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A STUDY OF SERUM LEVELS OF 25 (OH)VITAMIN D AND CALCIUM IN PRE-ECLAMPSIA, ECLAMPSIA AND NORMAL HEALTHY PREGNANT WOMEN

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ABSTRACT **BACKGROUND-** It is important to know the modifiable risk factors related to the occurrence of preeclampsia and eclampsia, which can help in its primary prevention. **OBJECTIVES-** To study the serum levels of 25(OH)Vitamin-D and Calcium in pre-eclampsia, eclampsia, and normal healthy pregnant women. **MATERIAL AND METHODS-** The prospective observational study was conducted from 2018-2021 in the Department of Obstetrics and Gynecology, Government Medical College, Northern India. Eighty women were divided into 3 groups: Group A- women with preeclampsia (30); Group B -women with eclampsia (30); Group C– normal healthy pregnant women (20). Investigations: 1. S.25(OH) VIT D level; 2. S. Calcium level. Results- The mean ± SD levels of vitamin D in women of Group A (preeclampsia) was 21.40 ± 7.11, in Group B (eclampsia) was 16.98 ± 6.62 and in Group C (normal healthy pregnant women) was 37.86 ± 11.34. This data is statistically significant (P=0.016). The mean ± SD of levels of serum calcium in women of Group A (preeclampsia) was 8.68 ± 0.63, in Group B (eclampsia) was 7.86 ± 0.90 and in Group C (normal healthy pregnant women) was 9.07 ± 0.50. The difference between groups was statistically significant (P=0.018). **CONCLUSION-**Both S. Vitamin D and S. Calcium levels have a negative correlation with systolic and diastolic blood pressure. Women having decreased levels of S. Vitamin D and S. Calcium are more prone to develop hypertensive disorders of pregnancy.

KEYWORDS : Preeclampsia, Eclampsia, S. 25(OH)Vitamin D, S. Calcium, Correlation, Feto-maternal outcome

INTRODUCTION

Hypertensive disorders complicate 5-10% of all pregnancies, and preeclampsia is identified in 4-5%of all pregnancies. Hypertensive disorders account for 16% of all maternal deaths and increased perinatal morbidity and mortality. Abnormal trophoblastic invasion, immune-mediated, endothelial cell activation and genetic factors are currently considered causative mechanisms.[1] Recent epidemiological studies emphasized the role of calcium and vitamin D deficiency in the etiology of pre-eclampsia. In developing countries, deficiency of essential trace elements is a common health problem, particularly among pregnant women because of the increased requirement of various nutrients during pregnancy.[2] Vitamin D deficiency is more common in pigmented individuals (melanin absorbs ultraviolet B rays). Deficiency is more common in winter. Pre-pregnancy obesity has been associated with low levels of vitamin D. Other factors associated with vitamin D deficiency are gastrointestinal conditions limiting fat absorption, immobility, etc.[3,4] Vitamin D is produced in the skin when exposed to ultraviolet light. The ultraviolet light acts on 7-dehydro cholesterol producing pre-vitamin D. Pre vitamin D is then converted to vitamin D which then enters circulation and travels to the liver. Vitamin D gets hydroxylated to form 25-hydroxy vitamin D, levels of which are measured to assess the levels of vitamin D in the body and is a precursor to the active metabolite 1,25-dihydroxy vitamin D (calcitriol).[5] Availability of vitamin D for various functions is dependent upon dietary intake of calcium and vitamin D as well as gut absorption and bone metabolism.[6,7] Prior vitamin D uptake is required for calcium absorption. For normal serum calcium levels kidney, intestinal tract, and bone work through strongly regulating ion transport, which is facilitated by calcemic hormones especially parathyroid hormone and vitamin D3.[8] Its deficiency during pregnancy has been linked with several serious short and long-term health-related problems in offspring also.[9] As compared to normal pregnancies, vitamin D metabolism gets altered in preeclampsia, due to reduced placental 1 alpha-hydroxylase activity that results in lowering the circulating calcitriol concentration compared to normotensive pregnant women.[10] Different studies have proposed a correlation between serum calcium levels and preeclampsia. The woman who is consuming less calcium in her diet is expected to develop an increase in blood pressure in her pregnancy.[11] It is important to know the modifiable risk factors related to the occurrence of preeclampsia and eclampsia, which can help in its primary prevention.[12] Discussion with members of the Nutrition Guidance Advisory Group and stakeholders highlighted the limited evidence available in some areas, meriting further research on calcium supplementation in pregnant women.[13] Thus the present study was done to evaluate the role of serum Vitamin D and Calcium in cases of preeclampsia, eclampsia, and normal healthy pregnant women. So, the results of this study can help in the future for the prevention of disease or at least in decreasing the fatality and severity of the disease to some extent.

