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LOW MATERNAL VITAMIN D STATUS AND ADVERSE PREGNANCY OUTCOME – A RETROSPECTIVE OBSERVATIONAL STUDY IN INDIAN POPULATION.

Obstetrics & Gynaecology

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ABSTRACT

Vitamin D has received worldwide attention not only for its importance for bone health in children and adults but also for reducing risk of many chronic diseases including autoimmune diseases, type 2 diabetes, heart disease, infectious diseases and cancers. The active form of vitamin D, 1,25-dihydroxyvitamin D3, has been shown to regulate the transcription and function of genes associated with placental invasion, normal implantation and angiogenesis.This nested case control study was done to find the association between early pregnancy maternal vitamin D level and adverse pregnancy outcome in terms of development of gestational hpertention, gestaional diabetes mellitus, fetal growth restriction and preterm labour In our study 68 of 78 subjects (87.13%) were found to be vitamin D deficient at a cutoff value of 25(OH)D level of <22.5 hg/ml . The mean 25(OH)D level in case group was 12.96±6.38 hg /ml, which is lower than the mean 25(OH)D level of 16.14±7.98 hg/ml among the control group(p value-0.025). Prevalence of severe vitamin D deficiency in case group was 43.6% of compared to 12.8% control group (<10ng/ml) hence severe vitamin D deficiency before 20 weeks of gestation increases the risk of development of adverse outcome by 5 fold (OR- 4.94, CI 1.44-19.35).hence early pregnancy low vitamin D status increases the risk of adverse pregnancy outcome in study population.

KEYWORDS

INTRODUCTION

In the recent years of fastest growing global economy, era of urbanization and socioeconomic transformation, vitamin D deficiency has emerged as a pandemic of modern world. Vitamin D has received worldwide attention not only for its importance for bone health in children and adults but also for reducing risk of many chronic diseases including autoimmune diseases, type 2 diabetes, heart disease, infectious diseases and cancers.[1,2] Vitamin D has emerged as an important regulator and determinant of pregnancy and child health. The active form of vitamin D, 1,25-dihydroxyvitamin D3, has been shown to regulate the transcription and function of genes associated with placental invasion, normal implantation and angiogenesis.[3] Hence maternal vitamin D status may have association with adverse outcomes of pregnancy, such as miscarriage, preeclampsia, intrauterine growth restriction (IUGR) and preterm birth. Low vitamin D levels have been linked to bacterial infections in the vagina in the first trimester of pregnancy. This can increase the risk of preterm birth and adverse pregnancy outcomes. There is a four times greater risk of caesarean section in women with low vitamin D levels and is believed to be due to the fact that skeletal muscle contains vitamin D receptors and deficiency can result in muscle weakness and poor strength in labor.[4] Women with deficient vitamin D levels have higher incidence small for gestational age (SGA) birth.[5] In utero or early life vitamin D deficiency has been linked to an increased risk of type 1 diabetes, asthma, and schizophrenia, in later life.[6,7,8]

Despite the protean role of vitamin D in various physiological processes, there is no universal definition for vitamin D deficiency and it seems that it varies in different populations.

Institute of Medicine (IOM) defined vitamin D deficiency as a 25-hydroxyvitamin D [25(OH)D] level of <20 ng/ml based on the population-based model in non-pregnant adults.[9] Another classification for vitamin D status in non-pregnant adults was given by Endocrine Society's Clinical Guidelines for vitamin D, based on prevention and treatment of vitamin D deficiency. Vitamin D deficiency be defined as a 25(OH)D ,<20 ng/ml, insufficiency as a 25(OH)D of 21–29 ng/ml and sufficiency as a 25(OH)D of 30–100 ng/ml.[10]

Vitamin D adequacy depends on both endogenous (UV-induced synthesis) and exogenous sources, *i.e.,* diet and supplements. Vitamin D synthesis depends firstly on the level of ambient UV-B light, which in turn depends on latitude and altitude of a place, time of the year and time of the day. Risk factors for vitamin D deficiency includes high latitude location, excessive covered clothing, habituated indoor activity, excessive use of sunscreen, dark skin, obesity, old age and malabsorption syndrome.

AIMS AND OBJECTIVE

To study the vitamin D status in pregnant women and determine the association of vitamin D deficiency and adverse pregnancy outcome in subgroup of Indian population.

MATERIAL AND METHOD

The study was conducted in the Department of Gynecology and Obstetrics at Nalanda Medical College and Hospital Patna, Bihar from May 2019 to November 2020.

