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Association between serum 25-hydroxyvitamin D levels measured 24 hours after delivery and postpartum depression

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Objective To assess the possible relationship between serum levels of 25[OH]D (25-hydroxyvitamin D) collected 24 hours after delivery and postpartum depression in a Chinese cohort sample.

Design Cohort study.

Setting One city hospital in Beijing, China.

Population Women delivering a full-term, singleton, live-born infant at one city hospital in Beijing between August 2013 and November 2013.

Methods Women were enrolled immediately postpartum. A blood sample was obtained 24–48 hours after childbirth to test serum levels of 25[OH]D. Participation consisted of a visit to an obstetric unit 3 months after delivery.

Main outcome measure At 3 months' postpartum, women were screened for depression using the Edinburgh Postnatal Depression Scale (EPDS). The primary outcome measure was a prespecified EPDS score of ≥12.

Results During the study period, 323 women were admitted. In all, 248 agreed to enrol and 213 completed 3 months' follow-up (21 were lost to follow-up and 14 withdrew). Of the 213 women who were included, 26 (12.2%) were considered to meet criteria for postpartum depression. Serum 25[OH]D levels in women with no postpartum depression were significantly higher than those in women with postpartum depression ($P < 0.0001$). Based on the receiver operating characteristic curve, the optimal cutoff value for serum 25[OH]D level as an indicator for screening for postpartum depression was estimated to be 10.2 ng/ml, with an area under the curve of 0.801 (95%CI 0.704–0.896). In multivariate analysis, there was an increased risk of postpartum depression associated with 25[OH]D levels ≤10.2 ng/ml (OR 7.17, 95%CI 3.81–12.94; $P < 0.0001$) after adjusting for possible confounders.

Conclusion Our study demonstrated that lower serum 25[OH]D levels were associated with postpartum depression. This association was independent of other possible variables.

Keywords 25-Hydroxyvitamin D, depression, postpartum, vitamin D.

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Introduction

Postpartum depression (PPD) is considered to be one of the most common psychiatric complications of childbirth and is a major cause of maternal mortality worldwide.[1,2] The risk of a woman developing PPD within the first year after childbirth is estimated to be approximately 10–40%, depending on the study sample and methodology.[3,4] Symptom onset in PPD is usually during the first 3 months' postpartum. The condition can last for a few weeks to 6 months or more and, if untreated, can increase the risk of serious outcomes – these include chronicity of the depression, suicide and infanticide, disruption of the marital relationship and adverse effects on child development.[5] However, PPD has received little attention from researchers and clinicians,[6] and only about 50% of women with significant symptoms of depression are recognised.[7]

Given the shortcomings of existing treatments for PPD, a mechanistic study of PPD has the potential not only to improve ontological classification but also to guide the development of more effective treatments.[8] Globally, the predictors of PPD vary; however, four main factors usually emerge – socio-economic status, demography, family history and maternal and social support. Additionally,

research has started to address gene–environment interactions,[9] hormonal factors,[10] the role of micronutrients,[11] inflammatory cytokines[12] and obstetric and biological factors as potential determinants in the aetiology of PPD.[13,14] Unfortunately, no clear biological measure has yet been identified as being causative or predictive of PPD.

Maternal vitamin D deficiency is common during pregnancy, and even with supplementation only a small percentage of women and babies are vitamin D-sufficient. Indeed, vitamin D deficiency during pregnancy is endemic in certain populations.[15] Vitamin D is not biologically active until it is metabolised in the liver into 25[OH]D (25-hydroxyvitamin D) and subsequently converted to 1,25 [OH]2D (1,25-dihydroxyvitamin D) in the kidneys. This active form of vitamin D then binds to vitamin D receptors (VDRs) to regulate cellular function in several body tissues, including brain neurons.[16] Vitamin D plays a role in a wide range of conditions such as osteoporosis, cancer, cardiovascular diseases and diabetes.[17]

Vitamin D concentrations have been shown to be low in people suffering from mood disorders and have been associated with cognitive function.[18] Some studies (in nonpregnant samples) have demonstrated a strong relation between vitamin D and depression,[19,20] whereas others have shown no relation.[21,22] Recent findings from a randomised trial suggested that high doses of supplemental vitamin D may improve mild symptoms of depression.[23] In addition, several studies have found that mood disorders are significantly associated with low levels of serum 25[OH]D, a reliable measurement of vitamin D.[24] There is little research in the literature exploring the implications of decreased levels of 25[OH]D on the prevalence of PPD. Therefore, the purpose of the present study was to assess a possible relationship between vitamin D status and PPD using the serum level of 25[OH]D collected 24–48 hours after delivery in a Chinese cohort sample.

