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CALCIUM AND PHOSPHATE METABOLISM AND RELATED DISORDERS DURING PREGNANCY AND LACTATION

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ABSTRACT

Pregnancy and lactation require women to provide calcium to the fetus and neonate in amounts that may exceed their normal daily intake. Specific adaptations are invoked within each time period to meet the fetal, neonatal, and maternal calcium requirements. During pregnancy, intestinal calcium absorption more than doubles, and this appears to be the main adaptation to meet the fetal demand for mineral. During lactation, intestinal calcium absorption is normal. Instead, the maternal skeleton is resorbed through the processes of osteoclast-mediated bone resorption and osteocytic osteolysis, in order to provide most of the calcium content of breast milk. In women this lactational loss of bone mass and strength is not suppressed by higher dietary intakes of calcium. After weaning, the skeleton appears to be restored to its prior bone density and strength, together with concomitant increases in bone volumes and cross-sectional diameters that may offset any effect of failure to completely restore the trabecular microarchitecture. These maternal adaptations during pregnancy and lactation also influence the presentation, diagnosis, and management of disorders of calcium and bone metabolism such as primary hyperparathyroidism, hypoparathyroidism, and vitamin D deficiency. Pregnancy and lactation can also cause pseudohyperparathyroidism, a form of hypercalcemia that is mediated by parathyroid hormone-related protein, produced in the breasts or placenta during pregnancy, and by the breasts alone during lactation. Although some women may experience fragility fractures as a consequence of pregnancy or lactation, for most women parity and lactation do not affect the long-term risks of low bone density, osteoporosis, or fracture.

INTRODUCTION

During gestation the average fetus requires about 30 g of calcium, 20 g of phosphorus, and 0.8 g of magnesium to mineralize its skeleton and maintain normal physiological processes. The suckling neonate obtains more than this amount of calcium in breast milk during six months of exclusive lactation. The adaptations through which women meet these calcium demands differ between pregnancy and lactation (Figure 1). Although providing extra calcium to the offspring could conceivably jeopardize the ability of the mother to maintain calcium homeostasis and skeletal mineralization, as this review will make clear, pregnancy and lactation normally do not cause any adverse long-term consequences to the maternal skeleton. The reader is referred to several comprehensive reviews for more details and extensive reference lists for the material covered in this chapter (1-7).

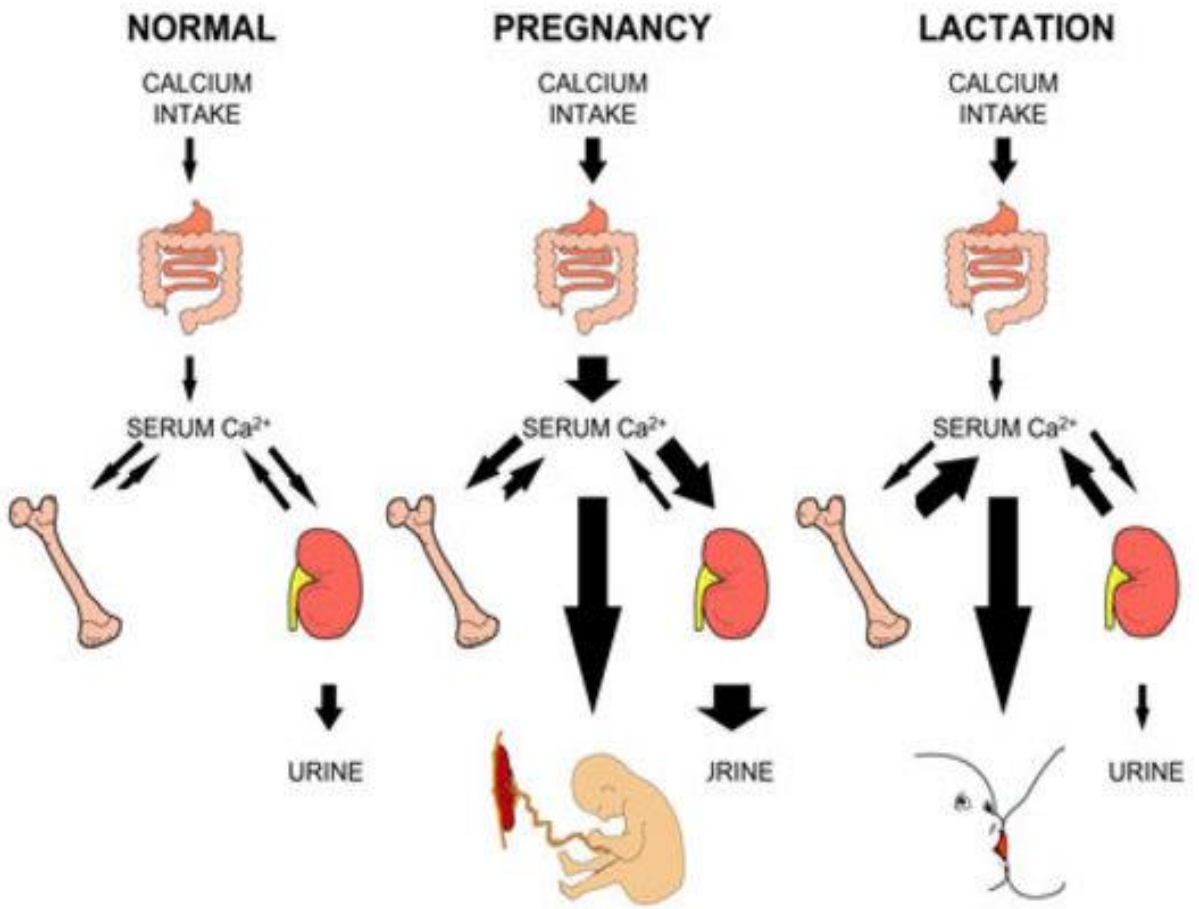

Figure 1. Schematic illustration contrasting calcium homeostasis in human pregnancy and lactation, as compared to normal. The thickness of arrows indicates a relative increase or decrease with respect to the normal and non-pregnant state. Although not illustrated, the serum (total) calcium is decreased during pregnancy, while the ionized calcium remains normal during both pregnancy and lactation. Adapted from ref. (8), © 1997, The Endocrine Society.

MINERAL PHYSIOLOGY DURING PREGNANCY

Calcium provided from the maternal decidua aids in fertilization of the egg and implantation of the blastocyst; from that point onward the rate of transfer from mother to offspring increases substantially. About 80% of the calcium and phosphate present in the fetal skeleton at the end of gestation crossed the placenta during the third trimester and is mostly derived from the maternal diet during pregnancy. Intestinal calcium and phosphate absorption doubles during pregnancy, driven by 1,25-dihydroxyvitamin D (calcitriol) and other factors, and this appears to be the main adaptation through which women meet the mineral demands of pregnancy.

Mineral Ions

There are several characteristic changes in maternal serum chemistries and calciotropic hormones during pregnancy (Figure 2), which can easily be mistaken as indicating the presence of a disorder of calcium and bone metabolism, especially since it is not common for clinicians to measure calcium,

phosphate, and calciotropic hormones during pregnancy (1). The serum albumin and hemoglobin fall during pregnancy due to hemodilution; the albumin remains low until parturition. In turn that fall in albumin causes the total serum calcium to decline to values that can be well below the normal range. The total calcium includes albumin-bound, bicarbonate-and-citrate-complexed, and ionized or free fractions of calcium. The ionized calcium, the physiologically important fraction, remains constant during pregnancy, which confirms that the fall in total calcium is but an artifact that can usually be ignored. However, that artifactual decline in total calcium means that the serum calcium cannot be relied upon to detect hypercalcemia or hypocalcemia. The ionized calcium should be measured or the albumin-corrected total calcium should be calculated to resolve any uncertainty about what the true serum calcium level is in a pregnant woman. Serum phosphate and magnesium concentrations remain normal during pregnancy.

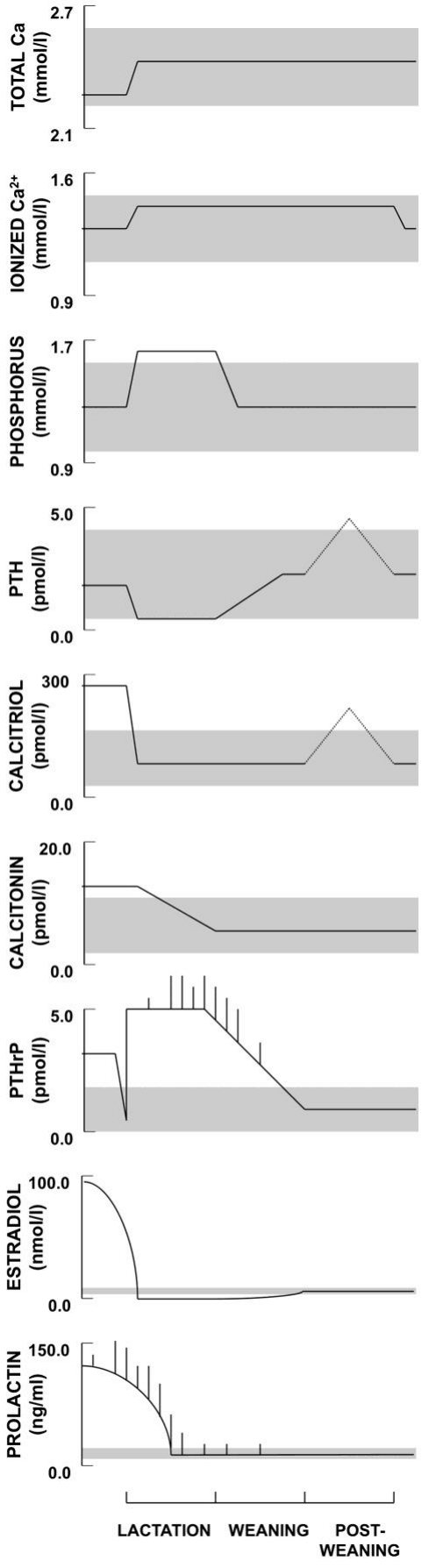
TOTAL Ca
(mmol/l)
2.7
2.1
IONIZED Ca2+
(mmol/l)
1.6
0.9
PHOSPHORUS
(mmol/l)
1.7
0.9
PTH
(pmol/l)
5.0
0.0
CALCITRIOL
(pmol/l)
300
0.0
CALCITONIN
(pmol/l)
20.0
0.0
PTHrP
(pmol/l)
5.0
0.0
ESTRADIOL
(nmol/l)
100.0
0.0
PROLACTIN
(ng/ml)
150.0
0.0
LACTATION
WEANING
POST-
WEANING

Figure 2. Schematic illustration of the longitudinal changes in calcium, phosphate, and calciotropic hormone levels that occur during pregnancy and lactation. Normal adult ranges are indicated by the shaded areas. PTH does not decline in women with low calcium or high phytate intakes, and may even rise above normal. Calcidiol (25OHD) values are not depicted; most longitudinal studies indicate that the levels are unchanged by lactation, but may vary due to seasonal variation in sunlight exposure and changes in vitamin D intake. PTHrP and prolactin surge with each suckling episode, and this is represented by upward spikes. FGF23 values cannot be plotted due to lack of data. Very limited data suggest that calcitriol and PTH may increase during post-weaning, and the lines are dashed to reflect the uncertainty. Adapted with permission from (1).

Parathyroid Hormone

Parathyroid hormone (PTH) was first measured with assays that reported high circulating levels during pregnancy. The finding of a low total serum calcium and an apparently elevated PTH led to the concept of “physiological secondary hyperparathyroidism in pregnancy.” This erroneous concept persists in some textbooks even today. Those early-generation PTH assays measured many biologically inactive fragments of PTH. When measured with 2-site “intact” assays or the more recent “bio-intact” PTH assays, PTH falls during pregnancy to the low-normal range (i.e. 0-30% of the mean non-pregnant value) during the first trimester, and may increase back to the mid-normal range by term. Most of these recent studies of PTH during pregnancy have examined women from North America and Europe who also consumed calcium-replete diets. In contrast, in women from Asia and Gambia who have very low dietary calcium intakes (and often high intakes of phytate that blocks dietary calcium absorption), the PTH level does not suppress during pregnancy and in some cases it has been found to increase above normal (1).

Vitamin D Metabolites

25-hydroxyvitamin D or calcifediol (25OHD) readily crosses the rodent hemochorial placenta (9) and appears to cross hemochorial human placentas just as easily because cord blood 25OHD levels generally range from 75% to near 100% of the maternal value (1,5). A common concern is that the placenta and fetus might deplete maternal 25OHD stores, but this does not appear to be the case. Even in severely vitamin D deficient women there was no significant change in maternal 25OHD levels during pregnancy (1,4,10,11).

Total calcitriol levels increase two to five-fold early in pregnancy and stay elevated until parturition, whereas measured free calcitriol levels were reported to be increased only in the third trimester (12). However, when the 20-40% increase in vitamin D binding protein and the decline in serum albumin during pregnancy are considered, that calculated free calcitriol should be increased in all three trimesters (11,13-16).There are several unusual aspects about this situation. PTH is normally the main stimulator of the renal 1alpha-hydroxylase; consequently, elevated calcitriol values are usually driven by high PTH concentrations. An exception to this is the ectopic expression of an autonomously functioning 1alpha-hydroxylase by such conditions as sarcoidosis and other granulomatous diseases. Another exception is pregnancy because the rise in calcitriol occurs when PTH levels are typically falling or quite low. Moreover, this increase in calcitriol occurs despite the ability of high levels of fibroblast growth factor-23 (FGF23) to suppress the synthesis and increase the catabolism of calcitriol, as shown in animal models of X-linked hypophosphatemic rickets (17-19). Evidence from additional

animal models suggest that it is not PTH but other factors, such as PTH-related protein (PTHrP), estradiol, prolactin and placental lactogen, which drive the 1alpha-hydroxylase to synthesize calcitriol (1).

The placenta expresses 1alpha-hydroxylase and it is often assumed that autonomous placental production of calcitriol explains why the maternal calcitriol level doubles; other sources such as maternal decidua and the fetus itself could conceivably contribute to the maternal value. However, it appears that any contributions of placenta and other extra-renal sources to the maternal calcitriol level are trivial. Animal studies indicate that the maternal renal 1alpha-hydroxylase is markedly upregulated during pregnancy (20,21) and that placental expression of 1alpha-hydroxylase is many-fold less than in the maternal kidneys (17). Clinical studies have revealed that anephric women on dialysis have very low circulating calcitriol levels before and during pregnancy (1,22), confirming that maternal kidneys must be the main source of the normal 2 to 5-fold increase in calcitriol during normal pregnancy. Rodent studies, including pregnancies in mice that lack the 1alpha-hydroxylase, have confirmed that there is a small contribution of fetal or placental calcitriol to the maternal circulation (1,23,24). However, it is not enough to account for the marked increase in maternal calcitriol that normally occurs during pregnancy.

Calcitonin

Serum calcitonin levels are increased during pregnancy and may derive from maternal thyroid, breast, decidua, and placenta. The importance of these extrathyroidal sites of calcitonin synthesis has been shown by serum calcitonin levels rising from undetectable to normal values in totally thyroidectomized women who become pregnant (25). Whether calcitonin plays an important role in the physiological responses to the calcium demands of pregnancy is unknown. It has been proposed to protect the maternal skeleton against excessive resorption during times of increased calcium demand; however, there are no clinical studies that have addressed this question. Study of pregnant women who lack the gene for calcitonin or the calcitonin receptor would be informative, but no such women have been identified. On the other hand, mice that lack the gene for calcitonin have normal calcium and bone metabolism during pregnancy (26,27).

Parathyroid Hormone-related Protein

PTHrP concentrations steadily increase in the maternal circulation, reaching the highest levels in the third trimester (1,11). The assays most commonly used in these studies detected PTHrP peptides encompassing amino acids 1-86, but PTHrP is a prohormone. It is cleaved into multiple N-terminal, mid-molecule, and C-terminal peptides, which differ in their biological activities and specificities. None of these peptides have been systematically measured during pregnancy. The commonly available $PTHrP^{1-86}$ assays do not measure $PTHrP^{1-34}$, which is likely the most abundant of the active, PTH-like, N-terminal forms of this protein. Moreover, in many clinical studies and case reports it is evident that inappropriate blood samples were used for assaying PTHrP. Special collection and handling are required because PTHrP is rapidly cleaved and degraded in serum. Blood samples should be collected in tubes containing EDTA and aprotinin (a protease inhibitor), kept chilled, and then centrifuged, separated, and frozen within 15 minutes of sample collection. Even with these rigorous standards, PTHrP has been found to begin degrading by 15 minutes after sample collection (28). Many studies did not use this method of sample collection and preparation, but used sera that had been allowed to clot at room temperature for up to 60 minutes. This likely explains why such studies found undetectable serum

concentrations of PTHrP, as compared to those that studied the plasma concentration of PTHrP during pregnancy. Individual case reports are also fraught with this problem, since standard blood collection protocols for hospital laboratories do not use the special handling described above.

