

# Osteopenia Of Prematurity Prevention And Treatment

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## Abstract

This paper examines Osteopenia of Prematurity (OOP) in a triplet child born at 24 3/7 weeks gestation. The infant required an extensive hospitalization in a Neonatal Intensive Care Unit (NICU) due to his prematurity. During his hospitalization, he was diagnosed with bronchopulmonary dysplasia, experienced multiple episodes of sepsis, and required long-term total parenteral and diuretic therapy. The differential diagnosis, pathophysiology, and prevention and treatment regarding insufficient bone mineralization in premature infants are discussed.

## INTRODUCTION

Osteopenia of prematurity (OOP) occurs when bone mineral content in an infant is significantly decreased compared to that seen in the fetus or infant of comparable size or gestational age. The incidence seen in very-low-birth-weight infants ((1250 grams) is approximately 30%<sup>2</sup>. The clinical onset of OOP usually occurs between the sixth and twelfth week postnatally and with infants born less than 28 weeks gestation. <sup>1</sup> OOP affects preterm infants with 1) chronic lung disease; 2) very-low-birth-weight; 3) long-term parenteral nutrition; 4) and use of certain medications (diuretics and corticosteroids) that affect mineral absorption.

OOP is the current term used for those infants showing evidence of decreased bone mineralization without radiological signs. The term Rickets is used when there is a chronic disorder of calcium metabolism characterized by radiological evidence of bone demineralization and elevated serum alkaline phosphatase levels. <sup>1</sup>

Rickets in newborns was first described in a study in 1919. All 668 low-birth-weight infants studied were found to have rickets. <sup>3</sup> During the time of this study, vitamin D deficiency was highly prevalent. Successful use of supplementation of Vitamin D did not start till the next decade. Today, with an increasing number of very-low-birth-weight infants surviving, the main pathogenic factor is an insufficient mineral intake of calcium and phosphorous. <sup>4</sup>

## CASE HISTORY

Infant boy FV was born as triplet "C" to a para 3 gravida 0 abortion 2 mother. Mother's prenatal history was

unremarkable except for the multiple gestation. FV was delivered by cesarean section due to premature labor. The amniotic fluid was clear and odorless. Estimated gestational age was 24 3/7 weeks with Apgar scores of 8 and 8 at 1 and 5 minutes, respectively. Birth weight was 633 grams. The infant was resuscitated and immediately intubated and placed on mechanically ventilation. He was transferred to the Neonatal Intensive Care Unit (NICU) for further evaluation and work up.

FV's long hospital course was very complex and included the following factors: 1) recurrent episodes of respiratory distress causing long-term need for mechanical ventilation; 2) multiple episodes of infection from multiple organisms ( E-Coli; Coagulase-negative Staph; and Candida Albicans) and from multiple sites (blood, trachea; skin and urinary tract); 3) long-term diuretic therapy (Lasix that was switched to Diurul on day of life 95); 4) long-term parenteral nutrition therapy; 5) corticosteroid therapy; 6) diagnoses of nephrocalcinosis and biliary atresia. Laboratory tests were routinely performed, as per standard of care in the NICU. Figures 1 and 2 demonstrate the significant lab data on calcium, phosphorus and alkaline phosphorus for this infant's hospital stay. After day of life 68, the infant's alkaline phosphorus level maintained a level that was greater than the standard normal range for infants (( 800 IU/L). On day of life 28, his parathyroid hormone level was 122 (normal 12-72). He was started on Vitamin D 400 units per day. Liver function tests were performed on multiple occasions and all were within normal limits for this infant.

Total parenteral nutrition (TPN) was initiated on day of life

2 through 26. He continued to require intermittent TPN due to episodes of multiple sepsis and possible gastrointestinal infection. When he was given oral nutrition, it was either fortified breast milk (4 packets on Enfamil Human Milk Fortifier per 100 cc of expressed breast milk) or Premature Enfamil 24 kcal/oz. with Iron.

Due to the consistent abnormal laboratory test results and concern for his overall nutrient status, a long extremity X-ray was performed on the 60th day of life. Results of this radiological examination showed questionable bowing of his left tibia. The infant was monitored closely throughout the remainder of his hospitalization to prevent fractures. Moreover, his nutritional status was monitored to promote an increase in his bone mineralization. Table 1 illustrates the sequelae of FV's prematurity and its effect on his overall health status.

### PATHOPHYSIOLOGY

The body distribution and regulation of the serum concentration of minerals such as calcium, phosphorus and magnesium determines overall bone mineralization. The renal regulation of these minerals is also essential to the ability of the infant to prevent bone demineralization. Chronic diseases (such as bronchopulmonary dysplasia), very low birth weight (( 1250 grams), and the use of long term total parenteral and diuretic therapy contribute to the increasing incidence of OOP and eventual Rickets in the preterm infant. <sup>2</sup>

Calcium is the most abundant mineral in the body. The average term newborn has accumulated between 20 and 30 grams of elemental calcium, 80% of which are accreted during the third trimester of pregnancy. Approximately 99% of this calcium is located in the skeleton; with only about one-third readily exchangeable with extracellular fluid. <sup>4</sup> The preterm infant is unable to accumulate the same amount as the term infant due to early extrauterine life.

