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ORIGINAL ARTICLE

Role of 25-Hydroxy Vitamin D Concentration in Early Pregnancy and Pregnancy Outcomes in Indian Population: A Prospective Observational Study

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ABSTRACT

Background: Pregnancy-related low levels of 25-hydroxyvitamin D [25(OH)D] are a common but avoidable issue. Neonatal 25(OH) D levels and the related health effects are directly impacted by low pregnancy 25(OH) D levels. There is little information and comprehension on the therapeutic significance and ramifications of these correlations.

Methods: This was a prospective observational study conducted among pregnant women over a period of 4 months. Serum vitamin D levels were measured in all the included subjects at the first interaction. Data on date of delivery, birth weight, length and gestational age were collected prospectively for all the patients at the time of delivery. Statistical analysis was performed using the SPSS 20 software database. The qualitative and quantitative data were presented as percentages and means ± SD, respectively. The risk factors were analysed univariately using the chi-square test and the student's "t" test. For multivariate analysis, every variable that had a P value less than 0.05 in the univariate analysis was chosen. A significance threshold of $p<0.05$ was established.

Results: The prevalence of vitamin D deficiency was 41%, of which nearly 14% had critically low levels, with a majority, 52%, belonging to the 25-35 years. Although the incidence of vitamin D deficiency (67/131), as well as critically low levels (23/47), was more frequent among gravida 2, the difference was not statistically

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significant (p = 0.13 and 0.09, respectively). There was no statistically significant difference in the maternal complications and outcomes between those with and without vitamin D deficiency. The maternal outcomes were not different even among women with critically low levels compared to those without. The incidence of low birth weight was significantly higher in the cohort with critically low levels of vitamin D (42% vs. 16%, p = 0.004). The incidence of other neonatal outcomes was not different.

Conclusion: The prevalence of vitamin D deficiency was higher among pregnant women aged 25-35 years. A higher incidence of low birth weight was observed.

KEYWORDS

• Vitamin D Deficiency • Pregnancy •Maternal • Neonatal • Outcome

INTRODUCTION

One of the main modifiable factors influencing newborn nutritional status and the health outcomes of both the mother and her offspring is maternal nutritional status. Pregnancy-related low levels of 25-hydroxyvitamin D (25(OH)D) are a prevalent but avoidable issue.[1,2] Vitamin D has an impact on immune system development and infection, cell proliferation and differentiation, and hormone pathways, all of which contribute to overall health and illness prevention. Furthermore, through calcium metabolism, vitamin D plays a crucial role in the skeletal system's growth and development. With vitamin D linked to placental and immune function, neurodevelopment, and lung development, low maternal 25(OH)D levels have also been linked to an increased risk of adverse maternal and neonatal outcomes, such as gestational diabetes, preeclampsia, preterm birth, and low-birth-weight infants.[3-5] For the best possible health of the mother, fetus, and newborn, adequate 25(OH)D levels must be maintained during pregnancy.[6] Maternal vitamin D levels during pregnancy play a major role in determining the vitamin D levels of the newborn.[7] Thus, low pregnancy-related 25(OH)D levels have a direct impact on neonatal 25(OH)D levels and the resulting health effects.

Low levels of 25-hydroxyvitamin D (25-OHD), the greatest indicator of vitamin D status in humans, have been linked to an increased risk of pregnancy complications, including gestational diabetes, pre-eclampsia, infections, caesarean delivery, and foetal growth limitation, according to observational data. Notwithstanding these results, nothing is known about the clinical significance and ramifications of these correlations. Determining the prevalence of vitamin D in pregnant women and its effect on feto-maternal outcomes was the study's goal.

METHODS

This was a prospective observational study conducted among pregnant women coming to the ESI hospital, Hyderabad, for antenatal visits at the first ANC visit over a period of 4 months from January 2022 to April 2022. Those with prior comorbid conditions, age < 18 years, and pregnant women lost to follow-up were excluded from the study. Serum vitamin D levels were measured in all the included subjects at the first interaction. Data on date of delivery, birth weight, length, and gestational age were collected prospectively for all the patients at the time of delivery. Statistical analysis was performed using the SPSS 20 software database. The quantitative variables were expressed as means ± SD and qualitative variables as percentages. The chi-square test and student's "t" test were used in the univariate analysis of the risk factors. For multivariate analysis, every variable that had a P value less than 0.05 in the univariate analysis was chosen. A significant threshold of $p < 0.05$ was established.