OBJECTIVES:

The aim of this study was to assess:

1. Serum 25 hydroxyvitamin D/25(OH) Vit D levels in women with preeclampsia, eclampsia, and healthy pregnant women.
2. Serum calcium levels in preeclampsia, eclampsia, and healthy pregnant women.
3. To evaluate the co-relation of 25(OH) Vitamin D and Calcium levels in preeclampsia, eclampsia, and normal healthy pregnant women.

METHODS

This prospective observational study was conducted from May 2018-April 2020 in the Department of Obstetrics and Gynecology, Government Medical College, Northern India.

INCLUSION CRITERIA:

- Pregnant women with preeclampsia and eclampsia after 28 weeks period of gestation.
- Healthy pregnant women after 28 weeks period of gestation with no co-morbidity as controls.
- Age 18-35 years.
- Willing to participate in study.

EXCLUSION CRITERIA:

- Pregnant women with chronic liver disease.
- Pregnant women with chronic kidney disease.
- Pregnant women on drugs like anticonvulsants, corticosteroids, thiazides, heparin.

After Ethical and IRC approval, total 80 pregnant women after 28 weeks of period of gestation were enrolled according to inclusion and exclusion criteria. After written informed consent, all the women (80) were divided into 3 Groups.

GROUP A- with preeclampsia (n=30).
GROUP B – with eclampsia (n=30)
GROUP C –Normal healthy pregnant (n=20)

After history taking, general physical examination was done followed by local examination and investigations.

Then, they were subjected to special investigations:
1.25(OH) VIT D level (ng/ml)- 25-OH Vitamin D was a solid phase ELISA based test on the principal of competitive binding.
Sufficient : 32-100
Insufficiency: 20-32
Deficiency : <20

2. S. Calcium level (mg/dl)- Arsenazo III combines with calcium ions at pH 6.5 to form a colored chromophore, the absorbance of which was measured at 650nm (600-660 nm) and was proportional to calcium concentration.

Normal: 8.6- 10.2 mg/dl

They were followed up throughout the antenatal period till delivery. Maternal and fetal outcome was noted, and data was analyzed statistically. Epi Info version 2 was used for Unpaired t-test and Chi-square test.

RESULTS

Following factors were evaluated and the determinants and consequences observed.

Table 1 shows comparison of Demographic and Clinical Variables. Most women were of 20-27 years age, educated up to 12th pass, housewives, lower and lower middle class socioeconomic status, had supplementation of Vitamin D and Calcium, non-smokers (passive only), no F/H of hypertension, medium complexion in all three Groups and no significant difference was observed P>0.05. However, they might not be compliant with supplementation intake, might not be able to talk correctly about F/H of hypertension and had similar complexion (all varying shades of brown) being from same geographical area P>0.05.

There were more rural women in both study Groups than control Group, similar parity women in study Group A and Group C but there were almost twice primigravida than multigravida women in Group B and no statistical difference was observed P>0.05.

There were more un-booked women, at period of gestation <37 weeks with spontaneous/induced labor as indicated, previous H/O hypertension, vegetarian habit, and higher BMI in both study Groups than control Group, all more in Group B than Group A. All were statistically significant P<0.05.

Our being a tertiary care institute majority of women were referral cases which were un-booked.

Booking status, period of gestation at first visit to us, dietary habits, pre-pregnancy BMI were the most significant factors followed by previous H/O of hypertension.

Table 2 shows comparison of Maternal Outcome. Both systolic and diastolic blood pressure (mm of Hg) were significantly higher in both study Group A and Group B than control Group C; P=0.003 HS and P=0.003 HS respectively.

