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RESEARCH ARTICLE
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A PROSPECTIVE STUDY ON VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH THE DEVELOPMENT OF PREECLAMPSIA IN PRIMIGRAVIDA IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND: Hypertension represents the most common medical complication of pregnancy affecting around 10% women. It is a dominant cause of maternal and perinatal morbidity. Abnormal placentation and impaired trophoblastic invasion are the triggering factors [1]. Vitamin D has immunomodulatory property on placental tissue and its deficiency plays an important role in preeclampsia pathogenesis. Objective of the study is to find the association between the deficiency of Vitamin D and preeclampsia development in primigravida.

METHODOLOGY: This is a prospective observational study done at a tertiary care hospital-Government Maternity Hospital (GMH), Tirupati, Andhra Pradesh, India. 200 antenatal women attending OPD were included in the study. At 12-20weeks of gestational age, their serum samples were taken and analysed for levels of vitamin D. They were categorized into 3 different groups based on serum levels of vitamin D, followed till delivery and were observed of development of preeclampsia and gestational hypertension. The association between vitamin D deficiency and the development of preeclampsia and gestational hypertension was analyzed with chi-square test.

RESULTS: At a cutoff value of 22.37, the ongoing investigation discovered that Vitamin D has a sensitivity of 85.06 percent and a specificity of 38.05 percent to predict preeclampsia Based on the findings of the current study, we conclude that vitamin D deficiency is associated with the development of preeclampsia and gestational hypertension.

KEYWORDS: Gestational hypertension, Preeclampsia, Primigravida Vitamin D Deficiency.

INTRODUCTION

Hypertension represents the most common medical complication of pregnancy affecting around 10% women. It is a dominant cause of maternal and perinatal morbidity. Abnormal placentation and impaired trophoblastic invasion are the triggering factors [1]. Vitamin D has immunomodulatory property on placental tissue. In normal pregnancy, cardiac output increases and as a result of

peripheral vasodilation, systemic vascular resistance decreases. These changes are mediated by nitric oxide, prostacyclin and progesterone [2]. Systolic blood pressure rises more quickly than diastolic, beginning around 8-10weeks and reaches a nadir by 22- 24weeks and attains pre-pregnancy level by term. Immediately after delivery, BP falls and then rises transiently for the first few days, due to vasomotor instability [3].

Vitamin D is a pleotropic steroid hormone mainly involved in calcium uptake and bone metabolism. Recent studies show that it is involved in immune function, cell proliferation and disease prevention. Vitamin D deficiency is prevalent in India, ranging in prevalence from 15% to 80% which is unexpected in a tropical country with good sunshine. [4] Ergocalciferol is found in plants and cholecalciferol found in animal tissues. In dermis and epidermis of human skin, 7-dehydrocholesterol intermediate product in cholesterol synthesis when exposed to sunlight is converted into cholecalciferol.[5]

In early pregnancy, Vitamin D deficiency affects placentation by its immunomodulatory effect. Vitamin D helps to stimulate T regulatory cells which are vital in supporting implantation of placenta by maintaining immune tolerance [6]. In deficiency of Vitamin D, inflammatory cytokines and TNF alpha are produced in increased amount, which plays a role in abnormal trophoblastic invasion. The need to study Vitamin D levels during early pregnancy and their association with the development of preeclampsia is crucial.[7]

Both the human endometrial decidua and the placenta produce Vitamin D. The enzyme 1 alpha hydroxylase, encoded by the CYP27B1 gene and present in the placenta, converts 25-hydroxy Vitamin D to its active form, 1,25-dihydroxy Vitamin D. This active form of Vitamin D has an immunosuppressive effect, facilitating proper trophoblast invasion and successful implantation. Low levels of Vitamin D disrupt the balance between T-helper 1 (Th1) and T-helper 2 (Th2) cytokines, leading to an increase in Th1 cytokine expression. This imbalance affects the immunological tolerance necessary for embryo implantation, potentially contributing to the development of preeclampsia.[8]

AIM OF THE STUDY

To study the association between the deficiency of Vitamin D and preeclampsia development in primigravida in a tertiary care hospital.

INCLUSION CRITERIA

All normotensive, nonproteinuric primigravida attending antenatal clinic between gestational age of 12 to 20 weeks are selected randomly. Those who are willing to give written informed consent were included in the study

EXCLUSION CRITERIA

Women with multiple pregnancy, Essential hypertension, Diabetes mellitus (type1, type2, gestational diabetes mellitus), Chronic renal disease (hydronephrosis, chronic glomerulonephritis), Molar pregnancy, Heart diseases like rheumatic heart disease.

