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Is first trimester vitamin D status in nulliparous women associated with pregnancy related hypertensive disorders?

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ABSTRACT

Objectives: this study aimed to explore if maternal vitamin D status in early pregnancy was associated with pre-eclampsia and pregnancy-induced hypertension. Relationships between vitamin D status and blood pressure at the start of pregnancy as well as the occurrence of a mid-pregnancy drop in blood pressure were also explored. This secondary analysis was completed to investigate a possible mechanism for the association between vitamin D status and pregnancy related hypertensive disorders.

Design and setting: data were obtained from the Amsterdam Born Children and their Development study, a prospective community-based cohort study based in Amsterdam, The Netherlands.

Participants: a total of 2074 nulliparous women without pre-existing hypertension and with a known vitamin D status before 17 weeks gestation were included in the study. Vitamin D status was categorized into four groups: "normal" (≥ 50 nmol/L), "insufficient" (30–49.9 nmol/L) "deficient" (20–29.9 nmol/L) or "severely deficient" (< 20 nmol/L).

Measurements: logistic regression analysis was used to investigate if vitamin D status was related to the odds of experiencing pre-eclampsia or pregnancy-induced hypertension. Models were corrected for maternal age, ethnicity, pre-pregnancy BMI, smoking and socioeconomic status. χ^2 and ANOVA tests were used to investigate relationships between vitamin D status and the blood pressure parameters.

Findings: when compared to women with a normal vitamin D status, women who were severely deficient had an increased risk for pre-eclampsia (OR 2.08; 95% CI, 1.05–4.13), but the association was rendered non-significant after correction (OR 1.88; 95% CI 0.79–4.48). There were no associations between vitamin D status and pregnancy-induced hypertension, starting blood pressure or the occurrence of a mid-pregnancy drop in blood pressure.

Key conclusions: no strong evidence was found for an association between first trimester vitamin D status and pregnancy related hypertensive disorders in nulliparous women.

Implications for practice: at this time, vitamin D supplementation is not warranted for the specific purpose of preventing pregnancy related hypertensive disorders.

Introduction

Hypertensive disorders during pregnancy are strongly related to both maternal and neonatal morbidity and mortality (Sibai et al., 2005; Netherlands Society of Obstetrics and Gynecology (NVOG), 2012). In the Netherlands the most common cause of immediate maternal death are pregnancy related hypertensive disorders (PRHD) (NVOG, 2012), which include pregnancy-induced hypertension (PIH), pre-eclampsia (PE), eclampsia and Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome. A

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number of variables have been identified as risk factors for PRHD including parity, age, obesity, pre-existent hypertension and several other co-morbid diseases (NVOG, 2005). An additional factor that may be related to hypertensive disorders during pregnancy is vitamin D status. Results from several international studies suggest that a low vitamin D status is a risk factor for developing hypertension in non-pregnant individuals (Pilz et al., 2009; Pilz and Tomaschitz, 2010; Min, 2013). The active form of vitamin D (1,25-dihydroxyvitamin D) appears to inhibit renin secretion from the kidneys (Li et al., 2002). This action suppresses the renin angiotensin aldosterone system (RAAS) to maintain a normotensive blood pressure. In non-pregnant individuals, deficiencies in vitamin D promote renin secretion, which may increase the risk of hypertension (Pilz and Tomaschitz, 2010). It is possible that vitamin D has a similar effect on the RAAS system in pregnant women, thus it is plausible that during pregnancy there is an increased risk of developing PRHD in individuals with a lower vitamin D status.

