Micronutrients and the Bone Mineral Content of the Mother, Fetus and Newborn

Ann Prentice

MRC Human Nutrition Research, Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, UK, CB1 9NL

ABSTRACT The fluxes of the primary bone-forming minerals, calcium, phosphorus, magnesium and zinc, across the placenta and through breast milk place considerable demands on maternal mineral economy. Increases in food consumption, elevated gastrointestinal absorption, decreased mineral excretion and mobilization of tissue stores are several possible biological strategies for meeting these extra mineral requirements. This paper presents a review of the evidence on the extent to which these strategies apply in the human situation, the mechanisms by which they occur, the limitations imposed by maternal diet and vitamin D status and the possible consequences for the growth of the infant and bone health of the mother. On the strength of current evidence it appears that pregnancy and lactation are associated with physiological adaptive changes in mineral metabolism that are independent of maternal mineral supply within the range of normal dietary intakes. These processes provide the minerals necessary for fetal growth and breast milk production without requiring an increase in maternal dietary intake or compromising maternal bone health in the long term. This may not apply to pregnant women whose mineral intakes or sunlight exposure are marginal. As a vehicle for promoting optimal growth and bone mineral content of infants, supplementation of lactating women with minerals or vitamin D is unlikely to prove effective. The situation in pregnancy is less certain. Until more studies have been conducted, a precautionary case can be made for targeted supplementation of pregnant women who have very low intakes of calcium or who are at risk of vitamin D deficiency. J. Nutr. 133: 1693S–1699S, 2003.

KEY WORDS: • bone mineral • breast milk • lactation • micronutrients • pregnancy

Calcium, phosphorus, magnesium and zinc are the primary bone-forming minerals. At birth an infant contains approximately 20–30 g calcium, 16 g phosphorus, 750 mg magnesium and 50 mg zinc, of which approximately 98%, 80%, 60% and 30%, respectively, are in the skeleton (1). Quantitatively, the greatest period of fetal mineral accretion takes place from midgestation and is maximal during the third trimester. For example, fetal accretion of calcium increases from around 50 mg/d at 20 wk gestation to 330 mg/d at 35 wk, averaging around 200 mg/d for the third trimester (2). After delivery, the mineral accretion accompanying skeletal and somatic growth continues, the rate being higher in the first months and slowing progressively with age. Typical whole-body mineral accretion rates for infancy are 140 mg/d calcium, 70 mg/d phosphorus, 3 mg/d magnesium and 0.4 mg/d zinc (1).

The flux of minerals across the placenta and through breast milk must be sufficient to match these accretion rates. Additionally, in the child the mineral supply must meet any requirements imposed by incomplete gastrointestinal absorption and obligatory losses. Breast milk mineral secretion averages about 200 mg/d calcium, 120 mg/d phosphorus, 25 mg/d magnesium and 1.6 mg/d zinc at peak lactation. However, there is considerable interindividual variation in mineral secretion. For calcium this can be as much as fivefold. This is due to differences in both the calcium concentration of breast milk and volume of milk consumed by the infant, there being no relationship between the two (3). Similar variations are likely for the other minerals. The concentrations of all four minerals in breast milk decrease after the first 3–6 mo (4,5) resulting inevitably in a decreased supply of minerals from breast milk during later infancy.

There are several biological strategies for meeting the extra demands that pregnancy and lactation impose on the mineral economy of the mother. An increase in mineral intake is one; physiological adaptations through elevated gastrointestinal absorption, decreased mineral excretion or mobilization of tissue stores is another. The following sections review the extent to which physiological adaptations occur during human reproduction and the importance of maternal diet and vitamin D status on the growth and bone development of the baby and the bone health of the mother.

Mineral and bone metabolism of the mother during pregnancy and lactation

Mineral absorption and excretion. Calcium absorption efficiency and urinary calcium excretion are approximately

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2 To whom correspondence should be addressed. Email: ann.prentice@mrc-ipsr.cam.ac.uk
Bone mineral content and bone turnover. The skeleton acts as a reservoir of essential minerals that potentially can be mobilized to buffer shortfalls in mineral supply. The extent to which bone mobilization occurs during human pregnancy and lactation has been a question of considerable research interest in the past few years. The most sensitive in vivo index of skeletal change is bone mineral content measured by absorptiometric techniques, such as single photon absorptiometry and dual-energy X-ray absorptiometry. Relatively few absorptiometric studies have been done of pregnant women, because the use of these instruments is avoided to minimize exposure to ionizing radiation, although the doses involved are very low. In addition, studies in women recruited when they are already pregnant are inconclusive because changes in bone metabolism occur from early pregnancy. As a result, investigations of bone response to pregnancy tend to be limited to estimating the integrated skeletal response by measuring bone mineral status before conception and after delivery. Studies of lactating women are not restricted in this way but are complicated by differences in lactation behavior and variations in the return of menses.

