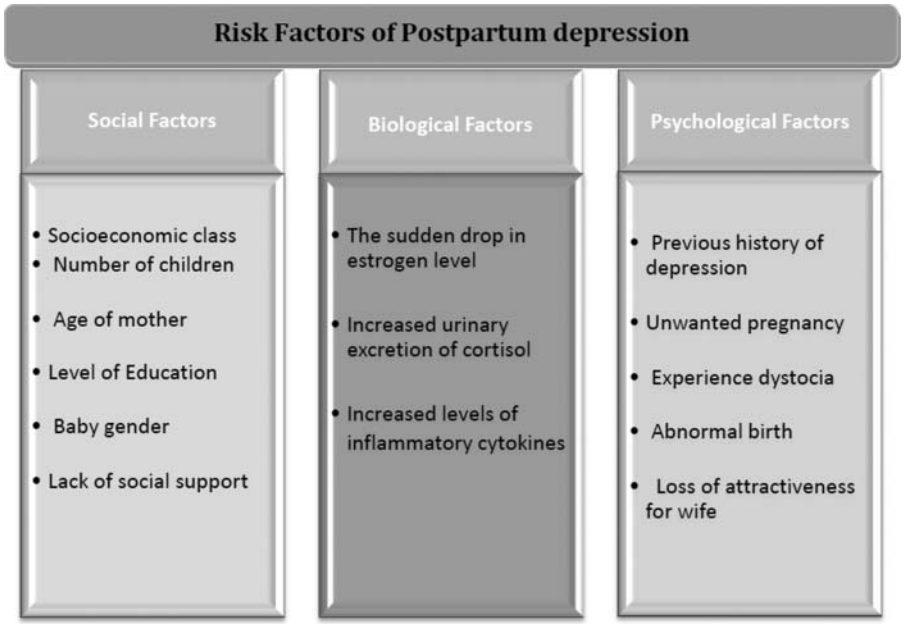

Figure 1. Risk factors associated with PPD (Beck 2008; Villegas et al. 2011).

functioning is probably involved in PPD. One of the major causes of PPD is the hyper-activation of the HPA axis with continuously enhanced levels of glucocorticoids. Most evidence demonstrates that normal glucocorticoid levels regulate synaptic plasticity and neuronal transmission; although, elevated levels are unusually recognized as a risk for depressive disorders (Hendrick et al. 1998). Cortisol levels increase during pregnancy and peak in late pregnancy as an outcome of placental production of corticotrophin-releasing hormone (CRH), falling abruptly at delivery (Obradovic et al. 2006). If the hypercortisolism that signals late pregnancy, and results from placental production of CRH, is sustained after delivery, may become intensive, and contribute to PPD (Tandon and Chintala 2001; Marian and Conn 1979). Thirdly, some studies have demonstrated a relationship between pro-inflammatory cytokines including, interlukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and PPD (Corwin and Pajer 2008; Corwin et al. 2003). Increased cytokines may be substantial in pathophysiology of PPD for two reasons. Pro-inflammatory cytokines may cause PPD due to

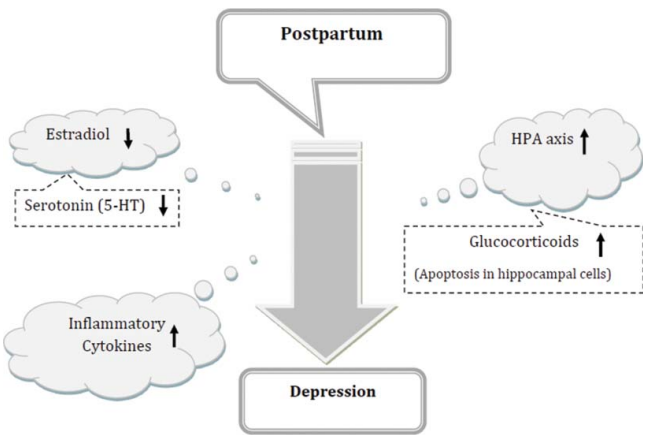

Figure 2. Proposed etiology of PPD (Ellsworth-Bowers and Corwin 2012).

