REVIEW

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A Narrative Review of Calcium, Phosphate, Magnesium and Vitamin D Metabolism in Breastfed Preterm Babies

Ayeni Victor A

Department of Paediatrics, Babcock University, Ilishan-Remo, Ogun State, Nigeria

Correspondence

Dr Victor A. Ayeni, Department of Paediatrics, Babcock University, Ilishan-Remo, Ogun State, Nigeria.
Email: tioluwa@hotmail.com.; ORCID – https://orcid.org/0000-0002-8626-7181.

Abstract

Calcium, magnesium, phosphate and Vitamin D metabolism is intricately interwoven in human beings. For the foetus, the accretion of these nutrients occurs mainly in the third trimester. Hence, babies who are delivered preterm are at risk of suffering a deficiency of these micronutrients. Inadequate micronutrients can impair the infants' cellular functions, growth and development. Hence, this paper reviews the determinants of plasma levels of the micronutrients and how they are mobilised. It also reviews the evidence about the quantities of the nutrients available in breast milk and how much of them are available to the infant at optimal breastfeeding volumes. The possible implications on growth and the argument for or against supplementation of the nutrients in pregnant women and their preterm neonates who are exclusively breastfed are also discussed.

Keywords: Breastfeeding, Breast milk, Calcium, Magnesium, Phosphate, Prematurity, Vitamin D, Vitamin supplementation.

Introduction

As far back as 1951, it was demonstrated in certain cornerstone studies that during the last three months of gestation, the fetal accretion of calcium, phosphorus, and magnesium is about 20 g, 10 g, and 700 mg, respectively, which represents accretion rates of approximately 100–120 mg/kg/day for calcium, 50–65 mg/kg/day for phosphorus, and 3–5 mg/kg/day for magnesium.[1] These findings were based on careful analyses of the body compositions of a large number of aborted fetuses at various gestational ages, including the exact mineral compositions of their ashes.[1] Several studies later have affirmed that 80% of calcium, magnesium, and phosphate accretion *in utero* occurs in the third trimester.[1–4] During the third trimester, calcium is transported by active transport against a concentration gradient of 1:4,[5] with relative hypercalcaemia in the foetus, leading to decreased bone resorption. The latter can be ascribed to a relatively low parathyroid hormone, low 1,25-dihydroxyvitamin D, and increased bone mineralisation. A relatively high foetal calcitonin level, as well as a possibly elevated level of 24,25-dihydroxy vitamin D, is thought to be responsible for this increased (foetal) mineralisation.[1,6]

The foregoing explanation about mineral accretion in the foetus during the third trimester implies that preterm infants are likely to miss, in part or entirely, the period of greatest mineral accretion and so are vulnerable to mineral deficiencies.[7,8] Breast milk's calcium, phosphate, and magnesium concentrations cannot match the intrauterine accretion rates at the highest possible extrauterine enteral feeding rates. This implies that preterm infants who are fed only breastmilk have the likelihood of developing deficiencies in plasma levels of the corresponding minerals.[1,7,9] Clinical evidence of mineral deficiency/deficiencies may occur in

as many as 30–50% of VLBW infants who are fed on breastmilk exclusively.[14]

Human breast milk contains little vitamin D3 (approximately 20IU/L), and very little 25-hydroxyvitamin D passes from the maternal circulation to breast milk.[10] The Vitamin D content of breast milk correlates with the serum levels of vitamin D in the mother. Preterm human milk contains approximately 220 mg/L of calcium, 125 mg/L of phosphorus, and 34 mg/L of magnesium.[11] These values increase slightly at 12 weeks after birth. Term human milk, on the other hand, contains relatively higher mean levels of calcium (261mg/L) and phosphorus (153mg/L) but no significant difference in magnesium levels.[11]

In a Taiwanese study, Hsu *et al*[12] demonstrated that there was no significant change in calcium levels over the first four weeks in the breast milk of mothers of preterm infants. Although there was an increase in the phosphate levels, these were still less than the corresponding phosphate levels in the breast milk of mothers who delivered babies at term. These findings were corroborated in a systematic review by Gidrewicz and Fenton,[13] involving studies done in North America, Europe, and Japan. However, as mentioned earlier, the values did increase at 12 weeks after delivery, but only slightly.[11]

