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Vitamin D study in pregnant women and their babies

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ABSTRACT

Background and objectives: Vitamin D deficiency is very common in pregnant women. Deficiencies have been prevalent even in studies where over 90% of the women took prenatal vitamins. The current guidelines for vitamin D intake during pregnancy of 200 – 400 IU has little scientific support and has been recently challenged. We conducted this study to determine the prevalence of vitamin D deficiency among pregnant women and to evaluate the effectiveness and level of weekly oral 50,000 IU of vitamin D supplementation for the mother and the newborn.

Setting and design: Prospective study at Hamad Medical Corporation outpatient unit and delivery room.

Patients and Methods: Ninety seven pregnant women were recruited in their first trimester between December 2007 and March 2010. Weekly oral vitamin D (50,000 IU) were prescribed after an initial testing for serum level of 25-hydroxyvitamin D, parathyroid hormone, calcium, phosphorus, total protein and albumin. Other multivitamins supplementations were allowed during pregnancy. The same tests were repeated at each trimester. Umbilical cords vitamin D levels were determined at birth.

Results: Out of 97 patients, 8 patients dropped out from the study for several reasons, and 19 patients had pregnancy loss. Data were available for 97 women in the first trimester, 78 women in the second trimester and 61 women in the third trimester. The mean level of vitamin D level in the first trimester and prior to starting vitamin D supplementation was 17.15 ng/ml, 29.08 ng/ml in the second trimester, 27.3 ng/ml in third trimester and 22.36 ng/ml in newborns. There were no toxic levels of vitamin D in any of the women at the second or third trimesters or in the newborns. The mean levels of vitamin D in the second and third trimester were not significantly different in those women who were taking multivitamin supplementation and those who were not.

Conclusion: Weekly doses of 50,000 vitamin D during pregnancy maintains acceptable vitamin D level during pregnancy and the newborn's vitamin D level correlates with the mother's levels.

INTRODUCTION

Vitamin D is an important hormone in the body. It is important for multiple physiologic processes, including calcium absorption. In recent years there has been an increased understanding of the role that vitamin D plays in regulation of cell growth, immunity, and cell metabolism. Vitamin D receptors can be found in most tissues and cells in the body, and the impact of a vitamin D deficiency on the developing fetus and maternal health is of significant concern.

Because 25-hydroxyvitamin D crosses the placenta,[1] and fetal and cord blood levels of the new born vitamin D status correlate with the mother levels of vitamin D,[2,3] a higher level of vitamin D in the fetus may raise the concern of possible potential fetal harm.

A high prevalence of vitamin D insufficiency was found in pregnant women in different studies with different ethnic and geographical backgrounds.[4–8] The average prenatal vitamins contain 400 IU of vitamin D, which partially explains this high prevalence of vitamin D insufficiency in pregnant women. Vitamin D supplementation during pregnancy remains controversial and the current recommended requirement for vitamin D during pregnancy (200 – 400 IU/d) has little scientific support. This is due to the misconception about potential harm to the fetus. A recent study showed that a daily supplement of 4000 IU of vitamin D was required to sustain normal metabolism in pregnancy and this dose was effective and safe.[9]

In this study we evaluated the prevalence of vitamin D deficiency in pregnant women and evaluated the effect of weekly oral 50,000 IU of vitamin D on mothers' and newborn's level of vitamin D.

METHODS

This is a prospective observational study conducted at a single center at Hamad Medical Corporation in Doha, Qatar. The study was conducted between December 2007 and March 2010. Approval of this study was granted by the research and ethics committee of Hamad Medical Corporation under number 7095/07.

Pregnant women were invited to participate in the study at primary health centers and government hospitals through local announcement and advertisement. Written consent forms were obtained from the participants. Pregnant women were enrolled in the study if they were in their first trimester before 14 weeks of gestation and were requested to continue their pregnancy supplements as prescribed by an obstetrician. During the study, all subjects were supplemented with vitamin D2 tablets (50,000 IU) to be taken orally once per week with calcium tablets at total dose of 1200 mg per day that was divided in two doses.

The subjects were interviewed at each trimester to ensure that they were taking the study supplements and to report any side effects. To ensure compliance, the research nurse called each participant monthly and reminded them of the importance of taking the vitamin D and calcium and tablets for their next appointment. Vitamin D was supplanted from the hospital to the subject free of charge.

Blood samples were obtained for serum levels of calcium, phosphorus, alkaline phosphatase, total protein and albumin, 25-hydroxyvitamin D level and parathyroid hormone (PTH). The same blood tests done at entry in the first trimester were repeated in 2nd trimester and 3rd trimester. Umbilical blood cord samples were extracted to measure the level of 25-hydroxyvitamin D levels in newborns. Vitamin D level was assayed by using a "DiaSorin Liaison 25OH Vitamin D TOTAL" machine using a chemiluminescence assay to detect total 25-hydroxyvitamin D levels.

