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Treatment and prevention of neonatal osteopenia

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Summary Osteopenia is a recognised cause of pathological fracture in preterm infants. The commonest etiology for osteopenia is mineral deficiency resulting in suboptimal bone formation. Various risk factors affecting bone growth have been implicated. Preterm infants who depend on prolonged total parenteral nutrition and have chronic co-morbidities, such as chronic lung disease and short-gut syndrome, are particularly vulnerable to this complication. Early detection by vigorous monitoring of bone homeostasis and prompt treatment of osteopenia are warranted in these high-risk infants. The aims of this article are to (1) identify infants who are prone to develop osteopenia, and (2) minimise its occurrence and complications.

Practice points

- The third trimester of pregnancy is critical for fetal bone mineralisation
- Premature infants, especially those who require prolonged total parenteral nutrition for feed intolerance, are most vulnerable to the development of osteopenia
- Medications such as diuretics, methylxanthines and corticosteroids can cause osteopenia
- Conventional radiographs are not sensitive enough to detect osteopenia until late stage disease
- Dual energy X-ray absorptiometry (DEXA) has been validated for use in determining bone mineral content in infants
- Vitamin D supplementation of 400 IU/day is adequate for bone mineralisation and higher dosage does not have additional benefit
- Provision of minerals in parenteral nutrition solution is limited by the solubility of calcium and phosphorus, which may be improved by using organic phosphates
- Use of alternate infusion of calcium and phosphorus in parenteral nutrition cannot improve mineral retention in preterm infants
- Enteral absorption of phosphorus is very efficient and hence oral supplementation should be started once enteral feeding is tolerated
- Maintaining serum calcium concentrations between 2.05 and 2.75 mmol/L and serum phosphate concentrations between 1.87 and 2.91 mmol/L by serial monitoring helps to prevent osteopenia in preterm infants

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Introduction

The integrity of the skeletal system depends on the strength of bones, which relies on the size, structure and degree of mineralisation. Osteopenia is due to a decrease in the amount of bone tissue and may result from insufficient bone deposition or increased bone reabsorption. Osteopenia with or without failure of bone mineralisation is a common cause of pathological fracture in newborns, in particular, preterm very low birth weight (VLBW) infants. The pathogenesis of osteopenia is usually multifactorial and may involve both prenatal and postnatal factors such as failure of transplacental mineral delivery, inadequate mineral intake and excessive mineral loss after birth. Although the incidence of osteopenia in neonates varies widely between different studies, it is inversely correlated with body weight and gestational age. Inadequate bone mineralisation has been reported in 30% of extremely low birth weight infants (birth weight <1000 g).[1] Osteopenia is associated with postnatal morbidities, including chronic lung disease (CLD) of prematurity, necrotising enterocolitis, prolonged parenteral nutrition and delay in achieving full enteral feeding.[2]

Pathophysiology of osteopenia in neonates

Fetal bone development

Skeletal development begins early in embryonic life but bone mineralisation occurs mainly during the third trimester of pregnancy. Protein and energy are required in a larger quantity for collagen matrix synthesis, and calcium and phosphorus for bone mineralisation.[3] Fetal skeletal growth and bone mineral accretion are dependent on maternal energy, protein and mineral supply and are directly affected by the net transfer of calcium and other minerals from mother to fetus. From the second trimester onwards, serum calcium and phosphorus concentrations are about 20% higher in the fetus than corresponding maternal levels,[4] suggesting an active transplacental transport of minerals. The increase in mineral demand on the mother is partially compensated for by an increased intestinal absorption of calcium[5] and possibly also by increased mobilisation of minerals from the maternal skeleton. Inadequate fetal bone mineralisation had been reported in mothers with extreme dietary restriction[6] and the condition could be improved by maternal calcium supplementation. Chronic maternal vitamin D deficiency may also affect fetal skeletal development.[6] The major metabolite that crosses the placenta is 25-OHD[7] and this is converted to 1,25-$(OH)_2$D in the fetal kidney.[8] However, the role of 1,25-$(OH)_2$D in fetal skeletal mineralisation and mineral homeostasis remains uncertain.

Postnatal bone development

The physical density of long bones decreases by 30% during the first 6 months of life. This is the result of a faster increase in bone marrow cavity than the increase of cross-sectional area of the cortex.[9] The reasons for this postnatal adaptation are postulated to be related to the difference in mechanical stress and pattern of hormonal stimulation before and after birth. Stimulation of cortex growth from resistance training by kicking against the muscular uterine wall is absent after birth. This postnatal adaptation process is similar between term and preterm infants. It has been shown that the substantial decrease in bone strength is associated with biochemical evidence for new bone formation in VLBW infants during the first 8 weeks of life.[10] This physiological reduction in bone strength together with inadequate mineral supply contribute to the development of osteopenia in VLBW infants.

Risk factors of neonatal osteopenia

Osteopenia in infants is multifactorial in origin. Identification of predisposing factors enables earlier monitoring, detection, treatment and prevention of the condition. Among the risk factors, prematurity is the most important. Intrauterine fetal accretion of calcium and phosphorus increases substantially from 24 gestational weeks onwards. During this period, fetal weight gain is about 30 g/day representing a consumption of 310 mg of calcium and 170 mg of phosphorus per day. Two-thirds of the total amount of calcium required by the human fetus is acquired during this period.[11] Infants born prematurely are likely to have lower stores of skeletal calcium and phosphorus at birth compared with term infants. The extra demand in minerals for rapid bone growth after birth in addition to the inadequate store in preterm infants will render them prone to the development of osteopenia.

Providing the intrauterine accretion rate of minerals in preterm infants has always been a challenge for neonatologists. Multiple restrictions have made this target very difficult to achieve. The