Original Research Article

To determine the prevalence of vitamin D among pregnant women and its impact on feto-maternal outcome

Ravi Kumar[1], Kajal Kunwar[2*], Anup Kumar[3], Nimisha Agrawal[4]

[1]Senior Resident, Department of Orthopaedics, Nalanda Medical College and Hospital,Patna,Bihar, India
[2]Senior Resident, Department of Obstetrics and Gynaecology, AIIMS Patna, Bihar,India.
[3]Additional Professor & Head, Department of Orthopaedics, AIIMS Patna, Bihar, India
[4]Assistant Professor, Department of Obstetrics and Gynaecology, AIIMS Patna, Bihar, India

Received: 07-10-2020 / Revised: 23-11-2020 / Accepted: 20-12-2020

Abstract

Background: Vitamin D deficiency is widely prevalent in all parts of the world. Pregnant women and neonates are highly vulnerable to vitamin D deficiency. The aim of our study was to determine the prevalence of vitamin D among pregnant women and its impact on feto maternal outcome. **Methods:** This was an observational study conducted in a government teaching hospital located in Patna,Bihar, India fromJanuary 2019 to March 2020. Total 100 pregnant women aged 18-40 years old with gestational age >28 weeks were included in this study. Blood sample was taken during routine blood collection at the first prenatal check-up. Reliable serum vitamin D was measured in the extra blood sample using an enzyme immunoassay method. **Results:** 100 pregnant women with aged 18-40 year participate in the study. Among study subjects 44% were multigravidae and 56% were primigravidae. All women recruited for the study were >32 weeks gestation. It was found that 52% had insufficient Serum 25(OH) D concentrations and 16% were deficient for Vitamin D.The lowest 25(OH) D concentrations (insufficient levels) were found in those with only 1-2 hours of sun exposure (60%), and 50% had deficient levels. Highest concentrations (12.5%) were found in those with 2-4 hours of sun exposure. It was found that 67% of women studied took regular calcium supplementation throughout pregnancy.There were no significant association between 25(OH) D concentrations and maternal outcome. While 89% with normal vitamin D levels had no complications, 81.25% with deficient levels were uncomplicated. However, among women with hypovitaminosis D, 20.19% developed PIH, 19.71% had pre term birth & 3.84% developed GDM. **Conclusion:** Treatment of vitamin D deficient women and vitamin D supplementation is safe and is recommended for all women who are pregnant or breastfeeding.

Keywords: Vitamin D, Pregnancy, Low birth weight, Preeclampsia, Preterm, GDM.

Introduction

Vitamin D status is a well-known determinant of bone health and is related with a risk of many diseases such as cancers, cardiovascular diseases and diabetes. The naturally occurring form of vitamin D in human beings is cholecalciferol or vitamin D3. Authors receive vitamin D from exposure to sunlight, diet and dietary supplements. The skin synthesis of vitamin D induced by ultraviolet B radiation is the main determinant of vitamin D status in the population because few food items contain or are fortified with vitamin D. Vitamin D2 or ergocalciferol is derived from plant sterols and is the form contained in most vitamin D supplements. Vitamin D is a steroid with hormone like activity that regulates the function of over 200 genes and is essential for growth and development of the body. Vitamin D deficiency is widely prevalent in the world[1].The South Asian population is at much higher risk due to dark skin pigmentation, limited dietary source of vitamin D and inadequate direct sunlight exposure. However, vitamin D deficiency is being

**Correspondence*
Dr Kajal Kunwar,
Senior Resident, Department of Obstetrics and Gynaecology, AIIMS Patna, Bihar, India.
E-mail:drkajalkunwar@gmail.com / k2.drravi@gmail.com

