International Journal Of

Recent Scientific Research

ISSN: 0976-3031
Volume: 7(5) May -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 5, pp. 10905-10908, May, 2016

International Journal of Recent Scientific Research

Research Article

PREVALENCE OF VITAMIN D DEFICIENCY AND ITS CUT OFF LEVEL PREDICTING ADVERSE PREGNANCY OUTCOME

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ARTICLE INFO

Article History:

Received 15th February, 2016
Received in revised form 21st March, 2016
Accepted 06th April, 2016
Published online 28th May, 2016

Keywords:

Vitamin D, deficiency, pregnancy induced hypertension, oligohydramnious, Fetal growth restriction, small for gestational age, cut off level.

ABSTRACT

Aims &Objectives: Maternal vitamin D deficiency is a major public health problem and can adversely affect pregnancy outcome. We aimed to assess the level of 25(OH) vitamin D in postnatal women within 72 hours of delivery, to find out the correlation of the pregnancy outcome with the level of vitamin D and to calculate the prevalence rate of this ailment.

Methods: The study was conducted from 06.06.2012 to 12. 09. 12 in the Department of O&G in collaboration with Rheumatology laboratory of IPGME&R, Kolkata. It is a crossectional observational study. Estimation of 25(OH) vitamin D was done by ELISA method with CPC Euroimmune kit.

Results: A total of 143 postnatal women with singleton pregnancy were regarded as subjects after exclusions. Among these 66 (46.15%) had deficiency. Fifty five (38.46%) and 22 (15.38%) women had suboptimal and optimal vitamin D level respectively. We observed the group with deficiency suffered from various adverse pregnancy outcome; oligohydramnios, small gestational age, fetal growth restriction, pregnancy induced hypertension and pre-eclampsia etc. Prevalence rate of vitamin D deficiency was 84%. Cut off level of 25 (OH)D was at $\leq$ 19.9ng/ml for predicting the adverse outcome. Cord blood estimated and observed to be also vitamin D deficient.

Conclusion: Vitamin D deficiency has to be addressed seriously in antenatal mothers. There should be routine estimation of vitamin D in antenatal and postnatal mothers.

INTRODUCTION

Pregnancy itself is pro for hypovitaminosis D. Fetus accretes 25-30gm of calcium by term. So to acclimatize the physiological demand intestinal absorption of calcium increases trimester by trimester. This upregulation of calcium synthesis requires increased prolactin, placental lactogen, calcitonin and 1.25 –dihydroxy vitamin D3 (calcitriol) also. Another theory depicts that calcium synthesis is independent of vitamin D. But trans placental transfer of 25(OH) D rapidly occurs to ensure adequate vitamin D status at birth. As 25(OH) D has short life span (2-3weeks), newborn concertation deceases rapidly unless an exogenous source of vitamin D is given. Thus if maternal level is at poor level, the low 25(OH) D level falls to a deficient range. Again during lactation mothers lose up to 210mg calcium daily and more when nursing multiple fetuses.

Deficiency of vitamin D is a major concern now a days worldwide. Many researchers from different global sectors have published their data regarding this issue and revealed high prevalence of the problem and poor pregnancy outcomes[1,2,3].

Vitamin D is a steroid prohormone which is produced in the skin by ultraviolet B (UVB) radiation. Major causes are low exposure to UVB rays, sunlight, inhibiting effect of dark skin on the uptake of UVB and inadequate dietary intake etc. It is well proven that prenatal vitamin D deficiency is prevalent among all racial groups but black women carry major burden [4]. We observed vitamin D status among institutional obstetric population to measure the prevalence and pregnancy outcome. Our aim was also to calculate a cut off level vitamin D which can predict the adverse outcome if any.

MATERIALS AND METHODS

This study was carried out in the Department of Obstetrics and Gynaecolgy, IPGME&R, Kolkata from 2012 June -2012 December in collaboration with Department of Rheumatology. It is a retrospective observational study. Ethical clearance was obtained, binding to the rules of Helsinki from IPGME&R

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ethical committee (Memo no. Inst/IEC/1626). With individual consent, 143 women in their last gestational weeks were included as subjects. Inclusion criteria was consecutive pregnant mothers attending labor room for delivery, who agreed to participate in the study. Mothers with previous cesarean sections, obesity, congenital anomalies of the fetus, chronic renal disease and hyperthyroidism etc. were excluded from the study.

