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CALCIUM IN PREGNANCY AND LACTATION

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■ **Abstract** Pregnancy and lactation are periods of high calcium requirement. This review highlights recent advances in our understanding of calcium and bone metabolism during human pregnancy and lactation and discusses the findings in relation to the calcium nutrition of the mother. The evidence indicates that pregnancy and lactation are characterized by physiological adaptive processes that are independent of maternal calcium intake and that provide the calcium necessary for fetal growth and breast-milk production without requiring an increase in maternal calcium intake. There are firm data that demonstrate that a low calcium intake during lactation does not lead to impaired lactational performance or to exaggerated bone loss. However, more research is required to define whether a low calcium intake prior to or during pregnancy can have deleterious effects on reproductive and lactational performance, and on the long-term health of the mother and child.

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INTRODUCTION

Pregnancy and lactation are periods of high calcium requirement. There is concern that if calcium in the diet is insufficient to meet this extra demand, the health of the mother and baby may be compromised because of bone loss from the maternal skeleton, reduced fetal growth and bone mineralization, and impaired breast-milk calcium secretion. The mechanisms by which calcium is supplied to the fetus and mammary gland have not been fully characterized. However, the past few years have seen an explosion of interest in defining the calcium response to pregnancy and lactation in humans. This is now known to differ substantially from the response in many other animal species (78), and studies of laboratory and domesticated animals have proved misleading. This review highlights the recent advances in our understanding of calcium and bone metabolism in human pregnancy and lactation and discusses the findings in relation to the calcium nutrition of the mother.

CALCIUM NUTRITION IN PREGNANCY

Calcium Requirements

The skeleton of a newborn baby contains approximately 20–30 g of calcium (43, 156). The bulk of fetal skeletal growth takes place from midpregnancy onward, with maximal calcium accretion occurring during the third trimester. The proportion of calcium in fetal ash increases during early gestation, plateauing at approximately 27% (g/g) by 4 months (43). The total calcium accretion rate of the fetus increases from approximately 50 mg/day at 20 weeks gestation to 330 mg/day at 35 weeks (35). For the third trimester of pregnancy, 200 mg/day is considered the average accretion rate.

Maternal Bone-Mineral Status

Direct investigations of changes in the maternal skeleton during pregnancy are limited by the fact that the most sensitive techniques for the direct assessment of bone-mineral status require the use of ionizing radiation and are unsuitable for measurements of the axial skeleton in pregnant women. Studies using these techniques are limited to estimates of the integrated skeletal response over the whole of pregnancy by measuring bone-mineral status before conception and after delivery. To date, only a few such prospective studies have been undertaken, on a relatively small number of individuals (18, 27, 61, 87, 104, 128, 139, 144). Three other studies have been described in preliminary abstracts (6, 9, 12). No consistent pattern has emerged. Increases in bone mineral in the total body and cortical bone sites have been reported in some studies (104) but not in others (128). Decreases in bone mineral in skeletal regions rich in trabecular bone, such as the spine and hip, have been noted (6, 9, 12, 27, 104), whereas other studies have observed either

no change in these regions (61, 128) or, in the case of women entering pregnancy during or after a period of extended lactation, substantial increases (87, 144).

Investigations of the pattern of skeletal response during pregnancy are confined to measurements at peripheral sites, using absorptiometry or bone ultrasonography (2, 15, 18, 39, 70, 77, 85, 160). Several of these studies recruited women who were already pregnant rather than women prior to conception, and consequently they are difficult to interpret because major changes in bone metabolism are known to occur in early pregnancy (121). Decreases in bone mineral over the course of pregnancy have been noted in ultradistal scans of the forearm, a region rich in trabecular bone, but not at more proximal appendicular sites (77, 85) and not in all studies (18, 70). Ultrasound studies of the os calcis and phalanges have demonstrated decreases in the speed of sound and broadband ultrasound attenuation in the later stages of pregnancy (39, 160). Although these parameters are regarded as indices of bone mineral density, the validity of this assumption during pregnancy, particularly in the presence of peripheral oedema, is not known.

It is possible that the maternal skeletal response during pregnancy is governed by a variety of influences, such as the mother's age or parity and her nutritional or endocrinological status prior to or after conception. Observations from studies of women who conceived during or shortly after a period of extended lactation demonstrated recovery of lactational bone loss during pregnancy, but those who conceived once this recovery had taken place showed little overall change in the subsequent pregnancy (87, 144). Slim pregnant women, those with a body mass index less than the median ($\sim$22), exhibited significant increases in bone mineral at the neck and Ward's triangle regions of the femur that were not observed in size-matched controls or in larger pregnant women (139). This finding was independent of weight gain during pregnancy.

