Calcium and Bone Disorders During Pregnancy and Lactation

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Mineral metabolism in the mother must adapt to the demand created by the fetus and placenta, which together draw calcium and other minerals from the maternal circulation to mineralize the developing fetal skeleton. Similarly, mineral metabolism must adapt in the lactating woman to supply sufficient calcium to milk and the suckling neonate. Potential adaptations include increased intake of mineral, increased efficiency of intestinal absorption of mineral, mobilization of mineral from the skeleton, and increased renal conservation of mineral. Despite a similar magnitude of calcium demand by pregnant and lactating women, the adjustments made in each of these reproductive periods differ significantly (Fig. 1). These hormone-mediated adjustments normally satisfy the needs of the fetus and infant with short-term depletions of maternal skeletal calcium content, but without long-term consequences to the maternal skeleton. In states of maternal malnutrition and vitamin D deficiency, however, the depletion of skeletal mineral content may be proportionately more severe and may be accompanied by increased skeletal fragility.

This article reviews present understanding of the adaptations in mineral metabolism that occur during pregnancy and lactation and how these adaptations affect the presentation, diagnosis, and management of disorders of calcium and bone metabolism. Animal data are cited to fill in the gaps where...
Adaptations during pregnancy

The developing fetal skeleton accretes about 30 g of calcium by term and about 80% of it during the third trimester. This demand for calcium is largely met by a doubling of maternal intestinal calcium absorption, mediated by 1,25-dihydroxyvitamin D$_3$ (1,25(OH)$_2$D$_3$), or calcitriol, and possibly by other factors.

Mineral ions and calcitropic hormones

Normal pregnancy results in altered levels of calcium and the calcitropic hormones as schematically depicted in Fig. 2 [1]. The ionized calcium (the physiologically important fraction of calcium) remains constant throughout pregnancy. In contrast, the total serum calcium (sum of the ionized, complexed, and albumin-bound fractions of calcium in the circulation) decreases in pregnancy secondary to a decline in serum albumin. In clinical practice, the total serum calcium is more commonly measured than the ionized calcium. The commonly observed decrease in total serum calcium should
Fig. 2. Longitudinal changes in calcium, phosphorus, and calcitropic hormone levels that occur during pregnancy and lactation. Normal adult ranges are indicated by the shaded areas. The progression in PTHrP levels is depicted by a dashed line to reflect that the data are less complete; the implied comparisons of PTHrP levels in late pregnancy and lactation are uncertain extrapolations because no reports followed patients serially. In both situations, PTHrP levels are elevated. (Adapted from Kovacs CS, Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium and lactation. Endocr Rev 1997;18:832–72. © 1997 The Endocrine Society; with permission.)
not be mistaken for evidence of “physiologic hyperparathyroidism of pregnancy,” an erroneous concept that has persisted in some modern texts [4,5]. The decline in total serum calcium is an unimportant artifact of a nonphysiologic measurement; the ionized calcium is the relevant measurement and always should be assayed if there is any doubt about the true value of the serum calcium during pregnancy (or at any time). Serum phosphorus levels also are normal during pregnancy.

As observed by longitudinal measurements during pregnancy with modern two-site “intact” immunoradiometric assays (IRMA), serum parathyroid hormone (PTH) decreases to the low-normal range (ie, 10–30% of the mean nonpregnant value) during the first trimester, then increases steadily to the mid-normal range by term [6–10]. As judged by the “intact” serum PTH level, the parathyroids are modestly suppressed beginning early in the first trimester and return to apparently normal function by the end of pregnancy. First-generation PTH assays in the 1970s and 1980s were insensitive and measured multiple, biologically inactive fragments of PTH; a few studies with these assays had detected higher levels of PTH during pregnancy in humans. Those early studies of PTH in pregnancy, combined with the observation that total serum calcium decreases during pregnancy, reinforced the erroneous concept that secondary hyperparathyroidism occurs during pregnancy. Modern “intact” assays have made it clear that in well-nourished women, ionized calcium is normal throughout pregnancy, and that PTH is suppressed during early pregnancy. “Bio-intact” PTH assays have been developed that detect true full-length PTH [11]; the levels are likely similar to levels obtained with the more widely used “intact” PTH assays, but no study has examined this. In contrast to the normal suppression of PTH during pregnancy, there is evidence that PTH may increase above normal in late pregnancy in women from Malay, who have very low intakes of calcium [12].

Total 1,25(OH)₂D₃ levels double early in pregnancy and maintain this increase until term; free 1,25(OH)₂D₃ levels are increased from the third trimester and possibly earlier. The increase in 1,25(OH)₂D₃ may be largely independent of changes in PTH because PTH levels typically are decreasing at the time of the increase in 1,25(OH)₂D₃. The maternal kidneys likely account for most, if not all, of the increase in 1,25(OH)₂D₃ during pregnancy, although the decidua, placenta, and fetal kidneys may contribute a small amount. The relative contribution of the maternal kidneys is based on several lines of evidence [1], including the report of an anephric woman on hemodialysis who had low 1,25(OH)₂D₃ levels before and during a pregnancy [13]. The renal 1α-hydroxylase may be upregulated in response to factors such as PTH-related protein (PTHrP), estradiol, prolactin, and placental lactogen (evidence from animal studies is reviewed by Kovacs and Kronenberg [1]). Serum calcitonin levels also increase during pregnancy, with the C cells of the thyroid, breast, and placenta possibly contributing to the circulating level of calcitonin. It has been postulated that calcitonin protects the maternal skeleton from excessive resorption of calcium, but this hypothesis is unproved.
No human studies have addressed the question, although studies in genetically engineered mice have shown that the absence of calcitonin does not impair the ability of mice to increase skeletal mineral content during pregnancy [14].

PTHrP levels are increased during late pregnancy, as determined by assays that detect PTHrP fragments encompassing amino acids 1 through 86. Because PTHrP is produced by many tissues in the mother and fetus (including the placenta, amnion, decidua, umbilical cord, fetal parathyroids, and breast), it is unclear which sources contribute to the increase detected in the maternal circulation. PTHrP may contribute to the elevations in 1,25(OH)₂D₃ and the suppression of PTH that are noted during pregnancy, although there is evidence that PTHrP may not be as potent as PTH in stimulating the renal 1α-hydroxylase in vivo [15]. PTHrP has other roles during pregnancy, including the regulation of placental calcium transport in the fetus [1,16]. PTHrP also may have a role in protecting the maternal skeleton during pregnancy because the carboxyl-terminal portion of PTHrP (“osteostatin”) has been shown to inhibit osteoclastic bone resorption [17].

Pregnancy induces significant changes in the levels of other hormones, including the sex steroids, prolactin, placental lactogen, and insulin-like growth factor type 1. Each of these may have direct or indirect effects on calcium and bone metabolism during pregnancy, but these issues have not been explored.