RESULTS

Majority 52% of the subjects belonged to the age group of 25-35 years, followed by 18–25 years, 41%, and more than 35 years, 6%. The prevalence of vitamin D deficiency was 41%, of which nearly 14% had critically low levels. There was no statistically significant difference between the age groups with respect to the prevalence of vitamin D deficiency and its criticality (p=0.13).

Table 1: Age Distribution

0.04	No. of Women (%)	No of Women Having Vit. D Deficiency (%)	Statistical Significance	No of Women Having Critically Low Levels of Vit. D (%)	Statistical Significance
18 -25	132 (41.5)	59 (44.69)		17 (12.8)	
25 - 35	166 (52.2)	66 (39.75)		26 (15.6)	
>35	20 (6.28)	6 (30)		4 (20)	
Total	318	131	P = 0.13	47	P = 0.133

Although the incidence of vitamin D deficiency (67/131), as well as critically low levels (23/47), was more frequent among gravida 2, the difference was not statistically significant (p = 0.13 and 0.09, respectively).

Table 2: Incidence with Respect to Parity

Parity	No. of Women	Incidence of Vit. D Deficiency	Statistical Significance	Critically Low Vit. D	Statistical Significance
Primi	136	58		18	
2	157	67		23	
3	18	4		4	
>3	7	2		2	
Total	318	131	p=0.12	47	p=0.09

There was no statistically significant difference in the maternal complications and outcomes between those with and without vitamin D deficiency pre-eclampsia (8% vs. 12%, p = 0.38), gestational diabetes (12% vs. 9%, p = 0.54), premature rupture of membranes (9% vs. 11%, p = 0.65), preterm labor (14% vs. 8%, p = 0.23), and cesarean section (68% vs. 66%). The maternal outcomes were not different even among women with critically low levels compared to those without.

Table 3: Maternal Complications among Vitamin D Deficiency Subjects

Maternal Outcome	Women with Vit. D Deficiency (%)	Women without Vit. D Deficiency (%)	Statistical Significance
Pre-eclampsia	8	12	Odds ratio= 0.6616 95 % CI: 0.2618 to 1.6716 Significance level P = 0.3824
Gestational diabetes mellitus	12	9	Odds ratio 1.3232 95 % CI: 0.5392 to 3.2469 Significance level P = 0.5409
Premature rupture of membranes	9	11	Odds ratio 0.8119 95 % CI: 0.3256 to 2.0247 Significance level P = 0.6550
Pre-term labor	14	8	Odds ratio 1.7366 95 % CI: 0.7047 to 4.2797 Significance level P = 0.2303
Caesarean section	68	66	Odds ratio 1.0224 95 % CI: 0.6741 to 1.5509 Significance level P = 0.9169

Table 4: Maternal Complications among Critically Low Levels of Vitamin D

Maternal Outcome	Women with Critically Low Vit. D	Women without Vit. D Deficiency	Statistical Significance
Pre eclampsia	4	12	Odds ratio 0.9147 95 % CI: 0.2799 to 2.9895 Significance level P = 0.8827
Gestational diabetes mellitus	5	9	Odds ratio 0.9835 95 % CI: 0.2976 to 3.2506 Significance level P = 0.9782
Premature rupture of membranes	4	11	Odds ratio 1.6005 95 % CI: 0.5077 to 5.0457 Significance level P = 0.4221
Pre-term labor	5	8	Odds ratio 1.8155 95 % CI: 0.5628 to 5.8559 Significance level P = 0.3182
Caesarean section	24	66	Odds ratio 1.0119 95 % CI: 0.5192 to 1.9721 Significance level P = 0.9724

With respect to neonatal outcomes, the incidence of low birth weight was significantly higher in the cohort with critically low levels of vitamin D (42% vs. 16%, p = 0.004). The incidence of other neonatal outcomes was not different— IUGR (35% vs. 34%, p = 0.91), admission to NICU (47% vs. 42%, p = 0.54), stillbirth/IUD (7% vs. 5%, p = 0.43).

Table 5: Foetal Complications among Vitamin D Deficiency Subjects

Fetal Outcome	Women with Vit. D Deficiency	Women without Vit. D Deficiency	Statistical Significance
Low birth weight	24(18.3)	21(16.1)	Odds ratio 1.1642 95 % CI: 0.6117 to 2.2158 P = 0.6433
IUGR	35	34	Odds ratio 1.0294 95 % CI: 0.5938 to 1.7847 Significance level P = 0.9178
Admission to NICU	47	42	Odds ratio 1.1723 95 % CI: 0.7023 to 1.9570 Significance level P = 0.5431
Still birth/IUD	7	5	Odds ratio 1.4113 95 % CI: 0.4362 to 4.5665 Significance level P = 0.5653

