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Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms

Authors and Affiliations

Dr Monique Robinson PhD [1]

A/Prof. Andrew J.O. Whitehouse PhD [1, 2]

Prof. John P. Newnham MD [3]

Dr Shelley Gorman PhD[1]

Mr Peter Jacoby MSc [1]

Mrs Barbara J. Holt BSc [1]

Mr Michael Serralha BSc[1]

Ms Jessica E. Tearne BA (Hons) Psych[1, 2]

Prof. Pat G. Holt PhD [1]

Prof. Prue H. Hart PhD [1*]

Dr Merci M.H. Kusel MD [1*]

[1]Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Australia
[2]School of Psychology, The University of Western Australia, Perth, Australia
[3]School of Women's and Infants' Health, The University of Western Australia, Perth, Australia
*equal last author

Corresponding Author:
Dr Monique Robinson
Telethon Institute for Child Health Research
PO Box 855, West Perth, WA 6872 Australia
email: moniquer@ichr.uwa.edu.au
Phone: +61 8 9489 7913
Fax: +61 8 9489 7700

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ABSTRACT

Purpose: Pregnancy is a time of vulnerability for vitamin D insufficiency and there is an emerging literature associating low levels of 25(OH)-vitamin D with depressive symptoms. However, the link between 25(OH)-vitamin D status in pregnancy and altered risk of postnatal depressive symptoms has not been examined. We hypothesise that low levels of 25(OH)-vitamin D in maternal serum during pregnancy will be associated with a higher incidence of postpartum depressive symptoms. **Method**: We prospectively collected sera at 18 weeks' gestation from 796 pregnant women in Perth (1989-1992) who were enrolled in the Western Australian Pregnancy Cohort (Raine) Study, and measured levels of 25(OH)-vitamin D. Women reported postnatal depressive symptoms at three days post-delivery. **Results**: Women in the lowest quartile for 25(OH)-vitamin D status were more likely to report a higher level of postnatal depression symptoms than women who were in the highest quartile for vitamin D, even after accounting for a range of confounding variables including season of birth, body mass index and sociodemographic factors. **Conclusion**: Low vitamin D during pregnancy is a risk factor for the development of postpartum depression symptoms.

Keywords: Vitamin D; postpartum blues; perinatal mental health; environmental exposure; postnatal depression

INTRODUCTION

The prevalence of 25(OH)-vitamin D deficiency and insufficiency is increasing in Western societies and is particularly common in women of childbearing age and during and after pregnancy (Gale et al. 2008; Tare et al. 2006; Ginde et al. 2010). While vitamin D can be found naturally in foods (e.g. salmon, liver, eggs), the major source is sun exposure (McCann and Ames 2008). Vitamin D from the skin and diet is metabolized in the liver to form 25(OH)-vitamin D, levels of which can be measured in the blood (Holick 2007). Pregnancy may be a time of particular vulnerability for vitamin D insufficiency due to diet and lifestyle changes in this period. Women are often advised to limit fish intake and liver products (e.g. paté) during pregnancy due to mercury and listeriosis concerns (Cannell 2008) and may be more likely to avoid sun exposure during pregnancy and spend more time indoors (Tare et al. 2006; Ginde et al. 2010; Holmes et al. 2009).

There is an emerging literature associating low levels of 25(OH)-vitamin D with increased depressive symptoms in the general population (Ganji et al. 2010; Howland 2011), but few studies have examined female populations (Murphy and Wagner 2008). Two recent randomised controlled trials assessing the effect of vitamin D supplementation on depressive symptoms in women presented differing results (Shipowick et al. 2009; Sanders et al. 2011). One study reported no effect of vitamin D3 supplementation on depressive symptoms (Sanders et al. 2011) while the other found that supplementation with vitamin D3 significantly reduced depressive symptoms over the Winter months (Shipowick et al. 2009). Only one study of which we are aware has examined postnatal mood disturbance (Murphy et al. 2010). That study examined 25(OH)-vitamin D levels postnatally and the risk for postpartum mood disorders and found that low levels of vitamin D were linked to greater reporting of postnatal depressive symptoms up to 7 months postpartum. However, the investigation was limited by a small sample size (n=97) and there was no prospective measure of 25(OH)-vitamin D during pregnancy (Murphy et al. 2010).