**Intestinal absorption of calcium**

Several clinical studies have shown that intestinal absorption of calcium is doubled during pregnancy from 12 weeks of gestation (the earliest time point studied); this seems to be a major maternal adaptation to meet the fetal need for calcium [1]. This increase may be the result of a 1,25(OH)₂D₃-mediated increase in intestinal calbindin₂₅K-D and other proteins. Based on evidence from limited animal studies [1], prolactin and placental lactogen (and possibly other factors) also may mediate part of the increase in intestinal calcium absorption. The increased absorption of calcium early in pregnancy may allow the maternal skeleton to store calcium in advance of the peak fetal demands that occur later in pregnancy.

**Renal handling of calcium**

The 24-hour urine calcium excretion is increased by 12 weeks of gestation (the earliest time point studied), and the amount excreted may exceed the normal range [1]. Because fasting urine calcium values are normal or low, the increase in 24-hour urine calcium likely reflects the increased intestinal absorption of calcium (absorptive hypercalciuria). The elevated calcitonin levels of pregnancy also may promote renal calcium excretion.

**Skeletal calcium metabolism**

Animal models indicate that histomorphometric parameters of bone turnover are increased during pregnancy, which could be interpreted to mean that
mineral is mobilized from the maternal skeleton to contribute to the fetal skeleton [18]. Serial measurements of bone mineral density by dual x-ray absorptiometry (DXA) in several strains of normal mice have shown, however, that bone mineral content increases by 5% to 10% during pregnancy [14,19], and the increased bone turnover of pregnancy might reflect (at least in rodents) an anabolic or bone formative state, as opposed to a net bone resorptive state. As noted later in the lactation section, a net loss of bone mineral content occurs during lactation in humans and rodents. An increase in bone mineral content during pregnancy might serve to protect the maternal skeleton against excessive demineralization and fragility during lactation.

Comparable histomorphometric data are not available for human pregnancy. In one study [20], 15 women who electively terminated a pregnancy in the first trimester (8–10 weeks) had bone biopsy evidence of increased bone resorption, including increased resorption surface, increased numbers of resorption cavities, and decreased osteoid. These findings were not present in biopsy specimens obtained from nonpregnant controls or in biopsy specimens obtained at term from 13 women who had elective cesarean sections.

Most human studies of skeletal calcium metabolism in pregnancy have examined changes in “bone markers,” that is, serum indices that reflect bone formation and serum or urine indices that reflect bone resorption. These studies have been fraught with numerous confounding variables that cloud the interpretation of the results, including the lack of prepregnancy baseline values; effects of hemodilution in pregnancy on serum markers; increased glomerular filtration rate (GFR) and renal clearance; altered creatinine excretion; placental, uterine, and fetal contributions to the markers; degradation and clearance by the placenta; and lack of diurnally timed or fasted specimens. Given these limitations, many studies have reported that urinary markers of bone resorption (24-hour collection) are increased from early pregnancy to mid-pregnancy (including deoxypyridinoline, pyridinoline, and hydroxyproline). Conversely, serum markers of bone formation (generally not corrected for hemodilution or increased GFR) often decrease from prepregnancy or nonpregnant values in early pregnancy or mid-pregnancy, increasing to normal or greater before term (including osteocalcin, procollagen I carboxy peptides and bone-specific alkaline phosphatase). It is conceivable that the bone formation markers are artifactually lowered by normal hemodilution and increased renal clearance of pregnancy, obscuring any real increase in the level of the markers. One study that adjusted for the confounding effects of hemodilution and altered GFR showed that osteocalcin production was not reduced in pregnancy [21]. Total alkaline phosphatase increases early in pregnancy largely because of contributions from the placental fraction and is not a useful marker of bone formation in pregnancy.

Based on the scant bone biopsy data and the measurements of bone markers (with the aforementioned confounding factors), one cautiously may conclude that bone turnover is increased in human pregnancy from 10 weeks of gestation. There is comparatively little maternal-fetal calcium
transfer occurring at this stage of pregnancy compared with the peak rate of calcium transfer in the third trimester. One might have anticipated that markers of bone turnover would increase particularly in the third trimester; however, no further increase was seen at that time.

Changes in skeletal calcium content have been assessed in humans through the use of sequential bone density studies during pregnancy. Because of concerns about fetal radiation exposure, few such studies have been done. Such studies are confounded by changes in body composition and weight during normal pregnancy, which can lead to artifactual changes in bone density. Using single-photon or dual-photon absorptiometry (SPA/DPA), several prospective studies did not find a significant change in cortical or trabecular bone density during pregnancy [1]. Several more recent studies have used DXA before conception (range 1–8 months prior, but not always stated) and after delivery (range 1–6 weeks postpartum) [21–27]. Most studies involved 16 or fewer subjects. One study found no change in lumbar spine bone density measurements obtained preconception and within 1 to 2 weeks postdelivery [23], whereas the other studies reported decreases of 4% to 5% in lumbar spine bone density with the postpartum measurement taken 1 to 6 weeks postdelivery. The puerperium is associated with bone density losses of 1% to 3% per month in women who lactate (see lactation section), and it is important that the postpartum measurement be done as soon as possible after delivery. Other longitudinal studies have found a progressive decrease during pregnancy in indices thought to correlate with bone mineral density, as determined by ultrasound measurements at a peripheral site, the os calcis [28]. Although the longitudinal studies with SPA/DPA suggested no change in trabecular or cortical bone density during pregnancy, the subsequent evidence from preconception and postdelivery DXA measurements and peripheral ultrasound measurements suggests that there may be a small net loss of maternal bone mineral content during normal human pregnancy. None of all the aforementioned studies could address the question as to whether skeletal calcium content increases early in pregnancy in advance of the third trimester, as has been observed in normal mice. Further studies, with larger numbers of patients, are needed to clarify the extent of bone loss during pregnancy.

It seems certain that any acute changes in bone metabolism during pregnancy do not normally cause long-term changes in skeletal calcium content or strength. Numerous studies of osteoporotic or osteopenic women have failed to find a significant association of parity with bone density or fracture risk [1,29]; however, a few studies of women with extremely low calcium or vitamin D intake found that pregnancy may compromise skeletal strength and density (see later). Although most clinical studies could not separate out the effects of parity from the effects of lactation, it may be reasonable to conclude that if parity has any effect on bone density or fracture risk, it normally must be only a modest effect. A more recent study of twins indicated that there may be a small protective effect of parity and lactation on maintaining bone mineral content [30].
Adaptations during lactation

About 280 to 400 mg of calcium is lost through breast milk daily, with losses of 1000 mg or more in women who are nursing twins. A temporary demineralization of the skeleton seems to be the main mechanism by which lactating women meet these calcium requirements. This demineralization does not seem to be mediated by PTH or calcitriol, but may be mediated by PTHrP in the setting of a decrease in estrogen levels.

