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ORIGINAL ARTICLE

Vitamin D deficiency and supplementation during pregnancy

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Summary

Objective Vitamin D is essential for skeletal health and prolonged deficiency results in infantile rickets and adult osteomalacia. The aim of this study is to determine the vitamin D status in pregnancy and to evaluate the effects of daily and of single-dose vitamin D supplementation.

Design A prospective randomized study at St Mary's Hospital London.

Patients A total of 180 women (Indian Asian, Middle Eastern, Black and Caucasian) were recruited at 27 weeks gestation and randomized into three treatment groups: a single oral dose of 200 000 IU vitamin D, a daily supplement of 800 IU vitamin D from 27 weeks until delivery and a no treatment group.

Measurements Vitamin D (25-hydroxyvitamin D), PTH and corrected calcium levels in mothers at 27 weeks and at delivery and cord 25-hydroxyvitamin D and corrected calcium levels.

Results The final maternal 25-hydroxyvitamin D levels were significantly higher in the supplemented group [daily dose (median) 42 (IQR 31–76) nmol/l, stat dose (median) 34 (IQR 30–46) nmol/l *vs.* median 27 (IQR 27–39) nmol/l in the no treatment; $P < 0{\cdot}0001$] and significantly fewer women with secondary hyperparathyroidism in the supplemented group (10% in daily dose *vs.* 12% in stat dose *vs.* 27% in the no treatment; $P < 0{\cdot}05$). Cord 25-hydroxyvitamin D levels were significantly higher with supplementation [daily dose median 26 (IQR 17–45) nmol/l, stat dose median 25 (IQR 18–34) nmol/l *vs.* median 17 (IQR 14–22) nmol/l in no treatment; $P = 0{\cdot}001$].

Conclusion Single or daily dose improved 25-hydroxyvitamin D levels significantly. However, even with supplementation, only a small percentage of women and babies were vitamin D sufficient. Further research is required to determine the optimal timing and dosing of vitamin D in pregnancy.

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Introduction

Vitamin D comes from both diet and the effect of sunlight on the skin. However, the majority of vitamin D comes from sunlight exposure and the main cause of vitamin D deficiency is lack of sunlight (half an hour of sunlight in the middle of the day during summer delivers approximately 50 000 IU of vitamin D in people with white skin). Dietary deficiency such as vegetarians and vegans compounds this, particularly among individuals with dark skin or with reduced exposure to sunlight.[1–4] Ethnic groups at risk of vitamin D deficiency include those from the Indian subcontinent and Middle East.[5–8] In recent years the prevalence of vitamin D deficiency has increased[9,10] and the incidence of rickets has risen in the UK and other developed countries.[11] There is a high prevalence of vitamin D deficiency in pregnant women from nonwestern countries residing in northern Europe,[12] indeed vitamin D deficiency during pregnancy is an ongoing epidemic.[13]

Vitamin D deficiency in pregnancy may affect women as well as their newborn. This can lead to high bone turnover, osteomalacia and hypovitaminosis D myopathy in the mother.[14,15] Maternal vitamin D deficiency during pregnancy can also affect calcium homeostasis, causing hypocalcaemia and craniotabes. Neonatal rickets is an uncommon consequence of vitamin D deficiency during pregnancy, whereas rickets in infants and children result from a combination of lack of exposure to vitamin D *in utero* and postnatally (due to lack of vitamin D in breast milk).[11] There is conflicting evidence regarding the effects of vitamin D on maternal weight gain and foetal growth.[16]

At present there is no enough evidence to evaluate the effectiveness of vitamin D in pregnancy and therefore, vitamin D supplementation is not routinely offered to all pregnant women. The Cochrane Database suggests more research is needed in vitamin D supplementation in pregnancy.[17]

Many studies have investigated vitamin D deficiency in pregnancy in different ethnic minority groups and the method of supplementation.[16] There is evidence that a stat dose is as effective as a daily dose with no adverse effects.[18,19]

The aim of this study is to compare the vitamin D status of pregnant women in four ethnic groups and to evaluate the effects of daily and of single-dose vitamin D supplementation in pregnant women and their babies at delivery.

Methods

The study was approved by St Mary's Hospital Ethics Committee (Ref: 06/Q0702/172) and the Medicines and Healthcare products

Regulatory Agency . The study took place between April 2007 and November 2007. No routine screening for hypovitaminosis D or routine supplementation with vitamin D was carried out at this antenatal unit.

Recruitment

Women attending the routine antenatal clinic at St Mary's Hospital were given a leaflet regarding the vitamin D study in pregnancy at their first clinic visit. Information leaflets were available in four different languages (English, Arabic, Bengali and Farsi). Women were recruited at the time of their routine glucose challenge test at 27 weeks and written consent was obtained.