PTHrP is produced by many tissues in the fetus and mother; consequently, it is uncertain which source(s) account for the rise in PTHrP in the maternal circulation. However, the placenta and breasts are likely the major sources of PTHrP. Whether circulating PTHrP has a role in maternal physiology during pregnancy is unclear, but its rise may stimulate the renal 1alpha-hydroxylase and contribute to the increase in calcitriol and, indirectly, the suppression of PTH. However, PTHrP appears less potent than PTH in stimulating the 1alpha-hydroxylase (29,30), which is why its contribution to the rise in calcitriol during pregnancy is uncertain. On the other hand, several case reports have clearly implicated breast- and placental-derived PTHrP as a cause of maternal hypercalcemia with elevated PTHrP and undetectable PTH, a condition called pseudohyperparathyroidism of pregnancy (see below). Since breasts and placenta were sources of excess PTHrP in these cases, those two tissues seem likely to be dominant sources of PTHrP during normal pregnancy. Moreover, since excess PTHrP impacted maternal calcium homeostasis to cause hypercalcemia in these cases, it is possible that the more modest elevations in circulating PTHrP seen during normal pregnancy also affect maternal calcium homeostasis.

A carboxyl-terminal form of PTHrP (so-called “osteostatin”) has been shown to inhibit osteoclastic bone resorption *in vitro*, and thus the notion arises that PTHrP may play a role in protecting the maternal skeleton from excessive resorption during pregnancy (31). Animal studies have shown that PTHrP has other roles during gestation such as regulating placental calcium transport in the fetus (1,32). Maternally produced PTHrP is not likely to regulate placental calcium transport since the protein should not be able to cross the placenta (1,5); instead, it is PTHrP produced within the fetus and placenta that is responsible for regulating placental calcium transport.

Fibroblast Growth Factor-23 (FGF23)

Intact FGF23 doubles its concentration in the mother’s circulation during rodent pregnancies (17-19), but whether such levels change during human pregnancy has not been reported. Within 24 hours after delivery, mean values in postpartum women were similar to non-pregnant women (33).

Other Hormones

This section has focused on changes in static concentrations of minerals and the known calciotropic hormones; there are no studies testing hormonal reserves or response to challenges such as hypocalcemia or hypophosphatemia. Pregnancy also induces significant changes in other hormones known to affect calcium and bone metabolism, including sex steroids, prolactin, placental lactogen, oxytocin, leptin, and IGF-1. Each of these – and possibly other hormones not normally associated with mineral and bone metabolism – may have direct or indirect effects on mineral homeostasis during pregnancy. However, this aspect of the physiology of pregnancy has been largely unexplored to date.

Prolactin and placental lactogen both increase during pregnancy and activate prolactin receptors. Osteoblasts express prolactin receptors, and prolactin receptor deficient mice show decreased bone formation (34). Suppressing the prolactin level with bromocriptine blunted a pregnancy-related gain in

bone mineral content in rats (35). These data are consistent with the notion that prolactin or placental lactogen regulate skeletal metabolism during pregnancy. Furthermore, prolactin can indirectly affect skeletal metabolism by stimulating PTHrP synthesis and release from the breasts (36-38).

Circulating oxytocin levels also rise during pregnancy (39), and the oxytocin receptor is expressed by osteoclasts and osteoblasts (40). Male and female mice lacking oxytocin or its receptor have an osteoporotic phenotype with low bone formation (41). Oxytocin has been shown to stimulate osteoblast differentiation and function, stimulate osteoclast formation, but inhibit osteoclast function and skeletal resorption (41,42). Taken together, these data predict that oxytocin may regulate bone metabolism during pregnancy, but this has not been directly studied *in vivo*.

Intestinal Calcium and Phosphate Absorption

Intestinal absorption of calcium doubles as early as 12 weeks of human pregnancy, as shown by clinical studies that used stable isotopes of calcium, and by other calcium balance studies (1). This increase in calcium absorption appears to be the major maternal adaptation to meet the fetal need for calcium. It has been generally believed that the doubling or tripling of calcitriol levels explains the increased intestinal calcium absorption and concurrent increases in the intestinal expression of calbindin$_{9k}$-D (S100G), TRPV6, Ca^{2+}-ATPase (PMCA1), and other genes and proteins involved in calcium transport. However, intestinal calcium absorption doubles in the first trimester, well before the rise in free calcitriol levels during the third trimester. Animal studies have indicated that placental lactogen, prolactin, and other factors may stimulate intestinal calcium absorption (1) and that calcitriol or the vitamin D receptor are not required for intestinal calcium absorption to increase during pregnancy (1,23,43-45).

The peak fetal demand for calcium does not occur until the third trimester, and so it is unclear why intestinal calcium absorption should be upregulated in the first trimester. It may allow the maternal skeleton to store calcium in advance of the peak demands for calcium that occur later in pregnancy and lactation; some studies in rodents have shown this to be the case with the bone mineral content rising significantly before term (17,26,45). Women have also been found to be in a positive calcium balance by mid-pregnancy (46), likely due to the effect of increased intestinal calcium absorption on skeletal mineralization.

Intestinal phosphate absorption also undergoes a doubling during rodent and other mammalian pregnancies (1), and presumably human pregnancy as well. However, no clinical studies have studied this.

Renal Handling of Calcium

The doubling of intestinal calcium absorption in the first trimester means that the extra calcium must be passed to the fetus, deposited in the maternal skeleton, or excreted in the urine. Renal calcium excretion is increased as early as the 12th week of gestation and 24-hour urine values (corrected for creatinine excretion) often exceed the normal range. Conversely, fasting urine calcium values are normal or low, confirming that this hypercalciuria is a consequence of the enhanced intestinal calcium absorption (1). This is absorptive hypercalciuria and will not be detected by spot or fasting urine samples that have been corrected for creatinine concentration. Absorptive hypercalciuria contributes to the increased risk of kidney stones during pregnancy.

This absorptive hypercalciuria also renders nomograms of fractional calcium excretion invalid for the diagnosis of familial hypocalciuric hypercalcemia during pregnancy (47,48).

Pharmacological doses of calcitonin promote renal calcium excretion, but whether the physiologically elevated levels of calcitonin during pregnancy promote renal calcium excretion is unknown.

Hypocalciuria during pregnancy has been associated with pre-eclampsia, pregnancy-induced hypertension, and low (equal to non-pregnant values) serum calcitriol (49-52). These changes appear largely secondary to disturbed renal function and reduced creatinine clearance, rather than being causes of the hypertension. However, calcium supplementation reduces the risk of pre-eclampsia in women within the lowest quintile of calcium intake, and so there is a pathophysiological link between calcium metabolism and pregnancy-induced hypertension (1).

Skeletal Calcium Metabolism and Bone Density/Bone Marker Changes

As mentioned earlier, some studies in rodents indicate that bone mineral content increases during pregnancy, and other studies have shown that histomorphometric parameters of bone turnover are increased at this time. Systematic studies of bone histomorphometry from pregnant women have not been done. However, one study of 15 women who electively terminated a pregnancy at 8-10 weeks found bone biopsy evidence of increased bone resorption, including increased resorption surface and increased numbers of resorption cavities (53). These findings were not present in biopsies obtained from 13 women at term, or in the non-pregnant controls. This study bears repeating but it does suggest that early pregnancy induces skeletal resorption.

Bone turnover markers – by-products of bone formation and resorption that can be measured in the serum or urine – have been systematically studied during pregnancy in multiple studies (1). In the non-pregnant adult with osteoporosis these bone markers are fraught with significant intra- and inter-individual variability which limit their utility on an individual basis. There are additional problems with the use of bone markers during pregnancy, including lack of pre-pregnancy baseline values; hemodilution; increased GFR; altered creatinine excretion; placental, uterine and fetal contributions; degradation and clearance by the placenta; and lack of diurnally timed or fasted specimens. Bone resorption has been assessed using urinary (deoxypyridinoline, pyridinoline, and hydroxyproline) and serum (C-telopeptide) markers, and the consistent finding is that bone resorption appears increased from early or mid-pregnancy (1). Conversely, bone formation has been assessed by serum markers (osteocalcin, procollagen I carboxypeptides and bone specific alkaline phosphatase) that were generally not corrected for hemodilution or increased GFR. These bone formation markers are decreased in early or mid-pregnancy from pre-pregnancy or non-pregnant values and rise to normal or above before term (1). The lack of correction for hemodilution and increased GFR means that the apparent decline in bone formation markers may actually occur despite no change or even an increase in bone formation. It should be noted that total alkaline phosphatase rises early in pregnancy due to the placental fraction and is not a useful marker of bone formation during pregnancy.

Overall, the scant bone biopsy data and the results of bone turnover markers suggest that bone resorption is increased from as early as the 10^{th} week of pregnancy, whereas bone formation may be suppressed (if the bone formation marker results are correct) or normal (if the bone formation markers are artifactually suppressed due to the aforementioned confounding factors) (1). Notably there is little

maternal-fetal calcium transfer occurring in the first trimester, nor is there a marked increase in turnover markers during the third trimester when maternal-fetal calcium transfer is at a peak. These findings may simply underscore that resorption of the maternal skeleton is a minor contributor to calcium homeostasis during pregnancy, whereas the upregulation of intestinal calcium absorption is the main mechanism through which the fetal demand for calcium is met.

Another way of assessing whether the maternal skeleton contributes to calcium regulation during pregnancy is to measure bone mineral content or density. A few sequential areal bone density (aBMD) studies have been done using older techniques (single and/or dual-photon absorptiometry, i.e., SPA and DPA), and none with newer techniques (DXA or qCT) due to concerns about fetal radiation exposure. Studies of aBMD are known to be confounded by changes in body composition, weight and skeletal volumes, and all three of these factors change during normal pregnancy. The longitudinal studies used SPA or DPA and found no significant change in cortical or trabecular aBMD during pregnancy (1). Most recent studies examined 16 or fewer subjects with DXA prior to planned pregnancy (range 1-18 months prior, but not always stated) and after delivery (range 1-6 weeks postpartum) [studies reviewed in detail in (54)]. One study found no change in lumbar spine aBMD measurements obtained pre-conception and within 1-2 weeks post-delivery, whereas the other studies reported 4-5% decreases in lumbar aBMD with the postpartum measurement taken between 1-6 weeks post-delivery. A large study from Denmark obtained DXA measurements of hip, spine, and radius at baseline (up to 8 months before pregnancy) and again within 15 days of delivery in 73 women (55). DXA of the radius was also obtained once each trimester. BMD decreased between pre-pregnancy and post-pregnancy by 1.8% at the lumbar spine, 3.2% at the total hip, 2.4% at the whole body, 4% at the ultradistal forearm, and 1% at the total forearm, whereas it increased by 0.5% at the proximal 1/3 forearm (55). All women went on to breastfeed, which means that the final BMD values were confounded by lactation-induced bone loss (see lactation section). These changes in BMD were statistically significant when compared to 57 non-pregnant controls who also had serial measurements done, but the magnitudes of change were small, and would not be considered statistically significant for an individual woman.

Ultrasound measurements of the os calcis and fingers have been examined in other longitudinal studies, which reported a progressive decrease in indices that correlate with volumetric BMD (1,54). Whether observed changes in the os calcis accurately indicate a true or clinically meaningful decrease in volumetric BMD, or imply that losses of BMD are occurring in the spine or hip during pregnancy, is not known. The reliability or relevance of data obtained from ultrasound is questionable since this technique failed to detect any change in volumetric BMD at the os calcis during lactation (56), even though substantial bone loss occurs at the spine and hip during lactation (see lactation section).

Overall, the existing studies have insufficient power to allow a firm conclusion as to the extent of bone loss that might occur during pregnancy, but it seems likely (especially when data from the Danish study are considered) that modest bone loss occurs, which would be difficult to discern on an individual basis. In the long term, pregnancy does not impair skeletal strength or lead to reduced bone density. Several dozen epidemiological studies of osteoporotic and osteopenic women have failed to find a significant association of parity with bone density or fracture risk (1,57), and many have shown a protective effect of parity (58-75).

DISORDERS OF CALCIUM AND BONE METABOLISM DURING PREGNANCY

Osteoporosis in Pregnancy

The occasional woman will present with a fragility fracture during the third trimester or puerperium, and low bone mineral density may be confirmed by DXA (76). In such cases it is not possible to exclude the possibility that low bone density or skeletal fragility preceded pregnancy. In favor of a genetic predisposition is the report that among 35 women who presented with pregnancy associated osteoporosis, there was a higher than expected prevalence of fragility fractures in their mothers (77). It is conceivable that pregnancy may induce significant skeletal losses in some women and, thereby, predispose to fracture. The normal pregnancy-induced changes in mineral metabolism may cause excessive resorption of the skeleton in selected cases, and other factors such as low dietary calcium intake and vitamin D insufficiency may contribute to skeletal losses (76). A high rate of bone turnover is an independent risk factor for fragility fractures outside of pregnancy, and so the apparently increased bone resorption observed during pregnancy may increase fracture risk. In favor of pregnancy inducing fragility through excess skeletal losses is an observational study of 13 women with pregnancy-associated osteoporosis who were followed for up to eight years. Since the bone mineral density at the spine and hip increased significantly during follow-up in these women, the investigators concluded that a large part of the bone loss must have been related to the pregnancy itself (78). Taken together, fragility fractures in pregnancy or the puerperium may result from the combination of abnormal skeletal microarchitecture prior to pregnancy and increased bone resorption during pregnancy.

Osteoporosis in pregnancy usually presents in a first pregnancy and there is no apparent increased risk with higher parity (76,78-80). About 60% of patients present with lower thoracic or lumbar pain that may be quite debilitating due to vertebral collapse (78-80). Most cases show normal serum chemistries and calciotropic hormone levels, but in a few, secondary causes of bone loss could be identified, including anorexia nervosa, hyperparathyroidism, osteogenesis imperfecta, inactivating mutations in *LRP5*, premature ovarian failure, and corticosteroid or heparin therapy (76,77,79-83). Bone biopsies have confirmed osteoporosis and the absence of osteomalacia, while bone density Z-scores are often lower than expected (78-80). The pain resolves spontaneously over several weeks in most cases while the bone density has been reported to improve in most women following pregnancy. Fractures tend not to recur in subsequent pregnancies. Thus, although myriad medical treatments (bisphosphonates, estrogen, testosterone, calcitonin, teriparatide, denosumab) and surgical interventions (kyphoplasty, vertebroplasty, spinal fusion) have been used in individual cases of pregnancy-associated osteoporosis (76), the tendency for this condition to spontaneously improve may make pharmacological treatment unjustified except for the severest cases. At the least, it may be prudent to wait 12-18 months to determine the extent to which the BMD recovers on its own after a pregnancy-associated vertebral fracture (76).

A distinct condition is focal, transient osteoporosis of the hip (76). This is rare, self-limited, and probably not a manifestation of altered calciotropic hormone levels or mineral balance during pregnancy. Instead, it may be a consequence of local factors. A variety of theories have been offered to explain this condition, including femoral venous stasis due to pressure from the pregnant uterus, Sudeck's atrophy or reflex sympathetic dystrophy (causalgia), 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 or puerperium (76,84-86). Radiographs and DXA indicate radiolucency and reduced bone density of the symptomatic femoral head and neck,

while MRI demonstrates increased water content of the femoral head and the marrow cavity; a joint effusion may also be present. The differential diagnosis of this condition includes inflammatory joint disorders, avascular necrosis of the hip, bone marrow edema, and reflex sympathetic dystrophy. It is a self-limiting condition with both symptoms and radiological appearance resolving within two to six months post-partum; conservative measures including bed rest are usually all that is required during the symptomatic phase (76). Of course, fractures of an involved femur require urgent arthroplasty or hip replacement. The condition recurs in about 40% of cases (not necessarily during pregnancy), unlike osteoporosis involving the spine, and this has prompted prophylactic hip arthroplasty to be done in a few cases where the opposite hip appears to be affected.