Mineral ions and calcitropic hormones

The normal lactational changes in maternal calcium, phosphorus, and calcitropic hormone levels are schematically depicted in Fig. 2 [1]. The mean ionized calcium level of exclusively lactating women is increased, although it remains within the normal range. Serum phosphorus levels also are higher during lactation, and the level may exceed the normal range. Because reabsorption of phosphorus by the kidneys seems to be increased, the increased serum phosphorus levels may reflect the combined effects of the increased flux of phosphorus into the blood from diet and from skeletal reabsorption in the setting of decreased renal phosphorus excretion.

"Intact" PTH, as determined by a two-site IRMA assay, has been found to be reduced 50% or more in lactating women during the first several months. It increases to normal at weaning, but may rise above normal after weaning (levels of bio-intact PTH have not been reported yet during lactation). In contrast to the high 1,25(OH)\(_2\)D\(_3\) levels of pregnancy, maternal free and bound 1,25(OH)\(_2\)D\(_3\) levels decrease to normal within days of parturition and remain there throughout lactation.

PTHrP levels are significantly higher in lactating women and mice than in nonlactating controls, as measured by two-site IRMA assays. The source of PTHrP seems be the breast or mammary tissue because PTHrP has been detected in milk at concentrations exceeding 10,000 times the level found in the blood of patients with hypercalcemia of malignancy or normal human controls. A small increase in the maternal level of PTHrP can be shown after suckling [31]. Blood levels of PTHrP were reduced in lactating mice that had the PTHrP gene ablated only from mammary tissue compared with normal lactating mice [32]. PTHrP seems to play several roles within the breast, as indicated by studies in animals that suggest PTHrP may regulate mammary development and blood flow. The calcium-sensing receptor is expressed in the breast during lactation, where it regulates PTHrP production and the calcium and water content of the milk (Fig. 3) [33].

PTHrP plays a key role during lactation in regulating the demineralization of the skeleton. In response to suckling [31] and in response to signaling from the calcium-sensing receptor expressed by lactating mammary tissue (see Fig. 3) [33], PTHrP reaches the maternal circulation from mammary
tissue and stimulates resorption of calcium from the maternal skeleton, renal tubular reabsorption of calcium, and (indirectly) suppression of PTH (Fig. 4). In a sense, the breast becomes an accessory parathyroid gland during lactation, but the “hyperparathyroidism” of lactation is increased secretion of PTHrP, not PTH. The strongest evidence in support of this model comes from the study of mice in which the PTHrP gene was ablated at the onset of lactation, but only within mammary tissue [32]. The lactational decrease in bone mineral content was significantly blunted in the absence of mammary gland production of PTHrP. Other evidence for the central role of PTHrP in lactation comes from humans, in that PTHrP levels correlate negatively with PTH levels and positively with the ionized calcium levels of lactating women [31,34], and that higher PTHrP levels correlate with greater losses of bone mineral density during lactation in humans [35]. Observations in aparathyroid women provide evidence of the impact of PTHrP in calcium homeostasis during lactation (see later).

Calcitonin levels are elevated in the first 6 weeks of lactation. Studies in mice lacking the gene that encodes calcitonin indicate that calcitonin may modulate the rate of skeletal resorption during lactation. Calcitonin-null mice lost more than 50% of skeletal mineral content during 3 weeks of
lactation, approximately twice that of normal littermate sisters [14,36]. The calcitonin-depleted mice still regained all of the lost mineral content after weaning, which indicates that although calcitonin is needed in the short-term to prevent severe losses of mineral content and potential skeletal fragility, calcitonin is not required in the long-term because the skeletal losses of mineral are restored anyway. The human equivalent of absence of calcitonin might explain some cases of osteoporosis of lactation (see later).

Intestinal absorption of calcium

Intestinal calcium absorption decreases to the nonpregnant rate from the increased rate of pregnancy. This decrease in absorption corresponds to the decrease in 1,25(OH)₂D₃ levels to normal.
Renal handling of calcium

In humans, the GFR decreases during lactation, and the renal excretion of calcium typically is reduced to very low levels. This situation suggests that tubular reabsorption of calcium must be increased, to account for reduced calcium excretion in the setting of increased serum calcium.

Skeletal calcium metabolism

Histomorphometric data from animals consistently show increased bone turnover during lactation, with losses of 30% of bone mineral achieved during 2 to 3 weeks of normal lactation in the rat [1], whereas a similar amount is lost in the lactating mouse within 21 days [19]. The loss is greatest in the trabecular bone of rats and mice. Comparative histomorphometric data are lacking for humans, and in place of that, serum markers of bone formation and urinary markers of bone resorption have been assessed in numerous cross-sectional and prospective studies of lactation. Some confounding factors discussed with respect to pregnancy apply to the use of these markers in lactating women. During lactation, GFR is reduced, and the intravascular volume is more contracted. Urinary markers of bone resorption (24-hour collection) increase two to three times above normal during lactation and are higher than the levels attained in the third trimester. Serum markers of bone formation (not adjusted for hemoconcentration or reduced GFR) are generally high during lactation and increase over the levels attained during the third trimester. Total alkaline phosphatase declines immediately postpartum owing to loss of the placental fraction, but still may remain above normal because of the elevation in the bone-specific fraction. Despite the confounding variables, these findings suggest that bone turnover is significantly increased during lactation.

In women, serial measurements of bone density during lactation (by SPA, DPA, or DXA) have shown a decline of 3% to 10% in bone mineral content after 2 to 6 months of lactation at trabecular sites (lumbar spine, hip, femur and distal radius), with smaller losses at cortical sites [1,29,37]. The peak rate of loss is 1% to 3% per month, far exceeding the rate of 1% to 3% per year that can occur in women with postmenopausal osteoporosis, who are considered to be losing bone rapidly. Loss of bone mineral from the maternal skeleton seems to be a normal consequence of lactation and may not be preventable by increasing the calcium intake above the recommended dietary allowance. Several studies have shown that calcium supplementation does not reduce significantly the amount of bone lost during lactation [38–41]. The lactational decrease in bone mineral density correlates with the amount of calcium lost in the breast milk [42].

The mechanisms controlling the rapid loss of skeletal calcium content are not fully understood. The reduced estrogen levels of lactation are important, but are unlikely to be the sole explanation. To estimate the effects of estrogen deficiency during lactation, it is worth noting the alterations in calcium...
and bone metabolism that occur in reproductive-age women who have estrogen deficiency induced by gonadotropin-releasing hormone agonist therapy for endometriosis and other conditions. Six months of acute estrogen deficiency induced by gonadotropin-releasing hormone agonist therapy leads to 1% to 4% losses in trabecular (but not cortical) bone density, increased urinary calcium excretion, and suppression of 1,25(OH)_{2}D_{3} and PTH levels [1]. During lactation, women are not as estrogen deficient, but they lose more bone mineral density (at trabecular and cortical sites), have normal (as opposed to low) 1,25(OH)_{2}D_{3} levels, and have reduced (as opposed to increased) urinary calcium excretion. The difference between isolated estrogen deficiency and lactation may be due to the effects of other factors (eg, PTHrP) that add to the effects of estrogen withdrawal in lactation (Fig. 5). The relative influences of estrogen deficiency and PTHrP have been partially discerned in normal mice, in which it has been shown that treatment with pharmacologic doses of estrogen blunted, but did not abolish, the normal demineralization that occurs during lactation [43].