The serum calcium exists in three separate fractions that are in dynamic equilibrium: 1) 40% protein-bound calcium (albumin representing the primary binding protein); 2) 10% complexed to a number of anions, such as citrate, phosphate, bicarbonate, and sulfate; and, 3) 50% free ionized calcium (the physiologically active form of calcium). <sup>5</sup> This serum concentration varies significantly in the newborn due to decreases over the first days of life, followed by a gradual increase to adult concentrations by the second or third week of life.

As with calcium, approximately 80% of the phosphorus in the term newborn is accumulated during the last trimester of pregnancy with 85% found in the skeleton. The phosphorous plasma concentrations in the newborn are maintained at concentrations greater than adults. Phosphorus is divided between the organic fraction and inorganic phosphate. <sup>4</sup>

Of the body's total magnesium content, about 60% is contained in the bone, another 29% in muscle, and the remainder is distributed through the soft tissues. The serum concentrations of magnesium are maintained within relatively tight limits and are essentially the same for newborns, infants, children, and adults. <sup>4</sup>

Serum calcium homeostasis is maintained primarily through the interaction of parathyroid hormone (PTH), calcitonin (CT), and vitamin D and their actions on the gastrointestinal tract, kidney, and bone. The kidney plays a very important role in calcium homeostasis. The movement of calcium from the gastrointestinal tract and bone determines the serum calcium concentration, but the kidney establishes homeostasis. The serum concentration of inorganic phosphate appears to be primarily regulated through the kidney by means of the tubular reabsorption of inorganic phosphate. The kidney also appears to be the primary site for regulation of serum magnesium concentration. <sup>1</sup>

The loop diuretics (Lasix) have been recognized to increase the urinary excretion of calcium. These agents act at the loop of Henle to inhibit the active reabsorption of sodium and chloride. Since calcium reabsorption in the ascending limb of the loop of Henle is dependent on the active reabsorption of these ions, calcium reabsorption is secondarily inhibited. The resulting hypercalciuria can place the infant at risk for development of nephrocalcinosis, and in very-low-birth-weight infants, can further impair an already marginal calcium balance. Chronic administration of thiazide diuretics, which are often used as an alternative to loop diuretics, is also known to increase urinary excretion of calcium.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for osteopenia of prematurity (OOP) versus Rickets is determined by routine and supplementary lab tests and examinations of bone density. OOP can generally be suspected when there is an elevated alkaline phosphatase activity (( 800 IU) or lowered serum phosphorus (<3.5 mg/dL). <sup>1</sup> Moderate increases in the alkaline phosphatase (400-800 IU) can be commonly seen in rapidly growing premature infants and warrants careful

monitoring of the infant’s mineral intake. The serum calcium level usually remains normal. 2

Supplementary tests include the Vitamin D levels (25-hydroxy-vitamin D and 1,25-hydroxy-vitamin D) and the parathyroid hormone (PTH). These tests reveal an increased level of 1,25-hydroxy-vitamin D and a depressed 25-hydroxy-vitamin D when OOP is present. The PTH will either be normal or high with OOP. 1

Most evaluations for bone demineralization, in premature infants with laboratory tests showing increased alkaline phosphorus, are performed using the standard radiograph of a long bone. This technique, unfortunately, does not detect mild OOP. 3 The radiograph of an infant with Rickets will exhibit: 1) a decrease in the long bone growth; 2) craniotabes; 3) nontraumatic palpable swelling of the costochondral junctions of the rib cage; 4) and, splaying of the metaphyseal ends of the long bones.

The presence of Rickets can be definitively assessed by direct evaluation with a bone mineral densinometer. 3 The bone density is calculated by applying a photon beam from a 125-Iodine source to the distal radius. The results are compared to standardized normal bone-density curves for different gestational ages. Since this technique is expensive, it is generally reserved for use as a research tool.

**PREVENTION AND TREATMENT**

Prevention is the best approach to Osteopenia of Prematurity (OOP) and resulting Rickets in the newborn. To prevent OOP, adequate amount and ratio (1.3-1.7:1) of Ca and P intake is needed together with an adequate caloric (> 80 Kcal/kg/d) and nutritional (2.5-3 g/kg/d amino acid and 400 IU/d vitamin D) intake. 4 When weaning from TPN to enteral feeding, high Ca and P content formulas should be used, such as: Similac Special Care, Enfamil Premature, or breast milk with Human Milk Fortifier (HMF). 3

Recommendations for the management of OOP complicated by medical conditions in the premature infant are presented in Table 2.

