Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies[1–4]

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ABSTRACT

During pregnancy and lactation, mothers require significant amounts of calcium to pass on to the developing fetus and suckling neonate, respectively. Given the dependence of adult calcium concentrations and bone metabolism on vitamin D, one might anticipate that vitamin D sufficiency would be even more critical during pregnancy and lactation. However, maternal adaptations during pregnancy and lactation and fetal adaptations provide the necessary calcium relatively independently of vitamin D status. It is the vitamin D–deficient or insufficient neonate who is at risk of problems, including hypocalcemia and rickets. Due to poor penetrance of vitamin D and 25-hydroxyvitamin D [25(OH)D] into milk, exclusively breastfed infants are at higher risk of vitamin D deficiency than are formula-fed infants. Dosing recommendations for women during pregnancy and lactation might be best directed toward ensuring that the neonate is vitamin D–sufficient and that this sufficiency is maintained during infancy and beyond. A dose of vitamin D that provides 25(OH)D sufficiency in the mother during pregnancy should provide normal cord blood concentrations of 25(OH)D. Research has shown that during lactation, supplements administered directly to the infant can easily achieve vitamin D sufficiency; the mother needs much higher doses (100 μg or 4000 IU per day) to achieve adult-normal 25(OH)D concentrations in her exclusively breastfed infant. In addition, the relation (if any) of vitamin D insufficiency in the fetus or neonate to long-term nonskeletal outcomes such as type 1 diabetes and other chronic diseases needs to be investigated. *Am J Clin Nutr* 2008;88(suppl):520S–8S.

INTRODUCTION

Calcium and bone metabolism in adults depend heavily on concentrations of vitamin D and its active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Without 1,25$(OH)_2$D, the body cannot absorb calcium and phosphorus adequately, secondary hyperparathyroidism supervenes, the skeleton loses mineral content (secondary osteoporosis), and new bone is not adequately mineralized (rickets or osteomalacia) (1). Hypocalcemia can occur, but secondary hyperparathyroidism supports blood calcium through skeletal resorption.

During pregnancy and lactation, mothers provide large amounts of calcium to the developing fetus and suckling neonate, respectively (2, 3). Given that adult calcium and bone metabolism depend on vitamin D sufficiency, vitamin D sufficiency would seem to be especially critical during pregnancy and lactation. However, as this review shows, maternal adaptations during pregnancy, lactation, and fetal development provide the necessary calcium relatively independently of vitamin D. It is only after birth that dependency on vitamin D becomes evident, at least with respect to calcium metabolism and skeletal health.

Due to the relative paucity of data obtained during human pregnancy and lactation, this review includes discussions of animal data on vitamin D's role in mammalian calcium metabolism. Studies in humans should confirm all pertinent findings from animal models, but this might never be possible for certain aspects of pregnancy and fetal development.

To avoid an unduly lengthy reference list, I direct the reader to a 1997 comprehensive review by Kovacs and Kronenberg (2), with >550 primary references on the issues discussed here, and several recent reviews that cite studies published since 1997 (3–8).

ADAPTATIONS DURING PREGNANCY

During gestation, the human fetus accretes 30 g Ca on average, of which 99% is contained within the skeleton. More than 150 mg/kg of this calcium is actively transferred each day across the placenta during the third trimester.

Serum calcium concentrations (which include ionized, protein-bound, and complexed fractions) fall early in pregnancy as a result of the drop in serum albumin. This artifact of pregnancy's hemodilution is physiologically unimportant and is not evidence of true hypocalcemia. Ionized calcium concentrations, the physiologically important fraction, do not change during pregnancy. Parathyroid hormone (PTH), as measured by "intact" assays, falls to the lower end of the normal range and can become undetectable in North American and European women (no studies have used the newer "bio-intact" PTH assays). In contrast, studies of women from Gambia, Asia, and other areas where calcium and vitamin D intake are low have found that PTH concentrations do not drop during pregnancy. Levels of other hormones with potential calcium-regulating effects—including estradiol, prolactin, placental lactogen, and the calcium-regulating hormone parathyroid hormone-related protein (PTHrP)—increase during pregnancy.