Inclusion criteria

We included pregnant women from the following ethnic populations; 45 Indian Asians, 45 Middle Eastern, 45 Black and 45 Caucasian women. Women who did not speak English were only included if a health advocate was able to interpret and a leaflet was provided in their language.

Exclusion criteria

Women with pre-existing sarcoidosis, osteomalacia, renal dysfunction and tuberculosis were excluded from the study.

Intervention

Women were randomized within each ethnic group to three arms; a daily dose of vitamin D (ergocalciferol) at 800 IU, a stat dose of 200 000 IU of (calciferol) or no treatment from 27 weeks until delivery. A previous supplementation study has shown that a stat dose of 200 000 IU is safe in pregnancy.[18]

Blood sampling

At 26–27 weeks gestation, the time of the glucose challenge test, maternal blood samples were taken to measure 25-hydroxyvitamin D, corrected calcium, PTH and alkaline phosphatase. A further blood sample was taken from the mother at the time of the delivery to measure 25-hydroxyvitamin D, corrected calcium and PTH levels in the mother and 25-hydroxyvitamin D, corrected calcium levels in the neonate. It was not feasible to measure PTH rp in the cord bloods due to cost.

Documentation

Each participant completed a lifestyle questionnaire. This included details regarding the ethnic group, maternal age, parity, height, weight, cigarette smoking, alcohol consumption (in units per week) or any use of recreational drugs. Ethnicity was self-reported. We also documented the estimated hours of daily sun exposure, clothing style (fully covered defined as burkha use and partially covered defined as use of headscarf), use of vitamins, diet (vegetarian or vegan) and clinical features suggestive of vitamin D deficiency.

Outcome measures

Primary outcome measure: Maternal and cord 25-hydroxyvitamin D levels at delivery.

Secondary outcome measure: Maternal PTH and corrected calcium levels at delivery.

Definitions

Previous supplementation studies suggest a 25-hydroxyvitamin D level below 50 nmol/l is insufficient for bone health in adults and children.[20–23] We define 25-(OH) D sufficiency as levels ≥ 50 nmol/l, insufficiency as levels 25–50 nmol/l and deficiency as levels < 25 nmol/l.[24] Small for gestational age was defined as birth weight less than the 10th percentile after adjustments for gestation at delivery, infant sex, maternal ethnicity, parity, height and weight.[25]

Method of randomization

Subjects were randomized within each ethnic group. Computer generated random number lists were drawn up by an independent researcher, with randomization in blocks of 15. All study personnel and participants were not blinded to treatment assignment. The person seeing the pregnant women allocated the next available number on entry to the trial, and each woman collected her tablets directly from the hospital pharmacy department or her local pharmacy. Women were given instructions to swallow the tablets whole and to avoid other multivitamin supplements that would lead to higher vitamin D intake.

Sample size

To determine the number needed to demonstrate a difference in the vitamin D levels in the no treatment group *vs.* the supplemented group is significant (Power 90%, test of significance at 5% level), we calculated that at least eight women in each ethnic group for each arm of treatment would be needed for the study.[18]

To account for drop-outs, preterm delivery, delivery at another hospital and the assumption that 75% of eligible patients will accept randomization, we considered 15 women in each ethnic group for each arm of treatment would be adequate for the study ($n = 180$).

Statistical analysis

Baseline data for the treatment groups were summarized by the mean (SD) or median (IQR) for normally and non-normally distributed data, respectively, and comparisons between groups were made by the Kruskal–Wallis for non-normally distributed data or by one-way ANOVA for normally distributed data. Univariate comparisons of dichotomous data were made using the χ^2- or Fisher's exact test as appropriate. The *P*-values for all hypothesis tests were two-sided and statistical significance was set at $P < 0{\cdot}05$. Multiple regression analysis was used to determine which maternal characteristics and obstetric history were significant predictors of vitamin D levels. The statistical software package SPSS 15·0 (SPSS Inc.,Chicago, IL) was used for all data analyses.

