Osteopenia of prematurity: Are we on the right track?

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Background

Modern advances in the care of preterm infants have significantly reduced the neonatal mortality rate universally. Among the Southeast Asian countries, Sri Lanka indicates the lowest neonatal mortality rate at 8.6% per 1000 live births. This achievement brings to attention the need to not just ensure the survival of the preterm infant but also the requirement to maintain better long term health outcomes and to manage associated co-morbidities relating to such newborn babies. Osteopenia of prematurity (OOP) in preterm infants is an important co-morbidity in its acute stage as well as long term as it is known to affect linear growth and lead to osteoporosis in patients in later life.

Premature infants are considered to be at high risk for developing osteopenia due to their reduced bone mineral content (BMC). Currently there are no standard practices relating to the screening, diagnosis or treatment of OOP around the world. At the neonatal intensive care unit (NICU) at Peradeniya Teaching Hospital in Sri Lanka we have observed clinical and radiological evidences of bony fractures due to reduced BMC which is very rare even in extremely premature babies. Most of the preterm infants in our unit were fed exclusively breast milk and parenteral nutrition was given only in selected cases.

Approximately 50% of very low birth weight (VLBW) neonates develop OOP with rickets which may eventually lead to spontaneous or traumatic fractures[1]. In the acute neonatal phase, reduced BMC can lead to fractures, which have been described in up to 10% of low birth weight (LBW) infants[2]. The clinical onset of OOP is usually between 6 and 12 weeks postnatally. Neonates who have suffered intrauterine growth retardation (IUGR) are also prone to reduced stores of calcium secondary to decreased placental nutrient transfer[3]. Compared with mature newborns at birth, premature babies have larger marrow cavities and lower bone density when they have reached expected term[4]. Rickets in newborns was first described in a study conducted in 1919. All 668 low-birth-weight infants studied at the time were found to have rickets[5]. There are several biochemical investigations, such as serum calcium, serum phosphate and alkaline phosphatase (ALP) that have been used to act as markers of bone mineralization and popular in screening for OOP.

Risk factors

The majority of bone mineralisation, along with calcium and phosphate accretion occurs during the third trimester of pregnancy. Infants born before the third trimester have decreased levels of these minerals. There are added factors that compound the risk of reduced bone mineralisation following premature delivery. There is evidence that the placenta has a role in BMC. Vitamin D is converted to 1, 25-dihydrocholecalciferol in the placenta which is important in the transfer of phosphate across the placenta to the fetus[6].

There is an association between neonatal rickets and pre-eclampsia[7]. Severe demineralisation has also been described in infants born to mothers with chorioamnionitis and placental infection[8]. There is a higher incidence of postnatal rickets in babies with IUGR, suggesting that chronic damage to the placenta may alter phosphate transport[9]. VLBW, delayed establishment of full enteral feedings and long term use of parenteral nutrition are risk factors for OOP. In exclusively breast fed infants OOP does not depend on the severity of the prematurity[10]. Common neonatal conditions such as sepsis, cerebral pathology, muscular disorders and paralysis may result in prolonged periods of immobility, well recognized as a risk factor for poor bone mineralization. Conditions such as bronchopulmonary dysplasia, cholestasis, acidosis and necrotizing enterocolitis are other well known risk factors. Medications frequently used such as steroids, methylxanthines and diuretics, can increase the risk of inadequate bone mineralisation.

Serum biochemical markers

Alkaline phosphatase (ALP)
ALP is a glycoprotein enzyme produced by a variety of tissues including bone, liver, kidney and intestine. Tissue nonspecific ALP is generally measured; however, 90% of ALP in infants is

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known to be of bone origin and it is considered to be an indicator of bone turnover. During the first 2-3 weeks after the birth of all newborn babies ALP increases and further rises if there is a lack of mineral supply. If there is an abnormal increase in bone activity due to factors such as rapid growth or a deficiency in mineral content a biochemical indicator can be of assistance in the diagnosis of osteopenia in newborn babies. However, there seems to be insufficient evidence and conflicting theories as to whether ALP is such an indicator. An ALP level of greater than five times the upper adult limit of normal is an indicator of the risk of rickets[11]. By using dual energy x-ray absorptiometry (DEXA) scan as a screening tool, Faerk et al concluded that bone mineralisation in premature infants cannot be predicted from serum ALP or serum phosphate[12]. However, ALP is still widely used because it is a readily available measurement and can be easily followed. Thus it is a frequently used screening tool for OOP which can generally be suspected when there is elevated ALP activity (>800 IU).

Calcium
Serum calcium cannot be regarded as a suitable method of screening as it can indicate normal values even though there may be a loss of bone calcium. The serum calcium level can also rise due to phosphorus depletion and hypophosphataemia.

Phosphate
Data has confirmed that although phosphate concentration is related to bone mineral density, it is not sensitive enough to identify infants with bone mineral deficits. It is however highly specific[13]. The use of serum phosphate levels in combination with ALP levels can significantly increase the sensitivity of the screening and identification of infants at risk of metabolic bone disease[14].