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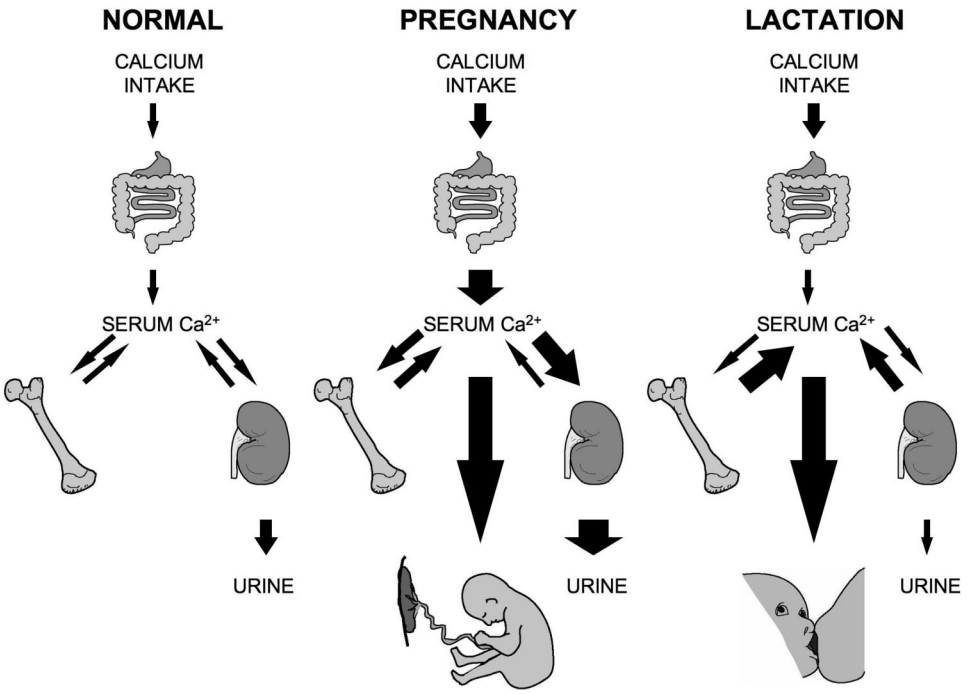

FIGURE 1. Schematic illustration contrasting calcium homeostasis in human pregnancy and lactation compared with normal. Arrow thickness indicates a relative increase or decrease with respect to the normal, nonpregnant state. Adapted from reference 2, copyright 1997, The Endocrine Society.

The pregnancy-induced adaptations to maternal calcium homeostasis are illustrated in **Figure 1**. Doubling the rate or efficiency of intestinal calcium absorption starting early in pregnancy appears to meet the fetal need for calcium. Skeletal resorption can also provide mineral to the circulation, but evidence is mixed on whether the maternal skeleton contributes substantial amounts of calcium to the fetus. Bone resorption markers are modestly increased during pregnancy (less than during lactation), and bone biopsies from women at the time of first-trimester abortions show histomorphometric evidence of increased bone resorption. Older, longitudinal studies of bone mineral density (BMD) during pregnancy (using single and dual-photon absorptiometry) showed no change in BMD. Studies using the more modern dual-energy X-ray absorptiometry 3–9 mo before planned pregnancies and 1–6 wk after delivery showed no change or a 1–4% decrease in BMD at the spine or hip between the first and second measurements. Serial ultrasound measurements at the heel have shown apparent BMD loss during pregnancy, but such peripheral measurements might have little relevance to the clinically and physiologically important content of the spine and hip. The maternal kidneys do not reclaim calcium avidly during pregnancy; instead, urinary calcium excretion increases in parallel with the increase in intestinal calcium absorption.

Rats and mice have a much shorter gestation period (22 and 19 d, respectively) and transfer 95% of their calcium to 8–12 fetuses per litter during the last 4–5 d of gestation. Ionized calcium levels are stable until late pregnancy, when they can drop during the rapid calcium transfer to the fetus. PTH is suppressed early in pregnancy but can increase in late pregnancy. Skeletal mineral content increases starting early in pregnancy, at least in certain strains of rats and mice.

VITAMIN D METABOLISM DURING PREGNANCY

25-Hydroxyvitamin D [25(OH)D], the storage form of vitamin D, readily traverses the hemochorial placentas of rats (9) and probably crosses the hemochorial human placenta readily, such that cord blood 25(OH)D concentrations are equal to or up to 20% lower than maternal concentrations (10, 11). Thus, for neonates to be born with adult-normal 25(OH)D concentrations, their mothers must be vitamin D–sufficient. Passage of 25(OH)D from mother to fetus could reduce maternal levels, especially if the mother is deficient in vitamin D; observational studies have shown either no change or a modest decline in maternal 25(OH)D concentrations during pregnancy (12, 13). No studies have addressed whether the ideal level of 25(OH)D during pregnancy should differ from the level considered sufficient for nonpregnant adults.

