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Maternal vitamin D levels in patients with hypertensive disorders of pregnancy

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Abstract
Objective: To evaluate maternal vitamin d levels in patients with hypertensive disorders of pregnancy.
Material and Method: The present case-control study was conducted among 150 pregnant women attending gynaecological OPD during July 2019-January 2020. On admission, patient demographic profile, complete history was recorded, and comprehensive clinical examination was done. In all the patients, blood samples for routine examination along with LFT, RFT, random blood sugar, serum electrolytes, serum uric acid and serum vitamin D were drawn, and serum levels of these biochemical parameters were determined according to standard laboratory procedures. Subjects were classified into four categories according to serum vitamin D level i.e. >20ng/ml (suboptimal to optimal), 10-20 ng/ml (mild deficiency), 5-10ng/ml (severe deficiency) and <5 ng/ml (very severe deficiency).
Results: Insignificant difference was found between case (hypertensive) and control (normotensive) group when compared in relation to age, education and socioeconomic status. Vitamin D<5 and >20ng/ml was revealed among 20%, 5.33% and 6.67%, 14.67% of the subjects in case and control group respectively. Mean vitamin level was 9.16±4.93 and 13.94±6.17 ng/ml in case and control group respectively with statistically significant difference as $p<0.05$. Mean serum calcium was found comparatively higher among control group (8.84±1.11) as compared to case group (8.21±1.34).
Conclusion: The results of the present study concluded that women with hypertension had significantly lower vitamin D level as compared to normotensive women.

Keywords: Vitamin D, pregnancy, hypertension

Introduction
Vitamin D3, also known as calciferol, is a prohormones that plays an important role in calcium homeostasis and bone health in addition to its neuromuscular functions [1]. Several studies reported the relationship between maternal Vitamin D deficiency and adverse maternal and fetal outcomes [2]. In the last two decades, the non-classical function of Vitamin D has been suggested; it regulates a large number of human genes (~200 genes), resulting in a wide range of autocrine effects in different tissues [3]. Beyond its well-established role in bone health, vitamin D has been studied as a potentially modifiable factor contributing to extra-skeletal health during pregnancy. During pregnancy, vitamin D may play a role in implantation and placental function potentially due to angiogenic, immunomodulatory and anti-inflammatory effects [4].
This explains the correlation of vitamin D deficiency to the potential risk of a series of conditions like hypertensive disorders, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, autoimmune and infectious diseases as well as depression. Hypertensive disorders of pregnancy are the most common medical complication of pregnancy and its association with vitamin D deficiency is worth discussing. Hypertensive disorders affect 7-15% of all gestations and account for potential maternal and perinatal risks and outcome [5]. It includes gestational hypertension, preeclampsia, eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension. In India incidence of preeclampsia is 5-15%, eclampsia is 1 in 500 to 1 in 30 [6]. About 16% of maternal deaths were attributed to hypertensive disorders in developed countries and over half of these were preventable [7].
Vitamin D deficiency has been widely reported among pregnant women in various countries. Some studies have shown association between vitamin D deficiency (VDD) and hypertension and other adverse pregnancy outcomes. Still there is paucity of literature pertaining to association between VDD and preeclampsia from sun-rich country of India and the available studies are quite old [2].

Hence the present study was planned to evaluate maternal vitamin d levels in patients with hypertensive disorders of pregnancy.

Material and Method: The present case-control study was conducted among pregnant women attending gynaecological OPD during July 2019-January 2020. The study protocol for all procedures was approved by the Institutional Review Board for Ethical Clearance of the institution and was performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration of Helsinki of 1975, as revised in 2000. All patients were asked to sign a written consent form prior to commencement of the study. The subjects were selected according to the following inclusion and exclusion criteria:

Inclusion criteria: Patients of pregnancy induced hypertension with and without treatment- gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome.

