REVIEW ARTICLE

Mineral and Bone Mass Changes During Pregnancy and Lactation

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INTRODUCTION

During the past decade many factors have come together to produce an explosive increase in investigations on bone and mineral metabolism during pregnancy and lactation. Among some populations, frequent pregnancies and long lactation periods may lead to severe skeletal damage in the mother.[1] For example, a case of severe after birth osteoporosis in a 30-y-old woman was described in 1948 in the classic book by Albright and Reifenstein.[2]

In the past decade, however, technology improvements have made it possible to quantify accurately the biochemical changes in bone formation and resorption markers and alterations in bone mass that occur within the different skeletal areas during a woman's reproductive life.

Likewise, the past decade has witnessed the eruption of descriptions of clinical cases in which the mother develops severe osteoporosis at the end of pregnancy or during the lactation period. Further, there is a growing need to determine whether pregnancy and lactation may become risk factors for the future development of postmenopausal bone fractures.

Several reviews,[3–7] including some that specifically examined reproductive bone health and as its relation to osteoporosis,[8] and others addressing the possibility of avoiding possible deleterious effects by increasing calcium intake[9–11] have been published recently.

The objective of this article is to review recent advances in bone changes that occur during pregnancy and lactation, with special emphasis on calcium balance and calcium needs during these periods of a woman's reproductive life.

PREGNANCY

Newborn Calcium Demand

The average calcium demand of the growing fetus is approximately 30 g until birth, with requirements of 5 g during the second trimester and 25 g during the third trimester.[12] Therefore, the daily average calcium transfers from the mother through the placenta to the fetus are approximately 50 mg/d during the second trimester and 250 mg/d during the third trimester.

Adaptative Changes That Normally Occur in Pregnant Women

During pregnancy there are many changes that occur in serum calcium, ionic calcium, urinary calcium excretion, and intestinal calcium absorption.[3,13–16] Although there is a decrease in serum calcium, this is usually attributed to a parallel decrease in serum albumin associated with hemodilution. Ionic calcium remains stable throughout the pregnancy. Urinary calcium excretion tends to increase gradually from an average of 160 mg/d[17,18] in a non-pregnant woman to 240 mg/d in the third trimester.[3,6,16,19,20] Intestinal calcium absorption increases from an average of 25%[17,18] in a non-pregnant woman to 50% by the end of pregnancy.[3,6,14,16,20] This increase in intestinal calcium absorption is already evident at the end of the first trimester[3] and suggests that during this stage there may be calcium storage in the maternal skeleton (see below).

There are also adaptive changes in the hormonal level of 1,25-dihydroxyvitamin D ($1,25[OH]_2D$).[3,15] There is a rapid increase in the first trimester, reaching the highest values at the end of the third trimester. Parathormone (PTH) does not show variation, with the exception of a moderate decrease after the second trimester.[19–22] PTH-related peptide (PTHrp) increases precociously and remains elevated throughout pregnancy.[19,22]

Other hormonal changes during pregnancy involve prolactin, estrogen, placental lactogen, placental growth hormone, and insulin-like growth factor-1.[3,4] They can induce changes in $1,25(OH)_2D$ synthesis, calcium absorption, and bone turnover. Placental lactogen exhibits many of the properties of growth hormone by inducing an increment of bone accretion and turnover and calcium absorption efficiency.[13]

Estrogens and prolactin are high during the second and third trimesters of gestation, and both hormones have been postulated to increase calcium absorption.[23,24]

Adaptative changes in the bone markers include a moderate increase in alkaline phosphatase during the first and second trimesters followed by a larger increase in the third trimester of pregnancy. Many studies have verified a significant increase in bone resorption markers after the first trimester[25] that peaks in the third trimester,[16,21,22,25,26] including the measurements of hydroxyproline, pyridinoline, C-terminal cross-linking telopeptide of type I collagen, or N-terminal cross-linking telopeptide of type I collagen. N-terminal cross-linking telopeptide of type I collagen increases from an average level of 30 mg/d in a young non-pregnant woman to 90 mg/d during the third trimester, showing a remarkable increase of bone remodeling, with predominance of resorption.[16,21,22,26]