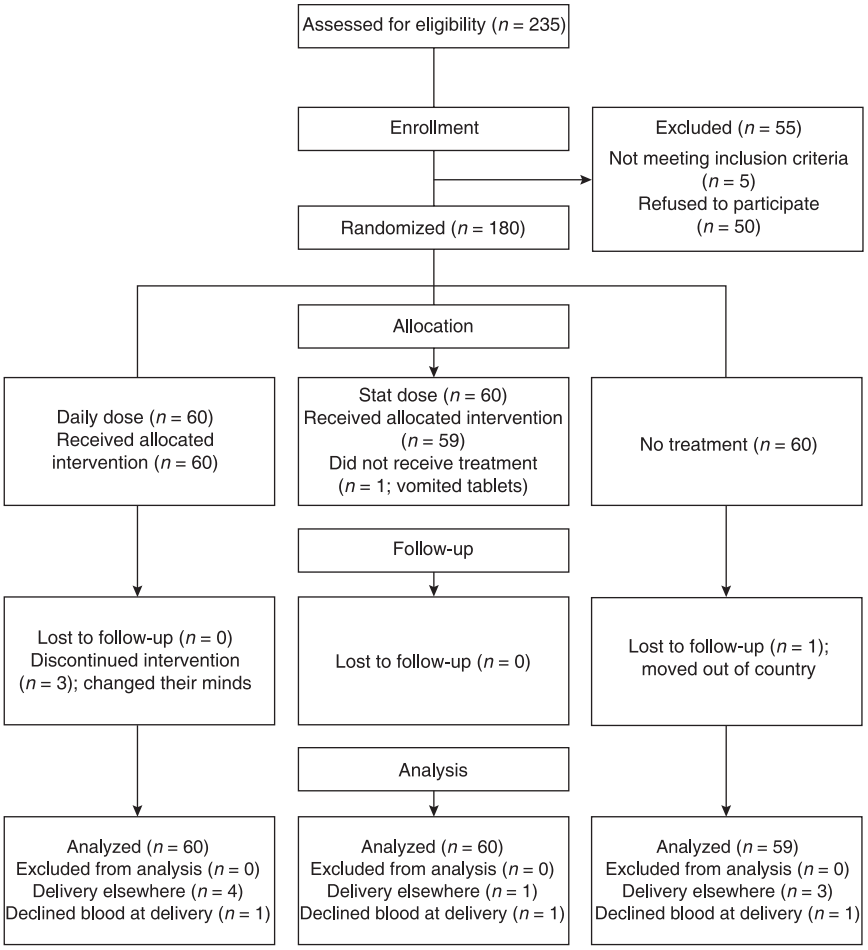

Fig. 1 Trial profile.

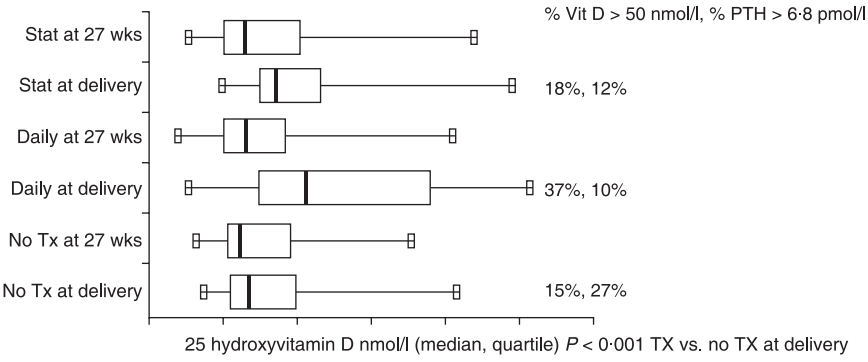

Fig. 2 Maternal 25-hydroxyvitamin D levels; % 25-hydroxyvitamin D ≥ 50 nmol/l; % PTH > 6·8 pmol/l according to each treatment group.

Compliance

Tel calls were made during the course of their pregnancy to check for compliance in all women on the daily treatment documenting the percentage of tablets actually taken. If the women in the nontreatment arm were found to be deficient in calcium, we would advise them to take supplementation. Any adverse effects would be reported to the Medicines and Healthcare Regulatory Agency.

Results

The trial profile is represented in Fig. 1. There was a correlation between maternal and cord vitamin D level at delivery ($r = 0{\cdot}45$; $P < 0{\cdot}0001$). All ethnic groups had normal calcium levels at 27 weeks and at delivery. The final maternal 25-hydroxyvitamin D levels at delivery were significantly higher in the supplemented group [daily dose median 42 (IQR 31–76) nmol/l, stat dose median 34 (IQR 30–46) nmol/l *vs.* median 27 (IQR 27–39) nmol/l in the no treatment; $P < 0{\cdot}0001$] (Fig. 2). Cord 25-hydroxyvitamin D levels were significantly higher in the supplemented groups [daily dose median 26 (IQR 17–45) nmol/l, stat dose median 25 (IQR 18–34) nmol/l *vs.* median 17 (IQR 14–22) nmol/l in no treatment; $P = 0{\cdot}001$] (Table 1).