Osteoporosis can occur in pregnancy, although the incidence is relatively rare (28, 100, 138). The condition frequently involves the hip or spine, is more common in the first pregnancy, and usually resolves spontaneously after a few months post-partum (100). Osteoporosis of pregnancy is generally idiopathic or secondary to clinical interventions such as warfarin and corticosteroid therapy (28, 138). Some studies have suggested that pregnancy may unmask rather than cause low-bone-mineral status and that fractures result from alterations in posture or load bearing (100, 129). There are no data to suggest that osteoporosis of pregnancy is either an exaggerated metabolic response to pregnancy or a consequence of dietary deficiencies. As a result, the fact that osteoporosis can occur in pregnant women cannot be taken as evidence either that bone mineral loss is a necessary corollary of normal pregnancy or that the condition can be prevented by alterations in diet and lifestyle.

The extent to which maternal calcium intake impacts bone mineral changes during pregnancy has not been investigated. Few longitudinal investigations have been conducted in women with a low customary calcium intake, and in most studies to date, the average intake of the group of subjects exceeded current dietary recommendations. No influence of calcium intake on changes in bone mineral at three femoral sites was noted in a study of American women consuming an average

of 1100–1350 mg/day (139). Greater decreases in ultrasonographic bone propagation velocity in the phalanges from the first to the third trimester were noted in Spanish women with a calcium intake below 1000 mg/day compared with those on a higher intake (2). However, in radiographic densitometry measurements of bone density of the hand in Indian women with a low calcium intake, no differences were observed between those women who received calcium supplements during pregnancy and those who did not (123). Increases in circulating lead concentrations occur during pregnancy, which is suggestive of lead release from the skeleton as a consequence of mineral mobilization, and these effects appear to be reduced in women with high calcium intakes or in those who take calcium supplements (50, 51, 84). It is not established whether this is a consequence of reduced pregnancy-associated bone changes in women with high calcium intakes, an alteration in the interplay between skeletal and dietary calcium that affects bone lead release, or an effect of calcium on lead absorption in the gastrointestinal tract (103).

Maternal Calcium and Bone Metabolism

Calcium absorption and urinary calcium excretion are higher during pregnancy than before conception or after delivery, by approximately twofold (18, 40, 55, 68, 78, 104, 128). The increases are evident by early to midpregnancy and precede the increased demand for calcium by the fetus for skeletal growth. Fasting calcium excretion, however, is normal or decreased, after correcting for creatinine excretion, indicating that the increased urine excretion reflects the combined effects of the increased glomerular filtration rate in pregnancy and the hyperabsorption of calcium (40, 63, 70, 100). Measured calcium balance in the later stages of pregnancy is generally positive, and retention approximates that required for fetal growth (108).

Bone resorption is elevated in pregnancy, as indicated histologically (121) and biochemically, by measurements of plasma markers such as tartrate-resistant acid phosphatase and by the urinary excretion of collagen cross-links, telopeptides or hydroxyproline (18, 104, 128). Bone formation also increases, after an initial decrease, as indicated by plasma markers such as bone alkaline phosphatase and procollagen peptides (18, 54, 104, 128, 131, 160). However, osteocalcin concentration, a commonly used plasma marker of bone formation, is reduced throughout pregnancy relative to preconception levels (18, 128), although concentrations in late gestation are higher than those earlier in pregnancy (16, 18, 104, 128). The reduced levels of circulating intact osteocalcin may be due to degradation or uptake of osteocalcin by the placenta (131, 132). Measurements of an osteocalcin metabolite (Ocf), adjusted for alterations in creatinine clearance, have indicated that despite the low measurable concentrations of the intact protein, osteocalcin production is not decreased in pregnancy (104).

The increases in bone turnover markers are apparent by early gestation, and their levels rise by 50%–200% during pregnancy (18, 104, 128, 160). The changes

in bone resorption markers are observed earlier than those in indices of bone formation (104). Part of the increase in resorption markers may reflect a contribution from the turnover of the fetal skeleton. However, a recent assessment of the ratio of α to β isomers of the C-terminal telopeptide of type 1 collagen (CTx) suggests that the fetal contribution to maternal CTx excretion is small, amounting to less than 10% of α-CTx and only 2% of β-CTx (104).

Total serum calcium concentration falls during pregnancy, with a slight rise toward the end of gestation. This pattern parallels the alterations in serum albumin concentration caused by the increased intravascular fluid volume of pregnancy and the resulting haemodilution (78, 110). In contrast, serum ionized calcium concentration decreases only slightly and remains within a narrow physiological range throughout. As a consequence, the proportion of total calcium circulating in the ionized form increases during pregnancy. Some studies have indicated a decrease in serum phosphorus concentration and in the renal phosphate threshold in the second and third trimesters of pregnancy, with a concomitant increase in urinary phosphate excretion (40), whereas others have shown no changes in phosphate metabolism (41, 70).