In sum, the premature infant needs more minerals than the term infant to develop appropriate bone mineral accretion. Osteopenia of prematurity (OOP) may result from the necessary care (long term total parenteral and diuretic therapy) required by these premature infants. The outlook for the resolution of OOP depends primarily on the causation for the decrease in bone mineralization. Infants exhibiting

OOP with elevated alkaline phosphatase, such as Baby Boy F., have the potential for a deficit in body length by 18 months of age. 1

**CLINICAL IMPLICATIONS**

Vigilant observation and evaluation by the health care team in the NICU is critical to prevent and treat OOP. Monitoring the infant’s nutritional status on a weekly basis is necessary to optimize bone mineralization. Maintaining calcium/phosphorus ratios of 1.3-1.7:1. in TPN will minimize bone demineralization during long term parenteral nutrition. Initiating enteral feedings with premature formulas or fortified breast milk as soon as medically stable will promote bone mineralization uptake.

Cautious handling of infants at risk for OOP will decrease the potential for fractures. Collaboration with physical therapy for range-of-motion exercises may enhance bone mineralization. However, replication studies evaluating the effect of physical therapy on bone mineralization in these premature infants are needed before physical therapy can be instituted as a standard of care. 4

**Figure 1**

Table 1

System	Effect Of FV's Prematurity On His Overall Health Status
Respiratory	Long-term mechanical ventilation resulting in Bronchopulmonary Dysplasia and extended diuretic therapy.
Fluid, Electrolyte and Nutrition	Feeding intolerance and multiple episodes of sepsis necessitating long-term parenteral nutrition resulting in biliary atresia.
Genitourinary	Long term diuretic therapy (Lasix) leading to electrolyte imbalances and nephrocalcinosis.
Infectious Diseases	Multiple episodes of sepsis from multiple organisms ( E-Coli, Coagulase-negative Staph, and Candida Albicans) and from multiple sites (blood, trachea; skin and urinary tract).
Orthopedics	Bowing of the left tibia seen on radiological exam.

**TABLE 2 :SUMMARY OF NURSING IMPLICATIONS**

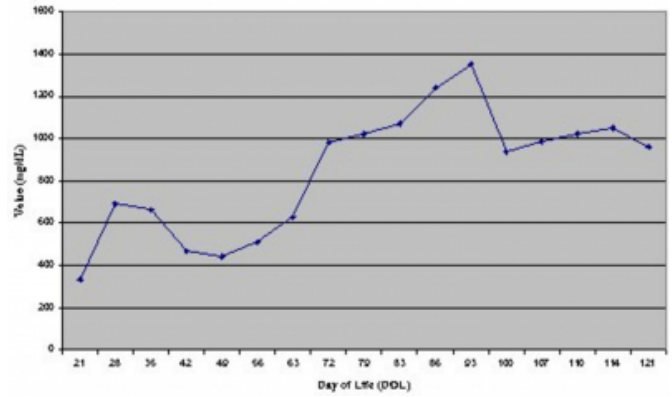
Prevention and Treatment of Osteopenia of Prematurity

Prevention & Treatment

1. Calcium and phosphorus in TPN at a ratio of 1.3-1.7:1 (calcium=9-10 mg/dl and phosphorus= 6-8 units/l) and initiating enteral feedings as soon as medically possible.
2. Optimizing enteral intake of calcium and

phosphorus by adding powdered fortifier to breast milk or using a formula made for premature infants.

3. Switching from Lasix to an anticalciuric diuretic, such as Chlorothiazide IV or PO as soon as medically possible.
4. Limiting the use of Aminophylline and Dexamethazone therapy by switching to Albuterol and weaning steroids as soon as medically possible.
5. Maintaining vitamin D intake of 400-IU per day.
6. Physical therapy (i.e., range-of-motion exercises of the upper and lower extremities) to enhance bone mineralization and bone mineral content in VLBW infants in stable condition.
7. Cautious handling in infants with nutritional rickets to avoid bone fractures.

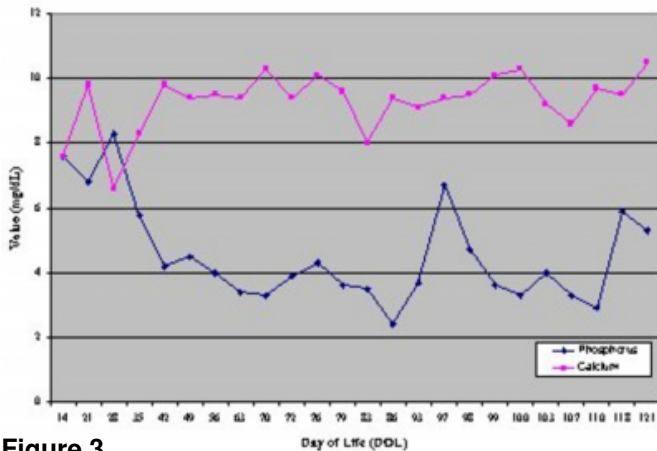


**Figure 2**

Figure 1: Calcium and Phosphorous Values for Baby Boy F

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**Figure 3**

Figure 2: Alkaline Phosphatase Values for Baby Boy F

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