

# **RESEARCH ARTICLE**

# Incidence and Risk Factors of Rachitic Genu Varus in Preschool Children in a Paediatric Health Institute in Egypt as One of the Developing Countries

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## Abstract:

#### Background:

Rachitic genu varus is one of the common conditions among the Egyptian children, despite the shinning sun of Egypt all the year.

#### Purpose:

The aim of the study was to estimate the incidence of rachitic genu varus among the Egyptian children, and to assess the risk factors contributing to it.

## Patients and Methods:

This prospective study recruited a total of 250 consecutive children, being 130 males and 120 females, with rachitic bow legs or genu varus, between 2 - 4 years of age, together with 250 controls of the same age group, out of a total number of 1900 children with other types of rickets, and other children's orthopaedic diseases, who presented to the National Institute of Neuromotor System in Egypt between September 2014 to September 2015. The cases and the controls were subjected to clinical, laboratory biochemical, and plain radiographic examinations. Their parents were subjected to epidemiological, maternal, and nutritional questionnaires.

## Results:

The calculations revealed high incidence (13.1%) of rachitic genu varus. The risk factors were low socioeconomic status, insufficient family income, poor housing conditions, lack of exposure to sunlight due to cultural practices, sole breast feeding, and inadequate supplementation of vitamin D to the children and the pregnant women. The *p* value was <0.05.

## Conclusion:

Vitamin D deficiency rachitic genu varus is a multifactorial condition in Egypt. Raising the standard of living, level of education, housings, and dietary supplementation of vitamin D to the pregnant women and infants are the solution.

Keywords: Genu varus, Malnutrition, Rachitic genu varus, Rickets, Vitamin D deficiency, Vitamin D supplementation.

## INTRODUCTION

Egyptian young children have a high incidence of vitamin D deficiency rickets, despite the ample sunlight of Egypt. The risk factors contributing to vitamin D deficiency rickets in the Egyptian children include the low socioeconomic status, the limited exposure to sunlight due to housing conditions and cultural practices, and the exclusive or prolonged

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breast-feeding without vitamin D supplements. A significant number of children have rachitic bow legs or genu varus [1 - 5].

The current study was a prospective one, designed and executed by the orthopaedic department of the National Institute of Neuromotor System in Egypt, a health institute which provides services to a large scale of Egyptian children and is in contact with the National Children's Council. The aim of study was to estimate the incidence of rachitic bow legs or genu varum in the Egyptian children, and the risk factors, with application of a scientific basis for prevention. The study was designed to compare affected versus unaffected children in Egypt taking into consideration the socioeconomic status, housing and nutritional history, clinical examination, laboratory biochemical serum calcium, phosphorus, alkaline phosphatase, and active vitamin D 1,25(OH)2D levels, and radiographic findings.

#### PATIENTS AND METHODS

A total of 250 consecutive children with vitamin D deficient rachitic bow legs or genu varus, being 130 males and 120 females, between 2 - 4 years of age, together with 250 non-rachitic controls of the same age group, out of a total number of 1900 children with other types of rickets, other rachitic deformity presentations, and other children's orthopaedic diseases, being 1000 males and 900 females, of similar and different ages, presented to the orthopaedic outpatient clinic of the National Institute of Neuromotor System of Imbaba, Egypt, between September 2014 to September 2015, were enrolled in the study. The institute provides health service to the skeletally disabled and handicapped children from all over Egypt that explains the relatively large number collected from a single centre, and supplying national data. The study fulfills the Egyptian's Ethics code of researches based on the institution and the National Children's Council.

#### **Inclusion Criteria**

The cases were children between 2 - 4 years of age with history, clinical, laboratory, and radiographic findings of vitamin D deficiency rickets causing bow legs or genu varus, not receiving therapeutic doses of vitamin D, with no history of prematurity, and not suffering any form of renal, liver, cardiac, bone (excluding rickets) disease or any form of chronic infection.

The controls were equal number of healthy children or with minor illness, at least non-rachitic, of the same age group; being brothers, sisters, or relatives of the cases or the other visitors of the paediatric orthopaedics outpatient clinic of the institute, after obtaining a written informed consent from their parents.

#### **Exclusion Criteria**

Children younger than 2 years and older than 4 years of age, with no history, clinical, laboratory, and radiographic findings of vitamin D deficiency rickets, or rachitic but with no bow legs or genu varus, receiving therapeutic doses of vitamin D, history of prematurity, and suffering any form of renal, liver, cardiac, bone (excluding rickets) disease or any form of chronic infection were rejected.