Table 6: Foetal Complications among Critically Low Levels of Vitamin D

Fetal Outcome	Women with Critically Low Vit. D	Women without Vit. D Deficiency	Statistical Significance
Low birth weight	20(42.5)	21(16.1)	Odds ratio 3.8448 95 % CI:1.8283 to 8.0853 Significance level P = 0.0004
IUGR	14	34	Odds ratio 1.9765 95 % CI:0.9336 to 4.1841 Significance level P = 0.0750
Admission to NICU	14	42	Odds ratio 0.8889 95 % CI:0.4304 to 1.8357 Significance level P = 0.7502
Still birth/IUD	2	5	Odds ratio 1.1111 95 % CI:0.2081 to 5.9313 Significance level P = 0.9019

DISCUSSION

Vitamin D deficiency is becoming more widely acknowledged as a public health issue since it has been linked to a number of harmful health effects, including pregnancy outcomes. Low levels of 25-hydroxyvitamin D (25-OHD), the greatest indicator of vitamin D status in humans, have been linked to an increased risk of pregnancy complications, including gestational diabetes, pre-eclampsia, infections, caesarean delivery, and fetal growth limitation, according to observational data.[8] Notwithstanding these results, nothing is known about the clinical significance and ramifications of these correlations.

Numerous studies have looked at variables related to pregnancy-related 25(OH) D levels.[9-11] Pregnancy-related 25(OH)D levels have been linked to a number of environmental factors, such as sun exposure (UVB radiation causes the skin to produce cholecalciferol), the time of year when blood is drawn (summer months are expected to have higher serum 25(OH)D concentrations), and other factors.[11] A prior study found that race was the most significant risk factor for vitamin D deficiency or insufficiency and that low 25(OH)D levels are more prevalent in non-white groups and those with higher melanin pigmentation.[2] Low 25(OH)D levels during pregnancy have also been associated with maternal alcohol and tobacco use, poorer educational attainment, and low dietary vitamin D intake and supplement use.[12,13]

Hyppönen *et al*. looked into the connection between early 25(OH)D consumption and the development of preeclampsia during pregnancy. They discovered that women who took regular 25(OH)D supplements throughout the first year of life had a halved risk of preeclampsia.[14] Additionally, Bener *et al*. observed a strong correlation between maternal 25(OH)D insufficiency during pregnancy and a higher risk of preeclampsia, anemia, and GDM (Gestational Diabetes Mellitus).[15] Scholl *et al*. discovered that secondary hyperparathyroidism, which was linked to a higher risk of preeclampsia, occurred in certain women with 25(OH)D insufficiency.[16]

The role of 25(OH)D concentration in preeclampsia or gestational hypertension was examined in recent research.17,18 The concentrations of the active form of 25(OH)D and $1,25(OH)_2D$ should be taken into account while discussing preeclampsia. 25(OH)D is changed into $1,25(OH)_2D$ by the enzyme 25-hydroxyvitamin D-1 alpha-hydroxylase (1 alpha-OHase). This enzyme is greatly diminished in the preeclamptic placenta, which may result in inadequate levels of 25(OH) D's active form.[19] Based on the information that is now available, low levels of 25(OH) D may not always translate into low levels of 1,25(OH)2D.[20] Nevertheless, research by Abbasalizadeh *et al*. discovered that a 25(OH) D shortage caused hypocalcemia, which raises the risk of preeclampsia by 8.5 times.[18]

In the present study, there was no statistically significant difference in the maternal complications and outcomes between those with and without vitamin D deficiency. Also, the maternal outcomes were not different even among women with critically low levels compared to those without. In contrast, women with low (as opposed to high) 25(OH) D levels during pregnancy had a statistically significant greater risk of preeclampsia in the Jensen *et al*. study;[21] in fact, none of the women in the high vitamin D group experienced preeclampsia. Preeclampsia rates were lower in women (40% with a self-reported history of physician-diagnosed asthma) with 25(OH)D levels ≥75 nmol/L in early and late pregnancy (10–18 and 32–38 weeks) compared to those who were insufficient at both time points (2.3 vs. 11.9%), according to a secondary analysis of an RCT of vitamin D supplementation during pregnancy.[22]

We did not find that people with vitamin D insufficiency had a higher incidence of gestational diabetes, in contrast to prior studies. Insulin resistance brought on by pregnancy and decreased compensatory insulin production are the causes of gestational diabetes. The relationship between the 25-OHD level and the risk of gestational diabetes may be explained by a number of factors. Research indicates that vitamin D increases insulin responsiveness to glucose transport, which in turn enhances insulin sensitivity. Furthermore, vitamin D may influence the development of pre-eclampsia by regulating and expressing genes that are involved in early placental development. It is unknown what biological basis there is for the relationship between birth weight and 25-OHD insufficiency, despite the fact that it may impact fetal growth through its impact on fetal bone development. The relationship between biomolecular mechanisms and pregnancy problems and fetal outcomes is currently poorly understood.[23,24]

