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Calcium homeostasis and bone mass during pregnancy and lactation in adult and adolescent women

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ABSTRACT

Physiological adaptations of calcium and bone metabolism during pregnancy and lactation in adults and adolescents are reviewed in this work, with emphasis on intestinal absorption, urinary excretion, bone turnover and hormonal regulation. Adjustments to maintain calcium homeostasis during pregnancy and lactation in adult women appear to have no long-term deleterious effect to maternal bone health under a wide range of calcium intake. Much less is known about the ability of adolescent women to adapt to the high calcium demands of pregnancy and lactation while preserving maternal bone mass. Calcium requirements may double when pregnancy and lactation are associated with adolescence and the homeostatic mechanisms may not be sufficient to ensure an adequate bone mass accretion of the young mother together with adequate fetal growth and milk production. The available evidence indicates that pregnancy and lactation are physiological conditions that may adversely affect bone mass acquisition of adolescent women when calcium intake is low. Long term studies are needed to evaluate the impact of pregnancy and lactation during adolescence on maternal bone mass at adulthood. Micronutrients other than calcium, gene polymorphisms, and other special maternal groups should also be considered in studies on bone mass during pregnancy and lactation.

KEY WORDS: *Pregnancy and lactation, adolescent mothers, calcium intake, bone, homeostasis.*

INTRODUCTION

Pregnancy and lactation are periods of high calcium demand for fetal development and milk production. The increased calcium needs during pregnancy must meet the requirement for fetal growth (50-330 mg/d) that accounts for a total of 25-30 g of calcium.[1] During lactation, the additional calcium demand corresponds to the requirement for milk production (≈210 mg/d)[2] accounting for up to 38 g of calcium transferred to breast milk during six months of full lactation[3]. In adolescent mothers, there is an additional calcium need for maternal bone mass accumulation (210-290 mg/d).[4,5] This means that calcium requirements of adolescent mothers may double during pregnancy and lactation.

The increase in calcium needs during pregnancy and lactation is met primarily by physiological adaptations that include changes in intestinal calcium absorption, renal calcium conservation, calcium-related hormones, bone turnover and a temporary loss

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of bone. The mechanisms for maintaining calcium homeostasis during these periods are adapted to ensure an adequate fetal skeletal formation and milk production. These mechanisms, that appear to be quite specific to each physiological period, have been studied mainly in adult women. Less is known about the adjustments in calcium homeostasis during pregnancy and lactation in adolescent women. Results from the few studies conducted with adolescent mothers indicate that the physiological adaptations during pregnancy and lactation in these women may not be sufficient to ensure an adequate bone mass accumulation of the young mother, together with adequate fetal growth and milk production.

Bone loss during pregnancy and lactation and recovery after weaning have been described in adult women and appear to be independent of calcium intake. Less is known about the ability of adolescent women to adapt to the increased calcium demands due to pregnancy and lactation while preserving their own bone mass acquisition.

Studies addressing physiological adaptations in calcium and bone metabolism during pregnancy and lactation are reviewed in this work (Tables 1 and 2). The possible implications of pregnancy and lactation during adolescence for bone mass in women are discussed, with special attention when calcium intake is low, as frequently seen in adolescents.

PHYSIOLOGICAL ADAPTATIONS DURING PREGNANCY AND LACTATION

Intestinal absorption

During pregnancy, there is an increased efficiency of intestinal calcium absorption, accompanied by an increase in 1,25-dihydroxivitamin D, that significantly contributes to meet the calcium needs.[6-8] In adult women with high calcium intakes (> 950 mg/d), calcium absorption increased substantially in the third trimester of pregnancy compared to the pre-gestational period, with final values between 54-62%.[6,7] In adult women with habitually low calcium intake (~500 mg Ca/d), calcium absorption also increased during pregnancy and appeared to be very efficient throughout pregnancy (66-98%).[8] Therefore, it is possible that the adaptation on the efficiency of intestinal calcium absorption during pregnancy is modulated by the habitual maternal calcium intake.

During lactation, the efficiency of intestinal calcium absorption returns to levels similar to those observed before pregnancy[6,7] or at early pregnancy[8], in adult women. Therefore, this mechanism does not appear to contribute to meet the increased calcium demand of lactation. However, the intestinal calcium absorption during lactation is very efficient (52-65%) in women accustomed to a low calcium diet (300-500 mg/d),[8,9] suggesting that the habitual calcium intake, together with other environmental and genetic factors, modulate the efficiency of intestinal calcium absorption during lactation.