Both S. Vitamin D (ng/ml) and S. Calcium(mg/dl) levels were significantly lower in both Study Group A and Group B than Control Group C; P=0.016 S and P=0.018 S respectively.

The number of caesarean-section in women having eclampsia was more than that of women in preeclampsia and control Group P=0.05
The data shows the higher risk of hypertensive disorders in mother P=0.003, and almost double the rate of caesarean deliveries in both Study Groups than Control Group P=0.05.

Table 3 shows comparison of Fetal Outcome. Both preterm (<37 weeks) and low-birthweight (<2500g) babies were significantly higher in both Study Groups than Control Group; P=0.001 HS and P= 0.0001 HS respectively. This led to increased NICU admissions and perinatal morbidity.

This data indicates that the complications and need of neonatal support was more in Group B followed by Group A than Group C; P=0.056 NS.

Table-1: Comparison Of Demographic And Clinical Variables

Demographic and Clinical Variables		Study Group		Control Group	
		Group A Preeclampsia N (30) 100%	Group B Eclampsia N (30) 100%	Group C Normal & Healthy N (20)100%	P Value <0.05 =S <0.01 HS >0.05 NS
Age Groups (Years)	<20	0 (00.00 %)	2 (6.67 %)	0 (00.00 %)	0.696 NS Fisher's Exact Test
	20-27	25 (83.33 %)	22(73.33 %)	16(80.00 %)	
	28-35	5 (16.67 %)	6 (20.00 %)	4 (20.00 %)	
	Mean± SD	25.23±2.87	24.57±4.41	25.50±2.30	
Residence	Rural	18 (60.00 %)	20(66.67 %)	8 (40.00 %)	0.614 NS
	Urban	12 (40.00 %)	10(33.33 %)	12 (60.00%)	
Education	Illiterate	5 (16.67 %)	6 (20.00 %)	2 (10.00 %)	0.284 NS
	Upto12th pass	19 (63.33 %)	22(73.33 %)	12(60.00 %)	
	Graduates	6 (20.00 %)	2 (6.67%)	6(30.00 %)	
Occupation	Housewife	27(90.00 %)	28(93.33 %)	16(80.00 %)	0.330 NS
	Working women	3 (10.00 %)	2 (6.67%)	4(20.00 %)	
Socioeconomic Class	Lower	9(30.00 %)	12(40.00 %)	7(35.00 %)	0.263 NS
	Lower Middle	15(50.00 %)	16(53.33 %)	7(35.00 %)	
	Upper Middle	6(20.00 %)	2 (6.67 %)	6(30.00 %)	
Booking History	Booked	4(13.33 %)	0(0.00 %)	11(55.00 %)	**0.0001 HS** Fisher's Exact Test
	Un-Booked	26(86.67 %)	30(100.00%)	9(45.00 %)	
Gravidity	Primigravida	14 (46.67 %)	19(63.33 %)	9(45.00 %)	0.324 NS
	Multigravida	16 (53.33 %)	11(36.67 %)	11(55.00 %)	
Period of Gestation	Mean± SD	36.27 ± 1.64	35.71 ± 1.74	38.17 ± 1.07	**0.0001 HS** ANOVA Test
Past H/O Hypertension	Yes	9(30.00 %)	6(20.00 %)	0 (0.00 %)	**0.02 S** Fisher's Exact Test
	No	21(70.00 %)	24(80.00 %)	20(100.00%)	
Diet	Vegetarian	24(80.00 %)	22(73.33 %)	8(40.00 %)	**0.008 HS**
	Non-vegetarian	6 (20.00 %)	8(26.67 %)	12(60.00 %)	
Calcium& Vit. D Supplementation	Yes	23(76.67 %)	18(60.00 %)	17(85.00 %)	0.123 NS
	No	7(23.33 %)	12(40.00 %)	3(15.00 %)	
H/O Smoking	Yes	0(00.00 %)	3(10.00 %)	0(0.00 %)	0.112 NS Fisher's Exact Test
	No	30(100.00 %)	27(90.00 %)	20(100.00%)	
F/H of Hypertension	Yes	5(16.67 %)	4(13.33 %)	1(5.00) %	0.466 NS
	No	25(83.33 %)	26(86.67 %)	19(95.00 %)	

