

# Rickets among a Group of Preterm Babies under the Age of Two Years at AL Ramadi Teaching Hospital for Maternity and Childhood

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## Abstract

**Background:** Rickets of prematurity is a familiar status that leads to pathological fractures. Deficiency of minerals leading to disturbed formation of bone is the most popular factor giving rise to disease and preterm infants are at increased risk of developing this condition.

**Objectives;** To identify the incidence of rickets in preterm babies, and studying the risk factor associated with this disease like age, gender, residence, type of feeding, and changes in some biochemical tests.

**Patients and Methods:** Across sectional study done in an outpatient clinic in maternity and childhood teaching hospital, cases included in this study were children below two years old and were delivered before 37 weeks of gestation. The diagnosis of rickets was done radiologically. All studied babies, data were collected by history about (gender, age, type of feeding, and residence). Cases which diagnosed radiologically as rickets, a serological test was done for (serum calcium, phosphorus, alkaline phosphatase, and vitamin D).

**Results:** (29.3%) of preterm babies were diagnosed as rickets of prematurity. The most common age reported with rickets was from 3months to less than13 months. Un-supplemented breast milk feeding was reported as a significant risk factor while residence and gender variation were not. High alkaline phosphatase level was reported in more than (90%) of rickety children.

**Conclusion:** A high incidence of rickets was found in preterm babies. Un-supplemented breastfeeding is an important risk factor for the disease. Alkaline phosphatase activity and radiological features are important for screening.

**Keywords:** Preterm babies, Rickets, Risk factors, West Iraq. Running title; Rickets in preterm babies at Ramadi city.

## Introduction

Prematurity is a live-born baby with a gestational age below 37 weeks.<sup>1</sup>

Definition of rickets is a bone disease distinguished by growth retardation related to the expansion of the hypertrophic chondrocyte layer of the growth plate and a defective mineralization of bone.<sup>2</sup>

Through pregnancy period, calcium and phosphorus are actively transmitted from the mother to her fetus, attaining the maximum increment rate at 32 to 36

gestational weeks for calcium of 100 to 130 mg/kg of the weight of fetus per day and phosphorus, 60 to 70 mg/kg of the weight of fetus per day<sup>2</sup>. Tremendous growth occurs during the 3rd trimester, and the higher increment rate is the result of the increase the need of the fetus for skeletal development.<sup>3</sup> As a result, calcium and phosphorus needs rise with lower age of gestation to compensate for the lack of these minerals accretion. Besides, human milk and standard formula have no sufficient calcium and phosphorus to provide the requirement of preterm infants<sup>2,4</sup>.

Most babies have no clinical signs and symptoms, and that x-ray finding and biochemical study established the diagnosis. Infants can have non-traumatic

fractures, mostly on the legs, arms, and ribs. Clinically Most fractures are not suspected.<sup>5</sup>

Measurement of serum levels of calcium is not a dependable tool for screening because those who are newly delivered can preserve normal calcium level in spite of a bone calcium wastage. The earliest indicator of mineral metabolism disruption is hypophosphatemia, serum phosphate levels <5.6 mg/dl have been highly linked with the existence of radiological finding of rickets in premature infants. Alkaline phosphatase is a bone turnover marker, values higher than 500 IU/L revealing bone homeostasis impairment and levels higher than 700 IU/L are correlated with bone mineral loss, in spite of the lack of clinical signs. Patients mostly have normal values of vitamin D. Low serum phosphorus level stimulates renal one alpha-hydroxylase, so levels of 1,25 vitamin D are high or high normal. Alkaline phosphatase values are elevated oftenly but may be at normal levels.<sup>3-5</sup>

The diagnosis is established by radiologic findings, which is best seen in wrists.<sup>6</sup> X-ray of the wrist demonstrates thickened growth plate, fraying, cupping, and widening of the metaphyseal distal end<sup>7</sup>.