The alterations in calcium and bone metabolism during pregnancy are accompanied by increases in the calciotropic hormone 1,25-dihydroxyvitamin D (18, 40, 83, 128). The increase in 1,25-dihydroxyvitamin D concentration is evident from the first trimester of pregnancy (40, 83) and is accompanied by increases in both free and protein-bound forms (70, 157). The mechanism mediating this increase is still unclear but may involve stimulation of renal 1-α-hydoxylase by a variety of pregnancy-associated hormones (see below), by placental synthesis of 1,25-dihydroxyvitamin D, or by an alteration in the balance between production of 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D (58, 78, 161).

In contrast to 1,25-dihydroxyvitamin D, there is no evidence of an increase in intact parathyroid hormone (PTH) concentration, or in nephrogenous cyclic adenosine monophosphate (NcAMP) production, a marker of PTH bioactivity (38, 40, 41, 70, 78). Indeed, some prospective studies have observed a decrease in circulating intact PTH compared with pre- or postpregnant levels (18, 128, 133). Early investigations that indicated high concentrations of PTH during pregnancy have had to be reinterpreted in the light of more recent studies using sensitive two-site immunoassays specific for the intact molecule (78). The discrepancies probably reflect detection by the early assays of multiple fragments of PTH, most of which are biologically inactive. Although these results cannot discount increased PTH turnover, it is clear that pregnancy is not associated with increased PTH bioactivity. Consequently, the view of pregnancy as a period of physiological hyperparathyroidism (22), driven by the fetal demand for calcium, is no longer tenable (40).

Parathyroid hormone–related protein (PTHrP), or more specifically its amino-terminal fragments, has PTH-like activity by virtue of the close homology in the N-terminal 1–34 amino acid sequence and the ability to activate the PTH/PTHrP receptor (158). Both PTH and PTHrP stimulate renal 1-α-hydoxylase activity and

NcAMP production, thus promoting 1,25-dihydroxyvitamin D synthesis and calcium reabsorption (62). Increasing levels of PTHrP have been detected in the maternal circulation during pregnancy (5, 38), potentially originating from fetal, placental, or mammary tissues (78). The role of PTHrP during pregnancy is unclear but may account for the rise in 1,25-dihydroxyvitamin D in the face of reduced intact PTH concentrations. Subcutaneous administration of PTHrP(1–36) to nonpregnant women produces elevations in 1,25-dihydroxyvitamin D, urinary calcium excretion, and NcAMP with no alteration in endogenous PTH or serum calcium (56), a response that is reminiscent of some of the biochemical changes observed in pregnancy. The likely consequences of increased concentrations of PTHrP during pregnancy on the maternal skeleton are unknown because although N-terminal PTHrP, like PTH, promotes bone resorption via the classical PTH/PTHrP receptor, the C-terminal fragment PTHrP(107–139) inhibits osteoclastic bone resorption through a different receptor (158).

Calcitonin (CT), the third classical calciotropic homone, is reported to be raised in pregnancy (24, 78, 155), although others have shown no changes (58, 111, 128), and it may be that the response is highly variable (111). During pregnancy, the breast and placenta are sites of extrathyroidal CT synthesis, and increases in circulating CT have been observed during pregnancy in thyroidectomized women (78). The physiological function of CT is not fully understood, although a role in protecting the maternal skeleton from resorption during pregnancy has been proposed (148).

In addition to PTHrP, many other hormones, growth factors, and cytokines are elevated in the maternal circulation during pregnancy that could stimulate or drive the observed changes in calcium absorption, 1,25-dihydroxyvitamin D synthesis, and bone turnover. These include prolactin, oestrogen, progesterone, placental lactogen, placental growth hormone, tumor necrosis factor alpha, and insulin-like growth factor-1 (54, 78, 104). Their relative contributions to calcium and bone metabolism in human pregnancy have yet to be established.

There have been no studies that have systematically investigated the relationship between calcium and bone metabolism in pregnancy and maternal calcium intake. An acute oral calcium load produces an exaggerated calcemic response in pregnant women compared with nonpregnant control subjects (40, 69), but pregnant women respond in the same way as control subjects in terms of increased urinary excretion and decreased bone resorption (69). This, coupled with fact that 1,25-dihydroxyvitamin D is elevated from early pregnancy with no concomitant rise in PTH suggests that pregnancy is a state of physiological hyperabsorption (40). As such, it seems unlikely that the observed biochemical changes imply an inadequacy of maternal dietary supply to meet the fetal demands for calcium. Pregnancy-associated changes in calcium and bone metabolism are evident in women with a high calcium intake, and although there is limited evidence, calcium supplements appear to have little effect on these changes in well-nourished women (18, 73). An abstract that provided preliminary data from a study in which pregnant women with a calcium intake of 1300 mg/day received either an extra

1000 mg/day or a placebo during pregnancy suggested that the increased calcium intake is associated with decreased PTH, decreased 1,25-dihydroxyvitamin D and urinary phosphate excretion, and increased total serum calcium, but unchanged bone turnover (57). Interpretation of this finding awaits publication of the full data.