METHODOLOGY

This was a prospective observational study done at a tertiary care hospital- Government Maternity Hospital (GMH), Tirupati, Andhra Pradesh, India. After taking informed consent, vitamin D2 levels were estimated in serum samples by chemiluminescent immunoassay at Multidisciplinary Research Unit (MRU).S.V.M.C Tirupati, using Beckman Coulter access 2 model. Target population were antenatal mothers with gestational age 12 to 20weeks. Serum samples of about 4ml are sent for assay. Depending on the serum vitamin D2 levels, pregnant women in the study were classified into following 3 groups, as follows, Vitamin D2 deficient group

10-19ng/ml Vitamin D2insufficient group 20-29 ng/ml Vitamin D2 optimum group >30ng/ml.
All the women in study population were advised regular antenatal check-ups to the hospital i.e., once in a month till 28 weeks , twice a month till 32 weeks and weekly thereafter. In every antenatal visit, Weight, blood pressure , urine protein estimation by dipstick were monitored. They were asked regarding development of pedal edema, any imminent signs of eclampsia like headache , blurring of vision ,abdominal pain, vomiting. General examination and per abdomen examination was done. Ultrasound for the presence of early diastolic notch was looked for. Based on blood pressure and proteinuria values, cases were categorized as gestational hypertension and preeclampsia and treatment was provided based on institutional protocols. Follow-up was done till delivery and mode of delivery was noted. The association between vitamin D deficiency and the development of preeclampsia and gestational hypertension was analyzed with chi-square test.

RESULTS

Majority of study population belong to age group less than 20years i.e. 94 (47%). Next in the order are individuals whose ages fall inside the 21-25 years i.e. 74 (37%). >25 years age group are least among study population i.e., 32 contributing to 16%. Mean age of study population was 21 years.

Table 1: Distribution based on Vitamin D levels

Vitamin D levels	Frequency	Percentage
<19ng/ml	107	53.5%
20–29ng/ml	80	40%
>30ng/ml	13	6.5%
Total	200	100%
Mean Vitamin D	18.62±7.46ng/ml	

Majority of study population were in Vitamin D deficiency group i.e., 107 (53.5%). 80 cases belong to vitamin D insufficient group contributing to 40%. Vitamin D optimum group contains only 13 cases contributing to 6.5%. Mean Vitamin D level among study population is18.62 ng/ml.

Prevalence of preeclampsia, Gestational Hypertension in the study population : Of the 200 study participants, 87 members developed preeclampsia, contributing to 43.5%, 78 cases developed gestational contributing to 39%.

Table 2: Age wise distribution of Preeclampsia

Age group in years	Pre – Eclampsia				Total	
	Yes		No			
	N	%	N	%	N	%
<20	37	42.5%	57	50.4%	94	47%
21–25	41	47.1%	47	41.6%	88	44%
>25	9	10.3%	9	8.0%	18	9%
Total	87	100%	113	100%	200	100%
Chi square test=1.30, p=0.52,Not statistically significant						

Only 87 out of 200 patients with preeclampsia were able to give birth. The age distribution was as follows: 37(42.5%) were less than 20 years old,41(47.1%) were Between 21 and 25 years old, and 9(10.3%) were older than 25. There is no statistically significant correlation between age and preeclampsia, according to the chi-square score of 1.3 and the p value of 0.52.

Table-3: Age wise distribution of Gestational Hypertension

Age in years	Gestational Hypertension				Total	
	Yes		No			
	N	%	N	%	N	%
<20	43	55.1%	51	41.8%	94	47%
21–25	31	39.7%	57	46.7%	88	44%
>25	4	5.1%	14	11.5%	18	9%
Total	78	100%	122	100%	200	100%
Chi square test=4.45,p=0.10,Not statistically significant						

Out of 200 cases, 78 had gestational hypertension, with 43 cases (55.1%) being identified. Of them, 31(or 39.7percent) belonged to the 21–25 age group, while 4 (or 5.1% of the total) were in the 25+ age group. Results are not statistically significant with a chi-square value of 4.4 and a probability value of 0.1 (more than 0.01). That gestational hypertension may happen at any age is shown by this.

Table-4: Distribution based on association between preeclampsia and Vitamin D levels

Vitamin D levels	Pre-Eclampsia				Total	
	Yes		No			
	N	%	N	%	N	%
<19ng/ml	52	59.8%	55	48.7%	107	53.5%
20–29ng/ml	35	40.2%	45	39.8%	80	40%
>30ng/ml	0	0%	13	11.5%	13	6.5%
Total	87	100%	113	100%	200	100%
Chi square test=11.14,p=0.003,Statistically significant*						

Out of 200 cases, 87 were preeclampsia. There were a total of 58.8% vitamin D deficient cases, 40.2% vitamin D insufficient cases, and 0% vitamin D optimal cases among them. With a p-value of 0.003, which is under 0.01, and a chi-square test worth of 11.14, there is a measurably critical relationship between lack of vitamin D and the development of preeclampsia.