#### Original Disease, History, Questionnaires, and Clinical Evaluation

#### History

The parents gave no history of knee deformity before the age of 2 years.

#### Questionnaires

The parents of all children were interviewed for epidemiological, maternal, and nutritional issues.

## Epidemiological Questionnaire

Socioeconomic status, geographic regions, housing conditions, exposure to sunlight, and child clothing type were assessed.

#### Maternal Questionnaire

The mothers of all children were inquired about the number of pregnancies, the intervals between pregnancies, maternal nutrition, and calcium and vitamin D supplementation during pregnancy.

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## Nutritional Questionnaire

A semi-quantitative food questionnaire was administered [6]. The nutritional status based on the body weight and the presence or absence of oedema was evaluated in all children [7]. Nutritional data included type of milk fed during infancy, dietary calcium intake, and calcium and vitamin D supplementation.

## **Clinical Evaluation**

All children were examined clinically both generally and locally for rachitic physical signs as fontanels closure, forehead bossing, dentition status, rachitic rosary of the ribs, Harrison's subcostal sulcus, barrel chest, pot-belly abdomen, broadening of the wrists and ankles, and skeletal deformities with stress on bow leg or genu varus deformities.

#### Laboratory Biochemical Findings

Serum calcium, phosphorus, alkaline phosphatase, and active vitamin D 1,25(OH)2D levels were measured by the standard methods. 1,25(OH)2D is the product of both liver and renal hydroxylation of vitamin  $D_3$  which is the most active metabolite of vitamin D. Its standard serum level ranges from 20 - 60 ng/dl.

#### **Radiographic Findings**

In all children, radiographic assessment of the severity of rickets was examined by standard plain radiography of both wrists and knees and classified into active with metaphyseal cupping and brush-border, healing with sclerotic metaphyseal sclerotic margin, and healed rickets, with assessment of the amount of the genu varus deformity (either mild  $<10^\circ$ , moderate  $<20^\circ$ , or severe  $>20^\circ$ ) [8].

#### Statistical Analysis

The clinical, laboratory, biochemical, and radiographic results were compared; and the differences were analyzed and defined as significant if the p value was < 0.05.

All the data were categorical in which quantitative and qualitative observation of events were made statistically, and were linear queues.

Intra-observer and inter-observer variability were studied. All children were examined and scored independently by four observers. On a separate occasion, two of the observers repeated the assessments of the same patients (one for the genu varus deformity, whether mild, moderate, or severe; and the other one for the other rachitic manifestations), in the absence of information from the initial observations. The overall intra-observer mean weighted kappa was  $\chi w = +0.45$  (range SE  $\chi = 0.015-0.055$ ) and the overall inter-observer mean weighted kappa was  $\chi w = +0.34$  (range SE  $\chi = 0.008-0.040$ ).

# RESULTS

The mean age of the rachitic genu varus cases was 3.1 years, and of the controls was 3.3 years (range of both groups 2 - 4 years). The incidence of vitamin D deficient rachitic genu varus was 13.1% of the children's orthopaedic diseases in the National Institute of Neuromotor System of Egypt, with 6.8% of the total being males and 6.3% females, *i.e.* 52% of the vitamin D deficient rachitic genu varus group being males and 48% females (Table 1). All children in the current study had both vitamin D deficiency and genu varus deformity secondary to it.

## Table 1. Gender distribution of rachitic cases and all children.

	Ge	T-4-1	
	Males	Females	Total
Rachitic Genu Varus Group	130	120	250
All children	1000	900	1900
Percentage to All Children	6.8%	6.3%	13.1%
Percentage to Rachitic Group	52%	48%	100%

As regards to their socioeconomic status, it comprised the family income, the level of parents' education and occupation. Of the 250 rachitic genu varus cases, 215 (86%) had insufficient income and 35 (14%) has sufficient income. The fathers of 230 cases (92%) received equivalent to high or middle school education; those of 18 cases