Each pregnant lady was allotted an individual case record form. Demographic variables such as age, weight, height, gravidity, socioeconomic status, exposure to sunlight and food habits etc. were noted down. Data regarding past history, present pregnancy, antenatal, intranatal, postnatal events and blood investigation reports were detailed out. Baby growth was measured by clinical parameters and serial ultrasonographies. Then pregnancy outcome were measured in terms of preterm labor, pregnancy induced hypertension (PIH), oligohydramnious, small for gestational age (SGA), fetal growth restriction (FGR) and low birth weight babies (LBW). All obstetric events were defined according to 24th edition William's Text Book of Obstetrics [5].

For vitamin D estimation 2ml of venous blood was drawn from each mother. Then blood was centrifuged to get the serum. With the help of 20µl serum by ELISA method 25(OH) vitamin D was estimated. The kit used was Euroimmun kit Medizinische Labordiagnostika AG. The tests were carried out in Institutional Rheumatology laboratory. This is one of our best laboratory which carries out all autoimmune disease related tests including 25(OH) vitamin D. Deficiency of vitamin D was considered at the level ≤19.9ng/ml, suboptimal range was 20-30 ng/ml and optimal level included the level ≥30ng/ml. All subjects were grouped into three categories to make the analysis comparable. All subjects and neonates observed with deficiency of vitamin D were treated with therapeutic dose of 1000IU in the caplet form per day to each mother for 6 weeks. Each neonate was treated with 400IU in the oral drop form daily. Mothers were also supplemented with vitamin D fortified foods. Follow up included overall health and vitamin D estimation.

Data were scrutinized and tabulated. Analysis was done by Chi-square tests. Kruskal-Wallis ANOVA followed by Dunn's post hoc test was used to compare the data overall and comparison among each parameter. A p value ≤ 0.05 was considered significant. Receiver operative characterstic (ROC) curve analysis was done to ascertain the is cut-off value of 25(OH) vitamin D in this present study cohort which imposes a high risk of adverse pregnancy outcome (composite of preterm labor , pregnancy induced hypertension, small for gestational age and fetal growth restriction). Bland-Altman plot was drawn to show the agreement between maternal and umbilical cord blood 25 (OH) vitamin D levels.

Software used were, Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001], MedCalc version 11.6 [Mariakerke, Belgium: MedCalc Software 2011], GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007].

RESULTS

A total of 143 women were included in the present study. All subjects were divided into three groups. Group of pregnant women with 25(OH)D deficiency range (46.15%), group with suboptimal range(38.46%) and another group with optimal range(15.38%). Demographic characteristics (Table1) of the study population did not show any statistical correlation in between the three groups. Mean age of the subjects was 23.64±1.95 years. The basal metabolic index of the whole subjects at 22.77±0.89. Almost 37.88% and 62.12% of women in the vitamin D deficiency group had nil and moderate exposure of sun respectively.

Tables1 Patient distribution, previous obstetric data and risk of study population

Characteristics	Deficient (n=66)	Suboptimal (n=55)	Optimal (n=22)	P value
Age in years				
Mean±SD	23.73±2.109	23.45±1.824	23.86±1.859	0.463
Median(IQR)	23(22-23)	23(22-25)	24(23-25)	
Primipara	30(45.45%)	25(37.87%)	13(59.09%)	
Multipara	36(54.54%)	30(54.54%)	9(40.9%)	
Urban	46(69.69%)	40(72.72%)	15(68.18%)	0.901
Rural	20(30.3%)	15(27.27%)	7(31.8%)	
BMI				
Mean±SD	22.83±0.796	22.78±0.917	22.55±1.101	0.599
Median(IQR)	23(22-23)	22(22-23)	23(22-23)	
GA* at delivery				
Mean±SD	37.45±1.711	38.2±1.282	38.64±1.049	0.003
Median(IQR)	38(37-39)	38(38-39)	39(38-39)	
Sun exposure				
Nil	25(37.88%)	16(29.09%)	4(18.18%)	0.02
Moderate	41(62.12%)	39(70.91%)	18(81.12%)	

*GA: Gestational age

Pregnancy outcome with vitamin D was shown in table-2. Mean gestational age at delivery was 37.92±1.95weeks. There was significance difference in between the groups regarding gestational age at delivery (37.45±1.71 vs38.2±1.28 vs 38.64± 1.04; p=0.003). The obstetric outcome of the subjects revealed majority of antenatal complications in the deficient group. These were oligohydramnious (33%vs 14.6%vs 0; p=0.001), PIH (23%vs 7%vs 5%; p=0.019), pre-eclampsia (9%vs 2%vs 0; p=0.217), small for gestational age (24%vs 7%vs5%; p=0.083), fetal growth restriction (24%vs7%vs0;p=0.003) and cesarean sections (60% vs 27% vs 45% ; p=0.001). The comparison of fetal outcome (table-3) among three groups observed a significant difference in birth weight (2.46±0.4 vs 2.69 ± 0.29± 2.91±0.32; p< 0.001) and in NICU admissions for more than seven days (17vs 7vs1; p=o.038).

