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ORIGINAL ARTICLE

Observational Study of Third-Trimester Vitamin D3 Supplementation and Implications for Mothers and Neonates at Term

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Abstract

Objective To determine 25-hydroxyvitamin D (25OHD) levels in pregnant women at 28 weeks and supplement based on these levels and check maternal and neonatal levels after delivery at term.

Design This is a prospective observational study wherein pregnant women aged 18–35 years received cholecalciferol from 28 weeks till delivery at term. Women with 25OHD levels $\geq$ 75 nmol/L received 12.5 µg/day, those with levels 50–74.9 nmol/L received 100 µg/day and those with levels $\leq$ 49.9 nmol/L received 1500 µg/week.

Results Of 555, 532 women (95.8%) completed the study. Of 532, 77 (14.5%) women had 25OHD $\geq$ 75 nmol/L at 28 weeks; 34/77 (44.15%) became deficient at term, and the mean 25OHD reduced from 99 ± 29.9 to 77 ± 30.4 nmol/L ($p < 0.0001$). One hundred and seventy-one women had 25OHD 50–74.9 nmol/L at 28 weeks; in 99 (57.89%), levels normalised at term, and mean

25OHD increased from 60.5 ± 7.5 to 78.2 ± 21.9 nmol/L ($p < 0.0001$). Two hundred and nineteen women had 25OHD 25–49.9 nmol/L at 28 weeks; in 135 (61.64%), levels normalised at term, and mean 25OHD increased from 36.6 ± 7.5 to 83.3 ± 32.7 nmol/L ($p < 0.0001$). Sixty-five women had 25OHD < 25 nmol/L at 28 weeks; In 39 (60.94%), levels normalised at term, and the mean 25OHD increased from 17.9 ± 5 to 80.6 ± 34.1 nmol/L ($p < 0.0001$). Seven neonates (1.3%) had cord blood ionised calcium values < 1 mmol/L, and all these had 25OHD < 50 nmol/L (mean 22.2 ± 2.5 nmol/L).

Conclusions Standard 12.5 µg/day supplementation in women with normal 25OHD levels at 28 weeks leads to deficiency in 44% women by term. Cholecalciferol in doses of 100 µg/day and 1500 µg/week leads to a significant increase in 25OHD levels in vitamin D-deficient pregnant women though nearly 40% may still have deficient levels at term along with their newborns. Only 1.3% of newborns had hypocalcaemia.

Keywords Neonates · Pregnancy · Vitamin D · 25-Hydroxy vitamin D · Cholecalciferol · Supplementation

Introduction

Vitamin D deficiency affects a significant portion of pregnant Indian women [1–3]. Maternal deficiency also affects the foetus, which is entirely dependent on the mother for its supply of 25-hydroxyvitamin D (25OHD) via transplacental transfer during the third trimester, and which establishes the foetal and neonatal stores [4].

However, there are differing views on the definition of vitamin D sufficiency and deficiency based on the serum 25OHD values [5]. The Institute of Medicine (IOM) considers 50 nmol/L as the lower limit of sufficiency [6], whereas the US Endocrine Society defines sufficiency as 75 nmol/L and above [7]. Other researchers consider levels of 80 nmol/L and above as optimal for pregnant women [8–11].

Apart from a well-acknowledged effect on bone and calcium metabolism, vitamin D and its related metabolites may possibly influence cardiovascular diseases, cancer, respiratory infections, asthma, conditions associated with pregnancy, like pre-eclampsia and gestational diabetes, and also birth outcomes [12]. It is therefore vital to determine the optimal antenatal vitamin D dose that would positively influence maternal, foetal and neonatal health outcomes without any adverse effects. A number of studies, employing a wide variety of antenatal vitamin D doses to prevent maternal and neonatal deficiency, have been conducted, yielding varied results [8–18].

However, most of these utilised a blanket supplemental dose that was given to all the women considered as deficient as per the study protocol. We conducted a prospective observational study to determine antenatal 25OHD levels in pregnant women at 28 weeks and to administer vitamin D3 (cholecalciferol) based on these levels: routine supplementary doses for those with normal levels and higher doses for those found insufficient and deficient. The 25OHD levels were rechecked when the women delivered at term, along with neonatal (cord) blood levels.