Several studies have explored the relationship between vitamin D and PE with conflicting results (Bodnar et al., 2007; Haugen et al., 2009; Baker et al., 2010; Shand et al., 2010; Hossain et al., 2011; Ullah et al., 2013; Wei et al., 2013; Burris et al., 2014). Some studies have observed strong relationships between low vitamin D status and increased risks for PE, but many of these studies had small sample sizes, followed case-control rather than prospective cohort designs or measured dietary vitamin D intake rather than serum vitamin D levels. Four separate systematic reviews have found that a relationship may exist between vitamin D status and PE, but strong conclusions were not possible because many of the reviewed studies had small sample sizes, inconsistent adjustment for confounding and large differences in racial composition (Christesen et al., 2012; Aghajafari et al., 2013; Wei et al., 2013; Harvey et al., 2014). All four systematic reviews concluded that more research is needed due to the variability in the evidence and the lack of high quality data. Also of note, limited attention has been given to the relationship between vitamin D and PIH. One small study observed no association (Shand et al., 2010), while a large American cohort study unexpectedly observed that for every 25 nmol/L increase in vitamin D there was a 33% higher risk of PIH (Burris et al., 2014). Due to these inconclusive findings, the association between vitamin D status and PRHD warrants further investigation.

Additionally, no studies have investigated the relationship between vitamin D status and established risk factors for PRHD. However, such an investigation is warranted because it could provide insight into the mechanisms involved in the potential association between vitamin D and PRHD. For example, higher systolic and diastolic blood pressure (SBP and DBP) at the start of pregnancy increase the risk of both PE and PIH (Magnussen et al., 2007; Cnossen et al., 2008; Macdonald-Wallis et al., 2012). Additionally, blood pressure typically drops in mid-pregnancy (Salles et al., 2014) and the absence of this drop may be a risk factor for developing PRHD (Moutquin et al., 1985; Silva et al., 2008; de Boer et al., 2011; Macdonald-Wallis et al., 2012). Because vitamin D status may be inversely associated with blood pressure, low vitamin D status may result in a higher blood pressure at the start of pregnancy as well as reduce the occurrence of a mid-pregnancy drop in blood pressure. This, in turn, could increase the risk of PRHD. Therefore, the current study investigated the relationship between first trimester vitamin D status and PRHD, as well as the relationship between vitamin D status and starting blood pressure and the occurrence of a mid-pregnancy drop in blood pressure. The aim was to determine if a relationship exists between vitamin D and PRHD and to understand the underlying mechanisms involved.

Methods

Study design and sample

Data were obtained from the Amsterdam Born Children and their Development (ABCD) study, a prospective, multi-ethnic, population-based cohort study in Amsterdam, the Netherlands (van Eijsden et al., 2011). Between January 2003 and March 2004 all pregnant women attending antenatal care in Amsterdam were invited to participate during their first antenatal check-up at approximately 12 weeks gestation. Women were asked to complete a questionnaire and during regular blood screening they were asked to provide additional blood samples. From these samples vitamin D status was determined at a median gestational age of 12 weeks (interquartile range 11.7–13.9 weeks). Data on PRHD outcomes were only available in nulliparous women, therefore all nulliparous women with a singleton pregnancy and whose vitamin D status was determined before 17 weeks of gestation were included in the study sample (Vollebregt et al., 2008). Women with pre-existing hypertension or who were missing data on pregnancy outcomes were excluded (Fig. 1). The ABCD study (project number MEC02/039#02.17.392) was approved by the Central Committee on Research Involving Human Subjects, the Medical Ethical Examining Committees of all Amsterdam hospitals and the Municipal Privacy Protection Committee of Amsterdam. All participants provided written informed consent.

Serum vitamin D

Blood samples were processed in the Regional Laboratory of Amsterdam. Samples were prepared through centrifugation (1600g for 10 minutes at room temperature) and stored as 1-mL aliquots at −80 °C until analysis. Analyses were performed at the National Institute for Public Health and the Environment in the Netherlands. Serum 25-hydroxyvitamin D (25OHD) was measured using an enzyme immunoassay method (OCTEIA AC-57F1; IDS Ltd, Boldon, UK). The reliability of the measurements was tested using the Haemolysis-icterus-lipidaemia (HIL) Index; no measurements were found to be unreliable. Vitamin D status was categorized based on the Dutch Health Council Guidelines (Health Council of the Netherlands, 2012) as normal ($\geq$ 50 nmol/L), insufficient (vitamin D 30–49.9 nmol/L), deficient (20–29.9 nmol/L) or severely deficient ($<$ 20 nmol/L).