Few investigations have been conducted of women with a customarily low calcium intake. Balance studies of Indian women show that they achieve calcium retention similar to that of their counterparts in other countries despite their lower plane of calcium nutrition (108, 135). A recent cross-sectional study of Malay women showed higher intact PTH and lower urinary calcium excretion by women in the third trimester compared with women at earlier stages of pregnancy (136). This is a different pattern of biochemical response to pregnancy from that seen in populations where average calcium intakes are higher, and it may indicate that PTH-induced renal conservation of calcium occurs in situations where maternal calcium intake is low.

Hypertensive Disorders of Pregnancy

Eclampsia and its precursor conditions, preeclampsia and pregnancy-induced hypertension, are associated with disturbances of calcium metabolism. In particular, women with preeclampsia have a relative hypocalciuria, coupled with higher intact PTH concentrations and lower ionized calcium and 1,25-dihydroxyvitamin D concentrations, than do women with normal pregnancies (37, 134, 149). Because eclampsia is more frequent in countries where the customary calcium intake is low (152), and because the risk of pregnancy-induced hypertension in American and Canadian women is higher among women with a low milk intake (<1 glass/day) than among those with a moderate intake (1–2 glasses/day) (96, 126), the hypothesis that dietary calcium deficiency is a primary factor in the pathogenesis of pregnancy-induced hypertension (109) has aroused considerable interest.

Early supplementation trials were inconsistent, but they largely indicated a beneficial effect on pregnancy-induced hypertension and related complications of consuming calcium supplements that supplied an extra 1000–2000 mg/day throughout the second half of pregnancy (10, 13, 113). Since that time, a large randomized control trial in the United States, involving 4589 nulliparous pregnant women, demonstrated that, in a population with an average calcium intake of 1100 mg/day, a calcium supplement of 2000 mg/day did not reduce the incidence of either preeclampsia or raised blood pressure (91). More recently, a randomized control trial in Australia has demonstrated positive benefits of a 1800-mg/day calcium supplement on the incidence of preeclampsia in nulliparous women with a similar customary calcium intake (20). In addition, positive effects have been reported from randomized control trials in India and Ecuador (95, 122) and from uncontrolled studies in Japan, China, and the Phillipines (159), populations where the customary calcium intake is lower than in Western countries. Recent systematic reviews of the evidence suggest that despite the negative findings of the large trial in the United States, routine calcium supplementation may be beneficial in

pregnant women with a high risk of hypertension or a low calcium intake (82, 151). In view of the uncertainties, a definitive randomized control trial of calcium supplementation in women with a low calcium intake would appear warranted.

Fetal Growth and Bone Mineralization

Maternal undernutrition has a major impact on fetal growth and birth weight, and hence on skeletal mass. Poor nutrition during pregnancy may reduce neonatal bone density as well as size (80). A detailed discussion of the relationship between maternal nutrition and fetal growth is outside the scope of this review, but interventions aimed at preventing or treating impaired fetal growth have recently been subjected to systematic analysis (49).

The question whether a low maternal intake of calcium can limit fetal growth or skeletal development in an otherwise healthily growing fetus has not been addressed. In an early study using radiographic densitometry, calcium supplementation of pregnant Indian mothers with a low calcium intake resulted in higher neonatal bone density compared with that in infants of control mothers, but it had no effect on birth weight or length (123). This finding has yet to be replicated, but the advent of sensitive absorptiometric techniques for measuring bone mineral content of small infants should now make such studies feasible.

CALCIUM NUTRITION IN LACTATION

Calcium Requirements

Calcium transfer between the mother and infant averages about 200 mg/day during full breast-feeding. There is wide variability in the amount of calcium secreted daily into breast milk, even among women who are exclusively breast-feeding, and can be as high as 400 mg/day in some individuals (116). For mothers who breast-feed for more than 3–6 months, the total calcium transfer via breast milk in one lactation period is greater than that transferred across the placenta during the whole of pregnancy.

