0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 6
Printed in U.S.A.

COMMENTARY

Calcium and Bone Metabolism in Pregnancy and Lactation*

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The adult skeleton contains approximately 99% of calcium in the body, and that content is perceived to be stable in the young to middle-aged adult female, unless ovarian failure and certain medications or illnesses have interfered. In fact, calcium and bone metabolism is substantially altered during the normal reproductive periods of pregnancy and lactation, and bone density can drop and regain 3–10% in the span of a few months in normal, healthy women. The primary cause for this disruption is, of course, the calcium requirements of the rapidly mineralizing skeleton of the fetus and neonate. The fetus and placenta actively pump calcium from the maternal circulation, while hormonal changes in the mother ensure a sufficient supply of calcium to the breast milk and, thereby, the nursing infant. Although the daily maternal calcium losses in the third trimester are similar to the daily calcium losses in breast milk of an exclusively lactating woman, it seems that the adjustments made in each of these reproductive periods differ significantly. This article summarizes what is currently known about altered calcium homeostasis in pregnancy and lactation; the interested reader is referred to a recent comprehensive review for more information and detailed references (1).

Pregnancy

The normal fetal skeleton has accreted about 30 g calcium by the end of gestation, but about 80% of the accretion occurs rapidly during the third trimester. This corresponds to a daily accretion rate of about 250–300 mg calcium by the fetal skeleton during the third trimester. The mother could theoretically meet this demand by increasing the intestinal absorption of calcium, decreasing renal calcium losses, and increasing the resorption of calcium from the maternal skeleton. The evidence indicates that alterations in intestinal calcium absorption may be a major adaptation in the pregnant woman, with possibly some contribution of calcium from the maternal skeleton as well.

Minerals and hormones

One of the earliest apparent changes in calcium balance in pregnancy is a fall in total serum calcium, which is physiologically unimportant. This fall is due to the decrease in serum albumin that accompanies the normal hemodilution of pregnancy; longitudinal studies have shown that the ionized calcium (the physiologically important fraction) remains constant throughout pregnancy. Serum phosphate levels are also normal. The serum PTH level, when measured with a two-site immunoradiometric assay (IRMA), falls to the low-normal range (*i.e.* 10–30% of the mean nonpregnant value) during the first trimester but increases steadily to the mid-normal range by term. Serum calcitonin levels are increased during pregnancy. Total 1,25-dihydroxyvitamin D levels double early in pregnancy and maintain this increase until term; free 1,25-dihydroxyvitamin D levels are increased from the third trimester and possibly earlier. The rise in 1,25-dihydroxyvitamin D may be largely independent of changes in PTH, because PTH levels are typically decreasing at the time that 1,25-dihydroxyvitamin D levels are increasing. The maternal kidneys likely account for most, if not all, of the rise in 1,25-dihydroxyvitamin D during pregnancy, although the decidua, placenta, and fetal kidneys may contribute a small amount. The relative contribution of the maternal kidneys is based on several lines of evidence (reviewed in Ref. 1), including the report of an anephric woman on hemodialysis who had low 1,25-dihydroxyvitamin D levels before and during a pregnancy, and an animal model (Hannover sow) of 1α−hydroxylase deficiency in which the homozygous mothers lack 1,25-dihydroxyvitamin D in the circulation even when carrying heterozygous fetuses (such fetuses have normal 1,25-dihydroxyvitamin D levels). The renal 1α−hydroxylase has been shown to be up-regulated in the mother, and it may be stimulated by such factors such as PTH-related protein (PTHrP), estradiol, PRL, and placental lactogen.

PTHrP levels have been found in several (but not all) studies to be increased during pregnancy, as measured in plasma by assays that detect PTHrP fragments encompassing amino acids 1–86. Many tissues in the fetus and mother produce PTHrP, and thus it is not clear which source(s) contributes to the rise detected in the maternal circulation.

Received January 22, 2001. Revision received March 12, 2001. Accepted March 17, 2001.

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* Supported in part by a Scholarship Award and research grant from the Canadian Institutes of Health Research (formerly Medical Research Council of Canada).

