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Comparative Study of Vitamin D Status and Fetomaternal Outcome in Preeclampsia/Eclampsia and Normal Pregnant Women at Term

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Abstract

Objective: To evaluate maternal vitamin D levels in term normotensive and pre-eclamptic/ eclamptic patients and to assess associated factors such as BMI, birth weight, and mode of delivery and fetomaternal outcome. *Method*: This was a prospective case control study carried out in Department of Obstetrics and Gynaecology, R.N.T. Medical College Udaipur from July 2017 to December 2017. 100 patients were divided into control and study groups of 50 each. Control group had normotensive term pregnant women while the study group had pre-eclamptic and eclamptic women. *Results:* We found more incidence of vitamin D deficiency (96%) in study group as compared to controls (82%). Vitamin D levels were lower in the study group (7.81±4.88ng/ml) compared to control group (12.94±6.72ng/ml) (P<0.001). Group with BMI >24.9 had the lowest vitamin D level (5.50±2.91ng/ml) (p<0.01). Mean Thyroid Stimulating Hormone (TSH) in study group was 4.71±1.51µIU/ml and in control was 3.0±1.11µIU/ml (p value<0.001). Incidence of hypothyroidism was 36% in study group and 12% in controls (p<0.05). The mean Vitamin D Levels in the two groups (TSH ≥4.5mIU/ml and TSH <4.5mIU/ml) were 5.60±3.08 ng/ml and 11.88±7.84ng/ml respectively (p<0.001). Study group had a SB rate of 20% vs 2% in controls and 12% neonatal mortality in NICU vs 8% in controls. Maternal vitamin D levels in patients with still borns was 5.71±2.22ng/ml in comparison to 10.95±7.71ng/ml in those with Live birth (p<0.001). Mean birth weight for study group was 2.04±0.60kg and control group was 2.63±0.37kg (p<0.01). Maternal Vitamin D level for neonates weighing >2.5kg was 12.76±3.91 ng/ml (p<0.01). Low BMI patients (<18.5) had a mean neonatal birth weight of 1.89±0.47kg. For Maternal BMI >24.9, the mean neonatal birth weight was 2.47±0.85kg (p<0.05). *Conclusion* : Low Maternal Vitamin D is associated with an increased risk of preeclampsia and poorer feto-maternal outcome. This could be a modiûable risk factor with important public-health implications.

Keywords: Vitamin D; Pre-Eclampsia; Eclampsia; Thyroid Stimulating Hormone (TSH).

Introduction

Maternal mortality still remains very high in developing countries including India. Maternal Mortality Ratio (MMR) in India is 174 per 1 lakh live births (2013) [1]. The incidence of preeclampsia in hospital practice varies widely from 5 to 15%. The incidence in primigravida is about 10% and in multigravida 5%. The hospital incidence of eclampsia in India ranges from 0.2 to 3.3%. After hemorrhage (38%), Anemia (19%), Sepsis (11%), Abortion (8%), Hypertension (5%) is the leading cause of maternal mortality (SRS survey 2001-2003)[2]. Besides maternal morbidity and mortality, it is also responsible for various fetal and maternal complications.

Vitamin D is a fat-soluble protein that has anti-inflammatory and immune modulation effects. Several large studies have showed

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the link between vitamin D deficiency and the increased incidence of pre-eclampsia [3]. Pre-eclampsia involves an exaggerated inflammatory process and the importance of immune factors in the disease pathogenesis, one could suggest the link between the two factors. Maternal vitamin D deficiency is common during pregnancy and a widespread public health problem [6].

There is increasing interest in vitamin D in pregnancy, including its effects on placental function and inflammatory response. Low status of vitamin D may result in low vitamin D activity and suppress the immune system and placental development. Therefore, a lack of vitamin D may be involved in the pathophysiology of preeclampsia [4].