Primigravidae with singleton pregnancy, between age 18 – 35 yrs and less than 20 weeks of gestation, registered in the antenatal clinic were screened. Subjects with history of current or past chronic medical disease or history of medication with drugs interfering with calcium and vitamin D metabolism like anticonvulsants, corticosteroids, thiazides, thyroxine and heparin were excluded. A total of 200 subjects were enrolled in the study after taking informed consent. Serum sample of the eligible primigravida were taken at 16-20 weeks of gestation, centrifuged and stored at -70°C for assessment of 25(OH)D levels at the end of the study. All the subjects completed their antenatal follow up with delivery done at the Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital Patna, Bihar. The detailed antepartum intrapartum and postpartum event of all the subjects were noted. Thirty nine subjects developed pregnancy complication during antenatal follow-up (gestational hypertension, gestational diabetes mellitus, preterm premature rupture of membranes and intra uterine fetal growth restriction) were included in case group.

A total of 157 subjects with uncomplicated ante partum, intrapartum and postpartum periods, were included in control group. Fifteen subjects were lost to follow up.

The 25(OH)D level was estimated in all cases (39) and equal number of matched controls(39) using 25(OH)D ELISA Kit. Serum 25(OH)D was assayed using a commercial Enzyme-linked immunosorbent assay kit (DLD Diagnostika GMBH, Germany).

In the present study, stages of vitamin D deficiency had been defined[11]

Severe vitamin D deficiency – serum 25(OH)D level of <10 ng/ml ,Vitamin D insufficiency- serum 25(OH)D level of 10-32 ng/ml ,Vitamin D adequacy - serum 25(OH)D level of 32-100 ng/ml, Vitamin

D toxicity- serum 25(OH)D level of >100 ng/ml.

DATA ANALYSIS

The Chi square test and Fischer Exact test were used for qualitative categorical data. Nonparametric Mannwhitney test and unpaire't' test were used for quantitative data. Odds ratio and its 95% confidence limit were computed for significant predictor of adverse pregnancy outcomes.

RESULT AND DISCUSSION

The present study was done in subjects representing the urban population of Bihar. Considered to be an area of adequate sunshine, vitamin D deficiency in healthy primigravidae was presumed to be unlikely. In contrast, the result of the present study contradicted the expected findings. The mean 25(OH)D level of 78 subjects, 39 being the cases and 39 being control group, was calculated to be 14.55±7.35 ng/ml with values ranging from 5.22 ng/ml - 49.48 ng/ml (Table 1).

Sachan A et al. (2005) studied the prevalence of vitamin D deficiency in 207 pregnant mothers and newborn at Lucknow and observed similar results with mean 25(OH) level of 14 ± 9.3 ng/ml, and cord blood 25(OH)D of 8.4±5.7 ng/ml.[12] In this study elevation of parathyroid hormone (PTH) was taken as a physiological indicator of vitamin D deficiency and normal vitamin D level was taken as 20-80 ng/ml. Accordingly, 84% of the women were found to be vitamin D–deficient taking the cut-off 22.5 ng/ml.[12] In our study, taking the same cut-off as proxy indicator, 68 of 78 subjects (89.74%) were found to be vitamin D deficient. Some other studies have been conducted in non-pregnant Indian population raising similar concern of low vitamin D status in Indian subcontinent. Harinarayan et al. (2011) have studied 25(OH)D levels and BMD (Bone mineral density) in women of reproductive (WR) age group in South India and reported vitamin D deficiency [25(OH)D <20 ng/ml] in 76% and insufficiency in 16.5% in WR.[13] Severe vitamin D deficiency (<10 ng/ml) was more frequent in subjects with higher weight at first visit than subjects with average weight (p value-0.018). Rest of the demographic parameters were comparable and there was no statistically significant difference on the basis of different 25(OH)D cut-off.

Of 235 subjects followed till delivery 11 subjects (4.6%) developed gestational hypertension, 8 subjects (3.4%) developed gestational diabetes mellitus, 8 (4.6%) developed preterm premature rupture of membranes and 10 (4.25 %) developed intrauterine growth restriction. The mean 25(OH)D level in case group was 12.96±6.38 ng/ml, which was significantly lower than the mean 25(OH)D level of 16.14±7.98 ng/ml among the control group (p value-0.025). The maternal serum concentration of 25(OH)D was 19.70 % lower on an average among the women who subsequently developed adverse maternal or fetal outcome compared with those having normal pregnancy outcome (Table 1).