Given that pregnancy may be a time of vulnerability to 25(OH)-vitamin D deficiency which in turn may lead to vulnerability for depressive symptoms, we examined the association between maternal serum 25(OH)-vitamin D at 18 weeks' gestation and the likelihood of developing postpartum depression symptoms in the first few days after birth in a cohort of Caucasian women enrolled in the Western Australian Pregnancy Cohort (Raine) Study. We hypothesised that low levels of 25(OH)-vitamin D in maternal serum during pregnancy would be associated with a higher incidence of postnatal depression symptoms.

METHOD

Participants

The Western Australian Pregnancy Cohort (Raine) Study enrolled 2,900 pregnant women with an average gestational age of 18 weeks between May 1989 and November 1991 at the state tertiary maternity hospital, King Edward Memorial Hospital (KEMH) in Western Australia. The full summary of enrolment methods has been published elsewhere (Newnham et al. 1993). All study participants provided data regarding psychosocial and demographic characteristics at enrolment, and a blood sample was taken from 929 randomly selected women, 796 of whom were Caucasian. Non-Caucasian women were excluded from the study due to potential confounding from differences in 25(OH)-vitamin D serum concentrations in dark-skinned and ethnic minority women (Whitehouse et al. 2012). A trained midwife recorded detailed obstetric data from the participants' medical records following delivery and women and their infants were followed up three days post-birth while still in hospital with a clinical examination and brief questionnaire. The protocols for the study were approved by the Human Research Ethics Committees at KEMH and/or Princess Margaret Hospital for Children in Perth, Western Australia.

Postpartum depression symptoms

Postpartum mood disturbance was measured three days after delivery by an index of six questions derived from the Edinburgh Postnatal Depression Scale (EPDS) assessing anxiety, sadness, mood fluctuations, teariness, appetite changes and sleep disturbances not related to caring for the baby (Cox et al. 1987). These six items were scored on a four-point Likert scale and summed to create a blues score where higher scores reflect poorer mood. As with the full EPDS scoring where from ten questions, a score of 10 or above can indicate possible mood disturbance, we created a cut-point from the six questions for a score of six or more to indicate possible mood disturbance (Cox et al. 1987).

Maternal 25(OH)-vitamin D

Venous blood was obtained at 18 weeks pregnancy in 796 randomly selected Caucasian women during the enrolment period, centrifuged, and serum collected and stored at -80^{o}C. As vitamin D concentrations in stored sera have been shown to remain stable for over three decades (Corder et al. 1993; Nomura et al. 1998), serum 25(OH)-vitamin D levels were measured in June 2011 using an enzyme immunoassay kit from Immunodiagnostic Systems Ltd (Scottsdale, Arizona, USA). Twenty-eight samples were also measured using isotope-dilution liquid chromatography-tandem mass spectrometry by RMIT Drug Discovery Technologies (Melbourne Australia) according to published methodology (Maunsell et al. 2005). The correlation of 25(OH)-vitamin D concentrations for samples assayed by both techniques was strong (r^2 = .87) and confirmed that there were no molecules (vitamin D metabolites or otherwise) in sera of 18-week pregnant women that interfered with the immunoassay of 25(OH)-vitamin D. The assay of 25(OH)-vitamin D by isotope-dilution liquid chromatography-tandem mass spectrometry gave concentrations of 25(OH)-vitamin D that were slightly higher than those measured by immunoassay (slope 0.95 $\pm$ 0.07). Given that overestimation of 25(OH)-vitamin D by the former assay has recently been reported (Carter 2011), we divided the 25(OH)-vitamin D levels in the serum into quartiles, which due to the strong correlative value was not influenced by the assay

used for the measure of serum 25(OH)-vitamin D concentration. In our final sample, the cut-points for quartiles of serum vitamin D levels were <47nmol/L (quartile 1), 47-58nmol/L (quartile 2), 59-70nmol/L (quartile 3) and >70nmol/L (quartile 4). The lowest quartile cut-point approximates the generally accepted cut-point for vitamin D deficiency of <50nmol/L (<20ng/ml) (Holick 2007).