Production of vitamin D in the decidua, placenta and the maternal kidneys increases during pregnancy [5]. When defining the level of vitamin D in the serum, though not standard, the cut-off level for vitamin D deficiency is acceptable at 20 ng/ml in the latest studies, although previously it was accepted at 15 ng/ml [6].

Pregnancy is a physiological state associated with many alterations in metabolic, biochemical, hematological and immunologic processes. Pregnancy can induce hypertension in previously normotensive women and aggravate hypertension in those who were hypertensive before pregnancy. Hypertensive disorders of pregnancy represent a group of conditions associated with high blood pressure during pregnancy proteinuria and in some cases convulsions. The National High Blood Pressure Education Program Working Group has classified hypertensive disorders during pregnancy into 4 categories,: 1) chronic hypertension, 2) preeclampsia-eclampsia, 3) preeclampsia superimposed on chronic hypertension, and 4) gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy). The most serious consequences for the mother and baby are result of pre-eclampsia and eclampsia [7].

Preeclampsia

The standard definition of pre-eclampsia being hypertension, proteinuria ± oedema occurring after 20 weeks gestation is universally accepted. The international society for the study of hypertension in pregnancy (ISSHP) defined pre-eclampsia as being:

Hypertension = Systolic Blood Pressure (SBP) >140mmHg and / or a Diastolic Blood Pressure (DBP) of > 90mmHg on two consecutive readings 6 hours apart.

Proteinuria ≥ 300mg/l/24 hrs or a protein: creatinine ratio of >30mg/mmol, and where this test is not available, a 1+ proteinuria on a urine dipstix, with both occurring after 20 weeks and returning to normal postnatally [9].

Severe Pre-Eclampsia

The National Institute for Health and Care Excellence (NICE) define severe pre-eclampsia as being pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment with a sub definition for severe hypertension as being a systolic BP ≥ 160mmHg and/or a diastolic blood pressure ≥ 110mmHg [8].

The American College of Obstetrics and Gynaecology (ACOG) define pre- eclampsia as "Blood pressure of 140 millimeters of mercury (mmHg) systolic or higher or 90 mmHg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria defined as urinary excretion of 0.3 grams (g) protein or higher in a 24-hour urine specimen". To be classified as severe they suggest one or more of the following features in a patient of pre eclampsia:

- Blood pressure of 160 mm Hg systolic or higher or 110 mm Hg diastolic or higher on two occasions at least 6 hours apart while the patient is on bed rest.
- Proteinuria of 5 g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart
- Oliguria of less than 500 millilitres (mL) in 24 hours
- Cerebral or visual disturbances
- Pulmonary edema or cyanosis
- Epigastric or right upper-quadrant pain
- Impaired liver function
- Thrombocytopenia
- Fetal growth restriction

The ISSHP have defined early onset pre-eclampsia as pre-eclampsia occurring less than 34 weeks of gestation, and late onset occurring after 34 weeks of gestation.

Effect of Pre Eclampsia on Fetus

The fetal risk is related to the severity of preeclampsia, duration of the disease and degree of proteinuria. The following hazards may occur:

1. Prematurity: either due to spontaneous onset of labor or due to preterm induction
2. Intrauterine growth restriction: due to chronic placental insufficiency
3. Asphyxia
4. Intrauterine death: due to spasm of uteroplacental circulation leading to accidental hemorrhage.

Aims and Objectives

1. Level of maternal vitamin D in patients of pre-eclampsia, eclampsia and normotensive pregnant patient at term.
3. Maternal and Fetal outcome in relation to vitamin D levels in both groups.
5. Correlation of maternal Vitamin D and maternal BMI.
6. Correlation of Vitamin D levels with serum TSH levels in mother.

Materials and Methods

This is an observational prospective case control study conducted on pregnant patients at Dept of Obs. & Gynae, R.N.T. Medical College, Udaipur, Rajasthan.

Preeclampsia was diagnosed if there was a blood pressure (BP) of 140/90 mmHg or greater, measured twice ≥ 6 hours apart, and consistent proteinuria of 300 mg/d or more or urine albumin >+1 by dipstick after the 20th gestational weeks at term or in labor (latent or active).