The WHO recommendations on optimal feeding of low-birth-weight infants in low- and middle-income countries include strong evidence for feeding the babies exclusively on breastmilk. On the other hand, the evidence for supplementation with anything other than breastmilk (including calcium, phosphate, and Vitamin D) is reportedly weak.[14] However, the absorption rates at the highest possible feeding rates approximate only about one-third of intrauterine bone mineral accretion rates.[7] These absorption rates also fall short of the 2022 updated recommendations for the daily requirements of calcium, phosphorus, and magnesium, made by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) for preterm neonates less than 1.8kg which are 3.0–5.0 mmol/kg/day, 2.2–3.7 mmol/kg/day, 0.4–0.5 mmol/kg/day respectively.[15] A recent survey of enteral feeding practices for very preterm babies in 50 neonatal units in Nigeria and Kenya found that the feeding practices varied widely, and 44% of the units gave calcium supplements. In contrast, only 10% gave phosphorus supplements.[16]

Therefore, this paper aims to review what is known from empirical studies and previous reviews of the interwoven subject of the metabolism of calcium, phosphate, magnesium, and vitamin D in breastfed preterm neonates and their possible clinical implications concerning the need for supplementation. It is hoped that it will thereby stimulate further research in local contexts, especially in Africa, where only a few studies have documented evidence on the subject.

Methods

Relevant publications were selected from searches of two medical databases, PUBMED and Web of Science. The search terms included ‘preterm’, ‘calcium’, ‘vitamin D’, ‘phosphate’, ‘magnesium’, and ‘breast milk’. Each of these key terms, with synonyms derived from MeSH headings, was used in the search. The search was delimited to the years between 1974 and 2024.

The search terms and synonyms were combined with the Boolean operators ‘OR’ and then ‘AND’. The search on the Web of Science returned 144 papers, while PubMed returned 190 papers. Publications on this review's subject matter were selected based on the title and abstracts. In addition, searches were made on Google, and in-text references of articles from the searches were also consulted for additional publications.

Determinations of Plasma Calcium, Phosphate and Magnesium

The interwoven nature of the physiology of these three substrates makes it difficult to

discuss them separately, as whatever affects one, directly or indirectly, affects the others. In a Canadian study involving 506 preterm neonates,[17] the authors reported that phosphate, magnesium, and alkaline phosphatase in cord blood serum decreased with gestational age, while calcium increased with gestational age. In the mentioned Canadian study, multiple births, small-for-gestational-age (SGA), and maternal pregnancy-induced hypertension (PIH) were also significant predictors of decreased calcium levels. However, their effects were found not to supersede the effect of gestational age.[17]

As the infant moves to an anabolic state (after the first few days of life) with cellular phosphorus uptake and without adequate phosphorus intake, the ensuing hypophosphataemia results in impaired bone deposition and hypercalcemia.[18] Plasma phosphate level is also known to vary considerably throughout life, with the highest values at the time of the fastest growth in early infancy.[19] There is a physiologic drop in plasma calcium levels in neonates, with a nadir at 24-48 hours.[20] Maternal diabetes in pregnancy is known to cause transient hypocalcaemia and hypomagnesaemia.[21,22]

Tocolysis (i.e. suppression of uterine contraction) using oral magnesium sulphate can result in maternal hypocalcaemia, as documented in an earlier case report from Lebanon.[23] This was conceivably attributable to a corresponding rapid suppression of parathyroid hormone release.[24] Transient hypermagnesaemia in the preterm infant is possible in preterm infants whose mothers had magnesium sulphate-induced tocolysis perinatally.[18] Prolonged tocolysis in the mother during pregnancy can result in osteopenia right from birth as a result of bone demineralisation in utero from magnesium toxicity.[25]