Exclusion criteria: Women with pre-existing medical conditions like rheumatoid arthritis, thyroid, hepatic or renal failure, metabolic bone disease, diabetes mellitus, malabsorption, chronic hypertension and lupus, or with multiple pregnancy, or history of intake of medications influencing bone, vitamin D or calcium metabolism e.g. Antiepileptic/theophylline/anti-tubercular drugs in the last 6 months were excluded.

Initially 350 pregnant females were screened of which 214 patients were enrolled on the basis of inclusion and exclusion criteria. Some were lost to follow up and finally 150 pregnant females, 75 each from normotensive (control group) and hypertensive group (case group) either preeclampsia or eclampsia were studied.

On admission, patient demographic profile, complete history was recorded, and comprehensive clinical examination was done. In all the patients, blood samples for routine examination along with LFT, RFT, random blood sugar, serum electrolytes, serum uric acid and serum vitamin D were drawn, and serum levels of these biochemical parameters were determined according to standard laboratory procedures. Serum vitamin D quantification was done by chemiluminescent assay. Those with diabetes mellitus, anemia, renal failure, hypothyroidism, multi-fetal gestation and immunosuppressive disorders were excluded from the study. Subjects were classified into four categories according to serum vitamin D level:

1. >20ng/ml: suboptimal to optimal
2. 10-20 ng/ml: mild deficiency
3. 5-10ng/ml: severe deficiency and
4. <5 ng/ml: very severe deficiency.

All the subjects were managed as per protocol of the institute. During the course of her pregnancy if the subject in control group developed preeclampsia then she was excluded from the control group and taken up as case.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

Results

Mean age in the case group was 24.11±3.77 and in the control group was 23.91 ± 3.89 years; the difference was not significant (p = 0.84). Maximum subjects in both the groups have studied upto high school i.e. 56% and 61.33% in case and control group respectively (table 1).

Table 2 shows the comparison of maternal serum vitamin D (ng/ml) between case and control group. Mean vitamin D level was 9.16±4.93 and 13.94±6.17 (ng/ml) in case and control group respectively with statistically significant difference as p<0.05. Vitamin D> 10ng/ml was revealed among 21.33% of the case group while it was found among 62.67% of the subjects in control group. When different categories of Vitamin D level was compared statistically among case and control group using chi square test, it was found to be statistically significant.

Mean birth weight (kg) and serum calcium level was 2.24±0.39, 8.21±1.34 and 2.54±0.44, 8.84±1.11 in case and control group respectively. When birth weight (kg) and serum calcium level was compared statistically among case and control group using t test, it was found to be statistically significant (table 3).

NICU admission was reported among 37.33% and 25.33% of the subjects in case and control group respectively with statistically insignificant difference as p>0.05 (table 4).

Table 1: Comparison of sociodemographic profile between case (hypertensive) and control group (normotensive).

Variables	Case Group (N=75)	Control Group (N=75)	Total	p value
Age (years), Mean±SD	24.11±3.77	23.91±3.89	24.01±3.82	0.84#
Education				
Illiterate, N (%)	28 (37.33)	23 (30.67)	51 (34)	0.23$
Up to high school, N (%)	42 (56.00)	46 (61.33)	88 (58.67)	
Above high school/graduate, N (%)	5 (6.67)	6 (8.00)	11 (7.33)	
Socioeconomic status				
Lower, N (%)	17 (22.67)	18 (24.00)	35 (23.33)	0.54$
Lower middle, N (%)	24 (32.00)	22 (29.33)	46 (30.67)	
Upper lower/middle, N (%)	32 (42.67)	34 (45.33)	66 (44.00)	
Upper, N (%)	2 (2.67)	1 (1.33)	3 (2.00)	

$Chi-Square test; #independent t-test

Table 2: Comparison of maternal serum vitamin D (ng/ml) between case and control group in relation to BP

Vitamin D (ng/ml)	Case Group N (%)	Control Group N (%)	p value
<5	15 (20.00)	5 (6.67)	<0.01*
5-10	44 (58.67)	23 (30.67)	
10-20	12 (16.00)	36 (48.00)	
>20	4 (5.33)	11 (14.67)	
Mean±SD#	9.16±4.93	13.94±6.17	<0.01*

