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Role of Vitamin-D Supplementation In Prevention of Preeclampsia

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Objectives:- *To assess whether Vitamin-D supplements given to women during pregnancy can safely improve maternal and neonatal outcome by preventing Preeclampsia.*
Materials And Methods: *This is an interventional and prospective study by including primi and multi gravida attending antenatal clinic-Dept. of OBG, Gandhi hospital, Secunderabad. Cases-50 pregnant women supplemented with Vit-D during antenatal period.Age and gravida matched controls-50 pregnant women not supplemented with Vit-D..For all the woman included in the study, that is, cases and controls vitamin- d level was estimated twice, once in 1st trimester and again in 3rd trimester. Supplementation of Vit-D was done to cases, Dosage- 60000IU sachets once a week for three months that is for entire second trimester. These woman were followed until delivery .Maternal and fetal outcome was noted in terms of mode of delivery, gestational age at delivery, birth weight of baby, Incidence of preeclampsia, eclampsia, GDM etc. Incidence of preeclampsia has been calculated among cases and controls.*
Results: *Among 100 cases and controls -4 cases and 9 controls developed preeclampsia in our study. Incidence of preeclampsia is 18%among controls ,8% among cases, more among controls in our study. p vaiue is 0.234 ,p value <0.05 is taken as significant. p value of our study is insignificant may be because of the small sample size. Incidence of mild preeclampsia-cases-6%,controls-8%,severe preeclampsia-cases-2%,controls 10%.Incidence of both mild and severe preeclampsia is more among controls than in cases.*
Conclusion: *Incidence of preeclampsia in our study is 13% (13 of 100) 4(incidence8%) cases and 9(incidence18%) controls developed preeclampsia. Incidence of mild and severe preeclampsia, abruption, eclampsia, LBW, GDM, operative delivery are more among controls though the p values are not significant which may be due to smaller sample size. Mean Vitamin D levels were lower in preeclamptic woman compared to normal woman with a statistically significant p value(p<0.05).Our study shows a positive association between vitamin D and preeclampsia .To establish a casual association between vitamin d deficiency and preecalmpsia ,a randomised control trial of vitamin D supplementation among woman with Vitamin D deficiency is needed.*

I. Introduction

We get Vitamin – D is a fat soluble vitamin, primarily from exposure to sunlight and foods such as fish oil, eggs, fortified diary products. Vitamin – D deficiency is common in India though it is a tropical country. Pre eclampsia is a form of hypertensive disorder unique to pregnancy, etiology has many factors both known and unknown, numerous suggested but not yet confirmed. Theories under consideration are Immunological disorder, genetic disorder and abnormal placentation. Vitamin D deficiency is one of the factors in etiology of Preeclampsia. Vitamin D deficiency is thought to be common among pregnant women. Supplementation during pregnancy has been suggested as an intervention to protect against adverse gestational outcome including Preeclampsia[1]. Maternal vitamin D levels have been shown to positively correlate with birthweight centile[2]. Hypovitaminosis D is associated with impaired glucose tolerance and diabetes in the general population[3]. However, the evidence for an association between low vitamin D levels and gestational diabetes mellitus (GDM) is conflicting. Vitamin D deficiency (< 37.5 nmol/l) has been associated with a fourfold increase risk of primary caesarean section[4].Vitamin D deficiency is associated with bacterial vaginosis in pregnant women[5].Neonatal vitamin D levels are correlated with those of their mother, with maternal vitamin D deficiency increasing the risk of neonatal vitamin D deficiency[6]. Vitamin D deficiency is a major cause of hypocalcaemic seizures in neonates and infants. Hypovitaminosis D is associated with impaired growth and bone development in the fetus[7]. Evidence is accruing to show that maternal 25(OH)D insufficiency may lead to suboptimal bone size and density after birth without overt rachitic change[7]. This is likely to lead to an increased risk of osteoporotic fracture in later life. Low maternal vitamin D intake in pregnancy is associated with wheeze and asthma in the offspring. Low cord blood 25(OH) D concentrations have been associated with respiratory syncytial virus bronchiolitis. Cord blood 25(OH) D is correlated with mononuclear cell release of IFN-γ and hence Th1 cell development[8].There is no data to support routine screening for vitamin D deficiency in pregnancy. As the test is expensive, universal supplementation is comparatively cost effective and safe.

