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Hypocalcaemia among children up to two years old in children Tripoli hospital

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Abstract: Hypocalcaemia is a state when serum calcium levels are < 7 mg/dl in preterm neonates and < 8 mg/dl in term neonates and < 8.5 mg/dl in older children. Prospective analytical study was performed in children, < 2 years, who admitted in Hospital with hypocalcaemia or discovered hypocalcaemia during admission. Biochemical serum investigations from the patients (S. Ca, Ph, alk ph, Mg, Hb, PTH, Urea and S. Cr) and X. ray of left hand wrist. 63 children (44 boys, 19 girls) the difference was statistically significant and age ranging from one day to 2 years with mean age of 5 ± 5.6 months, 46% of the patients are exclusive breast feeding and 41.4% of them are symptomatic at age between 6 to 12 months of age and most of bottle feeding babies (90%) are symptomatic early below 6 months of age. Most of the patients presented with abnormal movement (85.7%) and 12.7% are asymptomatic. 1.6% of the patients presented with bow legs, 14% of the patients were preterm, all of preterm patients are significantly presented early than term patients and 16% of the patients are IUGR, and they are significantly presented early and about 6% of the patients are infant of diabetic mother and significantly presented early, 73% of the mothers are multipara and 27% of the mothers are primigravida, 93.8% of primigravida mothers had normal. Serum calcium was compared with 80.5% of multiparty mothers; the difference was statistically not significant. All the patients had low serum calcium levels but serum phosphorous levels varied and about alkaline phosphatase, 62.7% of patients have high and 37.3% have normal serum alkaline phosphates, about 61% have high serum PTH. 37% have normal serum PTH and 2% have low serum PTH, 66.7% of breast feeding and 6.1% of bottle feeding patients have ricketic x-ray changes, this is not significant. 88.9% of babies of hypocalcemic mothers have ricketic bone changes; most of the babies of hypocalcemic mothers are presented early 77.8% less than 6 months of age. Thus, infants under 2 years of age are liable to have vitamin D deficiency rickets particularly if they are exclusively breastfed with reduced exposure to sunlight, seizures are the most important presented symptom of hypocalcaemia.

Introduction

Hypocalcaemia is state when serum calcium level is less than 7 mg/dl in preterm neonates and less than 8 mg/dl in term neonates and less than 8.5 mg/dl in older children (1). Various factors regulate the homeostasis of calcium. These include parathyroid hormone, vitamin D, hepatic function, renal function, phosphate level and magnesium levels (1). In newborns present with poor feeding, vomiting, cyanosis, seizures, apnea, or asymptomatic. In children present by lethargy, seizures, cramping, laryngospasm, tetany and signs of nerve irritability (such as the Chvostek sign, carpopedal spasm, and the Trousseau sign) (2).

In early neonatal period (first 72 hours of birth), hypocalcaemia caused by prematurity, congenital rickets (2), birth asphyxia, diabetic mothers, or intrauterine growth retardation. In late neonatal period (from 3 - 7 days until 6 weeks old) hypocalcaemia caused by feeding with phosphate-rich formula or cow's milk, magnesium deficiency, Transient hypopara-thyroidism or gentamicin use (3). In infants and children caused by hypoparathyroidism, vitamin D deficiency, abnormal vitamin D production or action, hyperphosphatemia or malabsorption syndromes. This study was aimed to estimate the occurrence of hypocalcaemia among children less than 2

years old. This study aimed to identify and differentiate the causes of hypocalcaemia among this age group.

Materials and methods

Prospective analytical study was performed on 63 children (< 2 years old), who admitted in Tripoli Children Hospital from October 2008 to March 2010 (with hypocalcaemia or discovered hypocalcaemia during admission). Biochemical investigations were taken from our patients (s. ca, s. ph, alk ph, mg, PTH) and X. ray of left hand wrist. Investigations were taken also from mothers (s. ca, s. ph, alk ph) then the data analyzed statistically.

Results

This study includes 63 patients with hypocalcaemia, the analysis of collected data will be presented as following: Socio-demographic characteristics of the patients and mothers. The age of the patients with hypocalcaemia under this study ranged between one day and 2 years with mean age of 5 ± 5.6 months, about half (43%) of the patients were aged from one month to 6 months, 27% were aged less than one month, 30% aged more than 6 months as shown in Figure 1.