dysregulation of the HPA axis. In stressful conditions, pro-inflammatory cytokines are released into the blood stream, which enhance the release of CRH, adrenocorticotropic hormone (ACTH), and cortisol by acting straightly on hypothalamic and pituitary cells (Dantzer et al. 1999; Vallières and Rivest 1999). Dysregulation of the HPA axis and increased cortisol levels are significantly associated with PPD (Dowlati et al. 2010). In addition, pro-inflammatory cytokines can induce the indoleamine-2,3-dioxygenase (IDO) enzyme, which accelerates the rate-limiting step in the synthesis of kynurenine from dietary tryptophan (Dowlati et al. 2010; Schröcksnadel et al. 2006). Pro-inflammatory cytokines reduce the level of tryptophan by increasing the expression of IDO in immune-competent cell types (Heyes et al. 1996; Mellor and Munn 1999). Finally, reduced levels of tryptophan and then serotonin in the brain, may lead to PPD.

Vitamin D is a steroid molecule and its concentration in the body depends on diet and exposure to the sun. Vitamin D can be obtained via diet as ergocalciferol (D2) from plant sources or cholecalciferol (D3) from animal sources. With the exception of fish oil, other foods are not rich in vitamin D. The synthesis of vitamin D in the epidermis is one of the greatest sources of vitamin D that depends on ultraviolet B (UV-B) radiation from sunlight (Norman 2008). UV-B radiation acts on a cholesterol metabolite (7-dehydroxycholesterol) in the skin, which leads to the generation of cholecalciferol. Cholecalciferol is metabolized in the liver into 25-hydroxyvitamin D (25[OH]D) and is then converted to 1,25-dihydroxyvitamin D (1,25[OH]2D) by 1-alphahydroxylase enzymes (CYP27B1) in the nephrons. 1,25[OH]2D then attaches to nuclear vitamin D receptors (VDRs) to modify gene transcription in various tissues (Zittermann 2003). Vitamin D has many physiological functions. One of the preliminary functions of vitamin D is the maintenance of calcium in body and the promotion of calcium homeostasis (Heaney and Weaver 2003). In addition to its classic functions in bone mineralization and calcium regulation

(Heaney and Weaver 2003), vitamin D can moderate immune function and regulate cell differentiation (Deluca and Cantorna 2001). There is evidence that vitamin D plays a role in the prevention of cancer, diabetes, cardiovascular diseases, liver diseases (Afshari et al. 2015; Przybelski and Binkley 2007; Sharifi et al. 2016), multiple sclerosis (MS) (Hejazi et al. 2014), central nervous system (Holick 2007), and it also acts as an antioxidant (Hejazi et al. 2014). Several studies have suggested a relationship between vitamin D deficiency and symptoms of depression (Lansdowne and Provost 1998; Bertone-Johnson 2009; Prohan et al. 2014).

However, little research has assessed the association between vitamin D deficiency and the occurrence of PPD, and it is still unclear how vitamin D relates to PPD. Prospective studies have suggested that vitamin D deficiency worsens symptoms of PPD. This review presents, the context data on the biological effects of vitamin D and pathophysiology of PPD, summarizes documents from studies in this field, and discusses the mechanisms for the possible effects of vitamin D deficiency on PPD.

Material and methods

For this systematic review, a comprehensive search strategy was used and 1,061 articles were downloaded from PubMed, Google Scholar, and EMBASE. Search took place with keywords such as the "Post-partum depression", "Vitamin D levels", "Vitamin D supplementation", "Inflammatory cytokines ", "Hormonal changes ", "Immune and inflammatory diseases", in the articles that were published from 1975 to 2017.

Criteria for selecting articles

In first screening, the articles' titles and abstracts were evaluated and irrelevant and duplicate titles were removed. Then, in the second phase of screening, full texts of all articles were checked. Two hundred and seventy-one articles were omitted due to not being written in English and trade publication. In addition, 66 articles were excluded because they were editorials, experimental and animal studies. Finally, seven articles which had the following eligibility criteria, "English language", "measurement of 25[OH]D levels" and "PPD scores with Edinburgh Postnatal Depression Scale (EPDS)" were selected for inclusion in the systematic review (Figure 3). From the included studies, six articles were prospective cohort and one was cross sectional. The studies were carried out in various countries: two studies from USA, two from Australia, and the others from Denmark, China and Turkey.

