

Calcium Supplementation during Pregnancy and Lactation: Implications for Maternal and Infant Bone Health

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29.1 Introduction

It is widely recognized that pregnancy and lactation are periods of high maternal calcium demands for fetal and infant skeletal growth and mineralization (Olausson *et al.*, 2012). During pregnancy, the fetus accumulates a total of 20–30 g of calcium at a rate up to 250–300 mg per day in the third trimester. During lactation, the rate of maternal calcium transfer to the mammary gland for breast milk secretion is 200–300 mg per day, thus providing a total of 35–50 g of calcium to the infant during 6 months of breastfeeding.

Considering that the skeleton of an adult woman contains 800–900 g of calcium, total maternal calcium losses during pregnancy and 6 months of lactation represent 3 and 5%, respectively, of total maternal bone calcium. In theory, mobilization of maternal bone calcium could supply the calcium required for the developing fetus and the lactating infant. In fact, temporary loss of maternal bone mass is a well-established physiological adaptation during human pregnancy and lactation.

Several stage-specific physiological adaptations are known to contribute to meet the increased calcium requirements for pregnancy and lactation. These adaptations have been extensively reviewed and recently summarized elsewhere (Olausson *et al.*, 2012). Briefly, during pregnancy, additional calcium is obtained primarily from increased efficiency of intestinal calcium absorption, and to some extent from increased maternal bone turnover, particularly during the last trimester. During lactation, conservation of renal calcium plays a role but the primary adaptation is mobilization of maternal bone calcium resulting in maternal bone loss that is recovered after weaning.

It is well accepted that in women with calcium intakes close to current recommendations (National Research Council, 2011), the physiologic adaptations for providing calcium to the fetus and infant are largely independent of calcium intake (Olausson *et al.*, 2012). In these women, there is no apparent bone benefit for the mother or infant of using calcium supplements. However, in women consuming low-calcium diets, maternal bone adaptations during reproduction have been found to respond to increased calcium intake or supplementation, although not always as expected. Moreover, fetal and infant skeletal development has been found to be positively associated with increased maternal calcium intake/supplementation during pregnancy in some but not all studies. These apparently inconsistent results are possibly due to the complex interactions between genetics, diet composition, environment and lifestyle on maternal and infant bone responses during pregnancy and lactation.

In this chapter, studies evaluating the effect of maternal calcium intake during pregnancy and lactation, from the diet and from supplements, on maternal bone outcomes and on fetal and infant bone growth are reviewed. The effects of other factors on bone outcomes and the possible implications for the maternal and infant bone health are considered.

29.2 Calcium Supplementation and Maternal Bone Outcomes

When interpreting maternal bone responses to calcium intake or supplementation, it is important to consider that bone outcomes during pregnancy and lactation are affected by multiple factors and that bone responses are difficult to fully evaluate because of limitations in study design, sample size and bone measurements. These limitations have been thoroughly discussed in a recent review (Olausson *et al.*, 2012). Measurement of BMC and BMD prior to

pregnancy and lactation is the ideal baseline but it is challenging to achieve in practice. Because of this difficulty only a few studies have used this approach (Ritchie *et al.*, 1998; Olausson *et al.*, 2008). Changes in bone mass and density are not generally measured during pregnancy due to poor precision of the ultrasound technique suitable for use in pregnant women, or to avoid unnecessary exposure of the fetus to ionizing radiation when using DXA. Bone measurements 1–3 weeks after delivery are generally assumed to reflect bone changes during pregnancy even in breastfeeding mothers. Serial bone measurements after delivery during breastfeeding, and after a period of time since cessation of breastfeeding are assumed to reflect bone responses to lactation and weaning, respectively. Comparisons over time with an appropriate control group (nonlactating postpartum or nonpregnant nonlactating) have been done only in few studies. In postweaning assessment, the time elapsed since onset of weaning may have not been sufficient to ensure that bone has reached a steady state. In many studies, bone outcomes are assessed indirectly by measuring changes in bone-turnover markers during pregnancy and lactation, assuming that changes in the dynamics of bone metabolism reflect changes in bone status. Confounding factors considered in some, but not all studies, include maternal age, parity, changes in body weight, vitamin D status, breastfeeding practice, hormone contraception, return of menses, and the residual effect of a previous recent pregnancy and lactation.

29.2.1 Effects of Calcium Supplementation during Pregnancy

There are several longitudinal studies relating maternal dietary calcium intake during pregnancy to maternal bone outcomes during pregnancy and postpartum although only a few studies have tested the effect of calcium supplementation during pregnancy in randomized placebo-controlled trials (Table 29.1).

Among observational studies, no effect (Olausson *et al.*, 2008) and positive effects (O'Brien *et al.*, 2003; Zeni *et al.*, 2003; O'Brien *et al.*, 2006; Avendaño-Badillo *et al.*, 2009) of dietary calcium intake during pregnancy on maternal bone have been described. No effect was found in a study in UK adult women with mean calcium intake ≥ 1000 mg per day, with comparison over time between pregnant and nonpregnant nonlactating groups (Olausson *et al.*, 2008). In this study, pregnancy was associated with substantial decreases in whole body (-1.7%) and regional (spine, -3.03% and total hip, -1.87%) BMC. Increase in body weight was a significant predictor of the skeletal changes but calcium intake did not affect bone responses to pregnancy in these women. On the other hand, in a study of adolescent women from the third trimester of pregnancy to early postpartum, with mean calcium intake of 1200 mg per day, lumbar spine Z scores postpartum were significantly associated with calcium intake during pregnancy ($R^2 = 0.355$, $P < 0.02$) (O'Brien *et al.*, 2003). Although dietary calcium was close to the 1300 mg per day reference intake for adolescents (National Research Council, 2011), a higher intake during pregnancy appeared to be protective against loss of trabecular bone in these young mothers.