Changes in Bone Mass

During the past 15 y, changes in bone mass during pregnancy have been studied with the limitation of not being able to use any radioactive or x-ray–based technique in pregnant women. Most recent studies in women before pregnancy and after the immediate puerperium (about 4 wk) have reported decreases of approximately 3% in bone mineral density (BMD) of the lumbar spine[27] and of a similar magnitude in the proximal femur.[21]

Studies of the total skeleton and its subareas before and after pregnancy have found a redistribution of bone mass, with a decrease of 3% in mineral density at the lumbar spine and pelvis and

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an increase in the areas where the cortical bone predominates.[25] The net balance of BMD of the total skeleton is then expected to be zero.

In light of these observations on the redistribution of the bone mass during pregnancy performed with modern methodology (dual-energy x-ray absorptiometry), it is of value to re-examine the data from studies done more than 30 y ago evaluating the changes that occur in long bones by micrometry (measure of bone diameter and cortical thickness on plain radiographs). Garn[28] observed that the number of pregnancies is inversely related to the width of the medullary cavity of the metacarpal bones, with each pregnancy stimulating the formation of the endosteal bone and, hence, increasing the cortical thickness.

Even more significant are the long-forgotten findings of Smith[29] who in 1967 reported the femoral cortical dimension of the femur in a large group of women from nulliparous to those who had more than four pregnancies. The external diameter of the femur increased from 31.1 mm in the nulliparous to 32.7 in women with an average of 5.5 offspring (~5.1% increment). In this same group, the cortical thickness increased from 17.6 mm to 19.3 mm (~9.5% increment). This very rigorous study showed that pregnancy (and perhaps lactation) increase the periosteal and endosteal appositions of the femur and probably of most long bones.

Ultrasound studies, because they are radiation free, can be performed throughout pregnancy and have shown a significant decrease in bone mass at the level of the calcaneus.[26]

In summary, most recent and exhaustive studies considered alongside studies done decades ago have shown a moderate loss of mineral density of the trabecular bone in the spine and pelvis during pregnancy and an increase in the cortical thickness of the long bones by endosteal and periosteal appositions. A possible explanation for these changes can be explained by the fact that the trabecular bone provides, by means of its fast resorption, the amount of calcium that the skeleton of the newborn requires. In addition, the endosteal apposition may be a mechanism for calcium storage that might be required during lactation. However, preliminary observations have suggested that this apposition of the endosteal bone may not be used during lactation and that resorption continues from the trabecular bone.[30]

Figures 1 and 2 summarize the metabolism of calcium by comparing what occurs in a young non-pregnant woman with what occurs in a pregnant one, specifically in the third trimester.

In the first case, there is an equilibrium (zero balance) based on the entry of approximately 250 mg/d of calcium from the food supply to the exchangeable calcium pool, balanced by a loss of approximately 100 mg of endogenous fecal calcium and a 150 mg loss through the kidney.

In the second case, even though the bone turnover increases,[16,21,22,25,26] the increased intestinal calcium absorption provides about 500 mg to the calcium pool,[3,19,20] which is equivalent to all calcium losses, including the (presumably diminished) endogenous fecal and higher urinary losses[3,6,16,19,20] and the needs of the fetus via the placenta without affecting the total bone calcium. Thus, under normal circumstances when there is sufficient calcium in the diet, final calcium bone balance probably equals zero.

In summary, during pregnancy there is a rapid increase in $1,25(OH)_2D$ levels and other hormones, thereby increasing intestinal calcium absorption. This increment in the intestinal absorption of calcium balances out the transfer of calcium from the mother to the fetus. The bone resorption markers increase after the first trimester and the markers of bone formation increase mainly during the third trimester, indicating a significant augmentation of bone turnover. The bone mass undergoes a redistribution, with a reduction of approximately 3% in the predominantly trabecular sites and an increase in the periosteal and endosteal surfaces of the predominantly cortical areas, with a total balance probably close to zero.