HIGH RISK GROUPS for vitamin D Deficiency - vitamin D deficiency is more common in pigmented women (Melanin absorbs UVB). Deficiency is more common in winter[9]. Pre pregnancy obesity has been associated with low levels of vitamin D[10]. Other factors associated with Vitamin D deficiency are gastrointestinal conditions limiting fat absorption, immobility, etc.,

Normal serum level of at least 20 ng/ml(50 nmol/l) is needed to avoid bone problems. When 25 (OH) D level < 20 ng/ml (50 nmol/l) leads to vitamin deficiency

Vitamin D insuffficiency 25 (OH) D level < 32 ng/ml (80 nmol/l)[11].

Recommended dietary allowences

VITAMIN D	PREGNANCY (Age 15 – 40)	LACTATION (Age 15 – 40)
	15 µg	15 µg (600 IU/day)

Recommendation measured as adequate intake by food and nutrition board at the Institute of Medicine 2011[12].

Safety And Toxicity:

Requirement of vitamin D in women may be upto 6000 IU/day. High risk woman are advised to take atleast 1000 IU/day. Supplemental doses of 4000 IU/day were safe and most effective in pregnant women compared to lower dose[13]. All pregnAnt women should take 400 IU(10µg) of vitamin D per day(NICE 2012). Vitamin D toxicity occurs at an intake of 10 – 100 times the RDA. In adults very high doses of vitamin D (3 – 5 lakh IU intramuscular bolus) may be associated with increased risk of fractures and such high doses are not recommended in pregnancy[14].

Regarding the role of Vitamin D in pathogenesis of pre eclampsia, there are several mechanisms by which vitamin D could potentially prevent or atleast delay the progression to preeclampsia.One potential mechanism relates to a defective control of effector T cells by regulatory T cells. This can lead to poor placental invasion,which in turn leads to release of placental derived vasoconstrictor factors[15].Vitamin D receptors on immune cells express key enzymes involved in hormonal activation(CYP2B1)and catabolism (CYP24A1) of vitamin D metabolites,suggesting that the availability and effectiveness of calcitriol can be directly regulated by cells of immune system.The net result of calcitriol on immune system is towards a more tolerogenic state[16].In vitro studies have demonstrated that calcitriol administration leads to upregulation of regulatory T cell responses while proinflammatory responses are downregulated .Vitamin D may help to control the hormones affecting blood pressure.The active form of vitamin D has been shown to regulate the transcription and function of genes associated with placental invasion ,normal implantation and angiogenesis[17]. Receptors for 1,25(OH)D have been found in target tissues that regulate blood pressure.Both hypocalcemia and hypercalcemia affect blood pressure and in both cases, vitamin D metabolism is involved .

It has been observed that decreased calcitriol levels during preeclampsia impair intestinal calcium absorption leading to hypocalcemia. As a compensatory mechanism there is increase in tubular reabsorption of calcium and it leads to hypocalciuria during preeclampsia[18] . It has been reported that hypocalciuria predicts preeclampsia long before clinical manifestation exist .Calcitriol has stimulatory effect on expression of VEGF in vascular smooth muscle cells.Calcitriol may be important in preventing cholesterol uptake by macrophages and vascular smooth muscle proliferation and atheromatous pathology[19].Vitamin D receptors on heart and blood vessels suggest vitamin D has a cardioprotective effect and has a role in controlling inflammation ,effects BP through influence on Reticulo endothelial system[20].Therefore vitamin D is likely to play an important role in immune and CVS changes necessary for healthy pregnancy.

Materials and Methods

This is an interventional and prospective study by including primi and multi gravida attending antenatal clinic-Dept. of OBG,Gandhi hospital,Secunderabad.Age and gravid matched pregnant women were taken as cases and controls according to inclusion and exclusion criteria after proper counseling.For cases vitamin D was supplemented and controls received only regular antenatal care.For all the women included in the study that is cases and controls vitamin- D level was estimated twice once in 1st trimester and again in 3rd trimester after taking consent of the patients. Period of study-January 2014 to August2015.This study has been approved by ethical committee of the Institution. Serum 25(OH)D level was measured by High performance liquid chromatography method .