Table 29.1 Studies relating dietary calcium or calcium supplementation during pregnancy and maternal bone outcomes.^a

References	Type of study	Country, maternal age and study groups (n)	Mean dietary Ca mg per day	Ca supplement mg per day	Maternal bone outcomes	Overall effect of calcium intake/ supplementation during pregnancy on maternal bone
Zeni <i>et al.</i> (2003)	Prospective cohort	Argentina, 17–30 years, Pregnant, 12 to 38 weeks (39) NPNL women (30)	790 530	—	Bone resorption markers increased during pregnancy; changes between the 3rd and 2nd trimester were negatively correlated with Ca intake	Positive
O'Brien <i>et al.</i> , 2003	Prospective cohort	US, 13–18 years, Pregnant, 3rd tri (23) to 1 month PP (15)	1200	—	LS BMD Z scores at postpartum positively associated with Ca intake during the third trimester of pregnancy	Positive
O'Brien <i>et al.</i> (2006)	Prospective cohort	Brazil, 21–34 years, Pregnant, 10–12 weeks pregnancy to 7–8 weeks PP (10)	460	—	Net balance in bone calcium turnover positively associated with dietary calcium intake during pregnancy and early lactation	Positive
Avendaño-Badillo <i>et al.</i> (2009)	Prospective cohort	Mexico, 15–43 years, Pregnant, 12 to 34 weeks (206)	998	—	Inverse association between dietary calcium intake and NTx (bone resorption marker) during pregnancy	Positive
Olausson <i>et al.</i> (2008)	Prospective cohort	UK, 23–37 years, Pregnant, prepreg. to 2 weeks PP (34) NPNL (84)	1008–1345 1001	—	Decrease in adjusted BMD and BMC at whole-body, spine and hip in the pregnant women, independent of Ca intake during pregnancy	No effect

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Table 29.1 (continued)

References	Type of study	Country, maternal age and study groups (n)	Mean dietary Ca mg per day	Ca supplement mg per day	Maternal bone outcomes	Overall effect of calcium intake/ supplementation during pregnancy on maternal bone
O'Brien <i>et al.</i> (2012)	Prospective cohort	Three cohorts Pre/early preg. to 3–10 weeks PP US, 13–18 years (23) US, 25–34 years (13) Brazil, 20–35 years (10)	1200 1200 450	—	At late pregnancy, inverse association between rate of bone calcium deposition and 1,25-(OH) ₂ D ₃ , particularly in the adolescents and low calcium cohorts. No association with calcium intake	No effect
Janakiraman <i>et al.</i> (2003)	RCO	Mexico, 15–43 years Pregnant, 25–35 weeks, treated during 20 days Calcium-Placebo (16) Placebo-Calcium (15)	1031 959	1200	14% decrease in NTx (bone resorption marker) in response to Ca supplementation compared to placebo (multivitamin)	Positive
Liu <i>et al.</i> (2011)	RCT	China, 24–31 years Pregnant, 20 weeks preg. to 6 weeks PP Control (12) Milk suppl. (12) Milk suppl. + Ca suppl. (11)	480 479 486	— 350 950	Higher total and LS BMD in women with calcium and milk powder supplementation than in those in the control group. Serum osteocalcin increased only in the calcium/milk intervention groups	Positive

Author (Year)	Study Design	Population	Intervention	Control	Sample Size	Outcomes
Diogenes <i>et al.</i> (2013)	RCT	Brazil, 13–19 years pregnant, treatment 26 weeks preg. to delivery	Ca suppl. (30)	Placebo (26)	500 743	At 20 weeks PP, higher BMC (13.9%), BA (6.2%) and BMD (10.6%) at the LS in the supplemented group. Less pronounced decrease in femoral neck BMD from 5 to 20 weeks PP in the supplemented (3.0%) than in the placebo (4.5%) groups
Jarjou <i>et al.</i> (2010)	RCT	The Gambia, 27.4 ± 7.5 years pregnant, treated 20 weeks preg. to delivery	Ca suppl. (61)	Placebo (64)	355 355	Lower size-adjusted BMC, BA, and BMD at the hip and greater decreases in BMC at LS and distal radius throughout 12 months lactation in the Ca-supplemented group
Jarjou <i>et al.</i> (2013)	RCT	The Gambia, 29 ± 8 years Treated 20 weeks to delivery in a previous pregnancy	Ca suppl. (31)	Placebo (28)	329	After 5 years, the lower maternal BMC in the calcium-supplemented group from the previous trial persisted over time irrespective of subsequent pregnancy and lactation
		Lact.	Ca suppl. (24)	Placebo (20)	330	Negative

*Overall effect of calcium intake/supplementation: positive when associated with preservation of bone, and negative with loss of bone. RCT, randomized controlled trial; RCO, randomized crossover trial; PP, postpartum; NPNI, nonpregnant nonlactating women; BMC, bone-mineral content; BMD, bone-mineral density; BA, bone area; LS, lumbar spine; UD, ultradistal.