Pregnancy related hypertensive disorders

The primary outcomes for this study were PE and PIH, which were defined on the basis of the guidelines from the Netherlands Society of Obstetrics and Gynaecology (NVOG, 2005), the Royal Dutch Organization of Midwives (de Boer et al., 2011) and the International Society for the Study of Hypertension in Pregnancy (Brown et al., 2001). PIH was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg measured by a trained maternal health-care provider after 20 weeks of gestation in a woman with a previously normal blood pressure. PE was defined as PIH in combination with proteinuria, which was indicated by $\geq$ 300 mg protein in a 24-hour urine sample, a protein-creatinine ratio of $\geq$ 30 mg/mmol or urine dipstick $\geq$ ++ after 20 weeks of gestation. Starting SBP and DBP were the blood pressure measurements obtained before 15 weeks of pregnancy. Occurrence of a mid-pregnancy drop was defined as a blood pressure measured between 18 and 22 weeks gestation that was lower than the starting blood pressure. Mid-pregnancy drops were defined separately for SBP and DBP because of differing results regarding whether a drop in SBP is more predictive of PRHD than a drop in DBP (Moutquin et al., 1985; Silva et al., 2008; Macdonald-Wallis et al., 2012). Data were available for starting SBP and DBP in 1695 women, and for the mid-pregnancy drops in 1372 women.

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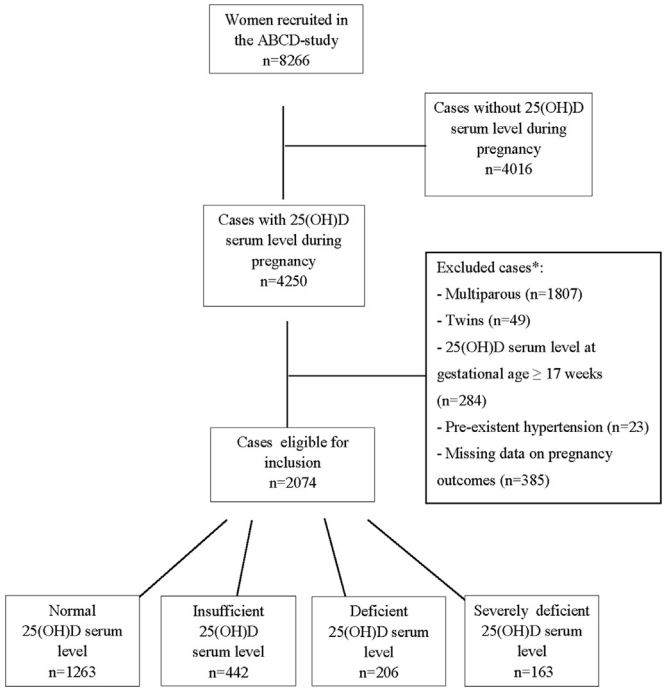

Fig. 1. Flowchart for study sample collection. *Sum of excluded data is greater than total excluded cases due to overlap in excluded variables. 25OHD=25-hydroxyvitamin D; ABCD=Amsterdam Born Children and their Development Study.

Covariates

Covariates were chosen after an extensive literature review to determine the variables most likely associated with vitamin D status and/or PRHD. They included maternal age (years), ethnicity (Dutch, Turkish, Moroccan, African-descent, other non-Western and other Western) pre-pregnancy BMI (kg/m^2) (pBMI), smoking status (yes/no) and maternal education level (years after primary school), with more years of education serving as an indicator of higher socio-economic status (Duckitt and Harrington, 2005; Magnussen et al., 2007; Vollebregt et al., 2008; Macdonald-Wallis et al., 2012; Vimaleswaran et al., 2013). Ethnicity was defined according to the birth country of the pregnant woman's mother. PBMI was calculated from pre-pregnancy weight and height. All covariates were self-reported in the pregnancy questionnaire. No adjustments were made in the primary analysis for maternal vitamin D supplement use or season of sampling because they are determinants of vitamin D and therefore adjustment for these covariates could contribute to overcorrection (Health Council of the Netherlands, 2012).