The efficiency of intestinal calcium absorption during pregnancy and lactation was measured in adolescent mothers in only one study.[10] These adolescents had high habitual calcium intake (~1200 mg/d). It was observed that during the third trimester of pregnancy intestinal calcium absorption was 60% higher than 3-4 wks postpartum, indicating that the increased efficiency of intestinal calcium absorption contributes to meet the calcium demands of pregnancy, but not of lactation, in adolescent mothers as also observed in adults. The efficiency of intestinal calcium absorption has not been measured in pregnant and lactating adolescents accustomed to low calcium diets.

Urinary calcium excretion

During pregnancy, an increase in urinary calcium excretion is frequently observed (100-300 mg/d)[6,7,11,12] due to the plasma volume expansion and the increased glomerular filtration rate. However, this increase appears to also reflect the concomitant increase in calcium intestinal absorption, since fasting urinary calcium concentrations are normal or slightly decreased.[13-15] The increase in urinary calcium excretion during pregnancy in adult women appears to be limited when calcium intake is habitually low.[8]

During lactation, glomerular filtration rate decreases and calcium tubular re-absorption increases resulting in reduced urinary calcium excretion which may be as low as 50 mg/d.[12] This reduction in urinary excretion occurs irrespective of habitual calcium intake[6-8,16] and appears to persist after weaning when maternal bone recovery takes place.[6] However, it is possible that at least part of this renal calcium conservation is a consequence of the postpartum state *per se*, as shown by studies comparing urinary calcium excretion between lactating and non-lactating postpartum adult women.[17,18]

Urinary calcium excretion in adolescent girls is usually found to be about half of that in adult women.[13,19,20] Few studies, however, measured urinary calcium excretion during pregnancy and lactation in adolescent women.[10,13] In adolescent mothers consuming ~1200 mg Ca/d, urinary calcium excretion was high during pregnancy and decreased about 75% in the postpartum period with no differences between lactating and non-lactating women.[10] A similar pattern of increase in urinary calcium excretion during pregnancy and decrease during lactation was observed in adolescent mothers consuming ~500 mg Ca/d.[13] However, comparison of these adolescents with corresponding groups of adult women indicated that the renal calcium conservation characteristic of adolescence is maintained during pregnancy and becomes even more efficient during lactation in adolescent mothers.[13] It is not known if similar results would be obtained at higher calcium intakes.

Bone turnover

Bone turnover is increased during pregnancy and lactation in adult women favoring a dynamic flux of minerals in and out of bone tissue that contributes to higher calcium availability for fetal growth and milk production.[12,21]

Studies in adult women indicate that levels of biochemical markers of bone turnover are high from early pregnancy and increase 50-200% at late pregnancy irrespective of maternal calcium intake.[6-8,11] The processes involved in bone remodeling appear to be decoupled during pregnancy since the alterations in bone resorption markers precedes those in bone formation markers.[11] This asynchrony appears to result in a fast bone mineral release that is followed by a gradual bone reconstitution.[1] During pregnancy, the levels of biochemical markers of bone resorption may triplicate while markers of bone formation remain at normal levels, slightly increased or decreased, such as observed for serum osteocalcin.[6,11] However, osteocalcin production is apparently not decreased during pregnancy[11] and the fall in its circulating levels appear to be due to an increase in degradation rate or placental uptake of osteocalcin.[1]

During early lactation in adult women, bone turnover is similar to or even more intense than in the third trimester of pregnancy[6-8,11,13] and decreases after six months postpartum.[22] Longitudinal studies have shown that serum osteocalcin increases during lactation, returning to pre-pregnancy levels.[6,11] The alterations observed in markers of bone metabolism are influenced by the intensity and duration of lactation and are more pronounced in those mothers who breastfed for longer periods.[1] As also observed during pregnancy, there is evidence of asynchrony between bone resorption and formation during lactation.[1] The levels of bone resorption markers peak a few weeks before the increase in those of bone formation, and are also the first ones to return to the normal pre-pregnancy levels.[18,23] Markers of bone resorption and formation are also elevated during lactation when habitual calcium intake is very low (<300 mg/d)[23] and are not influenced by calcium supplementation.[23]

Few studies measured biochemical markers of bone turnover in adolescent mothers.[13,24,25] A study comparing bone turnover markers in pregnant and lactating women, adolescents and adults, with low calcium intake,[13] indicated that the increase in bone resorption, typical of pregnancy and lactation, is less pronounced in adolescent mothers, possibly contributing to prevent an excessive loss of bone in these mothers.

Bone mass

Although techniques actually used to the direct evaluation of bone mass are considered non-invasive and of low exposition to radiation, they are not recommended for pregnant women. Therefore, the investigation of bone mass modifications during pregnancy is restricted to less sensitive techniques, such as ultrasonometry, or is limited to measurements before conception and immediately postpartum.