Studies in different populations with dietary calcium between 500 and 1000 mg per day indicate that increased calcium intake during pregnancy reduces maternal bone turnover and possibly bone calcium mobilization. In a longitudinal study in Argentina (Zeni *et al.*, 2003), a negative correlation was found between increase from the second to third trimester of pregnancy of different biochemical markers of bone turnover (NTx, β CTx, bone alkaline phosphatase) and calcium intake at late pregnancy. Similarly, an inverse association between dietary calcium, particularly from dairy products, and urinary levels of NTx was found during pregnancy in a study in Mexico (Avendaño-Badillo *et al.*, 2009). Consistent with these results, a crossover trial (Janakiraman *et al.*, 2003) showed that short-term use of calcium supplements during the third trimester of pregnancy decreased urinary NTx, a marker of bone resorption. Also, net balance in bone calcium turnover (deposition minus resorption) was positively associated with dietary calcium in a kinetic study during pregnancy and lactation in Brazilian women (O'Brien *et al.*, 2006). When three different cohorts of women were compared during pregnancy and postpartum using kinetic modeling (O'Brien *et al.*, 2012), elevated 1,25-(OH)₂D was associated with decreased rates of bone calcium deposition during late pregnancy, particularly in the adolescent US cohort and in the Brazilian adult cohort with low calcium intake.

Among randomized controlled trials studies, both positive (Liu *et al.*, 2011; Diogenes *et al.*, 2013) and negative (Jarjou *et al.*, 2010; Jarjou *et al.*, 2013) maternal bone outcomes in response to calcium supplementation during pregnancy have been described.

Positive effects have been found irrespective of maternal age. A dose-dependent relationship between calcium intake from midpregnancy to 6 weeks postpartum (usual diet supplemented with milk powder and calcium carbonate) and maternal BMD at postpartum was observed in adult Chinese women habitually consuming <500 mg per day dietary calcium. Maternal bone responses were site specific, being significant at the whole-body and spine, but not at the hip. Milk/calcium supplementation suppressed postpartum bone resorption (NTx) but serum osteocalcin (a marker of bone formation and bone calcium retention) was increased by supplementation in these women (Liu *et al.*, 2011). In a study of Brazilian adolescent mothers with habitual low calcium diets (\approx 600 mg per day), supplementation with calcium (600 mg per day) plus vitamin D (200 IU per day) during the third trimester of pregnancy resulted in higher lumbar spine bone mass at 5 and 20 weeks postpartum, and reduced rate of bone loss at the femoral neck during the first 20 weeks of lactation, compared to placebo (Diogenes *et al.*, 2013).

In contrast, calcium supplementation (1500 mg per day) during the second half of pregnancy of Gambian women with very low calcium diets (\approx 350 mg per day) resulted in lower BMC, BA and BMD at the hip throughout 12 months of lactation, compared to placebo. The supplemented group also had greater decreases in BMC at the lumbar spine and radius, and had biochemical changes consistent with greater bone mineral mobilization (Jarjou *et al.*, 2010). Serum 1,25-(OH)₂D decreased from 20 weeks pregnancy to 13

weeks lactation irrespective of treatment but to a larger extent in the calcium-supplemented women. A follow-up study conducted 5 years later in a subset from the same cohort scanned after a subsequent pregnancy and lactation indicated that the lower BMC in the calcium supplemented group from the previous trial persisted over time (Jarjou *et al.*, 2013). It was suggested that in these women accustomed to very low calcium intakes, the use of calcium supplementation during pregnancy disrupted the physiologic adaptation to conserve calcium for fetal and breast milk needs resulting in lower long-term maternal bone calcium. Besides habitual calcium intake, differences in diet composition, vitamin D status, breastfeeding practice, duration of lactation amenorrhea, physical activity, exposure to environmental pollutants, and genetics may explain differences in response to calcium supplementation between women from Gambia and from other countries, but further research is needed to confirm these hypotheses.

29.2.2 Effects of Calcium Supplementation during Lactation

Prospective cohort studies and randomized controlled trials have been done to test associations between calcium intake/supplementation during lactation and maternal bone outcomes (Table 29.2).

In general, studies in adult women consuming close to 1000 mg per day or higher dietary calcium indicate that there is no relationship between calcium intake and maternal bone outcomes during lactation and postweaning (Sowers *et al.*, 1993; Sowers *et al.*, 1995; Laskey *et al.*, 1998; Laskey *et al.*, 2011). It appears that in well-nourished adult women the physiological maternal bone loss during lactation and recovery after weaning is explained mostly by factors such as duration of breastfeeding, total breast-milk output, hormonal changes, resumption of menses, and changes in body weight, but not by different amounts of calcium intake close or higher than reference intakes during these periods. However, some studies provide evidence of positive effects of increasing calcium intake on maternal bone outcomes under certain conditions (Chan *et al.*, 1987; Krebs *et al.*, 1997; O'Brien *et al.*, 2012).

In a longitudinal study comparing three groups of well-nourished lactating women, adolescents and adults, from 4 weeks predelivery until 16 weeks postpartum (Chan *et al.*, 1987), BMC decreased during lactation in the adolescent group consuming 900 mg per day but not in the adult and adolescent groups consuming ≥ 1500 mg per day calcium. These results suggest that bone loss during lactation in adolescent mothers may be prevented by increased dietary calcium intake. Consistent with these results, in a kinetic study comparing three cohorts of women from different populations (O'Brien *et al.*, 2012), a higher calcium intake postpartum was associated with higher rates of bone-calcium deposition, particularly in the adolescent cohort and in the adult cohort accustomed to a low-calcium diet.