Primary Hyperparathyroidism

This is probably a rare condition but there are no firm data available on its prevalence. Two case series indicated that parathyroidectomies were done during pregnancy in about 1% of all cases (87,88). The diagnosis will be obscured by the normal pregnancy-induced changes that lower the total serum calcium and suppress PTH; however, finding the ionized or albumin-corrected calcium to be increased, and PTH to be detectable, should indicate primary hyperparathyroidism in most cases.

Primary hyperparathyroidism during pregnancy has been reported to cause a variety of symptoms that are not specific to hypercalcemia, and cannot be distinguished from those occurring in normal pregnancy (nausea, vomiting, renal colic, malaise, muscle aches and pains, etc.). Conversely the literature associates primary hyperparathyroidism with an alarming rate of adverse outcomes in the fetus and neonate, including a 10-30% rate for each of spontaneous abortion, stillbirth, and perinatal death, and 30-50% incidence of neonatal tetany (88-92). These high rates were reported in older literature; more recent case series suggest that the rates of stillbirth and neonatal death are each about 2%, while neonatal tetany occurred in 15% (89). The adverse postnatal outcomes are thought to result from suppression of the fetal and neonatal parathyroid glands; this suppression may be prolonged after birth for 3-5 months (89) and in some cases it has been permanent (89,91,93).

To prevent these adverse outcomes, surgical correction of primary hyperparathyroidism during the second trimester has been almost universally recommended. Several case series have found elective surgery to be well tolerated, and to dramatically reduce the rate of adverse events when compared to the earlier cases reported in the literature. In a series of 109 mothers with hyperparathyroidism during pregnancy who were treated medically (N=70) or surgically (N=39), there was a 53% incidence of neonatal complications and 16% incidence of neonatal deaths among medically treated mothers, as opposed to a 12.5% neonatal complications and 2.5% neonatal deaths in mothers who underwent parathyroidectomy (88). Choosing the second trimester allows organogenesis to be complete in the fetus and to avoid the poorer surgical outcomes and risk of preterm birth associated with surgery during the third-trimester (89,92,94,95).

Many women in the earliest published cases had a more severe form of primary hyperparathyroidism that is not often seen today (symptomatic, with nephrocalcinosis and renal insufficiency). While mild, asymptomatic primary hyperparathyroidism during pregnancy has been followed conservatively with successful outcomes, complications continue to occur, so that, in the absence of definitive data, surgery during the second trimester remains the most common recommendation (96). Milder cases diagnosed during the third trimester may be observed until delivery, although rapid and severe postpartum worsening of the hypercalcemia can occur (95,97-100). This postpartum “parathyroid crisis”

occurs because the placental calcium outflow has been lost, while surging PTHrP production in the breasts means an additional factor stimulating bone resorption.

There are no definitive medical management guidelines for hyperparathyroidism during pregnancy apart from ensuring adequate hydration and correction of electrolyte abnormalities (96). Pharmacologic agents to treat hypercalcemia have not been adequately studied in pregnancy. Calcitonin does not cross the placenta and has been used safely (96). Oral phosphate has also been used but is limited by diarrhea, hypokalemia, and risk of soft tissue calcifications. Bisphosphonates are relatively contra-indicated because of their potential adverse effects on fetal endochondral bone development, although a review of 78 cases of bisphosphonate use in pregnancy found no obvious problems in most cases (101). Denosumab crosses the placenta and has been shown to cause an osteopetrotic-like phenotype in fetal cynomolgus monkeys and rats (102,103), and so it should be avoided in human pregnancy. High-dose magnesium has been proposed as a therapeutic alternative which should decreases serum PTH and calcium levels by activating the calcium sensing-receptor, but it has not been adequately studied for this purpose (104,105). The calcium receptor agonist cinacalcet, which is used to suppress PTH and calcium in nonpregnant subjects with primary or secondary hyperparathyroidism and parathyroid carcinoma, has also been tried in pregnancy (106-109). However, since the calcium receptor is expressed in the placenta and regulates fetal-placental calcium transfer (110), the possibility of adverse effects of cinacalcet on the fetus and neonate remain a concern.

In any case that was followed medically, parathyroidectomy is recommended to be done postpartum, with monitoring in place to detect a postpartum hypercalcemic crisis.

Familial Hypocalciuric Hypercalcemia

Inactivating mutations in the calcium-sensing receptor cause this autosomal dominant condition which presents with hypercalcemia and hypocalciuria (111). As noted above, fractional excretion of calcium is not reduced during pregnancy in this condition, because it is overridden by the physiological increase in intestinal calcium absorption that in turn causes hypercalciuria (47,48). Pregnancy in women with familial hypocalciuric hypocalcemia may be uneventful for the mother, but the maternal hypercalcemia has caused fetal and neonatal parathyroid suppression with subsequent tetany in both normal and hemizygous children (5,112,113). A hemizygous neonate will later develop benign hypercalcemia, but if the baby has two inactivating mutations of the calcium receptor (most commonly from both parents being hemizygous for FHH), then the neonate may suffer a life-threatening hypercalcemic crisis (5).

Hypoparathyroidism

Hypoparathyroidism during pregnancy usually presents as a pre-existing condition that the clinician is challenged to manage. The natural history of hypoparathyroidism during pregnancy is confusing due to conflicting case reports in the literature [reviewed in (1,3)]. Early in pregnancy, some hypoparathyroid women have fewer hypocalcemic symptoms and require less supplemental calcium. This is consistent with a limited role for PTH in the pregnant woman, and suggests that an increase in calcitriol and/or increased intestinal calcium absorption occurs in the absence of PTH. However, other case reports clearly indicate that some pregnant hypoparathyroid women required increased calcitriol replacement in order to avoid worsening hypocalcemia. Adding to the confusion is that in some case reports, it appears that the normal, artifactual decrease in total serum calcium during pregnancy was the parameter that led to treatment with increased calcium and calcitriol supplementation; fewer cases reported that dose

increments in calcitriol and calcium were made because of maternal symptoms of hypocalcemia or tetany, or objective evidence of true hypocalcemia (ionized or albumin-corrected calcium). It is not possible to know in advance who will improve and who will worsen during pregnancy; the task is to maintain the albumin-corrected serum calcium or ionized calcium in the normal range for the duration of pregnancy. Maternal hypocalcemia due to hypoparathyroidism must be avoided because it has been associated with intrauterine fetal hyperparathyroidism and fetal death. Conversely, overtreatment must be avoided because maternal hypercalcemia is associated with the fetal and neonatal complications described above under Primary Hyperparathyroidism. Calcitriol and 1α-calcidiol are recommended due to their shorter half-lives, lower risk of toxicity, and the clinical experience with these agents.

Late in pregnancy, hypercalcemia may occur in hypoparathyroid women unless the calcitriol dosage and supplemental calcium are substantially reduced or discontinued. This effect appears to be mediated by the increasing levels of PTHrP in the maternal circulation in late pregnancy. Conversely, one case report of hypoparathyroidism in pregnancy found that there was a transient interval of increased requirement for calcitriol immediately after delivery and before lactation was fully underway (114). This may be the result of loss of placental sources of PTHrP followed by a surge in production of PTHrP by the lactating breast (see lactation section, below).

Pseudohypoparathyroidism

Pseudohypoparathyroidism is a genetic disorder causing resistance to PTH and manifest by hypocalcemia, hypophosphatemia, and high PTH levels. In two case reports of pseudohypoparathyroidism during pregnancy, the serum calcium normalized, PTH reduced by half, and calcitriol increased 2- to 3-fold (115). The mechanism by which these changes occur despite pseudohypoparathyroidism remains unclear. If maternal hypocalcemia persists during pregnancy, pseudohypoparathyroidism can lead to the same adverse fetal outcomes that have been associated with maternal hypoparathyroidism, including parathyroid hyperplasia, skeletal demineralization, and fractures (116,117). The maternal calcium concentration must be maintained in the normal range to avoid these fetal outcomes.

Pseudohyperparathyroidism

As mentioned above, pseudohyperparathyroidism is hypercalcemia that is caused by physiological release of PTHrP driving increased skeletal resorption, akin to how PTHrP also causes hypercalcemia of malignancy. In one such case the breasts were the source of PTHrP because the hypercalcemia and elevated PTHrP did not abate until a bilateral reduction mammoplasty was carried out (118,119). It has occurred in women who simply have large breasts (120,121). In another case the hypercalcemia, elevated PTHrP, and suppressed PTH reversed within a few hours of an urgent C-section, thereby confirming the placenta as the source (122). In all cases of pseudohyperparathyroidism, it should be anticipated that the cord blood calcium will also be increased, and that the baby is at risk for fetal and neonatal hypoparathyroidism with hypocalcemic tetany.

Vitamin D Deficiency and Insufficiency

There are no comprehensive studies of the effects of vitamin D deficiency or insufficiency on human pregnancy, but the available data from small clinical trials of vitamin D supplementation, observational studies, and case reports suggest that, consistent with animal studies, vitamin D insufficiency and

deficiency is not associated with any worsening of maternal calcium homeostasis (this topic is reviewed in detail in (1,4,7). Maternal hypocalcemia is milder with vitamin D deficiency due to the effects of secondary hyperparathyroidism to increase skeletal resorption and renal calcium reabsorption. Consequently, hypocalcemia due to vitamin D deficiency has not been clearly associated with the same adverse fetal outcomes that maternal hypoparathyroidism causes (reviewed in detail in (5,123)). The fetal effects of vitamin D deficiency, inability to form calcitriol, and absence of the vitamin D receptor have been examined across several animal species and all have indicated that the fetus will have a normal serum calcium and fully mineralized skeleton at term (reviewed in detail in (5,123)). Neonatal hypocalcemia and rickets can occur in infants born of mothers with severe vitamin D deficiency, but it is usually in the weeks to months after birth that this presents, after intestinal calcium absorption becomes dependent on calcitriol.

There has been much interest in studies that have inconsistently associated third-trimester measurements of 25OHD, or estimated vitamin D intakes during pregnancy or the first year after birth, with possible extraskeletal benefits in the mother (reduced bacterial vaginosis, pre-eclampsia, pre-term delivery) or in the offspring (lower incidence of type 1 diabetes, greater skeletal mineralization, etc.). These associational studies won't be discussed in detail (some are cited in: (1,5,124)) because they are confounded by factors which contribute to lower 25OHD levels (maternal overweight/obesity, lower socioeconomic status, poor nutrition, lack of exercise, etc.). It is necessary to test these associations in randomized clinical trials that compare higher versus lower intakes of vitamin D during pregnancy. At present the results of the associational studies are insufficient to warrant prescribing higher intakes of vitamin D during pregnancy to prevent these postulated outcomes.

Among many clinical trials of vitamin D supplementation that have been carried out (1), only a few have included over a 100 study participants who were vitamin D deficient at entry, while other recent studies that gained press attention did not include many vitamin D deficient subjects at all. Among the trials with over 100 participants (14,125-132), the two largest were from Bangladesh and UK with over 1,000 participants (131,132). Baseline maternal 25OHD levels were lowest (20-29 nmol/L) in trials from Bangladesh, UK, Iran, and UAE, and in the 40-60 nmol/L range in the remainder. Interventions consisted of placebo/no treatment versus low dose (400 IU/day) or high dose (1,000-5,000 IU/day) vitamin D supplementation, initiated before mid-pregnancy, and maintained until delivery. For most trials the primary outcomes were simply maternal and neonatal-cord blood 25OHD and calcium. The most recent and largest study was from Bangladesh, and the primary outcome was pre-specified as infant length-for-age z-scores at 1 year of age (132). Offspring anthropometric parameters and/or bone mineral content were pre-specified only in a few of the remaining studies (128,130,131).

In all studies vitamin D supplementation increased maternal serum and cord blood 25OHD, but there was no overall effect on cord blood calcium. The largest achieved difference in a single study was 16 nmol/L (6.4 ng/mL) in the untreated and 168 nmol/L (67 ng/mL) in vitamin D-supplemented mothers at term; however, there was no obstetrical or fetal benefit (125). The incidence of neonatal hypocalcemia was reduced in offspring of vitamin-D treated mothers, reflecting the role of vitamin D/calcitriol to stimulate postnatal intestinal calcium absorption (125). In the large Bangladesh study, there were no significant differences in infant anthropometrics or any other fetal, neonatal or maternal outcomes (132). In one US-based study there was no benefit on mode of delivery, gestational age at delivery, and preterm birth (14), while in another there was no benefit on mode of delivery, C-section rates, adverse events, hypertension, infection, gestational diabetes, still birth, gestational age at delivery, or combinations of these outcomes (127). The UK MAVIDOS trial reported no obstetrical benefit, and no

benefit to any of the primary (neonatal bone area, BMC, and BMD within the first 10-14 days after birth) or secondary outcomes (anthropometric and body composition parameters within 48 hours of birth). However, it received much publicity for a demonstrated increase in BMC and BMD in winter-born neonates of vitamin D-supplemented vs. placebo-treated mothers (131). Because the neonatal skeleton accretes 100 mg/day of mineral content after birth, this result may reflect improved intestinal mineral delivery over 14 days after birth, rather than a prenatal effect on skeletal mineralization (1,133,134). Curiously, autumn-born neonates of vitamin D-supplemented vs. placebo-treated mothers showed an adverse trend of similar magnitude on BMC and BMD, which suggests possible harm from vitamin D supplementation, or chance findings due to small numbers within the sub-groups (134). These sub-group analyses of treatment by season interaction were not specified outcomes in the trial registries (ISRCTN 82927713 and EUDRACT 2007-001716-23). In the UK study that achieved the greatest difference in 25OHD levels between untreated and vitamin D-treated mothers and babies, there was a trend for more small for gestational age babies born to mothers who did not receive antenatal vitamin D supplementation (28% vs. 15%, $p<0.1$), but the study was not powered for this outcome (125). In studies from the UAE, and Iran there was also no benefit on obstetrical outcomes (variably, mode of delivery, C-section rates, adverse events, stillbirths, gestational age at delivery) or neonatal anthropometric measurements and bone mass measurements (126,128,130).

The lack of any beneficial effect on maternal, immediate fetal/neonatal and neonatal outcomes (anthropometrics and cord blood calcium), even in studies that included mothers with some of the lowest 25OHD levels (125,128,130,132), suggests that vitamin D supplementation during pregnancy confers no benefit to the neonate. The most recent study was well-powered to demonstrate a beneficial effect on infant length and other fetal/neonatal outcomes, but did not yield any significant results, despite low vitamin D levels in the mothers at study entry (132).

Systematic reviews have used these and the results of smaller trials to examine the effect of vitamin D supplementation during pregnancy on maternal, fetal, and neonatal extra-skeletal outcomes (135-140). Vitamin D supplementation had no significant effect on pre-eclampsia in four (136,138-140) and a positive effect in two reviews (135,137), while combined vitamin D and calcium supplementation reduced the incidence of pre-eclampsia in three systematic reviews (135-137). No consistent effect was seen on other outcomes such as preterm birth, low birth weight, small for gestational age, infections, C-section rate, and newborn anthropometrics.

Overall, available data are insufficient from the individual clinical trials or these systematic reviews to conclude that vitamin D supplementation during pregnancy confers any proven obstetrical benefits.

Genetic Vitamin D Resistance Syndromes

Case reports and series have provided insight into the effect of pregnancy on genetic disorders of vitamin physiology. Pregnancies have generally been unremarkable in women with vitamin D-dependent rickets type 1 (VDDR-I) which is due to absence of Cyp27b1, and in women with VDDR-II that is due to absence of functional VDRs (141-143). In one such uneventful VDR-II pregnancy, the pre-pregnancy intake of supplemental calcium (800 mg) and high-dose calcitriol were maintained until her clinicians increased the dose of calcitriol later in pregnancy “because of the knowledge that the circulating 1,25-$(OH)_2$D concentration normally rises during pregnancy,” and not because of any change in albumin-adjusted serum calcium (142). Consequently, it’s unclear that any change was needed. However, it is reasonable to increase the dose of calcitriol to mirror the increase that happens

during normal pregnancy. In women with VDDR-I, the dose of calcitriol was unchanged in one-third of pregnancies but increased 1.5 to 2-fold in others (141).