At present, little is known about changes in bone mass during pregnancy in adult women. Some longitudinal studies observed bone losses during pregnancy,[11,26,27] whereas no modifications were observed by others.[6,7] Several factors contribute to the discrepancy of data, including different bone sites evaluated and the fact that some of these studies started at early pregnancy and not before conception.[11,26] Moreover, the maternal skeleton during pregnancy may be under the influence of several other factors including age, number of gestations and maternal nutritional status, that may affect the interpretation of results.

Losses of 3 to 9% in bone mineral content were observed after 2-6 months of lactation in adult women with calcium intake between 800-1400 mg/d,[7,17,28-30] with later bone mass recovery after weaning, specially after the return of menses.[7,17,28] The temporary loss of

Table 1
Physiological adaptations affecting calcium and bone homeostasis during pregnancy in adult and adolescent women

	Adaptation during Pregnancy*	
Mechanism	Adult women	Adolescent women
Efficiency of intestinal calcium absorption	Increased [6-8]	Possibly increased [10]
Urinary calcium excretion	Increased [6,7,11,12]	Increased [13]
Bone turnover	Increased [6-8,11]	Increased [13]
Bone mass	No change or decreased [6,11,26,27]	Possibly decreased [10,26]
Serum hormones		
PTH	No change or decreased [6,11,13]	Decreased [13]
PTH-rP	Increased [12,31]	nd†
1,25$(OH)_2$D	Increased [6,7,8,14]	nd
Estrogen	Increased [6,7]	nd
IGF1	Increased [8,11]	nd

* Compared to the non-pregnant non-lactating state.
† nd, no published data.

Table 2
Physiological adaptations affecting calcium and bone homeostasis during lactation in adult and adolescent women

	Adaptation during Lactation*	
Mechanism	Adult women	Adolescent women
Efficiency of intestinal calcium absorption	No change [6,7]	Possibly no change [10]
Urinary calcium excretion	Decreased [6-8,16]	Decreased [13]
Bone turnover	Increased [6-8,11,13]	Increased [13]
Bone mass	Decreased [7,17,28-30]	Possibly decreased [10,34]
Serum hormones		
PTH	No change or decreased [6,7,13,23,29]	No change [13]
PTH-rp	Increased[31]	nd†
1,25$(OH)_2$D	No change or decreased [6,7,23]	nd
Estrogen	Decreased[17,31]	nd
IGF1	No change[8,11]	nd

* Compared to the non-pregnant non-lactating state.
† nd: no published data.

bone mass during lactation was also observed in adult women with very low calcium intake (<300 mg/d) and was not influenced by calcium supplementation.[23] Changes in bone mineral density associated with lactation are, in part, mediated by the postpartum hormonal environment, in particular by parathyroid hormone-related peptide (PTHrP) and prolactin in the setting of a fall in estrogen levels.[31,32]

Few studies evaluated the effect of pregnancy and lactation in bone mass of adolescents.[10,26,33,34] Significantly higher bone losses in adolescent mothers compared to adult mothers were observed after pregnancy[26] and during lactation.[33] Chan et al[33] observed a significant reduction (up to 15%) in bone mineral content from the 2nd to 16th week of lactation in women younger than 18 years. Important deficits in bone mass were observed at early lactation in adolescent mothers with high[10] and low[34] calcium intakes.

Although the habitual calcium intake does not influence the loss of bone mass during pregnancy and lactation in adult women, it is possible that a higher calcium intake during these physiological periods contributes to minimize bone losses in adolescent women. Consistent with this hypothesis, a 10% decrease in bone mass during lactation was observed in adolescent mothers consuming 900 mg Ca/d whereas no bone loss was observed when the adolescents were supplemented with dairy products (1600 mg Ca/d).[35] Moreover, calcium supplementation with dairy products of pregnant adolescents resulted in higher newborn bone mineralization compared to control.[36] Also, in a study with adolescent mothers, bone mineral density measured at early lactation showed a positive correlation with calcium intake during pregnancy.[10] However, in spite of the high calcium intake of the adolescent mothers, net calcium retention during pregnancy was not sufficient to ensure the adequate bone calcium deposition of the young mothers together with the fetal growth,[10] suggesting a possible adverse effect in maternal bone mass.