Table-2 Pregnancy outcome according to vitamin D level

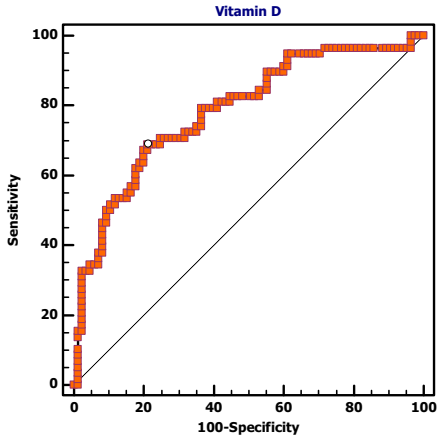
Characteristics	Deficiency(n=66)	Suboptimal(n=55)	Optimal(n=22)	Pvalue
Oligohydramnious	22(33.33%)	8(14.55%)	0	0.001
Preterm labor	4(6.06%)	1(1.82%)	0	0.281
PIH*	15(22.73%)	4(7.27%)	1(4.55%)	0.217
Pre eclampsia	6(9.09%)	1(1.82%)	1(4.55%)	0.217
SGA*	16(24.24%)	8(14.55%)	1(4.55%)	0.083
FGR*	16(24.24%)	4(7.27%)	0	0.003
Operative delivery	40(60.61%)	15(27.25%)	10(45.45%)	0.001

*PIH: Pregnancy induced hypertension, *SGA: Small for gestational age, *FGR: Fetal growth restriction

Table 2 Fetal outcome

Outcome	Deficiency(n=66)	Suboptimal(n=55)	Optimal(n=22)	pvalue
Baby weight				
Mean±SD	2.46±0.408	2.69±0.29	2.91±0.321	<0.001
Median (IQR)	2.6(2.2-2.7)	2.7(2.5-2.8)	2.85(2.8-3.1)	
NICU admission				
>7days	17(25.75	7(12.72	1	0.038
Apgarscore				
≥8/10	62(93.93	51(92.72	22(100	0.444

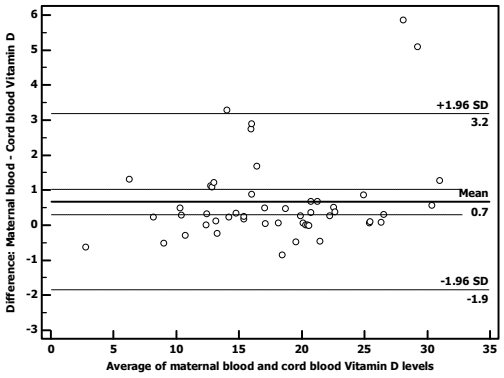
After correlating the major adverse outcomes with the each level of vitamin D (Figure-1) in the whole subjects, we could observe the cut off level at ≤19.05 ng/ml showed sensitivity and specificity of 68.97 and 78.82 respectively. It had a significant p value of <0.0001 (95% CI; 0.708 to 0.848).



Area under the ROC curve (AUC)	0.784
Standard Error [a]	0.0396
95% Confidence Interval [b]	0.708 to 0.848
z statistic	7.167
Significance level P (Area=0.5)	<0.0001

Figure 1 ROC Curve analysis (To ascertain if there is cut-off value of Vit D in this PP study cohort which imposes a high risk of adverse pregnancy outcome (composite of preterm labor, PIH, SGA and FGR)

Figure 2 revealed the correlated plot between maternal and cord blood vitamin D level. It showed a strong agreement between them revealing Interclass coefficient (ICC) at 0.97(0.94-0.99).



Intraclass Correlation Coefficient

	Intraclass correlation [a]	95% Confidence Interval
Single measures [b]	0.9745	0.9402 to 0.9875
Average measures [c]	0.9871	0.9692 to 0.9937

[a] The degree of absolute agreement among measurements.
[b] Estimates the reliability of single ratings.
[c] Estimates the reliability of averages of *k* ratings.