Pre-pregnancy BMI Kg/m^2	Mean± SD	26 .77± 1.59	25.59 ± 2.04	25.01± 1.01	**0.003 HS** Bartlett´s Test
Complexion	Dark	10(33.33 %)	12(40.00 %)	2(10.00 %)	0.110 NS
	Medium	17(56.67 %)	16(53.33 %)	13(65.00 %)	
	Fair	3(10.00 %)	2(6.67 %)	5(25.00 %)	

Table-2: Comparison Of Maternal Outcome

Maternal Outcome Variables		Study Group		Control Group	
		Group A Preeclampsia N (30) 100%	Group B Eclampsia N (30)100%	Group C Normal & Healthy N (20)100%	P Value <0.05 =S <0.01 HS >0.05 NS
Blood Pressure (Mean±SD) Mm of Hg	Systolic BP	158.60 ± 6.49	174.46 ± 6.98	119.60±3.28	**0.003 HS** Bartlett's Test
	Diastolic BP	110.00 ± 5.11	117.53 ± 3.22	79.50 ± 2.66	**0.003 HS** Bartlett's Test
S. Vitamin D(ng/ml)	<20	17(56.67 %)	21(70.00 %)	2(10.00 %)	**0.016 HS** Barlett's Test
	20-32	10(33.33 %)	7 (23.33 %)	5(25.00 %)	
	>32	3(10.00 %)	2(6.67)	13(65.00 %)	
	Mean ±SD	21.40 ± 7.11	16.98± 6.62	37.86 ±11.34	
S. Calcium (mg/dl)	<8.6	14(46.67 %)	22(73.33 %)	4(20.00 %)	**0.018 HS** Barlett's Test
	>8.6	16(53.33 %)	8(26.67 %)	16(80.00 %)	
	Mean±SD	8.68 ±0.63	7.86± 0.90	9.07 ±0.50	
Mode of Delivery	Caesarean Section	13(43.33 %)	16(53.33 %)	4(20.00 %)	0.05 NS Fisher's Exact Test
	Vaginal Delivery	17(56.67 %)	14(46.67 %)	16(80.00 %)	

Table-3: Comparison Of Fetal Outcome

Fetal Outcome Variables		Study Group		Control Group	P Value
		Group A Preeclampsia N (30) 100%	Group B Eclampsia N (30) 100%	Group C Normal& Healthy N (20) 100%	<0.05 =S <0.01 HS >0.05 NS
Period of Gestation (Weeks)	Pre-Term<37	14(46.67%)	20(66.67%)	3(15.00%)	**0.001 HS**
	Term =>37	16(53.33%)	10(33.33%)	17(85.00%)	
Fetal Weight (Kg)	Mean± SD	2260.66± 416.82	1834.56± 364.83	2778.70± 333.15	**0.0001 HS** ANOVA Test
Neonatal Outcome	Healthy	13(43.33 %)	3 (10.00 %)	17(85.00 %)	0.056 NS Fisher's Exact Test
	IUD	1(3.33 %)	5(16.67 %)	0(0.00 %)	
	Oxygen Support	11(36.67 %)	13(43.33 %)	2(10.00 %)	
	Still Birth	0(0.00 %)	1(3.33%)	0(0.00 %)	
	Ventilatory Support	5(16.67 %)	8(26.67 %)	1(5.00 %)	

Table 4 & Table 5 show: A positive correlation between S. Vitamin D and S. Calcium level P= 0.001 HS.

Both S. Vitamin D and S. Calcium levels; show a negative correlation with systolic and diastolic blood pressure; P=0.001 HS and P=0.001 HS respectively.

Both S. vitamin D and S. Calcium levels; show a positive correlation with period of gestation and fetal birth weight; P=0.001 HS and P=0.001 HS respectively.

