JKAU: Med. Sci., **Vol. 14, No. 2**, pp. 61-69 (1428 A.H./ 2007 A.D.)

Vitamin D Status in Term Newborn at King Abdulaziz University, Jeddah, Saudi Arabia

NADIA M. FIDA, MD
Department of Pediatrics, Faculty of Medicine
King Abdulaziz University, Jeddah, Saudi Arabia
nadiafida@hotmail.com

ABSTRACT. Vitamin D is required for normal bone growth and mineralization. The aim was to determine the prevalence of hypovitaminosis D in full term newborns. Serum calcium, inorganic phosphorus, 25 (OH) vitamins D (25OHD), alkaline phosphatase, parathyroid hormone levels were studied in 41 cord blood of full term newborns. According to 25OHD levels in cord blood, the newborns were divided into three groups: Group I [25OHD <25 nmol/L, n=2], Group II [25OHD (25-50 nmol/L) n=9] and Group III [25OHD > 50 nmol/L, n=30]. There was no significant difference in the demographic characteristics between the three groups. 25OHD level declined significantly in Group I compared to Groups II and III with ($p<0.01$, $p<0.000$) and in Group II compared to Group III ($p<0.000$). Meanwhile, calcium in Group II declined considerably compared to Group III with ($p<0.05$). In all newborn, there was a significant positive correlation between creatinine and albumin ($r=0.359$, $p<0.05$) and inorganic phosphorus ($r=0.324$, $p<0.05$) and negative correlation between calcium and parathyroid hormone ($r=-0.396$, $p<0.01$). We observed high prevalence of physiologically significant hypovitaminosis D among full tern newborns, the magnitude of which warrants further research.

Keywords: Vitamin D, Cord blood, Newborn, 25-hydroxyvitamin D, Vitamin D deficiency.

Introduction

Vitamin D (VITD) plays a key role in bone development by promoting calcium absorption in the gut. Its main source is synthesis in the skin after cutaneous exposure to ultraviolet B rays. When northern latitudes, darker skin, sun blocks or lifestyle choices limit the exposure to sunshine, VITD levels can be maintained through the intake of supplements and foods that contain natural or added VITD. Adequate VITD concentrations during pregnancy are crucial to provide the calcium needed for fetal bone mineral accretion, most of which occurs in the final trimester. A severe deficiency in VITD takes a heavy toll on the growing skeleton by causing impaired mineralization of bone tissue (leading to osteomalacia) and of the growth plate (which manifests as rickets). Profound VITD deficiency during pregnancy can result in neonatal rickets[1-3].

Correspondence & reprint requests to: Dr. Nadia M. Fida
P.O. Box 80215, Jeddah, 21589 Saudi Arabia
Accepted for publication: 18 June 2007. Received: 10 December 2006.

It is well known that the breast milk contents of VITD is low and contributes little to the infants' VITD status[4,5]. In early infancy, the VITD status of breast-fed infants depends mainly on the store of VITD gained across the placenta during intrauterine life[6,7]. It is also known that VITD is one of the preventable risk factors of osteoporosis[8]. Thus, maternal VITD status is important to the bone health of the mother and her baby[9].

Although people in Saudi Arabia have a great chance to have sufficient ultraviolet light to maintain adequate VITD status by dermal synthesis, it seems that most of the women cannot benefit because of their general traditional attire. Therefore, we investigated the 25-Hydroxyvitamin D (25OHD), Parathyroid Hormone (PTH), calcium, inorganic phosphorus and alkaline phosphatase status in the cord blood of healthy, full term newborns.

Material and Methods

Umbilical cord blood samples were obtained from 41 neonates with gestational age of 33 – 41 wks, born at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, from April 2001 to April 2002. Protocol of this cross-sectional study was approved by the Human Ethics Committee of KAUH. Only women giving birth to a clinically healthy, single infant were included in the study. Exclusion criteria were known preexisting hypertension or previous preeclampsia; liver, renal, heart, or endocrine disorders; and use of nutritional supplements (calcium or VITD), diuretics, any kind of hormonal treatment, or magnesium sulfate therapy. A detailed history was obtained from each mother: maternal age, number of pregnancies, maternal socioeconomic and educational status, housing and VITD supplement; Apgar score in neonate; weight, height and circumference and pattern of feeding. After cleaning the umbilical cord and avoiding contamination with maternal blood, (3 ml) cord blood samples were collected at delivery; after centrifugation, serum samples were aliquot and frozen at -20°C until assay. According to 25OHD levels in cord blood, the newborns were divided into three groups: Group I [25OHD <25 nmol/L, n=2]; Group II 25OHD [25-50 nmol/L, n=9]; and Group III [25OHD > 50 nmol/L, n=30].