Habitual use of fortified human milk or special premature formulas containing high mineral supplement has decreased the frequency of rickets with prematurity, especially in very low birth weight preterm newborns.<sup>8</sup> Many studies suggest giving preterm infants doses of calcium from 100-220mg/kg/day, and that of phosphate supplementation, most reports recommend doses from 75-140mg/kg/day,<sup>4,8</sup> and for the daily dose of vitamin D from 800-1000 IU/day.<sup>9</sup>

The present study was designed to describe the prevalence of rickets in premature babies, to identify age and sex distribution of rickets and some associated risk factors such as residence and types of feeding among Ramadi city population, and to identify the biochemical findings in positive cases.

### **Patient and Method**

Data was collected by direct interviews with the parents in the outpatient clinic and pediatrics ward

of Al-Ramadi Teaching Hospital for maternity and children, west of Iraq. The parents were given a full explanation about the purpose of the study and assurance about the confidentiality of the information and that the participation was completely optional.

After taking full permission from the director of the hospital a cross-sectional study started on children less than 2 years of age, who attending hospital during the period from the first of January 2020 to the last of June 2020 over 6 months selected randomly.

### **Exclusion criteria ;**

1. All children more than two years old.
2. Children on tonics and vitamin D supplements.
3. Children who were delivered  $\geq 37$  weeks of gestation.

A specially designed data papers was used to gather the information from parents or caregiver. The information contain data on; name, the age which categorized into 3 groups under 2 months, from 3months -<13 months and 13months -<25months, gender, residence whether rural or urban areas and duration of pregnancy to know whether the child is term or preterm. Also a detailed history of feeding; breast, bottle, or mixed feeding.

All cases sent for X-ray of the wrist, looking for signs of rickets which include; frying, cupping, widening of the wrist, decrease bone density. Wrist X-ray was done by an expert technician and reports of X-rays were done by an expert radiologist, In this study, the diagnosis of rickets depends on radiological findings.

Children who diagnosed radiologically as rickets, a serological investigation was done for calcium, phosphorus, alkaline phosphatase, and vitamin D levels.

The collected data were checked for accuracy by using the Statistical Package for Social Sciences (SPSS). Chi-square tests were used and a P-value level of <0.05 was considered as significant throughout the study.

### **Results**

The total studied cases were (140) preterm baby, 41(29.3%) of them were diagnosed by radiological

examination of the wrist as rickets. Boys were reported in (53.6%) of cases and girls (46.4%). As shown in Table 1.

Regarding age, most of the rickety preterm babies were reported from 3 months to less than 13 months old (78%). As shown in Table 2.

Regarding type feeding, most of the cases were reported in un-supplemented breastfeeding babies(53.6%). As shown in Table 3.

(58.5%) of rickety preterm babies were living in rural areas and (41.5%) of them were living in urban areas. As shown in Table 4.

Biochemical changes in diagnosed preterm rickets cases revealed that serum calcium was found to be low in only (10% ) of cases, serum phosphate level was recorded low in (59% ) of cases, while serum alkaline phosphatase level was recorded high in (90%) of cases. Serum vitamin D level was low in (32%) of cases. As shown in Table 5.

## Discussion

The metabolic bone disease of prematurity or rickets of prematurity is a complex metabolic bone disease characterized by inadequate postnatal bone mineralization compared with the rate of fetal mineral absorption.<sup>10</sup>

In this study, the incidence of rickets was (29.3%) among premature children, as a result of different definitions and no general agreement on diagnostic criteria, the incidence of rickets varies greatly from one study to another. Yet , the incidence of rickets of prematurity is related inversely to gestational age and weight at birth.<sup>11</sup> Results obtained that rickets of preterm babies occurs in 20-30% of newborn children under 1500 g and 50-60% of newborns weighing under 1000 g.<sup>12, 13</sup> Arani KS etal found that the incidence was 32.7%<sup>14</sup>, based on birth weight. While Mishra S etal study in Iran found the incidence was 23.3%<sup>15</sup>. In the present study, the higher rate of cases of rickets in preterm babies reflects the ignorance of the risk of this problem.

In the present study boys somewhat more than girls with non-significant statistically, other studies showed the same results<sup>1,6</sup>; but no another study showed a

significant variation in sex in rickets of prematurity.