PTHrP could play diverse roles in the mother during pregnancy. For example, the amino-terminal portions of PTHrP can stimulate skeletal calcium resorption and the renal 1α−hydroxylase; the midmolecular portions of PTHrP stimulate placental calcium transfer (1, 2) and the carboxy-terminal portions of PTHrP ("osteostatin") can inhibit osteoclastic bone resorption and could theoretically help protect the maternal skeleton from excessive resorption (3).

Other hormones are clearly in flux during pregnancy, such as estradiol, progestins, PRL, placental lactogen, and insulin-like growth factor I. Each of these may be having direct or indirect effects on maternal calcium and bone metabolism during pregnancy as well, but these issues have been relatively unexplored.

Intestinal calcium absorption

Intestinal absorption of calcium is doubled during pregnancy from as early as 12 weeks of gestation (the earliest time point studied); this is the most consistent finding in studies of maternal calcium metabolism during pregnancy. The increase in intestinal calcium absorption is associated with a doubling of 1,25-dihydroxyvitamin D levels and increased intestinal expression of the vitamin D-dependent calcium-binding protein calbindin$_{9K}$-D. There is also evidence from animal studies that PRL and placental lactogen (and possibly other factors) may also mediate part of the increase in intestinal calcium absorption. Because this increase in intestinal calcium absorption occurs in the first trimester, well before the peak fetal demands for calcium in the third trimester, it is conceivable that the maternal skeleton stores calcium (that is, increases bone density) in advance of the later demand. This is something that has been observed in some animal models, but has not been possible to directly assess in humans.

Renal calcium excretion

The 24-h urine calcium excretion is typically increased as early as the 12th week of gestation (the earliest time point studied), and the amount excreted may exceed the normal range. This increase is likely a consequence of the increased intestinal absorption of calcium, the increased renal filtered load of calcium, and the increased glomerular filtration rate (GFR) of pregnancy. The elevated calcitonin levels of pregnancy might also promote renal calcium excretion. In the fasted state, the calcium excretion is normal or even low.

Skeletal calcium metabolism

In normal pregnancy in the rat, histomorphometric parameters of bone turnover are increased during pregnancy, but the bone mineral content does not change (reviewed in Ref. 1). Comparable histomorphometric data are not available for human pregnancy. In one study (4), 15 women who electively terminated a pregnancy in the first trimester (8–10 weeks) had bone biopsy evidence of increased bone resorption, including increased resorption surface, increased numbers of resorption cavities, and decreased osteoid. These findings were not present in biopsies obtained from nonpregnant controls, or in biopsies obtained at term from 13 women who had elective cesarean sections.

Most human studies of skeletal calcium metabolism in pregnancy have examined changes in serum markers of bone formation and urine markers of bone resorption. These studies are fraught with a number of confounding variables, including lack of prepregnancy baseline values; effects of hemodilution in pregnancy on serum markers; increased GFR and renal clearance; altered creatinine excretion; placental, uterine, and fetal contribution to the markers; degradation and clearance by the placenta; and lack of diurnally timed or fasted specimens. Given these limitations, many studies have reported that urinary markers of bone resorption (24-h collection) are increased from early to midpregnancy (including deoxypyridinoline, pyridinoline, and hydroxyproline). Conversely, serum markers of bone formation (generally not corrected for hemodilution or increased GFR) are often decreased from prepregnancy or nonpregnant values in early or midpregnancy, rising to normal or above before term (including osteocalcin, procollagen I carboxypeptides, and bone-specific alkaline phosphatase). It is conceivable that the bone formation markers are artifactually lowered by normal hemodilution and increased renal clearance of pregnancy, obscuring any real increase in the level of the markers. Total alkaline phosphatase rises early in pregnancy due largely to contributions from the placental fraction; it is not a useful marker of bone formation in pregnancy.

