Serum Concentration of Vitamin D in Preeclampsia

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ABSTRACT:

BACKGROUND:

Preeclampsia, the *de novo* occurrence of hypertension and proteinuria after the 20th week of gestation, continues to exert an inordinate toll on mothers and children alike. Vitamin D, on the other hand, has direct influence on molecular pathways proposed to be important in the pathogenesis of preeclampsia, yet the vitamin D-preeclampsia relation has not been studied.

OBJECTIVE:

To assess the vitamin D status of preeclamptic women in different gestational period with respect to normal pregnancy.

PATIENT AND METHODS*:* the present study is a cross-sectional case-control study (2008-2009) At Al-Kadhimiya Teaching Hospital. Includes measurement of serum vitamin D3 in 60 patients with preeclampsia who were classified into two groups according to the gestational age:

- Preeclamptics in the second trimester G1: (n=30).
- Preeclamptics in the third trimester G2: (n=30,).

The results were compared with 60 apparently healthy pregnant women (as controls). They were classified according to the gestational age into two groups:

- Pregnants in the second trimester G3: (n=30).
- Pregnants in the third trimester G4: (n=30).

RESULTS:

Showed a significant decrease in serum vitamin D3 in the preeclamptics as compared with the controls ($p < 0.001$)this was accompanied by a significant reduction of this parameter with advancing gestational age in both preeclamptic and healthy pregnents.

CONCLUSION:

Preeclamptics (in different gestational age groups) experienced hypovitaminosis D when compared with healthy pregnant women matched with their age and gestational age; this can be explained partly by the reduction of insulin–like growth factor which has a stimulatory effects on vitamin D3 and partly explained on genetic defects affecting fetoplacental unit.

The above results were supported by the significant low level of s. vitamin D3; which call for the need for vitamin D supplementation in pregnancy.

KEYWORDS: *preeclampsia, vitamin D.*

INTRODUCTION:

A major contributor to complications during pregnancy and postpartum periods, pre-eclampsia, is a disorder characterized by sudden weight gain, fluid retention, high blood pressure, and swelling in the second and third trimesters. Other symptoms, including vision changes and headaches, may not always appear in rapidly advancing cases[(1)]. Pre-eclampsia affects 5-8% of all pregnancies and is the cause of 15% of premature births[1]. Preeclampsia can cause generalized damage to the kidneys, liver or blood vessels[2]. More seriously, it can progress into eclampsia, a potentially fatal condition that can cause seizures or severe damage to the blood, kidneys, liver, lungs and nervous system[(2]. Eclampsia may be the cause of 70 percent of deaths during pregnancy in Third World countries[(2)].

Pregnant women who are vitamin D deficient have five times the risk of suffering a potentially fatal condition known as preeclampsia[(3)].

Researchers also stressed that even slightly low Vitamin D measurements in pregnant women may double the likelihood of having the disorder. Even with prenatal vitamins, pregnant women remain at a high risk for the deficiency[(3)].

Additionally, the low availability of Vitamin D leads to an inefficient deposition of calcium in the

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bones. A recent publication from The New England Journal of Medicine also elaborates on the deficiency of this vitamin, which according to the article exposes millions of children and adults to several serious conditions, occasionally fatal, including cancer, infectious diseases and osteoporosis[4].

Moreover, the pathogenesis of preeclampsia involves a number of biological processes that may be directly or indirectly affected by vitamin D, including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, and hypertension[3].

The objectives of this study were to evaluate the vitamin D status of women with preeclampsia in different gestational periods.

SUBJECTS AND METHODS:

A-SUBJECTS

The study was a cross-sectional, case-control study conducted on 60 patients with preeclampsia (PE) attending the Obstetric Consultant-Clinic, Antenatal Clinic, and Labor Ward at Al-Kadhimiya Teaching Hospital, for re-evaluation of newly diagnosed PE, or for delivery during the period from November, 2008 till the end of March, 2009.

The diagnosis of PE was based on clinical criteria that were hypertension (absolute BP of 140/90 mmHg twice over 4 hr without prior comparison)[5] and proteinuria (21.5 mg of urinary protein per µmol creatinine)[6].

The exclusion criteria used for cases and controls were gestational or chronic hypertension, diabetes mellitus, renal disease, multifetal gestation, intrauterine fetal death, and pregnancy less than 20 weeks of gestation.

Depending on the gestational age, the 60 patients were divided into two groups:

1. Preeclamptics in the second trimester (G1): They were 30 with age range from 16 to 36 years (mean age ± SD = 25.1 ± 5.4 year) and gestational age range from 20 to 28 weeks (mean gestational age ± SD = 24.3 ± 1.6 week).

2. Preeclamptics in the third trimester (G2): They were 30 with age range from 18 to 38 year (mean age ± SD = 26.2 ± 6.7 year), and gestational age range from 29 to 40 weeks (mean gestational age ± SD = 36.5 ± 1.5 week).

The study included another 60 apparently healthy pregnant women attending the Antenatal clinic, and Labor Ward at Al-Kadhimiya Teaching Hospital, for re-evaluation of their pregnancy, or for delivery. They were included as normal controls. They were comparable with preeclamptic groups regarding the age and the gestational age. They were divided into two groups according to their gestational age:

1-Normal pregnant women in the second trimester (G3): They were 30 with age range from 15 to 38 years (mean age ± SD = 26.6 + 5.6 year) , and gestational age range from 20 to 28 weeks (mean gestational age ± SD = 24.7 ± 1.9 week).