$1,25(OH)_2D$ does not readily cross the placentas of rats (14), and $1,25(OH)_2D$ concentrations are normally lower than maternal values in fetal sheep, rats, mice, and humans (10, 11, 15, 16). The low fetal concentrations of $1,25(OH)_2D$ reflect the low fetal PTH and high phosphorus concentrations, which suppress renal 1α-hydroxylase. Although PTHrP is elevated in the fetal circulation, it appears to be less able to stimulate the renal 1α-hydroxylase than PTH (17, 18).

Total (free and bound) $1,25(OH)_2D$ concentrations double or triple in the maternal circulation starting in the first trimester, but studies have only shown increased free concentrations during the third trimester. This increase is due to maternal synthesis by the renal 1α-hydroxylase (19, 20). Some have suggested that the fetus and placenta contribute to the maternal rise, but this is not the case, as shown by both animal studies (reviewed in detail in reference 2) and a clinical case of an anephric woman who had

only a negligible increase in $1,25(OH)_2D$ concentrations during pregnancy (21).

Some researchers have argued that the doubled $1,25(OH)_2D$ concentrations explain the doubling of intestinal calcium absorption and indicate the maternal adaptation's dependence on vitamin D sufficiency, but this explanation might be incomplete. Intestinal calcium absorption doubles in humans and rodents early in pregnancy, well before free $1,25(OH)_2D$ concentrations increase late in pregnancy (2, 7). Furthermore, pregnant vitamin D–deficient rats and mice lacking the vitamin D receptor (VDR null) experience a marked up-regulation of intestinal calcium absorption to the same high rate as normal pregnant rats and mice (22–24). Animal studies indicate that prolactin and placental lactogen might stimulate intestinal calcium absorption independently of $1,25(OH)_2D$ (25, 26). Although the data show that pregnant animals do not require $1,25(OH)_2D$ and its receptor for intestinal calcium absorption doubling during pregnancy, no clinical study has compared intestinal calcium absorption during pregnancy in vitamin D–deficient and sufficient women.

VITAMIN D AND MATERNAL OUTCOMES FROM PREGNANCY

Animal data

Animal models used to examine vitamin D physiology during pregnancy and fetal development include severe vitamin D deficiency in rats (27–29), a naturally occurring null mutation of the 1α-hydroxylase in pigs (30), and VDR ablation in mice (24, 31). The 1α-hydroxylase has also been ablated in mice, but the null mice are infertile (32, 33).

In each of these models, the adult female has hypocalcemia, hypophosphatemia, rickets or osteomalacia, and reduced fertility with smaller litters. When such rats and mice do conceive, a few sporadic (possibly hypocalcemic) maternal deaths occur late in pregnancy during the interval of rapid calcium transfer to the fetus. Investigators have observed deaths in late pregnancy when giving rodents a low-calcium diet, which probably indicates that mothers rely on vitamin D and dietary calcium sufficiency to maintain their own blood calcium during ongoing rapid losses to multiple fetuses. In addition, vitamin D–deficient rats and VDR-null mice increased their skeletal mineral content during pregnancy (24, 29), although 1 study in vitamin D–deficient rats showed a small loss of skeletal mineral content during pregnancy (34). Studies in vitamin D–deficient rats and VDR-null mice have also shown that intestinal calcium absorption is upregulated to the normal pregnant level despite the respective absence of $1,25(OH)_2D$ or its receptor.

Human data

No studies have focused specifically on vitamin D deficiency during pregnancy; the available data come from observational studies (12, 13, 35–41) and a few clinical trials of vitamin D supplementation (42–50) in pregnant women ranging from vitamin D deficient to sufficient. Severe vitamin D deficiency causes modest hypocalcemia and secondary hyperparathyroidism in nonpregnant adults, but no reports have documented worsening during pregnancy. Collectively, serum calcium concentrations were normal in women ranging from vitamin D deficient to sufficient. Many observational and randomized trials of pregnant women consistently showed that daily or monthly vitamin D_2 or D_3 supplementation regimens can increase maternal 25(OH)D concentrations, but none has shown any maternal benefit from such supplementation beyond the increase in circulating 25(OH)D. If the animal data apply to humans, they suggest that intestinal calcium absorption increases during pregnancy in women with severe vitamin D deficiency.

