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Original Article

Correlation of Vitamin D Levels in Normotensive and Preeclamptic Patients in Labor

M. S. Krishnaveni

Assistant Professor, Department of OBG, Kakatiya Medical College, CKM Hospital, Warangal, Telangana, India

Abstract

Objective: The objective of the study was to evaluate maternal Vitamin D levels in term normotensive and preeclamptic patients in labor.

Materials and Methods: This was a case–control study carried out in the Department of Obstetrics and Gynaecology, CKM Hospital, Warangal. A total of 100 patients were divided into two equal groups (control and study groups of 50 each). Control group had women with singleton uncomplicated, term normotensive pregnant women in labor while the study group composed of term preeclamptic women in labor. A blood sample was collected by venepuncture. Serum 25 OHD (Serum 25 hydroxyl Vitamin D) concentrations were determined.

Results: Vitamin D levels were <15 ng/ml in 38 patients in the case group compared to 14 patients in the control group. Moreover, it was >15 ng/ml in 36 patients in the control group compared to 12 patients in the case group. This comparison of the Vitamin D (ng/ml) between the two groups shows that Vitamin D (ng/ml) is lower in case group which is statistically significant with $P < 0.001$. Comparison of Vitamin D based on severity of preeclampsia showed that as the severity of disease increases the vitamin level decreases which are evident from the comparison between preeclamptic and eclampic patient's Vitamin D levels which was statistically significant with $P < 0.001$.

Conclusion: From this study, Vitamin D deficiency is an independent modifiable risk factor for development of preeclampsia.

Key words: Preeclampsia, Vitamin D deficiency, Vitamin D

INTRODUCTION

Hypertensive disorders represent the most common medical complication of pregnancy affecting between 7 and 15% of all gestations and account for approximately a quarter of all antenatal admissions. According to the World Health Organization's (WHO) systemic review on maternal mortality worldwide, hypertensive disease remains a leading cause of direct maternal mortality.[1]

Hypertensive disorders are responsible for not only maternal deaths but also substantial morbidity for the pregnant women. Long-term impact of hypertension in pregnancy in the form of chronic hypertension and increased lifetime cardiovascular risk is also present. Hypertensive disorders also carry a risk for the baby.[1]

Hypertension and/or proteinuria are the leading single identifiable risk factor in pregnancy associated with stillbirth. Preeclampsia is strongly associated with fetal growth restriction, low birth weight, spontaneous or iatrogenic preterm delivery, respiratory distress syndrome, and admission to neonatal intensive care.[1]

Poor Vitamin D status, based on low circulating 25-hydroxy-Vitamin D (25 OHD) concentration, has been described in pregnant women in several countries. A lack of Vitamin D during pregnancy results in poor fetal and infant bone mineralization that may persist into later life. Low maternal Vitamin D has also been associated with an increased risk of preeclampsia. Vitamin D has direct influence on molecular pathways proposed to be important in the pathogenesis of preeclampsia. Serum 25OHD levels are associated with cardiovascular disease risk factors also. The placenta produces and responds to Vitamin D where Vitamin D functions as a modulator

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Corresponding Author: M. S. Krishnaveni, CKM Hospital, Warangal, Telangana, India.

of implantation, cytokine production, and the immune response to infection.

Low Vitamin D levels have been associated with a wide range of adverse maternal and child health outcomes. One of them is preeclampsia according to few studies. Preeclampsia is a pregnancy specific syndrome that affects approximately 3–7% of first pregnancies.[1]

Several prospective studies have suggested that Vitamin D deficiency predisposes individuals to increased risk of incident hypertension, IHD, sudden cardiac death, or heart failure.

There is conflicting evidence whether hypovitaminosis D in pregnancy is associated with hypertension and preeclampsia.

Objective

The objective of the study was to evaluate maternal Vitamin D levels in normotensive and preeclamptic patients in labor.

Vitamin D insufficiency affects almost 50% of the population worldwide.[2] An estimated 1 billion people worldwide, across all ethnicities and age groups, have a Vitamin D deficiency (VDD).[2-4] This pandemic of hypovitaminosis D can mainly be attributed to lifestyle and environmental factors that reduce exposure to sunlight, which is required for ultraviolet-B (UVB)-induced Vitamin D production in the skin. Black people absorb more UVB in the melanin of their skin than do white people and, therefore, require more sun exposure to produce the same amount of Vitamin D.[5]

The high prevalence of Vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population.[6] Emerging research supports the possible role of Vitamin D against cancer, heart disease, fractures and falls, autoimmune diseases, influenza, type-2 diabetes, and depression. Many health-care providers have increased their recommendations for Vitamin D supplementation to at least 1000 IU.