Inclusion Criteria

1. Age 20 to 30years
2. Primi and multi gravida attending antenatal clinic,Dept. of OBG,Gandhi hospital
3. Singleton pregnancy
4. Gestational age <12 weeks

Exclusion Criteria

1. Chronic hypertension cases
2. Gestational age >12 weeks
3. Medical disorders complicating pregnancy like Diabetes,SLEandRheumatoid arthritis.
4. Vitamin D deficient(frank deficiency less than 20ng/ml)as they have to be treated to avoid other complications due to vitamin D deficiency.
5. Previous history of pre eclampsia in a case of multigravida
6. Smokers

Supplementation of Vitamin D was done to ante natal mothers,in form of 60000IU sachets once a week for three months for entire second trimester.These women were followed until delivery .Maternal and fetal outcome was noted-mode of delivery,GA at delivery,birth weight of baby,Incidence of preeclampsia,eclampsia,GDM etc. Incidence of preeclampsia has been calculated among cases and controls.

RESULTS

Among 100 cases and controls -4 cases and 9 controls developed preeclampsia in our study.Incidence of preeclampsia was 12.6%(10 of 79) in age group 20-25, 14.2%(3 of 21) in age group 25-30.Our study included both primi and multi gravid(50 primi and 50 multi).There were 10 cases in primi incidence 20%,3 cases in multi incidence 6percent.Incidence is more in primi- primiparity is a known risk factor for preeclampsia. Obesity is taken as BMI>30.Prevalence of obesity is more among preeclamptic woman.Mean BMI Among preeclamptic woman is 24.1,among nonpreeclamptic woman is 21.8.Incidence of preeclampsia is 18%among controls ,8% among cases, more among controls in our study. p vaiue is 0.234 ,p value <0.05 is taken as significant. p value of our study is insignificant may be because of the small sample size. Incidence of mild preeclampsia-cases-6%,controls-8%,severe preeclampsia-cases-2%,controls 10%.Incidence of both mild and severe preeclampsia is more among controls than in cases.

II. Discussion

Our study is a prospective interventional case control study by including primi and multi gravida attending antenatal clinic-Dept. of OBG,Gandhi hospital,Secunderabad. Parity matched Cases and controls were chosen according to inclusion and exclusion criteria .Supplementation of Vit-D was done to cases,Dosage-60000IU sachets once a week for three months that is for entire second trimester.Serum vitamin D level was measured by HPLC method.During antenatal checkups along with regular obstetric examination BP and UA were measured.Diagnosis of preeclampsia was done according to ACOG 2013 task force criteria.Among 100 cases and controls -4 cases and 9 controls developed preeclampsia in our study

Incidence Of Preeclampsia Among Cases(Vitamin D Supplemented) And Controls(Non Supplemented) In Different Studies-Comparitive Table

STUDY	CASES	CONTROLS
ITO ET AL	10.9	16.9%
HCCSCA-CREIZEL ET AL	2.5%	3.06%
HAUGEN ET AL	5.1%	6%
CASECONTROL STUDY ,PGIMS-PARUL ET AL	4%	10%
OUR STUDY	8%	18%

In all the above studies incidence is lower in cases-vitamin D supplemented group than in non supplemented or control group.Our results are similar to the above mentioned studies.

Mean Vitamin D Level-First Trimester Among Preeclamptic And Normal Woman In Different Studies-Comparitive Table

Study	Mean vitamin D level in preclamptic woman	Mean vitamin D level in normal woman
CAMILLE ET AL	27.4ng/ml	28.8ng/ml
CASE CONTROL STUDY, QUEBEC-MADONNA ET AL	18.8	20.92
BAKER ET AL	30	39.2
PROSPECTIVE COHORT STUDY,CANADA-WEI ET AL	20.4	22.4
OUR STUDY	26ng/ml	37.7ng/ml

In all the above mentioned studies mean vitamin D level is low among preeclamptic woman than in normal womanOur results are similar to the above mentioned studies

Mean Vitamin D Value –Third Trimester Among Preeclamptic Woman And Normal Woman-Comparitive Table