Radiological investigations

X-ray
Osteopenia can be discovered as an incidental finding on a plain radiograph, showing 'thin bones' or healing fractures. Bone mineralization, however, needs to be decreased by at least 20–40% for these changes to be visible[15,16]

Single photon absorptiometry (SPA)
Data from SPA studies measuring BMC has been used to construct curves of intrauterine BMC. Such curves can subsequently be applied in longitudinal studies to compare the BMC in LBW infants with that of infants born closer to term[17]. Using this technology, many studies have documented delays in bone mineralisation in premature infants compared with the intrauterine curve of mineral accretion.

Dual photon absorptiometry (DPA)
DPA is a technique for quantifying both total skeletal and soft tissue masses. DPA is not used much in neonates due to time factors relating to the completion of a scan. DPA can take 20 to 50 minutes for a scan whereas SPA takes less than 5 minutes and therefore is considered a preferred method.

Dual-energy x-ray absorptiometry (DEXA)
It is becoming more widely used in infants but availability is limited. DEXA holds more promise for measuring BMC and assessing osteopenia in premature infants. DEXA uses two electronically generated x-ray beams of relatively high and low energy levels and can determine total body BMC as well as regional BMC with minimal tissue radiation. However, the scan time is still relatively lengthy (about 15 min for total body BMC), and the equipment is too cumbersome to be used at the bedside for studies of sick premature infants. Only a few studies using this technique in premature infants have been published and no standard reference values are available for preterm infants of different gestational ages[18]. DEXA scans are sensitive in detecting small changes in BMC and density, and can predict risks of fractures[19].

Quantitative ultrasound
Ultrasound gives measurements that are related to bone mineral density and structure. It is simple, non-invasive, and a relatively cheap bedside test[20]. Reference values are available for both term and preterm infants[21].

Urine analysis

Urinary excretion of calcium and phosphorus
Fetal bone mineral accretion has been achieved in preterm infants by establishing and maintaining a simultaneous slight excretion of calcium and phosphorus (urine concentrations of 1-2mmol/l) by means of an individual supplementation with calcium and/or phosphorus, resulting in a slight surplus supply. However, to date it has not been proven that these variables are a reliable substitute for direct measurement of BMC[22]. Phosphate is not bound in the plasma like calcium and so the percent tubular reabsorption of phosphate (TRP) is the best guide to adequacy of phosphate supplementation. A percent tubular reabsorption of >95% shows inadequate supplementation.

Current situation in Sri Lanka

We have collected the data using a standard questionnaire from 13 major neonatology units in Sri Lanka viz. Castle Street Hospital, De Soysa Maternity Hospital, Teaching Hospital Kalubowila, Sri Jayawardenepura General Hospital, Teaching

Hospital Karapitiya, Teaching Hospital Kandy, Teaching Hospital Kurunegala, Teaching Hospital Kegalle, Teaching Hospital Jaffna, General Hospital Ratnapura, Teaching Hospital Anuradhapura, General Hospital Ampara and General Hospital Polonnaruwa. Out of these only four units screened for OOP and all four units used serum ALP as the screening method and one unit used x-rays of both wrist joints in extremely premature babies to confirm the diagnosis. Only one unit did monitoring of ALP every 2 weeks while the other 3 units did it monthly. The values of ALP taken as positive varied from 400IU/L-1000IU/L. Treatment was started guided by the maturity of the neonate where the three units had different borderlines like 30 weeks, 32 weeks and 36 weeks irrespective of their weight. Most of the units started treatment at 2 weeks in premature babies thought to be at high risk. For treatment all the units used calcium supplements and vitamin D. None of the units used phosphate supplements.

Our survey showed that in Sri Lanka we do not have proper diagnostic criteria to diagnose OOP. Further, there is no clear opinion about when and what to use for treatment. However, the survey showed that the most popular and freely available screening tool for OOP is ALP as all three units used it for screening.

Calcium (Ca) content of breast milk rises from about 4mmol (160mg/L) in initial colostrum to 6.4mmol (256mg/L) by the third day and plateaus there for the first three months of nursing[23]. Milk from mothers giving birth prematurely ("preterm milk") is not significantly different in Ca content from term milk during the first month of nursing[24].

Recommended daily Ca intake is 140-160 mg /100kcal and for phosphate 95-108 mg/100kcal (American Academy of Paediatrics)[13]. Recommended daily intake of vitamin D for premature infants is 400IU. When mothers and their infants are exposed to biologically normal amounts of sunlight, human milk must be assumed to contain biologically normal amounts of vitamin D[25].

With the results of our survey we got to know that most of the units do not screen for OOP, and treatment is also not appropriate. After reviewing the current literature, in view of improving the screening and treatment methods of OOP we suggest the following guidelines:

Premature infants should be monitored for OOP if:
1. Period of gestation <34 weeks
2. Birth weight <1800g

Monitoring:
This should include weekly serum ALP, calcium (Ca), and phosphorus (P) (Normal values of ALP <800 IU/L, Ca- 2.26-2.69mml/L, P-1.74-2.66mml/L)

Suggested treatment:
1. Calcium 140-160mg/Kg daily
2. Phosphate 1-2mmol/Kg daily
3. Vitamin D 400IU daily

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