To date, relatively few prospective studies of the effects of pregnancy have been undertaken and these have involved only small numbers of women (6). Increases in bone mineral content in the total body and at cortical bone sites have been reported with decreases at trabecular bone sites, such as the spine, hip, and wrist, but not in all studies. Substantial increases have been reported at trabecular bone sites in women who entered pregnancy during or soon after a period of extended lactation but not in those women who conceived after the recovery of lactational bone loss (22,23).

The bone response to pregnancy, therefore, appears to differ between individual women and between skeletal sites, and as yet no consistent pattern has emerged. The changes in bone mineral content may be governed by a variety of influences, such as the mother’s age or parity and endocrinological status before or after conception. Nutritional status may also be influential. Increases in bone mineral content at the femoral neck and Ward’s region of the hip have been observed in pregnant women with a body mass index (expressed in kg/m²) <22 but not in women with a higher body mass index (24). The possible influence of dietary mineral intake on bone response is discussed later. Pregnancy may alter the architecture of trabecular bone without affecting bone mineral content. A bone biopsy study has suggested that bone loss in early pregnancy is associated with trabecular thinning whereas restoration of bone volume in later pregnancy is associated with the addition of new trabeculae, leading to a finer bone network with increased struts (25).

In contrast to the situation for pregnancy, there is now considerable evidence from prospective longitudinal studies that lactation is associated with significant reductions in maternal bone mineral content during the first 3–6 mo that are reversed in later lactation and after breastfeeding stops (6). These reductions are most marked at the spine and hip, where average decreases of 3–5% have been observed. The magnitude and duration of the skeletal response depend on the length of lactation and are attenuated or do not occur in mothers who do not breastfeed. These bone changes are highly variable, with some women experiencing decreases in bone mineral content at the spine of up to 10% whereas others appear to have little bone response despite exclusive breastfeeding (3,26). After breastfeeding has stopped for at least 2–3 mo, the bone mineral content at most skeletal sites is similar to or higher than that measured shortly after delivery (27,28). Exceptions are at the femoral neck and wrist, where bone mineral status in the immediate postlactation period tends to be lower than postpartum (27). Similar changes in bone mineral content are observed in women who do not breastfeed and there is no evidence that duration of lactation or even lactation itself influences bone mineral content postlactation (27,28).

Elevations in bone turnover support the likelihood that skeletal mineral is mobilized and restored during pregnancy and lactation. Indices of bone formation and resorption increase from early gestation (i.e., within the first trimester) (17,20,29–31). Their levels rise by 50–200% by the end of pregnancy. The exception is the commonly used formation marker serum osteocalcin concentration, which is decreased relative to preconception levels (17,20). This decrease is likely to be due to increased degradation or uptake of osteocalcin by the placenta (32) because measurements of a metabolite suggest that osteocalcin production is not decreased despite the low circulating concentrations of the intact protein (30).
The increases in markers of bone resorption occur before those of bone formation, which suggests that there is substantial uncoupling of bone remodeling (30,33). A study of women with multifetal pregnancies demonstrated that selective fetal reduction reduced circulating concentrations of the cross-linked carboxy-terminal telopeptide of type-I collagen, a marker of bone resorption, without corresponding changes in the carboxy-terminal propeptide of type I pro-collagen, an index of bone formation (31). This suggests that factors derived from the fetoplacental unit are involved in the stimulation of maternal bone turnover, primarily via an effect on bone resorption.