Methods

Subjects

From August 2013 to November 2013, eligible women giving birth at the Peking Union Medical College Hospital (PUMCH) were invited to take part in a study of PPD. This hospital is one of the best in China. The annual number of births there is approximately 2500. In fact, the hospital receives a particular group of pregnant women: almost half are high-risk and/or high-income women. The enrolled women were hospitalised for 24–48 hours after the delivery of a singleton, full-term (≥37 weeks' gestation), live-born infant. All participants were of Chinese family origin. Exclusion criteria were: (1) being under psychiatric care during pregnancy, (2) women with confidential personal data and (3) women with a stillborn infant or one that was immediately admitted to the neonatal intensive care unit. The ethics committee of the participating hospital approved the study. Participants gave written consent after a full explanation and understanding of the study protocols.

A blood sample was obtained 24–48 hours after the birth to avoid the intrinsic physiological changes that occur as a result of delivery but still allow collection before the mother and newborn left the hospital. Follow-up consisted of a visit to an obstetric unit 3 months after delivery for a semi-structured interview and tests. The structured questionnaires included questions on physical and socio-demographic characteristics, medical, psychiatric (depression during or prior to pregnancy based on self-reports), gynaecological and obstetric history variables, lifestyle, variables assessing social network and support, questions on breastfeeding,[2] and the Chinese version of the Edinburgh Postnatal Depression Scale (EPDS).[25] Variables concerning the delivery and neonatal outcome were retrieved from the medical records.

Symptoms of depression were assessed within 3 months after delivery using the Chinese version of the EPDS, a scale originally developed as a screening measure for depressed mothers. The EPDS is a screening tool indicating probable depression rather than diagnosing a depressive state in new mothers. Ten items dealing with typical symptoms of PPD are answered on a four-point scale. The EPDS has been used by many investigators in various countries, dividing the study sample into two groups, depressed and nondepressed, independently of evaluating the severity of the depressive state. The EPDS has been validated in numerous studies of postpartum women and has been shown to have a sensitivity of 86% and a specificity of 78%.[26] Similar to previous studies, a total score of 12 or more was considered a probable positive screen for PPD.[2,13] Reliability analysis of the EPDS (internal consistency) yielded a Cronbach's α of 0.79 in the pilot study.

Fasting blood samples were collected in 5-ml tubes within 24–48 hours postpartum at 07:00–08:00 hours. They were quickly centrifuged to separate the plasma and serum from the cells and were then immediately frozen at −80°C until analysis. All samples were analysed in duplicate. Serum 25[OH]D levels were measured on an E601 modular analyser (Roche Diagnostics, Mannheim, Germany) with a calibration range of 3–70 ng/ml. The intra-assay and inter-assay coefficients of variability were 1.5–4.6 and 2.8–5.1%, respectively. The 25[OH]D levels were therefore used to classify the vitamin D status as vitamin D-deficient (<20 ng/ml) or vitamin D-insufficient (20–30 ng/ml).[17]

Results were expressed as percentages for categorical variables and as medians (interquartile range, IQR) or means (standard deviation, SD) for the continuous variables. Shapiro–Wilk tests were used for the normal

distribution test. Univariate data on demographic and clinical features were compared by Mann–Whitney *U*-test or chi-square test as appropriate. Correlations among continuous variables were assessed by the Spearman rank-correlation coefficient as the data were skewed. The influence of 25[OH]D levels on PPD was tested by binary logistic regression analysis, which allows adjustment for possible confounding factors (age, breastfeeding, stressful life events, maternal education, family income, partner support, planned versus unplanned pregnancy, mode of delivery and previous psychiatric contact). Results were expressed as adjusted odds ratios (ORs) with the corresponding 95%CI. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of the use of serum 25[OH]D to predict PPD. Area under the curve (AUC) was calculated as a measurement of the accuracy of the test. All statistical analyses were performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Results

During the study period, 323 women were admitted. In all, 248 women agreed to enrol and 213 completed 3 months' follow-up (21 were lost to follow-up and 14 withdrew).