A meta-analysis published in 2007 showed that Vitamin D supplementation was associated with significantly reduced mortality.[7]

Biology of the Sunshine Vitamin

Vitamin D is unique because it can be made in the skin from exposure to sunlight. Vitamin D exists in two forms. Vitamin D2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms.[4,8,9] UVB light from the sun strikes the skin, and humans synthesize Vitamin D3, so it is the most – natural form. Human beings do not make Vitamin D2, and most oil-rich fish such as salmon, mackerel, and herring contain Vitamin D3. Vitamin D (D represents D2, or D3, or both) that is ingested is incorporated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood. Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver by the Vitamin D-25-hydroxylase (25-OHase) to 25(OH)D.[4] However, 25(OH)D requires a further hydroxylation in the kidneys by the 25(OH)D-1-OHase (CYP27B1) to form the biologically active form of Vitamin D 1,25(OH)2D. 1,25(OH)2D stimulates intestinal calcium absorption. Without Vitamin D, only 10–15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40% and 80%, respectively.[4]

Vitamin D receptor (VDR) is present in most tissues and cells in the body. 1,25(OH)2D has a wide range of biological actions, such as inhibition of cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production. The local production of 1,25(OH)2D may be responsible for regulating up to 200 genes 19 that may facilitate many of the pleiotropic health benefits that have been reported for Vitamin D.[4,8]

Vitamin D in Pregnancy

Introduction

Vitamin D has an increasingly recognized repertoire of non-classical actions such as promoting insulin action and secretion, immune modulation, and lung development. It, therefore, has the potential to influence many factors in the developing fetus. There is little information on Vitamin D intake in pregnancy and lactation and few studies on clinical outcomes. Some have suggested that the requirement for Vitamin D in these women may be up to 6000 iu/day 21 and the ideal Vitamin D regimen to prevent and treat Vitamin D insufficiency *in utero* is unknown.

VDD

Vitamin D and its active metabolite 1,25dihydroxyvitamin D (1,25(OH)2D) have classical actions of calcium balance and bone metabolism. Without sufficient 1,25(OH)2D, the intestine cannot absorb calcium and phosphate adequately, which leads to secondary hyperparathyroidism and a lack of new bone mineralization (rickets in children and osteomalacia in adults). Rickets is a childhood Vitamin D insufficiency and usually develops many months after delivery. However, the neonate is at risk of hypocalcemic tetany consequent on maternal hypovitaminosis D. Calcium levels are normal in utero when maternal Vitamin D is insufficient. However, when maternal calcium

delivery is interrupted at birth, the neonate may develop hypocalcaemia. While the developing fetus requires approximately 30 g of calcium, the maternal gut adapts and can overcome some Vitamin D insufficiency with increased calcium transport. VDD is common in northern Europe, especially in women with pigmented skin. In the general adult population, reduced Vitamin D concentrations are found in obese subjects. Prepregnancy obesity has been associated with lower levels of Vitamin D in both pregnant women and their neonates; 61% of women who were obese (body mass index [BMI] ≥30) before pregnancy were found to be Vitamin D deficient, compared to 36% of women with a prepregnancy BMI of less than.

Physiology

There are two forms of Vitamin D. Vitamin D3 (cholecalciferol) is produced from the conversion of 7-dehydrocholesterol in skin and Vitamin D2 (ergocalciferol) is produced in mushrooms and yeast. The biologically active form of Vitamin D is 1,25(OH)2D. This requires hydroxylation of Vitamin D in the liver to 25(OH) D (25-hydroxyvitamin D), which then undergoes renal hydroxylation to form 1,25(OH)2D. Although 25(OH)D has low biological activity, it is the major form of circulating Vitamin D. Serum 25(OH)D concentrations are generally thought to reflect nutritional status. Production of 1,25(OH)2D in the kidney is tightly regulated by plasma parathyroid hormone (PTH) as well as serum calcium and phosphate levels. The interaction of 1,25(OH)2D with nuclear VDRs influences gene transcription. Nuclear receptors for 1,25(OH)2D are present in a range of tissues including bone, intestine, kidney, lung, muscle, and skin. Similar to steroid hormones, 1,25(OH)2D acts through signal transduction pathways linked to VDRs on cell membranes. Major sites of action include intestine, bone, parathyroid, liver, and pancreatic beta cells. Its biological actions include increases in intestinal calcium absorption, transcellular calcium flux, and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle. The biological effects of 1,25(OH)2D are diverse. It inhibits PTH secretion and adaptive immunity, while promoting insulin secretion and innate immunity. It also inhibits cell proliferation and stimulates their differentiation. The largest source of Vitamin D in adults is synthesis from solar radiation; ½ h of sunlight delivers 50 000 iu of Vitamin D with white-complexioned skin. Dietary intake of Vitamin D makes a relatively small contribution to overall Vitamin D status as there is little Vitamin D that occurs naturally in the food supply. Melanin absorbs UVB from sunlight and diminishes cholecalciferol production by at least 90%. Dietary Vitamin D is absorbed from the intestine and circulates in plasma bound to a Vitamin D binding protein. Preeclampsia and neonatal hypocalcemia are the most prevalent complications of maternal hypocalcaemia and are clearly associated with substantial morbidity. A statistical association of glucose intolerance and hypovitaminosis D has been demonstrated. Maternal Vitamin D is important to fetal bone development. Fetal lung development and neonatal immune conditions such as asthma may relate in part to maternal Vitamin D levels. Although it is not clear whether maternal Vitamin D supplementation will prevent these conditions, a strategy for supplementation and treatment of maternal VDD is proposed.