Control Variables

We adjusted for a number of characteristics that have previously been associated with both our outcome and predictor variables; for example, maternal body mass index (BMI), cigarette smoking and alcohol use (Bertone-Johnson 2009). We also adjusted for other sample characteristics that could potentially confound our results including 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) (Blair et al. 2005). We also adjusted for season of birth to ensure that we were observing effects related to 25(OH)-vitamin D rather than other seasonal factors (Whitehouse et al. 2012).

Statistical Analyses

Given our predictor and outcome variables were measured across different seasons, we performed a calculation to remove the seasonal component of the 25(OH)-vitamin D data (van der Mei et al. 2007). These de-seasonalised data did not change our results, enabling us to proceed with our analyses adjusting for season of birth. Frequency data were compared for all predictor, outcome and control variables. We then used the total number of depressive symptoms reported as a continuous outcome in a general linear model to assess the impact on depressive symptoms of levels of vitamin D in quartiles 1-3 compared with quartile 4 (highest levels of vitamin D). The number of depressive symptoms was then summarized into a categorical variable reflecting endorsement of six or more depressive

symptoms compared with none, and then categorised again to reflect the experience of 1-5 depressive symptoms and six or more depressive symptoms compared with none. First we entered our predictor variables into a binary logistic regression model with the outcome of endorsing six or more depressive symptoms and reference category of no depressive symptoms reported. Second, we performed a multinomial logistic regression model comparing 1-5 depressive symptoms and six or more depressive symptoms with no depressive symptoms. SPSS 15.0 was used for the analyses (SPSS Inc. 2006).

RESULTS

Of the 2,454 Caucasian women in the analysis, 796 women provided sera at 18 weeks' gestation. Postnatal depression data were available for 706 women. The missing cases resulted from women who had left the hospital before the depression data could be collected on the third postpartum day. These 90 women did not differ significantly from the women who did complete the depression data in terms of vitamin D status, nor did they differ on any of the covariate data except for time in the special care nursery, with non-completers more likely to have a child in the special care nursery after delivery and hence not likely to be in their hospital room to complete the questionnaire.

A significant relationship was observed between increased experience of postnatal depressive symptoms and lower 25(OH)-vitamin D status (*p=0.017*), with those who scored in the range to indicate possible postnatal mood disturbance more likely to be in the lowest quartile for 25(OH)-vitamin D (Table 1). There was also a significant relationship between season of birth and 25(OH)-vitamin D measurements, where mothers who provided sera in the winter months (i.e. summer births) were more likely ($p<0.001$) to be in the lowest quartile for 25(OH)-vitamin D status. Those who smoked during the first four months of pregnancy were significantly more likely to be in the lowest quartile for 25(OH)-vitamin D levels, but there were no other significant associations between our control and predictor variables at (two-tailed) $p<0.05$. There was a non-significant association between

lower 25(OH)-vitamin D levels and having a total family income below the poverty line (<$24,000pa), being overweight or obese prior to pregnancy and drinking alcohol more frequently.

In our general linear model, in comparison with women in the highest quartile for 25(OH)-vitamin D levels, having a vitamin D level in the lowest quartile was associated with greater endorsement of postnatal depression symptoms (Table 2). This inverse association between 25(OH)-vitamin D and depression symptoms was significant at $p<0.05$ for women in the lowest quartile for vitamin D status ($b=0.93$, 95%CI= 0.27, 1.58), after adjustment for potential confounders.