Methods

Subjects

The study was conducted in the antenatal clinic of a tertiary-level mother and child care hospital in Bangalore, southern India. Pregnant women aged 18–35 years were offered inclusion in the study at 28 weeks of gestation. Gestational age was estimated based on the first day of the last menstrual period and correlated with a first-trimester ultrasound scan. Participant enrolment occurred from May 2014 to January 2015, and the pregnancies were completed between July 2014 and April 2015.

Subjects were excluded if they were already on vitamin D supplementation, anticonvulsants, or had any medical condition that affected calcium (Ca) and vitamin D metabolism, including renal and hepatic disease; haemoglobin < 70 g/L; systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; complicated medical or obstetric history; multiple gestation; reported prior history of delivery of an infant with a major congenital anomaly, birth asphyxia or perinatal death or thyroid surgery. Those who delivered before term (< 37 weeks) or were non-compliant with the regime were also excluded from the final analysis.

The baseline visit at 28 weeks consisted of a questionnaire, anthropometry and blood pressure measurement. The 25OHD levels were checked, and the women received cholecalciferol till delivery. At enrolment, the women were divided into 4 groups based on the levels of 25OHD: Group A (< 25 nmol/L), Group B (25–49.9 nmol/L), Group C (50–74.9 nmol/L) and Group D (≥ 75 nmol/L). Women in Group D were considered sufficient [6] and received 12.5 µg/day (500 IU/day) of cholecalciferol. Women in Group C received 100 µg/day (4000 IU/day). Women in Groups A and B received cholecalciferol 1500 µg/week (60,000 IU/week).

Thereafter, participants were contacted weekly at their homes and during antenatal visits to check compliance with the regime and symptoms related to pregnancy complications and hypocalcaemia or hypercalcaemia.

Maternal venous blood specimens for 25OHD were collected at the time of delivery, irrespective of when the last vitamin D dose was received. Cord blood specimens for 25OHD and ionised Ca levels were collected from the umbilical artery immediately after delivery of the placenta. Maternal and cord serum samples were dispatched to the laboratory (Techmed, Bangalore) immediately.

Serum 25OHD was quantified by chemiluminescent microparticle immunoassay (ARCHITECT i1000SR, Abbott Diagnostics, Lake Forest, IL, USA). Serum ionised calcium levels were checked using potentiometry (Gem Premier 3000, Instrumentation Laboratory, Bedford, MA, USA).

Ethical clearance for the study was obtained from the institutional review board.

Statistical Analysis

We utilised paired *t* test, ANOVA and Pearson's correlation coefficient using Epi Info 7.1.15 (Centers for Disease Control and Prevention, Atlanta, GA, USA) for statistical analysis.

Results

A total of 555 women were eligible for inclusion in the study, out of whom 532 (95.8%) completed the study. Eighteen women (3.2%) were excluded as they delivered prematurely and 5 (0.90%) due to non-compliance.

For the final analysis, 65 women from Group A, 219 from Group B, 171 from Group C and 77 from Group D were considered eligible, along with their newborns (Table 1).

Women in Group A received 1500 µg/week of cholecalciferol. In 39 (60%), levels normalised at term, in 18 (27.7%) rose to 50–74.9 nmol/L, in 5 (7.7%), rose to 25–49.9 nmol/L, and in 3 (4.6%) remained less than 25 nmol/L. The mean 25OHD level increased from 17.9 ± 5 to 80.6 ± 34.1 nmol/L ($p < 0.0001$).

Women in Group B received 1500 µg/week of cholecalciferol. In 135 (61.6%), the levels normalised at term, in 57 (26%) rose to 50–74.9 nmol/L, in 21 (9.6%) remained at 25–49.9 nmol/L, and in 6 (2.8%) reduced to less than 25 nmol/L. The mean 25OHD level of the cohort increased from 36.6 ± 7.5 to 83.3 ± 32.7 nmol/L ($p < 0.0001$).

Women in Group C received 100 µg/day of cholecalciferol, and In 99 (57.89%), the levels normalised at term, in 58 (33.91%) remained at 50–74.9 nmol/L, in 13, reduced to 25–49.9 nmol/L, and in 1, reduced to less than 25 nmol/L. The mean 25OHD level increased from 60.5 ± 7.5 to 78.2 ± 21.9 nmol/L ($p < 0.0001$).

In Group D, on routine 12.5 µg/day of cholecalciferol, 34 (44.15%) women became deficient at term. The remaining 43 women maintained levels ≥ 75 nmol/L. The mean 25OHD level reduced from 99 ± 29.9 to 77 ± 30.4 nmol/L ($p < 0.0001$).