Routine hematological and biochemical tests like total protein, albumin, calcium, inorganic phosphorous, and alkaline phosphatase were measured with Boehringer Mannheim Hitachi System in the hospital's central laboratories. The measurement of serum 25OHD (level was determined using radioimmunoassay kit (Gamma-B 25-OH Vitamin D Kits, Immunodiagnostic System, UK). Serum 25OHD levels were estimated in duplicates along with the standard supplied with the kit. The assay was run in accordance with the manufacturer's protocol.

In the current study, we defined VITD insufficiency as a serum 25OHD level below 5 mmol/L. Serum 25OHD levels below 25 nmol/L were considered to be VITD deficiency, even without clinical disease [9].

All statistical procedures were performed with the Statistical Package for Social Science (SPSS, Version 12, Chicago, IL, USA). One way ANOVA tests were used in comparisons between groups. Correlation analysis with Pearson's coefficient factors was applied to find the correlation between measured parameters. $P<0.05$ was considered statistically significant.

Results

The mothers' and their newborns' demographic characteristics are shown in Table 1. Between the three groups of newborns, no significant differences were noticed in gestational age, birth weight, APGAR score (1 min), APGAR score (5 min) of newborns or even age, Gravida, parity of their mothers.

Table 1. Demographic characteristics of the mothers and their babies.

Variable	Group I* (n=2)	Group II† (n=9)	Group III‡ (n=30)	P value
Gestational Age (weeks)	40 ± 0 (40 - 40)	40 ±0 (40-40)	39.46 ±1.62 (33-41)	p>0.05
Birth Weight (Kg)	4 ± 0 (4 - 4)	3.43 ±0.40 (3-4)	3.19 ±0.57 (2-4)	p>0.05
APGAR Score (1 min)	9 ± 0 (9-9)	7.89 ±2.26 (3-9)	8.89 ±0.32 (8-9)	p>0.05
APGAR Score (5 min)	10 ± 0 (10-10)	9.0 ±2.65 (2-10)	10.0 ±0.0 (10-10)	p>0.05
Age of Mother (years)	34 ± 0 (34-34)	30.86 ±5.93 (22-39)	25.92 ±5.97 (18-40)	p>0.05
Gravida	3 ± 0 (3-3)	3.13 ±1.73 (1-7)	2.54 ±1.67 (1-8)	p>0.05
Parity of Mother	2 ± 0 (2-2)	2.13 ±1.73 (0-6)	1.50 ±1.69 (0-7)	p>0.05

Data are expressed as mean ± SD, (range).
*(25OHD < 25 nmol/L)
†(25OHD = 25-50 nmol/L)
‡(25OHD > 50nmol/L)

In newborns, umbilical cord serum concentrations of 25OHD, PTH, calcium, inorganic phosphorus, alkaline phosphatase, albumin, and creatinine were [mean ±SD (ranged); 64.9 ±23.9 (4.5-104.5) nmol/L; 0.9 ±1.3 (0.3-8.1) μmol/L; 2.7 ±0.2 (2.3-3.2) mmol/L; 2.1 ±0.4 (1.3-3.2) nmol/L ; 196.4 ±53.8 (78.0-295.0) U/L; 38.7 ±2.9 (33.0-44.0) mg/L; 33.1 ±10.1 (7.0-53.0) mg/dL, respectively] (Table 2).

Table 2. Umbilical cord concentrations of different measured parameters.