diagnosed increasingly in pregnant woman, infants and children. Indian studies have shown the prevalence of vitamin D deficiency in pregnancy to be as high as 84% in both urban as well as rural areas[2,3]. Pregnant women, neonates and infants form the most vulnerable group for vitamin D deficiency. Apart from maternal skeletal preservation and fetal skeletal formation it may be linked with other disease susceptibility both in mother as well as fetus. Recent research has suggested that vitamin D deficiency may put pregnant women at risk for preeclampsia, preterm labour/preterm birth, gestational diabetes and infections, besides poor weight gain and myopathy. Clinical studies establishing an association between vitamin D level and adverse pregnancy outcomes such as preeclampsia, gestational diabetes, low birth weight, preterm labour, caesarean delivery and infectious diseases have shown conflicting results. Studies support the idea that lower vitamin D status may play a role in the development of preeclampsia. The active form of vitamin D (1,25 dihydroxy vitamin D) was proposed to be important for normal placentation, angiogenesis, and immunological tolerance. For example, 1,25 dihydroxy vitamin D is anti-inflammatory by down regulating the expression of Th1 - type cytokines and upregulating Th-2 type cytokines[4]. In pregnant women with GDM, pancreatic B cells fail to increase insulin secretion in response to the reduced insulin sensitivity during pregnancy. Both VDR and 1, α hydroxylase are expressed in pancreatic islets. Vitamin D is also known to improve insulin sensitivity by enhancing the expression of insulin receptors[5]. Vitamin D may reduce the risk of GDM by regulating insulin release and insulin sensitivity. Vitamin D may be relevant for preterm birth prevention. 1,25-dihydroxyvitamin D is known to reduce bacterial infections by inducing cathecidin in many tissues, including maternal and fetal cells of the placenta[6]. Vitamin D has a key role in fetal growth by its interaction with parathyroid hormone and Ca^{+2} homeostasis. Studies confirmed that insufficient prenatal and postnatal levels of vitamin D have great effects on bone mineralization which have significant association with small for gestational age (SGA) births[7]. SGA births are reported more frequent in pregnancies occurring in the winter with vitamin D deficiency. At present, there are fewer studies to assess the vitamin D status and its relationship with adverse effects in pregnancy in India. So, the aim of our study was to ascertain the prevalence of vitamin D among pregnant women and its impact on feto maternal outcome.

Material and methods

This was an observational study conducted in the This was an observational study conducted in a government teaching hospital located in Patna, Bihar, India from January 2019 to March 2020, after taking the approval of the protocol review committee and institutional ethics committee. Total 100 pregnant women aged 18-40 years old with gestational age >28 weeks were included in this study.Women with pre-existing medical disorders were excluded from the study.A questionnaire that covered socio-demographic data, religion, obstetric history, lifestyle, dietary habits and psychosocial factors were completed from all the women. Blood sample was taken during routine blood collection at the first prenatal check-up. Reliable serum vitamin D was measured in the extra blood sample using an enzyme immunoassay method. Data on date of delivery, infant sex, birth weight, length and gestational age (based on ultrasound or on the timing of the last menstrual period) were collected prospectively.Measurement of vitamin D (Independent variable) was done by an enzyme immunoassay method. At the laboratory, serum was prepared by centrifugation and stored as one ml aliquots at 280°C until analysis. Serum 25-hydroxyvitamin D (25(OH) D) level was measured using an enzyme immunoassay method. Outcome variables were birth weight, small for gestational age (SGA) and neonatal weight and length trajectories of neonates born at term (gestational age 37 weeks or more). An infant was considered SGA whenhis or her birth weight fell below the 10^{th} percentile of the most recent Indian reference values for that gestational age according to parity and sex. Neonatal weight and length trajectories were calculated by transforming each measurement into sex and age-specific standard deviation scores (SDS) based on the total research population.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. Test applied for the analysis was chi-square test.

Results

100 pregnant women participate in the study. Of these women, 3% were Christians, 81% were Hindus and 16% were Muslims. They belonged to the age group of 18-40 yrs. Among study subjects 44% were multigravidae and 56% were primigravidae. All women recruited for the study were >32 weeks gestation. The relation between vitamin D and ethnicity

was not confounded by socio economic status, religion, or parity (Table1).It was found that 52% had insufficient Serum 25(OH) D concentrations and 16% were deficient for Vitamin D.(Table 2)

The lowest 25(OH) D concentrations (insufficient levels) were found in those with only 1-2 hours of sun exposure (60%), and 50% had deficient levels. Highest concentrations (12.5%) were found in those with 2-4 hours of sun exposure (Table3.)

Table 1: Demographic profile of patients (n=100)

Parameter	%
Age: 18-40	**100**
Religion	
Christian	3%
Hindu	81%
Muslim	16%
Parity	
Multi	44%
Primi	56%
Gestational age	
<32weeks	0
32-37weeks	14%
37-40weeks	53%
>40 weeks	33%
BMI	
Underweight	2%
Normal	57%
Overweight	40%
Obese	1%

Table 2: Vitamin D3 levels in patients studied

Vitamin D3	N=100	%
Normal	32	32
Insufficiency	52	52
Deficiency	16	16

Table 3: Correlation of duration of exposure to sun according to Vitamin D3 levels in patients studied