Maternal and fetal complications

Preeclampsia

There is conflicting evidence whether hypovitaminosis D in pregnancy is associated with hypertension and preeclampsia. In three studies, women who developed preeclampsia were found to have lower levels of Vitamin D than women who did not 26–28 with levels <50 nmol/l associated with a five-fold increased risk of severe preeclampsia.

Low levels in the first half of pregnancy were related to the risk of developing preeclampsia and the neonates of these mothers had a two-fold increased risk of having Vitamin D levels <37.5 nmol/l (VDD).

In a case–control study, women with severe preeclampsia before 34 weeks of gestation had reduced levels of Vitamin D compared to control women. Furthermore, women with early-onset severe preeclampsia and a small-for-gestational-age (SGA) infant had significantly lower Vitamin D levels than those with early-onset severe preeclampsia but non-SGA infants.

However, many studies have shown a weak or no relationship between Vitamin D and hypertensive disorders in pregnancy.

A Canadian study showed that women with low circulating maternal Vitamin D levels are more likely to have hypertension in pregnancy in the univariate analysis, but not the multivariate analysis.

Another study failed to show any association between Vitamin D levels and the development of preeclampsia, gestational hypertension, or preterm birth.

A similar study from the USA also failed to demonstrate an association between maternal first trimester Vitamin D levels and the subsequent development of preeclampsia after controlling for BMI.

However, two meta-analyses, including a meta-analysis of 31 studies, demonstrated that Vitamin D insufficiency was associated with preeclampsia and SGA infants.

Low birth weight

Maternal Vitamin D levels have been shown to positively correlate with birth weight centile.

In a study from Holland, women with VDD had a 2.4-fold increased risk of having an SGA baby.

Another study found that maternal Vitamin D levels of <37.5 nmol/l in the first half of pregnancy were associated with an adjusted odds ratio of 7.5 for SGA infants in white women, but not in black women.

Australian researchers found that mean birth weight was 200 g lower ($P < 0.001$) in babies of Vitamin D deficient mothers.

However, other studies demonstrated no relationship between maternal Vitamin D levels in the first trimester and birth weight but did demonstrate that low Vitamin D levels in late pregnancy were associated with reduced intrauterine long bone growth and lower gestational age at delivery.

Impaired glucose tolerance in pregnancy

Hypovitaminosis D is associated with impaired glucose tolerance and diabetes in the general population. However, the evidence for an association between low Vitamin D levels and gestational diabetes mellitus (GDM) is conflicting. Low concentrations of 25(OH)D have been related to the risk of developing type II diabetes mellitus (T2DM) through effects on insulin secretion and insulin sensitivity.

However, not all studies support these findings. The Third National Health and Nutrition Examination Survey (NHANES III) did not demonstrate an association between 25(OH)D levels and diabetes or insulin resistance in African Americans, in contrast to Caucasians and Mexican Americans.

In another study of European Caucasian subjects, insulin secretion and action were not associated with levels of 25(OH)D.

It is vital that such studies are controlled for obesity, a risk factor itself for VDD. GDM is considered to share the same pathogenesis as T2DM and similar associations between 25(OH)D and the development of GDM have been sought. Maternal 25(OH)D concentrations have been related to the risk of developing GDM in various cohorts.

Depending on the diagnostic criteria used, it has been suggested that GDM complicates up to 16% of pregnancies, although the true incidence can be much greater in some ethnic groups.

There are some data to suggest that the association between 25(OH)D levels and GDM risk is specific to ethnicity. In a majority non-Hispanic white population, 25(OH)D concentrations at 16 weeks of gestation were significantly lower in GDM subjects than in controls, whereas no association was found in Indian mothers where 25(OH) D concentrations were measured at 30 weeks of gestation.

Some studies have investigated more than one ethnic group using statistical techniques to correct for the effect of ethnicity, but none have been designed to describe the association in specific ethnic populations.