The bone density losses of lactation are substantially reversed during weaning at a rate of 0.5% to 2% per month [1,29,40]. The mechanism for this restoration of bone density is uncertain and largely unexplored, but preliminary evidence from animal models suggests that PTH, calcitriol, calcitonin, and estrogen may not be required to achieve that restoration. In the long-term, the consequences of lactation-induced depletion of bone mineral seem clinically unimportant in most women. Most epidemiologic studies of premenopausal

Fig. 5. Acute estrogen deficiency (eg, gonadotropin-releasing hormone analogue therapy) increases skeletal resorption and raises the blood calcium; PTH is suppressed, and renal calcium losses are increased. During lactation, the combined effects of PTHrP (secreted by the breast) and estrogen deficiency increase skeletal resorption, reduce renal calcium losses, and raise the blood calcium, but calcium is directed into the breast milk. (From Kovacs CS. Kronenberg HM. Maternal-fetal calcium and bone metabolism during pregnancy, puerperium and lactation. Endocr Rev 1997;18:832–72. © 1997 The Endocrine Society; with permission.)
and postmenopausal women have found no adverse effect of a history of lactation on peak bone mass, bone density, or hip fracture risk [1,29].

**Disorders of bone and mineral metabolism during pregnancy and lactation**

As previously discussed, pregnancy is a state of hyperabsorptive hypercalciuria, characterized by high levels of calcitriol, increasing levels of PTHrP, suppressed PTH levels, stable serum ionized calcium levels, and enhanced urinary calcium excretion (see Fig. 2). Lactation is characterized by further increments in PTHrP levels, whereas calcitriol levels return to normal. The estimated daily increase in calcium requirements (0.3 g/d) to meet the fetal demands for bone mineralization and the maternal requirements for milk synthesis are largely through enhanced intestinal calcium absorption during pregnancy and through maternal bone resorption during lactation [42]. Disorders of bone and mineral homeostasis that occur in the nonpregnant state may manifest differently during pregnancy and lactation as a result of the differing hormonal changes that occur in these two distinct reproductive intervals.

**Primary hyperparathyroidism**

Primary hyperparathyroidism occurs rarely during pregnancy; the true incidence is unknown because hyperparathyroidism may remain asymptomatic and go undiagnosed in uncomplicated pregnancies. In the general population, the estimated incidence of hyperparathyroidism increased from 16/100,000 before 1974 (before routine automated screening) to a peak of 112/100,000 years later, then subsequently declined to 4/100,000 [44]. Most subjects were older than age 45 years [44]. The incidence of hyperparathyroidism in women of childbearing age in an older series was estimated to be approximately 8/100,000 per year [45]. Approximately 150 cases have been reported in the English literature to date [46,47]. Two studies retrospectively evaluated 850 parathyroidectomies during the period 1960–1991 and 750 parathyroidectomies during 1975–1996 and revealed that parathyroidectomies during pregnancies accounted for 1.4% and 0.8% of total surgeries [46,48]. The diagnosis may be obscured by the normal pregnancy-induced changes that decrease the total serum calcium and suppress PTH; finding the ionized calcium to be increased and the PTH to be detectable would indicate primary hyperparathyroidism in most cases.

Hyperparathyroidism in a pregnant patient can mean considerable morbidity for the mother and the fetus. Complications have been reported in 67% of mothers and 80% of fetuses and neonates [49], complications that are in large part due to maternal hypercalcemia. The histopathologic distribution in hyperparathyroidism of pregnancy is comparable to that reported in large series spanning all age groups [50]. A series of 100 cases of hyperparathyroidism diagnosed during pregnancy or postdelivery revealed adenomas in 89%, hyperplasia in 9%, and carcinoma in 2% [46].
Manifestations and complications in pregnant women

In a report of 45 pregnant women with hyperparathyroidism, 38% complained of nausea, vomiting, or abdominal pain; 24% reported renal colic; 22% had muscular weakness; 22% manifested mental symptoms; and 11% complained of skeletal pain or fatigue; only 20% were asymptomatic [51]. Other clinical manifestations included hyperemesis gravidarum, weight loss, seizure, or other symptoms mimicking preeclampsia [46,48]. Many of the aforementioned symptoms are nonspecific and could have been due to the pregnancy itself. Objective findings included the following: 24% had nephrolithiasis or nephrocalcinosis, 16% had urinary tract infections, 13% had bone disease on radiograph, and 11% had pancreatitis [51]. In another large series of 63 cases, 38% had evidence of bone disease, 54% had evidence of renal disease, and 30% had evidence of both [52]. The high prevalence of stone disease may be explained by pregnancy-induced hyperabsorptive hypercalciuria that augments the hypercalciuria that otherwise would occur secondary to hyperparathyroidism itself. The prevalence of pancreatitis complicating hyperparathyroidism varied among reports (range 6–13%) [51,53–55] and usually occurred during the second or third trimester [56]. In a series of 75 cases, pancreatitis was the presenting illness in 5 cases, 2 of which had concomitant hypercalcemic crisis [55]. Of the few other cases of acute parathyroid crisis reported during pregnancy [53,57], one became clinically apparent 3 days postpartum followed by rapid deterioration, pancreatitis, respiratory failure, shock, and unsuccessful resuscitation [57]. The patient had been hypercalcemic at 16 weeks of gestation, but was asymptomatic at that time, leading the authors to suggest that the increased fetal need for calcium may have protected the mother from severe hypercalcemia before delivery [57]. Susceptibility to fractures owing to hyperparathyroidism during pregnancy is uncommon. Bilateral femoral neck fractures and rib fractures have been reported in two cases of severe hyperparathyroidism diagnosed during pregnancy, wherein PTH levels were 20-fold above the upper limit of normal, and in one case, the hyperparathyroidism was due to parathyroid carcinoma [58,59].

Complications in Fetuses

The most frequent serious complications in fetuses include stillbirth, miscarriage, and neonatal tetany. The percentage of affected pregnancies terminating in stillbirth, neonatal death, and neonatal tetany declined over the decades from 13% to 2%, from 8% to 2%, and from 38% to 15% [52]. Perinatal death occurred in 25% to 30% of neonates, whereas neonatal complications were noted in 50%, with tetany being at the forefront in infants born to untreated mothers [46,60–62]. Neonatal tetany is a common presentation of unrecognized hyperparathyroidism during pregnancy. The pathophysiology of the hypocalcemia and tetany is the suppression of fetal parathyroid function from maternal hypercalcemia, which becomes clinically evident when the maternal calcium flow is interrupted at birth [63].
Although the neonatal hypocalcemia and hypoparathyroidism are usually transient, resolving with treatment within 3 to 5 months [52], it has been reported to occur initially as late as 2.5 months postpartum [64] and may be permanent [52,61,65]. Bottle-fed infants were more likely to develop hypocalcemia than breastfed ones because of the higher phosphate-to-calcium ratio in cow’s milk compared with breast milk [52].