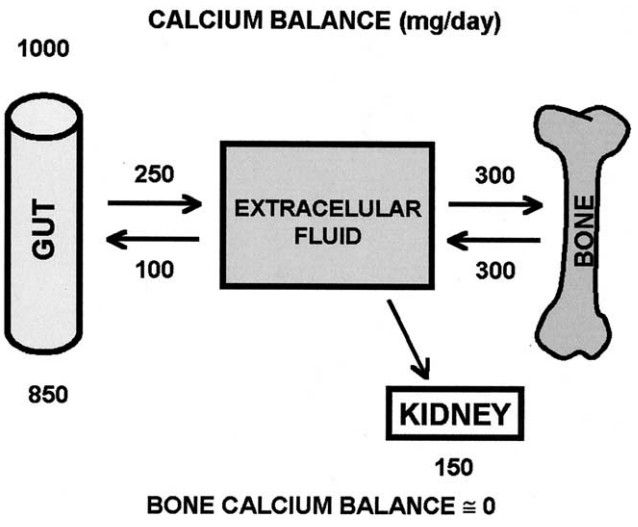

FIG. 1. Hypothetical average calcium balance (mg/d) in non-pregnant young women. The bone compartment does not lose calcium. The average figures are based on results reported by Broadus[17] and Auerbach et al.[18] In all figures, the numbers indicate average amounts of calcium (mg) exchanged per 24 h to and from the extracellular fluid from the gut, bone and kidney in white women because the vast majority of the studies have been done in white individuals.

Special Cases

There are many situations in which this balance may be altered. These include situations that involve:

1. Frequent pregnancies and short interpregnancy intervals
2. Low calcium intake during pregnancy
3. Pregnancy in adolescents
4. Multiple fetuses (twins, etc.)
5. Heparin treatment

FREQUENT PREGNANCIES. Hendersson et al.[31] recently studied a group of mothers, descendants of Finnish families living

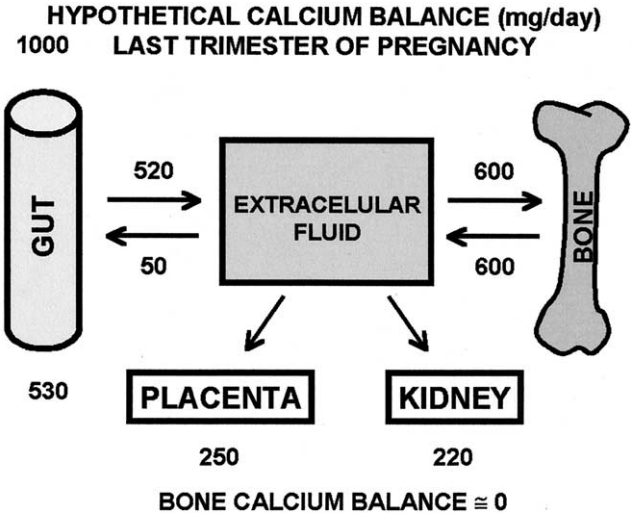

FIG. 2. Hypothetical average calcium balance (mg/d) during the last trimester of pregnancy in young women. The increased intestinal calcium absorption[3,6,14,16,20] balances out the urinary[3,6,16,19,20] and placental losses.[12] Despite an increased rate of bone remodeling,[16,21,22,25,26] the net balance of bone calcium is probably zero[25] (see caption to Figure 1 for further explanation).