None of the participants had a 25OHD value over 250 nmol/L (100 ng/mL). The highest value in a participant at 28 weeks was 241.5 nmol/L. The highest value observed in a mother at term was 233.2 nmol/L (33.5 nmol/L at 28 weeks). Her offspring also had the highest 25OHD level of 188.5 nmol/L among all the neonates.

The cord blood levels of 25OHD in the neonates correlated ($R = 0.83$) with those of the mothers at term (Fig. 1).

Among the neonates, only 7 had cord blood ionised calcium values less than 1 mmol/L and all these neonates had 25OHD levels below 50 nmol/L (mean 22.2 ± 2.5 nmol/L). Thirty-four had cord blood ionised

Table 1 Characteristics of the various groups of patients as per the 25OHD level at enrolment

25OHD levels at 28 weeks	Group A <25 nmol/L ($n = 65$)	Group B 25–49.9 nmol/L ($n = 219$)	Group C 50–74.9 nmol/L ($n = 171$)	Group D ≥75 nmol/L ($n = 77$)
Dose of cholecalciferol	1500 µg/week	1500 µg/week	100 µg/day	12.5 µg/day
Mean maternal age in years (SD)	30.8 (3.5)	30.7 (3.4)	29.9 (3.27)	29.8 (3.0)
Mean gestation in weeks (SD)	38.2 (1.4)	38.2 (1.2)	38.2 (1.4)	38.2 (1.2)
Mean maternal 25OHD levels at 28 weeks in nmol/L (SD)	17.9 (5)	36.6 (7.3)	60.5 (7.5)	99 (29.9)
Maternal 25OHD levels at delivery in nmol/L (SD)	80.6 (34.1)*	83.3 (32.7)*	78.2 (21.9)*	77 (30.4)*
Cord 25OHD levels in nmol/L (SD)	75.7 (29.7)$^{\#}$	74.4 (29.7)$^{\#}$	72.4 (21.7)$^{\#}$	68.9 (27.4)$^{\#}$
Cord ionised calcium in mmol/L (SD)	1.37 (0.09)	1.37 (0.14)	1.37 (0.11)	1.36 (0.13)
Mothers with 25OHD < 75 nmol/L at term	26 (40%)	85 (38.8%)	72 (42.1%)	46 (59.7%)
Neonates with 25OHD < 75 nmol/L at term	32 (49.3%)	112 (46.6%)	85 (49.7%)	47 (61%)

*$p < 0.001$; $^{\#}p < 0.001$ (compared with 28 weeks levels)

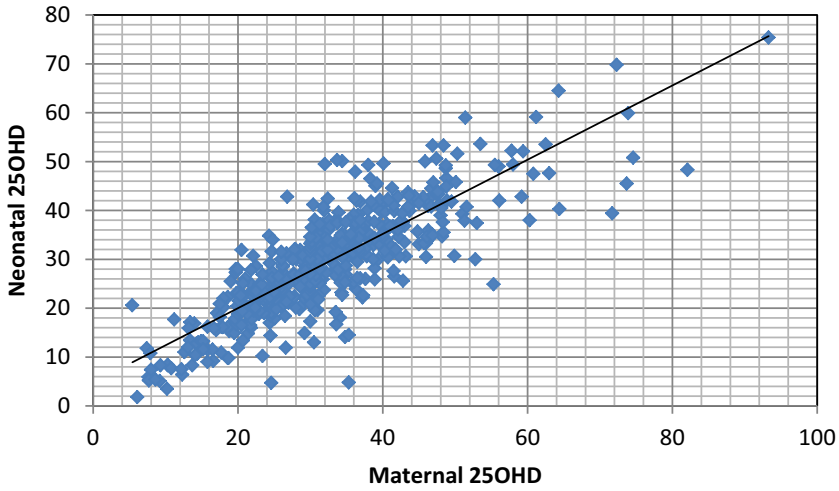

Fig. 1 Correlation between maternal and neonatal 25OHD levels

calcium values below 1.2 mmol/L, and all of them had 25OHD levels less than 50 nmol/L (mean 24.5 ± 2.5 nmol/L). None of the neonates in this cohort developed symptomatic hypocalcaemia.