Multiple pregnancies/births can cause foetal growth restriction,[26] although this should not significantly hamper adequate milk production for twins and triplets.[27] The possible effect(s) on foetal growth restriction might be associated with the background reduced mineral accretion rates, which predisposes the infant to metabolic bone disease of prematurity.[3] In a Swedish study[4] that compared blood concentrations of ionised calcium, phosphate and magnesium in preterm infants, appropriate for gestational age and small for gestational age infants, with those of a reference group of full-term newborns, the authors found SGA infants had lower phosphate values, than the reference group and the values correlated with the degree of growth retardation on the first day of life. This correlation of bone mineral content was similarly correlated with intrauterine growth status in a Finnish study.[28] The Swedish study[4] earlier mentioned also found that magnesium concentrations increased with time and did not differ significantly between the study and reference groups. There was no correlation between the serum magnesium, calcium, or phosphate values in that study. The reason(s) for this was/were not clear.

Hypocalcaemia with/without hyperphosphataemia may occur in infants with birth asphyxia.[29] This was conceivably attributed to increased phosphate load caused by tissue catabolism, decreased intake due to delayed initiation of feedings, renal insufficiency, and increased serum calcitonin concentration.[29] Furthermore, the practice of calcium administration during or after a session of exchange blood transfusion may contribute to an increase in plasma calcium levels.

In a study carried out a few decades ago on full-term neonates in Zaria, Nigeria, by Abdurrahman *et al*.,[30] there was a significant correlation between maternal calcium and phosphorus levels and neonatal calcium and phosphorus levels. Levels of calcium and phosphorus were significantly higher in the neonates than the corresponding levels of these minerals in the mothers.[30] This was thought to be due to a high foetal-maternal gradient brought about by a specific calcium transport mechanism. The other explanation considered was the possible elevated levels of parathormone. Still, this explanation could

hardly hold since the parathormone levels were low in the cord sera of the neonates in the same study.[30]

Calcium absorption from the small intestine is passive and may also occur through a vitamin D-dependent active transport mechanism. Phosphorus absorption takes place in the jejunum, and the quantity available regulates calcium absorption and retention; the higher the phosphorus content of the enteral feed(s), the higher the calcium retention.[5] It has been noted that the absorption of both calcium and phosphate improved with postnatal age, as it did with the intake of lactose, fat, and vitamin D.[31] Glucocorticoid use may directly inhibit intestinal absorption. In contrast, using phenytoin or phenobarbital in the infant may indirectly inhibit calcium absorption by interfering with vitamin D metabolism.[31] Conversely, in studies where supplementation of vitamin D was given,[3,16,48] the overall outcome on mineral status has not been significant compared with controls. Vitamin D levels in preterm neonates may not be important in regulating calcium, phosphate, and magnesium homeostasis beyond a certain level. Some available data suggest that 25-hydroxyvitamin D concentrations may remain adequate, even with relatively low dietary intake. Also, there was no demonstrable evidence of short- or long-term benefit(s) from high intakes of 25-hydroxyvitamin D on the minerals.[7] On the other hand, low concentrations of maternal 25-hydroxyvitamin D in pregnancy have been associated with lower bone mineral content and rickets in early infancy.[32]

Phototherapy is another factor known to induce hypocalcaemia. In a study by Yadav *et al.,* [33,] a significant fall in calcium level was observed in 80% of preterm and 66% of term neonates studied after 48 hours of phototherapy. In contrast, only seven per cent of term babies who had phototherapy developed hypocalcaemia in a more recent Iranian study.[34] The reason for this wide variance is not apparent. The reported hypocalcaemia was ascribed to the inhibitory effect of phototherapy on the pineal secretion of melatonin, thus blocking the effect of cortisol on bone calcium. The unchecked cortisol exerts a direct hypocalcaemic effect and increases bone uptake of calcium as well.[33] Another study on newborn rats proposes that it might be due to reduced secretion of parathormone.[35] The first hypothesis was tested by Asghar *et al,*[36] in a randomised controlled trial. In that study,[36] the authors found that phototherapy-associated hypocalcaemia can be prevented by covering the head during phototherapy. This finding supported the earlier (inhibition of pineal secretion of melatonin) hypothesis.