Bone turnover is also elevated in the first months of lactation (11,12,34). Duration of lactation influences the patterns of change of these markers, which occur for longer and are more pronounced in those who breastfeed for the longer time (34). Some increases are evident after delivery in women who do not breastfeed (14,15). Longitudinal studies suggest that bone turnover in early lactation is similar to or greater than at the end of pregnancy and is higher than preconception (17,20). Measured osteocalcin concentration is increased from the low concentrations observed in pregnancy to levels similar to those of prepregnancy (17,20). The concentrations of bone turnover markers decline after 6–12 mo even in women who continue to breastfeed for 18 mo or more (11). The levels also decline when lactation stops but some differences continue to be seen for several weeks between mothers who had lactated compared with those who had not (14,34). As with pregnancy, there is evidence of an asynchrony in the patterns of change between resorption and formation in lactation, with the peak of resorption preceding that of formation by several weeks (11,14). Such a pattern would allow for the rapid release of mineral from bone followed by its restitution after a period of time (11).

Calcitropic hormones and regulators of bone metabolism. The total concentrations of minerals in the circulation tend to decrease in pregnancy, often with a slight rise toward the end of gestation. These effects largely parallel the changes in concentration of serum proteins due to hemodilution; concentrations of the active, ionized forms are unchanged or only slightly decreased (6,7,17,35,36). The data on serum phosphate concentration are inconsistent and some studies have shown no changes in phosphate metabolism (17,37). After delivery, serum calcium, both ionized and total, and serum phosphate concentrations are raised compared with late pregnancy and with concentrations of normal control subjects (7,10–12,20,38). This appears to be the case for both lactating and nonlactating mothers at the same stage postpartum (14,15,35).

The control of calcium and phosphate metabolism in pregnancy and lactation is complex, and the roles of the three main calcitropic hormones, parathyroid hormone (PTH), 1,25–dihydroxyvitamin D (1,25D) and calcitonin, are altered. Recent data, collected with modern assay techniques, indicate that the changes in calcium and bone metabolism associated with human pregnancy and lactation are not driven by the classical PTH–vitamin D endocrine system and that other hormonal mechanisms must be involved. Despite the homeorhetic changes in calcium and bone metabolism, there is some evidence that PTH and 1,25D may continue to play a role in the regulation of serum calcium. There is also evidence that PTH and 1,25D may play a role during the recovery period toward the end of lactation and after breastfeeding stops or in situations where breast milk output is particularly high. However, current knowledge does not support the concept, accepted for many years, that pregnancy and lactation are periods of physiological hyperparathyroidism driven by a state of relative calcium deficiency (or deficiencies of phosphorus or magnesium) in the mother (6,36,39).

The evidence for this is as follows: serum PTH concentrations are not elevated in pregnancy or lactation and may be slightly depressed (11,17,20,40). Serum 1,25D concentrations are increased during pregnancy (7,8,20) through upregulation of renal hydroxylation, extrarenal synthesis or both in placental or fetal tissues but not during lactation (11,20), although the concentrations in lactating women may be higher than nonlactating women at the same stage postpartum (21). The response of calcitonin to pregnancy and lactation is variable, with high values reported in some studies during late pregnancy and early lactation but not in others (6). Increases in both PTH and 1,25D have been observed in the later stages of lactation and after breastfeeding stops (11,12,17) although this finding is not consistent (40,41). Serum calcitonin concentrations are not altered (11,15,20). Elevated PTH, 1,25D and calcitonin concentrations, in combination with raised serum calcium concentrations, were reported in mothers and nursing twins compared with those nursing single infants (42). Calcium supplementation during lactation causes a decrease in PTH concentration (14). These data suggest that the normal response to an increased calcium demand or a calcium load may remain intact in pregnancy and lactation.

Increased concentrations of parathyroid hormone-related protein (PTHrP) are detected in the maternal circulation during pregnancy (43), probably originating from fetal, placental or mammary tissues (7). PTHrP is also produced by the lactating mammary gland, possibly under the influence of prolactin; secreted into breast milk; and released in significant amounts into the maternal bloodstream (44,45). PTHrP can activate the PTH/PTHrP receptor (46) and consequently has PTH-like characteristics. PTHrP is regarded as a prime candidate for the role of principal regulator of calcium and bone metabolism in pregnancy and lactation (6,8,14). However, the evidence is not clearcut, not least because administration of PTHrP to nonpregnant, nonlactating women produces effects that resemble the response to pregnancy but do not resemble the changes seen in lactation (47). In addition, the circulating concentrations of PTHrP decrease rapidly in lactation (40) when changes in calcium and bone metabolism are still evident.