Discussion

In our study, we employed the US Endocrine Society recommendations of serum 25OHD of 75 nmol/L and above [7] for defining vitamin D sufficiency. Accordingly, 85.6% of women were found vitamin D-deficient at 28 weeks. This is similar to the findings of Hashemipour et al., who reported 81% deficiency among pregnant Iranian women at 26–28 weeks of gestation using similar cut-offs [13]. Kumar et al. [1] from our own city reported levels less than 50 and 75 nmol/L in 71 and 90% of pregnant Indian women, respectively, at term. Sahu et al. [2] found 74% of pregnant Indian women as having 25OHD levels below 50 nmol/L in their study. Marwaha et al. [3] reported 25OHD levels below 50 nmol/L in 96% of pregnant Indian women.

Among the 455 pregnant women with vitamin D levels less than 75 nmol/L at 28 weeks in our study, (Groups A, B and C), third-trimester cholecalciferol supplementation raised serum 25OHD concentrations in 59.8% of mothers and 51.9% of neonates above the cut-off. We supplemented women with sufficient 25OHD levels at 28 weeks with 12.5 µg/day, which corresponds to the 2010 IOM recommendations [6]. However, a significant number of these women (40%) became deficient at term. This suggests that the standard supplemental dose may not be adequate to prevent deficiency in the third trimester. Hollis et al. [8] reported 50% deficiency (< 80 nmol/L) in women receiving 10 µg/day of vitamin D3 from 16 weeks of gestation till delivery at term. Dawodu et al. [11] also administered 10 µg/day to pregnant women from 12 to 16 weeks and reported 25OHD levels below 80 nmol/L in 90.5% at term. However, these women had a baseline mean 25OHD level of 21.5 nmol/L.

In Group C, third-trimester supplementation of 100 µg/day raised serum 25OHD concentrations in 57.89% of mothers and 50.29% of neonates above 75 nmol/L. This raised the mean 25OHD from a baseline of 60.5 nmol/L at 28 weeks of gestation to 78.2 nmol/L for mothers and 72.4 nmol/L for neonates at term. Hollis et al. [8] administered 100 µg/day cholecalciferol to pregnant women with a baseline mean 25OHD level of 59.8 nmol/L, from 16 weeks till term, and reported that 83.9% achieved 25OHD levels above 80 nmol/L (mean 110.5 nmol/L) at term.

Among the 284 pregnant women with 25OHD levels below 50 nmol/L (Groups A and B), third-trimester supplementation of 1500 µg/week raised the levels in 249 (87.67%) mothers and 230 (80.99%) of neonates above the IOM cut-off for sufficiency (50 nmol/L) and in 174 mothers (60.9%) and 150 neonates (52.8%) above 75 nmol/L without inducing hypercalcaemia or any other apparent short-term clinical adverse effects. The supplementation raised mean 25OHD from a baseline value of 32.2 to 82.7 nmol/L. Hashemipour administered 1250 µg cholecalciferol/week for 8 weeks in the third trimester and found higher 25OHD levels as compared to the control group receiving 10 µg/day (119.5 and 39.8 nmol/L, respectively) [13]. Hossain et al. [14] reported that daily supplementation with 100 µg of cholecalciferol starting at 20 weeks of gestation elevated 25OHD levels beyond 75 nmol/L in only 15% of mothers and none of the neonates. In this study, the baseline mean 25OHD level was 11.8 nmol/L. Kalra et al. [15] administered 1500 µg once in the second trimester and 3000 µg twice, once each in the second and third trimester, to pregnant women with

baseline median 25OHD levels 32 and 31.8 nmol/L, respectively, and reported attainment of levels above 50 nmol/L in 27 and 62.5%, respectively. Roth et al. [16] found that 100% of women and 95% of neonates attained 25OHD levels higher than 50 nmol/L at term from a baseline level of 44 nmol/L with third-trimester supplementation of 875 μg/week (125 μg/day). Dawodu et al. [17] reported that 65% of mothers achieved levels above 80 nmol/L from a baseline 25OHD level of 19.6 nmol/L with cholecalciferol supplementation of 100 μg/day from 12 to 16 weeks till term. However, only 47.6% of neonates attained levels above 50 nmol/L with this dose. Sablok et al. [18] administered 1500 μg of cholecalciferol once to women with 25OHD levels above 50 nmol/L, twice to women with levels 25–50 nmol/L and 4 times to those with levels below 25 nmol/L, in the intervention group, and reported higher serum 25OHD levels and lower incidence of preterm labour, pre-eclampsia and gestational diabetes and higher neonatal birth weights in them as compared to those in the non-intervention group who did not receive any cholecalciferol. Grant et al. [19] administered placebo, 25 and 50 μg daily to three groups of women from 27 weeks of gestation and found that proportion with 25OHD $\geq$ 20 ng/mL was larger in both intervention groups at 36 weeks of gestation (50, 91, 89%, respectively) and in the cord blood (22, 72, 71%). Sahu et al. [20] administered either no cholecalciferol or 1500 μg in the fifth month of gestation or 3000 μg each in the fifth and seventh gestational months and found a significant increase in 25OHD levels at delivery only in the last group (40.1 nmol/L at baseline and 53.4 nmol/L after delivery). Sahoo et al. [21] supplemented pregnant women with oral cholecalciferol 1500 μg units 4 weekly, 8 weekly or placebo and reported improved cord blood 25OHD, but no improvement in bone mineral content or density in offspring at 12–16 months.