Effects of Obstetric Characteristics on Intrauterine Nutrition

The inter-pregnancy interval is known to affect the quantity of nutrients available for the infant and can indeed affect the pregnancy outcome.[37,38] Long intervals between pregnancies, especially lasting beyond 120 months, usually result in an end of the physiologic increase in uterine blood flow that follows the first pregnancy.[39] There is, however, a need for more data about the specific impact of this variable on the specific nutrient transfer of calcium, phosphate, and magnesium to the baby.

The level of magnesium in mothers is known to decrease with increasing parity, as was identified in a study done in India.[40] Also, a study in Northwestern Nigeria,[41], found a negative correlation between parity and serum calcium levels in pregnant women. Furthermore, a review by Olausson *et al*,[42] established that physiologic mechanisms are at play in the mother to mobilise nutrients from stores in bone and renal reabsorption to meet the growing foetus's increased demands. The occurrence of this in cycles may have a role to play in the relative plasma values of the relevant nutrients over time.

Advanced maternal age is known to result in age-related changes in the uterine vasculature and a possible corresponding poor placental perfusion that may interfere with the

transplacental transfer of nutrients.[43] However, there is a dearth of literature on the specific impact(s) of this variable (i.e. maternal age) on calcium, phosphate, and magnesium levels in preterm babies.

Vitamin D Mobilisation

Vitamin D sources in early infancy consist of transplacental transfer, breastmilk, and cutaneous production via sunlight. Maternal vitamin D status is essential in determining the amount of vitamin D transported across the placenta during foetal life and, therefore, the size of vitamin D reserves at birth.[44,45] Breastfed infants rely primarily on cutaneous synthesis (which should predictably be low because of minor exposure to sunlight) to maintain a normal vitamin D status; this is because the amount of vitamin D (which usually ranges between 12–60 U/L) obtained through human milk, is generally insufficient.[44]

The half-life of 25-hydroxyvitamin D is estimated to be approximately two to three weeks.[46] It is known that in pregnant women, 1,25-dihydroxyvitamin D levels are usually supraphysiologically high from 12 weeks gestation onwards, uncoupled from plasma calcium level. It has been suggested that this unusually high level is important for maternal tolerance to the "*foreign-body effect"* of the foetus.[47] These high levels of 1,25-dihydroxyvitamin D are presumed to be necessary for the normal physiology of pregnancy and also depend on a threshold plasma 25-hydroxyvitamin D level of at least 40ng/dL.[47] Hence, it will be preferable to measure 25-hydroxyvitamin D, rather than 1,25-dihydroxyvitamin D, to assess the true maternal plasma levels of Vitamin D.[48,49] Furthermore, the half-life of 1,25-dihydroxyvitamin D is only four hours, so it does not reflect the vitamin D stores in the body.[50] In the review by Mimouni *et al*.,[1] it was reported that there is no substantial evidence that the metabolism of vitamin D in preterm infants is any different from that of term infants, especially with respect to the intestinal absorption of vitamin D, and its 25- and 1α-hydroxylation.

Plasma Biomarkers of Metabolic Bone Disease

Plasma alkaline phosphatase (ALP) reflects the bone, liver, and intestinal isoforms, with the bone isoform contributing about 90% and representing a marker of bone mineralisation.[3] It has been shown in a study where the authors measured ALP serially that ALP concentration exceeding 700 IU/L at three weeks postnatal age was predictive of metabolic bone disease at term age (sensitivity, 73% and specificity, 73%).[51] However, another study[52] demonstrated that at three weeks postnatal age, an ALP level of 660 IU/L had a sensitivity of 29% and a specificity of 93% for severe metabolic bone disease. On the other hand, a PTH level of >180mg/dL or a phosphate level of <4.6mgdL yielded a sensitivity of 100 and specificity of 94 for severe metabolic bone disease. An observational study of 120 preterm infants in Cairo[53] put the optimal cut-off value of alkaline phosphatase, at which osteopaenia is detected at 500IU/L, with 100% sensitivity and 80.77% specificity. These inconsistencies suggest that alkaline phosphatase values should not be taken in isolation.