Management of the mother and neonate

Parathyroidectomy performed during pregnancy prevents fetal and neonatal morbidities. The first successful parathyroidectomy during pregnancy was performed by Petit and Clark in 1947 [66]. A review comparing the outcomes of 109 mothers with hyperparathyroidism during pregnancy who were treated medically (n = 70) or surgically (n = 39) revealed that neonates of mothers with untreated hypercalcemia run a greater risk of complications [46]. In patients treated medically, there were 53% neonatal complications and 16% neonatal deaths, as opposed to a 12.5% incidence of neonatal complications and 2.5% neonatal deaths in patients who underwent parathyroidectomy [46]. Parathyroidectomy is best performed during the second trimester, after completion of organogenesis in the fetus and to avoid the poor outcomes of surgery during the third trimester [51,52,54,62]. In one series, premature labor with neonatal death occurred in four of seven third-trimester surgeries [54]. Parathyroidectomy in the third trimester is warranted, however, when the risks outweigh the benefits, and the procedure has been performed successfully in such cases [47,67].

Treatment options for hyperparathyroidism in pregnancy are influenced by the symptoms and severity of disease and gestational age. Optimal management requires a multidisciplinary approach; surgery should be performed only by an experienced parathyroid surgeon. Symptomatic and severe disease should be treated surgically, preferably in the second trimester, whereas mild asymptomatic disease diagnosed in the third trimester may continue to be observed until after delivery. A consensus for other cases is missing, however. Medical treatment includes adequate hydration and correction of electrolyte abnormalities [49]. Pharmacologic agents to treat hypercalcemia have not been studied adequately in pregnancy. Calcitonin, a pregnancy category B medication of the US Food and Drug Administration, does not cross the placenta and has been used safely in pregnancy [49]. Oral phosphate, a pregnancy category C medication, has been used in pregnancy; its most common side effects are diarrhea and hypokalemia. It should be avoided in patients with renal failure or high serum phosphate because of the risk of soft tissue calcifications [49]. Bisphosphonates and mithramycin are contraindicated because of their adverse effects on fetal development; bisphosphonates in particular may interfere with normal endochondral bone development. High-dose magnesium has been suggested as a therapeutic alternative for hyperparathyroidism in pregnancy, although its effectiveness is uncertain. This divalent cation decreases serum PTH and calcium levels by activating the calcium-sensing
receptor, and at the same time it treats premature labor associated with hypercalcemia [68,69]. Experience with any of the aforementioned pharmacologic therapies is limited to individual case reports [49]; consequently, no medical therapy can be claimed to be better than any other. Medical therapy should be coupled with maternal surveillance and the monitoring of serum calcium and electrolytes and the initiation of antenatal testing with serial fetal ultrasound starting at 28 weeks of gestation. Parathyroidectomy is recommended postpartum in cases that were followed medically during pregnancy. Lactation is not contraindicated in women with untreated hyperparathyroidism, but worsening of hypercalcemia and accelerated skeletal losses may be anticipated because of the combined effects of PTHrP and hyperparathyroidism to stimulate bone resorption.

Neonatal hypoparathyroidism secondary to maternal hyperparathyroidism is usually transient (see earlier) and is treated with calcium supplementation and calcitriol. These neonates also should be fed milk formulas high in calcium and low in phosphate to minimize the risk of hypocalcemia. The prevalence and severity of complications from hyperparathyroidism in mothers and neonates have and will continue to decrease over time, owing to increased surveillance, earlier intervention, and improved surgical and anesthetic technology [52,60,61].

Familial benign hypocalciuric hypercalcemia

Familial benign hypocalciuric hypercalcemia (FBHH) is an autosomal dominant disorder that is caused by inactivating mutations in the calcium-sensing receptor that cause hypercalcemia and hypocalciuria [70,71]. In contrast to patients with hyperparathyroidism, patients with FBHH do not experience bone demineralization or nephrolithiasis. FBHH has been reported in pregnancy with no clinical sequelae in the mother [72]. As anticipated, maternal hypercalcemia has caused suppression of PTH synthesis in the fetus, however, and subsequent hypocalcemia and tetany in the neonate [72,73]. The treatment of neonates is similar to that of children born to mothers with hyperparathyroidism (see earlier).

The calcium-sensing receptor is expressed in the epithelial ducts of breast tissue and has been shown to modulate the production of PTHrP and the transport of calcium into milk in a mouse model [33]. Activating mutations of this receptor in women with FBHH theoretically could enhance the degree of skeletal demineralization during lactation and the calcium content of milk, but this has not been studied.

Hypoparathyroidism

Patients usually are known to have hypoparathyroidism or a parathyroidism before pregnancy, and the therapeutic dilemma revolves around adjustment of the treatment, which may vary widely. In 1966, O’Leary et al [74] reported two cases of hypoparathyroidism treated with high doses of
calcium and vitamin D wherein the mothers gave birth to healthy infants after uncomplicated pregnancies. Despite physiologic increments in endogenous calcitriol levels during pregnancy, several studies since have documented increased requirements for exogenous calcium and calcitriol therapy as pregnancy progressed in patients with hypoparathyroidism [75–78]. Conversely, in numerous other case reports, women with hypoparathyroidism have been reported to require less calcium and vitamin D supplementation during pregnancy [1]. Potential explanations for requiring less supplementation during pregnancy include pregnancy-induced increments in calcitriol from placental sources, the potential effect of PTHrP in the maternal circulation to stimulate the renal 1α-hydroxylase, and other pregnancy-related factors (eg, prolactin or placental lactogen) that may stimulate the renal 1α-hydroxylase or enhance intestinal calcium absorption independently of calcitriol. The last-mentioned has been reported exclusively in animal models [1]. In some case reports, it seems that the normal, artifactual decrease in total serum calcium during pregnancy was the parameter that led to treatment with increased calcium and calcitriol supplementation. Although few cases report measurements of ionized calcium, several do mention that the increments in vitamin D were due to maternal symptoms of hypocalcemia or tetany.