Women who were in the lowest quartile for 25(OH)-vitamin D status at 18 weeks' gestation were significantly more likely to report six or more depressive symptoms in the first days after birth (OR=2.19, 95%CI= 1.26, 3.78) compared with women in the highest quartile for vitamin D in our fully adjusted binary logistic regression model (Table 3). We then performed a multinomial logistic regression model to examine the effect of vitamin D levels on a greater frequency of depressive symptoms (Table 3). Women who were in the lowest quartile for 25(OH)-vitamin D were more likely to endorse between one and five depressive symptoms than women who were in the highest quartile (OR=1.43, 95%CI= 0.85, 2.40), although this difference was not significant at $p<0.05$. Women in the lowest 25(OH)-vitamin D category were significantly more likely to have endorsed six or more depressive symptoms compared with women in the highest quartile (OR=2.72, 95%CI= 1.42, 5.22). We observed an inverse association between 25(OH)-vitamin D levels and risk for postpartum depression with each quartile lower than quartile 4, although for sera vitamin D levels in quartile 2 and 3 these effect sizes were non-significant at $p<0.05$.

DISCUSSION

In this study of 706 women, a lower level of 25(OH)-vitamin D in serum at 18 weeks' gestation was associated with a greater risk for experiencing postnatal depression symptoms three days after birth. This is the first study of which we are aware to prospectively measure 25(OH)-vitamin D during pregnancy and the later early development of postnatal depression symptoms and provides a novel link in the understanding of the precursors to postnatal depression, as well as greater knowledge regarding the potential role of 25(OH)-vitamin D in depression more generally. Further, women in the lowest quartile for 25(OH)-vitamin D, which approximates the standard cut-point for 25(OH)-vitamin D deficiency, were at around twice the risk of those in the highest quartile of reporting six or more depression symptoms following birth after adjustment for potential confounders including season of birth. We did not observe a gradient effect of each lower quartile of vitamin D status resulting in a higher risk for postpartum depressive symptoms; therefore, we suggest our results are showing a threshold effect of low vitamin D and risk for postpartum depression.

The current study provides a new link between 25(OH)-vitamin D during pregnancy and later postnatal depressive symptoms and is the first study of which we are aware to prospectively collect 25(OH)-vitamin D in sera during pregnancy and assess later maternal psychological health. The study of vitamin D in this population is especially important as pregnant women are more likely to be deficient or insufficient in vitamin D (Gale et al. 2008) and because a number of studies have found that 25(OH)-vitamin D insufficiency is linked to later developmental difficulties for the offspring such as language delay and severe mental illness (Whitehouse et al. 2012; McGrath et al. 2010). Our findings support those of a smaller-scale study that reported a link between low levels of 25(OH)-vitamin D measured postnatally and increased risk for postpartum depression (Murphy et al. 2010). However, we have extended these findings further by prospectively assessing levels during pregnancy rather than at the time the depression data were collected. Furthermore we are reporting this relationship using a much larger sample, thus providing greater statistical power.

The strength of this study was the prospectively collected 25(OH)-vitamin D data from pregnancy prior to the measurement of depressive symptoms at 3 days postpartum, and the analysis of these data in quartiles so as to investigate the potential for a threshold effect of vitamin D levels in the deficiency range (<50nmol/L). We have also used well-validated techniques for analysing the collected serum and had extensive data on potential confounding and mediating factors. One limitation is the maternal self-report for depressive symptoms as women who are experiencing mental distress may provide less reliable data (Najman et al. 2001). We did not have a clinician rating of postnatal depression but the use of an abbreviated EPDS did allow us to examine what may be more subtle or sub-clinical effects of our exposure on the outcome, and some studies of vitamin D and depression have found results at a sub-clinical rather than clinical level (Bertone-Johnson 2009). We acknowledge that the use of an abbreviated EPDS is less desirable than the full scale. We did not have antenatal mental health data available in our study and therefore we cannot imply causation from this observational study as it is unknown whether the depression symptoms predated the measurement of vitamin D. It is also possible that vitamin D insufficiency is a surrogate for other lifestyle factors that may be associated with depression such as sedentary behaviour, smoking and a preference for staying indoors and although we adjusted for smoking we did not have data available regarding sedentary and indoor lifestyle (Robinson et al. 2011). Although we collected data regarding iron, folate and other vitamin supplements, we are unable to ascertain whether other vitamin supplements contained vitamin D; however, sunlight is the main source of vitamin D for Australians rather than supplements (Nowson and Margerison 2002). We acknowledge that in measuring vitamin D at 18 weeks' gestation we are assuming that levels remain relatively stable until our outcome of postpartum depressive symptomatology was measured shortly after birth and levels may have changed during that period (Milman et al. 2011; Viljakainen et al. 2010). We adjusted for season of birth to take account of this possibility as we did not have vitamin D data from later in pregnancy.