(7.2%) were illiterate; and those of 2 cases (0.8%) received university or higher education. The mothers of 200 cases (80%) received equivalent to high or middle school education; those of 48 cases (19.2%) were illiterate; and those of 2 cases (0.8%) received university or higher education. The occupations of the fathers of 192 cases (76.8%) were manual workers; those of 56 cases (22.4%) were employees; and those of 2 cases (0.8%) were professionals. The occupations of the mothers of 225 cases (90%) were house wives or non-workers; those of 23 cases (9.2%) were employees; and those of 2 cases (0.8%) were professionals. As regards to the geographic regions, 162 cases (64.8%) came from slum areas, 50 cases (20%) from rural areas, and 38 cases (15.2%) from urban areas. As regards to the housing conditions, 188 cases (75.2%) were inhabitants of poorly built houses in low stories, and 62 cases (24.8%) of well built houses in middle or upper stories. As regards to exposure to sunlight, 150 cases (60%) exposed to less than half an hour a day, and 100 (40%) to half an hour or more a day. The children were completely wrapped in 200 cases (80%), and partially wrapped in 50 cases (20%). A significance difference (p < 0.01) was present between the rachitic genu varus cases and the controls in the epidemiological questionnaire (Table **2**).

Item			Cases (Total 250)		ontrols tal 250)	P value Stats: Hypothesis
		No.	%	No.	%	test
Family Income	Insufficient	215	86%	25	10%	0.009
	Sufficient	35	14%	225	90%	0.009
	Illiterate	18	7.2%	5	2%	0.008
Father's Education	High or Middle School	230	92%	15	6%	0.0095
	University	2	0.8%	230	92%	0.0095
	Illiterate	48	19.2	34	13.6%	0.008
Mother's Education	High or Middle School	200	80%	16	6.4%	0.009
	University	2	0.8%	200	80%	< 0.007
Father's Occupation	Manual Worker	192	76.8%	10	4%	0.0095
	Employee	56	22.4%	10	4%	0.009
	Professional	2	0.8%	230	92%	0.0095
	House-wife	225	90%	40	16%	0.0095
Mother's Occupation	Employee	23	9.2%	20	8%	0.008
_	Professional	2	0.8%	190	76%	0.0095
	Slum	162	64.8%	10	4%	0.095
Geographic Region	Rural	50	20%	15	6%	0.0095
	Urban	38	15.2%	225	90%	0.009
	Poorly Built – Low Stories	188	75.2%	225	90%	0.008
Housing Conditions	Well Built – Middle or Upper Stories	62	24.8%	25	10%	0.0095
From a strong da Strong	Less than ½ h	150	60%	25	10%	0.0095
Exposure to Sun	<sup>1</sup> / <sub>2</sub> h or more	100	40%	225	90%	0.0095
01.41	Completely Wrapped	200	80%	25	10%	0.009
Clothing	Partially Wrapped	50	20%	225	90%	0.0095

# Table 2. Epidemiological questionnaire.

As regards to the maternal gestational conditions, the mothers of 175 cases (70%) had more than 3 pregnancies, compared to the mothers of 23 controls (9.2%); of 140 cases (56%) has less than 2-year interval between the pregnancies, compared to those of 14 controls (5.6%); of 200 cases (80%) exposed to less than half an hour a day, compared to the mothers of 50 controls (20%); of 155 (62%) with no food rich in vitamin D, nor calcium, nor vitamin D supplementation during pregnancy, compared to those of 10 controls (4%). A significance difference (p<0.05) was present between the rachitic genu varus cases and the controls in the maternal questionnaire (Table **3**).

As regards to the children nutrition, 170 cases (68%) had below average body weight, as compared with 20 controls (8%); all the 250 cases (100%) had no oedema, and also all the controls; 200 cases (80%) were only breast fed for the first 2 years of life, as compared to 50 controls (20%); 26 cases (10.4%) were breast and bottle fed (artificial milk), as compared to 200 controls (80%); 24 cases (9.6%) were breast, bottle, and solid food, compared to 230 controls (92%). All the 250 cases (100%) received calcium and vitamin D supplementations during infancy, and also all the controls. A significance difference (p<0.048) was present between the rachitic genu varus cases and the controls in the epidemiological questionnaire (Table 4).