The period of time needed to the total recovery of bone mass after pregnancy and lactation in adult women depends on several factors including duration of breastfeeding, duration of the postpartum amenorrhea and the skeletal site evaluated.[18] Studies in adult women have observed that bone density returns to pre-pregnancy levels after 12-18 months postpartum.[7,17,37]

Although maternal bone recovery after weaning appears to occur efficiently in adult women, there is evidence that this process may be compromised in adolescent mothers, at least when calcium intake is low.[34] Changes in bone mass from lactation to the post-weaning period were evaluated in adolescent mothers with calcium intake < 500 mg/d.[34] The lactation-induced bone loss was recovered after weaning in these adolescents as seen in adult women. However, the rate of bone accretion from lactation to post-weaning did not appear sufficient to ensure full bone mass recovery at levels similar to those in never pregnant adolescents.[34] It is possible that different results could have been obtained at higher calcium intakes. In fact, a study performed by secondary analysis of data from the NHANES III found that young adult women who breastfed during adolescence had greater bone mineral density than those who did not lactate and similar to that of nulliparous women.[38]

Additional considerations

Besides calcium, the intake of several other micronutrients may influence bone metabolism during pregnancy and lactation. Zinc, copper, magnesium and the vitamins C, A, D and K are also required for adequate synthesis of bone matrix constituents, bone cell differentiation and bone responses to growth factors.[39-41] Moreover, a sub-adequate intake of these micronutrients is frequently observed in women in developing countries, especially in adolescents.[42,43] The contribution of the nutritional status of micronutrients other than calcium on bone homeostasis during pregnancy and lactation needs to be investigated.

Several gene polymorphisms have been associated with calcium homeostasis and bone mineral density in different life stages.[44] The most investigated genes include those encoding for bone matrix proteins, for bone metabolism regulators and hormone receptors, especially the vitamin D receptor gene (VDR).[44,45] Although the contribution of genetic factors on the physiological responses to pregnancy and lactation may provide relevant information, genetic polymorphisms were poorly investigated in relation to bone mass and calcium homeostasis in these physiological states.[30,46] The results from the few studies in adult women indicate that the maternal skeletal response during lactation is not influenced by VDR polymorphisms.[30,46] However, VDR genotypes (*Apa1* and *Bsm1*) influenced total and lumbar spine bone mineral density, serum PTH and breast-milk calcium concentration in adolescent mothers,[47] consistent with the notion that the genetic contribution to bone mass may be more evident at younger age.[48-50]

The pubertal stage at conception also needs to be considered when evaluating bone loss during pregnancy and lactation and the recovery after weaning in adolescent mothers, since bone turnover is higher at early adolescence and bone mass accumulation peaks close to menarche.[51] However, very few studies addressed this effect. In one study,[34] the rate of bone calcium accretion from lactation to post-weaning in adolescent mothers decreased with the time elapsed since menarche. In contrast, O'Brien *et al*[10] observed that calcium absorption during pregnancy was not affected by maternal age across the range of 13-18y.

More studies are needed to evaluate the effect of the maternal pubertal stage on calcium and bone metabolism during pregnancy and lactation, and on lactational performance of adolescent mothers.

There are other special groups of women, besides adolescent mothers, for whom the process of bone loss during pregnancy and lactation and recovery after weaning may be compromised. These include women who breastfed multiple infants, women with closely spaced pregnancies and women with advanced maternal age, although information regarding these groups are limited.[3,52,53]

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RESUMEN

En este trabajo se hace una revisión de las adaptaciones fisiológicas del metabolismo del calcio y hueso durante el embarazo y lactancia en mujeres adultas y adolescentes, con énfasis en la absorción intestinal, la excreción urinaria, el recambio óseo y la regulación hormonal. En mujeres adultas los ajustes para mantener la homeostasis del calcio durante el embarazo y la lactancia parecen no tener ningún efecto nocivo a largo plazo en la salud ósea materna, dentro de un amplio intervalo de ingestión de calcio. En el caso de los adolescentes se sabe mucho menos sobre la capacidad de adaptación a las altas demandas de calcio durante el embarazo y la lactancia para preservar la masa ósea materna. Los requerimientos de calcio pueden duplicarse si el embarazo y la lactancia se asocian con la adolescencia y los mecanismos homeostáticos pueden no ser suficientes para asegurar un adecuado incremento de la masa ósea de la madre joven, junto con un adecuado crecimiento fetal y la producción de leche. La evidencia disponible indica que el embarazo y la lactancia son condiciones fisiológicas que pueden afectar la adquisición de masa ósea de mujeres adolescentes cuando la ingestión de calcio es baja. Se necesitan estudios a largo plazo para evaluar el impacto del embarazo y la lactancia durante la adolescencia en la masa ósea materna en la edad adulta. Los estudios acerca de la masa ósea durante el embarazo y la lactancia, deben considerarse el análisis del calcio, de otros micronutrientes, el polimorfismo genético, así como considerar el estudio de otros grupos vulnerables, como el materno.

PALABRAS GUÍA: *Embarazo y lactancia, madres adolescentes, ingestión de calcio, hueso, homeostasis.*

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