Table5: Distribution based on association between Vitamin D levels and gestational hypertension

Vitamin D levels	Gestational Hypertension				Total	
	Yes		No			
	N	%	N	%	N	%
<19ng/ml	52	66.7%	55	45.1%	107	53.5%
20–29ng/ml	25	32.1%	48	39.3%	73	36.5%
>30ng/ml	1	1.3%	19	15.6%	20	10%
Total	78	100%	122	100%	200	100%
Chi square test=14.55,p=0.0007,Statistically Significant*						

Out of 200 participants, 78 were found to have gestational hypertension. Out of the total, 52 individuals (66.7%) were determined to have insufficient vitamin D, 25 (32.1%) to have inadequate vitamin D and 1 (1.3%) to have appropriate vitamin D. With a p-value of 0.0007 (less than 0.01) and a chi-square value of 14.4, we may conclude that vitamin D plays a major role in the onset of gestational hypertension. Low blood vitamin D levels in mothers are associated with an increased risk of gestational hypertension.

Table 6: Distribution based on Mode of delivery and preeclampsia

Mode of delivery	Preeclampsia				Total	
	Yes		No			
	N	%	N	%	N	%
Normal Vaginal Delivery	40	46%	55	48.7%	95	47.5%
Elective LSCS	35	40.2%	34	30.1%	69	34.5%
Emergency LSCS	12	13.8%	24	21.2%	36	18%
Total	87	100%	113	100%	200	100%
Chi square test=3.05,p=0.21,Not Statistically Significant						

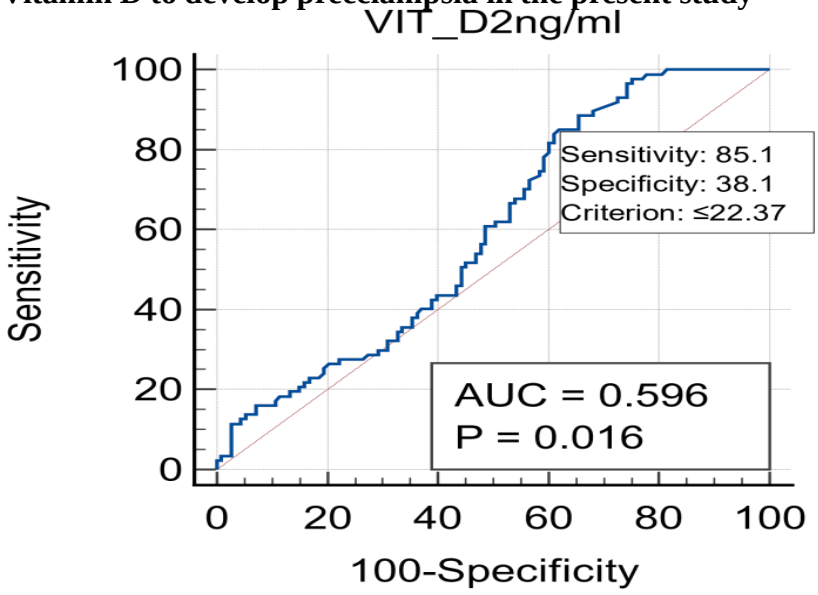
Out of 200 cases, 87 developed preeclampsia, of which 40(46%) delivered vaginally, 35(40.2%) delivered by elective caesarean section and 12(13.8%) delivered by emergency caesarean section.Chi-square value obtained was 3.05, with a p value=0.2 ,not statistically significant. Preeclampsia has no significant effect on mode of delivery.

Table 7: Distribution based on Mode of delivery and Gestational Hypertension

Mode of delivery	Gestational Hypertension				Total	
	Yes		No			
	N	%	N	%	N	%
Normal Vaginal Delivery	36	46.2%	59	48.4%	95	47.5%
Elective LSCS	27	34.6%	42	34.4%	69	34.5%
Emergency LSCS	15	19.2%	41	33.6%	36	18%
Total	78	100%	122	100%	200	100%
Chi square test=0.15,p=0.92,Not statistically significant						

Out of 200 patients, 78 developed gestational hypertension, of which 36 patients delivered vaginally (46.2%), 27 (34.6%) by elective caesarean section and 15(19.2%) delivered by emergency caesarean section. Chi-square value obtained was 0.15, with a p value=0.9, not statistically significant. This implies gestational hypertension has no significant effect on mode of delivery in study population.