The median age was 31 (IQR 29–32) years and 91.1% were Chinese Han. A total of 60.6% of the women had a vaginal delivery, 39.4% required assisted delivery (vacuum extraction or caesarean delivery) and 83.1% were breastfeeding their infant 6 weeks after the delivery. The median gravidity in this sample was 1 (IQR 1–2) and median parity was 1 (IQR, 1–1). The median EPDS score was 3 (IQR 2–7). The baseline characteristics of the women are shown in Table 1.

In our study sample, 82.6% of the women were vitamin D-deficient. The median serum level of 25[OH]D was 13.8 ng/ml (IQR 9.4–17.1). Levels of serum 25[OH]D were compared by the month in which the blood sample was taken. No significant differences in 25[OH]D levels were observed [analysis of variance (ANOVA); $P = 0.12$]. There was no correlation between levels of serum 25[OH]D and age ($P = 0.716$). There was a weak negative correlation between levels of 25[OH]D and the EDPS score ($r = -0.293$, $P < 0.0001$; Figure 1). There was still a significant negative correlation between serum 25[OH]D levels and EDPS score ($P = 0.006$) using linear regression after multivariate adjustment for possible confounders, for instance age, breastfeeding, stressful life events, maternal education, family income, partner support, planned or unplanned pregnancy, mode of delivery and previous psychiatric contact.

According to the EDPS score, 26 women (12.2%) were considered to have PPD at 3 months' follow-up. Serum 25 [OH]D levels in women with no PPD were significantly higher than those in women with PPD [14.3 (IQR 10.2–18.2) versus 8.3 (IQR 7.5–9.3) ng/ml; $P < 0.0001$; Figure 2]. With an unadjusted odds ratio of 0.74 (95%CI 0.64–0.85), serum

Table 1. Baseline characteristics of the enrolled women

Baseline characteristics	Total (n = 213)
Median age, years (IQR)	31 (29–32)
Han Chinese (%)	91.1
Gravidity (IQR)	2 (1–2)
Parity (IQR)	1 (1–1)
Education (%)	
Compulsory (up to 15 years of age)	13.1
High school or apprenticeship	18.3
University	68.6
Family's socio-professional category (%)	
Low	29.1
Middle	55.9
High	15.0
Delivery (%)	
Vaginal delivery	60.6
Assisted delivery	39.4
Breastfeeding 6 weeks after delivery (%)	83.1
Stressful life events (%)	16.9
Depression during or prior to pregnancy (%)	5.6
Planned pregnancy (%)	84.0
Partner support (%)	
None/little of the time	6.1
Some of the time	37.6
Most/all of time	56.3
The median EPDS score (IQR)	3 (2–7)
The median serum level of 25[OH]D, ng/ml (IQR)	13.8 (9.4–17.1)

EPDS, Edinburgh Postnatal Depression Scale.
Results are expressed as percentages or medians (IQR).

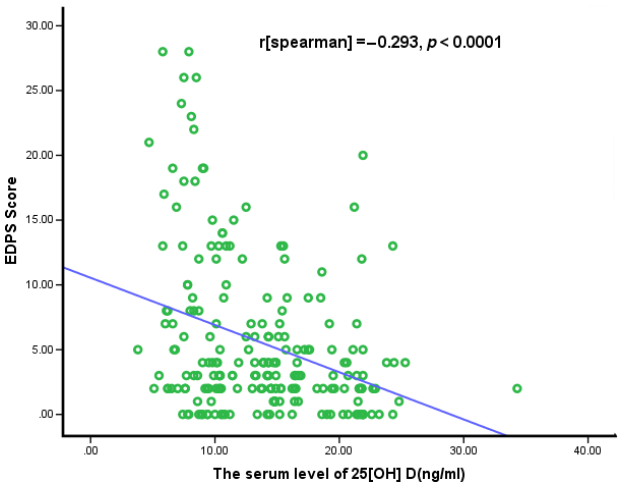

Figure 1. Correlation between serum 25(OH)D levels and the Edinburgh Postnatal Depression Scale (EPDS) score.

25[OH]D had a strong association with PPD. After adjusting for all other significant outcome predictors, serum 25[OH]D remained as an independent predictor of PPD with an adjusted odds ratio of 0.81 (95%CI 0.70–0.92; $P < 0.0001$). In addition, depression during or prior to pregnancy, stressful life events and less partner support were also predictors of PPD (Table 2).