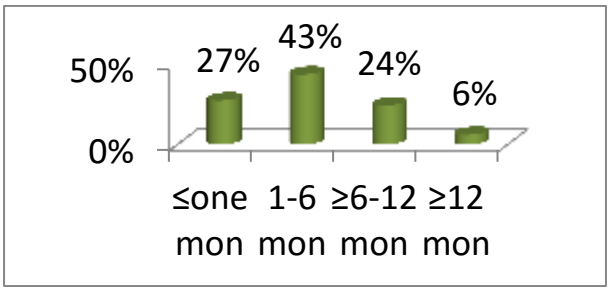

Figure 1: Age distribution of hypocalcaemic patients

Sex distribution: More than two thirds of the patients were males 44 from 63 making a percentage of 69.8%, females 19 from 63 made only 30.2% and by using nonparametric chi-square. It was found that the difference between the number of males and females was statistically significant (p = 0.003), Figure 2. Sex distribution of hypocalcemic patients (Children Tripoli Hospital 2009-2010).

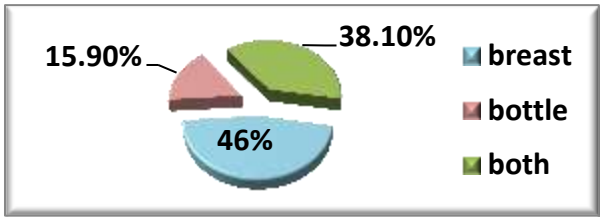

Figure 3: Mode of feeding in hypocalcaemic patients

Feeding history: 46% of the patients are exclusive breast feeding; only 15.9% are exclusive bottle feeding, and 38.1% of the patients are on both feeding.

Relation between mode of feeding and age of presentation, we found most of patients on exclusive breast feeding, 41.4% presented at age between 6 to 12 months of age, and most of patients on bottle feeding (90%) presented under 6 months of age, Table 1.

		nutritional			
		breast	bottle	both	Total
age of onset	<one mon	5 17.2%	5 50.0%	7 29.2%	17 27.0%
	1-6mon	11 37.9%	4 40.0%	12 50.0%	27 42.9%
	>6-12mon	12 41.4%	0 .0%	3 12.5%	15 23.8%
	>12mon	1 3.4%	1 10.0%	2 8.3%	4 6.3%
Total		29 100.0%	10 100.0%	24 100.0%	63 100.0%

Table 1: Percentage of each mode of feeding in different age of presentation.

Maternal history: 73% of the mothers are multipara (they have more than one child), and (27%) of the mothers are primigravida (they have only one child). It was found that the percent of mothers with pregnancy interval less than 2 years are equal to the percent of mothers more than 2 years, as shown figure 4, the difference is statistically is not significant (p = 0.2).

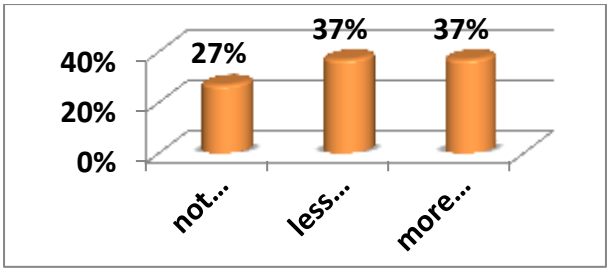

Figure 4: Distribution of pregnancy interval space among the mothers of hypocalcaemic patients.

Clinical features: Presenting symptoms of hypocalcaemic patients: as shown in Figure 5, most of the patients in this study (85.7%) presented to the hospital with abnormal movement.

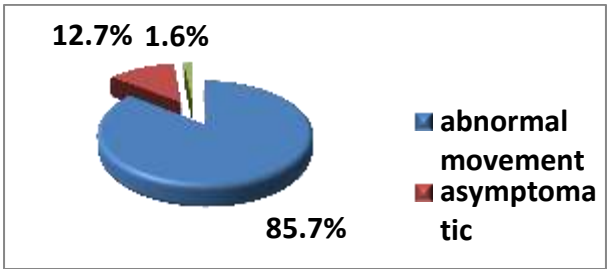

Figure 5: Presenting symptoms of hypocalcaemia patients

It was found that about half of the patients presented with abnormal movement are at age between one to 6 months of age all patients presented with bow legs are at age between 6 to 12 months of age and most of asymptomatic patients (87.5%) discovered hypocalcaemia are at age of less than one month of age.