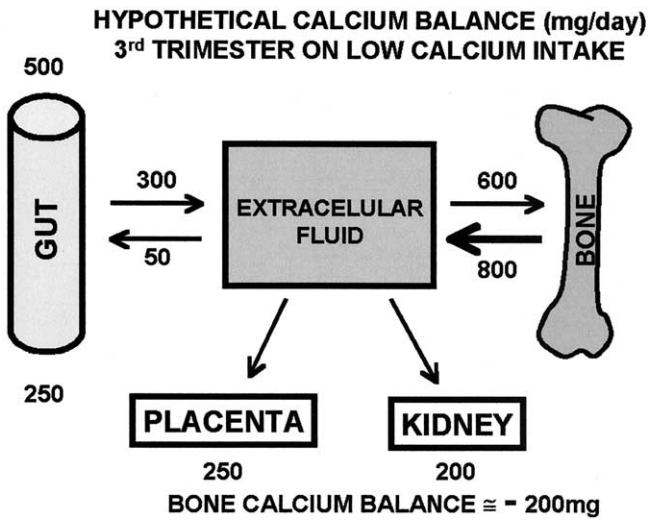

FIG. 3. Hypothetical calcium balance (mg/d) during the last trimester of pregnancy in young women on low calcium intake. The augmented fractional calcium absorption[3,6,14,16,20] does not compensate for urinary and placental losses,[12] probably causing a negative bone calcium balance (see caption to Figure 1 for further explanation).

in a community in the United States, who had multiple pregnancies and long lactation periods and compared their BMDs with women in the same community who had never been pregnant. This population's calcium intake was not specified. The investigators observed no difference between the women with multiple pregnancies (an average of six) and the ones who had never been pregnant. Therefore, this study found no evidence that multiple pregnancies have any effect on bone mass.

In a recent study on Japanese women, successive pregnancies did not reduce maternal BMD of the lumbar spine, although a BMD decrease was observed in older mothers.[32]

LOW CALCIUM INTAKE THROUGHOUT THE PREGNANCY. In theory, if total calcium intake is 500 mg/d, the sum of the losses through the placenta and the kidney would lead to a negative balance of about 200 mg/d. This amount of calcium would necessarily come from the skeleton (Figure 3), especially from the trabecular bone. During the third trimester, a calcium loss of approximately 150 to 250 mg/d from the skeleton would cause a net loss of calcium of approximately 13 to 22 g, which represents 1.5% to 2.5% of the total calcium from the mother's skeleton.

Nevertheless, if this percentage originates mainly from the trabecular bone, which is only 20% of the total skeleton, the loss in this sector can be 8% to 15%, a very important fraction of this compartment. A potential consequence of such a loss could be osteoporosis related to pregnancy (see below).

ADOLESCENT MOTHERS. Studies carried out by the same group of investigators evaluating the cortical bone from the forearm by single photon absorptiometry showed that adolescents (<18 y) during a lactation period of 4 mo can have a BMD loss of about 10%; in matched mothers older than 18 y, no change in the same area bone mass took place.[33,34] This loss was prevented in adolescents who had received, during those 4 mo of lactation, a diet rich in calcium (>1600 mg/d).[35]

We found no other studies investigating the effect of pregnancy on bone mass during the lactation period in teenage mothers using the currently available methodology.

MULTIPLE FETUSES. Georgino et al.[36] observed in 20 mothers who were pregnant with twins that the decrease of bone mass, evaluated by ultrasound of the calcaneus, was significantly higher than in mothers with single pregnancies. The researchers emphasized the importance of the care provided to mothers with multiple pregnancies, especially if there are other risk factors.

HEPARIN TREATMENT. Several cases of vertebral osteoporosis during pregnancy have been described in women who received heparin as a preventive treatment for venous thromboembolism or pregnancy loss secondary to antiphospholipid syndrome. This issue was reviewed by Haram et al.[37] In one study, 17% of the patients undergoing this treatment developed radiologically diagnosed osteopenia and 3% had multiple vertebral fractures.[38] The mechanism by which osteopenia is induced by heparin is not fully understood, but the most probable cause is the inhibition of the synthesis of $1,25(OH)_2D$,[39] which seems to interfere with the expected increase in intestinal calcium absorption that serves as the main homeostatic mechanism of calcium metabolism during pregnancy.