Based on the ROC curve, the optimal cutoff value of serum 25[OH]D as an indicator for screening of PPD was estimated to be 10.2 ng/ml, giving a sensitivity of 75.4% and a specificity of 84.6%, with an AUC of 0.801 (95%CI, 0.704–0.896) (Figure 3). Further, we found that an increased risk of PPD was 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, there was an increased risk of PPD associated with serum 25[OH]D levels ≤10.2 ng/ml (OR 7.17, 95%CI 3.81–12.94; $P < 0.0001$) after adjusting for the above possible confounders (Table 2).

Table 2. Multivariate analysis of factors associated with postpartum depression at 3 months

Parameter	OR*	95%CI	*P*
Chinese Han	0.66	0.34–1.25	0.201
Marital status	1.85	1.03–3.35	0.041
Employed	0.67	0.37–1.22	0.182
Parity	1.09	0.66–1.79	0.742
Gravidity	1.26	0.39–3.43	0.792
Gestational age (<37 weeks)	1.03	0.64–1.65	0.294
Age (>30 years)	1.22	1.01–1.47	0.004
Alcohol abuse	1.16	0.76–2.54	0.562
Smoking	1.18	0.89–1.89	0.296
Birthweight at delivery (<2500 g)	1.17	0.96–1.78	0.103
Body mass index at delivery	1.04	0.64–1.67	0.302
Maternal hospital readmission	3.02	1.46–6.24	0.003
No pregnancy planned	1.33	1.06–1.75	0.006
Stressful life events	2.01	1.25–3.21	0.004
Assisted delivery	1.74	1.09–2.79	0.021
Low income	1.62	1.19–2.75	0.003
Low education	1.15	1.04–1.28	0.006
Less partner support	3.15	2.33–4.27	<0.0001
Health problems during pregnancy	1.39	1.06–1.84	0.011
Not breastfeeding 6 weeks after the delivery	2.07	1.21–3.55	0.009
Depression during or before pregnancy	2.36	1.29–3.66	<0.0001
Serum 25(OH)D	0.81	0.70–0.92	<0.0001

*The odds ratio (OR) corresponds to a unit increase in the explanatory variable.
BMI, body mass index.

Discussion

Main findings

Although some studies have reported an association between serum 25[OH]D and PPD among White people [24], far fewer studies have addressed this association in other ethnic groups. In this study we report that serum 25 [OH] D levels after delivery were significantly lower in women with PPD than those without PPD. For the entire group, when adjusted for other possible risk factors, an elevated serum 25[OH]D level was an independent protective factor against PPD, and serum 25[OH]D levels ≤10.2 ng/

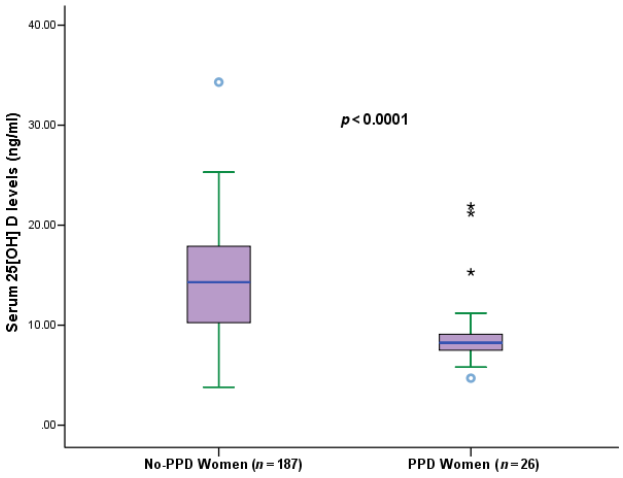

Figure 2. Serum 25(OH)D levels in women with postpartum depression (PPD) or no PPD. Mann–Whitney *U*-test. All data are medians and interquartile ranges (IQR). Serum 25(OH)D is significantly higher in women with no PPD than those with PPD ($P < 0.0001$).