In a study up to 7 months postpartum of lactating and nonlactating adult women consuming 1400 mg per day calcium (Krebs *et al.*, 1997), BMD at the lumbar spine in the lactating women was positively associated with the ratio

Table 29.2 Studies relating dietary calcium or calcium supplementation during lactation and maternal bone outcomes.^a

Reference	Type of study	Country, maternal age and study groups (n)	Mean dietary Ca mg per day	Ca supplement mg per day	Maternal bone outcomes	Overall effect of calcium intake/supplementation during lactation on maternal bone
Sowers <i>et al.</i> (1993)	Prospective cohort	US, 20–40 years Lactation and weaning 1 to 18 months PP (98)	>1500	—	5% bone loss at the spine and femoral neck at 6 months PP during lactation and complete recovery after weaning. No relationship with dietary calcium intake	No effect
Sowers <i>et al.</i> (1995)	Prospective cohort	US, 20–40 years Lactation and weaning 1 to 18 months PP (112)	1526–1830	—	Higher markers of bone turnover with longer duration of breastfeeding. No relationship with dietary calcium intake	No effect
Krebs <i>et al.</i> (1997)	Prospective cohort	US, 31 ± 4 years 0.5 to 7 months PP Lactating (27) NLPP (8)	1400 875	—	↓LSBMD only in the lactating women (4.0%); LSBMD positively associated with the ratio of calcium to protein intake	Positive
Laskey <i>et al.</i> (1998)	Prospective cohort	UK, 20–40 years 0.5 to 3 months PP Lactating (47) NLPP (11) NPNL (22)	1390 1180 960	—	↓BMC at spine (3.96%), femoral neck (2.39%), total hip (1.51%) and whole body (0.86%) only in the lactating group. No relationship with calcium intake	No effect
Laskey <i>et al.</i> (2011)	Prospective cohort	UK, 32 ± 4 years 2 weeks to 12 months PP Lactating (48) NPNL (23)	1254 904	—	Lactation was associated with significant but transient changes in hip BMD and measures of structural geometry. Bone changes were not associated with Ca intake	No effect

O'Brien <i>et al.</i> (2012)	Prospective cohort	Three cohorts Pre/early preg. to 3-10 weeks PP US, 13-18 years (23) US, 25-34 years (13) Brazil, 20-35 years (10)	1200 1200 450	—	During the postpartum period, positive association between rate of bone calcium deposition and dietary calcium	Positive
Chan <i>et al.</i> (1987)	Prospective cohort	US, Lactating 4 weeks prepartum to 16 weeks PP 19-35 years (12) 15-18 years (21) 15-18 years (15)	1500 >1600 900	—	10% decrease in BMC in the adolescent group consuming daily 900 mg Ca. No decrease in the high Ca groups. Positive correlation between dietary calcium intake and BMC in all adolescents	Positive
Cross <i>et al.</i> (1995)	RCT	US, 28 ± 1 years Lactating 2 weeks PP to 3 months and PW Ca suppl. (7) Placebo (8)	950	1000	Lactation: ↓LSBMD in both groups (Ca sup, -6.3%; placebo, -4.3%); ↑UDradius BMD (5.7%) only in the calcium group. After weaning compared to baseline: ↓UDradius BMD (-5.2%) only in the placebo group; no significant change in LSBMD in either group	Positive (slight)
Kalkwarf <i>et al.</i> (1997)	RCT	US, 21-40 years Lactation: 16 days to 6 months PP Lact. (97) NLPP (99)	821 650	1000 + vit D (400 IU) or placebo	Lactation study: ↓LSBMD only in the lactating women; slightly lower reduction with calcium supplementation: Ca sup, 4.2%; placebo, 4.9%. No effect in forearm BMD Weaning study: ↑LSBMD in both groups; slightly higher increase with calcium supplementation: Ca sup, 5.9%; placebo, 4.4%. No effect in forearm BMD	Positive (slight)

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Table 29.2 (continued)

Reference	Type of study	Country, maternal age and study groups (<i>n</i>)	Mean dietary Ca mg per day	Ca supplement mg per day	Maternal bone outcomes	Overall effect of calcium intake/supplementation during lactation on maternal bone
Kalkwarf <i>et al.</i> (1999)	RCT	US, 21–40 years Lactation: 16 days to 6 months PP Lact. (97) NLPP (99) Weaning: 6 to 12 months PP	860 699	1000 + vit D (400 IU) or placebo	Biomarkers of bone turnover higher in lactating than in nonlactating women during lactation and post weaning. No effect of Ca supplementation	No effect
Prentice <i>et al.</i> (1995)	RCT	Lact (95) NLPP (92) The Gambia, 16–41 years Lactating, 2 to 52 weeks PP	739 711	714 —	No significant differences in forearm BMC between Ca supplemented and placebo groups at any stage of lactation	No effect
Prentice <i>et al.</i> (1998)	RCT	Ca suppl. (30) Placebo (30) The Gambia, 16–41 years Lactating, 1.5 to 78 weeks PP Ca suppl. (30) Placebo (30)	275 288 278 288	714 — 714 —	Increased bone turnover markers and decreased serum PTH and 1,25-(OH) ₂ D during the first months of lactation; no effect of Ca supplementation	No effect

^aOverall effect of calcium intake/supplementation: positive when associated with preservation of bone, and negative with loss of bone. RCT, randomized controlled trial; PP, postpartum; PW, postweaning; NPNI, nonpregnant nonlactating; NLPP, nonlactating postpartum women; BMC, bone-mineral content; BMD, bone-mineral density; BA, bone area; LS, lumbar spine; UD, ultradistal.

of calcium to protein intake in the diet, suggesting that maternal bone loss during lactation may be attenuated by an increased intake of calcium relative to protein in populations with habitually high protein intake. It was hypothesized that in women with low calcium intakes, the effects of lactation on BMD could be attenuated by the fact that their habitual diet may be also low in protein (Krebs *et al.*, 1997).