Conversely, a well-conducted study has found no association between maternal 25(OH)D and the development of GDM.

A meta-analysis of 31 studies demonstrated vitamin D insufficiency was associated with a higher risk of GDM.

Other complications

VDD (< 37.5 nmol/l) has been associated with a four-fold increased risk of primary cesarean section (caesarean section performed for the 1st time), 52 although this has not been demonstrated in all studies.

VDD is also associated with bacterial vaginosis in pregnant women.

In conclusion, hypovitaminosis D may be associated with hypertension, preeclampsia, and increased cesarean section rates. There are no randomized trials showing that Vitamin D supplementation alters these putative risks.

Neonatal hypocalcemic seizures

Neonatal Vitamin D levels are correlated with those of their mother, with maternal VDD increasing the risk of neonatal VDD.

In an Australian study, hypovitaminosis D was found in 15% of pregnant women and 11% of neonates.

VDD is a major cause of hypocalcemic seizures in neonates and infants.

Hypocalcemia is not uncommon in neonates and is a potentially severe problem.

Mothers of babies who suffer hypocalcemic seizures are more likely to be VDD (85%) than mothers of babies who do not (50%).

In another study from Egypt, all mothers of babies with hypocalcemic seizures had severe VDD.

Maternal VDD is a common, and potentially preventable, cause of neonatal hypocalcaemia. This is especially common in South Asian women.

Skeletal development and growth

Hypovitaminosis D is associated with impaired growth and bone development in the fetus.

Evidence is accruing to show that less profound maternal 25(OH)D insufficiency may lead to suboptimal bone size and density after birth without overt rachitic change.

This is likely to lead to an increased risk of osteoporotic fracture in later life.

A retrospective cohort study showed that children who had received supplements with Vitamin D in the 1st year of life had a significant increase in femoral neck bone density at the age of 8 years compared to the group that did not receive supplements. In a UK mother–offspring cohort, 31% of the mothers had circulating concentrations of 25(OH)D in late pregnancy of 27–50 nmol/l.

There was a positive association between maternal 25(OH) D concentration in late pregnancy and whole body bone mineral content and density, assessed using dual energy X-ray absorptiometry, in the offspring at 9 years of age. Furthermore, maternal UVB exposure and Vitamin D supplementation were associated with the bone mass of the child ($P < 0.05$), while lower levels of umbilical-venous calcium were also associated with lower childhood bone mass, 58 suggesting a possible role for placental calcium transport in this process. In addition, maternal UVB exposure during pregnancy was positively associated with whole body bone mineral content in the off spring at the age of 9 years in the Avon Longitudinal Study of Parents and Children, 59 although later analysis does not confirm these data.

Similar findings have come from another UK cohort.

The Southampton Women's Survey, in which neonatal bone area and bone mineral content were reduced in the female offspring of mothers who had 25(OH)D concentrations <33 nmol/l in late pregnancy.

These findings of altered neonatal bone mass have been confirmed by a Finnish mother–offspring cohort in which babies born to mothers with circulating 25(OH)D status belo the median (42.6 nmol/l) had reduced tibial bone mineral content and cross-sectional area, measured by peripheral quantitative computed tomography.

In a follow-up study, a deficit in tibial cross-sectional area was still observed at 14 months' follow-up, 62 despite the low Vitamin D group catching up with the other group for the bone mineral content. Evidence that 25(OH)D-related changes may be detectable early in gestation has come from the Southampton Women's Survey.

In this cohort, fetal distal femoral metaphyseal cross-sectional area was increased relative to femur length at 19 and 34 weeks of gestation in those babies whose mothers had low levels of circulating 25(OH)D, changes reminiscent of those seen in postnatal rickets. These findings suggest that the adverse consequences of maternal VDD for the offspring are manifest early in pregnancy. There are no data from randomized controlled trials to show benefit from maternal Vitamin D supplementation in terms of fetal or longer term growth of the child.

Fetal lung development and childhood immune disorders

Low maternal Vitamin D intake in pregnancy is associated with wheeze and asthma in the off spring.

Low cord blood 25(OH)D concentrations have been associated with respiratory syncytial virus bronchiolitis and respiratory infections.

There are plausible physiological mechanisms for an association between prenatal Vitamin D status and immune development. The metabolite 1,25(OH)2D has been shown in animal and *in vitro* models to have an immune-modulatory role and low levels of neonatal Vitamin D have been linked to childhood asthma.

Maternal Vitamin D supplementation is associated with cord blood gene expression of tolerogenic immunoglobulin such as immunoglobulin-like transcripts 3 and 4 (ILT3 and ILT4).71 Cord blood 25(OH)D is correlated with mononuclear cell release of IFN-γ and hence Th1 cell development.