Based on the scant bone biopsy data, and the measurements of bone markers (with aforementioned confounding factors), one could cautiously conclude that bone turnover is increased in pregnancy, from as early as the 10th week of gestation. There is comparatively little maternal-fetal calcium transfer occurring at this stage of pregnancy, compared with the peak rate of calcium transfer in the third trimester. The pattern of bone markers has generally not shown a marked increase in the third trimester, which might be anticipated to occur if skeletal resorption were accelerated at that time to contribute to the peak rate of maternal-fetal calcium transfer.

Changes in skeletal calcium content have been assessed through the use of sequential bone density studies during pregnancy. Due to concerns about fetal radiation exposure, few such studies have been done. Such studies are confounded by the changes in body composition and weight during normal pregnancy, which can lead to artifactual changes in the bone density reading obtained. Using single and/or dual-photon absorptiometry (SPA and DPA), several prospective studies did not find a significant change in cortical or trabecular bone density during pregnancy (1). Three recent studies have used dual-energy x-ray absorptiometry (DXA) before conception and after delivery (5–7). In two of the studies, maternal lumbar spine bone density had dropped 4.5% and 3.5%, respectively, when preconception readings were compared with readings obtained within 4 weeks (5) and 6 weeks postpartum (6). The third study found no change in lumbar spine bone density measurements obtained before conception and within 1–2 weeks after delivery (7). Because the puerperium is associated with bone density losses of 1–3% per month (see *Lactation* below), it is possible that obtaining the second measurement relatively late after delivery confounded the first two studies. These two studies also examined changes in bone density at peripheral sites during pregnancy by DXA and obtained conflicting results, in that one found an increase in bone density at peripheral sites (5) and another found a decrease at peripheral sites (6). Other longitudinal studies have found a progressive de-

crease during pregnancy in indices thought to correlate with bone mineral density, as determined by ultrasonographic measurements at another peripheral site, the os calcis (8, 9). None of all the aforementioned studies can address the question as to whether skeletal calcium content is increased early in pregnancy in advance of the third trimester. Due to the conflicting results of the recent studies that used DXA, the question remains unsettled as to whether there is any net loss of skeletal calcium during pregnancy.

It seems certain that any acute changes in bone metabolism during pregnancy do not cause long-term changes in skeletal calcium content or strength. Numerous studies of osteoporotic or osteopenic women have failed to find a significant association of parity with bone density or fracture risk (1, 10). Although many of these studies could not separate out the effects of parity from those of lactation, it may be reasonable to conclude that if parity has any effect on bone density or fracture risk, it must be only a very modest effect.

Osteoporosis in pregnancy?

Occasionally, a woman will suffer an apparent fragility fracture during pregnancy or in the first few weeks after delivery, and a low bone mineral density reading will be obtained. In most instances, the possibility that the woman had low bone density before conception cannot be excluded. Some cases may be confounded by chronic therapy with heparin, anticonvulsants, or corticosteroids, among other causes of secondary osteoporosis. Due to the changes in mineral metabolism that occur during pregnancy, and other considerations such as low dietary calcium intake and vitamin D insufficiency, some women may experience excessive resorption of calcium from the skeleton. The apparently increased rate of bone turnover in pregnancy may contribute to fracture risk, because a high rate of bone turnover is an independent risk factor for fragility fractures outside of pregnancy. Therefore, fragility fractures in pregnancy or the puerperium may be a consequence of preexisting low bone density and increased bone turnover, among other possible factors. Additional changes in mineral metabolism occur during lactation, which may further increase the fracture risk in some women (see below).

Focal, transient osteoporosis of the hip is a rare, self-limited form of pregnancy-associated osteoporosis. It is likely not a manifestation of altered calcitropic hormone levels or mineral balance during pregnancy, but it is a consequence of local factors. The theories proposed to explain the condition include femoral venous stasis due to the gravid uterus, reflex sympathetic dystrophy, ischemia, trauma, viral infections, marrow hypertrophy, immobilization, and fetal pressure on the obturator nerve. These patients present with unilateral or bilateral hip pain, limp, and/or hip fracture in the third trimester. There is objective evidence of reduced bone density of the symptomatic femoral head and neck that has been shown by magnetic resonance imaging to be the consequence of increased water content of the femoral head and the marrow cavity; a joint effusion may also be present. The symptoms and the radiological appearance usually resolve within 2–6 months postpartum.