LACTATION

Calcium Demand During Lactation

During lactation, 250 to 350 mg of calcium is transferred daily from the mother to the neonate through the milk.[3,4,40] This means that, during a lactation period of 3 mo, the mother is going to transfer 25 to 30 g of calcium, which represents 3% of her total body calcium. If the lactation period should extend to 6 mo, this transfer would result in about 6% of the total body calcium.[12]

The concentration of calcium in the mother's milk is independent from the mother's calcium intake. In a study by Prentice,[4] the calcium concentration fluctuated between 275 and 315 mg of calcium per liter, even though the amount of calcium in the diet varied from an intake as low as 630 mg/d to one as high as nearly 2300 mg/d. In summary, the homeostatic mechanisms favors the newborn's skeleton calcification independent of the mother's calcium balance.

Biochemical Bone and Mineral Changes During Lactation

During lactation there are no variations in the serum levels of calcium, ionic calcium, or PTH. However, the urinary calcium excretion that increases during the last trimester of pregnancy decreases to levels similar to or lower than those observed during prepregnancy.[14,16,19,20] In contrast, the serum level of $1,25(OH)_2D$ that was high by the end of pregnancy gradually decreases to basal levels and, as a consequence, decreases intestinal calcium absorption.[14,20,41] Therefore, the most important calcium homeostatic mechanism found during pregnancy, the increase of the intestinal absorption secondary to the increase of $1,25(OH)_2D$, gradually disappears after childbirth and during lactation.

Other Hormonal Factors

PTHrP is produced by the lactating mammary gland, possibly under the influence of prolactin, and may play a role increasing bone turnover.[7] Other factors may be involved in regulating lactation-associated changes in calcium and bone metabolism. Prolactin and estradiol are modulators of calcium and bone metabolism, and the changes in bone mineral and bone turnover during lactation may be mediated by a decrease in estrogen levels and/or the elevated prolactin concentration observed in the early stages of lactation.[3] An early drop in serum estrogen during lactation may be responsible for increased bone turnover.[42] After weaning, restoration of ovarian hormone production and decreased production of PTHrP contribute to the recovery of bone mass.[7]

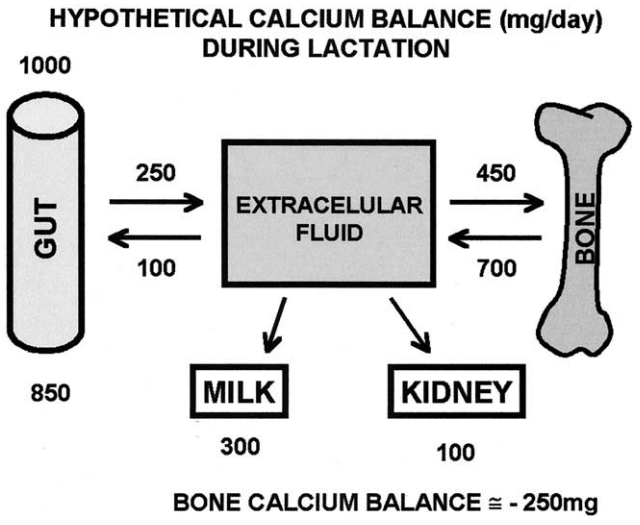

FIG. 4. Hypothetical calcium balance (mg/d) during lactation in young women. Bone remodeling remains elevated,[16,42,43] but in the face of a back-to-normal gut calcium absorption,[14,19,20,41] calcium loss through the milk[3,4,40] and urine produces a negative bone calcium balance[27,40,44,47–49] (see caption to Figure 1 for further explanation).

Bone Markers During Lactation

An investigation by Sowers et al.[43] clearly showed that, after childbirth, if the mother does not breastfeed or does it for a short period, bone formation and resorption markers rapidly decrease to basal levels. Conversely, in a mother who breastfeeds for about 6 mo, the bone remodeling markers, such as N-terminal cross-linking telopeptide of type I collagen, osteocalcin, and alkaline phosphatase remain high.[20,43,44] Likewise, there is a tendency for these biomarkers to gradually return to basal levels approximately 12 mo after childbirth.[43] In summary, lactation maintains a high level of bone turnover at least during the first 3 mo.[16,42,43]

Bone Mass During Lactation

Numerous investigators have studied the changes that occur in bone mass after childbirth and throughout lactation.[45] In general, after childbirth, in those women who do not breastfeed their babies, a recovery of the loss in BMD at the level of the spine produced during pregnancy can be observed.[46] Conversely, in those women who breastfeed their newborns for 6 mo, there is a highly significant decrease of approximately 5% in the BMD of the lumbar spine.[27,40,44,47–49] More et al.[46] observed in women who breastfed for near 12 mo that the decrease in the mineral density of the spine continues throughout lactation; sometimes the loss was up to 10% of the vertebral bone mass.