Cut off value for Vitamin D to develop preeclampsia in the present study



Area under the ROC curve(AUC)

Area under the ROC curve(AUC)	0.596
Standard Error[a]	0.0399
95% Confidence interval[b]	0.525to0.665
Z statistic	2.412
Significance level P(Area=0.5)	0.0159

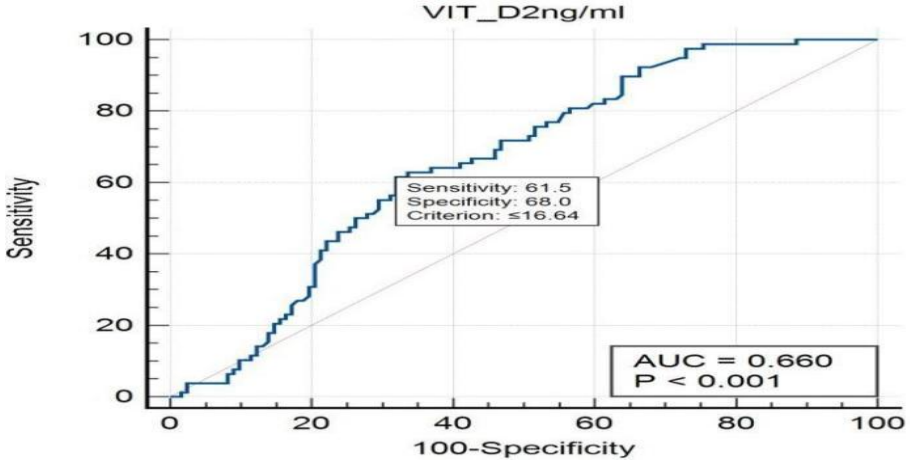
[a]DeLongetal.,1988 [b]Binomial exact

Youden index

Youden index J	0.2311
Associated criterion	≤22.37
Sensitivity	85.06
Specificity	38.05

In this study, out of 200 patients, 87 developed preeclampsia , with a sensitivity of 85.06 and specificity 38.05 and p value of 0.01. Cut-off value for the development of preeclampsia in the present study was 22.**37ng/ml.**

Cutoff value for Vitamin D to develop Gestational Hypertension in the present study



Area under the ROC curve (AUC)

Area under the ROC curve(AUC)	0.660
Standard Error[a]	0.0382
95%Confidenceinterval[b]	0.590to0.726
Z statistic	4.202
Significance level P (Area=0.5)	<0.0001

[a]DeLongetal.,1988 [b]Binomial exact

Youden index

Youden index J	0.2957
Associated criterion	≤16.64
Sensitivity	61.54
Specificity	68.03

In this study, out of 200 patients, 78 developed gestational hypertension, with a p value of <0.001, sensitivity of 61.54 and specificity of 68.03%.The cut-off value of vitamin D for the development of gestational hypertension in the present study was 16.64ng/ml.

DISCUSSION

The participants' average age was around 21.37 ±2.89 years, with 47% being under the age of 20, 37% being between the ages of 21 and 25 and 16% being beyond the age of 25. In the study done by Singh A et al.,[6] overall, 6.8% of the cases were under the age of 20, 55% were between the ages of 20 and 30, 32% were between the ages of 30 and 40, and 7% were beyond the age of 40, which aligns with the findings of the current investigation.

Prevalence of Pre-eclampsia and Gestational Hypertension:

Pre-eclampsia affected 43.5% of the participants in this study, and gestational hypertension was identified in 39% of the cases.

Vitamin D levels:

The mean vitamin D level was 18.62ng/ml, with 53.5 percent of subjects having levels below 19 ng/ml, 40 percent having levels between 20 and 29 ng/ml, and 6.5 percent having levels above 30 ng/ml. In the study done by Singh A et al.,[6]in accordance with the current study's findings, 53.5 percent of participants were found to be vitamin D deficient. Sahu M. et al.'s study found that ,[8] ninety percent of the pregnant women were found to be deficient in vitamin D.

It was seen that there was no measurably massive contrast in the age distribution among the cases who had preeclampsia. Among the cases who had Gestational Hypertension, 55.1% of the cases were <20years, 39.7% of the caseswerebetween21-25yearsand5.1%of them were >25 years. 41.8% of the cases who did not have gestational hypertension were under the age of 20, 46.7% were between the ages of 21 and 25, and 11.5 percent were over the age of 25. The age distribution of cases with gestational hypertension did not show a statistically significant difference in the current study.