Results

Seven studies have so far measured vitamin D levels during pregnancy or 24 hours after delivery in women and followed them up over time to recognize whether serum 25[OH]D levels are linked to a risk of developing PPD, and the results are conclusive (Table 1).

The results of all studies, but one, showed that lower 25[OH]D serum levels were related to the occurrence of PPD.

In a recent study on African-American women, Accortt et al. (2016) evaluated whether low prenatal serum 25[OH]D

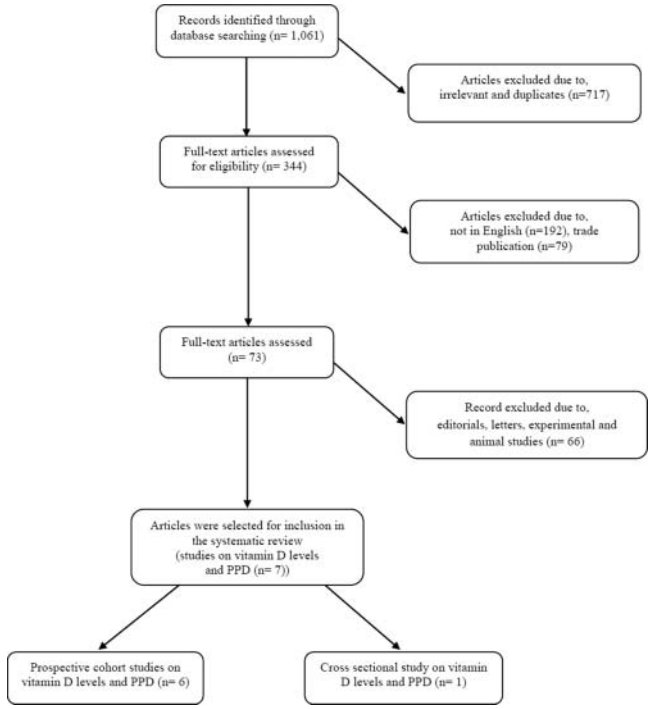

Figure 3. Flowchart of literature search and review.

and high levels of prenatal pro-inflammatory markers are related to the PPD symptoms in the pregnant women. In this prospective study, vitamin D status was measured in the first trimester, and pro-inflammatory cytokines were measured in the second trimester of pregnancy in 91 African-American pregnant women. PPD symptoms were examined at a post-partum visit using the EPDS questionnaire. The researchers reported an inverse association between prenatal log 25[OH]D and PPD symptomatology ($\beta = -0.209$, $P = 0.058$). Furthermore, in women with higher levels of pro-inflammatory cytokines, lower prenatal log 25[OH]D was associated with higher PPD symptoms ($P < 0.05$).

Similarly, Fu et al. 2015, in a Chinese cohort sample, assessed the possible relationship between serum concentrations of 25[OH]D and PPD. In this study, blood sample was taken 24 – 48 h post-delivery to measure serum levels of 25[OH]D. The women were re-visited three months after delivery. The results showed that serum 25[OH]D levels in women with PPD symptoms were significantly lower than those in healthy women ($P < 0.0001$). The optimal cutoff point for serum 25[OH]D levels as an indicator for screening for PPD was estimated to be 10.2 ng/mL. In multivariate analysis, after adjusting for possible confounders, there was an increased risk of PPD associated with 25[OH]D serum levels $\leq$ 10.2 ng/mL (OR: 7.17; 95% confidence interval [CI] 3.81-12.94; $P < 0.0001$).

Other studies have also assessed the relationship between vitamin D levels and PPD. Gould et al. 2015, for example, studying a large cohort of Australian women, evaluated the association between cord blood 25[OH]D at delivery and risk of PPD at six weeks and six months post-partum. In this study, cord blood specimens from 1,040 women participating in the docosahexaenoic acid randomized controlled trial were analyzed for 25[OH]D by mass spectroscopy. PPD symptoms were

Table 1. Summary of results from cohort and case – control studies of the relationship between vitamin-D and postpartum depression.