In the emerging literature examining the role of 25(OH)-vitamin D in depression, vitamin D has been termed a 'neurosteroid' for its effect on brain function (Bertone-Johnson 2009). Active vitamin D enhances glutathione metabolism in neurons, thereby promoting antioxidant activities that protect those cells from oxidative degenerative processes (Ganji et al. 2010). Vitamin D deficiency has also been linked to altered brain morphology and may regulate gene expression of tyrosine hydroxylase, an enzyme involved in the synthesis of neurotransmitters such as norepinephrine and dopamine (Ganji et al. 2010). Although as an observational study we were unable to determine causation, we suggest that the changes in neurotransmitter function enabled by sufficient vitamin D may have a protective effect on postpartum depression symptoms.

There is an established link between maternal depressive symptoms shortly after birth and the later development of clinical depression in the greater postnatal period (Henshaw et al. 2004). In turn, maternal depressive symptoms postnatally are linked to a higher risk for later child psychopathology and we have previously reported that a higher incidence of maternal baby blues predicts internalizing problems in preschool children (Robinson et al. 2008). Although we do not suggest that 25(OH)-vitamin D status is the only predictor of the later development of postnatal blues and postnatal depression, ensuring vitamin D levels in pregnancy are sufficient is a simple, cost-effective and safe method of protecting against the later development of postnatal blues and potentially postnatal depression (Tare et al. 2006). There is a growing field of literature suggesting positive health benefits of adequate 25(OH)-vitamin D both within pregnancy and beyond. With the majority of women accessing antenatal care during pregnancy, encouraging optimal levels of vitamin D during this important time, particularly in vulnerable populations may have considerable public health benefits.

CONCLUSION

In summary we have found that lower levels of 25(OH)-vitamin D in the second trimester of pregnancy are linked to a greater risk for reporting postnatal depressive symptoms in the first days following birth. Further, low 25(OH)-vitamin D levels were associated with an increased risk of reporting a greater level of symptomatology that may indicate mood disturbance. We suggest that in addition to the potential for positive impacts on health and development of the offspring, ensuring adequate intake of vitamin D during pregnancy may be one method of protecting against postpartum mood disturbance in mothers.

The authors have no conflicts of interest to declare.

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Table 1: Frequency data for predictor and control variables (N=796) [a]