		sings and symptoms			
		abnormal movement	bow legs	asyptomatic	Total
age of onset	<one mon	10	0	7	17
		18.5%	.0%	87.5%	27.0%
	1-6mon	26	0	1	27
		48.1%	.0%	12.5%	42.9%
	>6-12mon	14	1	0	15
		25.9%	100.0%	.0%	23.8%
	>12mon	4	0	0	4
		7.4%	.0%	.0%	6.3%
Total		54	1	8	63
		100.0%	100.0%	100.0%	100.0%

Table 2: Presenting symptoms of hypocalcaemic patients at different age of presentation.

Table 2 describes symptoms of hypocalcaemic patients at different age of presentation.

Mother's serum calcium: by study the relation between mother serum calcium level and her parity we found that 93.8% of prime mothers had normal serum Ca compared with 80.5% of multiparty mothers and by using chi-square test the difference was not statistically significant (p = 0.4). In relation between mother's serum Ca and age of onset of hypocalcaemia in children, it was found that most of the patients of hypocalcaemic mothers are presented early (77.8%) less than 6 months of age (p = 0.3) which is not statistically significant.

		age of onset				
		<one mon	1-6mon	>6-12mon	>12mon	Total
mother calciume	normal	14	18	13	3	48
		29.2%	37.5%	27.1%	6.3%	100.0%
	low	1	6	1	1	9
		11.1%	66.7%	11.1%	11.1%	100.0%
Total		15	24	14	4	57
		26.3%	42.1%	24.6%	7.0%	100.0%

Table 3: Relation between mother's serum calcium and age of onset of hypocalcaemia in hypocalcaemic patients.

Phosphorus levels: it was found that 70% of patients have normal phosphorus, 15% of patients have low phosphorus and 15% have high phosphorus.

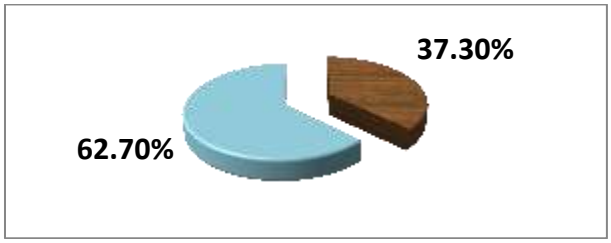

Figure 6: Distribution of serum alkaline phosphates in hypocalcemic patients.

Alkaline phosphates level:

Magnesium level: It was found that 21% of hypocalcaemic patients have low serum magnesium.

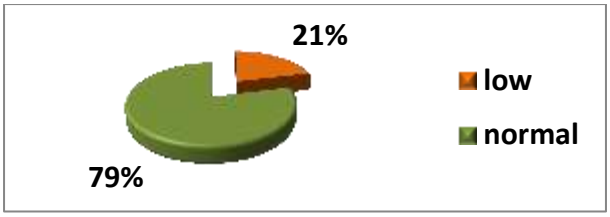

Figure 7: Distribution of serum magnesium in hypocalcaemicpatients

Parathyroid hormone level: When studying Parathyroid hormone level in these patients, we realize that about 60% of the patients have high serum parathyroid hormone, 37% of the patients have normal serum parathyroid hormone and 2% of patients have low serum parathyroid hormone.

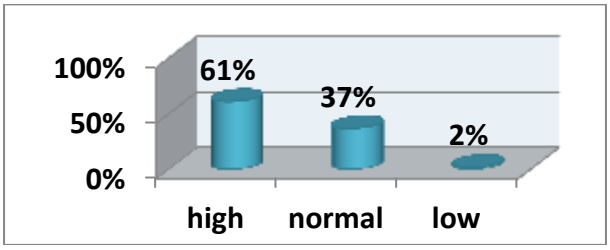

Figure 8: Distribution of parathyroid hormone in hypocalcemic patients.