24-Hydroxylase Deficiency

Loss of the catabolic effects of 24-hydroxylase causes high calcitriol and mild hypercalcemia in non-pregnant adults, which may be asymptomatic (144). But during pregnancy, the physiological 2 to 5-fold increase in calcitriol is unopposed by catabolism, which causes an exaggerated increase in calcitriol, followed by symptomatic hypercalcemia. Hypercalcemia can be quite marked, with suppressed or undetectable PTH, and calcitriol concentrations that exceed what is expected for pregnancy (145-147). Pregnant patients may also present with nephrolithiasis or acute pancreatitis (147,148).

Treatment of the hypercalcemia is difficult because the agents that could be used are not approved for pregnancy. Increased intestinal calcium absorption is the direct cause, and so use of increased hydration and a modestly restricted calcium diet, combined with phosphate supplementation to bind dietary calcium, are relatively safe management approaches. If PTH increases above normal, then dietary calcium restriction should be lessened to prevent maternal bone resorption and fetal secondary hyperparathyroidism. Other pharmacologic therapy should be reserved for the most severe cases and used with caution. This includes oral glucocorticoids, loop diuretics, calcitonin, and bisphosphonates; denosumab should not be used because of teratogenic effects observed in cynomolgus monkeys and mice (102,103). Cinacalcet will not be useful because PTH will already be suppressed due to the combined effects of pregnancy and hypercalcemia.

Low or High Calcium Intake

Through the doubling of intestinal calcium absorption during pregnancy, women have the ability to adapt to wide ranges of calcium intakes and still meet the fetal demand for calcium. It is conceivable that extremely low maternal calcium intakes could impair maternal calcium homeostasis and fetal mineral accretion, but there are scant clinical data examining this possibility (149). Among women with low dietary calcium intake, there are differing results as to whether or not calcium supplementation during pregnancy improved maternal or neonatal bone density (150). There is short term evidence that bone turnover markers were reduced when 1.2 gm of supplemental calcium was given for 20 days to 31 Mexican woman at 25-30 weeks of gestation; their mean dietary calcium intake was 1 gm (151). In a double-blind study conducted in 256 pregnant women, 2 gm of calcium supplementation improved bone mineral content only in the infants of supplemented mothers who were in the lowest quintile of calcium intake (152). Among cases of fragility fractures presenting during pregnancy, some women had very low calcium intakes (<300 mg per day), and in such cases substantial maternal skeletal resorption must be invoked in order to meet the fetal calcium requirement and maintain the maternal serum calcium concentration (76).

Overall the physiological changes in calcium and bone metabolism that usually occur during pregnancy and lactation are likely to be sufficient for fetal bone growth and breast-milk production in women with reasonably sufficient calcium intake (153). However, the use of calcium supplementation for pregnant women with low calcium intake can be defended by the links between low calcium intake and both preeclampsia and hypertension in the offspring (149). Clinical trials and meta-analyses have also demonstrated that supplemental calcium will reduce the risk of preeclampsia in women with low dietary calcium intakes, but not in those with adequate intake (154-157).

High calcium intake, similar to primary hyperparathyroidism, can cause increased intestinal calcium absorption, maternal hypercalcemia, increased transplacental flow of calcium, and suppression of the fetal parathyroids. Cases of neonatal hypoparathyroidism have been reported wherein women consumed 3 to 6 grams of elemental calcium daily as antacids or anti-nauseates (1).

Hypercalcemia of Malignancy

Hypercalcemia of malignancy is usually a terminal condition. When it has been diagnosed during pregnancy, in some cases the baby has been spared from chemotherapy, whereas in other cases the pregnancy was terminated (or ignored) so that chemotherapy could be administered in an attempt to prolong the woman's life. Half of published case reports haven't even mentioned the baby's outcome. A baby born of a mother with humoral hypercalcemia of malignancy may have a high concentration of calcium in cord blood, and is at high risk for fetal and neonatal hypoparathyroidism with hypocalcemic tetany.

FGF-23 Disorders

X-linked hypophosphatemic rickets (XLH) is caused by inactivating mutations in the *PHEX* gene, which lead to high circulating levels of FGF23. In turn this causes hypophosphatemia with rickets or osteomalacia. Pregnancies were normal in a mouse model of XLH. In particular, despite very high circulating levels of FGF23, which normally downregulate calcitriol synthesis and increase its catabolism, maternal serum calcitriol increased to the high levels normally seen during pregnancy (19,158). This rise in calcitriol should contribute to increased intestinal calcium and phosphate absorption. Several case reports documented persistent hypophosphatemia during pregnancy in women with XLH, but no adverse outcomes (159,160). Nevertheless, it is generally recommended to supplement with calcitriol and phosphate to keep the serum phosphate near normal during pregnancy.

Hyperphosphatemic disorders due to loss of FGF23 action have not been studied during human pregnancy, and animal data are also lacking because these conditions are lethal before sexual maturity. Renal insufficiency or failure causes hyperphosphatemia, and both animal and human data indicate that such renal disorders increase the risks of gestational hypertension, pre-eclampsia, eclampsia, and maternal mortality. However, the extent to which the hyperphosphatemia contributes to these risks is unknown.

MINERAL PHYSIOLOGY DURING LACTATION AND POST-WEANING

As lactation begins the mother is faced with another demand for calcium in order to make milk. The average daily loss of calcium into breast milk is 210 mg, although daily losses as great as 1000 mg calcium have been reported is some women nursing twins (1). Although women meet the calcium demands of pregnancy by upregulating intestinal calcium absorption and serum concentrations of calcitriol, a different adaptation occurs during lactation. A temporary resorption and demineralization of the maternal skeleton appears to be the main mechanism by which breastfeeding women meet these calcium requirements. This adaptation does not appear to require PTH or calcitriol, but is regulated by the combined effects of increased circulating concentrations of PTHrP and low estradiol levels.

Mineral Ions

The albumin-corrected serum calcium and ionized calcium are both normal during lactation, but longitudinal studies have shown that both are increased slightly over the non-pregnant values. Serum phosphate levels are also higher and may exceed the normal range. Since reabsorption of phosphate by the kidneys appears 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.

Parathyroid Hormone

PTH, as measured by 2-site “intact” or newer “bio-intact” assays, may be undetectable or in the lower quarter of the normal range during the first several months of lactation in women from North America and Europe who consume adequate calcium. PTH rises to normal by the time of weaning, and in two case series was found to rise above normal post-weaning. In contrast, and similar to findings during pregnancy, PTH did not suppress in several studies of women from Asia and Gambia who consumed diets that were low in calcium or high in phytate. The low PTH concentrations are an indication that PTH isn’t required for mineral homeostasis during lactation, and this is confirmed by hypoparathyroid and aparathyroid women in whom mineral and skeletal homeostasis normalize while they continue to breastfeed (see Hypoparathyroidism, below). The same is true of mice that lack the gene for parathyroid hormone. They are hypocalcemic and hyperphosphatemic when non-pregnant, but maintain normal serum calcium and phosphate concentrations while lactating and for a time during post-weaning (17).

Vitamin D Metabolites

A common concern has been that the suckling neonate will deplete maternal 25OHD stores, but this is not the case. 25OHD should not decline because it does not enter breast milk; conversely, although vitamin D can enter milk, it is present at very low concentrations because appreciable amounts exist in the maternal circulation for only a short postprandial interval. In observational studies and in the placebo arms of several clinical trials, there was either no change or at most a nonsignificant decline in maternal 25OHD levels during lactation, even in severely vitamin D deficient women (4). Calcitriol levels were twice normal during pregnancy but both free and bound calcitriol levels fall to normal within days of parturition and remain there in breastfeeding women (a single study found that women breastfeeding twins had higher calcitriol concentrations than women nursing singletons) (161). Animal studies show that severely vitamin D deficient rodents and mice lacking the vitamin D receptor are able to lactate and provide normal milk (4,45), thereby indicating that vitamin D and calcitriol are not required for lactation to proceed normally (at least in rodents). However, a more recent study found that mice lacking calcitriol produced milk with a lower calcium content (23).

Calcitonin

Calcitonin levels fall to normal during the first six weeks postpartum in women. Mice lacking the gene that encodes calcitonin lose twice the normal amount of bone mineral content during lactation, which indicates that physiological levels of calcitonin may protect the maternal skeleton from excessive resorption during this time period (26). Whether calcitonin plays a similar role in human physiology is unknown. Totally thyroidectomized women are not calcitonin deficient during lactation due to

substantial production of calcitonin by the breasts, which in turn leads to systemic calcitonin concentrations that are the same as in women with intact thyroids (25). Consequently, study of totally thyroidectomized women is not the equivalent of studying a calcitonin-null state when they are breastfeeding.

PTHrP

Plasma PTHrP concentrations are significantly higher in lactating women than in non-pregnant controls. The source of PTHrP appears to be the breast, which secretes PTHrP into breast milk at concentrations that are 1,000 to 10,000 times the level found in the blood of patients with hypercalcemia of malignancy or in normal human controls. The circulating PTHrP concentration also increases after suckling (162,163). Additional evidence that the breasts are the source of PTHrP include that ablation of the PTHrP gene selectively from mammary tissue resulted in reduced circulating levels of PTHrP in lactating mice (164). PTHrP also has an intimate association with breast tissue: in animals it has been shown to regulate mammary development and blood flow, and the calcium and water content of milk in rodents, whereas in humans it is commonly expressed by breast cancers.

Furthermore, as described in more detail below, during lactation PTHrP reaches 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, deletion of the PTHrP gene from mammary tissue at the onset of lactation resulted in more modest losses of bone mineral content during lactation in mice (164). In humans, PTHrP correlates with the amount of bone mineral density lost, negatively with serum PTH, and positively with the ionized calcium of lactating women (162,165,166). Lastly, clinical observations in hypoparathyroid and aparathyroid women demonstrate the physiological importance of PTHrP to regulate calcium and skeletal homeostasis during lactation (see Hypoparathyroidism, below).

Prolactin

Prolactin is persistently elevated during early lactation and spikes further upward with suckling. Later during lactation basal prolactin levels are normal but continue to spike with suckling. Prolactin is important for initiating and maintaining milk production (167), but it also alters bone metabolism by stimulating PTHrP production in lactating mammary tissue, inhibiting GnRH and ovarian function, and possibly (as noted earlier) through direct actions in osteoblasts that express the prolactin receptor.

Oxytocin

Oxytocin induces milk ejection by contracting myoepithelial cells within mammary tissue. If milk is not ejected, the pressure of milk stasis causes apoptosis of mammary cells, and lactation ceases. Oxytocin spikes in the maternal circulation within 10 minutes after the start of suckling (168). As noted earlier, the oxytocin receptor is expressed in osteoblasts and osteoclasts. But whether oxytocin plays a role in bone metabolism during lactation has proven difficult to determine because oxytocin null mice cannot lactate due to the lack of milk ejection (169).

Estradiol

In lactating women, estradiol levels fall and this stimulates RANKL and inhibits osteoprotegerin production by osteoblasts, thereby stimulating osteoclast proliferation, function, and bone resorption. Studies in mice have shown that increasing the serum estradiol concentration to 7 times the virgin level blunts the magnitude of bone loss during lactation (170), which confirms that estradiol deficiency plays a role in the skeletal resorption that occurs during lactation.

FGF23

FGF23 levels during lactation have not been reported. It is possible that FGF23 increases to compensate for the increased serum phosphate and low PTH that occur during lactation, but it's also possible that FGF23 is low and contributing to the high serum phosphate.

Other Hormones

Serotonin appears to be involved in regulating PTHrP and its effect to resorb the maternal skeleton (171,172). Lactation induces changes in myriad other hormones, such as luteinizing and follicle stimulating hormone, progesterone, testosterone, inhibins, and activins. Whether these play roles in regulating skeletal metabolism during lactation has not been investigated.

Intestinal Absorption of Calcium and Phosphate

Although intestinal calcium absorption was upregulated during pregnancy, it quickly decreases post-partum to the non-pregnant rate. This also corresponds to the fall in calcitriol levels to normal. This differs from rodents which maintain increased intestinal calcium absorption during lactation; their large litters sizes mandate the need to provide some of the calcium for milk production through this route.

Intestinal phosphate absorption has not been measured during human lactation, whereas in rodents it remains increased.

Renal Handling of Calcium and Phosphate

Renal excretion of calcium is typically reduced to about 50 mg per 24 hours or lower, and the glomerular filtration rate is also decreased. These findings suggest that the tubular reabsorption of calcium must be increased to conserve calcium, perhaps through the actions of PTHrP.

Renal tubular phosphate reabsorption is increased during lactation. Despite this, urine phosphate excretion may be increased, likely due to the large efflux of phosphate from resorbed bone, which exceeds what is needed for milk production.

Skeletal Calcium Metabolism and Bone Density/Bone Marker Changes

Histomorphometric data from lactating animals have consistently shown increased bone turnover, and losses of 35% or more of bone mineral are achieved during 2-3 weeks of normal lactation in rodents [reviewed in (1)]. There are no histomorphometric data from lactating women; instead, biochemical markers of bone formation and resorption have been assessed in numerous cross-sectional and prospective studies. Confounding factors discussed earlier for pregnancy need to be considered when assessing bone turnover markers in lactating women; in particular, opposing changes from pregnancy

include that the glomerular filtration rate is reduced and the intravascular volume is now contracted. Serum and urinary (24-hr collection) markers of bone resorption are elevated 2-3 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. The most marked increase is in the bone resorption markers, suggesting that bone turnover becomes negatively uncoupled, with bone resorption markedly exceeding bone formation, and thereby causing net bone loss. Total alkaline phosphatase falls immediately postpartum due to loss of the placental fraction, but may still remain above normal due to elevation of the bone-specific fraction. Overall, these bone marker results are compatible with significant increased bone resorption occurring during lactation.

Serial measurements of aBMD during lactation (by SPA, DPA or DXA) have shown that bone mineral content falls 3 to 10.0% in women after two to six months of lactation at trabecular sites (lumbar spine, hip, femur and distal radius), with smaller losses at cortical sites and whole body (1,57). These aBMD changes are in accord with studies in rats, mice, and primates in which the skeletal resorption has been shown to occur largely at trabecular surfaces and to a lesser degree in cortical bone, and as much as 25-30% of bone mass or aBMD is lost during three weeks of lactation in normal rodents. The loss in women occurs at a peak rate of 1-3% *per month*, far exceeding the 1-3% per year that can occur in postmenopausal women who are considered to be losing bone rapidly. This bone resorption is an obligate consequence of lactation and cannot be prevented by increasing the calcium intake in women. Several randomized trials and other studies have shown that calcium supplementation does not significantly reduce the amount of bone lost during lactation (173-176). Not surprisingly, the lactational decrease in bone mineral density correlates with the amount of calcium lost in the breast milk (177).

The skeletal losses are due in part to the low estradiol levels during lactation which stimulate osteoclast number and activity. However, low estradiol is not the sole cause of the accelerated bone resorption or other changes in calcium homeostasis that occur during lactation. It is worth noting what happens to reproductive-age women who have marked estrogen deficiency induced by GnRH agonist therapy in order to treat endometriosis, fibroids, or severe acne. Six months of GnRH-induced estrogen deficiency caused 1-4% losses in trabecular (but not cortical) aBMD, increased urinary calcium excretion, and suppression of calcitriol and PTH (Figure 3) [reviewed in (1,8)]. In contrast, during lactation women are not as estrogen deficient but lose more aBMD (at both trabecular and cortical sites), have normal (as opposed to low) calcitriol levels, and have reduced (as opposed to increased) urinary calcium excretion (Figure 3). The difference between isolated GnRH-induced estrogen deficiency and lactation appears to be explained by PTHrP. It stimulates osteoclast-mediated bone resorption and stimulates renal calcium reabsorption; by so doing, it complements the effects of low estradiol during lactation. Stimulated in part by suckling and high prolactin levels, PTHrP and estrogen deficiency combine to cause marked skeletal resorption during lactation (Figure 4).