## Table 3. Maternal questionnaire.

Item		Cases (Total 2		Controls (Cotol 250)		<i>p</i> value Stats: Hypothesis TEST
		No.	%	No.	%	
Number of Decementation	>3	175	70%	23	9.2%	0.046
Number of Pregnancies	<3	75	30%	227	90.8%	0.046
Internale hater an Decementic	<2 years	140	56%	14	5.6%	0.04
Intervals between Pregnancies	>2 years	110	44%	236	94.4%	0.04
Europura to Sunlight	Less than $\frac{1}{2}$ h	200	80%	50	20%	0.039
Exposure to Sunlight	More than 1/2h	50	20%	200	50%	0.039
Vitamin D. Supplementation	No supplements	155	62%	10	4%	0.04
Vitamin D Supplementation	Supplements	95	38%	240	96%	0.04

#### Table 4. Nutritional questionnaire.

Item		Cases (Total 250)		Controls (Total 250)		<i>p</i> value Stats: Hypothesis TEST
		No.	%	No.	%	
Dody woight	Below average	170	68%	20	8%	0.047
Body weight	Average	80	32%	230	92%	0.047
Oedema	Present	0	0%	0	0%	0.043
Oedellia	Absent	250	100%	250	100%	0.045
	Only Breast	200	80%	50	20%	
Feeding Breast &	Breast &Bottle	26	10.4%	200	80%	0.044
(during infancy)	+ Solid	24	9.6%	230	92%	0.044
	Vitamin D supplement	250	100%	250	100%	

Clinically, all the 250 rachitic genu varus cases (100%) had closed fontanels and forehead bossing; 75 cases (30%) had delayed or poor dentition; 112 cases (44.8%) had rachitic rosary; 5 cases (2%) had Harrison's subcostal sulcus; 5 cases (2%) had barrel chest; 7 cases (2.8%) had pot-belly abdomen, 158 cases (63.2%) had broaden wrists and ankles (Table 5).

## Table 5. Clinical evaluation.

Item		Cases (Total 250)			
	No.	%			
Closed Fontanels	250	100%			
Forehead Bossing	250	100%			
Delayed Dentition	75	30%			
Rachitic Rosary	112	44.8%			
Harrison's Sulcus	5	2%			
Barrel Chest	5	2%			
Pot-belly Abdomen	7	2.8%			
Broad Epiphyses	158	63.2%			
Genu Varus	250	100%			

The laboratory biochemical profile showed that 213 rachitic genu varus cases (85.2%) had serum calcium less than 9 mg/dl; 188 cases (75.2%) had serum phosphorus less than 3 mg/dl; 205 cases (82%) had serum alkaline phosphatase level more than 25K.U; and 163 cases (65.2%) had serum active vitamin D 1,25(OH)2D less than 15 ng/dl. The controls had normal values (Table 6).

The plain radiographic findings revealed that 225 cases (90%) had genu varus more than  $20^{\circ}$  (*i.e.* severe); 12 cases (4.8%) had genu varus less than  $20^{\circ}$  (*i.e.* moderate); and 13 cases (5.2%) had genu varus less than  $10^{\circ}$  (*i.e.* mild). As regards to the healing process, 238 cases (95.2%) were healed rickets; 7 cases (2.8%) were healing rickets; and 5 cases (2%) were still active rickets. The plain radiography of the controls was normal findings (Table 7).

#### Table 6. Laboratory biochemical profile.

ltem	Cases (Total 250)		
	No.	%	
Low serum calcium (<9mg/dl)	213	85.2%	
Low serum phosphorus (<3mg/dl)	188	75.2%	
High serum alkaline phosphatase (>25KU)	205	82%	
Low serum active vitamin D 1,25(OH)2D (<15ng/dl)	163	65.2%	

#### Table 7. Plain radiographic findings.

Item		(7)	Cases (Total 250)			
			%			
	Severe (>20°)	225	90%			
Genu Varus	Moderate (<20°)	12	4.8%			
	Mild (<10°)	13	5.2%			
Healing Process	Active	5	2%			
	Healing	7	2.8%			
	Healed	238	95.2%			

#### DISCUSSION

Nutritional vitamin D deficiency rickets still exists in Egypt with an overall incidence rate of 13.1%; although the sun is shining all the year [1].

The current prospective study was concerned of the incidence of vitamin D deficient rachitic genu varus in the Egyptian preschool children; which is the rate of occurrence of new cases. It is calculated as the number of new cases in a given period of time, usually a year, divided by the number of the initially disease free children's population. Whereas its prevalence, which was not concerned of in this current study, is the existent cases; and is calculated as the number of already existent cases at a given period of time divided by the number of all children examined [9]. The slightly higher incidence among males (6.8%) than females (6.3%), with males to females ratio being 1.1:1, is insignificant and in accordance to the normal Egyptian sex ratio which is 1.05:1 [10]. All of the children had no deformity before the age of 2 as given from the history.