Breastfeeding and Plasma Calcium, Phosphate, Magnesium, and Vitamin D

The sections above have highlighted why preterm neonates are especially prone to imbalance and low levels of essential minerals like calcium, magnesium, and phosphates. One of the reasons proffered is inadequate intake. The only source of these essential minerals after birth would be via parenteral nutrition or enteral feeding. The solubility of the different constituents of parenteral nutrition precludes adequate mineral nutrition through the parenteral route.[31] Hence, any infant with difficulty in establishing enteral nutrition is at risk of low levels of these mineral nutrients. Preterm infants fed with only breastmilk have better feeding tolerance and a lower incidence of necrotising enterocolitis (NEC) than those

fed preterm formula.[54] Exclusively breastfed preterm babies also recorded significantly shorter hospital stays,[55] and long-term benefits,[56] compared with their peers on formula feeds. However, several studies have reported that the amounts of calcium, phosphorus, protein, and other bone mineral nutrients in unfortified human milk are inadequate to meet the growth requirements of VLBW preterm infants.[6,56,57]

Postnatal Growth and Plasma Calcium, Phosphate, and Magnesium

Regarding calcium, magnesium, and phosphate, inadequate levels of these essential bone minerals will ultimately affect bone physiology and growth and hence, the linear growth of the preterm infant.[58] In contrast, the effect(s) of calcium and phosphorus supplementation was assessed in some groups of preterm infants, with no evidence of osteopaenia prevention or improvement in growth over six months.[59] This suggests that there may be no short-term effects of low levels of these nutrients on physical growth and development. However, it should be noted that the Swedish study that was mentioned earlier correlated low foetal levels of these nutrients with intrauterine growth restriction.[4]

Need for Supplementation of Vitamin D in Pregnancy and in Preterm Neonates

Studies done in the past have reported conflicting implications of maternal plasma vitamin D on preterm birth. Some studies reported that low maternal Vitamin D was associated with preterm birth 60,61. However, a study in China by Zhou *et al*. [62] found that a normal level of maternal plasma vitamin D, rather than low maternal plasma vitamin D levels, was associated with preterm birth. Furthermore, it is known that intrauterine growth restriction occurs in the babies of mothers whose plasma vitamin D levels were low,[63] and maternal plasma vitamin D levels had a direct positive correlation with bone mass at birth.[64,65]

Some systematic reviews showed that birth weight and birth length were significantly greater for neonates whose mothers had vitamin D supplementation in pregnancy. Still, the incidence of preeclampsia, gestational diabetes mellitus, small-for-gestational-age status. birth weight, preterm birth, and Caesarean section were not influenced by vitamin D supplementation.[66,67] Another more recent systematic review on preterm neonates or low birth weight infants who were fed with human milk showed an increase in weight-for-age z-scores and height-for-age z-scores at 6 months in the preterm babies who had Vitamin D supplementation, compared with those who did not have supplementation.[68]

Conclusion

Preterm neonates fed on only breastmilk may suffer deficiencies of the minerals, with possible effects on cellular metabolism, growth, and bone health. There is a need for local empirical data on the need or otherwise, for supplementation in pregnant women and fortification of breastmilk with Vitamin D, calcium, phosphate, and magnesium in exclusively breastfed preterm babies in different populations.

The limitations of this review include the few databases consulted, which may, therefore, miss some important studies. However, subjectivity was reduced by the structured search of the databases. The review has provided a basis to reconsider the WHO recommendations, which state that there is no strong evidence in favour of supplementation of breastmilk in preterm neonates with bone minerals. There is a need for more research to document the plasma levels of calcium, phosphate, magnesium and Vitamin D in pregnant women and their preterm neonates in African populations. Furthermore, the review has highlighted the need for trials to determine the impact or usefulness of supplementation with those nutrients in pregnant women and preterm babies who are exclusively breastfed

and also to determine the optimal doses in the context of African countries.

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