The mean standard deviation for continuous variables and frequency distribution with percentage for categorical variables was used in this study. Student – t-test: P value of 0.05 was considered as statistically significant level. SPSS 18.0 statistical package on Windows platform was used for this analysis.

RESULTS

Ninety-seven pregnant women were enrolled in the study. The age range was between 22 – 37 years. Forty-eight of the study subjects were Qatari and the rest were residents of Qatar. There was no difference in the vitamin D levels between the Qatari and the residents living in Qatar. Out of 97 women, 8 dropped out for different reasons, including leaving the country to their back home residency, and 19 subjects had pregnancy loss. The international figure for pregnancy loss ranges between 15 – 20%.

Data were available for 97 pregnant women in the first trimester, 78 pregnant women in the second trimester and 61 in the third trimester and their newborns.
A vitamin D level of less than 10 ng/ml was considered as deficiency and levels of more than 30 ng/ml were considered as insufficiency. Sixty-six patients (66/97) were found to have vitamin D levels of less than 20 ng/ml (58%), thirty one (31/97) 31.9% had levels less than 10 ng/ml.

Table 1. Levels of vitamin D, alkaline phosphatase, albumin, calcium level, total protein and PTH during all trimester, and baby vitamin D level.

	N	Minimum	Maximum	Mean	Std. Deviation
1st trimester results					
Total protein g/l	92	30	91	74.57	7.548
Alkaline phosphatase u/l	88	32	169	59.24	18.382
Albumin g/l	93	31	58	41.65	3.744
Calcium mmol/l	92	2.02	2.55	2.2773	.10,142
Phosphorus mmol/l	91	.81	71.00	1.9595	7.31,988
Vitamin D ng/ml	95	**3**	**48**	17.15	10.995
PTH ng/ml	86	3	191	39.90	27.726
2nd Trimester					
Albumin g/l	77	31	42	36.57	2.074
Calcium mmol/l	77	1.99	2.43	2.2177	.09209
Phosphorus mmol/l	76	.86	1.63	1.2216	.19,083
Vitamin D ng/ml	78	**5**	**70**	29.08	14.899
PTH ng/ml	76	7.00	152.00	35.2763	24.47,508
3rd trimester					
Total protein g/l	54	53	86	70.11	6.621
Alkaline phosphatase u/l	56	58	589	124.32	78.826
Albumin g/l	57	28	50	37.23	5.251
Calcium mmol/l	57	1.85	2.53	2.2449	.12,894
Phosphorus mmol/l	54	.87	1.78	1.2539	.16,761
Vitamin D ng/ml	61	**4**	**62**	27.38	12.411

Normal range for Table 1 parameters: Albumin 35 – 50 g/l, T.protein 60 – 80 g/l, alkaline phosphatase 40 – 129, corrected calcium 2.1-2.6 mmol/l, phosphorus 0.87 – 1.45, PTH 15 – 65 pg/ml.

During the first trimester, the lowest mean level of vitamin D was 3 ng/ml and the highest level was 48 ng/ml with a mean level of vitamin D level of 17.15 ng/ml. All other parameters were within normal range including calcium, phosphorus, alkaline phosphatase, albumin total protein and PTH. At the second trimester, the lowest vitamin D level was 5 ng/ml and highest was 70 ng/ml with a mean level of 29.08 ng/ml. At the third trimester, it was of 4 ng/ml and 59 ng/ml as the lowest and highest level respectively with a mean of 27.38 ng/ml. The range of vitamin D level in 61 umbilical cord blood samples of the newborns was 3 and 59 ng/ml with a mean level of 22.36 ng/ml (Table 1). During the study, calcium level was within normal range through out pregnancy, no hypercalcemia were observed, and the mean calcium levels were 2.27 mmol/l, 2.21 mmol/l and 2.24 mmol/l during first, second and third trimester respectively.

The mean parathyroid hormone level was within normal range (N: 15 – 65 ng/ml) during all trimesters except for one woman who had a high parathyroid hormone level; the level correlated with very low vitamin D levels. Her vitamin D level in the first trimester was 3 ng/ml and PTH was 191 ng/ml, vitamin D level was 5 ng/ml and PTH level was 152 ng/ml in the second trimester and in third trimester vitamin D was 4 ng/ml with a PTH level of 290 ng/ml, with normal level of calcium and alkaline phosphatase.

The level of vitamin D in newborns correlated with the mothers' 3rd trimester level with significant P value (Tables 1 and 2). Table 3 shows the level of vitamin D level in subjects who were on multivitamin supplement and those who were not on it before being recruited for

Table 2. Comparison of baby vitamin D to mothers 3rd trimester, it's correlated with significant P values.

	r	p-value
3rd trimester Vitamin D	0.63	<0.01

Table 3. Vitamin D levels between patients taking vitamin D before pregnancy and those not (0 means not on supplement, 1 means on supplement).

