Association between Vitamin D Deficiency and Preeclampsia: A Case Control Study

Thesis

Submitted for Partial Fulfillment of Master Degree

In Obstetrics and Gynecology

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Candidate

Mohamed Salah Sayed

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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

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Introduction

Preeclampsia is a multisystemic pregnancy disorder diagnosed clinically by new onset of gestational hypertension and proteinuria. It occurs in 3-5% of all pregnancies worldwide and is a major cause of maternal, fetal and neonatal morbidity and mortality ***(Roberts and Gammill, 2005).***

It occurs during second and third trimester of pregnancy. It is characterized by blood pressure of ≥140/90 mm Hg or rise in systolic blood pressure of more than 30 mmHg or diastolic blood pressure of more than 15 mmHg after 20 weeks of gestation, in conjugation with proteinuria ≥300 mg/24 hours ***(Lindheimer et al., 2009)***.

In the 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).***

Despite recent studies for understanding the pathophysiology of preeclampsia, the disorder remains a

challenge with no preventive therapy and the effective treatment limited to delivery to terminate pregnancy and the disorder . A current model of the pathophysiology of preeclampsia invokes a two stage model decreased placental perfusion usually secondary to abnormal trophoblastic invasion with consequent failed dilatory remodeling of maternal vessels perfusing the placenta that precedes and results in the clinical manifestations of preeclampsia. Multiple factors have been indicated in the initiation and progression of preeclampsia, including maternal constitutional factors, antiangiogenic factors, endothelial dysfunction, syncytiotrophoblast microparticles and inflammatory activation ***(Roberts and Hubel, 2009).***

More recently, vitamin D deficiency has been associated with several adverse pregnancy outcomes, including pre-eclampsia, gestational diabetes mellitus, intrauterine growth restriction and preterm birth ***(Robinson et al., 2010).***

Vitamin D is a seco-steroid pro-hormone which undergoes two successive hydroxylations, firstly to 25-hydroxyvitamin D, a nutritional biomarker for vitamin D status, and secondly to the active hormonal metabolite 1,25-dihydroxyvitamin D (calcitriol) that is the active form which exerts the hormonal action via binding to nuclear vitamin D receptors which are present throughout the body including pregnancy specific tissues such as the placenta and uterineplacental bed (decidua) ***(Zehnder et al., 2002; Barrera et al., 2008).***

The reasons for the increased vitamin D deficiency are unclear, but changes in lifestyle are likely to be important. In humans, the primary source of vitamin D is endogenous synthesis in the skin after exposure to ultraviolet rays of sunlight and the diet represents the secondary source. A combination of a change in lifestyle (with more daylight hours spent indoors), liberal use of sunscreens (mostly driven by concerns about the risk of skin cancer), and global environmental pollution might have contributed to the widespread increase in vitamin D deficiency ***(Hossain, 2011).***

There is a seasonal variation in 25(OH)D concentrations as the concentrations are highest in late summer and early autumn and lowest in late winter and early spring ***(Wortsman et al., 2000).***

Human trophoblasts both produce and respond to the active form of Vitamin D 1,25(OH)2D. The concentration of 1,25(OH)2D is tightly regulated by Vitamin D activating enzyme 1α-hydroxylase (CYP27B1) and the degradation enzyme 24-hydroxylase (CYP24A1). Both enzymes are expressed in human placenta. The activated 1,25(OH)2D mediates its actions through specific Vitamin D receptors (VDR), which are expressed in both decidua and trophoblasts. Recent pregnancy-related studies indicate that

Vitamin D inhibits the mRNA transcription of inflammatory cytokine genes (TNFα, IFNγ and IL-6) in trophoblast cell culture systems so it has an anti-inflammatory function in multiple organ systems including trophoblast cells and placenta ***(Diaz et al., 2009; 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 ***(Hyppo¨ nen, 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. This would have widespread maternal health implications as so far we do not have definitive preventive measures. So, this study will be conducted to determine the prevalence of vitamin D deficiency and its association with preeclampsia and with the disease severity.

Aim of the Study

To find out if lower levels of vitamin D is more prevalent in preeclamptic women.

Research hypothesis

In pregnant women with preeclampsia, vitamin D levels may be lower compared to controls.

Research question

Does vitamin D level is lower in pregnant women with preeclampsia than controls?

Patients and Methods

Study Design:

Case control study.

Study Site:

The study will be conducted at Ain Shams University Maternity Hospital from June 2015 to December 2015.

Sample Size Justification:

Sample size was calculated using stata program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study ***(Singla et al., 2014)*** showed that mean vitamin D level among preeclamptic women was 9.7± 4.95 ng/ml, while among controls it was 14.8± 6.68 ng/ml.Calculation according to these values produced a minimal sample size of **25** cases in each group.

Study population:

This study will be carried out on 90 pregnant women recruited at pre labour room at Ain Shams University Maternity Hospital. They will be divided into preeclamptic group and non preeclamptic group, 45 cases in each one.

Inclusion criteria:

- Parity: primigravida.
- Age: 18 - 35 years.

- Singleton pregnancy.
- Gestational age: 36-40 weeks.
- No past history of any medical disorder and with no other medical complications during pregnancy.

Exclusion criteria:

- Women with preexisting medical conditions like rheumatoid arthritis, thyroid, hepatic or renal failure, metabolic bone disease, diabetes mellitus, malabsorption and lupus.
- History of intake of medications influencing bone, vitamin D or calcium metabolism e.g. antiepileptic, theophylline, antitubercular drugs in the last 6 months.
- Women with multiple pregnancy.
- Women with congenital fetal malformation.
- Women with known thrombophilia.

<u>Case group</u>: Preeclamptic group

1. Blood pressure: greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation ***(Roberts et al., 2013).***
2. Proteinuria: dipstick screening test reading greater than or equal to (+1).