Epidemiologically, the risk factors are low socioeconomic status [11]. Most of the rachitic genu varus cases came from families having insufficient income (86%), living in slum areas (64.8%) where poverty, ignorance, and illiteracy prevail, suffering poor housing conditions (75.2%), lacking adequate exposure to sunlight (60%), and practicing unnecessary complete wrapping of the children (80%). This finding was supported by Majeed *et al.* (2007) [12],and Bakeit and Megeid (2012) [13] who found that lack of sunlight and complete wrapping of the child play an important role for the contribution of nutritional rickets.

Maternally, repeated pregnancies more than 3 gravida (70%), shortened pregnancy free intervals to less than 2 years (56%), lack of adequate sunlight exposure to less than half an hour (80%), and inadequate maternal gestational supplementation of calcium and vitamin D (62%) were contributing risk factors. This finding was in agreement with Baroncelli *et al.* (2008) [14] who reported that the mothers of rachitic children were exposed for shorter times to sunlight during pregnancy than those of non-rachitic children; and with Pehlivan *et al.* (2003) [15], Baroncelli *et al.* (2008) [14], and Bakeit and Megeid (2012) [13] who reported deficient maternal geastational supplementation of calcium and vitamin D deficiency rickets. Thacher *et al.* (2000) [16] found that maternal breast milk concentration of calcium is lower in rachitic than in healthy children.

Child feeding pattern imparted to the risk factors. Breast fed alone (80%) was the main contributing factor. This finding was in agreement with the study of Balasubramanian *et al.* (2008) [17] who revealed that most of the rachitic children were breast-fed; the incidence of vitamin D deficiency rickets is expected with icreasing rate of breast feeding. This finding was also supported by Lauer *et al.* (2006) [18], Ponnapakkam *et al.* (2008) [19], and Bakeit and Megeid

(2012) [13], who revealed that most of the rickets children were breast-fed which may lead to decreased vitamin D 25hydroxy vitamin D(25-OHD) intake from other sources and thereby causing rickets.

Vitamin D supplementation is essential preventive factor which came in agreement with study from China of Specker *et al.* (1992) [20] who observed that the breast- fed infant with insufficiency intake of vitamin D supplement are susceptible to nutritional rickets. Hollis and Wagner (2004) [21] noticed that although breast milk is adequate for growth and bone mineralization in the first year of life, it is lacking adequate concentration of vitamin D. Therefore, vitamin D supplementation must be necessary for breast-fed infants.

Limitations of the current study included, illiteracy of some parents particularly in dealing with the questionnaire, potential error in clinical evaluation particularly of fontanels' closure and dentitions, and observers judgments influencing the performance and scoring of tests.

## SUMMARY

Egyptian young children have a high incidence of vitamin D deficient rickets causing genu varus deformity.

A prospective study was made with 250 consecutive children between 2 - 4 years of age (130 males & 120 females) suffering vitamin D deficient rachitic genu varus, together with 250 non-rachitic controls of the same age group, out of a total number of 1900 children (1000 males & 900 females) who presented to the orthopaedic outpatient clinic in the National Institute of Neuromotor System of Imbaba, Egypt between September 2014 to September 2015.

Their parents were interviewed for epidemiological, maternal, nutritional and gestational issues through predesigned questionnaires. All of the cases and controls children were evaluated by clinical, laboratory, and radiographic examinations.

The incidence of vitamin D deficient rachitic genu varus was slightly greater in males (6.8%) than that in females (6.3%).

The risk factors included low socioeconomic status, nutritionally vitamin D deficient mothers, and prolonged breast feeding without vitamin D supplementation.

# CONCLUSION

Nutritional vitamin D deficiency rickets, causing rachitic genu varus deformity, is a multi-factorial condition comprising beside nutritional vitamin D deficiency, environmental and lifestyle factors. Several risk factors had important contributions, including low socio-economic status represented by low family income, low standard of education, poor housing conditions, lack of exposure to sunlight, nutritional status of mother, and prolonged breast-feeding without vitamin D supplementation. It was concluded that nutritional rickets is still a problem in Egypt and much effort should be done in order to combat it.