2-Normal pregnant during the third trimester **(G4):** They were 30 with age range from 18 to 35 year (mean age ± SD = 25.2 ± 6.5 year) and gestational age range from 29 to 40 weeks (mean gestational age ± SD = 37.6 ± 2.3 week).

B. Blood samples:

Ten milliliters of random venous blood were withdrawn from each patient and control, in supine position, without application of tourniquet. Samples were transferred into clean new plane tube, left at room temperature for 15 minutes for clotting, centrifuged, and the separated serum was transferred into Eppendrof tube and was used for measurement of vitamin D. The tubes were stored at –20^{o} C until analysis, which was done within one month after collection[7].

C-METHODS

Serum vitamin levels were separated by iso-cratic high performance liquid chromatography (HPLC) after pre-column extraction with hexane as described previously by Turpeinen, U. 2003[7].

D. Statistical analysis:

Statistical analysis was done using Excel system version 2003 and includes descriptive statistics (mean and standard deviation) and inferential statistics (*t-test*) to test the significancy of mean difference. When P-value was less than 0.05, the difference is considered statistically significant, and the difference is considered highly significant when P-value was less than 0.001.

RESULTS:

Serum vitamin D:

Serum vitamin D was significantly lower in preeclamptics (G1 &G2) compared with normal pregnants (G3 & G4) [P < 0.001 for both]. Moreover, serum vitamin D was significantly lower in third trimester preeclamptics G2 compared second trimester preeclamptics G1[P < 0.001]. Also, a significant difference was found between healthy pregnants G3 & G4, where serum vitamin D was significantly higher in second trimester group G3 compared with G4 [P < 0.001 for both] as in Table 1.

DISCUSSION:

The term *preeclampsia* refers to the new onset of hypertension (140/90 mmHg) and proteinuria after

20 week of gestation in previously normotensive, nonproteinuric women[2].

There are numerous biologically plausible mechanisms by which maternal vitamin D status could alter risk of preeclampsia. Preeclampsia is hypothesized to be a two-stage disorder[8]. Stage 1 is reduced placental perfusion, often secondary to abnormal implantation. The poorly perfused placenta is proposed to produce materials that, in an appropriate maternal environment, initiate the ensuing multisystem sequelae (stage 2). These pathophysiological changes are proposed to be secondary to abnormal endothelial function, which is a component of a generalized increase in the inflammatory activation that characterizes normal pregnancy[9]. The active form of vitamin D, 1,25-dihydroxyvitamin D3, has been shown to regulate the transcription and function of genes associated with placental invasion, normal implantation, and angiogenesis[10]. Furthermore, abnormal implantation is proposed to be mediated at least in part by an inappropriate immune response between mother and baby. The immunomodulatory properties of 1,25-dihydroxyvitamin D3 may be relevant in this regard[11].

Maternal vitamin D deficiency may likewise predispose to the increased inflammatory response[11]. Notably, vascular structure and function including vascular compliance, elasticity, and intima media thickness are more favorable among women supplemented with vitamin D[11]. Vitamin D deficiency may also elevate blood pressure[12]. Finally, the proteinuria of preeclampsia is thought to be mediated by renal vascular endothelial growth factor (VEGF). 1,25-Dihydroxyvitamin D3 has been shown to regulate angiogenic processes through direct effects on VEGF gene transcription[13].

The results of the present study confirmed previous observations regarding the lower maternal serum concentrations of 1,25-$(OH)_2$D3 in PE women compared with those in normal pregnant controls like Hypponen, et. Al[14]. and Bodnar[15] studies.

These results can be partly attributed to the fact that circulating *Insulin-like growth factor I (IGF-I)* and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] levels in maternal compartment are low in preeclampsia[16]. IGF-I stimulates renal and placental [1,25-(OH)2D] and is considered an important regulator of fetal growth[16].

The above results can also be attributed to *fetoplacental unit* which normally synthesizes 1,25-dihydroxyvitamin D3 and expresses the vitamin D receptor with the abundance of IGF-I mRNA[17] ,but in preeclampsia, the activity of enzyme 25-hydroxyvitamin D 1-alpha-hydroxylase (1-alpha-hydroxylase) is reduced to one-tenth the normal activity and did not respond to IGF-I, when compared with normal placenta; mostly attributed to hypermethylation of receptors regulating biologically active vitamin D3 (1,25-(OH)(2)D[17].

CONCLUSION:

Biochemical changes in preeclampsia appear to involve vitamin D metabolism leading to the appearance of the typical pattern which may cause vasospasm of eclampsia. These changes would include low serum level of vitamin D caused by different mechanisms; from the results of above study, vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia.

Table 1: The mean serum vitamin D in different preeclamptic and control groups (presented as mean ± SD).

Variable	G1	G2	G3	G4
s.Vitamin D (nmol/L)	30.3 ± 5.45*	14.2 ± 5.40**§	59.5 ± 1.16**	55 ± 1.33§§

(G1):Preeclamptics in the second trimester.
(G2): Preeclamptics in the third trimester.
(G3):Control pregnants in the second trimester.
(G4):Control pregnants during the third trimester.

* t-test: G1 versus G3, $p < 0.001$
** t-test: G2 versus G4, $p<0.001$
§ t-test: G2 versus G1, $p<0.001$
§§ t-tst: G4 versus G3, $p<0.001$

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