		Maternal Serum 25(OH)-vitamin D levels				
	n	**Quartile 1 <47nmol/L n=195 %**	**Quartile 2 47-58nmol/L n=185 %**	**Quartile 3 59-70nmol/L n=204 %**	**Quartile 4 > 70nmol/L n=212 %**	***p-value***
Postnatal depression symptoms						***0.017***
No symptoms	198	21.7	30.5	28.4	31.4	
1-5 symptoms	356	51.4	49.1	48.9	52.1	
6+ symptoms	152	26.9	20.4	22.7	16.5	
Maternal age						*0.424*
<20 years	72	7.2	7.0	10.3	11.3	
20-29.9 years	408	59.0	55.1	45.8	46.2	
30+ years	315	33.8	37.8	43.8	42.5	
Maternal education						*0.576*
<High school completion	518	65.1	67.6	65.0	63.2	
High school completion	277	34.9	32.4	35.0	36.8	
Maternal BMI						*0.182*
Underweight	92	13.3	12.4	8.4	12.3	
Healthy weight	583	70.8	68.1	75.4	78.3	
Overweight	77	9.2	11.4	13.8	4.7	
Obese	43	6.7	8.1	2.5	4.7	
Gender						*0.461*
Female	470	60.1	61.6	57.8	57.5	
Male	324	39.9	38.4	42.2	42.5	
Low family income						*0.222*
≤ $24,000 per annum	324	46.5	43.5	42.7	40.3	
>$24,000 per annum	426	53.5	56.5	57.3	59.7	
Smoking in pregnancy						***0.013***
None	547	61.5	70.8	67.6	74.5	
1+ daily	249	38.5	29.2	32.4	25.5	
Alcohol intake in pregnancy						*0.304*
None	409	53.3	57.3	48.0	47.6	
Once/week	200	22.6	23.8	27.5	26.4	
2-6 times/week	152	17.4	15.1	21.6	21.7	
Daily +	35	6.7	3.8	2.9	4.2	
Hypertensive diseases						*0.980*
None	615	75.4	77.8	79.4	76.4	
Gestational Hypertension	155	21.5	19.5	18.1	18.9	
Preeclampsia	26	3.1	2.7	2.5	4.7	
SCN admission						*0.874*
No	707	90.8	85.4	90.2	88.7	
Yes	89	9.2	14.6	9.8	11.3	
Season of birth						***<0.001***
Summer	275	56.9	41.6	25.0	17.0	
Autumn/Fall	206	22.1	20.0	34.3	26.4	
Winter	164	4.1	20.0	23.5	33.5	
Spring	151	16.9	18.4	17.2	23.1	
		Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Percentage of Optimal Birthweight						*0.741*
%	790	95.59 (13.12)	96.52 (13.70)	96.58 (13.72)	97.00 (11.55)	

[a]Caucasian women only, missing data not shown, row percentages for each variable presented, bolded values significant at two-tailed p<0.05; Perth, Western Australia 1989-1992

Table 2: Adjusted general linear model analysis showing effect of maternal serum 25(OH)-vitamin D levels on risk for postnatal depression symptoms

	Quartile 1 Regression coefficient b (95% CI) ***p***	**Quartile 2 Regression coefficient b (95% CI)** ***p***	**Quartile 3 Regression coefficient b (95% CI)** ***p***	**Quartile 4 Regression coefficient b (95% CI)** ***p***
Postnatal depression symptoms (increasing symptoms)	**0.93*** (0.27, 1.58) *0.005*	0.12 (-0.53, 0.77) *0.721*	0.38 (-0.26, 1.03) *0.245*	0.00 (ref)

*** significant at p<0.05**

Adjusted for pre-pregnancy body-mass-index, maternal age, maternal education, total family income, maternal smoking, maternal alcohol intake, hypertensive diseases of pregnancy, proportion of optimal birth weight, child gender, SCN admission and season of birth; Perth, Western Australia 1989-1992

Table 3: Adjusted binary and multinomial logistic regression analyses showing effect of maternal serum 25(OH)-vitamin D levels on risk for postnatal depression symptoms

	Quartile 1 OR (95% CI)[†] *p*	Quartile 2 OR (95% CI)[†] *p*	Quartile 3 OR (95% CI)[†] *p*	Quartile 4 OR (95% CI)[†] *p*
Binary logistic regression model				
Postnatal depression symptoms				
6+ symptoms	**2.19***	1.42	1.52	1.00
	(1.26, 3.78)	(0.80, 2.54)	(0.85, 2.72)	(ref)
	0.006	*0.236*	*0.158*	
Multinomial logistic regression model				
Postnatal depression symptoms				
1-5 symptoms	1.43	0.94	1.10	1.00
	(0.85, 2.40)	(0.57, 1.55)	(0.67, 1.82)	(ref)
	0.182	*0.811*	*0.696*	
6+ symptoms	**2.72***	1.37	1.61	1.00
	(1.42, 5.22)	(0.71, 2.63)	(0.83, 3.10)	(ref)
	0.003	*0.346*	*0.158*	

*** significant at p<0.05** [†]odds ratio and 95% confidence intervals

Adjusted for pre-pregnancy body-mass-index, maternal age, maternal education, total family income, maternal smoking, maternal alcohol intake, hypertensive diseases of pregnancy, proportion of optimal birth weight, child gender, SCN admission and season of birth; Perth, Western Australia 1989-1992