Duration of exposure to sun	Vitamin D3			Total
	Normal	Insufficiency	Deficiency	
<1/2 hour	4(12.5%)	8(15.38%)	4(25%)	16(16%)
1-2	21(65.62%)	31(63.46%)	8(50%)	60(60%)
2-3	4(12.5%)	7(13.46%)	2(12.5%)	13(13%)
3-4	3(9.38%)	6(11.53%)	2(12.5%)	11(11%)
Total	32(100%)	52(100%)	16(100%)	100(100%)

P=0.859, Not significant, Chi-square test

It was found that 67% of women studied took regular calcium supplementation throughout pregnancy.There were no significant association between 25(OH) D concentrations and maternal outcome. While 89% with normal vitamin D levels had no complications, 81.25% with deficient levels were uncomplicated. However, among women with hypovitaminosis D, 20.19% developed PIH, 19.71% had pre term birth &3.84% developed GDM (Table 4).

Table 4: Maternal complications according to Vitamin D2 levels in subjects studied

Maternal complications	Vitamin D3			Total (n=100)
	Normal (n=32)	Insufficiency(n=52)	Deficiency(n=16)	
No	29(90.63%)	47(90.38%)	13(81.25%)	89(89%)

Yes	3(9.39%)	5(9.62%)	3(18.75%)	11(11%)
Abruption placenta	0(0%)	2(3.84%)	2(12.5%)	4(4%)
GDM	0(0%)	2(3.84%)	0(0%)	2(2%)
PIH	0(0%)	4(7.69%)	2(12.5%)	6(6%)
Oligohydramnios	1(3.13%)	0(0%)	0(0%)	1(1%)
Pre term	4(12.5%)	7(13.46%)	1(6.25%)	12(12%)

P=0.652, Not significant, chi-square test

The analyses showed a significant association between a deficient vitamin D status (50%) and low birth weight (<2.5Kg) compared to 15.62% who had normal vitamin D levels. An insufficient vitamin D status was also related to a lower birth weight, but the association was not significant. Among normal birth weight (2.5-3.5 Kg) babies 81.25% of mothers had normal vitamin D status and 43.75% of them had deficient vitamin D levels (Table5)

Table 5: Correlation of Birth weight (kg) according to Vitamin D2 levels in subjects studied

Birth weight (kg)	Vitamin D3			Total
	Normal	Insufficiency	Deficiency	
<2.5	5	8	8	21
	(15.62%)	(25%)	(50%)	(21%)
2.5-3.5	26	41	7	74
	(81.25%)	(78.85%)	(43.75%)	(74%)
3.5-4.5	1	3	1	5
	(3.13%)	(5.77%)	(6.25%)	(5%)
Total	32	52	16	100
	(100%)	(100%)	(100%)	(100%)

P=0.033+, Significant, chi-square test

We did not find any significant association between Vitamin D levels and neonatal complications (Table 6).

Table 6: Fetal complications according to Vitamin D2 levels in subjects studied

Fetal complications	Vitamin D3			Total (n=100)
	Normal (n=32)	Insufficiency (n=52)	Deficiency (n=16)	
No	31	47	12	90
	(96.88%)	(90.38%)	(75%)	(90%)
Yes	1	5	4	10
	(3.12%)	(9.62%)	(25%)	(10%)
IUGR	0	2	0	2
	(0%)	(3.85%)	(0%)	(2%)
NICU	1	6	4	11
	(3.13%)	(11.54%)	(25%)	(11%)