Lactation

The typical daily loss of calcium in breast milk has been estimated to range from 280–400 mg, although daily losses as great as 1000 mg calcium have been reported. Again, the mother could theoretically meet this demand by increasing the intestinal absorption of calcium, decreasing renal calcium losses, and increasing the resorption of calcium from the maternal skeleton. A temporary demineralization of the skeleton seems to be the main mechanism by which lactating women meet these calcium requirements. This demineralization does not seem to be mediated by PTH or 1,25-dihydroxyvitamin D, but may be mediated by PTHrP in the setting of a fall in estrogen levels.

Minerals and hormones

The mean ionized calcium level of exclusively lactating women is increased, although it remains in the normal range. Serum phosphate levels are also increased and may exceed the normal range. Because reabsorption of phosphate by the kidneys seems to be increased, the increased serum phosphate levels may, therefore, reflect the combined effects of increased flux of phosphate into the blood from diet and from skeletal resorption in the setting of decreased renal phosphate excretion. Intact PTH, as determined by a two-site IRMA, has been found to be reduced 50% or more in lactating women in the first several months postpartum. It rises to normal at weaning, but may rise above normal postweaning. Calcitonin levels fall to normal after the first 6 weeks postpartum. In contrast to the high 1,25-dihydroxyvitamin D levels of pregnancy, maternal free and bound 1,25-dihydroxyvitamin D levels fall to normal within days of parturition and remain there throughout lactation.

PTHrP levels, as measured by two-site IRMAs, are significantly higher in lactating women than in nonpregnant controls. The source of PTHrP may be the breast, because PTHrP has been detected in breast milk at concentrations exceeding 10,000 times the level found in the blood of patients with hypercalcemia of malignancy or normal human controls. Indeed, a small rise in the maternal level of PTHrP can be demonstrated after suckling (11, 12). The primary role of PTHrP in the breast or breast milk is not clear. Studies in animals suggest that PTHrP may have a primary role in the breast to regulate mammary development and mammary blood flow. In addition, PTHrP may reach the maternal circulation from the lactating breast to cause resorption of calcium from the maternal skeleton, renal tubular reabsorption of calcium, and (indirectly) suppression of PTH. In support of this hypothesis, PTHrP levels have been found to correlate negatively with PTH levels and positively with the ionized calcium levels of lactating women (11, 13). Also, PTHrP levels correlate with the loss of bone mineral density during lactation in humans (14). Furthermore, observations in aparathyroid women may provide evidence of the impact of PTHrP in calcium homeostasis during lactation. Calcitriol requirements of hypoparathyroid women fall early in the postpartum period, especially if the woman breastfeeds, and hypercalcemia may occur if the calcitriol dosage is not substantially reduced (15). As observed in one recent case, this is consistent with PTHrP reaching the maternal circulation in amounts sufficient to allow stimulation of 1,25-dihydroxyvi-

tamin D synthesis, and maintenance of normal (or slightly increased) maternal serum calcium (16). This impact of lactation on calcium homeostasis does not occur in women with pseudohypoparathyroidism, who have resistance to the amino-terminal actions of both PTH and PTHrP.

Intestinal calcium absorption

The intestinal absorption of calcium is equal to the nonpregnant state and decreased from pregnancy. This change coincides with the fall in 1,25-dihydroxyvitamin D levels to normal.

Renal calcium excretion

The GFR falls during lactation to a level below the pregnant and prepregnant value, and the renal excretion of calcium is typically reduced to levels as low as 50 mg per 24 h. This suggests that the tubular reabsorption of calcium must be increased, to account for reduced calcium excretion in the setting of increased serum calcium.