More research is needed on the potential association between maternal Vitamin D in fetal lung development and childhood allergy; there are ongoing studies investigating long-term neonatal putative benefits of adequate maternal Vitamin D.

Screening for VDD in pregnancy

There are no data to support routine screening for VDD in pregnancy in terms of health benefits or cost effectiveness. There is an argument that some groups of women who are pregnant should have a screening test: for example, on the basis of skin color or coverage, obesity, risk of preeclampsia, or gastroenterological conditions limiting fat

absorption. As the test is expensive, offering it to all at-risk women may not be cost effective compared to offering universal supplementation, particularly as treatment is regarded as being very safe. At present, there are no data to support a strategy of measurement followed by treatment in the general female population.

Measurement of Vitamin D in a hypocalcemic or symptomatic woman as part of their management continues to be applicable. This includes women with a low calcium concentration, bone pain, gastrointestinal disease, alcohol abuse, a previous child with rickets, and those receiving drugs which reduce Vitamin D.

Supplementation and treatment in pregnancy

Daily Vitamin D supplementation with oral cholecalciferol or ergocalciferol is safe in pregnancy. The 2012 recommendation from UK Chief Medical Officers and NICE guidance state that all pregnant and breastfeeding women should be informed about the importance of Vitamin D and should take 10 μg of Vitamin D supplements daily.

Particular care should be taken over high-risk women. The recommendations are based on the classical actions of Vitamin D, although many of the non-classical actions of Vitamin D may be beneficial. As mentioned above, the review and meta-analysis by Aghajafari *et al*. found associations between Vitamin D insufficiency and risk of gestational diabetes, preeclampsia, bacterial vaginosis, and SGA infants.

Of course, this does not necessarily demonstrate that correction during pregnancy will reduce these risks.

Three categories of Vitamin D supplementation are recommended.

1. In general, Vitamin D 10 μg (400 units) a day are recommended for all pregnant women in accord with the national guidance. This should be available through the Healthy Start Programme
2. High-risk women are advised to take at least 1000 units a day (women with increased skin pigmentation, reduced exposure to sunlight, or those who are socially excluded or obese).

The RCOG has highlighted the importance of addressing suitable advice to these women. Seventy-eight women at high risk of preeclampsia are advised to take at least 800 units 79 a day combined with calcium.

Vitamin D may be inappropriate in sarcoidosis (where there may be Vitamin D sensitivity) or ineffective in renal disease. Deficient renal 1-α hydroxylation necessitates the use of active Vitamin D metabolites, such as 1α-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol. Specialist medical advice should be sought in such cases. The limitation to therapy compliance mostly relates to the calcium which has a side effect of tasting of chalk, rather than the vitamin D element of oral therapy. It is often more appropriate to give Vitamin D alone for patient acceptability. However, this is limited by the availability of suitable agents; Vitamin D cannot be prescribed at low doses without calcium. 800-unit formulations of cholecalciferol without calcium are available. There may be particular benefits of Vitamin D/calcium supplementation in women at risk of preeclampsia.

Treatment

For the majority of women who are deficient in Vitamin D, treatment for 4–6 weeks, either with cholecalciferol 20 000 iu a week or ergocalciferol 10 000 iu twice a week, followed by standard supplementation, is appropriate. For women who require short-term repletion, 20 000 iu weekly appears to be an effective and safe treatment of VDD. A daily dose is likely to be appropriate to maintain subsequent repletion (1000 iu daily). In adults, very high doses of Vitamin D (300 000–500 000 iu intramuscular [IM] bolus) may be associated with an increased risk of fractures and such high doses are not recommended in pregnancy. A 2011 study demonstrated that supplemental doses of 4000 iu cholecalciferol a day were safe in pregnant women and most effective compared to the lower doses.

A comment piece in the lancet argued that routine supplementation of Vitamin D should be reserved for at-risk women rather than for all women.

This was on the basis of a large prospective cohort study showing no association between maternal serum Vitamin D levels and bone mineral content in the children. However, large, this was not randomized, did not consider supplementation and only looked at one indication.

Safety of Vitamin D

In pregnancy, there is enhanced intestinal calcium absorption. Vitamin D toxicity is manifested through hypercalcemia and hypercalciuria. Therefore, there is a hypothetical concern that when secondary hyperparathyroidism follows VDD, calcium given with Vitamin D may be associated with temporary hypercalcemia. However, this is self-limiting due to the associated hungry bone and has not been demonstrated to represent a clinical problem.

