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Original Research Paper

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LOW MATERNAL VITAMIN D LEVELS AND RISK OF DEVELOPING HYPERTENSIVE DISORDERS OF PREGNANCY

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ABSTRACT Preeclampsia is thought to originate in abnormal angiogenesis and immunologic adaptation occurring during implantation and trophoblast invasion at the beginning of pregnancy. There is evidence that vitamin D affects transcription and function of genes responsible for trophoblast invasion, angiogenesis critical for implantation, and fetal allograft immunologic "tolerance".[1]

KEYWORDS :

This case control study was done in uncomplicated primigravidas of 18 to 25 years of age to find the association between early pregnancy maternal vitamin D level and risk of developing hypertensive disorders of pregnancy namely, gestational hypertension, preeclampsia and eclampsia. Early pregnancy vitamin D level of 21 cases developing hypertensive disorders of pregnancy were compared to control group who had uncomplicated pregnancy events.

The mean 25(OH)D level in subjects developing hypertensive disorders of pregnancy was 12.54±6.87 ng/ml as compared to 16.14±7.98 ng/ml among the control group, however the difference was not statistically significant. Severe vitamin D deficiency (25OH D level <10 ng/ml) in less than 20 week of gestation was significantly higher in subjects of case group as compared to the control group (63.6% vs. 12.8%) (p value-0.002) (OR-11.2). Risk of development of gestational hypertensive disorders were increased by aproximatly 6 fold in patients with severe vitamin D deficiency as compared to vitamin D insufficiency group.

Preeclampsia, as identified by new onset hypertension and proteinuria during pregnancy, is a serious disorder affecting 5–8% of pregnancies, and is alleviated only by delivery of the placenta. Preeclampsia is thought to originate in abnormal angiogenesis and immunologic adaptation occurring during implantation and trophoblast invasion at the beginning of pregnancy. There is evidence that vitamin D affects transcription and function of genes responsible for trophoblast invasion, angiogenesis critical for implantation, and fetal allograft immunologic "tolerance".[1] Vitamin D regulates angiogenic processes through direct effects on angiogenesis gene transcription, including vascular endothelial growth factor (VEGF).[2] One hypothesis is that low vitamin D levels impair the normal Th1 to Th2 cytokine balance, with higher Th1 cytokine expression adversely affecting the immunological tolerance of embryo implantation.[2] Some of the vitamin D supplementation studies to prevent preeclampsia showed protective effects of vitamin D.[3] The first known study in this context was a controlled trial in London in the 1940's -1950's with 5644 women in which a reduction of 31.5% in incidence of preeclampsia (PE) was seen in women who received a dietary supplement containing vitamins (2,500 IU vitamin D), minerals and fish oil in comparison to the control group who did not receive any supplement.[4] One small randomised control trial (RCT) conducted in India, however finds no association of vitamin D supplementation (1,200 IU vitamin D/day and 375 mg calcium/day) with a reduced risk for preeclampsia but a mean reduction of 8 mmHg in diastolic blood pressure was observed.[5] In a nested case-control study 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.[6] Although 2000 Cochrane Library review concluded that there is not enough evidence to evaluate the effect of prenatal vitamin D supplementation on adverse pregnancy outcomes.Seasonal patterns in preeclampsia support a role for vitamin D and sunlight. The highest incidence of preeclampsia has been observed in winter (when UVB light is limited), and lowest incidence in summer (when UVB light is plentiful).[6]Clear seasonal pattern in preeclampsia among the 20,794 white women in the cohort was substantially blunted among the 18,916 black women.[6] Taken together, the published literature suggests that there is substantial promise for vitamin D in the prevention of preeclampsia.

AIMS AND OBJECTIVE

To study the association of vitamin D levels in early pregnancy and risk of developing hypertensive disorder of pregnancy in subgroup of Indian population.

MATERIAL AND METHOD

The study was conducted in the Department of Gynaecology and Obstetrics at Nalanda Medical College and Hospital Patna, Bihar from May 2019 to March 2020. A total of 200 Primigravidae with singleton pregnancy, between age 18 – 35 yrs and less than 20 weeks of gestation were enrolled in the study after taking informed consent. 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. Serum sample 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. Twenty one subjects developed hypertensive disorder of pregnancy (gestational hypertension, 7 preeclampsia, 3 eclampsia) during antenatal follow up.

The 25(OH)D level was estimated in all cases (21) and equal number of matched control (not developing any complication) using 25(OH)D ELISA Kit. Serum 25(OH)D was assayed using a commercial Enzyme-linked immunosorbent assay kit (DLD Diagnostika GMBH, Germany).

RESULT AND DISCUSSION

Table 1: Comparative study of serum 25(OH) D levels between cases who developed hypertensive disorders of pregnancy and control group.