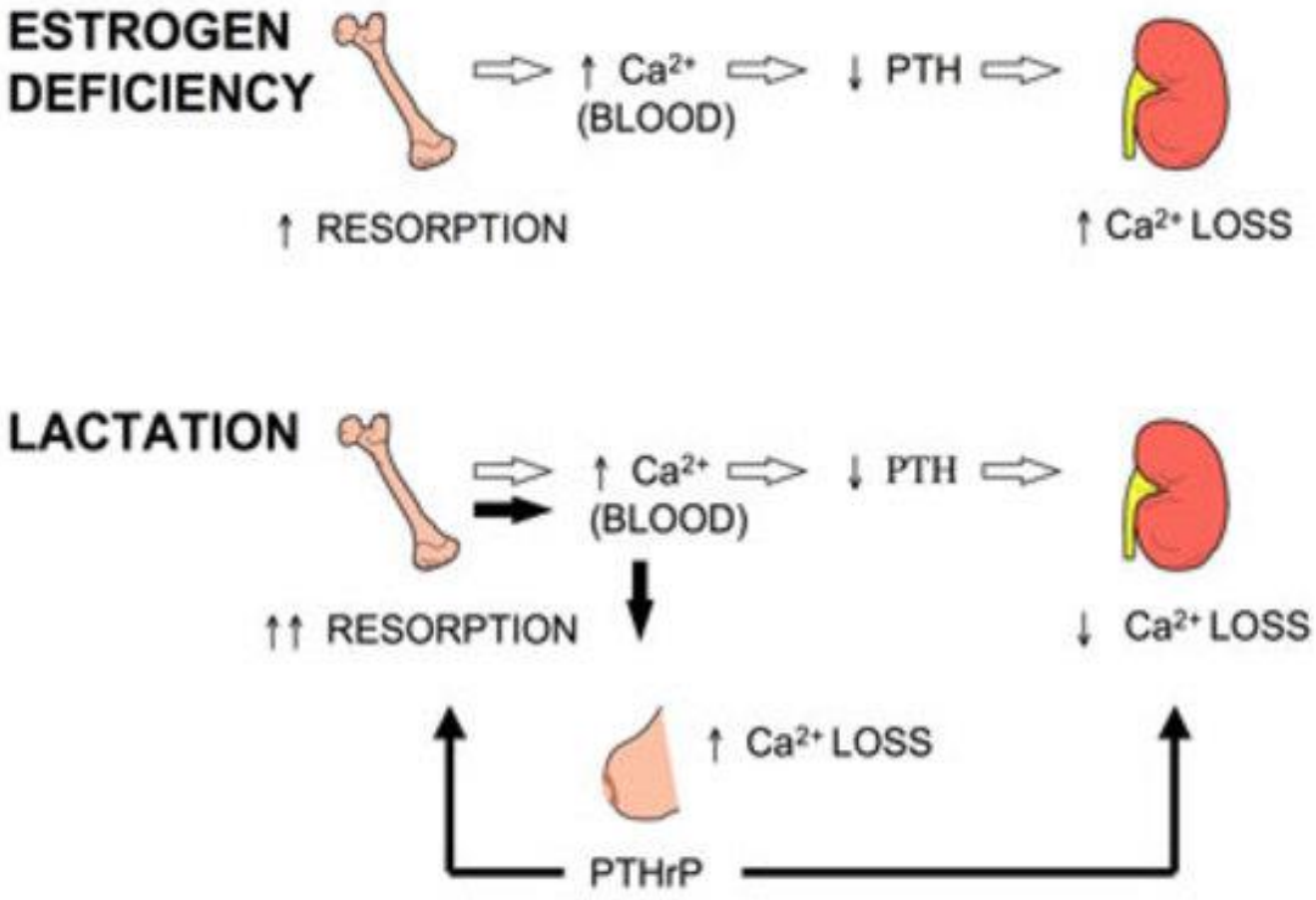

Figure 3. Comparison of the effects of acute estrogen deficiency vs. lactation on calcium and bone metabolism. Acute estrogen deficiency (e.g. GnRH analog therapy) increases skeletal resorption and raises the blood calcium; in turn, PTH is suppressed and renal calcium losses are increased. During lactation, 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. Reprinted from ref. (8), © 1997, The Endocrine Society.

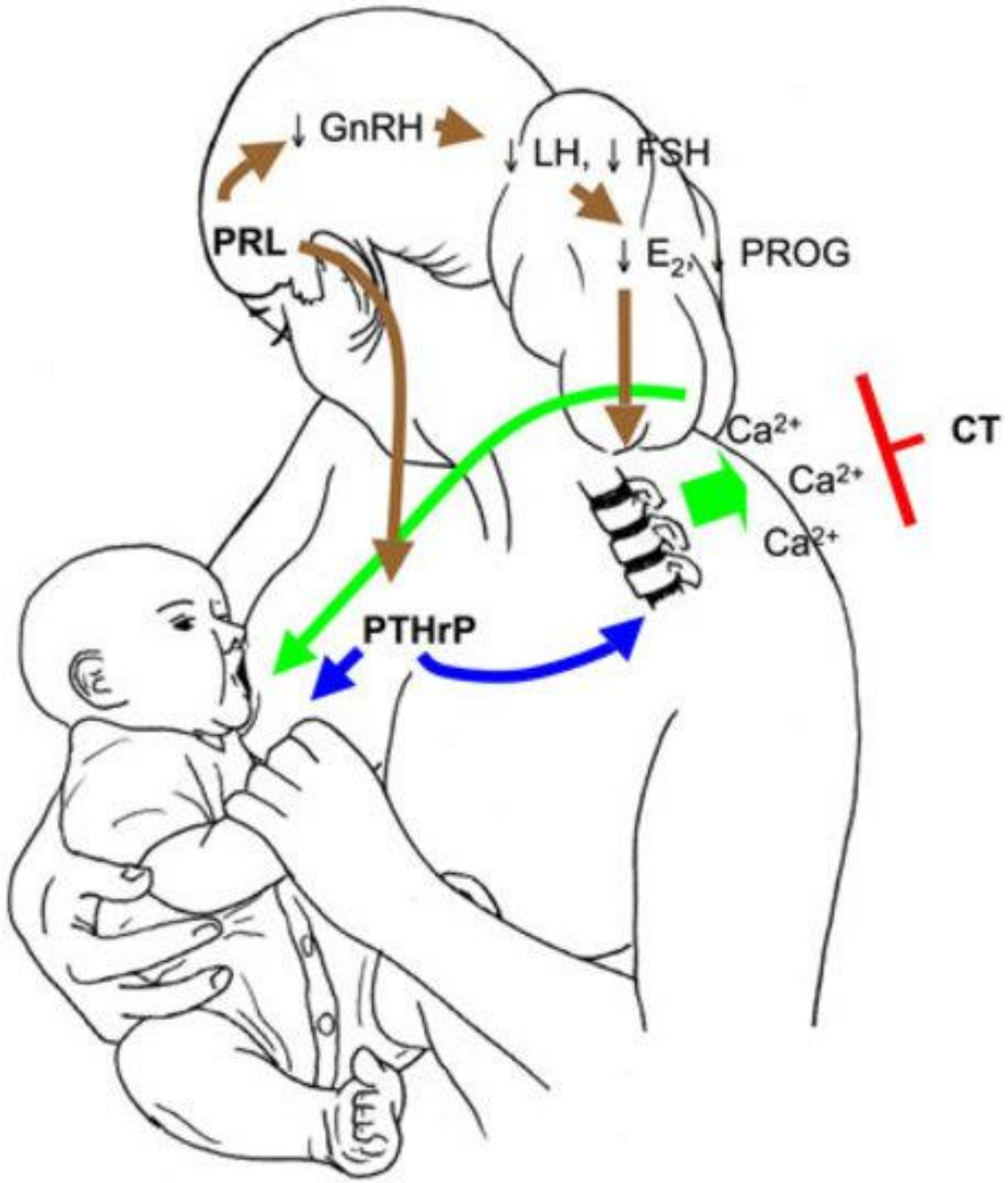

Figure 4. Brain-Breast-Bone Circuit. The breast is a central regulator of skeletal demineralization during lactation. Suckling and prolactin both inhibit the hypothalamic gonadotropin-releasing hormone (GnRH) pulse center, which in turn suppresses the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), leading to low levels of the ovarian sex steroids (estradiol and progesterone). PTHrP production and release from the breast is controlled by several factors, including suckling, prolactin, and the calcium receptor. PTHrP enters the bloodstream and combines with systemically low estradiol levels to markedly upregulate bone resorption. Increased bone resorption releases calcium and phosphate into the blood stream, which then reaches the breast ducts and is actively pumped into the breast milk.

PTHrP also passes into milk at high concentrations, but whether swallowed PTHrP plays a role in regulating calcium physiology of the neonate is unknown. Calcitonin (CT) may inhibit skeletal responsiveness to PTHrP and low estradiol. Not depicted are that direct effects of oxytocin and prolactin on bone cells are also possible. Adapted from ref. (26) © 2006, The Endocrine Society.

The mechanism through which the skeleton is resorbed has been shown in rodents to involve two processes, both osteoclast-mediated bone resorption (1) and osteocytic osteolysis, in which osteocytes function like osteoclasts to resorb the bone matrix that surrounds them (178). Both of these processes are dependent upon PTHrP. Conditional deletion of the PTHrP gene from mammary tissue reduced the amount of bone resorbed during lactation, whereas conditional deletion of the PTH/PTHrP receptor from osteocytes appeared to eliminate osteocytic osteolysis (179). Moreover, osteocyte-specific deletion of the PTH/PTHrP receptor resulted in a 50% blunting of the amount of BMD lost during lactation (179), which may indicate that osteocytic osteolysis and osteoclast-mediated bone resorption each contribute about half of the net bone loss achieved during lactation. To date no studies have examined whether osteocytic osteolysis occurs in lactating women.

The lactational bone density losses in women are substantially and completely reversed during six to twelve months following weaning (1,57,174). This corresponds to a gain in bone density of 0.5 to 2% per month in a woman who has weaned her infant. The mechanism for this restoration of bone density is unknown, but studies in mice have shown that it is not dependent upon calcitriol, calcitonin, PTH, or PTHrP (17,23,26,45,180,181); nor is it fully explained by restoration of estradiol levels to normal (1). The remarkable ability of the skeleton to recover is exemplified by mice lacking the gene that encodes calcitonin. They lose up to 55% of trabecular mineral content from the spine during lactation but completely restore it within 18 days after weaning (26).

Although aBMD appears to be completely restored after weaning in women and all animals that have been studied, more detailed examination of microarchitecture by μCT has shown variable completeness of recovery of microarchitecture by skeletal site. In rodents, the vertebrae recover completely while persistent loss of trabeculae is evident in the long bones (182). Studies in women have similarly shown that the trabecular content of the long bones also appears to be incompletely restored (1,57,174,183,184). However, in both women (74,184,185) and rodents (26,186,187) the cross-sectional diameters and volumes of the long bones may be significantly increased after post-weaning. Such structural changes potentially compensate for any reduction in strength that loss of trabecular microarchitecture might induce, because an increased cross-sectional diameter increases the ability of a hollow shaft to resist bending (cross-sectional moment of inertia) and torsional stress (polar moment of inertia). This is supported by the finding that the breaking strength of rodent bones returns to pre-pregnant values after weaning (1,180), and limited clinical studies that correlated the increased bone volumes achieved after reproductive cycles with increased bone strength (74,185). In women, the vast majority of several dozen 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 (1,7,54,57). In fact, multiple studies have suggested a protective effect of lactation on the future risk of low BMD or fragility fractures. Consequently, although lactational bone loss can transiently increase risk of fracture (see next section), it is likely unimportant in the long run for most women, in whom the skeleton is restored to its prior mineral content and strength.

DISORDERS OF CALCIUM AND BONE METABOLISM DURING LACTATION

Osteoporosis of Lactation

On occasion a woman will suffer one or more fragility fractures during lactation, and osteoporotic bone density will be found by DXA (76). As with osteoporosis presenting during pregnancy, this may represent a coincidental, unrelated disease; the woman may have had low bone density and abnormal skeletal microarchitecture prior to pregnancy. Alternatively, it is likely that some cases represent an exacerbation of the normal degree of skeletal demineralization that occurs during lactation, and a continuum from the changes in bone density and bone turnover that occurred during pregnancy. It may be somewhat artificial, therefore, to separate “osteoporosis of lactation” from “osteoporosis of pregnancy.” But since lactation normally causes a significant net loss of bone whereas pregnancy does not, it seems more likely for lactation to cause a subset of women to develop low-trauma fractures. For example, excessive PTHrP release from the lactating breast into the maternal circulation could conceivably cause excessive bone resorption, osteoporosis, and fractures. PTHrP levels were high in one case of lactational osteoporosis, and remained elevated for months after weaning (188).

The diagnostic and treatment considerations described above for osteoporosis of pregnancy also apply to women who are lactating (76).

Primary Hyperparathyroidism

When surgical correctional of primary hyperparathyroidism is not possible or advisable during pregnancy, it is normally carried out in the postpartum interval. A hypercalcemic crisis is possible soon after delivery due in part to loss of the placental calcium infusion, which represented a drain on the serum calcium. If a woman with untreated primary hyperparathyroidism chooses to breastfeed, the serum calcium should be monitored closely for significant worsening due to the effects of secretion of PTHrP from the breasts being added to the high concentrations of PTH already in the circulation. The potential impact of this is even more evident in women with hypoparathyroidism, as discussed below.

Familial Hypocalciuric Hypercalcemia

The calcium-sensing receptor is expressed in mammary epithelial ducts, and it modulates the production of PTHrP and calcium transport into milk during lactation in mice (189,190). Inactivating calcium-sensing receptor mutations increased mammary tissue production of PTHrP but decreased the calcium content of milk (190). These opposing changes meant that there was a further increase in bone resorption during lactation as compared to normal mice, and the serum calcium also became higher because of reduced output of calcium into milk. Conversely, a calcimimetic drug (similar to cinacalcet) caused increased milk calcium content (190). These data predict that women with FHH will have more marked skeletal resorption during lactation, lower milk calcium content, higher serum calcium, and a greater loss of BMD during lactation as compared to normal women. However, the effect of breastfeeding on mineral and skeletal homeostasis in women with FHH has not yet been described.

Hypoparathyroidism

As noted earlier, in the first day or two after parturition the requirement for supplemental calcium and calcitriol may transiently increase in hypoparathyroid women before secretion of PTHrP surges in the

breast tissue (114). The onset of lactation induces an important change in skeletal metabolism because the breasts produce PTHrP at high levels, some of which escapes into the maternal circulation to stimulate bone resorption and raise the serum calcium level. In women who lack parathyroid glands, the release of PTHrP into the circulation during lactation can temporarily restore calcium and bone homeostasis to normal. Levels of calcitriol and calcium supplementation required for treatment of hypoparathyroid women fall early and markedly after the onset of lactation, and hypercalcemia can occur if the calcitriol dosage and calcium intake are not substantially reduced (191-194). This decreased need for calcium and calcitriol occurs at a time when circulating PTHrP levels are high in the maternal circulation (191,194,195). As illustrated in one case, this is consistent with PTHrP reaching the maternal circulation in amounts sufficient to allow stimulation of calcitriol synthesis, and maintenance of normal (or slightly increased) maternal serum calcium (195).

Management of hypoparathyroidism during lactation requires monitoring the albumin-corrected calcium or ionized calcium, reducing or stopping the calcitriol and calcium as indicated, and planning to reinstitute both supplements in escalating doses as lactation wanes. However, production of PTHrP doesn't necessarily promptly cease around the time of weaning. The author is aware of a woman with hypoparathyroidism who required no supplemental calcium or calcitriol at all for about a year after her baby had been weaned. She thought that her hypoparathyroidism had been permanently cured by breastfeeding, until the abrupt recurrence of symptomatic hypocalcemia, and the need for pre-pregnancy doses of calcium and calcitriol, signaled the end of PTHrP production by her breasts. In another woman, lactation appeared to permanently cure her hypoparathyroidism (196), likely because of persistent production of PTHrP by her breasts.

Pseudohypoparathyroidism

The management of pseudohypoparathyroidism during lactation has been less well documented. Since these patients are likely resistant to the renal actions of PTHrP, and the placental sources of calcitriol are lost at parturition, the calcitriol requirements might well increase and may require further adjustments during lactation. Conversely, these patients do not have skeletal resistance to PTH, and so it is possible that calcium and calcitriol requirements may decrease secondary to enhanced skeletal resorption caused by the combined effects of high PTH levels, PTHrP release from the breast, and lactation-induced estrogen deficiency. Thus, women with pseudohypoparathyroidism might lose *more* bone density than normal during lactation, but this has not been studied.