It seems likely, therefore, that a complex interplay of different influences regulates calcium and bone metabolism in human pregnancy and lactation. The concentrations of many hormones, growth factors and cytokines that are elevated in the maternal circulation during pregnancy and lactation could stimulate or drive the observed changes in mineral absorption and excretion, bone turnover, and 1,25D synthesis. In pregnancy these include prolactin, estrogen, progesterone, placental lactogen, placental growth hormone, tumor necrosis factor–α and insulin-like growth factor–1 (7,30). In lactation the high prolactin concentrations and low estradiol levels may be particularly important. However, the concentrations of prolactin and estradiol tend to normalize as lactation progresses (40), and there is little evidence of synchronization between the skeletal response and the pattern of changes in these hormones. There is some evidence that breastfeeding mothers who have resumed menstruation, and therefore have normalized estrogen levels, have higher serum 1,25D concentrations than those who have not (14), but this has not been observed in all studies (19). In addition, estrogen deficiency in nonpregnant, nonlactating women of reproductive age resulting from gonadotropin-re-

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3 Abbreviations used: 1,25D, 1,25–dihydroxyvitamin D; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.
leaching hormone agonist therapy produces a metabolic response that does not resemble that seen in lactation (7,8). It is likely, therefore, that the observed changes in mineral metabolism in pregnancy and lactation represent an integrated picture across the effects of many different factors.

**Risk of osteoporosis.** In theory the mobilization of bone to support pregnancy and lactation could, if excessive or if insufficiently restored, increase the risk of osteoporotic fractures both during reproduction and in later life. Fragility fractures occur in pregnancy, although rarely (48,49). The condition generally involves the spine or hip, is more common in the first pregnancy and usually resolves a few months after delivery (49). Osteoporosis of pregnancy can be secondary to treatment with corticosteroids, magnesium or warfarin but is often idiopathic (48,50). There is no evidence that the risk of osteoporosis during pregnancy and lactation is a consequence of dietary deficiencies or other environmental factors. Some studies have suggested that pregnancy may unmask rather than cause low bone mineral content and that fractures result from alterations in load-bearing or posture (49,51). However, fractures can occur in the absence of low bone mineral status (52). Symptoms often develop during the postpartum period and are more common in women who are breastfeeding (53). A combination of a raised plasma PTHrP concentration and a low bone mineral density has been implicated in postpartum-onset osteoporosis (54). However, there have been no studies of whether women who fracture have an exaggerated metabolic response to pregnancy and lactation relative to other women.

Retrospective studies of older women have investigated the possible effect of pregnancy and lactation on postmenopausal osteoporosis risk but have produced conflicting results (6,55,56). The disparities may be due to the problems of defining reproductive and lactational history adequately; separating the effects of pregnancy and lactation; and controlling for possible confounders, such as socioeconomic factors and body size (3,55). Taken together, however, the evidence suggests that parity is not a risk factor for postmenopausal osteoporosis and may be protective whereas having breastfed has been associated variably with increased risk, decreased risk or no effect (6). The conclusion about parity has to be viewed with caution because nulliparous women may have hormonal or metabolic characteristics that independently place them at greater risk for osteoporosis in later life (55).

**Influence of maternal diet and vitamin D status**

**Mineral intakes.** The mineral fluxes from mother to child during gestation and breastfeeding represent a significant proportion of the mineral intakes of the mother, especially for calcium (56). Intakes of these minerals vary in different parts of the world and range widely between individuals, but average daily intakes for women are in the order of 300–1000 mg calcium, 1000 mg P, 250 mg magnesium and 10 mg zinc (35,57). The extent to which maternal mineral intakes during pregnancy affect bone mineral changes of the mother or fetal growth has not been fully investigated. In healthy women, metabolic adaptation during pregnancy probably ensures an adequate transfer of minerals to the fetus without necessitating an increase in maternal mineral intake (35,57).

In relation to calcium, most studies to date have been conducted in women with an average intake at or above current dietary recommendations. No influence of calcium intake on changes in bone mineral at the hip was noted in a study of U.S. women consuming an average of 1100–1350 mg/d calcium (24). Greater decreases in ultrasonographic bone propagation velocity were observed in the phalanges of Spanish women with a calcium intake <1000 mg/d compared with those with a higher intake (58). However, no differences in bone density of the hand, measured by radiographic densitometry, were observed in an Indian study between women with a low calcium intake and those who received calcium supplements during pregnancy (59).