Vitamin D		Number	Mean	Std. deviation	P value
1st trimester	0	38	8.71	4.099	<0.001
	1	46	24.64	8.875	
2nd trimester	0	36	23.86	12.545	<0.01
	1	38	33.58	16.018	
3rd trimester	0	29	26.31	12.349	0.52 NS
	1	30	28.37	12.840	

the study. Both groups had no significant differences in the level of vitamin D in the second and third trimester and in the newborns' vitamin D levels.

We observed no toxic levels of vitamin D during the study and non reached levels above (>80 ng/ml) during pregnancy as the highest vitamin D level was 70 ng/ml in pregnant mothers, and no toxic level reached in their new born with a highest level of 59 ng/dl.

DISCUSSION

Vitamin D deficiency during pregnancy is a worldwide epidemic; different studies reported a prevalence ranging from 18–84% depending on the country of residence and clothing customs.[4–8] In a study from Iran, Kazemi et al. found hypovitaminosis D in 86% of the pregnant women at the time of the delivery and 75% of the newborns during wintertime and 46% of the mothers and 35% of the newborns during summer. Newborns' vitamin D levels correlated positively with maternal 25-hydroxyvitamin D ($p < 0.001$).[10] In a study from China, Jing Wang et al., reported 57.1% of pregnant women and 44.2% showed deficiency, and 97.4% of women and 96.1% of neonates showed vitamin D insufficiency.[11]

Bodnar et al.,[12] reported the prevalence of vitamin D deficiency and insufficiency in 200 Caucasian and 200 African-American pregnant women and in the cord blood samples of their neonates. In African-American women, vitamin D deficiency occurred in 29.2% and insufficiency in 54.1%, compared with 5% and 42.1% of Caucasian pregnant women. Ninety percent of the study's participants were taking prenatal vitamins. At delivery vitamin D deficiency and insufficiency occurred in 45.6% and 46.8% of African-American neonates, respectively, compared to 9.7% and 56.4% of Caucasian neonates.

The importance of vitamin D for fetal and infant skeletal development has long been recognized. Several studies have reported association between infant size and vitamin D status.[13,14] Reduced concentration of 25-hydroxyvitamin D in mothers during late pregnancy is associated with reduced whole body and lumbar-spine bone mineral content in their children at the age of 9 years.[15] Several studies hypothesized that low prenatal and perinatal vitamin D concentrations affect the functional characteristics of various tissues of the body, which leads to greater risk in later life of multiple sclerosis, cancer, insulin-dependent diabetes mellitus and schizophrenia.[16,17]

The current recommended dose of vitamin D during pregnancy differs in different parts of the world. The recommended daily intake of vitamin D is 200 IU/day in the United States, Australia, New Zealand and Canada.[18–20] In the UK, the daily recommended dose is 400 IU/day.[21] Historically, vitamin D supplementation during pregnancy was thought to be a risk factor for supravalvular stenosis in infants, which was based on a 1964 case report.[22]

Different studies suggested that the daily use 1000 IU,[23–27] 2000 IU,[28] 4000 IU,[29] and 6400 IU[30] would help to eliminate vitamin D insufficiency without apparent toxicity in pregnant women and their infants. All of this supports that 400 IU of vitamin D may be inadequate to raise the maternal vitamin D level to optimum level particularly for women living in Northern latitude, women with darker skin or covered women, as well as for women who are not exposed to sunlight, not on dietary supplements or have absorption and metabolic problems.

We used a 50,000 IU dose, as per our previous studies, which demonstrated no toxicity when vitamin D deficient rheumatology outpatient and health care professional were supplemented this dose.[31–32]

The concern of using higher doses of vitamin D might cause hypercalcemia, hypercalciuria, renal calculi and soft tissue and vascular calcification toxicity is likely to worsen with calcium supplementation. Hypercalcemia, which is the most worrying toxicity, occurs with vitamin D levels of more than 80 or 100 ng/ml; and in our study no one reached this level through out

pregnancy and in newborns with normal levels of calcium in spite of supplementation. The highest dose of vitamin D studied during pregnancy was given to 15 hypoparathyroid women who received 100,000 IU/day in order to maintain serum calcium. No adverse effects were observed in these mothers or their infants.[33]

Our study demonstrated that low vitamin D level is common in pregnant mothers in Qatar. Routine supplementation of pregnant mothers with 50,000 IU vitamin D per week resulted in improvement of vitamin D levels. Newborns' vitamin D levels correlate with the vitamin D level of their mothers. At the present time vitamin D supplementation is not part of antenatal care program in Qatar.

One of the limitations of our study was that compliance of the patient was determined by phone calls. Moreover, given that Qatar is sunny all year, levels of vitamin D were not correlated with the season; we knew that from our previous study that most of the population has low vitamin D levels. We need RCT of vitamin D supplementation with measurement of 25-hydroxy-vitamin D to determine the baseline status, the level achieved on supplementation with appropriate design to avoid any confounder, and to assess what is the appropriate level of vitamin D during pregnancy and in newborns with no complications or toxicity through out. Studies are underway in the US to establish vitamin D requirements during pregnancy (http://clinicaltrials.gov#R01HD043921).

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