Result	Duration of follow-up	Design	n	Population	Country	Study, (year)
An inverse association between prenatal log 25[OH]D and PPD symptomatology was observed ($\beta = -0.209$, $P = 0.058$).	10 months	Cohort	91	African-American pregnant women	USA	Accortt *et al.* (2016)
Cord blood 25[OH]D 10–20, >20 ng/mL at childbirth was associated with reduced depressive symptoms at six weeks post-partum.	6 months	Cohort	1040	Australian newly delivered women	Australia	Gould *et al.* (2015)
In women with PPD, serum 25[OH]D levels were significantly lower than those women with no PPD ($P < 0.0001$).	3 months	Cohort	213	Chinese newly delivered women	China	Fu et al. (2014)
There is a significant relationship between low 25[OH]D levels in mid-pregnancy and severity of PPD, which was measured by EPDS questionnaire, in three follow-up periods ($P = 0.003$, $P = 0.004$ and $p < 0.001$, respectively).	6 months	Cohort	179	Pregnant women between 24- 28 gestational weeks	Turkey	Gur *et al.* (2014)
Women in the lowest quartile for vitamin D report more PPD symptoms than those with the highest quartile for 25[OH]D.	5 months	Cohort	796	Australian pregnant women	Australia	Robinson *et al.* (2014)
There is a significant relationship between low 25[OH]D levels in post-partum and high EPDS scores ($P = 0.02$).	7 months	Cohort	97	American newly delivered women	USA	Murphy *et al.* (2010)
No association between low 25[OH]D levels and risk of PPD ($P = 0.08$) and a significant increased risk of PPD among women with the highest 25[OH]D serum levels ($P = 0.04$).	—	Case-Control	1480 (605 PPD and 875 controls)	Danish pregnant women	Denmark	Nielsen *et al.* (2013)

EPDS: Edinburgh Postnatal Depression Scale; PPD: Postpartum Depression.

determined using the EPDS questionnaire six weeks and six months post-partum. The researchers found no association between cord blood 25[OH]D $\leq$ 10 ng/mL at childbirth and depressive symptoms at six months post-partum, but cord blood 25[OH]D 10–20 and > 20 ng/mL at childbirth was associated with reduced depressive symptoms six weeks post-partum.

Moreover, Gur et al. 2014, in a cohort health research study evaluated a probable dependence between serum levels of 25[OH]D, in 179 women during mid-pregnancy, and maternal PPD one week, six weeks, and six months post-delivery. They observed a significant relationship between low 25[OH]D levels in 24–28 weeks of pregnancy and high EPDS scores for all the three follow-up periods (r = -0.2, $P = 0.003$, r = -0.2, $P = 0.004$ and r = -0.3, $P < 0.001$, respectively).

In a similar study, Robinson et al. 2014, in a Western Australian pregnancy cohort study, measured the levels of 25[OH]D in 796 pregnant women during mid-pregnancy and assessed postnatal depressive symptoms three days post-delivery. After adjustment of confounding variables including socio-demographic factors, season of birth, and BMI, women in the lowest quartile for vitamin D reported more PPD symptoms than those with the highest quartile for 25[OH]D.

Finally, in an American cohort sample, a possible relationship between post-delivery serum concentrations of 25[OH]D and PPD was assessed among 97 American newly delivered women. The women were invited to attend monthly visits during seven months after delivery. The researchers observed a significant relationship between low 25[OH]D levels and high EPDS during this period ($P = 0.02$) (Murphy et al. 2010).

The study results were commonly consistent with previous studies, with the exception of Nielsen et al. 2013 study. The authors measured serum levels of 25[OH]D in 605 women with PPD and 875 controls at late pregnancy in the Danish National Birth Cohort. In this study, cases had non-significantly lowered 25[OH]D levels than their healthy controls. Odds ratio were computed for six levels of serum 25[OH]D in women with PPD. At the end of the study, the researchers found no relationship between low maternal vitamin D levels during pregnancy and risk of PPD ($P = 0.08$), and a significant increased risk of PPD among women with the highest 25[OH]D serum levels ($P = 0.04$). The authors did not express a clear interpretation of their results. They suggested that genetic variation can play a role in observing these results. A large number of women in this study had 25[OH]D levels over 50 nmol/L, which is defined as sufficient by the Danish National Board of Health (Dror and Allen 2010).