Statistical analysis

All variables of interest were analysed by the four vitamin D groupings to assess differences in demographics as a function of vitamin D status. The incidences of PIH and PE were also investigated across these four groupings using the χ^2 test to allow for a crude assessment of the associations. Multivariable logistic regression analyses were performed to estimate the odds of developing PIH or PE according to vitamin D status. This statistical method allows comparison of each vitamin D status category against a reference group, which, in this case, was the group with a normal vitamin D status. The odds of developing PIH or PE were then determined in comparison to this reference group. Models were analysed initially with no corrections to investigate the crude, unadjusted relationships. Then all covariates were included to create the fully adjusted models in order to correct for any confounding. The analysis of the relationship between PIH and vitamin D status excluded all PE cases and the analysis with PE as an outcome excluded all PIH cases.

Starting SBP and DBP and the occurrence of mid-pregnancy drop were then analysed for associations with maternal vitamin D status. The relationship between vitamin D status and the occurrence of mid-pregnancy drop in blood pressure was analysed with the χ^2 test, while the relationships between starting blood pressures and vitamin D status were tested with one-way ANOVA.

A sensitivity analysis was completed with adjustment for season and supplement use to investigate if the inclusion of these variables would alter the findings. p-values < 0.05 were considered significant. All statistical analyses were conducted using SPSS version 22.0 for Mac (SPSS Inc, Chicago, IL).

Results

The study population consisted mainly of women with Dutch ethnicity (65.2%). Mean pBMI was 22.4 kg/m^2, (standard deviation (SD) 3.3), mean education level was 9.8 years (SD 3.4) and mean vitamin D status was 60.0 nmol/L (SD 29.8) (Table 1). 60.9% of the women had a normal vitamin D status, 21.3% had an insufficient status, 9.9% had a deficient status and 7.8% had a severely deficient status. The women with a severely deficient status were generally of non-Dutch ethnicity, had higher pBMIs, smoked more often and had lower maternal education levels (Table 1). Among the total group, 132 (6.4%) women developed PIH and 82 (4.0%) developed PE (Table 2). The mean starting SBP and DBP were 113.1 mmHg (SD 11.7) and 66.9 mmHg (SD 8.4) respectively. 41.8% of women experienced a mid-pregnancy drop in SBP and 47.7% of women experienced a mid-pregnancy drop in DBP (Table 2).

Although there was a trend towards decreasing incidence of PIH with increasing severity of vitamin D deficiency (Table 2), there were no significant associations between any of the vitamin D groups and PIH in the unadjusted or adjusted models (Table 3). In the unadjusted model for PE, there were significantly increased odds for PE in severely deficient women compared to normal status women (OR 2.08; 95% CI 1.05–4.13) (Table 3). These results were rendered non-significant after adjustment (OR 1.88; 95% CI 0.79–4.48). When the inclusion of covariates was investigated separately, pBMI was observed to be the strongest confounder, followed by ethnicity and then years of education. No significant relationships between vitamin D status and either of the starting blood pressure parameters were observed (Table 2). There were also no differences between any of the vitamin D groups in the occurrence of a mid-pregnancy drop in either SBP or DBP (Table 2). Finally, in the sensitivity analysis that included adjustment for season and supplement use, there were minimal changes in the results and all investigated associations remained non-significant in this separate analysis.

Discussion

This study aimed to clarify whether a relationship exists between vitamin D status during early pregnancy and PRHD outcomes. To investigate a possible mechanism for this relationship, associations between vitamin D status and blood pressure parameters were also studied. No relationships between vitamin D status and any of the outcomes of interest were observed after correction for potential confounding variables. Thus, vitamin D status in early pregnancy does not appear to be related to PRHD or blood pressure risk factors for PRHD.