In our study, we used a cholecalciferol dose of 1500 μg/week. The subjects received 13,500–16,500 μg in total. A prospective pharmacokinetic study in vitamin D-deficient non-pregnant healthy adults demonstrated efficacy and safety of a single oral dose of 15,000 μg of cholecalciferol [22]. The same group also reported the efficacy of a single oral dose of 15,000 μg of cholecalciferol in enhancing 25OHD and reducing parathyroid hormone (PTH) in adults with vitamin D deficiency [23]. With our dosing regime, 40% of the mothers in Groups A and B remained deficient at term, as did nearly 50% of their newborns. With a total cholecalciferol dose of 6000 μg, Sahu et al. [19] reported only 20% of women as achieving levels > 80 nmol/L at delivery. While the optimal dosing regime for moderate and severe vitamin D deficiency in pregnancy needs to be determined, our study also demonstrates the safety and efficacy of this regime as none of the women in our study or their offspring developed toxic 25OHD levels ($\geq$ 250 nmol/L) [24].

We also found significant correlation between the cord and maternal 25OHD levels at term. Similar findings have been reported in other studies [1, 13, 14, 16, 18]. However, Abbasian et al. reported a weak significant relationship between cord and maternal 25OHD levels [25].

In our study, no correlation was found between the maternal and cord blood 25OHD levels and cord blood ionised calcium levels ($R = 0.003$ and 0.09, respectively). This is in contrast to the findings of Aly et al. who reported significant correlation between maternal 25OHD levels and cord blood calcium [26].

Among the 532 neonates, 498 (93.6%) had cord blood ionised calcium values above 1.2 mmol/L, and among the remaining 34, all had 25OHD levels less than 75 nmol/L (mean 24.5 ± 2.5 nmol/L). Also, 525 neonates (98.7%) had a cord blood ionised calcium value greater than 1 mmol/L, only 7 had a cord blood ionised calcium value less than 1 mmol/L, and all these neonates had a 25OHD level less than 50 nmol/L (mean 22.2 ± 2.5 nmol/L). There was, however, no difference between the ionised calcium levels of vitamin D-sufficient and vitamin D-deficient neonates (1.36 ± 0.13 vs 1.37 ± 0.11, $p = 0.1289$). Hashemipour et al. [11] reported significantly higher neonatal calcium level in the treatment group than that in the control group. Harrington et al. found higher cord blood total serum calcium in the supplemented group, but the difference in the albumin-adjusted calcium was not statistically significant [27].

Exact dietary intake of Ca or vitamin D was not calculated, but was assumed to be normal as the participants all belonged to a higher socio-economic status and were not found to be malnourished. We did not take into consideration the average sunlight exposure of the participants and also did not measure serum concentrations of 1,25-dihydroxyvitamin D, PTH or vitamin D-binding protein, but we believe these would not have significantly changed the conclusions.

Conclusions

This study in Bangalore determined that vitamin D deficiency is widespread among pregnant urban Indian women and that standard third-trimester supplementation in women with sufficient levels at 28 weeks may result in deficiency by term in 60% women and in their newborns.

Supplementation of 100 μg/day for mild deficiency and 1500 μg/week for moderate to severe deficiency helps correct the deficiency in 60% women and 50% of the newborns, and is safe in the third trimester and not associated with hypervitaminosis.

The current recommendations for antenatal vitamin D supplementation of pregnant women should be reviewed, and further studies are needed to establish the optimal treatment of vitamin D deficiency in pregnancy.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest

Human Rights All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments and comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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