In the Indian study, significant differences were noted in the bone density of the neonates depending on the mother’s calcium intake but not on neonatal weight or height (59). A possible effect of maternal calcium intake on fetal mineralization was also suggested from a study of U.S. women taking part in a calcium supplementation trial during pregnancy (2 g/d calcium or placebo from 22 wk gestation) (60). Neonates born to mothers with a low customary calcium intake (<600 mg/d) had a greater total bone mineral content than did those born to mothers in the placebo group, with no significant differences reported in infant size. No supplement effect was noted for mothers with higher calcium intakes (60).

With respect to the other minerals, no studies have examined the effect of dietary phosphorus on mineral economy in pregnancy or on health outcomes for the mother or child (35). In studies investigating the effect of magnesium supplementation on aspects of pregnancy outcome, such as preterm delivery and preeclampsia incidence, no effects of the supplement on fetal bone growth and intrauterine growth retardation have been detected (35). In addition, long-term use of intravenous magnesium sulfate therapy in pregnancy is associated with detrimental infant outcomes, such as neonatal hypermagnesemia and bone abnormalities (61,62). Poor maternal zinc status, as indicated, for example, by depleted leukocyte concentrations, has been associated with fetal growth retardation in some studies but not others (63). In randomized, controlled trials zinc supplementation of healthy pregnant mothers has not been shown to affect infant birth weight, crown-heel length or head circumference (63,64) but studies in African American women with a plasma zinc below the median and a body mass index <26 and in poor Indian women have demonstrated an effect of maternal zinc supplementation on birth weight (63–65).

In contrast to the inconclusive studies in pregnancy, compelling evidence exists that the bone mineral changes that accompany lactation are independent of the current calcium intake of the mother (6). The typical pattern of bone loss and gain is observed in lactating women with high customary calcium intakes and in those who consume calcium-rich supplements as well as in those with lower calcium intakes, and no correlations have been reported in most observational studies between the magnitude of lactational bone changes and maternal calcium intake (6). Four randomized, placebo-controlled studies have demonstrated little effect of calcium supplementation on the pattern of bone changes during and after lactation (66–69). The taking of calcium supplements results in a small increase in bone mineral status (28,67), but this occurs in both lactating and nonlactating women (67) and appears to be only a transient effect (28). Adolescent mothers may be an exception, because an American study reported that bone changes were attenuated in teenage lactating mothers consuming a high calcium diet compared with those with lower intakes (70). However, no differences were observed between teenage and adult lactating Gambian women in their response to calcium supplements despite their very low customary calcium intake (11,66).

Randomized, controlled intervention studies, conducted in women with high and low customary calcium intakes, have shown no effects of calcium intake in lactation on fractional calcium absorption, renal calcium handling, bone turnover or
serum mineral concentrations (11,14,19,66,69,71). In a small study no effect was detected of calcium supplementation on breast milk PTHrP concentration, suggesting that maternal calcium intake does not influence the production of this hormone in the mammary gland (45). Thus, the evidence suggests that the bone mineral changes are a physiological response to lactation that is independent of dietary calcium intake.

Similarly, breast milk calcium secretion does not appear to depend on the calcium intake of the breastfeeding mother (3). In particular, no changes in breast milk calcium concentration were observed in two randomized, controlled calcium supplementation studies of lactating mothers, even in women with a very low calcium intake (66,67). The calcium intake of the mother during pregnancy may predetermine the calcium concentration of breast milk (72), which would provide a link between the results of epidemiological and intervention studies. This hypothesis is currently undergoing formal testing, although preliminary results from a calcium supplementation study of Gambian women accustomed to a very low calcium intake suggest that breast milk calcium secretion may not be influenced by calcium intake in the second half of pregnancy (L.M.A. Jarjou, A. Prentice, J. Bennett, M.R.C. Keneba, The Gambia and MRC Human Nutrition Research, Cambridge, UK, personal communication, 2002). However, the extent to which breast milk calcium supply limits infant growth and bone mineral content is not known. In one study of Gambian children, no association was observed between breast milk calcium intake and infant bone growth at age 3 mo (3).