Opinion

Treatment of VDD women and Vitamin D supplementation is safe and is recommended for all women who are pregnant or breastfeeding. Low Vitamin D concentrations are present

in a significant proportion of the population. Women with pigmented or covered skin, obesity and immobility are at a higher risk. Low Vitamin D concentrations have been associated with a wide range of adverse maternal and offspring health outcomes in observational epidemiological studies. However, despite a dearth of interventional evidence supporting supplementation/treatment of Vitamin D in randomized controlled trial settings, it is generally accepted that supplementation/treatment is not harmful and may have some significant short- and long-term health benefits. Further research should focus on the potential benefits and optimal dosing of Vitamin D use in pregnancy.

Vitamin D and Preeclampsia

Vitamin D is a seco-steroid pro-hormone which, for biological activation, undergoes two successive hydroxylations, first to 25-hydroxyvitamin D (25(OH)D), a nutritional biomarker for Vitamin D status, and second to the active hormonal metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D), that is, calcitriol. Calcitriol exerts the hormonal action through binding to nuclear VDRs, which are present throughout the body, including pregnancy-specific tissues such as the placenta and uterine placental bed (decidua). The placenta and decidua as well as other important target cells such as immune and endothelial cells have the molecular machinery for local production of calcitriol.

Preeclampsia is thought to originate in early pregnancy when the maternal immune system limits placental citriol can be considered a pregnancy-supporting factor that could work through several mechanisms to reduce preeclampsia risk, including a direct influence of calcitriol on implantation, placental invasion, and angiogenesis. It is also believed to be important in directing immune responses by dendritic cells and macrophages at the fetal-placental interface as well as immunological adaptation by the mother to reduce the risk of infection and inflammation.

Compared to normal pregnancies, Vitamin D metabolism is markedly altered in preeclampsia. This may be due to reduced placental 1α-hydroxylase activity resulting in lower circulating calcitriol concentrations compared to normotensive or chronically hypertensive pregnant women. Vitamin D status is reportedly lower in preeclamptic mothers at the time of diagnosis, but also before disease onset in some studies [Table 1].

MATERIALS AND METHODS

Source of Data

The study was conducted in pregnant patients in labor room, diagnosed as preeclampsia and normotensive patients in first stage of labor, of CKM Hospital, Warangal, between September 2019 and February 2020.

Method of Collection of Data (Including Sample Procedure if Any)

Study type: Comparative case–control study.

Inclusion Criteria

Case	Control
Age : 18–35 years of age	Age: 18–35 years of age
Singleton	Singleton
Preeclamptic patients in labor (defined as BP ≥140/90 mm Hg after 20 weeks of gestation and proteinuria ≥1+dipstick)	Uncomplicated Normotensive patients in labor

Exclusion Criteria

The following criteria were excluded from thr study:

- Patients who have taken Vitamin D prophylaxis.
- Patients with any other co-morbidities affecting Vitamin D levels.

METHODOLOGY

The women were included in the study on the basis of the inclusion and exclusion criteria were asked to give their consent for the test to be done for the purpose of this study.

The women were first screened for preeclampsia and accordingly included into _Case "and _Control" groups.

A blood sample was collected by venepuncture. Serum 25 OHD (serum 25 hydroxyl Vitamin D) concentrations were determined.

VDD defined as 25(OH)D levels below 15 ng/ml. (37.5 nmol/l).

Sample Size Estimation

Sample size is 100. The sample size was determined using the formula:

$n = 2(Z\alpha+Z\beta)^2\sigma^2/d^2$.

where,

n = sample size.

$Z\alpha = 1.96$ at 95% confidence interval.

$Z\beta = 1.2816$, at 90% power.

d = x1 - x2.

$\sigma = \sqrt{\sigma 1^2 + \sigma 2^2}/2$.

Cases – 50 patients diagnosed as preeclampsia in labor.

Controls – 50 normotensive patients in labor.

Statistical Methods

Independent –*t* test.

Pearson's Chi-square test.

OBSERVATION AND RESULTS

Comparison of the AGE between the two groups shows that AGE is higher in control group which is statistically not significant with $P = 0.542$. Hence, the first demographic factor age is comparable in cases and controls.

Comparison of the parity between the two groups shows that parity is statistically not significant with $P = 0.480$.

4B) Demographic factor – Period of Gestation

Comparison of the POG (Wks) between the two groups shows that POG (Wks) is higher in control group with a t value of 2.652 and is statistically significant with $P = 0.009$. The difference in the period of gestation in the cases and control was significant might be because of induction of preeclamptic patients in the earlier gestation than normotensive patients.

The maternal Vitamin D levels in the study group (cases) were relatively lower with a median value of 11.12 ng/ml as compared to 18.12 ng/ml in the control group. This difference in the median maternal Vitamin D levels of both the groups was found to be statistically significant with $P < 0.001$.