When comparing the final maternal 25-hydroxyvitamin D levels between the two methods of supplementation, although the *P*-value was close to 0·5 ($P = 0{\cdot}07$), suggesting a difference, it did not reach significance at the 5% level. However, with supplementation, we have

Table 1. Median maternal and cord 25-hydroxyvitamin D, the percentage of cord 25-hydroxyvitamin D ≥ 50 nmol/l, the incidence of vitamin D deficiency, PTH and incidence of secondary hyperparathyroidism at 27 weeks and at delivery and according to treatment groups

	Maternal 25-hydroxyvitamin D Median, (IQR) nmol/l		Cord 25-hydroxyvitamin D		25-hydroxyvitamin D < 25 nmol/l *n*, (%)		PTH pmol/l Median (IQR)		PTH > 6·8 pmol/l *n*, (%)	
Treatment	27 weeks	At delivery	Median, (IQR) nmol/l	≥ 50 nmol/l *n*, (%)	27 weeks	At delivery	27 weeks	At delivery	27 weeks	At delivery
None	25 (21–38)	27 (27–39)	17 (14–22)	0	30/60 (50%)	20/60 (40%)	4·6 (2·6–7·6)	4·7 (2·55–18·7)	18/60 (30)	16/60 (27)
Daily	26 (20–37)	42 (31–76)***	26 (17–45)***	8/60 (13)*	27/60 (45%)	7/60 (13%)***	3·8 (2·4–6·6)	2·6 (1·5–14·4)**	14/60 (23)	6/60 (10)**
Stat	26 (21–41)	34 (30–46)**	25 (18–34)***	2/60 (3)	25/60 (42%)	4/60 (7%)***	4·4 (2·6–6·8)	3·3 (1·4–16·6)**	14/60 (23)	7/60 (12)*

Comparison with no treatment group: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

only achieved vitamin D sufficiency > 50 nmol/l in 30% of women treated with supplementation and only 8% of babies were vitamin D sufficient at term in the treatment group. There were significantly fewer women with secondary hyperparathyroidism in the supplemented group compared to no treatment group (10% in daily dose *vs.* 12% in stat dose *vs.* 27% in the no treatment; $P < 0·05$) (Table 1).

Maternal characteristics according to each ethnic group are shown in Table 2. There was no significant difference in the baseline characteristics across the three treatment groups. The mean gestational age at randomization was 27 weeks (26–29 weeks). There was a significant difference in the 25-hydroxyvitamin D and PTH levels in Asian, Middle Eastern and Black women compared with the Caucasian women. Asian (47%), Middle Eastern (64%) and Black women (58%) were vitamin D deficient compared with Caucasian women (13%); $P < 0·0001$. Secondary hyperparathyroidism (PTH levels > 6·8 pmol/l; $n = 46$) was significantly higher in Asian (27%), Middle Eastern (49%) and Black women (24%) compared to Caucasian women (2%); $P < 0·05$. Multiple regression analysis showed ethnic group, age, parity and daily sun exposure to be significant predictors of vitamin D levels (Table 3).

There was no significant difference in the gestational age at delivery, birth weights or number of infants with a birth weight less than the 10th percentile in the supplemented group compared to the no treatment group [15% in daily dose *vs.* 13% in stat dose *vs.* 17% in the no treatment ($P = 0·7$)]. There was one unexplained stillbirth at 41 weeks and one neonatal death at day two as a result of meconium aspiration; both cases were in the no treatment arm of the Asian group.

One woman developed significant proteinuria and was diagnosed with nephritic syndrome, therefore her vitamin D treatment was stopped. One woman had vomited her tablets 15 min after taking her stat dose. In the daily treatment, three women changed their minds and three women reported nausea and vomiting. Overall, the average percentage of tablets taken was 60% in the daily vitamin D regime.

Discussion

This is the first study to compare 25-hydroxyvitamin D levels and the effects of a daily *vs.* a single-dose vitamin D supplementation in pregnant women of four ethnic groups. Within each ethnic group, the supplemented groups all had significantly higher vitamin D levels compared with the no treatment group. However, even with supplementation, we have only achieved vitamin D sufficiency in 30% of treated women. Our choice of single dose of vitamin D (800 IU) may be inadequate during pregnancy to raise the levels sufficiently. The other reason may be due the reference range for vitamin D deficiency may be different during pregnancy. One criticism of this study may be in the method of randomization. The treatment was not blinded to the women or doctor and there was no placebo tablet. Seasonal variation can impact upon the change in 25-hydroxyvitamin D levels in the no treatment group. However, the enrolment was similar in each month both across the ethnic groups with no significant difference between the treatment groups.