Breast-Milk Calcium Secretion

The total amount of calcium transferred from mother to infant during breast-feeding depends on the calcium concentration of the milk and on the amount of milk produced, with no relationship between the two (86, 90, 116). The calcium concentration of breast milk remains relatively constant during the first 6–12 weeks of lactation but declines progressively thereafter (90, 116, 150). There are regional variations in breast-milk calcium concentration, with average values at 2–3 months of lactation ranging from approximately 200 mg/liter in parts of Africa and Asia to approximately 300 mg/liter in regions of the United States and Europe (114, 116). In addition, there are differences in breast-milk calcium concentration

between individuals that are maintained throughout the lactation period (116). Typically, there is a twofold range of calcium concentrations between women in the same community at the same stage of lactation, a variation that increases to threefold when women are compared across regions. After taking into consideration variations in breast-milk volume, the differences in breast-milk calcium secretion between women can approach fivefold during exclusive breast-feeding (116).

Breast-milk calcium concentrations tend to be lower in countries where the customary diet is low in calcium (116), a fact that has suggested that maternal calcium intake may be an important factor in determining breast-milk calcium secretion. In the past, this possibility was supported (*a*) by a few observational studies reporting significant associations between maternal calcium intake and breast-milk concentration (46), (*b*) by early, uncontrolled intervention studies involving small numbers of subjects (127), and (*c*) by the observation that Dutch mothers consuming a calcium-poor, macrobiotic diet have lower breast-milk calcium concentrations than do omnivorous women (23). However, the accumulating evidence no longer supports this view. Moderate-to-high calcium concentrations have been recorded in some countries where the maternal diet is low in calcium, such as Egypt, Nepal, and Pakistan (116), and most observational studies have not found relationships between maternal calcium intake, or the use of calcium supplements, and breast-milk calcium concentration (33, 86, 150). More recently, two randomized controlled intervention studies have demonstrated that an increase in calcium intake by lactating women does not alter their breast-milk calcium concentration (65, 118), even in women with a very low calcium intake (300 mg/d) (118).

It would, therefore, appear that breast-milk calcium concentration is independent of the mother's calcium intake during the period of breast-feeding. However, observational evidence suggests that her calcium intake in the previous pregnancy may influence breast-milk calcium concentration (106, 117). This hypothesis requires formal testing, and studies are in progress.

Maternal Bone-Mineral Status

Prospective longitudinal studies have demonstrated that lactation is accompanied by significant reductions in maternal bone mineral content during the first 3–6 months (1, 17, 65, 72, 77, 79, 88, 94, 112, 118, 142). The reductions are most marked in the axial skeleton, where average decreases of 3%–5% have been observed at the spine and hip. These rates of change are remarkable, given the fact that rates of postmenopausal bone loss at these sites are typically 1%–3% per annum. The magnitude and duration of the decreases are greater the longer a woman breast-feeds (88, 143) and are attenuated or do not occur in mothers who do not breast-feed at all (65, 88). These bone changes are highly variable, with some women losing up to 10% at the spine and others having little bone loss, despite exclusive breast-feeding (116). To date, only breast-milk volume and maternal height have been identified as predictors of bone loss during early lactation (89).

Recovery of lactation-associated bone loss is observed during late lactation and after weaning (88, 118, 142). For women who conceive during lactation, increases in bone mineral are observed during pregnancy (87). At most skeletal sites, bone-mineral status is higher once breast-feeding has been stopped for at least 2–3 months than it is shortly after delivery (88, 112). The exception is at the femoral neck and wrist, where bone-mineral status shortly after weaning tends to be lower than immediately postpartum (88). Similar changes are observed in women who do not breast-feed, and there is no evidence that duration of lactation, or even lactation itself, is a determinant of the mother's postlactational bone-mineral status (88, 112).

There has been much debate about whether the recovery of bone mineral is related to cessation of breast-feeding or to the return of ovarian function and menstruation. However, the strong interrelationship between length of lactation and duration of amenhorrea makes it difficult to examine the influence of each independently on bone-mineral status, and it is possible that neither factor is directly involved, but that instead they provide information about some aspect of lactation behavior, such as suckling frequency or intensity (88). This makes interpretation of long-term bone changes difficult because different studies have variously defined the timing of the final measurement relative to cessation of breast-feeding, to onset of regular menstruation, or to delivery, with no control of the other variables (60, 61, 77, 88, 94, 128, 142). However, in a recent Italian study, all women fully breast-fed for 6 months and weaned their babies at 7 months, at which point lactation was suppressed pharmacologically (112). Those with an early return of menses had smaller bone loss from the spine after 6 months of lactation but gained less afterward, so that by 18 months there was no difference relative to women with a later return of menses. This emphasizes that there are different patterns of bone loss and gain, depending on a number of reproductive and lactation-associated factors.