Exclusion Criteria were

1 Chronic hypertension or history of hypertension before 20 wks,
2 Pre-existing diabetes,
3 History of renal disease or liver disease,
4 Multiple pregnancies,
5 Chronic medical conditions
6 Heart disease

In the study, 100 patients were enrolled from July 2017 to December 2017. The patients were divided equally into study and control groups. In the study group we included, patients having preeclampsia (defined as BP 140/90 mm Hg after 20 weeks of gestation and proteinuria +1 dipstick) and eclampsia (women who met the criteria for pre eclampsia and experienced convulsions in the antenatal period). In control group, patients included were normotensive (defined as BP< 140/90 after 20 weeks of gestation and proteinuria <1 dipstick) at term. On admission, brief history and clinical examination followed by an initial screening for inclusion and exclusion criteria and after obtaining informed written consent, qualified volunteers were scheduled for testing.

At the beginning of the study, venous blood sample (5cc) was taken and subjected to biochemical studies. During the same time, all patients underwent anthropometric measurements.

Weight was measured without shoes and in light clothing using a digital scale with a precision of 0.1 kg (SECA 707; HH, Modena, Italy). Standing height was measured without shoes, using a stadiometer to the nearest 0.1cm precision.

$$BMI = \frac{\text{Body weight (kg)}}{\text{Height square (meter square)}}$$

BMI	Weight Status
Below 18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
30.0 and Above	Obese

The systolic and diastolic blood pressure (SBP and DBP) (5 min seated rest, mean of two readings) were measured with a mercury sphygmomanometer.

Biochemical Measurements

Quantitative determination of total 25 hydroxyvitamin D in human serum and plasma. Test principle is competition principle. Total duration of assay is 27 minutes.

1st incubation: By incubating the sample (15microL) with pre-treatment reagent 1 (Dithiothreitol) and 2 (sodium hydroxide), bound vitamin D(25-OH) is released from the vitamin D binding protein.

2nd incubation: By incubating the pre-treated sample with the ruthenium labelled vitamin D binding protein, a complex between the vitamin D (25-OH) and the ruthenylated vitamin D binding protein is formed.

3rd incubation: after addition of streptavidin-coated microparticles and vitamin D (25-OH) labelled with biotin, unbound ruthenium labelled vitamin D

binding proteins became occupied. A complex consisting of the ruthenylated Vitamin D binding protein and the biotinylated Vitamin D (25-0H) is formed and becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/Procel M. Application of voltage to the electrode then induces chemiluminescent emission which is measured by a photomultplier.

Results are determined by a calibration curve which is instrument specifically generated by a two point calibration and a master curve provided via the reagent barcode.

The measuring range is 3.00 to 70.0ng/ml or 7.50 to 175 nmol/L.

Informed consent was taken from patients. The study protocol was approved by the Ethical Committee of the R.N.T. Medical College, Udaipur.

Data showing a normal distribution were presented as mean±standard deviation (SD). The socio demographic characteristics of the groups were evaluated using the chi-square test. The independent sample *t*-test and Chi-Square test was used to compare the groups in a parametric or nonparametric way whichever applicable. Statistical analyses were performed using SPSS 20. A value of $p < 0.05$ was considered as significant in all statistical analyses.

Results & Discussion

In our study, 78% of the study group and 68% of the controls were in the age group of 21-30 years. Also, the mean age of the study group was 24.82±4.27 years and 24.70±4.55 years among the controls respectively which was almost equivalent and hence, statistically insignificant (p > 0.05).

Patients with parity ≥ 2 had lowest vitamin D levels, i.e. 8.01±3.68ng/ml. this shows lower vitamin D levels are associated with higher parity. The mean vitamin D level of total patients was 10.38±7.49ng/ml (Table 1).