Mode of delivery:

Among the cases who had Pre-eclampsia, 46% of the cases had Normal vaginal delivery, 40.2% of the cases had Elective LSCS and 13.8% of the cases had emergency LSCS. Among the cases who didn't have preeclampsia, 48.7% of the cases had normal vaginal delivery, 30.1% of the cases had Elective LSCS and 21.2% of the cases had emergency LSCS and it was seen that there was no genuinely critical relationship between the mode of delivery and preeclampsia. In the study done by Arora S et al.,[9] they have observed and stated that the LSCS rate was significantly higher among them who had vitamin D deficiency. Among the cases who had Gestational Hypertension, 46.2% of the cases had normal vaginal delivery, 34.6% of the cases had Elective LSCS and 19.2% of the cases had emergency LSCS. Among the cases who didn't have gestational hypertension, 48.4% of the cases had Normal vaginal delivery, 34.4% of the cases had Elective LSCS and33.6% of the cases had emergency LSCS.

Impact of Vitamin D on pre-eclampsia and Gestational Hypertension:

In the present study, among the cases with pre-eclampsiaamong59.8%ofthe cases had vitamin D levels <19 ng/ml, among 40.2% of the cases vitamin D values were between 20-29 ng/ml and among none of the cases Vitamin D was >30ng/ml. Among the cases who did not have pre-eclampsia, 48.7% of the cases had vitamin D levels <19 ng/ml, among 39.8% of the cases vitamin D values were between 20-29 ng/ml and among 11.5% of the cases Vitamin D was >30ng/ml. In the cases who had pre-eclampsia, the mean Vitamin D level was observed to be 16.83 ± 6.06ng/ml and among those who were normal the mean value was observed to be 19.99 ± 8.14ng/ml here it was seen that the mean vitamin D levels were fundamentally lower among the individuals who had preeclampsia when contrasted with the people who didn't have preeclampsia.

In the present study, among the cases with Gestational Hypertension among 66.7% of the cases had vitamin D levels <19 ng/ml, among 32.1% of the cases vitamin D values were between 20-29ng.ml and among 1.3% of the cases Vitamin D was >30ng/ml. Among the cases who did not have

Gestational Hypertension, 45.1% of the cases had vitamin D levels <19 ng/ml, among 39.3% of the cases vitamin D values were between 20-29 ng.ml and among 15.6% of the cases Vitamin D was >30ng/ml.

In the cases who had Gestational Hypertension, the mean Vitamin D level was observed to be 16.09 ± 5.44 ng/ml and among those who were normal the mean value was observed to be 20.3 ±8.12ng/ml. In this study, it was found that pregnant women with Gestational Hypertension had significantly lower mean vitamin D values than those without the condition.

Diagnostic accuracy of Vitamin D in diagnosing Pre-eclampsia and Gestational Hypertension:

At a cutoff value of 22.37, the ongoing investigation discovered that Vitamin D has a sensitivity of 85.06 percent and a specificity of 38.05 percent to predict preeclampsia. The area under the curve was 0.59,withp=0.0001The ongoing investigation discovered that foreseeing gestational hypertension with vitamin D at a cutoff value of 16.64 has a sensitivity of 61.54 percent and a specificity of 68.03 percent, p=0.0001*, the area below the curve was 0.66. In the study done by Sahu M et al.,[8]**,** they stated that the cutoff value for vitamin D deficiency was considered to be acceptable at 20 ng/ml in the most recent studies, whereas previously 15 ng/ml were considered to be the cutoff for vitamin D deficiency. In a similar vein, the cutoff value of 22 ng/ml was found to have better diagnostic accuracy for vitamin D deficiency. It was observed that a staggeringly high 90% of the women had vitamin D deficiency

LIMITATIONS OF THE STUDY

Sample size of this study was 200, indicating a smaller size, which produces less reliable results when compared to larger studies.Study period was only 1year.Lack of availability of Vitamin D estimation in our setup makes it difficult to evaluate all antenatal cases for Vitamin D levels.

CONFLICTS OF INTEREST: No conflict of interest

CONCLUSION

This study shows that the association between vitamin D deficiency and development of preeclampsia is statistically significant. Also significant association was found between vitamin D deficiency and development of gestational hypertension. In this study, it was found that there is more association between vitamin D deficiency and development of gestational hypertension when compared to vitamin D deficiency and development of preeclampsia. Vitamin D being an immunomodulator with calming impact can moderate pathways prompting the improvement of toxaemia. Pregnancy-related hypertensive disorders may be independently linked to vitamin D deficiency. So the supplementation of Vitamin D to maintain optimum serum levels can prevent the development of preeclampsia and gestational hypertension thereby improving maternal and foetal health.

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