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Table 1
Maternal demographic characteristics within groupings of maternal 25-hydroxyvitamin D status during the first trimester of pregnancy for women in the Netherlands in 2003/2004.

	Total	Maternal 25-hydroxyvitamin D status			
		Normal	Insufficient	Deficient	Severely Deficient
	n=2074	n=1263 (60.9%)	n=442 (21.3%)	n=206 (9.9%)	n=163 (7.9%)
25-hydroxyvitamin D (nmol/L) Mean (SD)	60.0 (29.8)	78.4 (22.5)	41.0 (5.6)	24.7 (2.9)	14.3 (3.7)
Maternal age (years) Mean (SD)	30.2 (4.6)	31.1 (3.8)	29.8 (4.8)	28.2 (5.3)	26.3 (5.4)
Ethnicity No. (%)					
Dutch	1351 (65.2)	992 (73.4)	262 (19.4)	77 (5.7)	20 (1.5)
Turkish	58 (2.8)	4 (6.9)	6 (10.3)	16 (27.6)	32 (55.2)
Moroccan	86 (4.2)	11 (12.8)	22 (25.6)	21 (24.4)	32 (37.2)
African	96 (4.6)	24 (25.0)	23 (24.0)	27 (28.1)	22 (22.9)
Other Non-Western	145 (7.0)	25 (17.2)	47 (32.4)	32 (22.1)	41 (28.3)
Other Western	335 (16.2)	207 (61.8)	82 (24.5)	31 (9.3)	15 (4.5)
BMI (kg/m^2) Mean (SD)	22.4 (3.3)	22.1 (2.9)	22.8 (3.6)	22.9 (4.0)	23.2 (4.3)
Smoking No. (%)					
Non-smoker	1891 (91.2)	1173 (62.0)	403 (21.3)	175 (9.3)	140 (7.4)
Smoker	183 (8.8)	90 (49.2)	39 (21.3)	31 (16.9)	23 (12.6)
Maternal education level (years)* Mean (SD)	9.8 (3.4)	10.4 (2.9)	9.6 (3.5)	8.7 (3.7)	6.9 (4.3)
Season at start of pregnancy No. (%)					
Spring	515 (25.0)	252 (48.9)	136 (26.4)	65 (12.6)	62 (12.0)
Summer	429 (20.8)	315 (73.4)	68 (15.9)	25 (5.8)	21 (4.9)
Autumn	487 (23.6)	363 (74.5)	71 (14.6)	30 (6.2)	23 (4.7)
Winter	633 (30.7)	328 (51.8)	166 (26.2)	84 (13.3)	55 (8.7)
Vitamin D supplementation during pregnancy No. (%)					
No supplementation	1441 (69.8)	800 (55.5)	327 (22.7)	175 (12.1)	139 (9.6)
With supplementation	624 (30.2)	458 (73.4)	113 (18.1)	30 (4.8)	23 (3.7)

SD=Standard Deviation.

* years of education after primary school.

Table 2
Association between maternal 25-hydroxyvitamin D status during early pregnancy in nulliparous women in the Netherlands in 2003/2004 and the incidence of pregnancy related hypertensive disorders and associated blood pressure risk factors.

	Total	Maternal 25-hydroxyvitamin D status				*p*-Value
		Normal	Insuffi-cient	Deficient	Severely deficient	
PRHD diagnosis	*n*=2074	*n*=1263	*n*=442	*n*=206	*n*=163	
None (%)	89.7	89.8	89.4	90.3	89.0	0.24
PIH (%)	6.4	6.8	6.3	5.3	4.3	
PE (%)	4.0	3.4	4.3	4.4	6.7	
Starting blood pressure (mmHg) Mean (SD)	*n*=1695	*n*=1048	*n*=370	*n*=160	*n*=117	
SBP (mmHg)	113.1 (11.7)	112.9 (11.5)	113.8 (11.3)	112.4 (12.8)	113.4 (13.3)	0.46
DBP (mmHg)	66.9 (8.4)	66.8 (8.3)	67.7 (8.2)	66.3 (9.0)	66.7 (8.7)	0.26
Mid pregnancy drop	*n*=1372	*n*=832	*n*=305	*n*=131	*n*=104	
SBP drop (% present)	41.8	42.2	41.6	39.7	42.3	0.96
DBP drop (% present)	47.7	47.8	49.3	45.5	45.2	0.84