Table 1: Correlation of 25(OH)D, serum calcium, serum albumin & serum alkaline phosphatase levels between cases and controls

	Cases N=39	Controls N=39	p-value
25(OH)D levels (ng/ml) Mean ± SD (Range)	12.96 ± 6.38 (5.22-31.94)	16.14 ± 7.98 (7.16-49.48)	**0.025***
Serum Calcium levels (mg) Mean ± SD (Range)	9.41 ± 1.17 (6-11)	9.44 ± 1.07 (8-12)	0.97
Serum Albumin levels (g%) Mean ± SD (Range)	3.77 ± 0.60 (2.2-5.0)	3.68 ± 0.54 (2.2-4.8)	0.49
Serum alkaline phosphatase (IU/ml) Mean ± SD (Range)	44.78 ± 48.36 (16-243)	32.25 ± 8.26 (28-56)	0.11
25(OH)D levels on basis of vitamin D deficiency N(%)			
<10 ng/ml 10-32 ng/ml 32-100 ng/ml	17 (43.6%) 22 (56.4%) 0 (0%)	05 (12.8%) 32 (82.1%) 02 (5.1%)	**0.003*(a)**

* p-value significant; OR - odds ratio; CI - confidence interval
(a) OR=4.94 95% CI (1.44 - 19.35)

In the study done by Mulligan et al. (2010), severe vitamin D deficiency has been taken as serum 25(OH) vitamin D level of less than 10ng/ml.[14] In the present study prevalence of severe vitamin D deficiency in the study population has been found to be 54.69 % which is a matter of great concern.

It was observed that the prevalence of severe vitamin D deficiency 25(OH)D level < 10 ng/ml) was 43.6% in cases group, where as it was only 12.8% in control group.(Table- 1) The difference was statistically significant (p value = 0.003) (Table 3). Hence severe vitamin D deficiency increases the risk of development of adverse outcome by 5 fold (OR- 4.94, CI 1.44-19.35). However no statistically significant difference was seen in mean serum calcium levels (mg) among cases and control (9.41 ± 1.17 Vs 9.44 ± 1.07, p value 0.97). In a similar study by Bodnar et.al. (2007), vitamin D deficiency in pregnancy < 50 nmol/l (20 ng/ml) of 25(OH)D3 was associated with an almost 4-fold odds of severe preeclampsia and vitamin D deficiency < 37.5 nmol/l (15 ng/ml) was even associated with a 5- fold risk of developing preeclampsia.[15]

A higher incidence of gestational hypertension was observed in severe vitamin D deficiency group than in vitamin D inadequacy group (p value 0.01) (Table 2). Risk of development of gestational hypertension was increased by approximately 6 fold in patients with severe vitamin D deficiency as compared to vitamin D insufficiency group. However no statistically significant association was observed between severe vitamin D deficiency and occurrence of GDM (Gestational diabetes mellitus), PPROM (Preterm premature rupture of membrane) and IUGR (Intrauterine growth restriction).

Table 3: Adverse pregnancy outcome based on 25(OH)D levels

Adverse outcome	25(OH)D levels <10 ng/ml N=22	25(OH)D levels 10-32 ng/ml N=54	p-value
Gestational hypertension N(%)	07 (31.8%)	04 (7.4%)	**0.01* (a)**
GDM N(%)	04 (18.2%)	04 (7.4%)	0.22
PPROM N(%)	00 (0%)	08 (14.8%)	0.09
IUGR N(%)	05 (22.7%)	05 (9.3%)	0.14
IUGR + PPROM N(%)	0 (0%)	01 (1.9%)	1.00
PIH + IUGR N(%)	01 (4.5%)	0 (0%)	1.00

* p-value significant; GDM - Gestational diabetes mellitus, PPROM – Preterm premature rupture of Membrane; IUGR - Intrauterine growth restriction; OR - odds ratio; CI - confidence interval
(a) **OR=5.83 95% CI (1.25 - 30.21)**

CONCLUSION

Prevalence of severe vitamin D deficiency (<10 ng/ml) in early pregnancy was calculated to be 54.69 % which is a matter of great concern. There is paucity of well-defined clinical guidelines classifying vitamin D status in Indian population. Larger studies are needed to standardize the population based values of vitamin D levels in both pregnant and non pregnant Indian population as well as to quantify the burden of the disease. In view of the global prevalence of vitamin D deficiency among women in childbearing age and infants it would be desirable to initiate simple and rapid assays for quantification of vitamin D, and 25(OH)D, levels in general population, both in rural and urban areas. Recent guideline advocates supplementation of oral cholecalciferol during pregnancy both for therapeutic and prophylactic purposes.in general 400IU is recommended for all low risk women, those high risk for developing preeclampsia should be supplemented with 800 IU/ day.[16] There is a need to develop similar guidelines specific for Indian women owing to different demographic, socioeconomic and geographic status of India. Improving vitamin D level in pregnant women as well as other age groups by simple measures like adequate sun exposure, dietary calcium intake, taking vitamin rich foods, lifestyle modification, periconceptional vitamin D supplementation and food fortification of vitamin D is also desired.

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