P=0.132, Not Significant, chi-square test

Discussion

Prevalence of vitamin D deficiency varies widely across various populations. International comparison of the prevalence of Vitamin D deficiency is difficult because of variation in the definition of vitamin D deficiency in reported studies. Also prevalence of vitamin D deficiency is influenced by ethnicity, food habits, clothing, climate and exposure to sun.Vitamin D deficiency is common in Northern Europe, especially in women with pigmented skin. Vitamin D deficiency is three times more common in the winter and spring compared to the summer and autumn in the UK[8]. In a London antenatal population, a vitamin D level of less than 25 nmol/l was found in 47% of Indian Asian women, 64% of Middle Eastern women, 58% of black women and 13% of Caucasian women[9].Pre-eclampsia and neonatal hypocalcaemia 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 [10,11]. 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 vitamin D deficiency is proposed [12].There are no data to support routine screening for vitamin D deficiency 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 colour or coverage, obesity, risk of pre-eclampsia 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[13]. Measurement of vitamin D in a hypocalcaemic 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.Treatment of vitamin D deficient 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. A review and meta-analysis by Aghajafari et al. found associations between vitamin D insufficiency and risk of gestational diabetes, pre-eclampsia, bacterial vaginosis and SGA infants[14].However, despite a dearth of interventional evidence supporting supplementation/treatment of vitamin D in randomised controlled trial settings, it is generally accepted that supplementation/treatment is not harmful and may have some significant short- and long-term health benefits. 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 micrograms of vitamin D supplements daily.[15,16] This does not necessarily demonstrate that correction during pregnancy will reduce these risks.Three categories of vitamin D supplementation are recommended by RCOG. 1.In general, vitamin D 10 micrograms (400 units) a day is recommended for all pregnant women[15]. 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 orobese)[17,18]. 3.Treatment for the majority of women who are deficient in vitamin D, treatment for four-six weeks, either with cholecalciferol 20 000 IU a week or ergocalciferol 10 000 IU twice a week, followed by standard supplementation, is appropriate[19,20]. 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[21]. 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-hydroxycholecalciferolor1,25-dihydroxy chole-calciferol. Specialist medical advice should be sought in such cases [22,23]. In pregnancy there is enhanced intestinal calcium absorption. Vitamin D toxicity is manifested through hypercalcaemia and hypercalciuria. Therefore, there is a hypothetical concern that when secondary hyperparathyroidism follows vitamin D deficiency, calcium given with vitamin D may be associated with temporary hypercalcaemia. However, this is self-limiting due to the associated hungry bone and has not been demonstrated to represent a clinical problem[12]

Conclusion

Treatment of Vitamin D deficient 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 our population.

References

1. Mithal A, Wahl DA, Bomjour JP. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009;20:1807-20.
2. Balasubramanian K, Rajeshwari J, Gulab, Govil YC, Agarwal AK, Kumar A. Varying role of vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. Clin Endocrine. 2009;70:680-4.
3. Sahu M, Bhatia V, Agarwal A, Rawat V, Saxena P, Pandey A. Vitamin D deficiency in rural girls and pregnant women despite adequate sunshine in northern India. Clin Endocrino. 2009;680-684.
4. Diaz L, Noyola-Martinez N, Barrera D, Hernandez G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-alphainduced inflammatory cytokines in human trophoblasts. J ReprodImmunol. 2009;81(1):17-24.
5. Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev. 2009;22(1):82-92.

6. Hewison M. Antibacterial effects of vitamin D. Nat Rev Endocrinol. 2011;7(6):337-45.
7. Karim S, Nusrat U, Aziz S. Vitamin D deficiency in pregnant women and their newborns as seen at a tertiary - care center in Karachi, Pakistan. Int J Gynaecol Obstet. 2011;112:59-62.
8. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007;85:860-8.
9. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. Clin Endocrinol (Oxf).2009;70:685-90
10. Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. J Clin Endocrinol Metab.2006;91:906-12.
11. Mahon P, Harvey N, Crozier S, Inskip H, Robinson S, Arden N, et al. Low maternal vitamin D status and fetal bone development: cohort study. J Bone Miner Res.2010;25:14-9.
12. Vitamin D in Pregnancy. RCOG Scientific Impact Paper No. 43.2014:2,3.
13. Sattar N, Welsh P, Panarelli M, Forouhi NG. Increasing requests for vitamin D measurement: costly, confusing, and without credibility. Lancet. 2012;379:95-6.
14. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes:systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169.
15. Chief Medical Officers for the United Kingdom. Vitamin D - advice on supplements for at risk groups. Cardiff, Belfast, Edinburgh, London: Welsh Government, Department of Health, Social Services and Public Safety, The Scottish Government, Department of Health. 2012.
16. National Institute for Health and Clinical Excellence. Antenatal care. NICE clinicalguideline 62. Manchester: NICE. 2008.
17. Hollis BW. Vitamin D requirement during pregnancy and lactation. J Bone Miner Res. 2007;22(2):39-44
18. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16:713-6.
19. Saadi HF, Dawodu A, Afandi BO, Zayed R, Benedict S, Nagelkerke N. Efficacy of daily and monthly high-dose calciferol in vitamin D-deficient nulliparous and lactating women. Am J Clin Nutr. 2007;85:1565-71.
20. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc. 2010;85:752-7.
21. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res. 2011;26:2341-57.
22. Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and vitamin D3 in an antenatal protocol. Int J Gynaecol Obstet. 1994;47:115-20.
23. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2010;(8):CD001059.

Conflict of Interest: Nil
Source of support:Nil