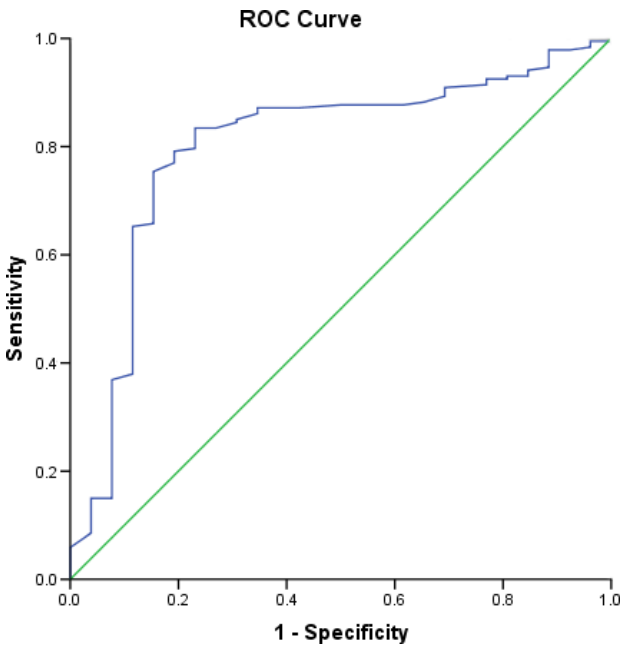

Figure 3. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of serum 25(OH)D levels in predicting PPD.

ml were associated with a 7.17-fold increase in the risk of PPD. Similarly, Robinson et al.[27] reported that women in the lowest quartile for 25(OH)D status were more likely to have a higher level of PPD symptoms than were women who were in the highest quartile, even after accounting for a range of confounding variables. In contrast, a study by Nielsen et al.[28] in Denmark found an increased risk of PPD reported among women with the highest vitamin D concentrations. Further, we found that the serum 25[OH]D level increased with decreasing severity of PPD symptoms as defined by the EDPS score.

Serum 25[OH]D levels can be influenced by season (accounting for the amount and strength of UVB exposure) and vitamin D supplementation. PPD also can be influenced by many factors – for example socio-economic status, demographics, family history, depression state during or before pregnancy, maternal and social support. Skouteris et al.[29] reported that symptoms of depression during or before pregnancy can predict higher PPD symptoms. Similarly, our findings also suggested that depression during or prior to pregnancy can be seen as a predictor of PPD. Interestingly, in this study, when controlling for the above-mentioned variables, a significant relationship over time was found between high EPDS scores and low vitamin D levels during the first 3 months postpartum ($P = 0.006$). Therefore, if a pregnant or postpartum woman is identified to have an insufficient level of vitamin D, she may be more at risk of developing symptoms associated with PPD.

Bodnar et al.[30] found that approximately 54% of Black women and 47% of White women had serum 25[OH]D levels indicative of vitamin D insufficiency. The prevalence of vitamin D deficiency (82.6%) in our study was in the range of a recent study done in a sample of pregnant women at the Medical University of South Carolina in Charleston, SC, USA, which reported that 82% of women had insufficiency and/or deficiency.[24] The mean 25[OH]D levels in pregnant African-American, Hispanic and White women were 15.5 $\pm$ 7.2, 24.1 $\pm$ 8.7 and 29.0 $\pm$ 8.5 ng/ml, respectively.[31] The median serum level of 25[OH]D in our sample was 13.8 (IQR 9.4–17.1) ng/ml.

The overall proportion (12.2%) of women screening positive for PPD in this study was in the range of estimates of PPD in the literature. A systematic review of studies has reported that the point prevalence of major depressive disorder and minor depression ranges from 6.5 to 12.9% through the first 6 postpartum months, peaking at 2 and 6 months after delivery.[32] Other studies have reported a prevalence of PPD within the range 5.85–38%.[5,11,33–36] PPD is a major health concern for women from diverse cultures.[37] Internationally, the prevalence of PPD ranges from almost 0% in Singapore to nearly 57% in Brazil.[38] Overall, this range of prevalence rates for PPD may be due to cross-cultural variables, screening methods, differences in the perception of mental health, time periods for inclusion after delivery and differences in socio-economic background.

Strengths and limitations

There have been several papers in the literature linking vitamin D deficiency and depression, but fewer linking such deficiency to PPD and, as far as we could find, none in an ethnic Chinese sample. As such, this paper makes a significant addition to the literature, especially as people of ethnic Chinese origin make up such a large proportion of the world's population and the results are likely to be generalisable to a non-Chinese population. In addition, this is a prospective study and we were able to control for multiple variables. Lastly, we sought to elucidate putative causative mechanisms for a very important postpartum disorder. This is especially the case for this study, as vitamin D supplementation would be relatively easy and cheap to test in a randomised controlled trial.