VITAMIN D AND FETAL OUTCOMES

Animal data

Studies of severely vitamin D–deficient rats (28, 51, 52), 1α-hydroxylase-deficient pigs (30), and VDR-null mice (31) have consistently shown strikingly normal fetal blood calcium, phosphorus, and PTH concentrations; fetal weight; and skeletal mineral and calcium content. 1α-Hydroxylase-null mice are normal at birth, but the literature includes no extensive studies of their fetal chemistries and skeletal mineral content (32, 33). Researchers have assayed placental calcium transfer from mother to fetus indirectly in vitamin D–deficient rats (53) and directly in VDR-null fetuses (31); calcium concentrations were normal to nonsignificantly increased in both. Clearly, fetal calcium homeostasis and skeletal development and mineralization are independent of vitamin D, $1,25(OH)_2D$, and its receptor. The placenta provides calcium without relying on vitamin D metabolites, and vitamin D–deficient and VDR-null placentas express normal concentrations of the vitamin D–dependent factors calbindin-D-9K and Ca^{2+}-ATPase, which are important for intestinal calcium absorption and calcium homeostasis in adults (31, 53, 54).

Offspring of VDR-heterozygous mice (wild-type, heterozygous-deleted, and VDR-null fetuses) were indistinguishable with respect to calcium homeostasis, weight, skeletal size, morphology, and mineral content. Fetuses of VDR-null mothers had a lower birth weight than did those with VDR-heterozygous mothers, but their proportionately smaller skeletons had a normal mineral content (31). Researchers did not observe this global reduction in fetal size and weight from VDR-null mothers in vitamin D deficiency models, which could indicate that absence of VDR affects fetal growth in a way that absence of vitamin D does not.

In animal models of maternal hypoparathyroidism, fetuses can develop secondary hyperparathyroidism, skeletal demineralization, and fractures (2). Researchers have not observed this with vitamin D deficiency, perhaps because the maternal calcium level is usually less low from vitamin D deficiency than from hypoparathyroidism.

Human data

No systematic studies have examined skeletal mineral content among normal, vitamin D–insufficient, and vitamin D–deficient fetuses; thus, we do not know whether vitamin D–deficient or –insufficient human fetuses have normal skeletal mineral content as studies have shown for vitamin D–deficient animals. Clinical experience reported in textbook chapters and reviews indicates that fetuses with severe vitamin D deficiency are generally born with normal serum calcium concentrations and skeletal morphology, and rickets does not develop (or clinicians do not recognize it) until weeks to months after birth (55–57). The observational and clinical studies of human pregnancy cited above showed no relation of cord blood 25(OH)D concentrations to cord blood calcium or PTH concentrations.

Those observational studies and clinical trials showed that providing vitamin D to pregnant mothers increases cord 25(OH)D concentrations at term but has no effect on fetal weight or skeletal parameters. Several studies found no effect of maternal vitamin D supplementation on cord blood calcium concentrations (42, 48, 49), but 2 small studies in Asian women showed a small but significant increase in cord calcium concentrations (46, 47). Another study compared administration of 1200 mg Ca and 10 μg (400 IU) vitamin D (as dairy) or 1200 mg Ca alone (as orange juice) with placebo and found greater birth weight and total body calcium levels in the fetuses whose mothers received the dairy product but no change in other skeletal variables such as length and head circumference (50). The authors do not know whether the results were due to the dairy product's vitamin D content or its nutritional content compared with the supplement.

Studies of mother-infant pairs have shown no convincing relation between maternal vitamin D sufficiency and fetal outcomes at birth. One study found no association between third-trimester maternal 25(OH)D concentrations and any fetal measurement, but offspring of women with 25(OH)D concentrations <25 nmol/L during the third trimester had a knee-heel length 2.7 mm shorter (not statistically significant) after the authors corrected for gestational length (39). Another study found no association of third-trimester 25(OH)D concentrations with any fetal measurement, including weight, head circumference, arm circumference, and length (40, 41). No systematic study has investigated skeletal lengths and calcium content (by dual-energy X-ray absorptiometry) in newborns stratified by vitamin D status, but the available animal and human data indicate that vitamin D status should have little or no effect on the fetal skeleton's length and mineral content.