Pseudohyperparathyroidism

Severe, PTHrP-mediated hypercalcemia during lactation was first noted to occur in women with large breasts, but it has also developed in women with average-sized breasts in whom milk let-down took place but the baby's illness prevented breastfeeding (120). This represents an exaggeration of normal lactational physiology, which benefits hypoparathyroid women, but in some normal women can overwhelm the normal regulatory pathways and cause potentially severe hypercalcemia. Cessation of lactation should reverse the condition, but a reduction mammoplasty or mastectomy has proved necessary for recalcitrant hypercalcemia.

Vitamin D Deficiency and Insufficiency, and Genetic Vitamin D Disorders

The available data from small clinical trials, observational studies and case reports indicate that lactation proceeds normally regardless of vitamin D status, and breast milk calcium content is unaffected by vitamin D deficiency or supplementation in doses as high as 6,400 IU per day given to the mother, and achieved maternal 25OHD blood levels of 168 nmol/L (topic reviewed in detail in (1,4,5,7,123)). This is likely because maternal calcium homeostasis is dominated by skeletal resorption induced by estrogen deficiency and PTHrP, with vitamin D/calcitriol playing no substantial role in lactational mineral homeostasis. It is the neonate who will suffer the consequences of being born of a vitamin D deficient mother. This is especially true if the infant is exclusively breast fed, since both vitamin D and 25-hyroxyvitamin D are normally present at very low concentrations in breast milk.

The high-dose (6,400 IU) vitamin D supplementation strategy raises the maternal vitamin D concentration substantially for hours and, in turn, this increases the penetration of vitamin D into milk. Consequently, breastfed babies whose mothers consumed 6,400 IU per day achieved the same 25OHD level as babies who received a 300 IU dose of vitamin D directly (197). The potential advantage of this approach is that all of the neonate's nutrition can then come from breast milk, rather than requiring that breastfed babies receive a vitamin D supplement. Further study is needed regarding the safety of this approach for the mothers and their babies.

A misconception about vitamin D and milk often arises because marketed forms of cow's and goat's milk contain approximately 100 IU of vitamin D per standard serving, but that is a synthetic vitamin D supplement which is added to the milk after the pasteurization stage. It is not put there by the cow or goat.

Given that vitamin D deficiency does not affect breast milk content in humans, it is likely that genetic absence of VDR or calcitriol also does not affect milk calcium, but this has not been studied.

Whether vitamin D deficiency impairs the ability of the maternal skeleton to recover post-weaning has not been examined in any clinical study. However, studies in mice lacking the vitamin D receptor or Cyp27b1 to synthesize calcitriol, indicate that these mice are able to fully remineralize their skeletons after lactation (23,45).

24-Hydroxylase Deficiency

Hereditary absence of Cyp24a1 reduces calcitriol catabolism, which can lead to very high calcitriol concentrations and marked maternal hypercalcemia during pregnancy. But calcitriol production falls to non-pregnant levels during normal lactation, and the same should be true in women with 24-hydroxylase deficiency. Consistent with this, in one affected woman who breastfed, calcitriol was normal and hypercalcemia was milder compared to pregnancy (145).

Low and High Calcium Intakes

The calcium content of milk appears to be largely derived from skeletal resorption during lactation, a process that cannot be suppressed in women by consuming greater amounts of calcium (however, it can be suppressed in rodents by high calcium intakes). It shouldn't be surprising, therefore, that low calcium intake does not impair breast milk quality, nor does it accentuate maternal bone loss (153). Even in women with very low calcium intakes, the same amount of mineral was lost during lactation from the skeleton as compared to women who had supplemented calcium intakes, and the breast milk

calcium content was unaffected by calcium intake or vitamin D status (198-200). Conversely, since randomized trials and cohort studies have shown that high calcium intakes do not affect the degree of skeletal demineralization that occurs during lactation (173-176), it is unlikely that increasing calcium supplementation well above normal would affect skeletal demineralization either.

There is a lingering concern that adolescent mothers with low calcium intakes may not achieve normal peak bone mass as a consequence of lactation-induced bone loss. In fact the adolescent skeleton appears to recover fully from lactation (201), and adolescent women who breastfed have higher BMD than those who did not breastfeed or had not been pregnant as adolescents (202). However, it remains reasonable to give a calcium supplement to adolescents who lactate in order to ensure that the needs of adolescent growth are met and that peak bone mass is achieved (153,201).

IMPLICATIONS

During pregnancy and lactation, novel regulatory systems specific to these settings complement the usual regulators of mineral homeostasis. Intestinal calcium absorption more than doubles from early in pregnancy in order to meet the fetal demand for calcium. In comparison, skeletal calcium resorption is a dominant mechanism by which calcium is supplied to the breast milk, while renal calcium conservation is also apparent. Calcium supplementation during pregnancy will result in a woman absorbing more calcium, but it is clear from clinical trials and observational studies that calcium supplements have little or no impact on the amount of bone lost during lactation.

The skeleton appears to recover promptly from lactation to achieve the pre-pregnancy bone mass through mechanisms that remain unclear. The transient loss of bone mass during lactation can at least temporarily compromise skeletal strength and lead to fragility fractures in some women. Furthermore, full recovery of mineral content and bone strength may not always be achieved after weaning. But the majority of women can be assured that the changes in calcium and bone metabolism during pregnancy and lactation are normal, healthy, temporary, and without adverse consequences in the long-term.

REFERENCES

1. Kovacs CS. Maternal Mineral and Bone Metabolism During Pregnancy, Lactation, and Post-Weaning Recovery. Physiol Rev 2016; 96:449-547
2. Wysolmerski JJ. Conversations between breast and bone: physiological bone loss during lactation as evolutionary template for osteolysis in breast cancer and pathological bone loss after menopause. BoneKEy 2007; 4:209-225
3. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. Endocrinol Metab Clin North Am 2011; 40:795-826
4. Kovacs CS. The Role of Vitamin D in Pregnancy and Lactation: Insights from Animal Models and Clinical Studies. Ann Rev Nutr 2012; 32:9.1-9.27
5. Kovacs CS. Bone Development and Mineral Homeostasis in the Fetus and Neonate: Roles of the Calciotropic and Phosphotropic Hormones. Physiol Rev 2014; 94:1143-1218
6. Kovacs CS. Physiology of calcium, phosphorus, and bone metabolism during pregnancy, lactation, and post-weaning. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology: Physiology, Pathophysiology, and Clinical Management. San Diego: Academic Press; 2019:in press.

7. Kovacs CS, Chakhtoura M, El-Hajj Fuleihan G. Disorders of mineral and bone metabolism during pregnancy and lactation. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology: Physiology, Pathophysiology, and Clinical Management. San Diego: Academic Press; 2019:in press.

8. Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. Endocr Rev 1997; 18:832-872

9. Haddad JG, Jr., Boisseau V, Avioli LV. Placental transfer of vitamin D_3 and 25-hydroxycholecalciferol in the rat. J Lab Clin Med 1971; 77:908-915

10. Hillman LS, Slatopolsky E, Haddad JG. Perinatal vitamin D metabolism. IV. Maternal and cord serum 24,25-dihydroxyvitamin D concentrations. J Clin Endocrinol Metab 1978; 47:1073-1077

11. Ardawi MS, Nasrat HA, HS BAA. Calcium-regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and postpartum: a longitudinal study. Eur J Endocrinol 1997; 137:402-409

12. Bikle DD, Gee E, Halloran B, Haddad JG. Free 1,25-dihydroxyvitamin D levels in serum from normal subjects, pregnant subjects, and subjects with liver disease. J Clin Invest 1984; 74:1966-1971

13. Zhang JY, Lucey AJ, Horgan R, Kenny LC, Kiely M. Impact of pregnancy on vitamin D status: a longitudinal study. Br J Nutr 2014; 112:1081-1087

14. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 2011; 26:2341-2357

15. Markestad T, Ulstein M, Aksnes L, Aarskog D. Serum concentrations of vitamin D metabolites in vitamin D supplemented pregnant women. A longitudinal study. Acta Obstet Gynecol Scand 1986; 65:63-67

16. Ritchie LD, Fung EB, Halloran BP, Turnlund JR, Van Loan MD, Cann CE, King JC. A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. Am J Clin Nutr 1998; 67:693-701

17. Kirby BJ, Ma Y, Martin HM, Buckle Favaro KL, Karaplis AC, Kovacs CS. Upregulation of calcitriol during pregnancy and skeletal recovery after lactation do not require parathyroid hormone. J Bone Miner Res 2013; 28:1987-2000

18. Cooke-Hubley S, Kirby BJ, Suppiah S, Simmonds CS, Karaplis AC, Kovacs CS. Circulating FGF23 is regulated by PTH and calcitriol during fetal development but low FGF23 does not significantly alter fetal phosphorus metabolism. IBMS BoneKEy 2013; 10:S95

19. Ma Y, Samaraweera M, Cooke-Hubley S, Kirby BJ, Karaplis AC, Lanske B, Kovacs CS. Neither absence nor excess of FGF23 disturbs murine fetal-placental phosphorus homeostasis or prenatal skeletal development and mineralization. Endocrinology 2014; 155:1596-1605

20. Fenton E, Britton HG. 25-hydroxycholecalciferol 1 alpha-hydroxylase activity in the kidney of the fetal, neonatal and adult guinea pig. Biol Neonate 1980; 37:254-256

21. Kubota M, Ohno J, Shiina Y, Suda T. Vitamin D metabolism in pregnant rabbits: differences between the maternal and fetal response to administration of large amounts of vitamin D_3. Endocrinology 1982; 110:1950-1956

22. Turner M, Barre PE, Benjamin A, Goltzman D, Gascon-Barre M. Does the maternal kidney contribute to the increased circulating 1,25-dihydroxyvitamin D concentrations during pregnancy? Miner Electrolyte Metab 1988; 14:246-252

23. Gillies BR, Ryan BA, Tonkin BA, Poulton IJ, Ma Y, Kirby BJ, St-Arnaud R, Sims NA, Kovacs CS. Absence of Calcitriol Causes Increased Lactational Bone Loss and Lower Milk Calcium but Does

Not Impair Post-lactation Bone Recovery in Cyp27b1 Null Mice. J Bone Miner Res 2018; 33:16-26

24. Ryan BA, Alhani K, Sellars KB, Kirby BJ, St-Arnaud R, Jones G, Kovacs CS. Mineral homeostasis in murine fetuses is sensitive to maternal calcitrio, but not to absence of fetal calcitriol. J Bone Miner Res 2018:in press

25. Bucht E, Telenius-Berg M, Lundell G, Sjoberg HE. Immunoextracted calcitonin in milk and plasma from totally thyroidectomized women. Evidence of monomeric calcitonin in plasma during pregnancy and lactation. Acta Endocrinol (Copenh) 1986; 113:529-535

26. Woodrow JP, Sharpe CJ, Fudge NJ, Hoff AO, Gagel RF, Kovacs CS. Calcitonin plays a critical role in regulating skeletal mineral metabolism during lactation. Endocrinology 2006; 147:4010-4021

27. Woodrow JP. Calcitonin modulates skeletal mineral loss during lactation through interactions in mammary tissue and directly though osteoclasts in bone [PhD thesis] [PhD]. St. John's, Newfoundland: Biomedical Sciences, Faculty of Medicine, Memorial University of Newfoundland; 2009.

28. Hutchesson AC, Hughes SV, Bowden SJ, Ratcliffe WA. In vitro stability of endogenous parathyroid hormone-related protein in blood and plasma. Ann Clin Biochem 1994; 31 (Pt 1):35-39

29. Horwitz MJ, Tedesco MB, Sereika SM, Hollis BW, Garcia-Ocana A, Stewart AF. Direct comparison of sustained infusion of human parathyroid hormone-related protein-(1-36). J Clin Endocrinol Metab 2003; 88:1603-1609

30. Horwitz MJ, Tedesco MB, Sereika SM, Syed MA, Garcia-Ocana A, Bisello A, Hollis BW, Rosen CJ, Wysolmerski JJ, Dann P, Gundberg C, Stewart AF. Continuous PTH and PTHrP infusion causes suppression of bone formation and discordant effects on 1,25(OH)2 vitamin D. J Bone Miner Res 2005; 20:1792-1803

31. Cornish J, Callon KE, Nicholson GC, Reid IR. Parathyroid hormone-related protein-(107-139) inhibits bone resorption in vivo. Endocrinology 1997; 138:1299-1304

32. Kovacs CS, Lanske B, Hunzelman JL, Guo J, Karaplis AC, Kronenberg HM. Parathyroid hormone-related peptide (PTHrP) regulates fetal-placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. Proc Natl Acad Sci U S A 1996; 93:15233-15238

33. Ohata Y, Arahori H, Namba N, Kitaoka T, Hirai H, Wada K, Nakayama M, Michigami T, Imura A, Nabeshima Y, Yamazaki Y, Ozono K. Circulating levels of soluble alpha-Klotho are markedly elevated in human umbilical cord blood. J Clin Endocrinol Metab 2011; 96:E943-947

34. Clement-Lacroix P, Ormandy C, Lepescheux L, Ammann P, Damotte D, Goffin V, Bouchard B, Amling M, Gaillard-Kelly M, Binart N, Baron R, Kelly PA. Osteoblasts are a new target for prolactin: analysis of bone formation in prolactin receptor knockout mice. Endocrinology 1999; 140:96-105

35. Suntornsaratoon P, Wongdee K, Goswami S, Krishnamra N, Charoenphandhu N. Bone modeling in bromocriptine-treated pregnant and lactating rats: possible osteoregulatory role of prolactin in lactation. Am J Physiol Endocrinol Metab 2010; 299:E426-436

36. Thiede MA. The mRNA encoding a parathyroid hormone-like peptide is produced in mammary tissue in response to elevations in serum prolactin. Mol Endocrinol 1989; 3:1443-1447

37. Ratcliffe WA, Thompson GE, Care AD, Peaker M. Production of parathyroid hormone-related protein by the mammary gland of the goat. J Endocrinol 1992; 133:87-93

38. Stiegler C, Leb G, Kleinert R, Warnkross H, Ramschak-Schwarzer S, Lipp R, Clarici G, Krejs GJ, Dobnig H. Plasma levels of parathyroid hormone-related peptide are elevated in hyperprolactinemia and correlated to bone density status. J Bone Miner Res 1995; 10:751-759

39. Dawood MY, Ylikorkala O, Trivedi D, Fuchs F. Oxytocin in maternal circulation and amniotic fluid during pregnancy. J Clin Endocrinol Metab 1979; 49:429-434

40. Colucci S, Colaianni G, Mori G, Grano M, Zallone A. Human osteoclasts express oxytocin receptor. Biochem Biophys Res Commun 2002; 297:442-445

41. Tamma R, Colaianni G, Zhu LL, DiBenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, Colucci S, Grano M, Faccio R, Liu X, Li J, Usmani S, Bachar M, Bab I, Nishimori K, Young LJ, Buettner C, Iqbal J, Sun L, Zaidi M, Zallone A. Oxytocin is an anabolic bone hormone. Proc Natl Acad Sci U S A 2009; 106:7149-7154

42. Liu X, Shimono K, Zhu LL, Li J, Peng Y, Imam A, Iqbal J, Moonga S, Colaianni G, Su C, Lu Z, Iwamoto M, Pacifici M, Zallone A, Sun L, Zaidi M. Oxytocin deficiency impairs maternal skeletal remodeling. Biochem Biophys Res Commun 2009; 388:161-166

43. Halloran BP, DeLuca HF. Calcium transport in small intestine during pregnancy and lactation. Am J Physiol 1980; 239:E64-E68

44. Brommage R, Baxter DC, Gierke LW. Vitamin D-independent intestinal calcium and phosphorus absorption during reproduction. Am J Physiol 1990; 259:G631-G638

45. Fudge NJ, Kovacs CS. Pregnancy up-regulates intestinal calcium absorption and skeletal mineralization independently of the vitamin D receptor. Endocrinology 2010; 151:886-895

46. Heaney RP, Skillman TG. Calcium metabolism in normal human pregnancy. J Clin Endocrinol Metab 1971; 33:661-670

47. Walker A, Fraile JJ, Hubbard JG. "Parathyroidectomy in pregnancy"-a single centre experience with review of evidence and proposal for treatment algorithim. Gland Surg 2014; 3:158-164

48. Morton A. Altered calcium homeostasis during pregnancy may affect biochemical differentiation of hypercalcaemia. Intern Med J 2004; 34:655-656; author reply 656-657