DBP=diastolic blood pressure; PE=pre-eclampsia; PIH=pregnancy-induced hypertension; PRHD=pregnancy related hypertensive disorders; SBP=systolic blood pressure, Analysis of continuous outcomes was completed using one-way ANOVA and analysis of categorical outcomes was completed using χ^2 testing.

Previous research

The results of this study contradict many of the findings from previous studies on PE. However, this study addressed many of the concerns from previous systematic reviews. Several studies have observed strong associations between vitamin D levels below 50–75 nmol/L and increased odds for PE, but many of these studies utilised case-control designs, had small sample sizes and inconsistently corrected for important confounders (Aghajafari et al., 2013; Harvey et al., 2014). In the systematic review by Aghajafari et al. (2013), they conducted stratified analyses: one with just the studies that controlled for confounding and one with just the studies that did not utilise case-control designs. No significant relationships between vitamin D status and PE were found in these analyses, suggesting previous positive findings may be a result of study design and quality. Although several small studies have observed very strong, inverse relationships between vitamin D status and PE, the standard errors in these studies were much greater than the current study, resulting in less reliable results (Bodnar et al., 2007; Baker et al., 2010; Hossain et al., 2011). Only one other cohort study investigated a large sample of 1591 women and, similar to the current study, observed no relationship between vitamin D status and PE (Burris et al., 2014). Finally, one small randomized controlled trial observed no reduction in the incidence of PE in women supplemented with vitamin D and

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Table 3
Multivariate logistic regression analysis of the association between maternal 25-hydroxyvitamin D status during early pregnancy in nulliparous women in the Netherlands in 2003/2004 and the incidence of pregnancy related hypertensive disorders.

	Unadjusted OR	95% CI	Adjusted* OR	95% CI
PIH				
Maternal 25-hydroxy-vitamin D status				
Normal $n=1216$	1		1	
Insufficient $n=420$	0.94	0.60–1.46	0.99	0.62–1.55
Deficient $n=194$	0.79	0.41–1.51	1.00	0.50–2.01
Severely deficient $n=146$	0.66	0.30–1.46	1.07	0.42–2.71
PE				
Maternal 25-hydroxy-vitamin D status				
Normal $n=1173$	1		1	
Insufficient $n=411$	1.27	0.73–2.21	1.19	0.67–2.10
Deficient $n=192$	1.29	0.62–2.70	1.19	0.53–2.66
Severely deficient $n=150$	**2.08**	1.05–4.13	1.88	0.79–4.48

OR= odds ratio; CI=confidence interval. PE=pre-eclampsia; PIH=pregnancy-induced hypertension.

* Adjusted for age, ethnicity, pre-pregnancy BMI, smoking and years of education after primary school.

calcium (Marya et al., 1987). Therefore, the positive results observed in the previous studies may have been spurious findings.

Few studies have investigated the relationship between vitamin D status and the development of PIH, even though PIH may progress to fulminant PE (Barton et al., 2001). Burris et al. (2014) unexpectedly observed a positive relationship between serum vitamin D and the odds for PIH. Prior to correction in the current study, a trend was observed for lower odds of PIH in severely deficient women, although this finding was eliminated after adjustment. It is difficult to know whether the association observed by Burris et al. was a chance finding (Burris et al., 2014), but their results emphasise the importance of further investigation into the associations between vitamin D status and PIH, particularly if vitamin D supplementation has potential harmful effects.