Table 2. Maternal characteristics and biochemical results at 27 weeks according to each ethnic group

Characteristics	Indian Asian	Middle Eastern	Black African	Caucasian
Age mean, (range)	29 (19–44)**	31 (20–37)	31 (18–45)*	33 (22–42)
Daily sun exposure < 1 h *n*, (%)	30 (67)***	26 (58)**	13 (29)	9 (20)
Clothing restriction				
None *n*,(%)	24 (53)***	13 (29)***	30 (67)**	42 (93)
Partially covered *n*, (%)	15 (33)**	23 (51)***	12 (27)**	2 (4)
Fully covered *n*, (%)	6 (13)	9 (20)*	3 (7)	1 (2)
> 50% of tablets taken; *n*, (%)	11 (73)	9 (64)	7 (47)*	12 (80)
Vitamin D deficient < 25 nmol/l *n*, (%)	21 (47)***	29 (64)***	26 (58)***	6 (13)
Vitamin D insufficient ≥ 25–50 nmol/l *n*, (%)	23 (51)	15 (33)*	16 (36)*	27 (60)
Biochemical results median, (interquartile range)				
Maternal results at 27 weeks				
25-hydroxyvitamin D (nmol/l)	25 (19–32)***	21 (18–28)***	23 (20–27)***	42 (29–50)
PTH (pmol/l)	5·5 (4·0–7·0)***	6·7 (4·4–8·9)***	3·1 (2·3–6·2)*	2·5 (1·7–3·8)
Corrected calcium (mmol/l)	2·3 (2·3–2·4)	2·3 (2·3–2·4)	2·3 (2·3–2·4)	2·3 (2·3–2·4)
Alkaline phosphatase (μmol/l)	81 (71–97)***	77 (66–104)*	77 (67–87)	72 (59–80)
Glucose (mmol/l)	6·6 (5·2–8·2)*	5·8 (5·2–7·0)	5·7 (4·8–6·5)	5·5 (4·8–6·2)

Comparison with Caucasian group: *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.

Table 3. The results of multiple regression analysis in the prediction of 25-hydroxyvitamin D with correlation coefficient, 95% CI and *P* values

Variable	Correlation coefficient	95% CI		*P* value
Racial origin				
Asian	–0·127	–0·200	–0·053	0·0008
Middle Eastern	–0·175	–0·248	–0·103	< 0·0001
Black	–0·155	–0·226	–0·085	< 0·0001
Sun exposure				
1–2 h	0·064	0·001	0·128	0·046
2–4 h	0·112	0·051	0·173	0·0004
More than 4 h	0·129	0·020	0·238	0·020
Age	0·007	0·003	0·011	0·001
Parity	–0·064	–0·115	–0·013	0·014

A study of 90 healthy lactating and 88 nulliparous women carried out in United Arab Emirates compared the efficacy of daily and monthly vitamin D supplementation in vitamin D deficient pregnant women and found the monthly dosing to be a safe and effective alternative to daily dosing especially in nonconcordant patients.[19] In this study, there was a wide interquartile range in the daily dosing group compared to the stat dose. This may reflect the compliance of the women with treatment.

This study has shown that vitamin D deficiency and secondary hyperparathyroidism are more common in the non-Caucasian ethnic groups. This finding is consistent in previous studies.[5–8] In this study, 13% of the Caucasian group is also found to be vitamin D deficient. This figure is similar to the recent epidemiological data that vitamin D deficiency is not only confined to at risk ethnic groups.[26]

Long-term vitamin D deficiency results in increased PTH concentrations, which in turn leads to osteomalacia.[16] This study has demonstrated secondary hyperparathyroidism to be significantly higher among ethnic minority groups, particularly the Asian and Middle Eastern groups confirming the vitamin D deficiency to be clinically significant. Our study has shown that after vitamin D supplementation, there was a significant reduction in the total number of women with secondary hyperparathyroidism at delivery. However, a reasonable proportion of women still had secondary hyperparathyroidism and only a small percentage of women were vitamin D sufficient despite supplementation (daily dose 37%, stat dose 18% *vs.* 15% in no treatment group). As for the neonate, only 8% of babies were found to be vitamin D sufficient in mothers that were supplemented.

Conclusion

Vitamin D deficiency is a large and growing problem in some ethnic groups in the UK. All pregnant women may benefit from vitamin D supplementation in pregnancy and in the postpartum period and this could be administered as a single dose. Further research is needed to determine the long-term consequences of maternal and neonatal vitamin D deficiency and the optimum timing and dosing of vitamin D in pregnancy.

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