About 42% of the patients in the study group were found to be severely Vitamin D deficient (Vitamin D levels <10 ng/ml) as compared to 6% of the patients in the control group. This difference in the number of patients with severe VDD among the two groups was also statistically significant with $P < 0.001$

Vitamin D levels were <15 ng/ml in 38 patients in the case group compared to 14 patients in the control group. Moreover, it was >15 ng/ml in 36 patients in the control group compared to 12 patients in the case group. This comparison of the Vitamin D (ng/ml) between the two groups shows that Vitamin D (ng/ml) is lower in case group which is statistically significant with $P < 0.001$.

Comparison of Vitamin D based on severity of preeclampsia showed that as the severity of disease increases the vitamin level decreases which are evident from the comparison between preeclamptic and eclampic patient's Vitamin D levels which was statistically significant with $P < 0.001$.

DISCUSSION

In our study, age and parity did not effect the Vitamin D levels. Hence, it is an independent risk factor for development of preeclampsia.

In our study, the difference in the period of gestation in the cases and control was significant might be because of induction of preeclamptic patients in the earlier gestation than normotensive patients.

Parameters	*P* value
Age	0.542
Parity	0.480
Gestational age	0.009

For this study, 100 women were selected and divided into two groups, the control group comprised 50 normotensive pregnant women, and the study group is comprised 50 diagnosed PE cases.

In our study, the cutoff for VDD taken was 15 ng/ml. Study done by Ringrose *et al.* has taken a cut off of 50 nmol/l (20 ng/ml).

In the contrast study by Shand *et al.*, the serum 25OHD concentration levels at the cutoff points of <37.5(15 ng/ml), <50, or <75 nmol/l.

Sample size	Cases		Controls
Robinson *et al.* (2010)	150	50	100
Ringrose *et al.* (2011)	187	78	109
Gupta *et al.* (2016)	100	50	50
Our study	100	50	50

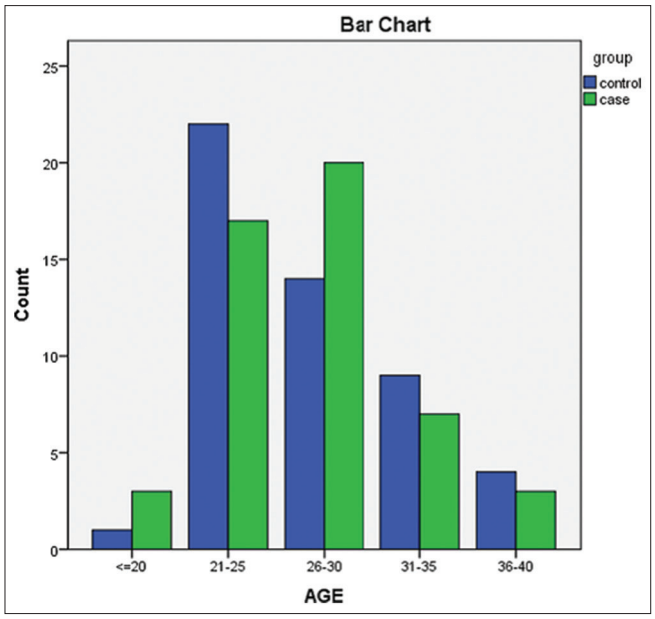
In the present study, the serum Vitamin D levels were relatively lower with a median value of 11.12 ng/ml as compared to 18.12 ng/ml in the control group. This difference in the median maternal Vitamin D levels of both the groups was found to be statistically significant with $P < 0.001$. The supporting studies with our study were by Bodnar *et al.*, Ringrose *et al.*, Gupta *et al.*, and contrary to our study, were studies done by Shand *et al.*, Powe *et al.*

Study	Significance *P* value
Bodnar *et al.* (2007)	<0.05
Ringrose *et al.* (2011)	0.046
Shand *et al.* (2010)	0.21, 0.41
Gupta *et al.* (2016)	<0.001
Our study	<0.001

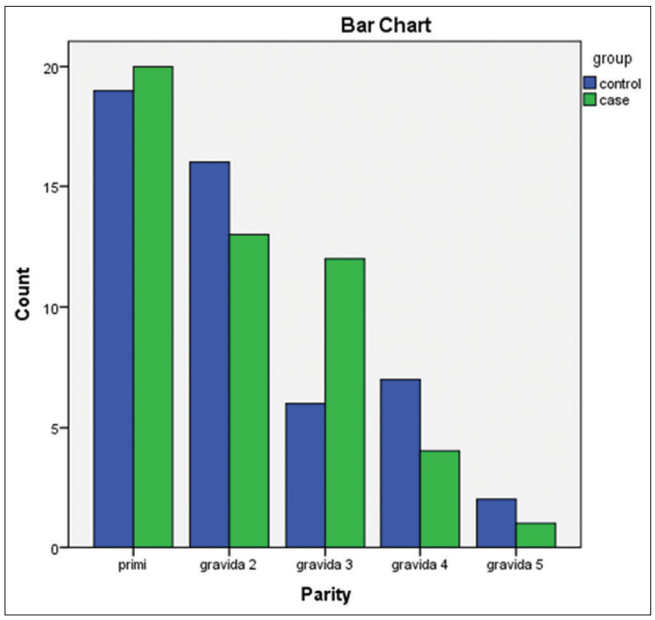
However, the limitations of this study were small sample size, and selection bias in selecting significant number of eclamptic patients.