Relation between parathyroid hormone and age of onset of hypocalcaemia: It is found that 47.1% of the patients with normal parathyroid hormone are at age below one month of age, one patient with low parathyroid hormone are at age between 1 and 6 months of age and 46.4% of the patients with high parathyroid hormone are at age between 1 and 6 months of age, Table 4.

		parathyroid hormone			
		normal	low	high	Total
age of onset	<one mon	8	0	4	12
		47.1%	.0%	14.3%	26.1%
	1-6mon	4	1	13	18
		23.5%	100.0%	46.4%	39.1%
	>6-12mon	3	0	9	12
		17.6%	.0%	32.1%	26.1%
	>12mon	2	0	2	4
		11.8%	.0%	7.1%	8.7%
Total		17	1	28	46
		100.0%	100.0%	100.0%	100.0%

Table 4: Relation between parathyroid hormone and age of onset of hypocalcemia.

Relation between mode of feeding and ricketic x. ray changes: It is found that 66.7% of breast feeding patients have left wrist x. ray changes, and 6.1% of bottle feeding patients have left wrist x. ray changes, this difference is statistically significant (p = 0.002).

		nutritional			
		breast	bottle	both	Total
lt wrist x ray	no ricketic changes	7	8	15	30
		23.3%	26.7%	50.0%	100.0%
	ricketic changes	22	2	9	33
		66.7%	6.1%	27.3%	100.0%
Total		29	10	24	63
		46.0%	15.9%	38.1%	100.0%

Table 5: Relation between mode of feeding and ricketic x ray.

Relation between mother serum calcium level and patients with x. ray changes of rickets: It can be noticed that 88.9% of the patients of hypocalcaemic mothers have ricketic bone changes on left wrist x. ray and only 50% of patients of normal calcium mothers have ricketic bone changes, p = 0.06.

		mother calciume		
		normal	low	Total
lt wrist x ray	no ricketic changes	24	1	25
		50.0%	11.1%	43.9%
	ricketic changes	24	8	32
		50.0%	88.9%	56.1%
Total		48	9	57
		100.0%	100.0%	100.0%

Table 6: The relation between mother`s serum calcium and ricketic x ray changes.

Causes of hypocalcaemia: Figure 9 shows that 53% of the patients have Ricketes (16%) are intrauterine growth retardation, 6% are infants of diabetic mothers, 14% are preterm, and 11% of the patients have unclear causes (some of them have history of drug intake as diuretics or phenobarbiton or history of blood transfusion).

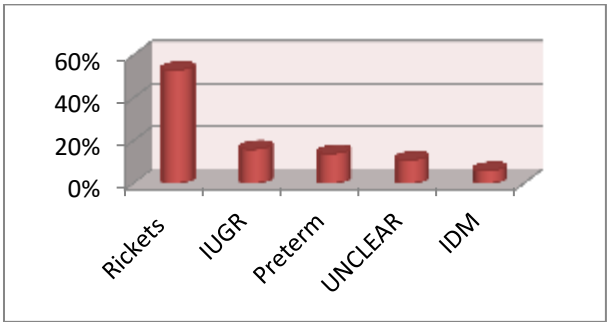

Figure 9: Distribution of possible causes of hypocal-caemia in hypocalcaemic patients.

The Relation between causes of hypocalcaemia and age of presentation : It is found that all of the preterm patients are significantly presented early than term patients p = 0.014 (Mann-Whitney U test) mean age of onset of the preterm babies is 1.5 month, about 45% of the preterm patients presented below one month of age and 100% of the preterm patients are presented below 6 months of age, and in term patients mean age of onset is 5.4 months about 40% are presented between one to six months of age.

		gestational age		
		term	preterm	Total
age of onset	<one mon	13	4	17
		24.1%	44.4%	27.0%
	1-6mon	22	5	27
		40.7%	55.6%	42.9%
	>6-12mon	15	0	15
		27.8%	.0%	23.8%
	>12mon	4	0	4
		7.4%	.0%	6.3%
Total		54	9	63
		100.0%	100.0%	100.0%

Table 7: Percent of term- and pre-term patients at different age of the among hypocalcaemic patients.

IUGR patients: We found that all IUGR patients, 100% are presented early below 6 months of age, IUGR patients are significantly presented early p = 0.028 (Mann-Whitney U test).

		intrauterine growth retardation		
		no IUGR	IUGR	Total
age of onset	<one mon	14	3	17
		26.4%	30.0%	27.0%
	1-6mon	20	7	27
		37.7%	70.0%	42.9%
	>6-12mon	15	0	15
		28.3%	.0%	23.8%
	>12mon	4	0	4
		7.5%	.0%	6.3%
Total		53	10	63
		100.0%	100.0%	100.0%

Table 8: Age of presentation in IUGR and non IUGR patients among hypocalcaemic patients.