Randomized controlled studies indicate that calcium supplementation during lactation has no effect on maternal bone outcomes during lactation and postweaning, both in women accustomed to dietary calcium ≥ 800 mg per day (Cross *et al.*, 1995; Kalkwarf *et al.*, 1997; Kalkwarf *et al.*, 1999) and in women on very low dietary calcium (≈ 300 mg per day) (Prentice *et al.*, 1995; Prentice *et al.*, 1998). However, subtle positive effects have been described in some of these studies (Kalkwarf *et al.*, 1997; Prentice *et al.*, 1998).

When well-nourished Caucasian women received 1000 mg per day calcium (together with vitamin D, 400 IU per day) or placebo during 6 months postpartum, the decrease in lumbar spine BMD seen in the lactating women was slightly but significantly lower in the calcium supplemented (-4.2%) than in the placebo (-4.9%) group (Kalkwarf *et al.*, 1997). In the same study, when cohorts were treated during weaning, lumbar spine BMD increased slightly more in the calcium supplemented ($+5.9\%$) than in the placebo ($+4.4\%$) group. Therefore, calcium supplementation did not prevent bone loss during lactation in these women but slightly reduced loss and enhanced regain in bone density after weaning.

In lactating Gambian women, providing calcium supplement to increase calcium intake to about 1000 mg per day proved to be of no benefit for maternal BMC at the radius midshaft and wrist (Prentice *et al.*, 1995), neither modified the increased bone turnover (Prentice *et al.*, 1998) during several months of lactation. But, at 52 weeks postpartum bone alkaline phosphatase was significantly lower in the calcium-supplemented group compared to placebo, suggesting a reduction in bone turnover during lactation by use of the supplemental calcium. On the other hand, at 13 weeks postpartum, and irrespective of calcium supplementation, Gambian mothers had higher serum PTH, $1,25\text{-(OH)}_2\text{D}$, and osteocalcin than British lactating women with greater habitual dietary calcium (>1000 mg per day), suggesting differences in the magnitude of adaptive mechanisms between these two populations. As previously mentioned, ethnic, genetic, life style, and environmental differences could be underlying factors.

29.3 Calcium Supplementation and Fetal/Infant Bone Growth

It is well accepted that calcium homeostasis during pregnancy and lactation is overwhelmingly in favor of the fetus/neonate (Prentice, 2003). Nevertheless, fetus and neonate are dependent on maternal calcium and it is plausible to expect that changes in maternal calcium intake may affect intra-uterine and/or postnatal bone development through changes in placental

calcium transfer and/or breast-milk calcium content. Studies evaluating the influence of maternal calcium intake from diet or from supplements during pregnancy on fetal and infant skeletal development are summarized in Table 29.3. Studies of calcium supplementation during lactation have been mainly focused on breast-milk calcium.

Increasing maternal calcium intake during pregnancy, through diet or supplements, has been shown to positively affect newborn bone mineral mass in some (Koo *et al.*, 1999; Chang *et al.*, 2003; Chan *et al.*, 2006; Young *et al.*, 2012), but not all studies (Jarjou *et al.*, 2006; Abdel-Aleem *et al.*, 2009; Abalos *et al.*, 2010). Many factors possibly contribute to different observations, such as differences in study design, methods used for fetal/infant bone assessment, timing of fetal/infant bone evaluation, genetic background, maternal age, maternal gestational weight gain, overall maternal nutritional state, and more specifically maternal habitual calcium intake.

29.3.1 Fetal Bone Growth

Fetal growth rate is the highest throughout lifespan, even greater than during puberty. The fetus typically accumulates about 30 g of calcium during intra-uterine life, of which 80% is in the third trimester. These means that an average daily calcium transfer of 200 mg from mother to fetal skeleton is needed during this period and may reach 330 mg per day at 35 weeks of gestation (Prentice, 2003).

In the final third of pregnancy, calcium transfer through the placenta occurs at a rapid rate by active transport (Abrams, 2011). Multiple calcium-binding proteins are involved in this process, but hormonal regulation is still unclear. Parathyroid hormone-related protein (PTHrP), which is produced in several fetal tissues and the placenta, appears to be the main determinant of fetal calcium levels. Furthermore, it is possible that vitamin D increases the synthesis of various calcium-binding proteins (Abrams, 2011).

It appears that efficient mechanisms for fetal calcium conservation operate in late gestation, including fetal intestinal absorption of calcium present in amniotic fluid that is predominantly originated from fetal urine and available for reuse (Done, 2012). As observed in extrauterine life, 1,25-(OH)₂D, produced by both the placenta and the fetus, exerts positive influence in calcium intestinal absorption and may play an important role in fetal calcium reutilization (Done, 2012). Moreover, it appears that maternal vitamin D status is an important factor affecting fetal bone development.

29.3.2 Evaluation of Fetal and Infant Bone Outcomes

Measuring multiple fetal ultrasound parameters is considered an effective way for evaluation of fetal growth. Selection of a single biometric parameter depends on the timing and purpose of the measurement. Biparietal diameter (BPD) better correlates with gestational age; abdominal circumference is the

Table 29.3 Studies relating maternal calcium from diet or supplements during pregnancy and fetal/infant bone-growth outcomes.^a