Variable	Reference Range	Cord Blood (n=41)
25OHD nmol/L)		
Mean ±SD		64.9 ±23.9
range	(12-46)	(4.5-104.5)
Parathyroid hormone (µmol/L)		
Mean ±SD		0.9 ±1.3
range	(1.0-5.0)	(0.3-8.1)
Calcium (mmol/L)		
Mean ±SD		2.7 ±0.2
range	(2.2-2.7)	(2.3-3.2)
Phosphorus (nmol/L)		
Mean ±SD		2.1 ±0.4
range	(1.2-2.6)	(1.3-3.2)
Alkaline phosphatase (U/L)		
Mean ±SD		196.4 ±53.8
range	(50.0-165.0)	(78.0-295.0)
Albumin (mg/L)		
Mean ±SD		38.7 ±2.9
range		(33.0-44.0)
Creatinine (mg/dL)		
Mean ±SD		33.1 ±10.1
range		(7.0-53.0)

Table 3 showed comparisons between different measured parameters in the three groups of newborns. VITD declined significantly in Group I compared with Group II and III ($p<0.01$, $p<0.000$). Also, VITD lessened in Group II compared with Group III ($p<0.000$). Meanwhile, calcium levels were significantly declined in Group II (25OHD=25-50) compared to Group III (25OHD>50 nmol/L) with ($p<0.05$).

Table 3. Umbilical cord concentrations of different measured parameters in different conditions of $VITD_3$ concentrations.

Variable	Group I* (n=2)	Group II† (n=9)	Group III‡ (n=30)
25 OHD nmol/L)	8.50 ±5.66 (4.50-12.50)	39.44 ±6.72 (26.00-46.00) **[1]p<0.01**	76.27 ±14.74 (51.00-104.00) **[1]p<0.000** **[2]p<0.000**
Parathyroid Hormone (µmol/L)	0.36 ±0.03 (0.33-0.38)	1.22 ±1.21 (0.36-4.22) [1]p>0.05	0.86 ±1.42 (0.30-8.11) [1]p>0.05 [2]p>0.05
Calcium (mmol/L)	2.63 ±0.12 (2.54-2.71)	2.55 ±0.16 (2.32-2.80) [1]p>0.05	2.71 ±0.18 (2.37-3.24) [1]p>0.05 **[2]p<0.05**
Phosphorus (nmol/L)	1.70 ±0.41 (1.41-1.99)	1.98 ±0.39 (1.55-2.78) [1]p>0.05	2.11 ±0.45 (1.31-3.21) [1]p>0.05 [2]p>0.05
Alkaline Phosphatase (U/L)	236.50±34.65 (212.00-261.00)	211.56 ±56.96 (255.34-129.00) [1]p>0.05	189.21 ±53.11 (78.00-295.00) [1]p>0.05 [2]p>0.05
Albumin (mg/L)	38.50 ±0.71 (38.00-39.00)	38.11 ±0.03 (36.00-41.00) [1]p>0.05	38.00 ±3.21 (37.70-40.09) [1]p>0.05

			[2]p>0.05
Creatinine (mg/dL)	38.00 ±8.49 (32.00-44.00)	30.11 ±6.64 (21.00-44.00) [1]p>0.05	33.70 ±11.01 (7.00-53.00) [1]p>0.05 [2]p>0.05

Data are expressed as Mean ±SD (range); [1]p: significance versus VitD<25 nmol/L; [2]p: significance versus VitD 25-50 µmol/L

*(25OHD < 25 nmol/L)

†(25OHD = 25-50 nmol/L)

‡(25OHD > 50nmol/L)

In all groups of newborns, a significant positive correlation was found between creatinine and albumin ($r=0.359$, $p<0.05$) and inorganic phosphorus ($r=0.324$, $p<0.05$). Meanwhile, a significant negative correlation was found between calcium and PTH ($r=-0.396$, $p<0.01$).

Discussion

VITD and PTH have important roles in calcium-phosphorus homeostasis and bone mineralization[10]. During pregnancy, maternal serum concentrations of 25OHD, the circulating form of vitamin D, correlate with dietary VITD intake. The neonates derive the VITD through the trans-placental passage of VITD metabolites during intrauterine life. The major metabolites to cross the placenta are 25OHD with cord levels being approximately two-thirds of those found in the mothers[11,12].