Infant of diabetic mother: About 5% of the patients are infant of diabetic mother. We found that IDM are presented early, 75% at less than one month of age and all of IDM patients, 100% are presented at less than 6 months of age and statistically IDM patients are significantly presented early p = 0.030.

		infant of diabetic mother		
		yes	no	Total
age of onset	<one mon	3	14	17
		75.0%	23.7%	27.0%
	1-6mon	1	26	27
		25.0%	44.1%	42.9%
	>6-12mon	0	15	15
		.0%	25.4%	23.8%
	>12mon	0	4	4
		.0%	6.8%	6.3%
Total		4	59	63
		100.0%	100.0%	100.0%

Table 9: Percent of hypocalcaemic patients with IDM in different age of onset.

Discussion

Symptomatic hypocalcemia may be caused by low concentration of ionized calcium resulting from vitamin D deficiency which is caused by nutritional deficiency, malabsorption or abnormal metabolism of vitamin D; hypocalcemia may also be a result of hypoparathyrodism, hyperphosphatemia and magnesium deficiency. The neonate is particularly susceptible to hypocalcemia associated with hypoparathyroidism, abnormal vitamin D metabolism, a low calcium intake, or a high phosphate intake (4). Hypocalcemic patients in our study males are more affected than females by 44: 19 and the mean age is 5 + 5.6 months, same results achieved by study for prevalence of hypocalcemia in the Specialized Pediatric Center in Sana'a city, Yemen during the 4 year period 1999 to 2003, the median age of the patients was 5 months, with minimum age of one day and maximum age of 4 years. Sixty percent of them were males and 40% were females (5) and another study which was done in Royal Alexandra Hospital for Children, Sydney. With hypocalcaemia in infancy, 36 infants who presented with hypocalcaemia in the first 2 years of life males outnumbered females 28: 8 (6). We noticed that babies who have hypocalcaemia generally they are more among breast feeding than bottle feeding babies as result of vit D deficiency, in this study 46% are exclusive breast feeding. This supported with study was conducted in Pakistan the department of Pediatrics, King Edward Medical University / Mayo hospital Lahore

from March 1998 to January 2001. 120 children (72 boys & 48 girls) ranging from 2 months to 3.5 years which showed infants under 2 years of age are liable to have vitamin D deficiency rickets particularly if they are exclusively breastfed or received fresh milk with reduced exposure to sunlight (7). This is also supported by the study which was done in India from the Kanchi Kamakoti Childs Trust Hospital. Hypocalcaemia due to vitamin D deficiency in exclusive breastfed infants; during the period from January 2002 - 2004. This report is based on observations during the conduct of the study 50 cases, 13 exclusively breast fed infants less than 6 months of age 8 were males and 5 were females manifesting with hypocalcemic seizures were confirmed to have vitamin D deficiency. All the mothers of these 13 infants had low levels of 25 (OH) Vit D3. Mothers of 5 infants had reported reduced exposure to sunlight due to religious reasons. This report emphasizes the need to supplement vitamin D in exclusively breast fed infants and also to encourage exposure to sunlight in them and their mothers (8).

Although human milk contains less calcium than cow's milk, but the calcium in human milk has over twice the bioavailability of the calcium in cow's milk. Increasing mother's calcium intake does not increase the amount of calcium in her milk-mother's milk has the right amount of calcium even if mothers do not get enough in her diet (9). However hypocalcaemia presented among bottle feeding babies at age under 6 months and that could be explained by improper bottle feeding due to high phosphorus content more than breast feeding. Also the explanation in Late-onset hypocalcaemia (3-7 days after birth), is usually ingestion of cow's milk or formula with a too high PO4 load; elevated serum PO4 leads to hypocalcaemia (10), examples for some artificial formula, see the figure