49. Pedersen EB, Johannesen P, Kristensen S, Rasmussen AB, Emmertsen K, Moller J, Lauritsen JG, Wohlert M. Calcium, parathyroid hormone and calcitonin in normal pregnancy and preeclampsia. Gynecol Obstet Invest 1984; 18:156-164

50. Frenkel Y, Barkai G, Mashiach S, Dolev E, Zimlichman R, Weiss M. Hypocalciuria of preeclampsia is independent of parathyroid hormone level. Obstet Gynecol 1991; 77:689-691

51. Seely EW, Wood RJ, Brown EM, Graves SW. Lower serum ionized calcium and abnormal calciotropic hormone levels in preeclampsia. J Clin Endocrinol Metab 1992; 74:1436-1440

52. Lalau JD, Jans I, el Esper N, Bouillon R, Fournier A. Calcium metabolism, plasma parathyroid hormone, and calcitriol in transient hypertension of pregnancy. Am J Hypertens 1993; 6:522-527

53. Purdie DW, Aaron JE, Selby PL. Bone histology and mineral homeostasis in human pregnancy. Br J Obstet Gynaecol 1988; 95:849-854

54. Kovacs CS, El-Hajj Fuleihan G. Calcium and bone disorders during pregnancy and lactation. Endocrinol Metab Clin N America 2006; 35:21-51

55. Moller UK, Við Streym S, Mosekilde L, Rejnmark L. Changes in bone mineral density and body composition during pregnancy and postpartum. A controlled cohort study. Osteoporos Int 2012; 23:1213-1223

56. To WW, Wong MW. Changes in bone mineral density of the os calcis as measured by quantitative ultrasound during pregnancy and 24 months after delivery. Aust N Z J Obstet Gynaecol 2011; 51:166-171

57. Sowers M. Pregnancy and lactation as risk factors for subsequent bone loss and osteoporosis. J Bone Miner Res 1996; 11:1052-1060

58. Kreiger N, Kelsey JL, Holford TR, O'Connor T. An epidemiologic study of hip fracture in postmenopausal women. Am J Epidemiol 1982; 116:141-148

59. Aloia JF, Vaswani AN, Yeh JK, Ross P, Ellis K, Cohn SH. Determinants of bone mass in postmenopausal women. Arch Intern Med 1983; 143:1700-1704
60. Aloia JF, Cohn SH, Vaswani A, Yeh JK, Yuen K, Ellis K. Risk factors for postmenopausal osteoporosis. Am J Med 1985; 78:95-100
61. Hreshchyshyn MM, Hopkins A, Zylstra S, Anbar M. Associations of parity, breast-feeding, and birth control pills with lumbar spine and femoral neck bone densities. Am J Obstet Gynecol 1988; 159:318-322
62. Dequeker J, Tobing L, Rutten V, Geusens P. Relative risk factors for osteoporotic fracture: a pilot study of the MEDOS questionnaire. Clin Rheumatol 1991; 10:49-53
63. Feldblum PJ, Zhang J, Rich LE, Fortney JA, Talmage RV. Lactation history and bone mineral density among perimenopausal women. Epidemiology 1992; 3:527-531
64. Cumming RG, Klineberg RJ. Breastfeeding and other reproductive factors and the risk of hip fractures in elderly women. Int J Epidemiol 1993; 22:684-691
65. Berning B, van Kuijk C, Schutte HE, Kuiper JW, Drogendijk AC, Fauser BC. Determinants of lumbar bone mineral density in normal weight, non-smoking women soon after menopause. A study using clinical data and quantitative computed tomography. Bone Miner 1993; 21:129-139
66. Cure CC, Ramirez PC, Lopez-Jaramillo P. Osteoporosis, pregnancy, and lactation. Lancet 1998; 352:1227-1228
67. Cure-Cure C, Cure-Ramirez P, Teran E, Lopez-Jaramillo P. Bone-mass peak in multiparity and reduced risk of bone-fractures in menopause. Int J Gynaecol Obstet 2002; 76:285-291
68. Bjornerem A, Ahmed LA, Jorgensen L, Stormer J, Joakimsen RM. Breastfeeding protects against hip fracture in postmenopausal women: the Tromso study. J Bone Miner Res 2011; 26:2843-2850
69. Chapman DJ. Longer cumulative breastfeeding duration associated with improved bone strength. Journal of human lactation : official journal of International Lactation Consultant Association 2012; 28:18-19
70. Canal-Macias ML, Roncero-Martin R, Moran JM, Lavado-Garcia JM, Costa-Fernandez Mdel C, Pedrera-Zamorano JD. Increased bone mineral density is associated with breastfeeding history in premenopausal Spanish women. Archives of medical science : AMS 2013; 9:703-708
71. Heidari B, Heidari P, Nourooddini HG, Hajian-Tilaki KO. Relationship between parity and bone mass in postmenopausal women according to number of parities and age. J Reprod Med 2013; 58:389-394
72. Schnatz PF, Marakovits KA, O'Sullivan DM. Assessment of postmenopausal women and significant risk factors for osteoporosis. Obstet Gynecol Surv 2010; 65:591-596
73. Schnatz PF, Barker KG, Marakovits KA, O'Sullivan DM. Effects of age at first pregnancy and breast-feeding on the development of postmenopausal osteoporosis. Menopause (New York, NY) 2010; 17:1161-1166
74. Specker B, Binkley T. High parity is associated with increased bone size and strength. Osteoporos Int 2005; 16:1969-1974
75. Crandall CJ, Liu J, Cauley J, Newcomb PA, Manson JE, Vitolins MZ, Jacobson LT, Rykman KK, Stefanick ML. Associations of Parity, Breastfeeding, and Fractures in the Women's Health Observational Study. Obstet Gynecol 2017; 130:171-180
76. Kovacs CS, Ralston SH. Presentation and management of osteoporosis presenting in association with pregnancy or lactation. Osteoporos Int 2015; 26:2223-2241
77. Dunne F, Walters B, Marshall T, Heath DA. Pregnancy associated osteoporosis. Clin Endocrinol (Oxf) 1993; 39:487-490
78. Phillips AJ, Ostlere SJ, Smith R. Pregnancy-associated osteoporosis: does the skeleton recover? Osteoporos Int 2000; 11:449-454

79. Khovidhunkit W, Epstein S. Osteoporosis in pregnancy. Osteoporos Int 1996; 6:345-354
80. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. Pregnancy-associated osteoporosis. Quarterly Journal of Medicine 1995; 88:865-878
81. Campos-Obando N, Oei L, Hoefsloot LH, Kiewiet RM, Klaver CC, Simon ME, Zillikens MC. Osteoporotic vertebral fractures during pregnancy: be aware of a potential underlying genetic cause. J Clin Endocrinol Metab 2014; 99:1107-1111
82. Cook FJ, Mumm S, Whyte MP, Wenkert D. Pregnancy-associated osteoporosis with a heterozygous deactivating LDL receptor-related protein 5 (LRP5) mutation and a homozygous methylenetetrahydrofolate reductase (MTHFR) polymorphism. J Bone Miner Res 2014; 29:922-928
83. Khastgir G, Studd JW, King H, Abdalla H, Jones J, Carter G, Alaghband-Zadeh J. Changes in bone density and biochemical markers of bone turnover in pregnancy-associated osteoporosis. Br J Obstet Gynaecol 1996; 103:716-718
84. Lakhanpal S, Ginsburg WW, Luthra HS, Hunder GG. Transient regional osteoporosis. A study of 56 cases and review of the literature. Ann Intern Med 1987; 106:444-450
85. Arayssi TK, Tawbi HA, Usta IM, Hourani MH. Calcitonin in the treatment of transient osteoporosis of the hip. Semin Arthritis Rheum 2003; 32:388-397
86. Curtiss PH, Jr., Kincaid WE. Transitory demineralization of the hip in pregnancy. A report of three cases. The Journal of bone and joint surgery American volume 1959; 41-A:1327-1333
87. Kort KC, Schiller HJ, Numann PJ. Hyperparathyroidism and pregnancy. Am J Surg 1999; 177:66-68
88. Kelly TR. Primary hyperparathyroidism during pregnancy. Surgery 1991; 110:1028-1033; discussion 1033-1034
89. Shangold MM, Dor N, Welt SI, Fleischman AR, Crenshaw MC, Jr. Hyperparathyroidism and pregnancy: a review. Obstet Gynecol Surv 1982; 37:217-228
90. Wagner G, Transhol L, Melchior JC. Hyperparathyroidism and pregnancy. Acta Endocrinol (Copenh) 1964; 47:549-564
91. Ludwig GD. Hyperparathyroidism in relation to pregnancy. N Engl J Med 1962; 267:637-642
92. Delmonico FL, Neer RM, Cosimi AB, Barnes AB, Russell PS. Hyperparathyroidism during pregnancy. Am J Surg 1976; 131:328-337
93. Bruce J, Strong JA. Maternal hyperparathyroidism and parathyroid deficiency in the child, with account of effect of parathyroidectomy on renal function, and of attempt to transplant part of tumor. Q J Med 1955; 24:307-319
94. Kristoffersson A, Dahlgren S, Lithner F, Jarhult J. Primary hyperparathyroidism in pregnancy. Surgery 1985; 97:326-330
95. Carella MJ, Gossain VV. Hyperparathyroidism and pregnancy: case report and review. J Gen Intern Med 1992; 7:448-453
96. Schnatz PF, Curry SL. Primary hyperparathyroidism in pregnancy: evidence-based management. Obstet Gynecol Surv 2002; 57:365-376
97. Matthias GS, Helliwell TR, Williams A. Postpartum hyperparathyroid crisis. Case report. Br J Obstet Gynaecol 1987; 94:807-810
98. Clark D, Seeds JW, Cefalo RC. Hyperparathyroid crisis and pregnancy. Am J Obstet Gynecol 1981; 140:840-842
99. Salem R, Taylor S. Hyperparathyroidism in pregnancy. Br J Surg 1979; 66:648-650
100. Nilsson IL, Adner N, Reihner E, Palme-Kilander C, Edstrom G, Degerblad M. Primary hyperparathyroidism in pregnancy: a diagnostic and therapeutic challenge. J Womens Health (Larchmt) 2010; 19:1117-1121

101. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis GG, Papaioannou NA, Tournis S. The use of bisphosphonates in women prior to or during pregnancy and lactation. Hormones (Athens, Greece) 2011; 10:280-291
102. Boyce RW, Varela A, Chouinard L, Bussiere JL, Chellman GJ, Ominsky MS, Pyrah IT. Infant cynomolgus monkeys exposed to denosumab in utero exhibit an osteoclast-poor osteopetrotic-like skeletal phenotype at birth and in the early postnatal period. Bone 2014; 64:314-325
103. Okamatsu N, Sakai N, Karakawa A, Kouyama N, Sato Y, Inagaki K, Kiuchi Y, Oguchi K, Negishi-Koga T, Takami M. Biological effects of anti-RANKL antibody administration in pregnant mice and their newborns. Biochem Biophys Res Commun 2017; 491:614-621
104. Rajala B, Abbasi RA, Hutchinson HT, Taylor T. Acute pancreatitis and primary hyperparathyroidism in pregnancy: treatment of hypercalcemia with magnesium sulfate. Obstet Gynecol 1987; 70:460-462
105. Dahan M, Chang RJ. Pancreatitis secondary to hyperparathyroidism during pregnancy. Obstet Gynecol 2001; 98:923-925
106. Horjus C, Groot I, Telting D, van Setten P, van Sorge A, Kovacs CS, Hermus A, de Boer H. Cinacalcet for hyperparathyroidism in pregnancy and puerperium. J Pediatr Endocrinol Metab 2009; 22:741-749
107. Gonzalo Garcia I, Robles Fradejas M, Martin Macias MLA, Biain Ciganda A, Bustinza Beaskoetxea Z, Ruiz Perez E, Fernandez Matia G, Martinez Guisasola J. Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report. J Obstet Gynaecol 2018; 38:132-134
108. Vera L, Oddo S, Di Iorgi N, Bentivoglio G, Giusti M. Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report and review of the literature. Journal of medical case reports 2016; 10:361
109. Nadarasa K, Bailey M, Chahal H, Raja O, Bhat R, Gayle C, Grossman AB, Druce MR. The use of cinacalcet in pregnancy to treat a complex case of parathyroid carcinoma. Endocrinol Diabetes Metab Case Rep 2014; 2014:140056
110. Kovacs CS, Ho-Pao CL, Hunzelman JL, Lanske B, Fox J, Seidman JG, Seidman CE, Kronenberg HM. Regulation of murine fetal-placental calcium metabolism by the calcium-sensing receptor. J Clin Invest 1998; 101:2812-2820
111. Brown EM, Pollak M, Seidman CE, Seidman JG, Chou YH, Riccardi D, Hebert SC. Calcium-ion-sensing cell-surface receptors. N Engl J Med 1995; 333:234-240
112. Powell BR, Buist NR. Late presenting, prolonged hypocalcemia in an infant of a woman with hypocalciuric hypercalcemia. Clin Pediatr (Phila) 1990; 29:241-243
113. Thomas BR, Bennett JD. Symptomatic hypocalcemia and hypoparathyroidism in two infants of mothers with hyperparathyroidism and familial benign hypercalcemia. J Perinatol 1995; 15:23-26
114. Sweeney LL, Malabanan AO, Rosen H. Decreased calcitriol requirement during pregnancy and lactation with a window of increased requirement immediately post partum. Endocr Pract 2010; 16:459-462
115. Breslau NA, Zerwekh JE. Relationship of estrogen and pregnancy to calcium homeostasis in pseudohypoparathyroidism. J Clin Endocrinol Metab 1986; 62:45-51
116. Glass EJ, Barr DG. Transient neonatal hyperparathyroidism secondary to maternal pseudohypoparathyroidism. Arch Dis Child 1981; 56:565-568
117. Vidailhet M, Monin P, Andre M, Suty Y, Marchal C, Vert P. [Neonatal hyperparathyroidism secondary to maternal hypoparathyroidism]. Arch Fr Pediatr 1980; 37:305-312

118. Khosla S, van Heerden JA, Gharib H, Jackson IT, Danks J, Hayman JA, Martin TJ. Parathyroid hormone-related protein and hypercalcemia secondary to massive mammary hyperplasia. N Engl J Med 1990; 322:1157
119. Jackson IT, Saleh J, van Heerden JA. Gigantic mammary hyperplasia in pregnancy associated with pseudohyperparathyroidism. Plastic and reconstructive surgery 1989; 84:806-810
120. Sato K. Hypercalcemia during pregnancy, puerperium, and lactation: review and a case report of hypercalcemic crisis after delivery due to excessive production of PTH-related protein (PTHrP) without malignancy (humoral hypercalcemia of pregnancy). Endocr J 2008; 55:959-966
121. Marx SJ, Zusman RM, Umiker WO. Benign breast dysplasia causing hypercalcemia. J Clin Endocrinol Metab 1977; 45:1049-1052
122. Eller-Vainicher C, Ossola MW, Beck-Peccoz P, Chiodini I. PTHrP-associated hypercalcemia of pregnancy resolved after delivery: a case report. Eur J Endocrinol 2012; 166:753-756
123. Kovacs CS, Ward LE. DIsorders of calcium, phosphorus, and bone metabolism during fetal and neonatal development. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology: Physiology, Pathophysiology, and Clinical Management. San Diego: Academic Press; 2019:in press.
124. Rosen CJ, Adams JS, Bikle D, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS. The Nonskeletal Effects of Vitamin D: an Endocrine Society Scientific Statement. Endocr Rev 2012; 33:456-492
125. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, Robinson VP, Winder SM. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. Br Med J 1980; 280:751-754
126. Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, Baqui AH. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. Nutrition journal 2013; 12:47
127. Wagner CL, McNeil R, Hamilton SA, Winkler J, Rodriguez Cook C, Warner G, Bivens B, Davis DJ, Smith PG, Murphy M, Shary JR, Hollis BW. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. Am J Obstet Gynecol 2013; 208:137.e131-113
128. Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. J Clin Endocrinol Metab 2013; 98:2337-2346
129. Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, Wall C, Mitchell EA, Crengle S, Trenholme A, Crane J, Camargo CA, Jr. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. Pediatrics 2014; 133:e143-153
130. Vaziri F, Dabbaghmanesh MH, Samsami A, Nasiri S, Shirazi PT. Vitamin D supplementation during pregnancy on infant anthropometric measurements and bone mass of mother-infant pairs: A randomized placebo clinical trial. Early Hum Dev 2016; 103:61-68
131. Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, Fraser R, Gandhi SV, Carr A, D'Angelo S, Crozier SR, Moon RJ, Arden NK, Dennison EM, Godfrey KM, Inskip HM, Prentice A, Mughal MZ, Eastell R, Reid DM, Javaid MK, Group MS. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. The Lancet Diabetes & Endocrinology 2016; 4:393-402
132. Roth DE, Morris SK, Zlotkin S, Gernand AD, Ahmed T, Shanta SS, Papp E, Korsiak J, Shi J, Islam MM, Jahan I, Keya FK, Willan AR, Weksberg R, Mohsin M, Rahman QS, Shah PS, Murphy

KE, Stimec J, Pell LG, Qamar H, Al Mahmud A. Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth. N Engl J Med 2018; 379:535-546

133. Kovacs CS, Ward LE. Physiology of calcium, phosphorus, and bone metabolism during fetal and neonatal development. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology: Physiology, Pathophysiology, and Clinical Management. San Diego: Academic Press; 2019:in press.

