COMMENTARY

How Important Is Vitamin D for Calcium Homeostasis During Pregnancy and Lactation?

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Pregnancy and Lactation: Major Challenges for Calcium Homeostasis

The vitamin D endocrine system originated during the early evolution of the vertebrates. It plays an important role in calcium homeostasis, mainly by increasing the absorption of calcium either in the gills of fish or in the intestine of other vertebrates. By optimizing intestinal calcium transport and thus the availability of calcium, the vitamin D endocrine system is also important for bone homeostasis, because lack of vitamin D or the vitamin D receptor (VDR) causes rickets or osteomalacia. On the other hand, in case of insufficient intestinal calcium absorption, levels of the active vitamin D hormone, 1,25(OH)_{2}D, will increase and, together with increased PTH levels, will give priority at maintaining serum calcium levels even at the expense of bone calcium content.

Pregnancy and lactation are stress situations for calcium and bone homeostasis in women. Indeed, during the last weeks of human pregnancy, about 30 g or more of calcium is transferred to the fetus, and during a 6-month to 9-month lactation period an additional 30 g of calcium is provided via the milk to the neonate. This corresponds to a mean calcium transfer rate to the fetus of 30 to 50 mg/day during pregnancy (60 mg/per day at mid-term and 300 mg/day during last weeks) and of 200 mg/day through the milk to the neonate. However, the impact on the skeleton is much more pronounced than in pregnancy. Indeed, bone loss in the lumbar spine is 25% to 35% in lactating rodents and 5% to 10% in breastfeeding mothers, whereas no or only a modest decrease in bone mass occurs in late pregnancy in rodents and humans. The highest relative calcium requirements in vertebrates are probably observed in the egg-laying hen, which needs several grams of calcium per day.

Different Importance of Vitamin D Action During Pregnancy Versus Lactation

Successful reproduction is extremely essential for the survival of the species and it is therefore no surprise that sophisticated adaptive mechanisms have been developed to cope with these calcium stress situations. In this issue of the Journal of Bone and Mineral Research, Gillies and colleagues describe the consequences of the absence of 1,25(OH)_{2}D during pregnancy and lactation, by investigating calcium handling in Cyp27b1 null mice, which are unable to synthesize 1,25(OH)_{2}D. To prevent hypocalcemia and rickets, mice were given a calcium rescue diet (2% calcium and 20% lactose) before pregnancy, although the diet was not able to fully restore calcium and bone homeostasis, a finding that is not yet fully understood. During pregnancy, maternal serum calcium homeostasis and bone mass was not altered in wild-type mice, and even improved in the absence of 1,25(OH)_{2}D signaling. These observations indicate that the increase in intestinal calcium absorption during pregnancy can be regulated by other factors or hormones besides 1,25(OH)_{2}D action. During lactation, as expected, wild-type mice lost a substantial amount of trabecular and a marginal quantity of cortical bone. However, the absence of 1,25(OH)_{2}D aggravated trabecular as well as cortical bone loss in the mother and even caused severe histological osteomalacia despite the rescue diet. Therefore, the authors conclude that 1,25(OH)_{2}D activity is essential for calcium and bone homeostasis during lactation. The calcium content of the mother’s milk was also decreased, but the authors did not report the consequences for bone development and mineralization in their offspring. Finally, a few weeks after weaning, bone mass was restored in wild-type as well as in Cyp27b1 null mothers, indicating that the absence of 1,25(OH)_{2}D action does not impair the postlactation bone recovery in mice.

Vitamin D–Independent Effects Contribute to Calcium Homeostasis During Pregnancy

This study attracts our attention to the adaptive mechanisms used during the calcium stress of reproduction. Total 1,25(OH)_{2}D levels increase early during human pregnancy, largely due to increased serum vitamin D binding protein (DBP) concentrations, whereas free 1,25(OH)_{2}D only increases (+22%) in the third trimester when the majority of the calcium transfer...
Vitamin D Is Critical for Intestinal Calcium Absorption and Thus Bone Health During Lactation, But Not Postweaning

Lactation is a short (3 weeks) but intensive calcium stress for rodents because they usually have a large number of pups. Loss of mainly trabecular bone is a general phenomenon and may result in a loss of 25% to 35% of spinal trabecular bone mass.\(^\text{5}\) Thus, bone mass can be considered as a storehouse for calcium to meet these calcium requirements.\(^\text{8}\) This observation is in line with the evolutionary principle of serum calcium homeostasis being better defended than bone calcium content.\(^\text{1}\) Women who breastfeed exclusively for up to 6 months might lose 5% to 10% of trabecular spine whereas there is less bone loss at cortical sites.\(^\text{5}\) Bone loss during lactation is due to osteoclastic and osteocytic bone resorption, but the relative contribution of each of these mechanisms is unclear. The osteocytic bone resorption requires the action of PTH/PTHrP receptor in osteocytes\(^\text{17}\) and involves the activation of proton pumps (vacuolar ATPase) and other genes that were originally identified in relation to osteoclastic bone resorption.\(^\text{17,18}\) Whether the vitamin D endocrine system plays an essential role for bone homeostasis during lactation is disputed.\(^\text{5,12,13,19}\) The new data from Kovac’s group indicate that 1,25(OH)\(_2\)D is implicated in bone loss during lactation because absence of Cyp27b1 aggravates bone loss and induces osteomalacia in the nursing mother. Whether the fetal calcium and bone homeostasis is normal was not further evaluated. The results in Vdr null mice are contradictory; in the Boston mice total body or spine BMC was not different in wild-type or Vdr null mice during and after lactation, when given the rescue diet.\(^\text{13}\) Lactating Leuven Vdr null mice lost more trabecular bone (−52%) than wild-type mice (−30%), but they were switched to a normal diet after being fed the rescue diet during pregnancy.\(^\text{10}\) Overall, it seems that the absence of VDR action aggravates bone loss, most likely due to poor intestinal calcium absorption.