An additional explanation for the null results of this study may be the role of pBMI in the relationship. In the relationship between severely deficient vitamin D status and PE, pBMI was responsible for the largest attenuation in the strength of the relationship, which may be explained in two possible manners. Firstly, vitamin D may lie along the causal pathway between pBMI and risk of PE. Previous research suggests that increasing BMI is causally related to lower vitamin D levels (Vimaleswaran et al., 2013) and higher pBMIs are related to increased risks of PE (Duckitt and Harrington, 2005). Alternatively, there may be interaction between vitamin D status and pBMI, meaning that the relationship between vitamin D status and PE differs depending on pBMI. Therefore, an inverse relationship between vitamin D and PE could exist in overweight or obese women, even if no relationship exists in normal weight women. The pathophysiology of PE is not fully understood, but abnormalities within the placenta, including abnormal inflammatory responses, are observed in PE cases (Sibai et al., 2005). Both vitamin D and elevated pBMI have been related to placental inflammation and dysfunction (Heerwagen et al., 2010; Shin et al., 2010; Liu et al., 2011; Kim et al., 2014). Perhaps if interaction exists between vitamin D and pBMI, the combination of low vitamin D status and elevated pBMI may be sufficient to cause PE. The possibility of mediation or interaction via pBMI has not been investigated in previous research, perhaps because most studies have simply considered pBMI as a confounder. Therefore, this alternative role for pBMI in the relationship between vitamin D status and PRHD warrants further investigation in studies with larger sample sizes.

The lack of an association between vitamin D status and the blood pressure parameters suggests that if a relationship does exist between vitamin D and PRHD, the mechanism does not involve these blood pressure parameters. While it is possible that vitamin D is inversely related to blood pressure in the general population (Pilz et al., 2009; Pilz and Tomaschitz, 2010; Min, 2013), vitamin D does not appear to mediate a relationship between blood pressure and the risk of PRHD.

Strengths and limitations

One strength of this study was the large sample size. Few studies to date have investigated such a large sample of women and therefore this study had much more power to detect a true relationship. The current study was also based on a prospective observational cohort and the analysis benefited from investigation into the mechanisms behind the possible relationship. These characteristics would have strengthened the argument for causality had a relationship between vitamin D status and PRHD been found.

The current study may be limited by selection bias. Participation rates by non-Western women and women with lower education levels were lower in the ABCD cohort (van Eijsden et al., 2011). Therefore, a potential relationship between vitamin D status and PRHD may have been missed due to the limited participation by women with greater risks for PRHD, especially because these women also often have severe vitamin D deficiencies. Perhaps future studies could investigate the relationship in a large cohort of high-risk women. Finally, the current study utilised ELISA assay techniques for 25OHD measurement, which is no longer the ideal method due to issues with reliability of values at the extremes of the 25OHD range. As a result, the results may be difficult to compare with studies utilising modern analysis techniques, such as high performance liquid chromatography.

Implications

At this time, it is not recommended to use vitamin D supplementation as a preventive measure for PRHD. The only randomized controlled trial to date did not show a reduction in PE incidence with vitamin D supplementation (Marya et al., 1987) and too many inconsistent results remain in the current literature to warrant a change to antenatal care. Additionally, the possible direct relationship between vitamin D and risk of PIH emphasises the importance of additional research prior to recommending supplementation. Future studies should focus on the role that pBMI plays to provide a better understanding of whether or not a relationship exists between vitamin D and PRHD.

Conclusion

No strong evidence was found for an association between vitamin D status in the first trimester of pregnancy and PRHD in nulliparous women. Previous positive results may have arisen from methodological problems in the study designs. Future research should investigate whether there is a relationship between vitamin D status and PIH, as well as what role pBMI plays in the relationship between vitamin D status and PRHD.

Conflicts of interest

None to declare.

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Author contributions

BW, DB and EJH contributed to the study design, analysed the data and led the writing of the article. TV contributed to the study design and assisted in the data analysis. AO contributed to the data collection and assisted in the data analysis. EM contributed to the study design. All of the authors contributed to interpretation of the results and the writing of the article, and all authors approved the final version.

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