Consequently, there is no established therapeutic regimen for the treatment of hypoparathyroidism during pregnancy, but numerous principles exist that help to guide treatment decisions. Calcitriol levels normally increase during pregnancy and contribute (at least in part) to the enhanced intestinal calcium absorption of pregnancy; most women should receive an increase in the dosage of calcitriol at least initially. The total serum calcium is less informative, and the ionized calcium should be monitored in these patients. Undertreatment results in maternal hypocalcemia; increases the risk of premature labor and of neonatal secondary hyperparathyroidism; and may lead to neonatal skeletal demineralization, subperiosteal bone resorption, and osteitis fibrosa cystica [79]. Conversely, overtreatment may lead to maternal hypercalcemia and neonatal hypoparathyroidism and raises the potential concerns of teratogenicity that has been shown using older vitamin D preparations [80,81]. The active forms of vitamin D, such as calcitriol and 1α-calcidiol, have the advantages of a shorter half-life and lower risk of toxicity. A study reported the outcome of pregnancy in 10 women treated with calcitriol at doses of 0.25 μg/d to 3.25 μg/d [75]. In 8 of 10 pregnancies, healthy infants were delivered. In two cases, serious adverse events occurred, including premature closure of the frontal fontanelle and stillbirth, but the causative role of calcitriol could not be established [75]. Details regarding nine additional cases of hypoparathyroidism and vitamin D–resistant rickets were provided in the same publication and confirmed the lack of toxicity or teratogenicity from vitamin D supplementation during pregnancy [75].

In contrast to the conflicting literature on the effects of pregnancy on hypoparathyroidism, calcium and vitamin D or calcitriol requirements in
hypoparathyroid patients have been shown consistently to decrease during lactation [77,78], such that the patients become hypercalcemic unless the supplements are reduced substantially or discontinued. The decreased requirement for calcium and calcitriol occurs at a time when circulating PTHrP levels are high in the maternal circulation of these hypoparathyroid women [76,82,83]. PTHrP may stimulate endogenous calcitriol formation; in one patient, the calcitriol level initially declined below the lower limit of normal when calcium and calcitriol were discontinued, but thereafter the calcitriol level remained in the lower half of the normal range as lactation proceeded [82]. PTHrP also facilitates maternal bone resorption in the presence of postpartum estrogen deficiency. The aforementioned activity may explain why lactation can eliminate temporarily the requirement for supplemental calcium and calcitriol in hypoparathyroid women.

The management of hypoparathyroidism during pregnancy and lactation is challenging. The use of calcium supplementation with calcitriol is recommended, along with monitoring of symptoms of hypocalcemia and of serum ionized calcium levels (not the total serum calcium) to titrate the calcitriol dose as pregnancy progresses. In general, the requirements in calcitriol vary during the second half of pregnancy, but are expected to decrease during lactation.

Pseudohypoparathyroidism

In case reports of pseudohypoparathyroidism, a state characterized by inherited resistance to PTH, patients have hypocalcemia, hypophosphatemia, and high PTH levels. Such patients have been reported to become normocalcemic during pregnancy without ingesting therapeutic amounts of calcium and vitamin D [84]. The mechanism by which pseudohypoparathyroidism is improved in pregnancy is unclear. It may include increased placental secretion of calcitriol, wherein levels have been reported to double or triple in two case reports during the second and third trimesters [84].

The impact of lactation on calcium metabolism in pseudohypoparathyroidism is less well documented. These patients do not have skeletal resistance to PTH, and it is possible that calcium and vitamin D requirements may decrease secondary to enhanced skeletal resorption owing to the combined effects of endogenous high PTH levels, increasing PTHrP release from the breast, and lactation-induced estrogen deficiency. Women with pseudohypoparathyroidism might be expected to lose more bone density than normal during lactation, but this has not been studied.

Osteoporosis associated with pregnancy and lactation

Osteoporosis associated with pregnancy and lactation has been recognized for more than 5 decades [85] and usually presents during late pregnancy or early postpartum [85–88]. It is still debatable whether pregnancy
and lactation are causal or accidentally associated with the condition. It is equally unclear whether these osteoporotic fractures reflect architectural deterioration of a previously abnormal skeleton or whether pregnancy and lactation themselves account in large part for the bone loss and fragility fractures, situations that may be compounded by low calcium intake and vitamin D deficiency. As reviewed previously, skeletal demineralization normally occurs during lactation as a consequence of the actions of mammary gland-derived PTHrP in the setting of low estradiol levels and is not preventable by increased calcium intake; osteoporotic fractures may occur in some women during lactation when the demineralization is excessive or the skeleton is unable to tolerate the normal lactational losses of mineral. PTHrP levels were high in one case of lactational osteoporosis and were found to remain elevated for months after weaning [89]. One study, which followed 13 women with pregnancy-associated osteoporosis for 8 years, showed that bone mineral density at the spine and hip increased significantly, leading the investigators to conclude that a large part of the bone loss had been related to the pregnancy itself [86]. Conversely, a high prevalence of fractures in 35 subjects presenting with pregnancy-associated osteoporosis raised the possibility of a genetic factor [90]. The recognition that absence of endogenous calcitonin in mice more than doubles the lactational losses raises the consideration that some women might have a genetic deficiency in calcitonin, its receptor, or some other factor [14,36]. Because bone density is not normally measured in premenopausal women, the bone density before pregnancy or at the end of lactation is usually unknown, and the debate regarding the relative contribution of pregnancy or lactation-associated bone changes versus preexisting abnormalities in the skeleton will continue.

**Clinical features**

Patients present at a mean age of 27 to 28 years, usually in the setting of a first pregnancy, and no clear association with parity has been found [86–88]. In more than 60% of cases, patients complain of back pain in the lower thoracic or lumbar area, pain that can be quite debilitating secondary to vertebral collapse [86–88]. In such cases, the pain usually improves spontaneously over weeks, but in a few the severe pain may persist for several years [87]. Others present with hip pain, otherwise known as transient osteoporosis of the hip, as part of a syndrome of monarticular or polyarticular pain over other lower extremity joints, including the ankles, which is accentuated with the use of the joint [86–88,91]. Of the more than 200 cases of transient osteoporosis of the hip that have been reported, one third occurred in women in their third trimester of pregnancy or in the early postpartum period [91–93]. The differential diagnosis of this condition includes inflammatory joint disorders, avascular necrosis of the hip, bone marrow edema, and reflex sympathetic dystrophy. In contrast to the last-mentioned condition, patients with transient regional osteoporosis of the hip lack a history of trauma and the typical physical findings of muscle spasm and skin changes
In contrast to vertebral osteoporosis, recurrences in transient regional osteoporosis of the hip have been described in 40% of total cases, but no series has described this syndrome exclusively in pregnant women [91].

Pathogenesis and laboratory findings
The pathogenesis of pregnancy-associated osteoporosis (presenting with vertebral compression fractures) and transient osteoporosis of the hip differs. In a few cases of the former, secondary causes of bone loss could be identified, including anorexia nervosa, hyperparathyroidism, osteogenesis imperfecta, and corticosteroid or heparin therapy [87,88,90]. One report described pregnancy-associated osteoporosis after oocyte donation in a woman with ovarian failure [94]. Serum calcium and phosphate levels were normal, and no consistent abnormalities in the calcitropic hormones were reported [87,88]. Bone biopsy specimens obtained in some cases have confirmed the diagnosis of osteoporosis, and no osteomalacia was found [87,88]. Bone density tended to be low when measured [86,88]. In a series of 24 patients, the mean Z-score was $-1.98 \pm 1.5, n = 15$ at the lumbar spine and $-1.48 \pm 1.5, n = 15$ at the total hip [88]. In transient osteoporosis of the hip, radiographs or MRI revealed reduced bone density and increased water content of the marrow cavity [91].