The rapid recovery of bone after weaning, or restoration of bone mass to prepregnancy levels, is a most remarkable phenomenon. This return to baseline levels happens in mice and women; however, it requires only weeks in mice but up to a year in most women. The mechanisms involved in this rapid recovery of bone after weaning are largely unknown except for the sudden drop in PTHrP and restoration of estrogen status, both leading to rapid apoptosis of osteoclasts. The mechanisms involved in the restoration of osteocytic bone loss are also largely unexplained. From animal studies, however, a number of mechanisms are excluded such as PTH/PTHrP or estrogens.\(^\text{5}\) The vitamin D endocrine system is also redundant because Vdr and Cyp27b1 null mice can indeed rapidly restore bone mass after weaning. Because the Cyp27b1 null mice had severe osteomalacia during lactation (58% of bone surface covered by osteoid), mineralization of osteoid may have contributed to this rapid bone gain and even overcompensate bone mass, as demonstrated in vitamin D deficient rats exposed to long term intravenous calcium infusions.\(^\text{20}\) This process remains remarkable, because we are not aware of a similar rapid gain of bone even when using the most potent bone anabolic agents.

Summary and Outstanding Questions

In summary, the new data in Cyp27b1 null mice and older data in Vdr null mice or vitamin D–deficient rodents all confirm that bone mass can be maintained or even strengthened during pregnancy despite the calcium transfer to the fetus, providing dietary calcium supply is sufficient. The data, however, should not be interpreted as that vitamin D action is totally redundant during pregnancy because the Cyp27b1 or Vdr null mice were fed a nonphysiologic rescue diet to compensate for the lack of vitamin D. Rather, the findings demonstrate that the presence of VDR is not essential to maintain healthy bone during pregnancy. Lactation, however, results in a large transfer of bone calcium to the circulation to allow adequate supply of calcium in milk. Absence of Cyp27b1 or Vdr aggravates this calcium loss in bone during lactation, most likely due to deficient upregulation of intestinal calcium absorption. Remarkably, the postlactation gain of bone is not dependent on Cyp27b1\(^\text{7}\) and has been insufficiently evaluated in Vdr null mice.

There are many remaining questions, such as what are the compensatory mechanism(s) allowing the gain of bone during pregnancy or after weaning. The most important question, however, is the short-term and especially the long-term outcome in the offspring exposed to poor vitamin D action during the perinatal period. Indeed, a large percentage of pregnant and lactating women around the world have a poor
vitamin D status, and the limited data so far indicate that this may have health consequences for the mother as well as their offspring.\(^{21–23}\)

What are the potential implications of these studies for human reproduction? Simply extrapolating the mouse data to pregnant or lactating women would imply that maternal bone could be more or less maintained in the absence of vitamin D action by using very high pharmacologic amounts (several grams per day) of calcium. In daily life, taking into account the rather low calcium intake in general, these findings indicate that vitamin D is essential for maternal calcium and bone homeostasis, and even more during lactation than during pregnancy. A poor vitamin D status is highly prevalent around the world, and therefore the question of the health consequences of such deficiency for mothers and infants is highly relevant. Epidemiologic data associate a poor vitamin D status with increased risk for maternal (preeclampsia and gestational diabetes) and neonatal consequences (lower body weight, hypocalcemia, and lower bone mass, but only very exceptionally neonatal rickets). Moreover, such deficiency is also associated with long-term health consequences in the offspring of vitamin D–deficient mothers, such as atopic diseases, asthma, lower bone mass, autoimmune diseases (including multiple sclerosis and type 1 diabetes) and maybe even cognitive impairment.\(^{5,21–23}\)

Unfortunately, most randomized controlled trials (RCTs) are so far limited to small-scale studies with inconsistent results. Several recent extensive reviews\(^{5,21–24}\) therefore concluded that there is a trend for some beneficial effects of vitamin D supplementation during pregnancy but that the current evidence does not allow a definite answer. In the meantime, it seems wise to implement the existing guidelines (such as formulated by the Institute of Medicine [IOM] and WHO) regarding calcium and vitamin D.

**Disclosures**

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