In this study, the most common presented symptoms among the patients, 85.7% is convulsion, this supported by prospective study was performed on 400 children in Al-Jahra Hospital, Kuwait, between the ages of 1 month and 13 years with a history of convulsions, admitted during a 2-year period. There were more males than females, hypocalcaemia with or without rickets (5.7%), and hypocalcaemia and lead intoxication were found to be significant causative factors for convulsions in children less than 2 years of age (11). So, it can be explained by the presentation of hypocalcaemia in breast feed babies who are under 6 months because of osteomalacic mothers as presented in our study most of the patients of hypocalcaemic mothers are presented early. 77.8% less than 6 months of age and this was supported by retrospective study was done in Royal Melbourne Hospital from June 1994 to February 1999. To identify infants treated for vitamin D deficiency rickets, and to determine the incidence of vitamin D deficiency in their mothers, the result showed 55 children with vitamin D deficiency rickets, 31 of the 55 mothers (56%) with osteomalacia. Twenty-four of the 55 children (44%) were aged less than 12 months and, out of these, 23 were exclusively breast fed at the time of diagnosis vitamin D stores at birth are dependent on maternal stores (12). The present study showed that about 52.4% (33 out from 63) of the patients have bone changes and 88.9% of hypocalcaemic mothers their babies have ricketic changes and mean age of bone changes is 7.6 months, no clear data from literature reviewing regarding presence of bone deformities apart from one study was done in Nigeria by using semi structured questionnaires to know maternal knowledge about Ricketic changes, causes and treatment of rickets, they found about 60.% and 36.5% of the mothers were aware of children with knee deformity and rickets, respectively. 22.6% mothers had the correct knowledge and perception of the true meaning of rickets (13). This study also indicates that 14% of the patients are preterm most of them presented

	Human milk	Formula 1	Formula 2	Formula 3
Calcium	30 mg/100ml	59.7 mg 100ml	50 mg/100ml	51 mg/100ml
Phosphate	15 mg/100ml	29.8 mg/100ml	28 mg/100ml	28.6 mg/100ml

early, 44.4% below one month and 100% presented under 6 months of age and this supported with study was done in Northern Ireland studied 35 infants < 1500 gm, exposed to antenatal steroids and 15 term controls.

Total Ca, ionized Ca, Mg, P, Parathyroid Hormone (PTH) were measured in cord blood and at 24 hours of age and the results in preterm infants, from birth to 24 hours, both ionized Ca and total decreased significantly. Corresponding values in term controls were: ionized Ca and total Ca. The magnitude of ionized Ca decrease was virtually identical n infants < 1000 g, the rate of hypocalcemia was 20%. In the subset of infants < 1000 g (N: 17), PTH increased in all infants. At 24 hours PTH was higher in infants < 1000 g (181 pg/ml) than in infants 1000-1499 g (140 pg/ml) and term controls (58 pg/ml). so the Conclusions was VLBW and ELBW infants have a much lower rate of early hypocalcemia than previously reported, respond to decreasing serum ionized Ca with an adequate PTH surge (14). 6% of the patients are infant of diabetic mothers when compared this study with the one which was done in Montreal, Shriners Hospital Neonatal Unit and Department of Pediatrics, 22 infants of diabetic mothers (IDM) were studied and were divided into two groups: a first group of 14 IDM did not receive vitamin D_3 and was studied at birth and at 2, 24, 48 and 120 hours; a second group was given daily dosage of 60 μg of vitamin D_3 from 3 hours to 120 hours and was studied at 2 hours and 120 hours, in the first group, serum calcium levels decreased markedly during the first 24 hours of life and remained low at 5 days, in group II, serum 25O-HD levels and 1.25 OH2 D levels increased significantly ($p < 0.001$) respectively to 27.2 ± 2.7 ng/ml and 114 ± 20 pg/ml at 5 days. The results of this study show hypocalcemia to be a common event in IDM during the first days of life (15).

In conclusion**,** hypocalcaemia represents a major health problem in Libyan children. Infants under 2 years of age are liable to have vitamin D deficiency rickets particularly if they are exclusively breastfed with reduced exposure to sunlight. Seizures are the most important presenting symptom of hypocalcaemia.

Recommendations: All pregnant and lactating mothers should be educated about vitamin D deficiency & supplemented with vitamin D. Vitamin D supplementation of all infants should begin during the first days of life in exclusively breast-fed specially if the mother's diet is deficient in vitamin D or the infant's sun exposure is limited because of deeply pigmented skin coloration or inadequate sunlight exposure.

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