Regarding the type of feeding, in this study, un-supplemented breastfeeding infants were more liable to have rickets of prematurity than those with formula milk. Siddhartha S etal<sup>16</sup> study reports the same result. Human milk is recommended for enteral feeding of all premature infants; however, it supplies deficient amounts of various nutrients, including calcium and phosphorus, to meet the needs estimated for these infants. This is an important reason to use breast milk supplements.<sup>17</sup>

In the present study, the most reported age of diagnosis of rickets in preterm babies was from 3 months to less than 13 months, similar results were obtained by Rustico S E etal .<sup>18</sup> Other researches demonstrate that the time of appearance of rickets of prematurity usually varies between postnatal 6th and 12th weeks.<sup>19</sup> Researches showed that in premature infants with gestational age under 32 weeks, bone mineral content was found to be 25% to70 % lower than term infants<sup>20</sup>.

Regarding biochemical results, calcium serum level was reported low in (11%) of rickety preterm babies, phosphate serum level was reported low in (59%) of rickety preterm babies, and that alkaline phosphatase serum level was high in (90%) of those babies while vitamin D serum level was low in only (32%) of cases. Pieltain C etal in Hong Kong<sup>21</sup> and Bozzetti V, Tagliabue P in Italy<sup>22</sup> also reported similar results. Studies showed that rickets in Infancy associated with normal levels of serum calcium and a low or low normal level of serum phosphorus .<sup>23</sup> In the majority of cases of rickets in preterm babies, vitamin D levels are normal<sup>18,24</sup>, but in opposite Al-Mustafa Z H etal study on term babies in Saudi Arabia<sup>25</sup> demonstrate (75%) with a low level of vitamin D in patients with rickets. Alkaline phosphatase serum levels are usually raised in infants with active rickets, and that authors have recommended that sequential estimations might help anticipate disease.<sup>26</sup>

All diagnosed rickety babies in this study had some degree of radiological changes proposal of rickets, for example, cupping, fraying, widening of the epiphyseal growth plate, and poor mineralization of trabecular bone. The radiological test very helpful for early diagnosis; however, screening test requires both radiological and alkaline phosphatase activity measurement to enable

neonatologists to minimize risk factors and optimize nutrition and mineral supplementation.<sup>19</sup>

No considerable variation was reported between provincial and urbanized cultures as a risk for rickets in preterm babies. No other study was found a significant difference in residence, and this can be explained by that rickets of prematurity had certain etiologies other than exposure to sunlight. However; in term babies, Al-Dalla Ali F J a study in Iraq<sup>27</sup> revealed that children living in urban areas are at risk for rickets explaining that via inadequate sunlight exposure.

### Conclusion

This study concluded that there is a high incidence of rickets among preterm babies in Ramadi city. Increase serum alkaline activity is a remarkable indicator in rickets diagnosis. Supplementation with vitamin D, calcium, and phosphate for premature babies is a must. Appropriate screening tests for preterm infants by x-ray and serological tests for early detection and treatment of patients is recommended. The use of the Quantitative Ultrasound which recently more widely used to estimate bone density is recommended.