Study	Mean vitamin D value in preeclamptic woman	Mean vitamin D value in normal woman
UK STUDY(2005-8)-LECHTERMANN ET AL	18.21	49.2
PROSPECTIVECOHORT STUDY,CANADA-WEI ET AL	19.56	22.8
OUR STUDY	30.4ng/ml	44ng/ml

In all the above mentioned studies mean vitamin D level is low among preeclamptic women than in normal women Our results are similar to the above mentioned studies Kaur et al, found that supplementation of vitamin D in 60,000 IU during 6th and 7th month of pregnancy increases protein, DNA and RNA content of placenta and improved the placental growth[21]. Recent studies have also demonstrated the reno-protective effects of Vitamin D analogs . In a controlled trial of 5644 women in the United Kingdom, those receiving a dietary supplement of halibut liver oil containing 900 IU of vitamin D per day starting at 20 wk gestation demonstrated a 32% decreased odds of preeclampsia compared with women who did not receive the supplement[22].Dose dependent association between vitamin D level and preeclampsia was established by Hollis and Wagner[23]. Olafsdottir et al-an observational study in Icelandic woman, showed a U shaped relation between vitamin D intake at 11-15 weeks gestation and risk of hypertensive disorders[24].Various recent studies have demonstrated a negative association between albuminuria and Vitamin D levels[25].

Our study has demonstrated a positive association between vitamin D level and preeclampsia.Strengths of our study are it is a prospective study-vitamin D levels were measured and supplementation was given before the onset of preeclampsia,vitamin D level measurement is a better biomarker of status than food quesstionaries as used in some studies,vitamin d level is measured twice before and after supplementation –longitudinal status and effect on early and late gestation could be evaluated.Vitamin D value was measured by high performance liquid chromatography method which has acceptable accurancy. Confounding factors were minimized to the possible extent - cases and controls were age and parity matched. Though vitamin D supplementation-role in preeclampsia is not yet established, supplementation has other advantages in pregnancy both to mother and growing fetus without any toxicity and side effects.

Vitamin D supplementation has effect both in early and late stages of pregnancy. Vitamin D is important for fetal and childhood bone development. New research has shown that it plays a wider role in health and disease prevention. In normal pregnancies, circulating maternal concentration of 1,25 $(OH)_2D$ is elevated from the first trimester onwards[26]. Local production of 1,25$(OH)_2D$ may be important for its increased concentration in the early stage of pregnancy, this has been suggested to influence implantation, partly through the immunomodulatory effect and partly by regulation of the target genes associated with implantation. The elevation of 1,25 $(OH)_2D$ in the early stage of pregnancy could reflect its role in implantation, as demands to meet increased calcium requirements for the fetal skeletal development come later in pregnancy. Vitamin D might also be important for the maintenance of a normal pregnancy through its impact on the maternal immune response to the fetus[27].

III. Conclusion

Incidence of preeclampsia in our study is 13% (13 of 100) 4(incidence8%) cases and 9(incidence18%) controls developed preeclampsia. In our study incidence is more in primigravida .Incidence of preeclampsia is similar among different age groups,different occupations and different communities included in our study. Majority of cases had onset of preeclampsia after 34 weeks of gestation. Preeclamptic woman had increased rate of obstetric and neonatal complications and increased rate of operative delivery. Mean Vitamin D levels were lower in preeclamptic women compared to normal women with a satistically significant p value($p<0.05$).Our study shows a positive association between vitamin D and preeclampsia .To establish a casual association between vitamin D deficiency and preeclampsia,a randomised multicentric control trial of vitamin D supplementation among woman with Vitamin D deficiency is needed.

Limitations of our study are it is a case control study-can overestimate the effect size of the association and makes temporal association less clear, selection bias and confounding factors cannot be eliminated totally. Sample size is small –overestimates the prevalence rates, it includes similar population. Vitamin D deficient group is excluded from our study as it is unethical to leave them untreated as controls as vitamin d deficiency has other side effects on pregnancy if not preeclampsia, the present study included only insufficient and sufficient group.Consensus for vitamin D levels(normal ,insufficiency,deficiency)are taken according to non pregnant levels as there are no specific guidelines for vitamin D values in pregnant woman.

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