Diagnostic studies and therapeutic interventions
Patients should be screened for secondary causes of bone loss, a large proportion of which may be treatable. Most cases improve symptomatically within a few weeks with conservative measures [87,91]. Myriad pharmacologic agents have been used in individual cases, including calcium, vitamin D, testosterone, estrogen, calcitonin, and bisphosphonates, with increments in bone mineral density reaching 27% at the spine and 7% at the hip in patient case treated with alendronate for 6 months [87]. Because these are usually reports on individual cases and lack controls, the efficacy of such interventions is unproved, and the interventions are not warranted.

In severe cases of osteoporosis, it may be prudent to discourage breastfeeding, the rationale being that the skeleton may not be able to tolerate the normal demineralization that lactation would induce. Patients should be cautioned against carrying heavy weights to avoid additional stress on the spine, and the use of a supportive corset may be helpful. Patients should be reassured that substantial increments in bone mineral density will occur over time [86], and that the condition in cases of vertebral collapse is unlikely to recur. In cases of transient osteoporosis of the hip, patients usually do well with conservative measures, including bed rest. Symptoms and radiograph abnormalities resolve within a few months of their onset [91], but may recur, in contrast to cases with vertebral fracture symptoms, which usually do not recur.
Disturbances in bone and mineral metabolism from the administration of magnesium sulfate during pregnancy

The administration of intravenous magnesium sulfate for 24 to 72 hours is one of the mainstay therapies for the treatment of preterm labor and for the treatment of preeclampsia and eclampsia. Its effect is mediated by action on the myoneural junction. In vitro at high doses, magnesium suppresses PTH levels, similarly to other divalent and trivalent cations, albeit with a lower potency than calcium. This effect now is recognized to occur through the calcium-sensing receptor, a receptor heavily expressed in the parathyroid glands and kidneys [70,95]. Long-term tocolytic therapy using magnesium sulfate generally has been considered safe [96], although few reports have raised concerns about its safety to mothers and neonates.

Maternal complications

Hypocalcemia has been described in several cases in which the women received magnesium to suppress premature labor [97–99]. In a study of seven such cases, a loading dose of 6 g of intravenous magnesium sulfate followed by a maintenance dose of 2 g/h resulted in a rapid increase in the mean serum magnesium level from 2 mg/dL to 6 mg/dL within 1 hour, coupled with an almost concomitant decline in the serum PTH levels, which only partially recovered in 3 hours despite substantial decrements in total and ionized serum calcium levels below the lower limit of normal [98]. A similar pattern for maternal and neonatal profiles was noted in a study of 15 women treated with magnesium sulfate [99]. A Medline literature search for articles published in English in the period 1966–2002 on magnesium sulfate and hypocalcemia revealed four cases of maternal symptomatic hypocalcemia, with serum calcium levels reaching 5.3 mg/dL in one case. Two mothers had a positive Chvostek and Trousseau sign or tetany; three of these cases were noted to have concomitant low PTH levels [100].

Although the short-term administration of magnesium sulfate may lower maternal serum calcium through an effect on PTH secretion, long-term administration for 2 to 3 weeks was associated with increments in serum PTH levels, possibly as an appropriate adaptive mechanism to prolonged hypocalcemia. It has been suggested that urinary loss of calcium may be a major pathophysiologic mechanism for the hypocalcemia and in such instances may result in ultimate impairment of bone mineralization [101]. In a study of 20 subjects given intravenous magnesium sulfate for premature labor, serum magnesium and phosphorus levels increased, serum calcium levels decreased concomitantly with an increase in serum PTH, and substantial increments in urinary magnesium and calcium were noted, reaching mean levels two to three times the upper limit of normal [101]. Prolonged magnesium administration for several weeks also has been associated with maternal forearm bone loss prospectively, osteoporosis by bone mineral density, and bilateral calcaneal stress fractures postpartum [101–103].
Neonatal complications

Administration of intravenous magnesium to mothers before delivery increased neonatal serum magnesium and decreased PTH levels, whereas the effect on neonatal total and ionized calcium levels varied [97,99]. Studies evaluating the impact of neonatal hypermagnesemia on neonatal outcomes have yielded conflicting results [97,104–106]. Respiratory depression and hypotonia were reported in 16 cases of neonatal hypermagnesemia [106]. A follow-up study of 35 infants born to toxemic mothers treated with magnesium sulfate for 2 to 4 days suggested that neonates whose mothers had received prolonged administration may be more likely to manifest respiratory depression [105]. Cord blood and neonatal serum magnesium levels were of little diagnostic value to the clinical picture except in cases of severe hypermagnesemia [105,107], confirming the general observation that circulating serum magnesium levels do not reflect intracellular and total body magnesium stores. Conversely, a study of 118 infants born to mothers who had received intramuscular magnesium in doses of 10 to 95 g concluded that the neonatal death rate was lower than that of the total newborn population [104]. Respiratory depression, hypotonia, and need for intubation were not evaluated in that report, however [104]. Neonatal bone abnormalities have been reported with long-term use of magnesium sulfate. The first report by Lamm et al [108] described a congenital form of rickets manifested by defective ossification of bone and enamel in the teeth of the offspring of mothers who had received magnesium sulfate during pregnancy. Several cases of abnormal mineralization of metaphyses since have been reported in neonates born to mothers who received prolonged intravenous magnesium and had high serum magnesium levels [109–111]. The proposed mechanism for defective mineralization of bones involves the inhibition of calcification of osteoid in which calcium-binding sites are occupied by magnesium [109,110].

Some of these conflicting findings regarding neonatal morbidity from maternal administration of magnesium sulfate may be explained by the route and duration of magnesium sulfate administration, by the variability in the ranges of cord magnesium levels reached, and by the gestational age of the neonates. Postdelivery, there was a delay in normalization of the serum magnesium level for a few days resulting from the limitation of magnesium excretion by the newborn’s immature kidneys [97].

Management issues

There are no guidelines for the monitoring of pregnant women receiving magnesium sulfate. Neonates born to mothers receiving long-term magnesium sulfate and experiencing severe hypermagnesemia (> 7 mg/dL) are more likely to have hypotonia, respiratory depression, and bone abnormalities [97,105,107,111]. Subjects receiving such therapy for periods exceeding 1 or 2 days should be monitored carefully, with the measurement of maternal serum calcium and magnesium levels, coupled with monitoring the fetal movement. Symptomatic neonates can be managed by maintaining
ventilation for 24 to 48 hours and providing intravenous fluids for electrolyte balance for a few days, after which marked clinical improvement is usually noted [105]. Intravenous calcium to antagonize the central nervous system depression and peripheral neuromuscular blockade has been used, with careful monitoring of the heart rate [105].