Compared with calcium, there have been few studies of the effect of the maternal diet on the metabolism or breast milk concentrations of phosphorus, magnesium and zinc. However, the limited evidence suggests that dietary intakes of these minerals have little influence on breast milk composition (73,74). Zinc balance, including zinc secreted into breast milk, has been shown to be maintained in women with a low customary intake of zinc (18). Zinc supplementation may slightly attenuate the decrease in breast milk zinc concentration in later lactation (74) but the significance of this for infant growth and bone development is unclear (73).

Few studies have investigated the possibility that pregnancy and lactation may be risk factors for later osteoporosis in women with a low intake of minerals or with other potentially adverse diet and lifestyle characteristics. In those that have attempted to explore such interactions for calcium, no effects of a low intake have been identified (75). However, it should be remembered that women in developing countries who have had many children, lactated for long periods and had lower mineral intakes than women in Western countries are not at increased risk (76,77).

The studies reviewed here investigated the importance of maternal dietary intake during established pregnancy and lactation, and no information exists about the relevance of the micronutrient intake of the mother during adolescence and before conception to the bone health of the mother and child. More research is needed into the effects of nutrition of the mother before and at conception on the effectiveness of the adaptive mineral responses during pregnancy and lactation.

**Vitamin D status.** Vitamin D is intimately linked with mineral and bone metabolism. Vitamin D deficiency in pregnant mothers is associated with congenital rickets and craniofacies in the newborn (78) and with rickets in infancy, especially when the child is exclusively breast-fed (79,80). There is evidence that poor maternal vitamin D status at a level above that associated with rickets in the child can adversely affect fetal and infant skeletal growth and ossification, tooth enamel formation and calcium handling (78). Seasonal variations in maternal vitamin D status are reflected in neonatal bone mineral content (81,82). Vitamin D supplementation of pregnant mothers at risk of vitamin D insufficiency produced higher neonatal serum calcium concentrations, smaller fontanelles and a trend toward higher birth weight in the neonates and greater weight and length at age 1 y (83–86).

The current consensus is that the vitamin D status of the infant is more influenced by the vitamin D status of the mother during pregnancy and by the infant’s sunshine exposure than by maternal vitamin D status during lactation (35,78). Although concentrations of 25–hydroxyvitamin D in breast milk parallel those in the mother’s circulation, this does not affect the vitamin D status of the infant unless the mother is consuming high doses of supplemental vitamin D (35,78). Whether this applies when the infant has limited exposure to sunlight of the correct wavelengths is not known.

There is no evidence that pregnancy or lactation imposes an increased requirement for vitamin D on the mother (78). The transfer of vitamin D and its metabolites across the placenta and into breast milk is small and considered unlikely to compromise the vitamin D status of the mother (35,78). Pregnant and lactating women who receive regular sunlight exposure during the summer months are not at risk of vitamin D deficiency, but women who wear concealing clothes, are housebound or for other reasons do not receive adequate sunlight exposure are at risk (35,87). It is considered prudent for pregnant and lactation women to consume dietary vitamin D; the recommended intake varies among countries but is generally 5–10 μg/d (200–400 IU/d).

**Likely benefits of micronutrient supplementation on the bone mineral content of the mother, fetus and newborn**

On the strength of the preceding evidence, it is clear that programs aimed at improving the growth and bone mineral content of the infant or the bone health of the mother by supplementing the breast-feeding mother with minerals and vitamin D or with general nutritional supplements are unlikely to prove efficacious. Similar conclusions can be reached for pregnant women in populations with moderate to high mineral intakes and adequate exposure to sunlight. However, there are data, albeit limited, that suggest that a low calcium intake may limit the bone mineral accretion of the fetus and alter the bone metabolism of the mother. The data on phosphorus, magnesium and zinc are too limited to enable conclusions to be drawn. Until more data are available from well-constructed studies, inclusion of calcium in micronutrient supplementation programs for pregnant women with low calcium intakes could be defended on a precautionary principle. The possible link between a low calcium intake in pregnancy and preeclampsia in the mother and raised blood pressure in the offspring (88) would add weight to this conclusion. Concerns about possible detrimental interactions with other minerals, such as iron, would need to be addressed (89,90). Vitamin D supplementation of pregnant women at risk of vitamin D deficiency would reduce the incidence of rickets and other problems of calcium handling in the newborn and might promote infant growth.

**LITERATURE CITED**