Some limitations of this study should be noted. First, a single blood sample was taken immediately following delivery. Our finding needs to be confirmed in future studies with more than one 25[OH]D assessment over the course of pregnancy. It would have been useful to know whether vitamin D was low during the pregnancy and not just in the 24 hours after delivery – this would be a better guide for possible interventions. However, for the purposes of assessing the clinical utility of 25[OH]D as a marker for PPD this is a reasonable approach because more demanding measurement protocols would not be practical in a clinical setting.

Secondly, although the cohort studied reflects the overall largely Han race/ethnicity of Beijing, these results may not be generalisable to more ethnically diverse populations. Although this study excluded women taking medication for depression at enrolment, women could have been untreated or undiagnosed during pregnancy, and less frequently before pregnancy, and still remain in the study cohort. This would give rise to a higher rate of PPD.

Thirdly, although the outcome measure of major depression was assessed with a valid and reliable self-report measure (EPDS), all rating scales have limitations and the diagnosis of depression was not confirmed with structured clinical interviews. In addition, data on depression during or prior to pregnancy were collected based on self-reports. This will induce bias.

Fourthly, we did not have the resources to measure serum vitamin D-binding protein in our samples. Vitamin D-binding protein increases during gestation, whereas 25[OH]D remains constant. Future studies with data on calcium intake and vitamin D status will be needed to further disentangle the effect of each on depression risk.

Fifthly, future studies should clarify whether the association between 25[OH]D and depressive symptoms during

the postpartum period remains stable beyond the first 3 months up to several months postpartum, and whether this relationship holds true for individuals with screening episodes of PPD.

Finally, our study involved a small sample (n = 213) and was not replicated, and this needs to be highlighted. Therefore, our findings may not be generalisable to other patients. Further research is needed to find out whether serum 25[OH]D is a reliable marker of PPD that can be used in clinical practice in other cohorts.

Interpretation

The biological mechanism linking vitamin D and PPD is still unclear. There are numerous biologically plausible mechanisms by which maternal vitamin D status could alter the risk of depression. First, this mechanism could be related to the location of VDRs 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.[39] Relations between VDRs and the regulation of glucocorticoid signalling in rat models[40] and bone mineral density[41] have been reported. Those factors have been implicated in major depressive disorder, and it is possible that inadequately saturated VDRs are also the culprit in this recent finding.

Secondly, vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development,[42] making it biologically plausible that this vitamin might be associated with depression. Thirdly, calcitriol regulates intra- and extracellular calcium concentrations in neurons, consequently reducing toxicity caused by excess calcium.[43] Moreover, it has been shown that vitamin D is involved in the synthesis of norepinephrine and dopamine.[44]

Fourthly, active vitamin D enhances glutathione metabolism in neurons, therefore promoting the antioxidant activities that protect them from oxidative degeneration.[43] Because vitamin D regulates calcium homeostasis, membrane permeability and axonal conduction, it is thought to have an indirect role in the regulation of neurotransmission.

Lastly, VDRs and catalytic enzymes are colocalized in areas of the brain involved in complex planning, processing and the formation of new memories.[45]

Conclusion

In line with our hypothesis, we have shown that serum 25 [OH]D levels after delivery are negatively associated with a positive screen on the EPDS (a score of ≥12), indicating a higher risk for the development of PPD. If vitamin D can be identified as a risk factor for PPD, vitamin D supplementation may reduce the incidence of PPD in those women who are at risk of developing PPD because of their low vitamin D status.

Disclosure of interests

None.

Contribution to authorship

Tu WJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Tu WJ, Fu CW, Liu JT, Yang JQ, Cao Y. *Acquisition of data:* Tu WJ, Fu CW, Cao Y. *Analysis and interpretation of data:* Tu WJ, Fu CW, Liu JT. *Drafting of the manuscript:* Tu WJ. *Critical revision of the manuscript for important intellectual content:* Tu WJ, Fu CW. *Administrative, technical or material support:* Fu CW, Liu JT, Yang JQ. *Study supervision:* Tu WJ.

Details of ethics approval

The ethics committees of the Peking Union Medical College Hospital approved the study (PUMCH-2014101). Participants gave written consent after a full explanation and understanding of the study protocols.

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