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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

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Elevated Liver enzymes and Low Platelets (HELLP) syndrome. A 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 (1600*g* 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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