Reference	Study type	Country, maternal age and study groups (n)	Mean dietary Ca mg per day	Ca supplement mg per day	Fetal/infant outcome measurements	Overall effect of Ca intake/supplementation on fetal/infant bone growth
Raman <i>et al.</i> (1978)	RCT	India, 16–32 years placebo (38) Ca suppl. G1 (24) Ca suppl. G2 (25)	Not informed	300 (G1) or 600 (G2) from 18–22 weeks ges- tation until parturition	In both 300 and 600 mg Ca-supple- mented groups, neonate densities of ulna, radio, tibia and fibula bones were higher than those of the neo- nates born to nonsupplemented mothers	Positive
Koo <i>et al.</i> (1999)	RCT	US, 19.5 ± 0.4 years Placebo (48) Ca suppl. (43)	1035 1010	2000 from ~22 weeks ges- tation until parturition	No differences between treatment groups in birth weight or length, and in TB or LS BMC at 1st weeks postpartum Higher TB BMC at 1st weeks post- partum in infants born to Ca-sup- plemented mothers in the lowest quintile (<600 mg per day) of dietary Ca intake	Positive
Chang <i>et al.</i> (2003)	Retrospec- tive cohort	US African Ameri- can, ≤17 years Groups by dairy intake: Low (180) Medium (86) High (84)	Dairy intake (servings per day): Low – <2 Medium – 2 to 3 High – >3	—	Dairy intake not associated with: biparietal diameter, abdominal circumference and head cir- cumference at 20–34 weeks of gestation High dairy intake associated with greater femur length after adjust- ment for gestational age, maternal age, maternal height, prepreg- nancy BMI, and biparietal diameter	Positive

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Table 29.3 (continued)

Reference	Study type	Country, maternal age and study groups (n)	Mean dietary Ca mg per day	Ca supplement mg per day	Fetal/infant outcome measurements	Overall effect of Ca intake/supplementation on fetal/infant bone growth
Chan <i>et al.</i> (2006)	RCT	US, 15–17 years Control (23) Ca fortified orange juice (24) Dairy (25)	835 856 817	~1200 during pregnancy	Infants in the dairy group were heavier and had higher total body Ca at birth than infants in the control and orange juice plus calcium groups	Positive
Jarijou <i>et al.</i> (2006)	RCT	The Gambia, 27.4 ± 7.6 years Placebo (64) Ca suppl. (61)	363 345	1500 from ~20 weeks gestation until parturition	No differences between the 2 groups for birth weight and infant weight, body length and head circumference at 2 weeks postpartum Slower rate of increase in infant BMC and bone area from 2 to 52 weeks in the Ca supplement group compared to placebo	Negative
Abdel-Aleem <i>et al.</i> (2009)	RCT	Egyptian, 20.5 ± 3.0 years Placebo (48) Ca suppl. (43)	Estimated <600	1500 from ~20 weeks gestation until parturition	No differences between placebo and supplemented groups for: biparietal diameter, femur length, humerus length and abdominal circumference from 20 to 36 weeks gestation No differences between placebo and supplemented groups for: weight, length, head circumference and abdominal circumference at birth	No effect

Abalos <i>et al.</i> (2010)	RCT	Argentina, 20.5 ± 4.6 years Placebo (230) Ca suppl. (231)	Estimated <600	1500 from ~20 weeks ges- tation until parturition	No differences between placebo and supplemented groups for: head circumference, biparietal diameter, abdominal circumference, femoral diaphysis length, humeral diaphysis length from 20 to 36 weeks gestation	No effect
Young <i>et al.</i> (2012)	Prospective cohort	US, ≤18 years (171)	917	—	No differences between placebo and supplemented groups for: weight, length, head circumference and abdominal circumference at birth Mothers consuming >1050 mg Ca per day had fetuses with higher femur and humerus Z scores at 34 weeks than those consuming <1050 mg Ca per day Maternal dietary Ca intake and 25-(OH)D status interacted to affect bone-length outcomes Mothers consuming >1100 mg Ca per day delivered longer neonates compared to mothers consuming <1100 mg Ca per day	Positive

^aOverall effect of calcium supplementation: positive when associated with increased bone growth; negative, with decreased bone growth. RCT, randomized control trial; BMC, bone mineral content; BMI, body-mass index; TB, total.

most useful dimension to evaluate overall fetal growth, and femur length is the best parameter in the evaluation of skeletal development (Degani, 2001). This set of information has been used to evaluate patterns of intrauterine growth and response to interventions. However, it is important to note that ultrasound measurements are often subjected to observer error, and systematic variations in measurement accuracy may exist between different studies. For this and other reasons, when investigating the effect of nutrient intervention during pregnancy on the offspring, a number of studies evaluate only birth or neonatal outcomes that are also known to reflect fetal growth and development (Done, 2012).

More sophisticated methods for the assessment of infant bone accrued during pregnancy include radiograph and DXA, both restricted to postpartum measurement. DXA has been used for the evaluation of bone mineral content, area and density in infants and, if the assessment is done during the first days postpartum, it reflects bone accretion during gestation. The main limitation appears to be the difficulty in preventing the infant from moving during measurement in order to obtain images that are technically satisfactory without movement artifacts.

29.3.3 Effects of Maternal Calcium Supplementation during Pregnancy on Fetal and Infant Bone Growth

The influence of maternal calcium intake or calcium supplementation during pregnancy on fetal growth has been approached with different methodologies. The first study evaluating the effect of calcium supplementation during pregnancy on bone measurements of neonates was done in an underprivileged population (Raman *et al.*, 1978). In this study, bone densities (evaluated by X-ray) at ulna, radius, tibia and fibula of neonates from mothers supplemented with 300 or 600 mg daily calcium from 18–22 weeks of gestation until parturition were higher than bone densities of neonates from nonsupplemented mothers. More recently, the effect of calcium supplementation (2000 mg Ca per day) during pregnancy on neonatal bone mass at the first weeks postpartum was tested in overall well-nourished mothers, in a placebo-controlled study (Koo *et al.*, 1999). Habitual maternal calcium intake was on average close to 1000 mg per day at midpregnancy and all women received a prenatal supplement containing 400 IU D₂ during pregnancy. Maternal calcium supplementation was found to be associated with increased DXA measurements of total body BMC only in newborns whose mothers were in the lowest quintile (<600 mg) of habitual daily calcium intake during pregnancy. Considered together, the results of both studies suggest that bone growth of neonates benefits from additional calcium when their mothers consume low-calcium diets.