Data of the present study demonstrated that a large percentage of neonates are deficient in VITD. These results highlight an important nutritional problem for mothers and their infants. The endogenous stores of VITD in these neonates are low. Thus, unless exogenous VITD is provided, VITD of neonates will drop as its half life is only 3–4 wks. Most neonates were breast-fed for a prolonged period of time. The VITD content of breast milk has been estimated to be between 20 and 60 IU/L[5] which is not adequate for meeting the requirement of a growing baby[13]. Thus, unless these infants are supplemented, they will become depleted in VITD and subsequently develop rickets[14]. The infants of the mothers with adequate 25OHD will improve their VITD status faster than those of the mothers with lower serum 25OHD level[14].

Studies from different countries suggest that VITD deficiency in children is a global problem, including in the Middle East[14]. VITD insufficiency and deficiency during pregnancy are reflected in lower maternal weight gain and biochemical evidence of disturbed skeletal homeostasis in the infant, with, in extreme situations, reduced bone mineralization, radiologically evident rickets, and fractures[15].

The cause of persistent VITD deficiency among women[16] and infants[17] throughout the world is not entirely clear. Several studies from the Middle East, North America, and northern Europe have highlighted

the prevalence of low circulating concentrations of 25OHD during pregnancy. Factors found to be important risk factors include increased skin pigmentation, immigration from non-European countries to countries of high latitude, limited skin exposure as a result of religious and social customs, and vegetarian diets[18,19]. Several studies underline the importance for the newborn of the mother's VITD status during pregnancy. The fight against rickets has to start with the pregnant woman. In this respect, Weiler *et al.*[20] reported that the causes of persistent VITD among women and infants throughout the world is not clear, deficiency persists despite consumption by some women of more than 2000 IU of VITD per day, as documented in other studies.

Calcium homeostasis is a complex process involving calcium and other involved ions, and three calcitropic hormone, PTH, calcitonin and 1,25 dihydroxy $VITD_3$. The principle maternal adjustment during pregnancy is an increasing PTH secretion which maintains serum calcium concentration in the face of increasing renal excretion and placental calcium transfer. The placenta transports calcium ions actively making the fetus hypercalcemic relative to its mother, which in turn stimulates calcitonin release and perhaps suppresses PTH secretion by the fetus. A unique extra renal system for 1α hydroxylation of 25 hydroxy VitD3 exists in placenta and/or deciduas, providing a source for 1, 25 dihydroxy cholecalciferol for the fetus. With the abrupt cessation of the placental source of calcium at birth, the neonatal calcium levels fall for 24-48 hrs, then stabilizes and rises slightly[21]. Hypocalcaemia and increased PTH secretion induce synthesis of 1, 25-dihydroxyvitamin D after birth in both full-term and preterm neonates. Nevertheless, serum concentrations of 25OHD are a rate-limiting factor in the synthesis of 1, 25-dihydroxyvitamin D[22].

In this study, levels of PTH were detectable in all samples of cord blood. In contrast to this present study, Hillman *et al.*[23] found 9 of 10 term infants had undetectable PTH concentrations in cord sera. In this study, a negative correlation was found between calcium and PTH in cord blood. Meanwhile, Hillman *et al.*[23] found a weak positive correlation between 25-OHD and cord calcium.

VITD deficiency is a systemic disease. There are biochemical determinants of 25OHD deficiency before the clinical signs of nutritional rickets become evident. Therefore, supplementation should be initiated early before the infant presents clinical signs of rickets. Most the authors recommend that the pregnant mother should receive 2000 IU of 25OHD daily during the third trimester[24]. Neonates should receive 400 IU of 25OHD daily and children with high risks of developing VITD deficiency should also receive similar supplementation in addition to taking VITD -enriched infant formula[25].