Overall, whereas animal studies have shown normal serum calcium concentrations, skeletal lengths, and skeletal mineral content in fetuses despite extreme disturbances in vitamin D physiology, none of the human studies has approached this level of careful, systematic investigation. Consequently, the possibility remains that the human studies lacked the power or sensitive outcome measures required to detect differences among normal, vitamin D–insufficient, and vitamin D–deficient fetuses.

ADAPTATIONS DURING LACTATION

Near-exclusive breastfeeding for 6 mo leads, on average, to maternal calcium loss 4 times higher than in pregnancy because lactation can require 150–300 mg Ca $\cdot$ kg^{-1} $\cdot$ d^{-1}. Characteristic findings (2, 3, 5) in the blood chemistries of healthy lactating women include that serum calcium and ionized calcium concentrations are normal, although some reports suggest that ionized or corrected serum calcium concentrations rise slightly but stay within the normal range. Phosphorus can rise above the normal range, probably because of accelerated resorption from the skeleton (discussed below). PTH concentrations, as measured by "intact" assays, fall to the lower end of the normal range or below, except in women known to have a low calcium or vitamin D intake, including women from Asia and Gambia. Estradiol concentrations are low and near menopausal values. Prolactin concentrations increase at each suckling, but the basal concentrations between feeds decline with time postpartum. PTHrP concentrations are higher than PTH concentrations in nonpregnant women and show some pulsatility in response to suckling.

The lactation-induced adaptations to maternal calcium homeostasis are illustrated in Figure 1. As described in detail elsewhere (5, 6, 8), PTHrP (produced by the lactating breast) in combination with low estradiol concentrations appears to drive the main physiologic adaptation to meet the calcium demands of lactation (**Figure 2**). Suckling and prolactin both inhibit ovarian function and stimulate PTHrP. Together, PTHrP and low estradiol concentrations stimulate skeletal resorption, and bone mineral content declines by 5–10% over 2–6 mo of near-exclusive lactation. Bone resorption markers show marked elevation without a compensatory increase in bone formation. Intestinal calcium absorption rates drop to the normal range after delivery. Renal calcium reabsorption rates increase, presumably due to PTHrP, which mimics the actions of PTH on the renal tubules.

Lactating rodents have a similar adaptive mechanism and lose 25–35% of their trabecular bone mineral content during 3 wk of lactation. Similarly, PTH concentrations are usually low but increase with litter size, estradiol concentrations are low, and PTHrP concentrations are high. Intestinal calcium absorption rates are still approximately double those of nonpregnant animals (22, 58), which might be necessary to meet the proportionately greater calcium demands of multiple suckling pups. Animal models also show that local actions of the calcium receptor and PTHrP within mammary tissue regulate milk's calcium content, at least partly.

VITAMIN D METABOLISM DURING LACTATION

Vitamin D passes readily into breast milk, 25(OH)D passes very poorly, and $1,25(OH)_2D$ does not appear to pass at all (2). $1,25(OH)_2D$ concentrations fall rapidly after pregnancy and are normal during lactation, except in women nursing twins, who have increased $1,25(OH)_2D$ concentrations (2). 25(OH)D concentrations were stable in 1 study (59) but fell during lactation in another (60). Breast milk should only account for a small loss of 25(OH)D; seasonal variation and differences in vitamin supplement use before and after pregnancy might have confounded the results. In lactating rats and mice, $1,25(OH)_2D$ concentrations remain elevated until weaning (2).

VITAMIN D AND MATERNAL OUTCOMES FROM LACTATION

Animal data

Not only are $1,25(OH)_2D$ concentrations elevated during lactation in normal rodents, but the concentrations respond to varying lactation demands. When stressed by a low-calcium diet or large litter size, $1,25(OH)_2D$ concentrations increase even further (61, 62), perhaps because a mechanism increases intestinal calcium absorption further when the mother faces extra demands. However, mothers do not require vitamin D sufficiency or responsiveness to $1,25(OH)_2D$ for normal lactation. Vitamin D–deficient rats and VDR-null mice lactate normally and experience similar skeletal losses to controls (24, 29, 34), although 1 study found that vitamin D–deficient rats lose more skeletal mineral content than do normal rats (63). Intestinal calcium absorption in lactating vitamin D–deficient rats is upregulated to the same level as in vitamin D–sufficient rats (22, 58).