Skeletal calcium metabolism

Histomorphometric data from animals consistently show increased bone turnover during lactation, and losses of 35% or more of bone mineral are achieved during 2–3 weeks of normal lactation in the rat (reviewed in Ref. 1). Comparative histomorphometric data are lacking for humans, and, in place of that, serum markers of bone formation and urinary markers of bone resorption have been assessed in numerous cross-sectional and prospective studies of lactation. Some of the confounding factors discussed with respect to pregnancy apply to the use of these markers in lactating women. In this instance, the GFR is reduced and the intravascular volume is more concentrated. Urinary markers of bone resorption (24-h collection) have been reported to be elevated 2- to 3-fold during lactation and are higher than the levels attained in the third trimester. Serum markers of bone formation (not adjusted for hemoconcentration or reduced GFR) are generally high during lactation and increased over the levels attained during the third trimester. Total alkaline phosphatase falls immediately postpartum due to loss of the placental fraction, but may still remain above normal due to the elevation in the bone-specific fraction. Considering the confounding variables, these findings suggest that bone turnover is significantly increased during lactation.

Serial measurements of bone density during lactation (by SPA, DPA, or DXA) have shown a fall of 3–10.0% in bone mineral content after 2–6 months of lactation at trabecular sites (lumbar spine, hip, femur, and distal radius), with proportionately smaller losses at cortical sites (1, 10). The loss occurs at a peak rate of 1–3% per month, far exceeding the rate of 1–3% per year that can occur in women with postmenopausal osteoporosis who are considered to be losing bone rapidly. Loss of bone mineral from the maternal skeleton seems to be a normal consequence of lactation and may not be preventable by raising the calcium intake above the recommended dietary allowance. Several recent studies have demonstrated that calcium supplementation does not significantly reduce the amount of bone density lost during lactation (17–20). Not surprisingly, the lactational decrease in bone mineral density correlates with the amount of calcium lost in the breast milk output (21).

The mechanisms controlling the rapid loss of skeletal calcium content are not well understood. The reduced estrogen levels of lactation are clearly important, but are unlikely to be the sole explanation. In the studies of lactational bone density changes, no study has adequately addressed the relative role of estrogen withdrawal during lactation in a definitive way, because no study has manipulated estrogen independently of lactation. Such a study might, for example, require that lactating women be randomized to the use of an oral contraceptive *vs.* a placebo. In the studies that have been done, earlier resumption of menses (and, by implication, earlier restoration of estrogen levels) is associated with smaller decreases in bone density during lactation; conversely, a longer duration of amenorrhea correlates with a greater degree of bone loss during lactation (14, 19, 20, 22). At first glance this might seem to solely implicate estrogen; however, it must also be remembered that the duration of amenorrhea correlates with the intensity of lactation. Women who lactate more intensely (*i.e.* infant exclusively breastfed, more frequent feedings, greater breast milk output, etc.) can be expected to have greater net calcium losses and lose more bone, and that is not necessarily due to estrogen deficiency alone.

To estimate the effects of estrogen deficiency during lactation, it is worth noting the alterations in calcium and bone metabolism that occur in reproductive-age women who have estrogen deficiency induced by GnRH agonist therapy for endometriosis and other conditions. Six months of acute estrogen deficiency induced by GnRH agonist therapy leads to 1–4% losses in trabecular (but not cortical) bone density, increased urinary calcium excretion and suppression of 1,25-dihydroxyvitamin D and PTH levels (1). In lactation, women are not as estrogen deficient but lose more bone mineral density (at both trabecular and cortical sites), have normal (as opposed to low) 1,25-dihydroxyvitamin D levels, and have reduced (as opposed to increased) urinary calcium excretion. The difference between isolated estrogen deficiency and lactation may be due to the effects of other factors (such as PTHrP) that add to the effects of estrogen withdrawal in lactation (Fig. 1).

The bone density losses of lactation seem to be substantially reversed within 3–6 months of cessation of lactation, irrespective of how much bone density was lost initially (1, 10, 19). This corresponds to a gain in bone density of 0.5% to 2% per month in the woman who has weaned her infant and far exceeds the rate of bone density increases achieved with approved treatments for osteoporosis. The mechanism for this restoration of bone density is uncertain and largely unexplored. A few studies have observed that levels of PTH and 1,25-dihydroxyvitamin D may be higher after weaning and during the time frame when bone mass is being accreted by the maternal skeleton (23), but the significance of these observations is uncertain. In the long-term, the consequences of lactation-induced depletion of bone mineral content seem clinically unimportant. The vast majority of epidemiologic studies of pre- and postmenopausal women have found no adverse effect of a history of lactation on peak bone mass, bone density, or hip fracture risk.