There is compelling evidence that the bone mineral changes that accompany lactation are independent of the current calcium intake of the mother (115, 116). The typical pattern of bone loss and gain has been observed in lactating women with high customary calcium intakes and in those who consume calcium-rich supplements (17, 77, 94, 112). Four randomized placebo-controlled studies have demonstrated little effect of calcium supplementation on the pattern of bone changes during and after lactation (17, 65, 71, 118). The taking of calcium supplements has been shown to lead to a small increase in bone-mineral status (65, 112), but this occurs in both lactating and nonlactating women (65) and appears to be only a transient effect (112). Most observational studies have found no correlation between the magnitude of lactational bone changes and maternal calcium intake (77, 88, 89, 94, 142). Associations that have been recorded (79, 101) have been with overall bone mineral status and not with the magnitude of change experienced during lactation. These associations are likely to reflect the interrelationships between bone mineral density, as commonly measured by dual-energy x-ray absorptiometry (DXA), with body size and dietary intake (120). Thus there

is little evidence to suggest that lactation-associated bone mineral changes are a manifestation of an inadequate dietary calcium intake by the mother. Adolescent mothers may be an exception, because a study in the United States indicated that bone changes were attenuated in teenage lactating mothers consuming a high-calcium diet compared with those with lower intakes (14). However, no differences have been observed between teenage and adult lactating Gambian women in their response to calcium supplements, despite their very low customary calcium intake (118, 119).

Maternal Calcium and Bone Metabolism

Calcium absorption and urinary calcium excretion, which are elevated in pregnancy, return to prepregnancy levels postpartum (66, 68, 128, 147). The reduction in urinary calcium output reflects the reduction in glomerular filtration rate after delivery. For women who breast-feed, some studies have reported further decreases in urinary calcium output, which is suggestive of increased tubular reabsorption of calcium (24, 75, 118, 128, 147), but others studies have not (18, 79). The possibility that lactation is associated with renal conservation of calcium is supported by the fact that breast-feeding women have raised serum ionized calcium and lower fasting calcium excretion compared with nonlactating control subjects (72, 78), although, again, the data are not consistent (92). In addition, lactating women have reduced urinary phosphate excretion and elevated serum phosphate concentrations, which is indicative of renal phosphorus conservation (72, 92, 119). Decreases in calcium excretion have been reported after breast-feeding has stopped (18, 72), but the data are inconsistent and some studies indicate that urinary calcium output increases toward nonpregnant, nonlactating levels during long lactation and after weaning (75, 119, 128). Increased calcium absorption efficiency has been observed in the postweaning period (2–3 months after stopping breast-feeding) (66), but not in all studies (18, 128) and not 6 or more months postweaning (147). Interpretations of these results may be complicated by alterations in maternal dietary calcium intake during and after lactation and, in some studies, by small subject numbers, but they suggest that late lactation and the period immediately postweaning may be a time of recovery, when calcium retention is increased.

Biochemical markers of bone resorption and formation are elevated in the first months of lactation (1, 72, 140) but decrease after 6–12 months, even in women who continue to breast-feed for 18 months or more (119). Longitudinal studies suggest that bone turnover in early lactation is similar to that at the end of pregnancy and higher than that in prepregnancy (18, 128). As in pregnancy, measured osteocalcin concentrations are at variance with those of other markers, with an increase during lactation from the low concentrations observed in pregnancy to levels similar to those prepregnancy (16, 18, 128). Duration of lactation influences the patterns of change of these markers, which are longer and more pronounced in those who breast-feed for longer periods (140, 160), but some changes are evident after delivery even in women who do not breast-feed (79). There is evidence of

an asynchrony in the patterns of change between resorption and formation in the postpartum period, with the peak of resorption preceding that of formation by several weeks (26, 119), a pattern that would allow for the release of mineral from bone followed by its restitution at a later stage (119).

It is not clear what hormonal mechanisms are responsible for these changes in calcium and bone metabolism. Raised CT levels in early lactation followed by a decrease to normal levels have been reported in some studies (24, 119) but not others (47, 128). However, the other classical calciotropic hormones, PTH and 1,25-dihydroxyvitamin D, are not elevated in lactation compared with concentrations measured before conception or in nonpregnant, nonlactating control women and are, if anything, slightly depressed (18, 119, 128, 145, 147, 157). In contrast, the later stages of long lactation and the weaning period have been associated with increased PTH and 1,25-dihydroxyvitamin D (18, 72, 119), although this finding is not consistent (145, 146). Elevated PTH, 1,25-dihydroxyvitamin D, and CT concentrations, in combination with raised serum calcium concentrations, have been reported in mothers nursing twins compared with those nursing single infants (45). In general, however, postpartum changes in the three calciotropic hormones do not correlate with those in bone turnover markers, breast-milk calcium, or bone-mineral status (47, 119, 145). It is clear, therefore, that other hormonal mechanisms must be involved in regulating the homeorhetic changes in calcium and bone metabolism associated with lactation, although PTH and 1,25-dihydroxyvitamin D may play a role during the period of recovery postweaning or in situations where the demand for breast-milk production is particularly high. However, as with pregnancy, the proposition that human lactation is a period of physiological hyperparathyroidism (124) is not supported by current evidence.