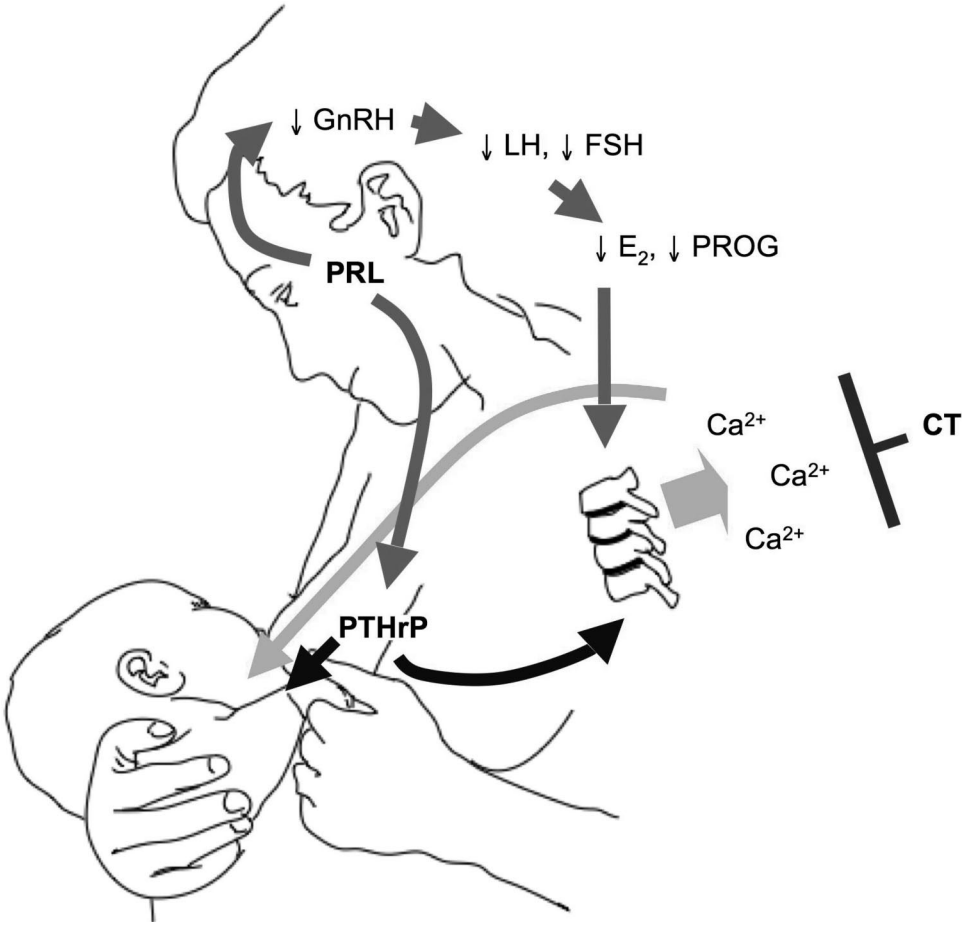

FIGURE 2. The breast is a central regulator of skeletal demineralization during lactation. Suckling induces prolactin (PRL) release. Suckling and prolactin both inhibit the hypothalamic gonadotropin-releasing hormone (GnRH) pulse center, which in turn suppresses the gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)], leading to low levels of the ovarian sex steroids [estradiol (E_2) and progesterone (PROG)]. Several factors control parathyroid hormone-related protein (PTHrP) production and release from the breast, including suckling, prolactin, and the calcium receptor. PTHrP enters the bloodstream and combines with systemically low estradiol concentrations to markedly up-regulate bone resorption. Increased bone resorption releases calcium and phosphate into the bloodstream, which then reaches the breast ducts and is actively pumped into the breast milk. PTHrP also passes into milk at high concentrations, but we do not know whether swallowed PTHrP plays a role in regulating the neonate's calcium physiology. Calcitonin (CT) might inhibit skeletal responsiveness to PTHrP and low estradiol. Reprinted from reference 8, copyright 2005, with kind permission of Springer Science and Business Media B.