*: statistically significant, $Chi-Square test; #independent t-test

Table 3: Comparison of mean birth weight (kg) and serum calcium level of babies born in case and control group

Variables	Case Group, Mean±SD	Control Group, Mean±SD	p value
Birth Weight (kg)	2.24±0.39	2.54±0.44	0.03*
Serum Calcium	8.21±1.34	8.84±1.11	0.02*

*: statistically significant

Table 4: Comparison of NICU admission among the case and control group

NICU	Case Group, N (%)	Control Group, N (%)	Chi Square	P value
Yes	28 (37.33)	19 (25.33)	1.98	0.37
No	47 (62.67)	56 (74.67)		

Discussion

Preeclampsia is associated with high maternal and fetal morbidity and mortality. Recent research has pointed towards some role of vitamin D deficiency in pathogenesis of preeclampsia [8]. While we have a fair number of studies from developed countries, but very few investigators have studied the relation between vitamin D deficiency and preeclampsia from India. Therefore this study was conducted to evaluate maternal vitamin d levels in patients with hypertensive disorders of pregnancy.

First of all, our study showed alarmingly high prevalence of vitamin D deficiency among pregnant women. Nearly, 95% and 85% of the women among case and control group respectively were deficient in vitamin D. Similar results were reported by Rimpi Singla *et al.* [9] in their study. Mahija Sahu *et al.* [10] in their study revealed that 75% of the patients in the hypertensive group with either preeclampsia or eclampsia were found to have very severe deficiency (<5 ng/ml) as compared to 25% of those in the healthy normotensive group. Robinson *et al.* [11] carried out a study to assess the levels of total 25-hydroxyvitamin D (25-OH-D) at diagnosis of early-onset severe preeclampsia and found reduced total 25-OH-D levels in comparison to healthy controls (P <0.01). Further supporting our results, Gupta *et al.* [12] estimated serum vitamin D level in term normotensive and preeclamptic. All the patients enrolled in both the study and control group were found to be vitamin D deficient. They found more incidence of severe vitamin D deficiency (90%) in preeclamptic patients as compared to normotensive patients (62%). This difference in the median maternal vitamin D levels of both the groups was found to be statistically significant. Contrary to that Canadian researchers Baker AM *et al.* [13] did a nested case control study and found no association between 25-OH-D and preeclampsia at 16-18 weeks.

The reasons may be lack of sun exposure and fortification of food with vitamin D, and irregular intake of prenatal vitamins. Urban women had better vitamin D status than rural women; this may be due to more of outdoor activity in urban women than their rural counterparts during pregnancy.

In the present study, mean birth weight (kg) and serum calcium level was 2.24±0.39, 8.21±1.34 and 2.54±0.44, 8.84±1.11 in case and control group respectively with statistically significant difference. Mahija Sahu *et al.* [10] in their study reported similar results. They found that out of the 24 babies born to very severe vitamin D deficient mothers, 14 (58.3%) were low birth weight (<2.5 kg) which is in line with what has been mentioned in earlier literature that there is a higher incidence of low birth weight neonates in vitamin D deficient mothers. Calcium deficiency (<8.4 mg/dl) in the neonates was 64.2% and 25.9% with serum vitamin D 5-10 and <5 ng/ml respectively. In a 2-year retrospective study by Taema FH *et al.* [14], all newborns presenting to the pediatric emergency centers with symptomatic hypocalcemia were admitted and their maternal serum vitamin D level was estimated. They found a positive association between the two. This was supported by Mehrotra *et al.* [15] too.

Conclusion

The results of the present study establish a consistent association of maternal serum vitamin D deficiency with hypertensive disorders. This study has also raised the intriguing possibility of association of maternal serum vitamin D deficiency with that of neonatal calcium deficiency and reduced birth weight. The present study serves as a need for larger randomized controlled studies and Meta analyses to confirm the findings. It is suggested that those in the risk group of vitamin D deficiency can be prevented from having hypertensive disorders in pregnancy through a simple step of vitamin D supplementation during pregnancy.

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