In conclusion, subclinical VD is not uncommon in full term babies in Saudi Arabia, and is not likely to be uncommon in other developing countries as well. Clinical rickets and osteomalacia represent only the tip of the iceberg; the real problem is the extent of undiagnosed VD in infants and women at reproductive ages. One of the risks of chronic low vitD status may be its negative influence on bone mass; this issue needs further exploration. It is a serious health problem, and pediatricians, obstetricians, and general practitioners in developing countries should be aware of this condition. The impact of VITD deficiency during fetal development and the growing years may well prove to extend beyond rickets. It is now recognized that attention to bone development during the years when the skeleton is "under construction" is the key to the optimization of bone health throughout the lifespan. To this end, the long-term impact of VITD deficiency during fetal and childhood skeletal development, and the most appropriate dose and timing for VITD supplementation, remain important areas for study.

Acknowledgement. The author would like to **thank** Professor Suhad Bahijri for evaluating the lab results and, also, Dr. Wafaa Sait for reviewing clinical data.

References

[1] **Russell JG, Hill LF.** Tue fetal rickets. *Br J Radiol* 1974; **47**(562): 732-734.

[2] **Moncrieff M, Fadahunsi TO.** Congenital rickets due to maternal vitamin D deficiency. *Arch Dis Child* 1974; **49**(10): 810-811.

[3] **Andiran N, Yordam N, Ozon A**. Risk factors for vitamin D deficiency in breast-fed newborns and their mothers. *Nutrition* 2002; **18**(1): 47-50.

[4] **Hollis BW, Roos BA, Draper HH, Lambert PW.** Vitamin D and its metabolites in human and bovine milk. *J Nutr* 1981; **111**(7): 1240-1248.

[5] **Ala-Houhala M, Koskinen T, Parviainen MT, Visakorpi JK.** 25-Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. *Am J Clin Nutr* 1988; **48**(4): 1057-1060.

[6] **Gupta MM, Kuppuswamy G, Subramanian AR**. Transplacental transfer of 25-hydroxycholecalciferol. *Postgrad Med J* 1982; **58(681)**: 408-10.

[7] **Fraser DR.** Vitamin D. *Lancet* 1995; **345**(8942): 104-107.

[8] **Deal CL**.Osteoporosis: prevention, diagnosis and management. *Am J Med* 1997; 27; 102(1A): 35s-39s.

[9] **Salle BL, Glorieux FH, Lapillone A.** Vitamin D status in breastfed term babies. *Acta Paediatr* 1998; **87**(7): 726-727.

[10] **Pehlivan I, Hatun S, Aydogan M, Babaoglu K, Gokalp AS**. Maternal vitamin D deficiency and vitamin D supplementation in healthy infants. *Turk J Pediatr* 2003; **45**(4): 315-320.

[11] **Reeve LE, Chesney RW, DeLuca HF.** Vitamin D of human milk: identification of biologically active forms. *Am J Clin Nutr* 1982; **36**(1): 122-126.

[12] **Nishimura K, Shima M, Tsugawa N, Matsumoto S, Hirai H, Santo Y, Nakajima S, Iwata M, Takagi T, Kanda Y, Kanzaki T, Okano T, Ozono K.** Long-term hospitalization during pregnancy is a risk factor for vitamin D deficiency in neonates. *J Bone Miner Metab* 2003; **21**(2): 103-108. Erratum in: *J Bone Miner Metab* 2003; **21**(4): 253.

[13] **Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL, Wilkinson EM, Forfar JO, Barrie WJ, McKay GS, Pocock SJ.** Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. *Br Med J* 1980; **281**(6232): 11-14.

[14] **Molla AM, Al Badawi M, Hammoud MS, Molla AM, Shukkur M, Thalib L, Eliwa MS.** Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int* 2005; 47(6): 649-652.

[15] **Pawley N, Bishop NJ.** Prenatal and infant predictors of bone health: the influence of vitamin D. *Am J Clin Nutr* 2004; **80**(Suppl 6): 1748S-1751S **.**

[16] **Weisman Y.** Maternal, fetal and neonatal vitamin D and calcium metabolism during pregnancy and lactation. *Endocr Dev* 2003; **6**: 34-49.

[17] **Dawodu A, Agarwal M, Hossain M, Kochiyil J, Zayed R.** Hypovitaminosis D and vitamin D deficiency in exclusively breast-feeding infants and their mothers in summer: a justification for vitamin D supplementation of breast-feeding infants. *J Pediatr* 2003; **142**(2): 169-173.