S. Calcium had a positive correlation with age P=0.018 S and no correlation with BMI; P=0.729 NS.

Table-4: Correlation Of Serum Vitamin D Level With Serum Calcium Level Age, Bmi, Systolic Bp, Diastolic Bp, Fetal Weight And Period Of Gestation

Correlation between	Pearson's Correlation coefficient	p-value	
Serum Vitamin D and Calcium	0.397**	0.001	Highly significant
Serum Vitamin D and Age	0.087	0.442	Not significant
Serum Vitamin D and BMI	-0.158	0.161	Not significant
Serum Vitamin D and Systolic BP	-0.705**	0.001	Highly significant
Serum Vitamin D and Diastolic BP	-0.705**	0.001	Highly significant
Serum Vitamin D and Period of Gestation	0.370**	0.001	Highly significant
Serum Vitamin D and Fetal Weight	0.453**	0.001	Highly significant

Table-5: Correlation Of Serum Calcium Level With Serum Vitamin D, Age, Bmi, Systolic Bp, Diastolic Bp, Fetal Weight And Period Of Gestation

Correlation between	Pearson's Correlation coefficient	p-value	
Serum Calcium and Vitamin D	0.397**	0.001	Highly significant
Serum Calcium and Age	0.263*	0.018	Significant
Serum Calcium and BMI	-0.039	0.729	Not significant
Serum Calcium and Systolic BP	-0.537**	0.001	Highly significant
Serum Calcium and Diastolic BP	-0.514**	0.001	Highly significant
Serum Calcium and Period of Gestation	0.394**	0.001	Highly significant
Serum Calcium and Fetal Weight	0.450**	0.001	Highly significant

In our study S. Vitamin D and S. Calcium level are found significantly lower in pre-eclampsia and eclampsia than normal healthy pregnant mothers and thereby poses increased risk to both mother (pre-eclampsia and eclampsia, and increased rate of caesarean delivery), and the fetus (preterm and low birth weight babies) with consequent higher neonatal complications and poor feto-maternal outcome

DISCUSSION

The present study was conducted to find out the relation of S. Vitamin D and Calcium levels with hypertensive disorders of pregnancy. Along with that, fetal indices and prognosis has also been studied along with maternal parameters. We report in our study that S. Vitamin D and Calcium levels are found significantly lower in pre-eclampsia and eclampsia than normal healthy pregnant mothers and the adverse impact on maternal and neonatal health outcome. We emphasize on booking status, period of gestation at first visit, dietary habits, BMI followed by previous H/O of hypertension.

In this study the mean age (years) of women enrolled in the Group A was 25.23 ± 2.87, in Group B was 24.57 ± 4.41 and in Group C was 25.50 ± 2.30 which was non-significant(P>0.05). Our study is like studies by Aghade SM et al (2017)[14] and by Bakacak M et al (2015).[15] However, Kumar N et al (2017)[16] found the mean age of preeclampsia study Group was 27.14 ± 3.64 and of eclampsia study Group was 24.73 ± 4.01 (P =0.004) which was statistically significant.

In our study 57.5% women belonged to rural area and 42.5% women belonged to urban area since a higher percentage of population in India is still living in rural areas.

In the studies by Hamedanian L et al (2019) [17] and Sahu M et al (2017) [12] the maximum number of women were also educated up to 12th standard, like our study.

In the present study, most of women belong to lower and lower middle-class families. This data was also statistically non-significant (P>0.05). However, this is also a fact that this study was conducted in a government sector hospital where most of the women came from poor strata with low socioeconomic status.

We had relatively more primigravida (63.33%) in eclampsia Group than multigravida women (36.67%) P>0.05 NS. However, Ullah M.I et al (2013)[24] reported an almost equal distribution.

Hamedanian L et al (2019) [17] observed only 8.3%, Logan G.G. et al 2020 [18] (21.6%) women having pre-eclampsia had positive family history of hypertension unlike us (16.67%) with this history though statistically non-significant.

In our study no booked woman had eclampsia however 13.33% booked women had preeclampsia and 55% booked women were normal and healthy (P=0.0001) which is highly significant. As booked women had regular antenatal visits and diagnosed in early stages so severity of disease can be prevented. Similar findings are noted by Sahu M et al (2017) [12], Gogaram et al (2018) [19]and Jido A.T et al (2012) [20]

Bakacak M et al (2015) [15] reported the mean gestational age in preeclampsia study Group was 35.3 ± 1.43, in eclampsia Group 34.1 ± 3.87 and in control Group was 38.5 ± 1.43 (P<0.01) which was statistically significant and consistent with our study. Sah S et al (2018) [21] reported higher mean gestational age in preeclampsia Group, was statistically non-significant. Aghade SM et al (2017)[14] reported lower mean gestational age which was statistically non-significant.

