Association between Preeclampsia and vitamin D Deficiency

Thesis

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Evian Hadi Mahdi

List of Contents

List of Abbreviations

Abbr.	Full-term
ALT	**:** Alanine aminotransferase
Ang-II	**:** Angiotensin-II
AST	**:** Aspartate aminotransferase
CBC	**:** Complete blood count
DBP	**:** Vitamin D binding protein
ELISA	**:** Enzyme-linked immunosorbent assay
ET-1	**:** Endothelin-1
hCG	**:** Human chorionic gonadotropin
HO-1	**:** Heme oxygenase-1
IL	**:** Interleukin
PAI	**:** Plasminogen activator-inhibitor
PCOS	**:** Polycystic ovary syndrome
PE	**:** Preeclampsia
PTH	**:** Parathormone
RIA	**:** Radioimmuno assay
sEng	**:** Soluble endoglin
sFlt1	**:** Soluble fms-like tyrosine kinase 1
STOX1	**:** Storkhead box 1
TNF	**:** Tumor necrosis factor
UVB	**:** Ultraviolet B radiation
VDD	**:** Vitamin D deficiency
VDR	**:** Vitamin D receptors
VEGF	**:** Vascular endothelial growth factor
SPSS	**:** Statistical package for Social Science
NVD	**:** Normal vaginal delivery
LSCS	**:** Lower segment cesarean section

List of Tables

List of Figures

Introduction

Preeclampsia is pregnancy-specific syndrome, characterized by high blood pressure induced and proteinuria after 20 weeks of gestation. Although preeclampsia is something more than simple gestational hypertension with proteinuria, development of proteinuria is still one significant and objective diagnostic measure of this disorder. Proteinuria is defined as excretion of more than 300 mg of protein in 24-hour urine collection ***(Williams, 2014).***

In absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100.000/microliter), impaired liver function (elevated concentration of liver transaminases to twice the normal concentrations), renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or doubling of serum creatinine in the absence of other renal disease), pulmonary edema or new onset of cerebral or visual symptoms ***(Roberts et al., 2013).***

Disorders of calcium metabolism, including hypocalciuria and low vitamin D level, have been consistently described, during in the course of pregnancy of women who later developed preeclampsia ***(Forman et al., 2007; Steegers et al., 2010).***

Factors contributing to preeclampsia are diabetes, chronic hypertension before pregnancy, chronic kidney diseases, nulliparity, twin or multiple pregnancy, family history of preeclampsia or eclampsia, obesity, immune disorders and a personal history of preeclampsia, or eclampsia. The occurrence of preeclampsia in one pregnancy does not necessarily predict the occurrence of preeclampsia in subsequent pregnancies. However, its initial development is associated with a higher probability of its occurring in subsequent pregnancies ***(English et al., 2015).***

Vitamin D is especially important during pregnancy as low maternal vitamin D stores may contribute to problems such as low birth weight and small for gestational age infants, as well an increased risk of maternal comorbidities ***(Hollis et al., 2011).***

Vitamin D deficiency is worldwide epidemic, with a prevalence that ranges from 18% to 84% depending on the country of residence, ethnicity, and local clothing customs and dietary intake ***(Ponsonby et al., 2010; Sharma et al., 2016).***

Clinical studies establishing an association between vitamin D levels and adverse pregnancy outcomes such as preeclampsia, gestational diabetes, and low birth weight, preterm labor, and caesarean delivery have conflicting results ***(Morley et al., 2006).***

Vitamin D is a prohormone that is derived from cholesterol. The nutritional forms of vitamin D include D3 (cholecalciferol), which is generated in the skin of humans and animals, and vitamin D2 (ergocalciferol), which is derived from plants; both forms can be absorbed in the gut and used by humans ***(Mulligan et al., 2010).***

The reasons for the increased vitamin D deficiency are unclear. A combination of a change in lifestyle and global environmental pollution might have contributed to the widespread increase in vitamin D deficiency ***(Hossain, 2011).***