It has been hypothesized that single-nucleotide polymorphisms (SNP) in some populations may impair the transformation of 25[OH]D to the active structure. As a result, despite the high serum levels of 25[OH]D, in these populations, the levels of 1,25 [OH]2D remain lower than optimal, leading to increased risk of PPD (McGrath et al. 2010).

Alternatively, different results may reflect discrepancies among methodology, race, blood samples, time point of assessments, control of confounders and measures of PPD.

Conclusion

Our review identified one case-control study and six cohort studies investigating the association between vitamin D deficiency and PPD; however, no randomized controlled trial has been done. Recent studies have shown that vitamin D plays an important role in brain development and is perhaps directly involved in the paracrine and/or autocrine regulation of the brain. 25[OH]D levels have been shown to be low in people with depression (Newmark and Newmark 2007), and vitamin D deficiency during pregnancy is prevalent in some societies (Buell and Dawson-Hughes 2008).

The biological evidence for the role of vitamin D in PPD are corroborated by the presence of vitamin D receptors (VDR) in the zones of the brain that are implicated in PPD (Newmark and Newmark 2007), the presence of vitamin D response elements (VDRE) in the promoter of serotonin gene (Borges et al. 2011),

and the interactions between glucocorticoid receptors and vitamin D receptors in the hippocampus (Obradovic et al. 2006).

According to *in vitro* documents, there is cross-talk between glucocorticoid receptors and VDR in the zones of the brain that are implicated in PPD and vitamin D is required in differentiation and apoptosis of neurons in this area. Researchers have proposed that vitamin D interacts with the function of the HPA axis and glucocorticoids (Obradovic et al. 2006). In normal conditions, glucocorticoids hamper the differentiation of neurons in hippocampus and, whenever glucocorticoids stimulate the cells for long-terms, apoptosis happens. When hippocampal cells were exposed to vitamin D before exposure to glucocorticoids for long-term periods, the extent of apoptosis significantly decreased (Ellsworth-Bowers and Corwin 2012).

The function of hypothalamic-pituitary-gonadal (HPG) axis has effects on women's reproductive cycles. Pulsed secretion of gonadotropin-releasing hormone (GnRH) plays a role in the physiological regulation of neuronal activity and fertility cycle. Physiological secretion of GnRH releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH), consequently leading to an increase in estrogen levels. Calcium is an important second messenger to induce intracellular signal ions, in cell types. Studies show that calcium, as a second messenger for the release of gonadotropins, is effective in rhythmic stimulation of GnRH (Marian and Conn 1979; Tandon and Chintala 2001). Most women receive calcium less than the required daily amount (i.e. 1,000-1,300 mg/d) by diet (Christakos et al. 2011). Following delivery and a sudden drop in estrogen, reducing maternal calcium deposits can affect GnRH and have a role in low estrogen levels and PPD. One of the preliminary functions of vitamin D is the maintenance of calcium in tissues. Vitamin D plays an essential role in calcium homeostasis by enhancing the calcium absorption from the intestine, and calcium reabsorption from the kidney. Through its effect on genome, 1,25 [OH]2D, is the most important stimulator of active intestinal calcium absorption (Catterall 1995). Moreover, some studies have demonstrated a relationship between pro-inflammatory cytokines including (TNF-α, IL-6) and PPD (Corwin et al. 2003; Corwin and Pajer 2008; Eyles et al. 2005). Recent studies have suggested that vitamin D decreases the pro-inflammatory cytokines production by reducing the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in macrophages (Vieth et al. 2007; Wang et al. 2005). (Figure 4)

In this systematic review, six articles were prospective with approximately long duration of follow-up, considering the short duration of PPD, e.g., Accortt et al.'s (2016) with 10 month and Murphy et al. (2010) with a 7-month follow-up. In addition, Gould et al.'s (2015) study has a high sample size (n = 1040), which makes the studies credible. The only case-control study which was examined in our review has a high sample size (n = 1480) (Nielsen et al. 2013).