Rural subjects had a mean Serum Vitamin D level of 9.49±7.13ng/ml whereas the urban community had a mean Vitamin D level of 11.54±7.87ng/ml. No significant statistical difference was observed in both the groups (p=0.18) (Table 1).

The Lower Socioeconomic group had the lowest mean Vitamin D level of 9.62±7.90ng/ml. The mean vitamin D levels in Lower middle group and upper Lower group were 9.68±5.35 and 11.13±7.97ng/ml respectively (Table 1).

Patients with eclampsia had the lowest mean Vitamin D level of 6.97±3.27ng/ml. The Pre eclampsia group and severe pre eclampsia group had a mean Vitamin D level of 8.48±7.55 and 8.40±4.97 ng/ml respectively.

Table 1: Association of Mean Vitamin D levels with Parity, Community and Socio-Economic Status

		Vitamin D levels(ng/ml) Mean	SD
Parity	Nulli	10.75	7.75
	Primi	10.94	8.36
	Multi	8.01	3.68
Community	Rural	9.49	7.13
	Urban	11.54	7.87
Socio-economic status	Lower	9.62	7.90
	Upper Lower	11.13	7.97
	Lower Middle	9.68	5.35

Table 2: Mean Serum Vitamin D Levels in both groups

Type of Patients	Vitamin D levels(ng/ml) Mean	SD	P value
Eclampsia	6.97	3.27	ANOVA
PET	8.48	7.55	>0.05 (NS)
Severe PET	8.40	4.97	
Total Study group	7.81	4.88	<0.001 (HS)
Total Control group	12.94	6.72	

Mean vitamin D level of the study group was 7.81±4.88ng/ml in comparison to the Control group which had a mean Vitamin D level of 12.94±8.72ng/ml. The difference between the two groups was statistically highly significant (Table 2).

Obese group (BMI >24.9) had the lowest vitamin D level of 5.50±2.91ng/ml. The Mean vitamin D level in normal BMI group was 12.09±3.73ng/ml in comparison to 10.29±4.62ng/ml in the Low BMI group. This shows that Vitamin D levels are lower in high BMI patients (Table 3).

Table 3: Association of Mean Vitamin D levels with BMI and TSH in both groups

		Vitamin D levels(ng/ml) Mean	SD
BMI	<18.5	10.29	4.62
	18.5-24.9	12.09	3.73
	>24.9	5.50	2.91
TSH	<4.5	11.88	7.84
	≥4.5	5.60	3.08

Bodnar et al. [10] noted that there is a twofold increase in maternal and neonatal vitamin D deficiency as maternal BMI increases from 22 to 34 kg/m^2. Josefson et al. [15] observed maternal serum 25-OHD was lower by 0.40 ng/ml for BMI higher by 1 kg/m^2 ($p<0.001$) in an adjusted model and concluded that maternal levels of 25-OHD are associated with maternal BMI.

The mean Vitamin D Levels in the two groups (TSH ≥ 4.5mIU/ml and TSH < 4.5mIU/ml) was 5.60±3.08ng/ml and 11.88±7.84ng/ml respectively. This difference was statistically highly significant ($p<0.001$) which shows Lower Vitamin D levels in hypothyroid patients (Table 3).

Dr. Mackawy et al. [13] 2013 observed Serum 25(OH) vitamin D was significantly lower in hypothyroid patients than in controls (t=11.128, P =0.000) and concluded patients with hypothyroidism suffered from hypovitaminosis D with hypocalcaemia that is significantly associated with the degree and severity of the hypothyroidism.