**Ethical Clearance:** The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

**Conflict of Interest:** None

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### References

1. Julie-Anne Quinn, Flor M. Munoz; Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data; *Vaccine*; 2016; Dec 1; 34(49): 6047–6056.
2. Hung-Yi Chen, Li-Chien Chiu, Yung-Lee Yek, Yi-Ling Chen; Detecting rickets in premature infants and treating them with calcitriol: Experience from two cases; *Kaohsiung Journal of Medical Sciences*; 2012; 28, 452e456.
3. Faienza MF, D'Amato E, Natale MP, Grano M, Chiarito M, Brunetti G, and D'Amato G; Metabolic Bone Disease of Prematurity: Diagnosis and Management. *Front. Pediatr.* 2019; 7:143.
4. Vachharajani A.J., Mathur A.M., Rao R. Metabolic bone disease of prematurity. No reviews ; 2009;10:e402–e411.
5. Larry A. Geenbaurt: Nelson Textbook of Pediatrics, 20th ed, Philadelphia. WB Saunders 2015; 51:331-341.
6. Alessandro Rubinacci, Guido E Moro; Quantitative ultrasound for the assessment of osteopenia in preterm infants. *European Journal of Endocrinology*; 2003; 149 307–315.
7. Valeria Anna Manfredini<sup>1</sup>, Chiara Cerini; Metabolic Bone Disease of Prematurity: A Review of Minerals Supplementation and Disease Monitoring. *J Neonatal Biol*; 2015; 4:3.
8. Uauy R, Koletzko B. Defining the nutritional needs of preterm infants. *World Rev Nutr Diet*; 2014; 110:4–10.
9. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr*; 2010; 50: 85-91.
10. Maria Livia Ognean, Oana Boantă, Gabriel Grădinariu; Metabolic bone disease of prematurity; *Neonatology*; 2010; Volume II No 4.
11. Chan GM, Armstrong C, Moyer-Mileur L, et al. Growth and bone mineralization in children born prematurely. *J Perinatol*; 2008; 28(9):619–623.
12. Ali E, Rockman-Greenberg C, Moffatt M, et al. Caffeine is a risk factor for osteopenia of prematurity in preterm infants: a cohort study. *BMC Pediatr*; 2018; 18(1):9.
13. Daiva Gorczyca<sup>1</sup>, Hanna Cebula; Osteopenia of Prematurity in an Extremely Low-Birth-Weight Infant. *American Journal of Medical Case Reports*; 2013; Vol. 1, No. 1, 12-15.
14. Arani KS, Lotfi A, Jahangir M. Metabolic bone disease in very low birth weight neonates. *Iranian neonatal*; 2015; 6(2):7-13.
15. Mishra S, Biswal S, Parida P. Osteopenia of prematurity: Assessment of Biochemical parameters in Very low birth weight preterm neonates: *Int J Pediatr Res*; 2016; 3(3):137-142.
16. Sanjay Siddhartha<sup>1</sup>, Shobha Sharma; Metabolic bone disease in low birth weight babies between 1500 and 2000 g on exclusive breastfeeding; 2014; Volume: 1 Issue: 2 Page: 75-79.
17. Harding JE, Wilson J, Brown J. Calcium and

- phosphorus supplementation of human milk for preterm infants. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD003310.
18. Stacy E. Rustico, MDa,c, Andrew C. Calabria; Metabolic bone disease of prematurity; *J Clin Transl Endocrinol*; 2014; 1(3): 85–91.
  19. Heves Kırmızıbekmez, Gül Yeşiltepe Mutlu; Metabolic Bone Disease of Prematurity: Report of Four Cases; *J Clin Res Pediatr Endocrinol*. 2014 Jun; 6(2): 111–115.
  20. Miller ME, The bone disease of preterm birth: a biomechanical perspective. *Pediatr Res*;2003; 53 (1). 10-15.
  21. Pieltain C, de Halleux V, Senterre T, Rigo J, Prematurity, and bone health. *World Rev Nutr Diet*;2013; 106. 181-188.
  22. Bozzetti V, Tagliabue P, Metabolic Bone Disease in preterm newborn: an update on nutritional issues. *Ital J Pediatr*;2009; 35. 20.
  23. panel stay E.RusticoMD.A metabolic bone disease of prematurity; *Journal of Clinical & Translational Endocrinology*; 2014; Volume 1, Issue 3, Pages 85-91.
  24. Mimouni FB. Vitamin D in the newborn, part II: bases for current dietary recommendations in term and preterm neonates. No reviews; 2014;15(5): e193e8.
  25. Al-Mustafa Z H etal; Vitamin D deficiency and rickets in the Eastern Province of Saudi Arabia; Article *in Annals of Tropical Paediatrics International Child Health*; 2007;27(1):63-7 ·
  26. Hung YL, Chen PC, Jeng SF, Hsieh CJ, Peng SS, Yen RF, Chou HC, Chen CY, Tsao PN, Hsieh WS. Serial measurements of serum alkaline phosphatase for early prediction of osteopenia in preterm infants. *J Paediatr Child Health*. 2011;47:134–139.
  27. Fakhri Jamil Al-Dalla Ali; Prevalence of Rickets and Certain Associated Risk Factors Among Children Under Five Years of Age Attending the Outpatient Clinic of Maternity and Children Teaching Hospital in Ramadi City; *Anbar medical journal*; 2011 Volume: 9 Issue: 1 Page: 1-13