On the other hand, the effect of calcium supplementation (1500 mg per day) during pregnancy on fetal and infant growth that was investigated in Gambian mothers accustomed to very low calcium intakes (300–400 mg per day) produced different results (Jarjou *et al.*, 2006). In this randomized, placebo-controlled trial, there was a trend to a slightly higher BMC and bone area

in neonates (~2 weeks postpartum) whose mothers received calcium supplements during pregnancy. However, this trend was not sustained over time and it was actually reversed, resulting in a lower bone accretion rate over the first year of life. Therefore, it appears that the low maternal calcium intake was not the primary determining factor of infant calcium accretion in this population.

The effect of prenatal calcium supplementation was investigated in two other studies resulting in no beneficial effect for fetal growth (Abdel-Aleem *et al.*, 2009; Abalos *et al.*, 2010). These studies were subsets of a WHO multicenter randomized trial of calcium supplementation among low-calcium intake pregnant women for the prevention of pre-eclampsia and preterm delivery. Mothers received a calcium supplement (1500 mg) or placebo daily from ~20 weeks of pregnancy until parturition. Fetal growth was monitored by five ultrasound examinations at 20, 24, 28, 32 and 36 weeks. In both studies, no differences in fetal biometric measurements (BPD, humerus length, abdominal circumference and femur length) at any stage of gestation were observed between fetuses of women who were supplemented with calcium and those who were not (Abdel-Aleem *et al.*, 2009; Abalos *et al.*, 2010). Also, neonatal outcomes (birth weight, length, head circumference, abdominal and thigh circumferences) were similar between the groups, regardless of the supplementation status.

Interestingly, studies focusing on pregnant adolescents are not controversial and provide consistent results irrespective of study design. The effect of maternal dairy intake at early pregnancy on fetal femur development during gestation was investigated in a retrospective cohort study of African-American adolescents (Chang *et al.*, 2003). Dairy intake was considered to be high in those pregnant adolescents consuming 3 or more servings per day, medium in those consuming 2 to 3 servings per day and low if consumption was less than 2 servings per day. High maternal dairy intake at entry into prenatal care was associated with greater fetal femur length evaluated between 20 and 34 weeks of pregnancy, after adjustment for gestational age, maternal age, maternal height, prepregnancy BMI, and fetal BPD. Pregnant adolescents with high dairy intake had fetuses with significantly longer femurs than did those with low dairy intake, suggesting a dose–response relation.

Another study focusing in pregnant adolescents in the US tested the effect of calcium intervention through fortified orange juice or dairy products during the second half of pregnancy on newborn anthropometric data and total bone calcium content, estimated by DXA (Chan *et al.*, 2006). Calcium intake was increased to >1200 mg per day in the supplemented groups compared to ~860 mg per day in the control group. Newborns from mothers receiving dairy products during pregnancy were heavier at birth and had higher total bone calcium content than those born from mothers receiving fortified orange juice or placebo. The hypothesis was that consumption of dairy products increased also the intake of vitamin D, that in turn may have contributed to a better utilization of the extra calcium provided, and probably promoted a higher fetal calcium accretion.

More recently, maternal vitamin D status and calcium intake were found to interact in the effect on fetal skeletal growth in pregnant adolescents (Young *et al.*, 2012). In this prospective longitudinal designed study, fetal femur and fetal humerus *Z* scores were singly associated with maternal calcium intake and serum 25-(OH)D, with higher scores at maternal calcium intake ≥ 1050 mg per day or maternal serum 25-(OH)D > 50 nmol L⁻¹. When the interaction between the two nutrients was evaluated, calcium intake remained associated with fetal outcomes only when maternal 25-(OH)D was < 50 nmol L⁻¹. Similarly, maternal 25-(OH)D was associated with fetal measurements only when maternal calcium intake was < 1050 mg per day. These results suggest that, in adolescent mothers, both adequate maternal calcium intake or sufficient 25-(OH)D status have positive effects on fetal skeletal development and there is a capacity for compensation when intake or status of the other nutrient is limited. The associations and interactions observed *in utero* remained evident at delivery, as indicated by significant differences in neonatal birth length. Adolescents consuming higher amounts of calcium delivered neonates that were longer at birth, especially when maternal 25-(OH)D was suboptimal (Young *et al.*, 2012).

29.3.4 Effects of Maternal Calcium Supplementation on Breast-Milk Calcium Concentration

Most reports on breast-milk calcium concentration and its relationship with mother's calcium intake were published several years ago. In general, these studies suggest that there is no influence of maternal calcium intake during lactation, through diet or supplements, on breast-milk calcium concentrations, even in women consuming very low calcium diets (Prentice *et al.*, 1995; Kalkwarf *et al.*, 1997; Laskey *et al.*, 1998; Jarjou *et al.*, 2006).

It has long been hypothesized that calcium intake during pregnancy, rather than during lactation, may influence breast-milk calcium concentration and hence the calcium intake of breastfed infants. This hypothesis was tested in Gambian mothers that received calcium supplementation (1500 mg per day) from 20 weeks of gestation until delivery (Jarjou *et al.*, 2006). No significant differences between supplemented and nonsupplemented mothers were observed in breast milk concentrations of calcium or calcium-to-phosphorus ratio at 2, 13 and 52 weeks of lactation. Also, no effect of calcium supplementation (1000 mg per day) from 28 weeks gestation until parturition was observed on breast-milk calcium concentrations in Iranian mothers (Karandish *et al.*, 2007). However, in a longitudinal study from the third trimester of pregnancy to 40 days lactation done in Spain (Ortega *et al.*, 1998) it was found that mothers consuming less than 1100 mg per day calcium during pregnancy had significantly lower calcium concentration in mature milk than those consuming > 1100 mg per day, suggesting that breast fed babies of mothers with lower calcium intakes during pregnancy may receive less calcium from mother's milk.