[18] **Mukamel MN, Weisman Y, Somech R, Eisenberg Z, Landman J, Shapira I, Spirer Z, Jurgenson U.** Vitamin D deficiency and insufficiency in Orthodox and non-Orthodox Jewish mothers in Israel. *Isr Med Assoc J* 2001; **3**(6): 419-421.

[19] **Datta S, Alfaham M, Davies DP, Dunstan F, Woodhead S, Evans J, Richards B.** Vitamin D deficiency in pregnant women from a non-European ethnic minority population--an interventional study. *BJOG* 2002; **109**(8): 905-908.

[20] **Weiler H, Fitzpatrick-Wong S, Veitch R, Kovacs H, Schellenberg J, McCloy U, Yuen CK.** Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. *CMAJ* 2005; **172**(6): 757-761.

[21] **Pitkin RM.** Calcium metabolism in pregnancy and the perinatal period: a review. *Am J Obstet Gynecol* 1985; **151**(1): 99-109.

[22] **Salle BL, Delvin EE, Lapillonne A, Bishop NJ, Glorieux FH.** Perinatal metabolism of vitamin D. *Am J Clin Nutr* 2000; **71**(5 Suppl): 1317S-1324S.

[23] **Hillman LS, Rojanasathit S, Slatopolsky E, Haddad JG**. Serial measurements of serum calcium, magnesium, parathyroid hormone, calcitonin, and 25-hydroxy-vitamin D in premature and term infants during the first week of life. *Pediatr Res* 1977; **11**(6): 739-744.

[24] **Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J.** Maternal compared with infant vitamin D supplementation. *Arch Dis Child* 1986; 61(12): 1159-63.

[25] **Hillman LS.** Mineral and vitamin D adequacy in infants fed human milk or formula between 6 and 12 months of age. *J Pediatr* 1990; **117**(2 Pt 2): S134-142.

JKAU: Med. Sci., **Vol. 14, No. 2**, pp. 61-69 (1428 A.H./ 2007 A.D.)

مستوى فيتامين د في الأطفال كاملي النمو مواليد جامعة الملك عبد العزيز ، جدة – المملكة العربية السعودية

نادية محمد فدا

قسم طب الأطفال ، كلية الطب

جامعة الملك عبدالعزيزو جدة – المملكة العربية السعودية

المستخلص: لفيتامين "د" دور مهم في النمو السليم للعظام. تهدف هذه الدراسة إلى معرفة مدى انتشار نقص فيتامين "د" في المواليد مكتملي النمو. تم قياس الكالسيوم والفوسفات وهرمون د (25) والفوسفات القلوي وهرمون الغدة الجار درقية في دم الحبل السري للمواليد كاملي النمو. وقد قسمت الحالات إلى ثلاث مجموعات، المجموعة الأولى (عدد = 2) مستوى الهرمون د (25) أقل من 25 ملي مول/ لتر والمجموعة الثانية (عدد = 9) مستوى هرمون د (25) من 20 -25 ملي مول/لتر والمجموعة الثالثة (عدد = 30) مستوى هرمون د (25) أكثر من 25 ملي مول/لتر. وقد لوحظ عدم وجود فروق ذات دلالة احصائية في التغيرات الديموغرافية بين المجموعات ولكن هناك فروقاً ذات دلالة احصائية بين المجموعات في مستوى نقص هرمون د (25) وقد أظهرت النتائج انخفاض مستوى كالسيوم المجموعة الثانية مقارنة بالمجموعة الثالثة . وقد كان هناك علاقة إيجابية ذات دلالة احصائية في جميع المواليد بين مستوى الكرياتنين والأليبومين والفوسفات وعلاقة سلبية بين مستوى الكالسيوم وهرمون الغدة الجار درقية .

ولقد تم استنتاج وجود مستويات منخفضة للفيتامين "د" بين المواليد كاملي النمو وهذا يستدعي القيام بدراسات أكثر.

Correspondence & reprint requests to: Dr. Nadia M. Fida
P.O. Box 80215, Jeddah, 21589 Saudi Arabia
Accepted for publication: 18 June 2007. Received: 10 December 2006.