Osteoporosis of lactation?

Rarely, a woman will suffer a fragility fracture during lactation, and osteoporotic readings will be confirmed by

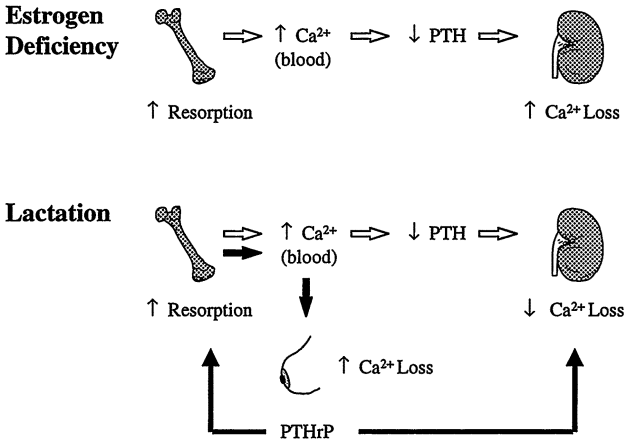

FIG. 1. Acute estrogen deficiency (*e.g.* GnRH analog therapy) increases skeletal resorption and raises the blood calcium; in turn, PTH is suppressed and renal calcium losses are increased. During lactation, the combined effects of PTHrP (secreted by the breast) and estrogen deficiency increase skeletal resorption, reduce renal calcium losses, and raise the blood calcium, but calcium is directed into breast milk. [Reproduced with permission from C. S. Kovacs and H. M. Kronenberg: *Endocrine Reviews* 18:832–872, 1997 (1). © The Endocrine Society.]

DXA. Like osteoporosis in pregnancy, this may represent a coincidental, unrelated disease; the woman may have had low bone density before conception. Alternatively, some cases might represent an exacerbation of the normal degree of skeletal demineralization that occurs during lactation, and a continuum from changes in bone density and bone turnover that may have occurred during pregnancy. For example, excessive PTHrP release from the lactating breast into the maternal circulation could cause excessive bone resorption, osteoporosis, and fractures in some of these cases. PTHrP levels were high in one case of lactational osteoporosis and were found to remain elevated for months after weaning (24). However, the extent to which PTHrP contributes to the reduction of bone density during lactation has yet to be established.

Implications of these studies

The studies of pregnant women suggest that the fetal calcium demand is met in large part by intestinal calcium absorption, which more than doubles from early in pregnancy. The studies of biochemical markers of bone turnover, DXA, and ultrasound are not conclusive, but are compatible with the possibility that the maternal skeleton does contribute calcium to the developing fetus. In comparison, the studies in lactating women suggest that skeletal calcium resorption is a dominant mechanism by which calcium is supplied to the breast milk, while renal calcium conservation is also apparent. These observations indicate that the maternal adaptations to pregnancy and lactation have evolved differently over time, such that dietary calcium absorption dominates in pregnancy, whereas the temporary borrowing of calcium from the skeleton appears to dominate during lactation. Lactation seems to program an obligatory skeletal calcium loss irrespective of maternal calcium intake, but the calcium is completely restored to the skeleton after weaning. The rapidity of calcium loss and regain by the skeleton of the lactating woman are through mechanisms that are at best, only partly understood. A full elucidation of the mechanisms of bone loss and restoration in the lactating woman might lead to the development of novel approaches to the treatment of osteoporosis and other metabolic bone diseases. Finally, although it is apparent that some women will experience fragility fractures as a consequence of pregnancy or lactation, the majority of women can rest assured that the changes in calcium and bone metabolism during pregnancy and lactation are normal, healthy, and without adverse consequences in the long term.

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