Figure-2 Bland-Altman plot showing agreement between maternal Vit D levels and umbilical cord blood Vit D levels

DISCUSSION

Prevalence of vitamin D deficiency was 84% in the present set up. Which is very high almost like other studies. Whereas Northern India revealed 96% prevalence[6]. Another Southeast country reported 78% prevalence[7]. Developed regions like Australia has also similar picture of vitamin D deficiency prevalence [8]. A study from Turkey stated 46% of prevalence, but contradicting to other authors they did not find any association with maternal age, gravidity, skin phenotype, benefiting from ultraviolet index and educational status of the cases [9]. We also did not also observe any relation to age, BMI, urban or rural setting and parity.

Sixty two percent of vitamin deficient women underwent cesarean section then followed by oligohydramnious was observed in 33% and followed by FGR in 24%, PIH in 23%, and preeclampsia in 9%. Even when we compared the composite adverse outcome among all pregnant women, more cases from the group with deficiency showed poor outcome (61%vs 27%vs9%; p, 0.001). This high rate of cesarean sections related to development of PIH, pre eclampsia, FGR, oligohydramnious and poor Doppler and biophysical profile of fetuses in ultrasonography. Marewood *et al* had shown similar significant association of vitamin D deficiency with primary cesarean section[10]. They stated that pregnant women with 25(OH) D less than 37.5nmol/l were almost four times likely to have cesarean sections than women with ≥37.5nmol/l. According to them deficiency of vitamin D results in disturbed calcium homeostasis which in turn might affect the labor process. Thus these women with cesarean sections might have specific indications like; non progress of labor and cephalopelvic dispropertion etc.

Thomas *et al* studied 99 mothers with mean 25(OH)D 48 nmol/l. Maternal complications recorded were premature rupture of membrane, pre eclampsia, postpartum haemorrhage, antepartum haemorrhage, oligohydramnious, cholestasis, gestational diabetes mellitus and also operative delivery [8]. Bodenar LM *et al* carried out vitamin D estimation in <22 weeks gestation and observed 28.6% pre eclampsia when 25(OH)D was <37.5nmol/l , 23% when 37.5-75nmol/l and 12% when >75nmol/l[11]. It is hypothesized that deficiency of vitamin D plays vital role in reducing placental perfusion , regulating genes responsible for implantation, angiogenesis and reduction of vascular endothelial growth factor(VEGF) [11,12].It also elevates the blood pressure by down regulation of renin in the kidney[13].

Other prominent complications in the present study were small for gestational age and fetal growth restricted babies. Another author from Pittsburg analyzed the SGA fetuses and observed a modest increased risk coexisting with higher serum value of 25(OH) D also (≥75 nmol/l with 54% SGA babies)[14]. Pathogenesis of vitamin D deficiency relating to FGR explains that vitamin D influences placental villous development by activating enzymes CYP27B1and VDR. It also regulates human chorionic gonadotropin expression and secretion in human placenta [15]. Because it helps in calcium synthesis, there way directly affects skeletal muscle and bone growth[16].

We determined a cut off level where the risk of adverse pregnancy outcome was more. This step may be a necessary step in a set up like ours as most of patients feel it to be a less important issue and also most of clinicians are not aware of the outcome as well as management. If timely therapeutically given vitamin D to deficient mothers, it may improve the present result. In a randomized trial all pregnant mothers were subjected to the dose of vitamin D 400IU, 2000IU, 4000IU per day until delivery from first trimester onwards, those who had highest dose of vitamin D improved to good 25(OH)D level.

No adverse outcome related to the drug was noticed[17,18]. However they did not comment regarding the pregnancy outcome. So further studies are required to know how much should be the dose of vitamin D, when should be it started and whether estimation should be routinely implemented.

Strength of the present study was because of these observations and determining cut off level we can aware our pregnant mass and clinicians to start at least empirical treatment from early weeks.

Limitation was the small sample size and long term follow up of neonates and mothers were not present.

Prevalence of vitamin D deficiency was high among pregnant mothers even when supplemented with calcium and vitamin D3 combinations by available brands. This only necessitates the requirement of therapeutic dose of vitamin D. Low vitamin D level may be more likely develop pregnancy and birth complications. Deficient mothers give birth to deficient neonates. So this issue should be addressed seriously and routine estimation antenatally is desirable.

Acknowledgement

We are grateful to staffs of Rheumatology Laboratory and to Professor Alokendu Ghosh for allowing us in their laboratory.

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How to cite this article:

Debasmita Mandal *et al*.2016, Prevalence of Vitamin D Deficiency And Its Cut off Level Predicting Adverse Pregnancy Outcome. *Int J Recent Sci Res.* 7(5), pp. 10905-10908.

TSSN 0976-3031