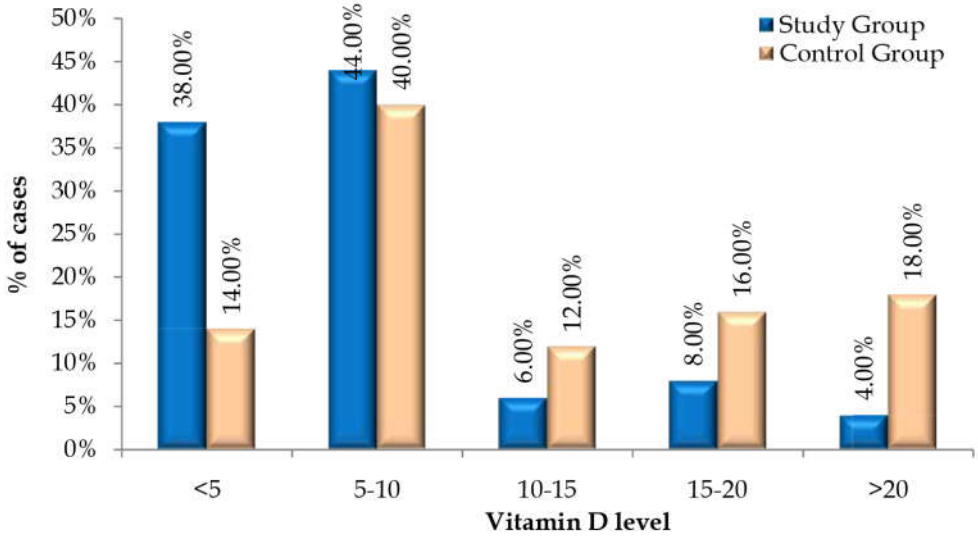
These findings supported the report that pre-eclamptic woman had higher incidence of biochemical hypothyroidism compared with normotensive pregnant woman (Kumar et al. [5] 2005 40% v/s 12.2%). These findings are in concordance with Kumar et al, Lao et al. [6]. On the other hand Khadim et al. [7], Qublan et al. [8] observed insignificant TSH value. 89% of the patients had a Vitamin D Level of ≤ 20ng/ml, indicating a high incidence of Vitamin D deficiency. 96% of the study group had Deficient vitamin D levels of ≤ 20ng/ml in comparison to 82% in the controls. 38% patients in the study group and 14% in the controls had very severe Vitamin D deficiency (<5ng/ml). 44% of the study group patients had severe vitamin D deficiency (5-10ng/ml) in comparison to 40% of the controls. Mild Vitamin D deficiency (10-20) was present in 14% of the study group and 28% of the controls. The difference in Vitamin D levels of both the groups was statistically significant ($p<0.01$).

Mahija Sahu et al. (2017) only 10% had suboptimal to optimal vitamin D level while 90% had vitamin deficiency. The hypertensive group had lower mean serum vitamin D level (9.06±5.20 ng/ml) as compared to normotensive group (13.67±7.24 ng/ml).

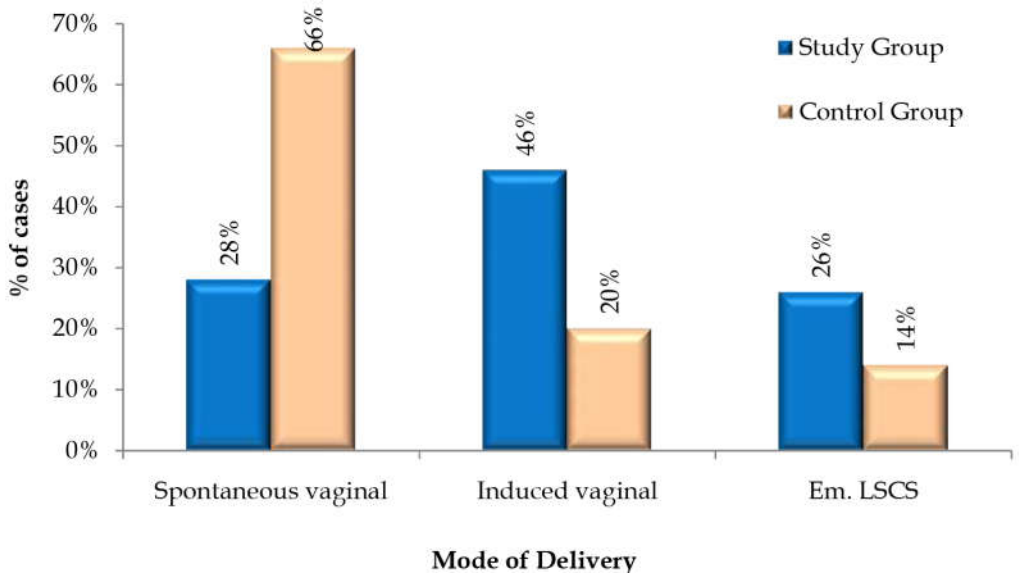
Madhu Jain et al in 2015 in Banaras, India did a study and found a high incidence of vitamin D deficiency (72.8%) in pregnancy. Recent studies have shown a strong association between vitamin D deficiency and preeclampsia with an odds ratio of 2.09 (95% CI 1.50-2.90)