PTHrP is produced by the lactating mammary gland, possibly under the influence of prolactin, and is secreted in significant amounts into breast milk (11, 19). Mammary gland PTHrP, released into the maternal circulation, is a leading contender as the primary stimulus for lactation-associated changes in calcium and bone metabolism (48, 92, 143). The possibility that PTHrP replaces PTH as a principal regulator of calcium homeostasis during lactation is supported by a clinical case report of a woman with parathyroid deficiency whose requirement for supplemental calcium and 1,25-dihydroxyvitamin D abated during lactation, a circumstance that was attributed to her elevated concentrations of PTHrP (97). However, the evidence is not consistent. One study of lactating women showed that higher PTHrP concentrations were associated with higher prolactin and lower oestradiol concentrations, and with greater bone mineral changes at the spine and hip, but no correlations were observed with calciotropic hormone concentrations (143, 145). In contrast, an earlier study found no correlations during established lactation between PTHrP and other biochemical indices or bone mineral changes (26) but demonstrated an inverse correlation with PTH during the initiation of lactation (2–3 days postpartum) (26). In addition, subcutaneous administration of PTHrP(1–36) to nonpregnant, nonlactating women results in increases in 1,25-dihydroxyvitamin D, urinary phosphate, and calcium excretion,

with decreases in serum phosphate (56), a pattern of changes that does not resemble the metabolic response to lactation. However, PTHrP has a complex biology and is, in fact, a family of closely related peptides, all originating from the PTHrP gene but each with its own distinct physiological functions (158). It is likely that investigations of PTHrP in relation to lactation have been limited by the assay systems used, and more studies are needed.

Many other factors may be involved in regulating lactation-associated changes in calcium and bone metabolism. For example, elevated prolactin and low oestradiol levels are characteristic of the early stages of lactation and both are known modulators of calcium and bone metabolism. However, their concentrations tend to normalize as lactation progresses (145), and there is little evidence of synchronization between the observed changes in bone-mineral status and bone turnover with the pattern of changes in these hormones.

As with lactation-associated changes in bone-mineral status, there is no evidence that maternal calcium intake modulates the biochemical response to lactation. Although lactating women have an exaggerated reduction in urinary hydroxyproline excretion and decreased calciuric response to an acute oral calcium load, but a similar calcemic response compared with nonpregnant, nonlactating control women (69), there is no indication that this pattern differs depending on the mother's calcium intake. Randomized, controlled intervention studies of women with high and low customary calcium intakes have shown no effects of an increased calcium supply on bone turnover markers, plasma minerals, calciotropic hormone concentrations, fractional calcium absorption, or renal calcium handling (17, 29, 66, 118, 119). In addition, in a small pilot study, breast-milk PTHrP concentration was not altered by calcium supplementation, which suggests that maternal calcium intake does not influence the production of this hormone in the mammary gland (19).

LONG-TERM EFFECTS ON THE MOTHER

The possibility that the calcium requirements of human reproduction may be met by mobilization of calcium from the maternal skeleton has led to concerns that a woman's risk of osteoporosis in later life may be increased as a result of pregnancy and lactation, especially if her dietary calcium supply is poor. Retrospective studies in peri- and postmenopausal women have attempted to relate bone-mineral status or fracture incidence to number of pregnancies and to lactation history. Pregnancy has been associated with increased bone mineral in the forearm (36, 141), the effect increasing with each additional birth (36), whereas a negative effect of parity has been reported at the femoral neck (64). Others have observed positive associations between parity and bone-mineral status at a range of skeletal sites, including the hip (102). However, other studies have reported no consistent effects of parity on bone mineral in various regions of the skeleton (81, 99), and there is no evidence that women who have become pregnant but miscarried have altered bone-mineral

status (53). Attempts to relate parity directly to fracture incidence have also produced ambiguous results (141). A protective effect on hip fracture of having had a baby has been reported in some studies (59, 107) but not others (3, 21, 125).

Similarly, there are conflicting reports that lactation history and duration of breast-feeding are associated, at a range of skeletal sites, with increased bone mineral (31, 64, 99), with decreased bone mineral (44, 93, 154), or with no effect (36, 76, 99, 137). No association has been observed between lactation history and risk of spinal deformity (105), but women who breast-fed have been reported to be at lower risk of hip fracture than women who had children but did not breast-feed, the protective effect increasing with duration of lactation (3, 21, 67).