There were limitations in some of the reviewed studies. In Accortt et al.'s (2016) and Murphy et al.'s (2010) studies, the sample size was small (n = 91 and n = 97 respectively). In Gould *et al's* (2015) study, 25[OH]D was measured only in the cord blood sample, and the authors did not have maternal blood samples. It is unclear whether concentrations of vitamin D in cord blood were equal to 25[OH]D in maternal blood. Both Robinson et al. (2014) and Gur et al. (2014), used the

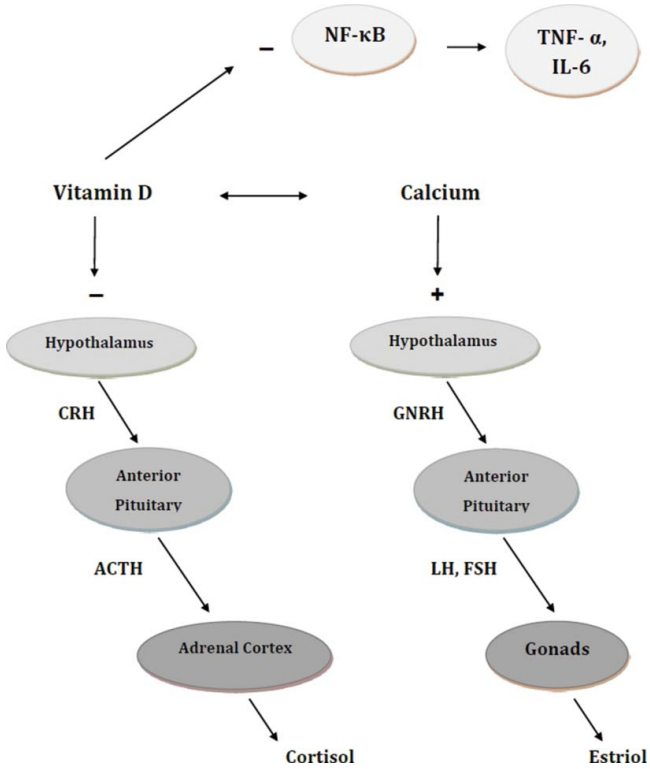

Figure 4. Proposed mechanism that vitamin D may affect on PPD (Marian and Conn 1979; Tandon and Chintala 2001; Christakos et al. 2011; Vieth et al. 2007; Wang et al. 2005).

EPDS questionnaire within one week of birth, while the use of this questionnaire is not appropriate within 14 days of delivery (Cox et al. 1987).

Strengths and limitations

This is the first systematic review that has investigated the relationship between vitamin D deficiency and PPD. The authors used an extensive assessment to identify articles in this field, to determine their eligibility, extract the necessary data and assessed risk of bias in each study. Lastly, in this review, we proposed scientific mechanisms for the effect of vitamin D on PPD. Our review, however, has several limitations. Firstly, at the time of our study, there was no clinical trial of vitamin D supplementation for PPD, hence our review was limited to prospective and case-control studies, in which results are usually less credible than randomized controlled trials (RCTs). Secondly, in our examined studies, the risk factors and etiology of PPD maybe various, thus it may lead to bias. Thirdly, the difference in the vitamin D intake patterns in different countries and races maybe influence the results of studies regarding the relationship between vitamin D and PPD.

In conclusion, vitamin D plays a significant role in brain function and development in women with PPD. It is, however, uncertain whether vitamin D is robustly involved in increasing estradiol, reducing the activation of NF-κB in macrophages, and/or decreasing the pro-inflammatory cytokines production in women with PPD. Overall, evidence suggests a relationship between levels of 25[OH]D and PPD. Since results from RCT studies are not available and women be to modest sun exposure, it could be recommended to use the dose of 1,000-2,000

IU of vitamin D per day that is safe and has positive effect on health to achieve low risk of PPD symptoms.

Conflicts of interest

The authors declare no conflict of interest.

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