	Hypertensive disorders of pregnancy N=21	**Control group** N=21	p-value
25(OH)D levels (ng/ml) Mean ± SD (Range)	12.54 ± 6.87 (5.22-26.57)	16.14 ± 7.98 (7.16-49.48)	0.18
25(OH)D levels on the basis of months of sample collection (ng/ml)			
March-June Mean ± SD (Range)	10.45 ± 2.52 (8.93-13.36)	16.98 ± 9.27 (9.64-49.48)	**0.03***
July-October Mean ± SD (Range)	8.35 ± 2.11 (5.22-9.72)	16.83 ± 7.93 (7.16-34.82)	**0.001***
November-February Mean ± SD (Range)	18.3 ± 8.76 (7.68-26.57)	14.13 ± 5.78 (7.19-22.21)	0.06
25(OH)D levels on basis of vitamin D deficiency N(%)			
<10 ng/ml 10-32 ng/ml 32-100 ng/ml	13 (63.6%) 08 (36.7%) 0 (0%)	02(12.8%) 17 (82.1%) 02 (5.1%)	**0.002*(α)**

* p-value significant; OR – odds ratio; CI - confidence interval

(α) OR= 11.2, 95% CI (1.88 - 69.96)

The mean 25(OH)D level in subjects developing hypertensive disorders of pregnancy was 12.54±6.87 ng/ml as compared to 16.14±7.98 ng/ml among the control group, however the difference was not statistically significant. It was also observed that women serum 25OHD concentration was significantly less in months of March-June and July-October who developed hypertensive disorders of pregnancy (p value 0.03 and 0.001 respectively). Severe vitamin D deficiency (25OH D level <10 ng/ml) in less than 20 week of gestation was significantly higher in subjects of case group as compared to the control group (63.6% vs. 12.8%) (p value-0.002) (Table 1) (OR-11.2).

Hence severe vitamin D deficiency before 20 weeks of gestation increases the risk of occurrence of gestational hypertension by 11.2 fold [(OR-11.2)(CI 1.88-69.66)]. No significant difference in occurrence of gestational hypertension was found among different months of sample collection. It was also observed that serum 25OHD concentration was comparatively less in months of March-June and July-Oct in subjects who developed gestational hypertension as compared to subjects with normal pregnancy outcomes (p value 0.03 and 0.001) (Table 1). A higher incidence of gestational hypertension was observed in severe vitamin D deficiency group than in vitamin D inadequacy group (p value 0.01). Hence risk of development of gestational hypertensive disorders was increased by aproximatly 6 fold in patients with severe vitamin D deficiency as compared to vitamin D insufficiency group.

In one prospective cohort study done by Shand et al (2004-2007) in British Columbia no association between low serum 25(OH) concentrations in the first half of pregnancy and subsequent risk of preeclampsia or adverse pregnancy outcomes was seen.[7] On the other hand a nested case-control study among 1198 nulliparous pregnant women conducted by Lisa M. Bodnar et al (1997–2001), the adjusted serum 25(OH)D concentrations in early pregnancy were lower in women who subsequently developed preeclampsia compared with controls [geometric mean, 45.4 nmol/ L, and 95% confidence interval (CI), 38.6 –53.4 nmol/L, vs. 53.1 and 47.1–59.9 nmol/L; $P < 0.01$]. There was a monotonic dose-response relation between serum 25(OH)D concentrations at less than 22 week and risk of preeclampsia. After confounder adjustment, a 50-nmol/l decline in 25(OH)D concentration doubled the risk of preeclampsia (adjusted odds ratio, 2.4; 95% CI, 1.1–5.4).[6]

While studies in the second and third trimester of pregnancy suggest an association of hypovitaminosis D and preeclampsia, a nested-case control study conducted by Powe et al. in first trimester suggested that, total and free 25 (OH)D3 levels were not independently associated with subsequent preeclampsia.[8] Robinson et al. (2010) measured maternal plasma 25(OH)D concentrations of 50 women at the time of diagnosis of early-onset severe preeclampsia (EOSPE)—severe preeclampsia diagnosed before 34 weeks of gestation—and compared these with the concentrations of the 100 control pregnant women. They reported a 63% decreased odds of EOSPE with every 25-nmol/L increase in the plasma 25(OH)D concentrations of the EOSPE patients.[9]

Vitamin D supplementation studies to prevent PE showed protective effects of vitamin D. In a cohort study by Haugen et al. (2009) of over 23000 nulliparous women, a higher total vitamin D intake of 15-20 mg/day compared with <5mg/day had lower rate of preeclampsia (OR 0.76,95% CI 0.6- 0.9).[10] One small RCT conducted in India, however finds no association of vitamin D supplementation (1,200 IU vitamin D/day and 375 mg calcium/day) with a reduced risk for PE but a reduction in diastolic blood pressure of 8 mmHg was observed.[11] The cited studies on vitamin D and preeclampsia are not only conducted in different populations but also differ considerably in their experimental set-up, definition of vitamin D deficiency, inclusion criteria and possible confounders so that the discrepancy in study results cannot easily be explained and large-scale clinical trials are awaited to clarify this issue.

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