Nasrin Khalessi (2015) mean maternal vitamin D level was 31.46 nmol/L. Forty eight percent of mothers had vitamin D deficiency, 27.5% had vitamin D insufficiency and 24.5% were normal.

In the control group 66% of the patients had spontaneous delivery in comparison to only 28% of patients in the study group. Emergency LSCS was done in 26% of patients in the study group, whereas in the controls Em. LSCS was required in only 14% of the patients ($p<0.01$). Patients that were admitted for elective LSCS were not included in the study.



Graph 1: Distribution of Vitamin D Levels in the patients



Graph 2: Distribution of patients according to the Mode of Delivery

Murat Bakacak et al. [12] 2015 the rate of cesarean section was found to be higher in pre-eclamptic and eclamptic patients (p<0.001).

The still birth rate in the study group was 20%, whereas it was only 2% in the controls. 12% of the newborns of the study group expired in nursery compared to 8% in the controls. 90% of the babies were stable and alive at the time of discharge in the control group which was higher as compared to 68% in the study group (Table 4).

The Mean maternal vitamin D levels in the group of patients with still born deliveries was 5.71±2.22ng/ml in comparison to 10.95±7.71ng/ml in the group of patients that had Live births. The difference was statistically highly significant (p<0.001), depicting poorer perinatal outcomes with lower vitamin D levels.

De-Regil et al. [11] attempted to review the evidence on vitamin D and stillbirth and uncovered one trial that had investigated the relationship with their results suggesting that vitamin D supplementation is unlikely to prevent stillbirth (RR = 0.17; 95% CI: 0.01, 4.06).

It can be seen that with increasing Maternal Vitamin D levels, the neonatal birth weight also increased. In case of VLBW babies (≤1.5kg), the mean Maternal vitamin D level was 6.19±1.73ng/ml, and for LBW (1.6-2.5kg) neonates it was 9.16±3.16ng/ml. Maternal Vitamin D level for neonates weighing >2.5kg was 12.76±3.91ng/ml (Table 6).

Table 4: Neonatal Outcome of the Study Population

Condition of Baby at Discharge	Study Group		Control Group		Total	
	No.	%	No.	%	No.	%
Discharged with mother	34	68%	45	90%	79	79%
Still Birth	10	20%	1	2%	11	11%
Expired in Nursery	6	12%	4	8%	10	10%
Total	50	100%	50	100%	100	100%

p<0.01 (S)