# **CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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## REFERENCES

- Bereket A. Rickets in developing countries. In: Hochberg Z, Ed. Vitamin D and rickets. Basel, Switzerland: Karger 2003; Vol. 6: pp. 220-32. [http://dx.doi.org/10.1159/000072778]
- [2] Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? Am J Clin Nutr 80 2004; (Suppl 6): 1725-9.
- Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets around the world: causes and future directions. Ann Trop Paediatr 2006; 26(1): 1-16.
   [http://dx.doi.org/10.1179/146532806X90556] [PMID: 16494699]
- [4] Hochberg Z. Rickets. Past and present. In: Hochberg Z, Ed. Vitamin D and rickets. Basel, Switzerland: Karger 2003; Vol. 6: pp. 1-13. [http://dx.doi.org/10.1159/000072763]
- [5] Awwaad S, Khalifa AS, Naga MA, et al. A field survey on child health in a rural community in Egypt. J Trop Med Hyg 1975; 78(1): 20-5.
   [PMID: 1121039]

- [6] Rockett HR, Breitenbach M, Frazier AL, et al. Validation of a youth/adolescent food frequency questionnaire. Prev Med 1997; 26(6): 808-16. [http://dx.doi.org/10.1006/pmed.1997.0200] [PMID: 9388792]
- [7] [No Authors Listed]. Wellcome Trust Working Party. Classification of infantile malnutrition. Lancet 1970; 2(7667): 302-3.
   [PMID: 4194372]
- [8] Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 2000; 46(3): 132-9. [http://dx.doi.org/10.1093/tropej/46.3.132] [PMID: 10893912]
- [9] Last JM. A Dictionary of Epidemiology. 4<sup>th</sup> ed. New York: Oxford University Press 2001.
- [10] el-Kholy MS, Abdel Mageed FY, Farid FA. A genetic study of vitamin D deficiency rickets: 2-sex differences and ABO typing. J Egypt Public Health Assoc 1992; 67(1-2): 213-22. [PMID: 1295947]
- [11] Manaseki-Holland S, Zulf Mughal M, Bhutta Z, Qasem Shams M. Vitamin D status of socio-economically deprived children in Kabul, Afghanistan. Int J Vitam Nutr Res 2008; 78(1): 16-20.
   [http://dx.doi.org/10.1024/0300-9831.78.1.16] [PMID: 18654949]
- [12] Majeed RY, Memon MK, Majeed M, Usman A, Rajar U. Contributing factors of rickets among children at Hyderabad. J Liaquat Uni Med Health Sci 2007; 6(2): 60-5.
- [13] Megeid FYA. Study of risk factors of rickets in children. World Appl Sci J 2012; 17(11): 1386-93.
- Baroncelli GI, Bereket A, El Kholy M, *et al.* Rickets in the Middle East: role of environment and genetic predisposition. J Clin Endocrinol Metab 2008; 93(5): 1743-50.
   [http://dx.doi.org/10.1210/jc.2007-1413] [PMID: 18285415]
- Pehlivan I, Hatun S, Aydoğan M, Babaoğlu K, Gökalp AS. Maternal vitamin D deficiency and vitamin D supplementation in healthy infants. Turk J Pediatr 2003; 45(4): 315-20.
   [PMID: 14768796]
- Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Chan GM. Case-control study of factors associated with nutritional rickets in Nigerian children. J Pediatr 2000; 137(3): 367-73.
   [http://dx.doi.org/10.1067/mpd.2000.107527] [PMID: 10969262]
- [17] Balasubramanian S, Ganesh R. Vitamin D deficiency in exclusively breast-fed infants. Indian J Med Res 2008; 127(3): 250-5. [PMID: 18497439]
- [18] Lauer JA, Betrán AP, Barros AJ, de Onís M. Deaths and years of life lost due to suboptimal breast-feeding among children in the developing world: a global ecological risk assessment. Public Health Nutr 2006; 9(6): 673-85. [http://dx.doi.org/10.1079/PHN2005891] [PMID: 16925871]
- [19] Ponnapakkam T, Ravichandran A, Bradford E, Tobin G, Gensure R. Breast-feeding and vitamin D supplementation rates in the ochsner health system. Ochsner J 2008; 8(3): 146-50. [PMID: 21603467]
- [20] Specker BL, Ho ML, Oestreich A, et al. Prospective study of vitamin D supplementation and rickets in China. J Pediatr 1992; 120(5): 733-9. [http://dx.doi.org/10.1016/S0022-3476(05)80236-7] [PMID: 1578308]
- Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 2004; 79(5): 717-26.
   [PMID: 15113709]

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