The inconclusive results of these retrospective studies may lie in the lack of consistent definitions and in the failure to adequately control for confounding factors such as obesity and estrogen use (116, 141). Women who have never been pregnant may differ from those who have in their ability to conceive and maintain a viable fetus, calling into question the use of nulliparity as the referent for fracture-risk studies (141). The term lactation encompasses a spectrum of breast-feeding behaviors that differ in the duration of exclusive and partial breast-feeding, the number of breast-feedings given per day, the time at which weaning foods are introduced, the extent to which they are used, and the lactational performance of the mother. Failure to adequately define lactation history may mask underlying relationships with bone-mineral status and fracture risk. There are marked social class differentials in breast-feeding incidence and in body size that could result in spurious associations emerging between bone-mineral status and lactation history (81, 116, 120). In addition, few studies have investigated the possibility that pregnancy and lactation may pose a risk for later osteoporosis only in women with a low intake of calcium or with other potentially adverse diet and lifestyle characteristics. In those who have attempted to explore such interactions, no effects of low calcium intake have been identified (74). However, in a global context, it is recognized that women with low customary calcium intakes who have many children and long lactation periods are not at increased risk of low-bone-mineral status or osteoporotic fractures in later life (8, 153).

LONG-TERM EFFECTS ON THE CHILD

Maternal nutrition during pregnancy and lactation may impact the growth and long-term health of the offspring via programming effects in utero or during the first year of life. There is evidence of long-term effects on vascular disease (coronary heart disease, hypertension, and stroke) and diabetes, as well as on osteoporosis risk (30). There is some evidence to suggest that maternal intake of calcium may influence childhood blood pressure and the development of hypertension. Inverse associations have been observed between blood pressure in young children and maternal calcium intake during pregnancy (98) and calcium intake in early childhood (42). A recent follow-up of the offspring of women involved in a randomized,

controlled trial of calcium supplementation during pregnancy has demonstrated lower blood pressure at 5–9 years of age in association with the higher maternal calcium intake, especially in those children with body mass indexes above the median (7). Whether maternal calcium nutrition affects the growth and bone mineral development of infants and their risk of osteoporosis in later life has yet to be explored experimentally.

IMPLICATIONS FOR CALCIUM RECOMMENDATIONS

During pregnancy and lactation, calcium is needed for fetal growth and breast-milk production. The amount required, approximately 200 mg/day, is substantial in relation to the daily calcium intake for many women, and it has long been assumed that the extra calcium needed for pregnancy and lactation must be satisfied by an increase in dietary calcium intake. This has been the basis of dietary recommendations in many countries over the years (113), supported by data from animal studies. However, the recent evidence, detailed in this review, is that human pregnancy and lactation are accompanied by physiological changes in calcium and bone metabolism that are sufficient to make calcium available for fetal growth and breast-milk production without necessitating increases in maternal calcium intake. Physiological hyperabsorption of calcium occurs in pregnancy, preceding the demands of the fetus for calcium, whereas renal conservation of calcium and temporary liberation of calcium from the skeleton occur in lactation.

In lactation, increases in calcium intake have no impact on these physiological changes or on the transfer of calcium into breast milk, even in women with a low customary calcium intake, and they result only in increased excretion of the mineral. Limited evidence in pregnancy suggests that pregnant women may be equally impervious to the effects of changes in dietary calcium supply, although more experimental data are required. There is some evidence to suggest that a low calcium intake during pregnancy may increase the predisposition to hypertensive disorders, may reduce fetal mineralization, and decrease breast-milk calcium concentrations in the subsequent lactation. However, for women on a moderate-to-high plane of calcium nutrition, an increase in calcium intake at a time of calcium hyperabsorption could potentially lead to hypercalciuria and an increased risk of kidney stones and urinary tract infections (4, 32) and might reduce the absorption of other minerals, such as iron and zinc (52, 130).

It would appear, therefore, that pregnancy and lactation in humans are characterized by physiological adaptive processes that provide the calcium necessary for fetal growth and breast-milk production and that no extra calcium is needed from the diet. Two advisory committees that have recently reviewed the evidence have either removed the recommendation that calcium intakes for adult women should be increased during pregnancy and lactation or have indicated that such increments may not be necessary (25, 34). An increase in calcium intake is recommended for

adolescent mothers to meet the dual needs of calcium for reproduction and maternal growth (34).

Because the homeorhetic changes in maternal physiology occur independently of current calcium intake, it may be important to optimize dietary calcium intake of women prior to conception. This suggests that messages about appropriate calcium nutrition should be focused on young women before childbearing rather than targeting pregnant and lactating women, as is common practice currently. More research is required to define whether low calcium intakes prior to and during pregnancy have deleterious effects on reproductive and lactational performance, and on the long-term health of the mother and child. However, there is now firm evidence that a low calcium intake during lactation does not lead to impaired lactational performance or to exaggerated bone loss, and that there is no reason why women with a customary diet that is poor in calcium should be discouraged from breast-feeding.

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