Human data

Observational studies (59, 60, 64–67) and clinical trials (68–75) have generally shown that providing vitamin D to lactating mothers increases their 25(OH)D concentrations but has no significant effect on any other maternal outcome (68, 69, 72–74). Randomized trials and observational studies of dietary calcium intake's effect on skeletal resorption during lactation in North American and Gambian women have consistently shown that very low to well-above-normal calcium intakes had no effect on skeletal demineralization during lactation but did increase urinary calcium excretion (76–81). Most of these studies compared calcium intake and did not manipulate vitamin D intake directly, but a test of vitamin D supplementation during lactation would probably find no effect on skeletal resorption. Limited studies of lactating adolescents have reported greater skeletal losses than in older women, perhaps due to poor calcium intake and nutrition in the adolescents (82, 83). In other studies, maternal vitamin D status or vitamin D supplementation did not affect breast milk calcium content (73, 84).

Thus, while one might expect that low vitamin D and calcium intakes would accentuate skeletal losses to maintain breast milk calcium content, most studies suggest otherwise. This is consistent with the animal studies and might indicate that skeletal resorption provides most of the calcium needed during lactation, regardless of dietary calcium intake. The obligatory rise in PTHrP and fall in estradiol programs the lactational loss of skeletal calcium content (Figure 2), and vitamin D status does not influence this loss. Increasing calcium and vitamin D intake during lactation might simply increase urinary calcium excretion and, thereby, kidney stone risk.

VITAMIN D AND NEONATAL AND INFANT OUTCOMES

Animal data

In vitamin D–deficient rats (51, 52), 1α-hydroxylase-null pigs (30), VDR-null mice (85, 86), and 1α-hydroxylase-null mice

(32, 33), rickets and failure to thrive are not apparent until near weaning. Studies of vitamin D–deficient rats and VDR-null mice confirm that skeletal mineral content is normal at birth and during the first 2 wk after birth, after which the animals develop progressive hypocalcemia, hypophosphatemia, and histomorphometric evidence of rickets. The sequence of events parallels the maturation of intestinal calcium absorption postnatally, which develops from nonsaturable passive absorption facilitated by lactose to an active, saturable process that depends on $1,25(OH)_2D$ (87–89).

Human data

No systematic studies have addressed the effects of vitamin D status on neonatal or infant calcium and bone status parameters; case reports and clinical experiences described in textbook chapters constitute the main data. Vitamin D deficiency predisposes newborns to neonatal hypocalcemia, and clinicians do not usually diagnose (or recognize) rickets for several months after birth (55–57). However, in areas where vitamin D deficiency is endemic and clinical awareness is high, clinicians often identify the characteristic changes of rickets soon after birth (90, 91).

After birth, serum calcium concentrations drop from their high fetal levels to a trough below the adult level, followed by a gradual recovery over several days to the adult level (2, 92). Although vitamin D deficiency increases neonatal hypocalcemia risk, it is unclear whether vitamin D insufficiency causes hypocalcemia. Vitamin D supplementation during pregnancy reduced blood calcium excursion in neonates in 1 study and reduced hypocalcemia incidence in another (42, 48, 49).

Standard 10 μg (400 IU) vitamin D supplements given to lactating mothers do not increase infant 25(OH)D concentrations because of 25(OH)D's poor penetrance into milk; a dose of 100 μg (4000 IU) per day was required to raise neonatal 25(OH)D concentrations to the perceived sufficient range of >75 nmol/L (72). Dosing the infant directly with smaller doses of vitamin D produces normal 25(OH)D concentrations but vitamin D supplementation in otherwise healthy infants (via mother's milk or directly to the infant) did not improve the infants' blood calcium concentrations, length, weight, or other parameters.

One study found no association between third-trimester maternal 25(OH)D concentrations and newborn weight, length, or head circumference indexes (40). Follow-up assessments of these children also found no effect at 9 mo or 9 y of age (40, 41). However, bone mineral content was apparently lower in 9-y-old children whose mothers had had low 25(OH)D (<20 nmol/L) concentrations during the third trimester (40), which might indicate the effect of in utero vitamin D status to program peak bone mass that will be achieved later in life (93, 94). Because the investigators did not measure bone mineral content at birth or 9 mo, it is not clear whether this is truly a mechanistic association [low fetal 25(OH)D programming low bone mineral content] or is related to environment and nutrition [because a pregnant woman with a low 25(OH)D level might be more likely to provide poor nutrition to her child, have lower socioeconomic status, etc].