**Low calcium intake**

There are limited data that low calcium intake in the mother may adversely affect fetal mineral accretion and maternal bone mineral metabolism [112]. In women with low dietary calcium intake, there are differing results as to whether or not calcium supplementation during pregnancy improved maternal or neonatal bone density [3]. There is short-term evidence that maternal turnover was reduced when 1.2 g of calcium was given for 20 days to 31 Mexican women with a mean calcium intake of 1 g during weeks 25 to 30 of gestation [113]. In a double-blind study conducted in 256 pregnant women, 2 g of calcium supplementation improved bone mineral content in infants of supplemented mothers who were in the lowest quintile of calcium intake [114].

During lactation, there is no firm evidence that low calcium intake leads to impaired breast milk quality or accentuates maternal bone loss [115]. Even in women with very low calcium intakes, the same amount of mineral was lost during lactation from the skeleton compared with women who had supplemented calcium intakes, and the breast milk calcium content was unaffected by calcium intake or vitamin D status [116–118]. Conversely, because high calcium intakes do not affect the degree of skeletal demineralization that occurs during lactation [38–41], it is unlikely that increasing calcium supplementation above normal would affect skeletal demineralization.

In general, the physiologic changes in calcium and bone metabolism that usually occur during pregnancy and lactation are likely to be sufficient for fetal bone growth and breast milk production in women with reasonably sufficient calcium intake [115]. The inclusion of calcium supplementation for pregnant women with low calcium intake could be defended, however, and is strengthened further by the possible link between low calcium intake, preeclampsia, and increased blood pressure in the offspring [112]. Increased calcium intake also is recommended in adolescent mothers to meet the need of reproduction and maternal bone growth [115]. There is evidence that the skeleton of an undernourished adolescent recovers fully from lactational losses, but there is some concern that peak bone mass might not be attained subsequently [119].

**Vitamin D deficiency**

In humans and in animal models, vitamin D deficiency or the absence of the vitamin D receptor can lead to adverse neonatal outcomes, including neonatal rickets, craniotabes, decreased wrist ossification centers, and
impaired tooth enamel formation [120]. These features generally are not present at birth, but appear postnatally as intestinal calcium absorption becomes vitamin D dependent. Although vitamin D supplementation of pregnant mothers at risk for vitamin D deficiency improved neonatal serum calcium concentrations and resulted in a trend for greater height and length in the offspring [112], a Cochrane review of 232 women in two trials reported conflicting results [121]. Although there is no evidence to indicate a beneficial effect of vitamin D supplementation during pregnancy above the amounts needed to prevent vitamin D deficiency, optimal levels for vitamin D supplementation are unclear [122]. An arbitrary daily recommended intake has been set at 400 IU/d, but likely needs revision upward [123]. Recommendations for vitamin D supplementation either for women of childbearing age or for lactating women were not mentioned in the new US dietary guidelines issued in 2005 [124].

Scientific data pertaining to vitamin D supplementation during lactation are even scarcer than data on vitamin D supplementation during pregnancy. An arbitrary daily recommended intake has been set at 400 IU/d, but may be insufficient [123]. Whether vitamin D deficiency impairs the ability to restore maternal skeleton postweaning is unclear [1]. Lactating mothers supplemented with 1000 IU to 2000 IU of vitamin D for 15 weeks experienced increments in circulating maternal 25-hydroxyvitamin D₃ levels of 16 ng/mL to 23 ng/mL [122]. It has been suggested that vitamin D supplementation of lactating mothers would improve vitamin D nutrition in the mother and the breastfeeding infant; this has not been shown yet, but is currently under investigation [122]. Breastfed infants of vitamin D–deficient mothers should receive vitamin D supplementation to avoid nutritional rickets [125]. There is low penetrance of vitamin D into breast milk, and it is more efficient to give the vitamin D supplement directly to the infant, although supplementing the mother with high doses has been shown to work [126].

Hypercalcemia of malignancy

Hypercalcemia of malignancy, an extremely rare occurrence, has been reported in two cases—one in metastatic breast cancer and the other in renal cell carcinoma [127,128]. In both reports, the disease was rapidly progressive and resulted in premature delivery at 29 and 32 weeks of gestation and maternal demise within 4 months postpartum. On the first day postdelivery, both infants were hypercalcemic, and one subsequently developed hypocalcemia from transient hypoparathyroidism. Intravenous pamidronate was used shortly before delivery in one case with normalization of maternal serum calcium within 5 days of pamidronate administration [128]. Treatment in such cases includes adequate aggressive hydration with close monitoring, furosemide, and possibly calcitonin. Because bisphosphonates cross the placenta, their use should be reserved for life-threatening situations.
Neonatal hypoparathyroidism from maternal therapy with radioactive iodine

Inadvertent maternal therapy with radioactive iodine during pregnancy may result in neonatal hypoparathyroidism, similar to what has been reported in adults treated with high-dose radioactive iodine. A mother was reported to have received 103 mCi of iodine-131 ($^{131}\text{I}$) for thyroid carcinoma at 10 weeks of gestation when she was unaware of her pregnancy. Her neonate experienced occasional episodes of stiffening and turning blue during the first 2 months that accelerated and led to a hospital admission for respiratory distress, tonic-clonic seizures, and ultimate tracheostomy [129]. The infant was found be hypocalcemic, with documented hypoparathyroidism and severe hypothyroidism. The infant was discharged after 1 month of hospitalization with a tracheostomy and ongoing treatment with calcium, dihydrotachysterol, and thyroid hormone. It is likely that the fetal thyroid gland accumulated sufficient amounts of $^{131}\text{I}$ to result in destruction of fetal thyroid and parathyroid tissue from the emitted $\beta$ particles [129].

Summary

Studies of pregnant women indicate that the fetal calcium demand is met largely by intestinal calcium absorption, which from early pregnancy onward more than doubles. The studies of biochemical markers of bone turnover, DXA, and ultrasound are inconclusive, but suggest that the maternal skeleton also contributes calcium to the developing fetus. In contrast, during lactation, skeletal calcium resorption is the dominant mechanism by which calcium is supplied to the breast milk; renal calcium conservation is also apparent. Lactation produces an obligatory skeletal calcium loss regardless of maternal calcium intake, but the calcium is completely restored to the skeleton after weaning through mechanisms that are not understood. The adaptations during pregnancy and lactation lead to novel presentations and management issues for known disorders of calcium and bone metabolism, such as primary hyperparathyroidism, hypoparathyroidism, and vitamin D deficiency. Finally, although some women experience fragility fractures as a consequence of pregnancy or lactation, in most women the changes in calcium and bone metabolism during pregnancy and lactation are normal and without adverse consequences in the long-term.

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