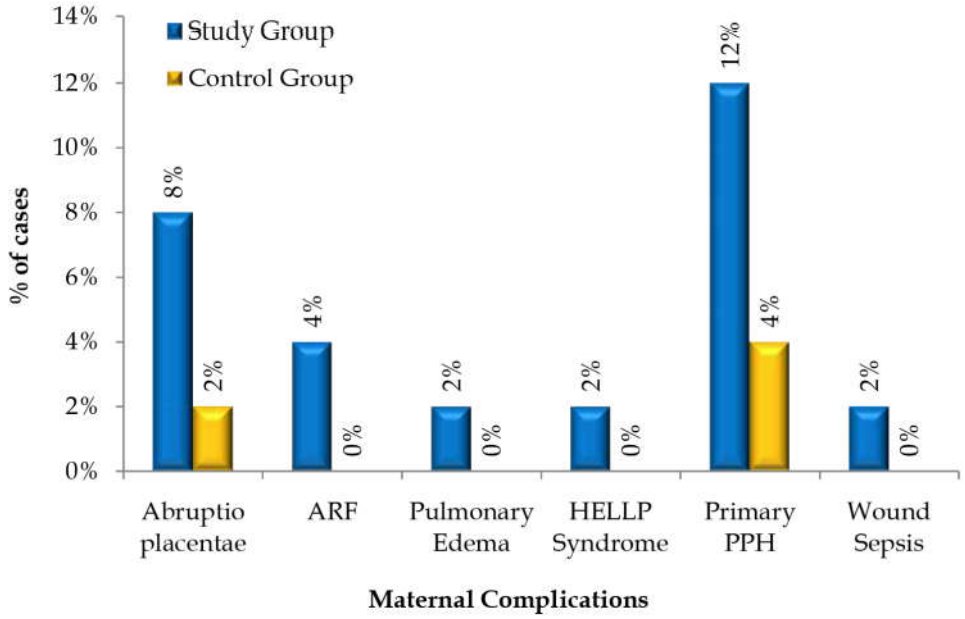
Table 5: Perinatal Outcome Associated with Maternal Vitamin D levels

Live/ Still Birth	Vitamin D levels of mother	
	Mean	SD
Live	10.95	7.71
Still Birth	5.71	2.22
Total	10.38	7.49

p<0.001 (HS)

Table 6: Association of Neonatal Birth Weight and Maternal Vitamin D Levels

Birth Weight (Kg)	Vitamin D levels of mother	
	Mean	SD
≤1.5	6.19	1.73
1.6-2.5	9.16	3.16
>2.5	12.76	3.91



Graph 3: Maternal Complications

Yuan-Hua Chen et al. [14] in their studies in relation to vitamin D levels in the cohort of 3658 patients and birth weight of their newborns showing threshold of about 40 ng/ml for normal birth weight. With addition of 1 ng/ml of 25 (OH) D in maternal serum will increase the birth weight by 23.66 gms, showing the close association between maternal serum vitamin D and birth weight.

Nasrin Khalessi [16] 2015 mean maternal vitamin D (vitamin D) level was 31.46 nmol/L. Mean maternal vitamin D level of LBW neonates was lower than other group; 25.05 vs. 38.13 (p = 0.001).

In the Study group 30% of the patients had complications in comparison to only 6% of the patients in the control group. 8% of the patients in the study group developed abruptio placentae whereas this number was only 2% in the controls. In the study group, ARF occurred in 4% of the patients, pulmonary edema occurred in 2% of the patients, HELLP Syndrome occurred in 2% of the patients and wound sepsis occurred in 2% of the patients. In comparison to the study group, in the controls none of the patients had these complications. Primary PPH occurred in 12% of the patients in the study population in comparison to 4% of the patients in the controls. This data can be interpreted as higher maternal complications being present in the study group as compared to the control group. No maternal death occurred in any of the groups (Graph 3).

Conclusion

Maternal Serum Vitamin D level <20 ng/ml was seen to be constantly associated with an increased risk of preeclampsia and poorer feto-maternal outcome. If we consider maternal serum Vitamin D deficiency to be a modifiable risk factor for pregnancy induced hypertension then we should include Serum Vitamin D level estimation in routine antenatal tests and if that is not feasible, routine Vitamin D supplementation should be given in all pregnant women in a low resource developing country like India. Patient should be advised to increase the intake of vitamin D rich foods like fish, eggs and milk, and

to increase sun exposure at noon time as the UV B rays (290-320 nm) responsible for Vitamin D production are highest during this time.

The present study can serve as a starting point for larger randomized controlled studies with more number of patients so as to validate the results obtained so far.

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