Human trophoblasts both produce and respond to the active form of Vitamin D 1,25(OH)2D which mediates its actions through specific Vitamin D receptors (VDR), which are expressed in both decidua and trophoblasts ***(Liu et al., 2011).***

Furthermore, 1,25-dihydroxyvitamin D stimulates the activity of T-regulatory cells, which are vital in supporting placental implantation through immune tolerance ***(Hypponen, 2005)***. In preeclampsia, the metabolism of vitamin D in placental tissue is altered, and these differences may play a role in the abnormal trophoblastic invasion found in these pregnancies ***(Fischer et al., 2007).***

Given the demonstrated anti-inflammatory function of Vitamin D in multiple organ systems including trophoblast

cells and placenta, some authors hypothesized that Vitamin D deficiency contributes to the development of preeclampsia through increased inflammation ***(Liu et al., 2011)***.

Finding relation between vitamin D deficiency and preeclampsia may lead us to a non-expensive preventive measure. So, this study was conducted to study this relationship which would have widespread maternal health implications ***(Singla et al., 2015).***

Aim of the Study

The aim of this study is to investigate the serum vitamin D levels in preeclampsia and healthy normotensive pregnant women .

Preeclampsia

Preeclampsia is a common complication of pregnancy associated with high maternal morbidity and mortality and intrauterine fetal growth restriction. There is extensive evidence that the reduction of uteroplacental blood flow in this syndrome results from the toxic combination of hypoxia, imbalance of angiogenic and anti-angiogenic factors, inflammation, and deranged immunity ***(Eiland et al., 2012).***

Definition:

Preeclampsia is defined as the presence of a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg, on 2 occasions at least 4 hours apart in a previously normotensive patient. In addition to the blood pressure criteria, proteinuria of ≥ 0.3 grams in a 24-hour urine collection, a protein (mg/dl)/creatinine (mg/dl) ratio of 0.3 or higher, or a urine dipstick protein of 1+ is required to diagnose preeclampsia**. Eclampsia** is defined as seizures that cannot be attributable to other causes, in a woman with preeclampsia ***(American College of Obstetricians and Gynecologists, 2013).***

Two types are recognized: mild and severe preeclampsia. The severity of preeclampsia is assessed by the frequency and intensity of abnormalities.

Severe features of preeclampsia:

Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg and proteinuria (with or without signs and symptoms of significant end-organ dysfunction).

Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without proteinuria) and one or more of the following signs and symptoms of significant end-organ dysfunction:

New-onset cerebral or visual disturbance, such as: - Photopsia (flashes of light) and/or scotomata (dark areas or gaps in the visual field). - Severe headache (ie, incapacitating, "the worst headache I've ever had") or headache that persists and progresses despite analgesic therapy. - Altered mental status.

Severe, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis or serum transaminase concentration ≥2 times upper limit of normal for a specific laboratory, or both. • <100,000 platelets/microL

Progressive renal insufficiency (serum creatinine >1.1 mg/dL [97.3 micromol/L]; some guidelines also include doubling of serum creatinine concentration in the absence of other renal disease ***(Phylliy and Baha, 2018).***

Epidemiology

Overall, 10%–15% of maternal deaths are directly associated with preeclampsia and eclampsia. Some epidemiological findings support the hypothesis of a genetic and immunological etiology. The risk of preeclampsia is 2 to 5 times higher in pregnant women with a maternal history of this disorder. Depending on ethnicity, the incidence of preeclampsia ranges from 3% to 7% in healthy nulliparous and 1% to 3% in multiparas ***(Uzan et al., 2011).***

Risk Factors: *(Phylliy and Baha, 2018).*

A past history of preeclampsia increases the risk of developing preeclampsia in a subsequent pregnancy eightfold compared with women without this history.

Preexisting medical conditions:

Pregestational diabetes – This increase has been related to a variety of factors, such as underlying renal or vascular disease, high plasma insulin levels/insulin resistance, and abnormal lipid metabolism.

Chronic hypertension Blood pressure ≥130/80 mmHg at the first prenatal visit has also been reported to increase risk.