134. Kovacs CS. Analysis of the MAVIDOS trial. The Lancet Diabetes & Endocrinology 2017; 5:328

135. Khaing W, Vallibhakara SA, Tantrakul V, Vallibhakara O, Rattanasiri S, McEvoy M, Attia J, Thakkinstian A. Calcium and Vitamin D Supplementation for Prevention of Preeclampsia: A Systematic Review and Network Meta-Analysis. Nutrients 2017; 9

136. De-Regil LM, Palacios C, Lombardo LK, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev 2016; 1:Cd008873

137. Hypponen E, Cavadino A, Williams D, Fraser A, Vereczkey A, Fraser WD, Banhidy F, Lawlor D, Czeizel AE. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. Annals of nutrition & metabolism 2013; 63:331-340

138. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatric and perinatal epidemiology 2012; 26 Suppl 1:75-90

139. Roth DE, Leung M, Mesfin E, Qamar H, Watterworth J, Papp E. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. Bmj 2017; 359:j5237

140. Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, Cole Z, Tinati T, Godfrey K, Dennison E, Bishop NJ, Baird J, Cooper C. Vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess 2014; 18:1-190

141. Edouard T, Alos N, Chabot G, Roughley P, Glorieux FH, Rauch F. Short- and long-term outcome of patients with pseudo-vitamin D deficiency rickets treated with calcitriol. J Clin Endocrinol Metab 2011; 96:82-89

142. Marx SJ, Swart EG, Jr., Hamstra AJ, DeLuca HF. Normal intrauterine development of the fetus of a woman receiving extraordinarily high doses of 1,25-dihydroxyvitamin D3. J Clin Endocrinol Metab 1980; 51:1138-1142

143. Malloy PJ, Tiosano D, Feldman D. Hereditary 1,25-Dihydroxyvitamin-D-Resistant Rickets. In: Feldman D, Pike JW, Adams JS, eds. Vitamin D, Third Edition. San Diego, CA: Academic Press; 2011:1197-1232.

144. Carpenter TO. CYP24A1 loss of function: Clinical phenotype of monoallelic and biallelic mutations. J Steroid Biochem Mol Biol 2017; 173:337-340

145. Shah AD, Hsiao EC, O'Donnell B, Salmeen K, Nussbaum R, Krebs M, Baumgartner-Parzer S, Kaufmann M, Jones G, Bikle DD, Wang Y, Mathew AS, Shoback D, Block-Kurbisch I. Maternal Hypercalcemia Due to Failure of 1,25-Dihydroxyvitamin-D3 Catabolism in a Patient With CYP24A1 Mutations. J Clin Endocrinol Metab 2015; 100:2832-2836

146. Dinour D, Davidovits M, Aviner S, Ganon L, Michael L, Modan-Moses D, Vered I, Bibi H, Frishberg Y, Holtzman EJ. Maternal and infantile hypercalcemia caused by vitamin-D-hydroxylase mutations and vitamin D intake. Pediatr Nephrol 2015; 30:145-152

147. Woods GN, Saitman A, Gao H, Clarke NJ, Fitzgerald RL, Chi NW. A Young Woman With Recurrent Gestational Hypercalcemia and Acute Pancreatitis Caused by CYP24A1 Deficiency. J Bone Miner Res 2016; 31:1841-1844

148. Kwong WT, Fehmi SM. Hypercalcemic Pancreatitis Triggered by Pregnancy With a CYP24A1 Mutation. Pancreas 2016; 45:e31-32

149. Prentice A. Micronutrients and the bone mineral content of the mother, fetus and newborn. J Nutr 2003; 133:1693S-1699S
150. Prentice A. Pregnancy and lactation. In: Glorieux FH, Petifor JM, Jüppner H, eds. Pediatric bone: biology & diseases. New York: Academic Press; 2003:249-269.
151. Janakiraman V, Ettinger A, Mercado-Garcia A, Hu H, Hernandez-Avila M. Calcium supplements and bone resorption in pregnancy: a randomized crossover trial. Am J Prev Med 2003; 24:260-264
152. Koo WW, Walters JC, Esterlitz J, Levine RJ, Bush AJ, Sibai B. Maternal calcium supplementation and fetal bone mineralization. Obstet Gynecol 1999; 94:577-582
153. Prentice A. Calcium in pregnancy and lactation. Annu Rev Nutr 2000; 20:249-272
154. Hofmeyr GJ, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2006; 3:CD001059
155. Kumar A, Devi SG, Batra S, Singh C, Shukla DK. Calcium supplementation for the prevention of pre-eclampsia. Int J Gynaecol Obstet 2009; 104:32-36
156. Hiller JE, Crowther CA, Moore VA, Willson K, Robinson JS. Calcium supplementation in pregnancy and its impact on blood pressure in children and women: follow up of a randomised controlled trial. Aust N Z J Obstet Gynaecol 2007; 47:115-121
157. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, Purwar M, Hofmeyr J, Nguyen TN, Campodonico L, Landoulsi S, Carroli G, Lindheimer M. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol 2006; 194:639-649
158. Ohata Y, Yamazaki M, Kawai M, Tsugawa N, Tachikawa K, Koinuma T, Miyagawa K, Kimoto A, Nakayama M, Namba N, Yamamoto H, Okano T, Ozono K, Michigami T. Elevated fibroblast growth factor 23 exerts its effects on placenta and regulates vitamin d metabolism in pregnancy of hyp mice. J Bone Miner Res 2014; 29:1627-1638
159. Jonas AJ, Dominguez B. Low breast milk phosphorus concentration in familial hypophosphatemia. J Pediatr Gastroenterol Nutr 1989; 8:541-543
160. Reade TM, Scriver CR. Hypophosphatemic rickets and breast milk. N Engl J Med 1979; 300:1397
161. Greer FR, Lane J, Ho M. Elevated serum parathyroid hormone, calcitonin, and 1,25-dihydroxyvitamin D in lactating women nursing twins. Am J Clin Nutr 1984; 40:562-568
162. Dobnig H, Kainer F, Stepan V, Winter R, Lipp R, Schaffer M, Kahr A, Nocnik S, Patterer G, Leb G. Elevated parathyroid hormone-related peptide levels after human gestation: relationship to changes in bone and mineral metabolism. J Clin Endocrinol Metab 1995; 80:3699-3707
163. Yamamoto M, Duong LT, Fisher JE, Thiede MA, Caulfield MP, Rosenblatt M. Suckling-mediated increases in urinary phosphate and 3',5'-cyclic adenosine monophosphate excretion in lactating rats: possible systemic effects of parathyroid hormone-related protein. Endocrinology 1991; 129:2614-2622
164. VanHouten JN, Dann P, Stewart AF, Watson CJ, Pollak M, Karaplis AC, Wysolmerski JJ. Mammary-specific deletion of parathyroid hormone-related protein preserves bone mass during lactation. J Clin Invest 2003; 112:1429-1436
165. Kovacs CS, Chik CL. Hyperprolactinemia caused by lactation and pituitary adenomas is associated with altered serum calcium, phosphate, parathyroid hormone (PTH), and PTH-related peptide levels. J Clin Endocrinol Metab 1995; 80:3036-3042
166. Sowers MF, Hollis BW, Shapiro B, Randolph J, Janney CA, Zhang D, Schork A, Crutchfield M, Stanczyk F, Russell-Aulet M. Elevated parathyroid hormone-related peptide associated with lactation and bone density loss. JAMA 1996; 276:549-554

167. Kelly PA, Bachelot A, Kedzia C, Hennighausen L, Ormandy CJ, Kopchick JJ, Binart N. The role of prolactin and growth hormone in mammary gland development. Mol Cell Endocrinol 2002; 197:127-131
168. Dawood MY, Khan-Dawood FS, Wahi RS, Fuchs F. Oxytocin release and plasma anterior pituitary and gonadal hormones in women during lactation. J Clin Endocrinol Metab 1981; 52:678-683
169. Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, Matzuk MM. Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. Proc Natl Acad Sci U S A 1996; 93:11699-11704
170. VanHouten JN, Wysolmerski JJ. Low estrogen and high parathyroid hormone-related peptide levels contribute to accelerated bone resorption and bone loss in lactating mice. Endocrinology 2003; 144:5521-5529
171. Hernandez LL, Gregerson KA, Horseman ND. Mammary gland serotonin regulates parathyroid hormone-related protein and other bone-related signals. Am J Physiol Endocrinol Metab 2012; 302:E1009-1015
172. Horseman ND, Hernandez LL. New concepts of breast cell communication to bone. Trends Endocrinol Metab 2014; 25:34-41
173. Kolthoff N, Eiken P, Kristensen B, Nielsen SP. Bone mineral changes during pregnancy and lactation: a longitudinal cohort study. Clin Sci (Lond) 1998; 94:405-412
174. Polatti F, Capuzzo E, Viazzo F, Colleoni R, Klersy C. Bone mineral changes during and after lactation. Obstet Gynecol 1999; 94:52-56
175. Kalkwarf HJ, Specker BL, Bianchi DC, Ranz J, Ho M. The effect of calcium supplementation on bone density during lactation and after weaning. N Engl J Med 1997; 337:523-528
176. Cross NA, Hillman LS, Allen SH, Krause GF. Changes in bone mineral density and markers of bone remodeling during lactation and postweaning in women consuming high amounts of calcium. J Bone Miner Res 1995; 10:1312-1320
177. Laskey MA, Prentice A, Hanratty LA, Jarjou LM, Dibba B, Beavan SR, Cole TJ. Bone changes after 3 mo of lactation: influence of calcium intake, breast-milk output, and vitamin D-receptor genotype. Am J Clin Nutr 1998; 67:685-692
178. Teti A, Zallone A. Do osteocytes contribute to bone mineral homeostasis? Osteocytic osteolysis revisited. Bone 2009; 44:11-16
179. Qing H, Ardeshirpour L, Pajevic PD, Dusevich V, Jahn K, Kato S, Wysolmerski J, Bonewald LF. Demonstration of osteocytic perilacunar/canalicular remodeling in mice during lactation. J Bone Miner Res 2012; 27:1018-1029
180. Kirby BJ, Ardeshirpour L, Woodrow JP, Wysolmerski JJ, Sims NA, Karaplis AC, Kovacs CS. Skeletal recovery after weaning does not require PTHrP. J Bone Miner Res 2011; 26:1242-1251
181. Collins JN, Kirby BJ, Woodrow JP, Gagel RF, Rosen CJ, Sims NA, Kovacs CS. Lactating Ctcgrp nulls lose twice the normal bone mineral content due to fewer osteoblasts and more osteoclasts, whereas bone mass is fully restored after weaning in association with up-regulation of Wnt signaling and other novel genes. Endocrinology 2013; 154:1400-1413
182. Liu XS, Ardeshirpour L, VanHouten JN, Shane E, Wysolmerski JJ. Site-specific changes in bone microarchitecture, mineralization, and stiffness during lactation and after weaning in mice. J Bone Miner Res 2012; 27:865-875
183. Bjornerem A, Ghasem-Zadeh A, Wang X, Bui M, Walker SP, Zebaze R, Seeman E. Irreversible Deterioration of Cortical and Trabecular Microstructure Associated With Breastfeeding. J Bone Miner Res 2017; 32:681-687

184. Brembeck P, Lorentzon M, Ohlsson C, Winkvist A, Augustin H. Changes in cortical volumetric bone mineral density and thickness, and trabecular thickness in lactating women postpartum. J Clin Endocrinol Metab 2015; 100:535-543
185. Wiklund PK, Xu L, Wang Q, Mikkola T, Lyytikainen A, Volgyi E, Munukka E, Cheng SM, Alen M, Keinanen-Kiukaanniemi S, Cheng S. Lactation is associated with greater maternal bone size and bone strength later in life. Osteoporos Int 2012; 23:1939-1945
186. Bowman BM, Miller SC. Skeletal adaptations during mammalian reproduction. J Musculoskelet Neuronal Interact 2001; 1:347-355
187. Vajda EG, Bowman BM, Miller SC. Cancellous and cortical bone mechanical properties and tissue dynamics during pregnancy, lactation, and postlactation in the rat. Biol Reprod 2001; 65:689-695
188. Reid IR, Wattie DJ, Evans MC, Budayr AA. Post-pregnancy osteoporosis associated with hypercalcaemia. Clin Endocrinol (Oxf) 1992; 37:298-303
189. VanHouten J, Dann P, McGeoch G, Brown EM, Krapcho K, Neville M, Wysolmerski JJ. The calcium-sensing receptor regulates mammary gland parathyroid hormone-related protein production and calcium transport. J Clin Invest 2004; 113:598-608
190. Ardeshirpour L, Dann P, Pollak M, Wysolmerski J, VanHouten J. The calcium-sensing receptor regulates PTHrP production and calcium transport in the lactating mammary gland. Bone 2006; 38:787-793
191. Caplan RH, Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. Obstet Gynecol 1990; 76:485-489
192. Salle BL, Berthezene F, Glorieux FH, Delvin EE, Berland M, David L, Varenne JP, Putet G. Hypoparathyroidism during pregnancy: treatment with calcitriol. J Clin Endocrinol Metab 1981; 52:810-813
193. Sadeghi-Nejad A, Wolfsdorf JI, Senior B. Hypoparathyroidism and pregnancy. Treatment with calcitriol. JAMA 1980; 243:254-255
194. Shomali ME, Ross DS. Hypercalcemia in a woman with hypoparathyroidism associated with increased parathyroid hormone-related protein during lactation. Endocr Pract 1999; 5:198-200
195. Mather KJ, Chik CL, Corenblum B. Maintenance of serum calcium by parathyroid hormone-related peptide during lactation in a hypoparathyroid patient. J Clin Endocrinol Metab 1999; 84:424-427
196. Rideout KL. When endocrine disorders disrupt pregnancy: perspectives of affected mothers. In: Kovacs CS, Deal CL, eds. Maternal-Fetal and Neonatal Endocrinology: Physiology, Pathophysiology, and Clinical Management. San Diego: Academic Press; 2019:in press.
197. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med 2006; 1:59-70
198. Prentice A, Jarjou LM, Cole TJ, Stirling DM, Dibba B, Fairweather-Tait S. Calcium requirements of lactating Gambian mothers: effects of a calcium supplement on breast-milk calcium concentration, maternal bone mineral content, and urinary calcium excretion. Am J Clin Nutr 1995; 62:58-67
199. Prentice A, Jarjou LM, Stirling DM, Buffenstein R, Fairweather-Tait S. Biochemical markers of calcium and bone metabolism during 18 months of lactation in Gambian women accustomed to a low calcium intake and in those consuming a calcium supplement. J Clin Endocrinol Metab 1998; 83:1059-1066

200. Prentice A, Yan L, Jarjou LM, Dibba B, Laskey MA, Stirling DM, Fairweather-Tait S. Vitamin D status does not influence the breast-milk calcium concentration of lactating mothers accustomed to a low calcium intake. Acta Paediatr 1997; 86:1006-1008

201. Bezerra FF, Mendonca LM, Lobato EC, O'Brien KO, Donangelo CM. Bone mass is recovered from lactation to postweaning in adolescent mothers with low calcium intakes. Am J Clin Nutr 2004; 80:1322-1326

202. Chantry CJ, Auinger P, Byrd RS. Lactation among adolescent mothers and subsequent bone mineral density. Arch Pediatr Adolesc Med 2004; 158:650-656