Prentice[4] observed in those women who breastfed their babies for less than 6 mo that the loss of bone mass at the level of the proximal femur is similar to the one at the spine, and that the total skeleton has a global decrease of approximately 2% of the prelactation levels, with full recovery after 1 y.

Laskey et al.[50] analyzed the changes in the different subareas of the total skeleton and found that the density decrease affects only the trabecular component and can be seen in the dorsal and lumbar vertebrae, the pelvis, and the ribs, with no loss at the level of the long bones of the arms and the legs.

Calcium Balance During Lactation

Figure 4 shows the calcium balance in a mother who is breastfeeding and has a dietary intake of 1000 mg of calcium per day. The calcium absorption from the intestine is less than that observed during the last trimester of the pregnancy and similar to the absorption efficiency in the non-pregnant control women.[14,19,20,41] Therefore, during lactation the intestinal calcium absorption does not compensate for the amounts of calcium delivered in the mother's milk. As a consequence, there is a calcium bone loss to maintain the serum calcium within normal levels, of about 200 to 250 mg/d. This loss, if maintained for 6 mo, may cause a significant decrease of the trabecular bone, especially at the vertebral level.

In summary, during lactation the most important calcium homeostatic mechanism that operates during pregnancy, greater intestinal absorption of calcium, ceases to function. The increase in intestinal calcium absorption, secondary to the increase of $1,25(HO)_2$ D levels, is not seen during lactation. Instead, a high level of bone turnover is maintained, probably by the combined influence of PTHrP and prolactin. To maintain normal levels of calcium in the extracellular fluid, bone resorption predominates over bone accretion, thereby compensating for the losses to the mother's milk and the kidney. A bone mass of about 5% is lost in 6 mo. It should be kept in mind that the calcium concentration in the mother's milk is independent of the calcium content in her diet. Thus, the calcium stored in the trabecular bone has to be removed to keep an adequate concentration of calcium in the milk. The bone loss is likely greater if dietary calcium intake is low.

The re-establishment of the trabecular bone mass at the spine seems to be complete within 6 mo to 1 y in mothers who breastfeed for less than 6 mo. Increased secretion of estrogen and diminished PTHrP play a significant role for bone restoration after weaning. There are no studies indicating whether bone mass recovery in mothers who breastfeed for longer periods is complete, even after 12 mo after lactation. However, it is expected that, unless other events occur such as a new pregnancy and lactation, the recovery of bone mass would also be complete over time.

OSTEOPOROSIS ASSOCIATED WITH PREGNANCY AND LACTATION

It is important to mention that there are infrequent cases of women with osteoporotic fractures that occur by the end of pregnancy or during lactation.[19,51,52] The most frequent findings in these patients are multiple vertebral crushes or fractures at the level of the hip.

The physiopathology is not clearly defined. It may be that these women have a low bone mass due to inherited or acquired factors and that, if an exaggerated physiologic decrease of the trabecular bone occurs at the vertebral or femoral level, the bone mass is reduced below the theoretical fracture threshold. An extremely low calcium level has been observed in many of the cases.[53,54]

EFFECT OF PREGNANCY AND LACTATION ON THE RISK OF OSTEOPOROTIC FRACTURES LATER IN LIFE

One of the main areas of investigation centers on determining whether the calcium demands of pregnancy and lactation might increase the risk of osteoporotic fractures later in life.[41,55] Many studies have focused on this issue and have confirmed the observations of no increased risk made initially by Hoffman et al.[56] and most recently in studies by Hillier et al.,[57] Petersen et al.,[58] and Nguyen et al.[59] The consensus in these findings is that women who have one or more pregnancies during their lives actually have a diminished risk of hip and possibly vertebral fractures.