Observational studies have shown that up to 95% of children with vitamin D–deficient rickets had been breastfed (95), which is consistent with the milk's low vitamin D and 25(OH)D contents unless the woman takes supplements aggressively. Supplementing the mother during pregnancy to provide the infant with normal 25(OH)D stores at birth or supplementing the infant directly can prevent childhood rickets.

Increasing evidence from observational studies indicates that vitamin D deficiency and insufficiency at older ages might increase the risk of chronic diseases such as type 1 diabetes and multiple sclerosis. In many of these diseases, the association is with latitude and, by inference, with vitamin D status. For most of these associations, no specific data relate the disease to fetal or neonatal vitamin D sufficiency. However, observational studies indicate that vitamin D insufficiency during pregnancy is associated with increased prevalence of islet cell antibodies in offspring, and a history of vitamin D supplementation in pregnant women (96, 97) or infants (98) is associated with lower childhood incidence of type 1 diabetes. Investigators need to conduct randomized trials on this association before clinicians recommend vitamin D to reduce the incidence of type 1 diabetes. Although human fetuses might suffer no skeletal problems from vitamin D deficiency and insufficiency, they could have an increased risk of nonskeletal problems, such as type 1 diabetes, in childhood.

POSTWEANING SKELETAL RECOVERY

After weaning, the maternal skeleton rapidly recovers the mineral content lost during lactation. In clinical studies, the recovery apparently occurred within 3–6 mo, although many studies did not follow the women after weaning. Observational studies generally indicate that a history of lactation confers no increased risk of low bone mass, fractures, or osteoporosis (2, 99).

This recovery is especially remarkable when one considers that the adult skeleton normally recovers incompletely, if at all, from bone mass losses induced by weightlessness, bed rest, corticosteroid therapy, estrogen deficiency, etc. We do not know what mechanism explains skeletal recovery after lactation. One observational study showed that intestinal calcium absorption was upregulated by 19% during postweaning recovery (71), but the investigators assayed only 1 time point and the magnitude was quite modest.

Lactating rodents recover completely within 10–21 d, depending on the rodent strain and technique used. No studies have systematically measured intestinal calcium absorption or calciotropic hormone concentrations during the recovery interval.

Animal data

Two studies of vitamin D–deficient rats noted some recovery of mineral content after lactation, with the final value exceeding the prepregnancy value in 1 study (29, 34). In preliminary studies of VDR-null mice, skeletal recovery after lactation was complete and final bone mineral content exceeded the prepregnancy level by 50% (24). Thus, animal studies suggest that vitamin D status plays no role in skeletal recovery after lactation.

Human data

No study has examined the impact of vitamin D deficiency or insufficiency on the skeleton's ability to recover from lactational losses. One study of lactating women observed that PTH and $1,25(OH)_2D$ concentrations were higher than normal at 1 time point assayed during postweaning recovery (100). No other study has examined this, so we do not know whether the skeleton requires vitamin D sufficiency to recover. Vitamin D requirements might be higher during postweaning recovery than after, but this is also speculation.

CONCLUSIONS

Vitamin D deficiency during pregnancy and lactation can lead to hypocalcemia and rickets in neonates and, especially, infants, but animal data and limited human data suggest that fetuses are protected from the adverse skeletal effects of vitamin D deficiency. Adaptations in maternal calcium and bone metabolism appear to occur independently of vitamin D status. Careful study of newborns with vitamin D–deficient mothers might reveal deficits in skeletal mineral content by dual-energy X-ray absorptiometry. Given the apparent relative protection of mothers and fetuses from severe vitamin D deficiency, vitamin D insufficiency probably does not harm the fetus, infant, or mother. Dosing recommendations for mothers during pregnancy should be aimed at preventing problems in neonates and infants, and a vitamin D dose sufficient for the mother during pregnancy should produce normal cord blood 25(OH)D concentrations at birth. Giving relatively small doses of vitamin D directly to the infant or supplementing the mother with 100 μg (4000 IU) vitamin D daily should maintain normal 25(OH)D concentrations in exclusively breastfed infants without harming the mother. Researchers need to study aspects of the role of vitamin D sufficiency and supplementation in pregnancy and lactation, especially the relation (if any) between vitamin D insufficiency in utero and infancy and long-term outcomes such as type 1 diabetes, multiple sclerosis, and other chronic diseases.

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