Verma MK M.I et al (2017) [22] and Madhu Jain et al (2015) [23] found significantly higher vegetarian women having pre-eclampsia 62.8% and 93% respectively like our study (80%).

Like our study, Ullah M.I et al (2013) [24] reported the mean of pre-pregnancy BMI in preeclampsia study Group was 18.39 ± 0.51, in eclampsia Study Group 16.34+-0.21 and in Control Group was 18.92 ± 0.51 (P<0.001) which was statistically highly significant. But Bakacak M et al (2015)[15] reported higher BMI and Aghade SM et al (2017) [14] lower BMI- both statistically non-significant.

The mean of systolic blood pressure in our study in Group A (preeclampsia) was 158.60 ± 6.49, in Group B was 174.46 ± 6.98 and in Group C (normal healthy pregnant women) was 119.60+-3.28; (P= 0.003) which was statistically significant, like other studies [14,15]. However, Sah S et al (2018) [21] reported the mean of systolic blood pressure in preeclampsia study Group was 153.2+-11.37, and in control Group was 114.7 ± 8.1 (P>0.05) which was statistically non-significant.

The mean of diastolic blood pressure in our study in Group A(preeclampsia) was 110.00 ± 5.11, in Group B was 117.53 ± 3.22 and in Group C (normal healthy pregnant women) was79.50 ± 2.66(P<0.05) which was statistically significant like other studies.[14,15] Sah S et al (2018) [21] observed the mean of diastolic blood pressure in preeclampsia study Group was 97.5 ± 7.16, and in control Group was 74.6 ± 5.69 (P>0.005) which was statistically non-significant.

In the present study the mean S. Vitamin D levels in Group A was 21.40 ± 7.11, in Group B was 16.98 ± 6.62 and in Group C (normal healthy pregnant women) was 37.86 ± 11.34. (P<0.05) which is statistically significant, like other studies [15,24] and Singla M et al (2019) [25]. All these studies were showing the negative correlation between S. Vitamin D levels and severity of disease.

In the present study the mean S. Calcium levels in Group A was 8.68 ± 0.63, in Group B was 7.86 ± 0.90 and in Group C was 9.07 ± 0.50 (P<0.05) which is statistically significant and like other studies [14,16]and by Deshpande HG et al (2018) [26]. These studies show negative correlation between serum calcium and the severity of disease. However, study conducted by Sah S et al (2018) [21] found similar results which were statistically non-significant.

The rate of caesarean-section was more in only eclampsia Group in this study, whereas many other studies [15,16] found the rate of caesarean-section more in both pre-eclampsia and eclampsia Groups.

In present study the mean fetal weight in Group A was 2260 ± 416.82, in Group B was 1834.56 ± 364.83 and in Group C was 2778.70 ± 333.15 (P<0.001) which is statistically significant, like other authors [15,16]

In our study, IUD (3.33%) and still birth (0.00%) rate in preeclampsia is very less and both these (0.00%) in normal healthy pregnant women as compared to a study done by Kumar N et al (2017) [16]. In women having eclampsia still birth rate is (3.33%) but rate of IUD (16.67%) is nearly equal to that study[16].

Strength: Majority educated up to 12th pass-better information

Limitation: Sample collection with many confounding factors and effect modifiers. Majority referred/or un-booked in emergency

Future: Multicentric trials with large sample size

CONCLUSION

Immunomodulatory properties of vitamin D have been reported to play a key role in the development of immunological tolerance in pregnancy and a major role in mediating endothelial function. We have found that both S. Vitamin D and Calcium levels have a negative **correlation with** systolic and diastolic blood pressure and a positive correlation with period of gestation and fetal birth weight. So, we conclude that the women having low level of S. Vitamin D and Calcium are more prone to develop hypertensive disorders of pregnancy which may lead to poor pregnancy outcome both in mother and fetus. Thus**,** education and testing in periconceptional period or at the first antenatal visit **(**early booking) and supplementation may lead to decreased incidence of preeclampsia and eclampsia and better feto-maternal outcome.

Ethical issues: The study was conducted after approval from ethical and protocol review committee of the institute: Yes

Permission from IRB: Yes

Funding: Nil

Conflict of interest: Nil

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