The study by Hillier et al.[57] followed for almost 10 y 9700 women older than 65 y and found that 5% of the women who had children developed hip fracture as opposed to the age-matched 9.1% of nulliparous women. Vertebral fractures also were more frequent in this group: 7.3% versus 4.9% of the women who had

children. Each pregnancy decreases the risk of a hip fracture by approximately 9%. Curiously, Petersen et al.[58] reported that men who have children also have a lower risk of hip fractures than do men who have never had children, which suggests the existence of an environmental component.

In the studies by Hillier et al.,[57] Nguyen et al.,[59] and Paton et al.,[60] the bone density of the hip of women who had children equaled the bone density of nulliparous women. However, the risk of hip fractures was significantly lower in those women who have had one or more pregnancies. Therefore, a possible hypothesis to explain the decrease of the risk of hip fractures without any variation in the BMD would be that each pregnancy produces a change in the proximal femur's dimension with an enlargement of the external diameter and a consequent increase in the cortical thickness of the femur that provides protection against hip fractures. Changes in the pelvic geometry should be studied as a possible explanation of the observed results.

In summary, studies done in postmenopausal women have shown that the BMD of women who have had one or more pregnancies during their lives is not different from the BMD of nulliparous women. This has been a very consistent finding, especially at the hip level. However, women who had children had a significantly lower risk of a hip fracture than did the nulliparous women. The protective effect seems to be proportional to the number of pregnancies. Each pregnancy likely produces changes that improve the biomechanical resistance of the upper femur. Expansion of the outer diameter of the femur, increased cortical bone thickness, or changes in the pelvic geometry are possible explanations that should be studied.

EFFECT OF CALCIUM SUPPLEMENTATION ON AXIAL BONE MASS DURING LACTATION AND WEANING

Although this is an important issue,[9,10] we found only two studies addressing the effect of calcium intake on axial bone mass in white women during lactation and weaning.[42,61]Prentice et al.[62] observed that the administration of 714 mg/d of calcium in lactating Gambian women had no effect on the bone mass of the radius. However, the results are not easily extrapolated to the studies made in white women due to the extremely low calcium diet of that population and to the known differences in mineral and bone metabolism of whites and blacks. Cross et al.[42] studied the effect of supplementation with 1 g of calcium during lactation in eight women versus seven on placebo. The baseline calcium intake in both groups was very high, approximately 1300 mg of calcium per day. No difference was observed in lumbar spine bone loss (~5%) between groups. The main criticisms of this study are the small number of subjects and their high baseline calcium intake.

Kalfwarf et al.[61] performed a somewhat similar study with a much larger group of women (~100/group) and lower baseline calcium intake (~650 to 820 mg/d). The BMD of the lumbar spine decreased by 4.2% in the lactating women receiving calcium and by 4.9% in those receiving placebo and increased by 2.2% and 0.4%, respectively, in the non-lactating women ($P < 0.01$ for the effect of calcium). After weaning, the BMD of the lumbar spine increased by 5.9% in the lactating women receiving calcium and by 4.4% in those receiving placebo; it increased by 2.5% and 1.6%, respectively, in the non-lactating women ($P < 0.001$ for the effects of calcium). If both studies are compared, it seems that calcium supplementation has some protective effect when the calcium intake is below approximately 800 mg/d.

CALCIUM RECOMMENDATIONS FOR WOMEN DURING PREGNANCY AND LACTATION

Current Dietary Reference Intakes (DRI) daily calcium recommendations of 1300 mg for mothers younger than 18 y and 1000 mg for women 19 to 50 y old[63] seem adequate to maintain bone health during pregnancy and lactation in most women. However, the calcium requirements for special cases such as adolescent mothers, multiple pregnancies, frequent pregnancies with prolonged lactation, or low calcium diets has yet to be studied. In such cases it is necessary to determine the preventive measures that can be implemented to avoid damage to the current and future bone health of the mothers.

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