In contrast to most studies in adult mothers, teenage motherhood was found to consistently affect calcium concentration in breast milk. Moreover, it was suggested that lower maternal calcium intake results in lower calcium concentrations in the milk secreted by adolescent mothers, but not by adult mothers (Vítolo *et al.*, 2004).

29.4 Conclusions

Several potential interacting factors may explain different results between studies testing the effects of maternal calcium supplementation on maternal and infant bone responses during pregnancy and lactation. Maternal age merits special attention considering that the adolescent pregnant body may compete with her fetus for the nutrients required for optimal bone mineralization. Therefore, adolescent pregnant women and their infants may be particularly benefited by a higher maternal calcium intake during pregnancy and lactation. Other aspects requiring attention when examining the effects of maternal calcium supplementation include limited or inexistent data on dietary habits and vitamin D status. This is an important issue since responses to a calcium-supplement intervention certainly depend on the initial nutritional and bone status of the mother to which her body is already adapted. Additionally, in populations with restricted access to a variety of foods, the concomitant deficiencies of calcium and other nutrients need to be considered. Besides calcium, dietary intake of several nutrients and food components affecting bone health should be examined when evaluating the maternal bone responses to pregnancy and lactation. Finally, interpretation of results depends on the study design and techniques used for assessment of maternal and infant bone mass, and fetal and neonatal bone growth, each one with specific limitations.

The available evidence indicates that use of calcium supplementation, particularly during pregnancy, may have a protective effect on maternal bone mass and may benefit fetal and neonatal bone growth in certain (but not all) populations with habitual calcium intakes <1000 mg per day, and in adolescent mothers. Bone benefits appear to be site specific and the responsiveness of bone sites varies among different populations. Additional research is required before making public-health recommendations for use of calcium supplementation during pregnancy and lactation aiming at maternal and infant bone health. It is likely that recommendations may vary for different population groups.

Summary Points

- It is well accepted that in women with calcium intakes close to current recommendations there is no apparent bone benefit for the mother or infant of using calcium supplements.
- However, in women consuming low-calcium diets, and in adolescent mothers, maternal bone adaptations during reproduction have been found to respond to increased calcium intake or supplementation, although not always as expected.

- Fetal and infant skeletal development has been found to be positively associated with increased maternal calcium intake or supplementation during pregnancy in some but not all studies.
- Inconsistent results across studies of maternal and infant bone responses to calcium supplementation may be due to complex interactions between genetics, diet composition, calcium intake, vitamin D status, environment, and lifestyle.
- Bone effects of calcium supplementation during pregnancy and lactation appear to vary for different population groups.

Key Facts of Bone

1. Adult bone is composed of 32–36% calcium deposited as mixed-phosphate salts within a protein matrix.
2. Bone mineral content and density can be measured by dual-energy-X-ray absorptiometry.
3. Bone serves two main body functions: to provide structural support and to contribute to calcium homeostasis.
4. Bone tissue is continuously renewed during a lifetime through processes of resorption and deposition known as bone turnover.
5. Bone turnover can be indirectly measured by biochemical markers such as osteocalcin and crosslinked *N*-telopeptide of type-I collagen.
6. Bone turnover is increased during pregnancy and lactation.

Definitions of Key Terms

1,25-(OH)₂D – 1,25-Dihydroxyvitamin D. Hormonal form of vitamin D that becomes active after two sequential hydroxylations at liver (25C position) and kidneys (1C position).

25-(OH)D – 25-Hydroxyvitamin D. Main circulating form of vitamin D, considered the best marker of nutritional status.

Bone mineral content. Total amount of mineral matter that is present in bones, expressed in g.

Bone-mineral density. Amount of bone mineral per unit of bone area scanned, expressed in g cm⁻².

Bone turnover. A continuous process of bone remodeling that consists in removal of old bone and replacement with new bone matrix and minerals.

DXA – dual-energy X-ray absorptiometry. X-ray based image technique considered the gold standard for bone-mineral density evaluation.

Fetal biometry. Measurements obtained by ultrasound examination often used to estimate gestational age, fetal growth and skeletal development. Main measurements include abdominal circumference, biparietal diameter and femoral length.

PTH – parathyroid hormone. Polypeptide hormone secreted by the parathyroid glands that has a critical role in calcium and bone homeostasis.

PTHrP – parathyroid hormone-related peptide. Polypeptide hormone produced by tumors and some tissues under specific conditions that exerts biological actions similar to PTH.

Z score. Indicates the number of standard deviations a single measurement distances from a given mean of an age-matched population.

List of Abbreviations

1,25-(OH)₂D	1,25-Dihydroxyvitamin D
25-(OH)D	25-Hydroxyvitamin D
BA	Bone area
BPD	Biparietal diameter
BMC	Bone-mineral content
BMD	Bone-mineral density
BMI	Body-mass index
DXA	Dual-energy X-ray absorptiometry
LS	Lumbar spine
NLPP	Non lactating postpartum women
NPNL	Nonpregnant nonlactating women
NTx	Crosslinked N-telopeptide of type-I collagen
PP	Postpartum
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
PW	Post weaning
RCO	Randomized crossover trial
RCT	Randomized controlled trial
TB	Total body
UD	Ultradistal
WHO	World Health Organization
βCTx	Carboxyterminal telopeptide of type-I collagen

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