Table 1: Number of cases and controls

Groups	Number
Cases	50
Controls	50



AQ9 **Figure 1:** Demographic factors – age



AQ9 **Figure 2:** Demographic factor – parity

SUMMARY

Hypertensive disorders represent the most common medical complication of pregnancy affecting between 7 and 15% of all gestations and account for approximately a quarter of all antenatal admissions.

There is conflicting evidence whether hypovitaminosis D in pregnancy is associated with hypertension and preeclampsia.

Hence, this study deals with the levels of Vitamin D in preeclamptic patients compared to normotensive patients.

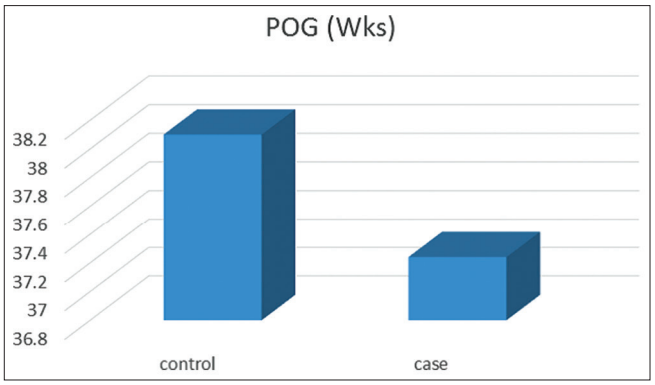


Figure 3: Demographic factor – period of gestation AQ9

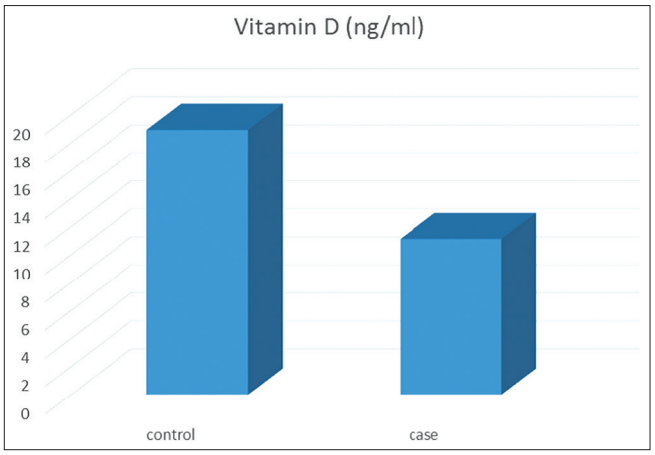


Figure 4: Vitamin D correlation AQ9

The study was conducted in pregnant patients in labor room, diagnosed as preeclampsia and normotensive patients in first stage of labor, of CKM Hospital, Warangal, between September 2019 and February 2020.

The women were first screened for preeclampsia and accordingly included into _Case "and _Control" groups. A blood sample was collected by venepuncture between of gestation. Serum 25 OHD (serum 25 hydroxyl Vitamin D) concentrations were determined. VDD defined as 25(OH) D levels below 15 ng/ml.

Cases – 50 patients diagnosed as preeclampsia in labor. Controls – 50 normotensive patients in labor.

Age, parity demographic features were comparable in both case and control groups. Period of gestation was higher in the control group might be because of induction of preeclamptic patients in the earlier gestation than normotensive patients.

Vitamin D levels were <15 ng/ml in 38 patients in the case group compared to 14 patients in the control group. Moreover, it was >15 ng/ml in 36 patients in the control group compared to 12 patients in the case group. This

comparison of the Vitamin D (ng/ml) between the two groups shows that Vitamin D (ng/ml) is lower in case group which is statistically significant with $P < 0.001$.

Comparison of Vitamin D based on severity of preeclampsia showed that as the severity of disease increases the vitamin level decreases which are evident from the comparison between preeclamptic and eclampic patient's Vitamin D levels which was statistically significant with $P < 0.001$.

CONCLUSION

From this study, VDD is an independent modifiable risk factor for development of preeclampsia.

Future research is needed to determine the effect of Vitamin D supplementation on the incidence of gestational hypertension and preeclampsia.

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Author Queries???
AQ9: Kindly cite Figures 1-4 in the text part