Serum 25-OHD levels and the incidence of gestational diabetes were found to be significantly inversely correlated in a recent systematic study.[25] Additional research on this subject has been published since the release of this review, with additional clinically significant findings that have not yet been succinctly summed up. With respect to neonatal outcomes, in the present study, the incidence of low birth weight was significantly higher in the cohort with critically low levels of vitamin D. The incidence of other neonatal outcomes was not different.

The fetus develops, and the risk of unfavorable pregnancy outcomes is reduced when 25(OH)D concentrations and the ideal quantity of its metabolites are present. Pregnant women who have low levels of 25(OH)D in their bodies are more likely to experience health issues for both themselves and their unborn children. Numerous negative neonatal outcomes are linked to inadequate levels of 25(OH)D, including low birth weight, premature and small-for-gestational-age births, head development limitation, and the length and weight of the fetus during the third trimester. Asthma and wheezing in children, respiratory syncytial infection in children at 1 year of age, the decline in respiratory status, BPD in preterm newborns, and Apgar score at 1 and 5 minutes < 7 points have also been noted. Since 25(OH)D affects the synthesis of surfactant, which has the ability to stimulate the formation of peptides (β2-defensins and cathelicidins) with pronounced bactericidal activity, a deficiency during pregnancy affects fetal skeletal formation and reduces fetal bone mass. It also has an effect on the child's susceptibility to diseases immediately after birth. Additionally, in the fetal–maternal interface, 25(OH)D can control both innate and adaptive immune responses.

Despite the fact that prior meta-analyses have discovered a correlation between low birth weight and preterm birth in pregnant women with vitamin D insufficiency (<50 nmol/L).[26,27] In our investigation, Jensen *et al*.,[21] did not find a difference in these results. Although it was not statistically significant, they did note a clinically significant difference between the low and high vitamin D groups in terms of NICU admissions and infant respiratory distress. More than half of prematurely born children had a 25(OH)D deficit (less than 20 ng/mL), according to a study. Fariba Aghajafari *et al*.,[28] also discovered a link between 25-OHD insufficiency and unfavorable pregnancy outcomes and birth characteristics in a systematic review and meta-analysis. According to a study by Vasilyeva *et al*., supplementing with 25(OH) D at a concentration of 4000 IU/day has been shown to reduce negative neonatal outcomes, including fetal growth retardation, hypoxia, fetal cerebral damage, and 25(OH) D deficit.[29] However, not every researcher has discovered a link between newborn outcomes and 25(OH)D insufficiency. Cooper *et al*. (2016) showed that the whole-body bone mineral content in infants born to mothers administered cholecalciferol 1000 IU/day was not significantly different from that in infants born to mothers administered with a placebo.[30]

Vitamin D supplementation may be a simple way to reduce the risk of these adverse outcomes. According to a recent comprehensive analysis, there is insufficient data to assess how supplementing during pregnancy affects the health of the mother, fetus, or newborn. Notwithstanding this drawback, the researchers demonstrated that low birth weight was protected by daily vitamin D treatment (800–1000 IU/day).[31] Together with our findings, these data imply that low levels of 25-OHD may be a modifiable risk factor during pregnancy and that medical professionals should at the very least advise expectant mothers to adhere to the most recent recommendations regarding daily doses of vitamin D. Although this seems like a straightforward recommendation, there is ongoing discussion on the proper amount of vitamin D to consume during pregnancy, as bodies that advise on best practices in prenatal care recommend between 600 and 2000 IU/day.

The limitations of the present study were the small study sample and short duration of the study. Also, it was a hospital and not a community-based study, and the pool of patients was diverse. Large, carefully planned randomized controlled trials are still required to ascertain whether methods to maximize maternal 25-OHD levels are beneficial in enhancing pregnancy and neonatal outcomes, even though small trials of vitamin D supplementation during pregnancy have shown a decrease in the risk of having small for gestational age infants.

CONCLUSION

The prevalence of vitamin D deficiency was higher among pregnant women aged 25-35 years. A higher incidence of low birth weight was observed. The literature on vitamin D insufficiency in pregnancy is growing rapidly, with several studies examining a variety of populations and outcomes. This literature requires comprehensive review to characterize the associations of vitamin D insufficiency with the outcomes.

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