Chapter 21

Disorders of Mineral and Bone Metabolism During Pregnancy and Lactation

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Common Clinical Problems

- Multiple vertebral crush fractures can occur in association with pregnancy, especially with lactation; pharmacotherapy has an uncertain benefit in these cases.
- Physiological hypercalciuria during pregnancy will mask the diagnosis of familial hypocalciuric hypercalcemia (FHH), while physiological hypocalciuria during lactation can mask the diagnosis of primary hyperparathyroidism.
- Mild primary hyperparathyroidism can cause a sudden hypercalcemic crisis in the third trimester or puerperium, as well as fetal parathyroid suppression that leads to prolonged neonatal hypocalcemia.
- Hypercalcemia can also occur during pregnancy due to excess calcitriol (from 24-hydroxylase deficiency) or excess parathyroid hormone-related protein (PTHrP) arising from the breasts, placenta, or both.
- Hypoparathyroidism can improve during pregnancy (requiring less supplemental calcium or calcitriol), but in some instances the condition can worsen (requiring increased doses of supplements).
- Lactation improves or normalizes mineral homeostasis in hypoparathyroidism, such that severe hypercalcemia can ensue if supplemental calcium and calcitriol are not reduced or stopped.

21.1 INTRODUCTION

As discussed in Chapter 5, specific adaptations are invoked to meet the increased mineral requirements of the developing fetus and neonate. Increased intestinal absorption of calcium and phosphorus is the main adaptation during pregnancy, while increased skeletal resorption of minerals predominates during lactation. In turn, these adaptations can influence the presentation, diagnosis, and management of disorders of bone and mineral metabolism that may predate pregnancy or onset for the first time during a reproductive cycle.

For more detailed citation of more than 1000 papers of primary animal and human data relevant to this subject, the reader is referred to a recent comprehensive review.[1] We have updated the results of this review with a systematic search conducted in PubMed and Medline current to April 2018. Due to restrictions on the length of the reference list, only selected recent papers will be cited herein.

21.2 DISORDERS OF BONE AND MINERAL METABOLISM DURING PREGNANCY

21.2.1 Osteoporosis in Pregnancy

The first description of osteoporosis occurring in association with pregnancy is often attributed to Albright and Reifenstein in 1948,[2] although low bone mineral density (BMD) and vertebral fractures have been recognized in Egyptian mummies and other archaeological remains of women who were 16–30 years of age at the time of their deaths several millennia ago.[3] Fragility fractures rarely occur during pregnancy, but they are somewhat more common during lactation, as described in Section 21.3. Although fragility fractures may occur at any skeletal site, two presentations have generally been reported in association with pregnancy: vertebral compression fractures and transient osteoporosis of the hip.[4]

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21.2.1.1 Vertebral and Appendicular Fractures in Pregnancy

Fragility fractures during pregnancy are rare, but among them, vertebral compression fractures have been described most often. The condition may be underrecognized and underreported, given how often back pain is reported with pregnancy. In general, case reports and series have emphasized women who presented with a cascade of multiple compression fractures.[4,5] However, one recent retrospective study spanning 17 years suggested that ankle and other lower limb fractures (67%) may be more common during pregnancy, usually occurring with falls, whereas vertebral fractures occur without much trauma.[6]

Pregnancy-related fractures typically occur in women not previously known to have any abnormality of bone or mineral metabolism.[1,7,8] Consequently, a BMD reading prior to pregnancy is usually unavailable. Investigations typically reveal normal serum chemistries and bone-relevant hormones. However, BMD is usually low at diagnosis and shows spontaneous improvement afterward, thereby implicating that transient bone loss occurred during pregnancy. Of the small number of bone biopsies that have been reported, the methodology was not detailed, publication preceded the standardized histomorphometry nomenclature for reporting,[9] the timing since delivery varied, some had no tetracycline label uptake, and a few reported findings consistent with mild osteoporosis.[10–12]

Fractures may occur because skeletal fragility preceded pregnancy or significant bone loss occurred during pregnancy. Table 21.1 lists the conditions that have been reported among women with pregnancy- or lactation-associated osteoporosis.

Insufficient calcium absorption can cause substantially increased skeletal resorption in order to meet the fetal and maternal requirements for calcium. Poor dietary calcium intake, lactose intolerance, vitamin D deficiency, celiac disease, and other malabsorptive disorders can all lead to the same outcome. For example, a woman's habitual intake of only 229 mg of calcium was likely a substantial factor resulting in high skeletal resorption, especially during the third trimester, to meet her own calcium needs and those of her baby, and thus leading to the cascade of vertebral compression fractures experienced during pregnancy.[4]

Parathyroid hormone-related protein (PTHrP) concentrations rise progressively in the maternal circulation during pregnancy. In some women, the release of PTHrP has been excessive, leading to high circulating levels, hypercalcemia, and even fractures (a condition called pseudohyperparathyroidism; see Section 21.2.6). While this is a relatively extreme situation, it is conceivable that less marked elevations in PTHrP may also occur, thereby inducing bone loss without causing symptomatic hypercalcemia.

The available data come largely from individual case reports, and mostly from small retrospective case, or case control, series.[4,5] Fractures typically occur in a first pregnancy, during the third trimester or the first few months in the postpartum period; are not necessarily associated with higher parity; and have a low risk of recurrence with future pregnancies.[4,13–17] For example, in a retrospective series of 52 patients with pregnancy-associated osteoporotic fractures, only 2 saw recurrence of a fracture during a second pregnancy.[5] The low risk of recurrence may imply that treatable factors (such as nutritional deficiencies) were corrected after the first pregnancy.

21.2.1.2 Transient Osteoporosis of the Hip

Transient osteoporosis of the hip is a rare condition causing skeletal fragility localized to one or both hips.[4,18] It may be a form of chronic regional pain syndrome 1 or reflex sympathetic dystrophy. Risk factors include pregnancy, alcohol, nicotine, corticosteroid, abnormal vascularity, drugs, inflammation, metabolic derangement, mechanical injury, neurologic deficit, and osteogenesis imperfecta.[4,18] Although the condition is more common in men, in women, it often onsets during the third trimester or puerperium with unilateral hip pain, limping, or a hip fracture; it may be bilateral at presentation or become so later. The femoral head and neck are osteopenic and radiolucent, while the hip BMD is usually quite low and out of keeping with the lumbar spine measurement. Magnetic resonance imaging (MRI) studies have revealed an edematous femoral head and neck. Prophylactic arthroplasties have been carried out in some cases. In women who were not operated on and did not fracture, the MRI and BMD abnormalities typically resolved within 3–12 months, accompanied by 20%–40% increases in femoral neck BMD. The question of whether these changes in BMD represent real changes in mineralization or artifacts resulting from changes in the marrow remains uncertain.

Several theories have been advanced to explain why pregnancy might increase the risk, including femoral venous stasis caused by pressure from the pregnant uterus, reduced activity or bed rest, and fetal pressure on the obturator nerve. It is not associated with systemic skeletal resorption, and thereby it appears to be distinct from the form of osteoporosis described previously, which leads to vertebral compression fractures. It may appear in any pregnancy and can recur in the opposite hip in a subsequent pregnancy. A few reported cases have involved women who had both vertebral compression fractures and transient osteoporosis of the hip, and thus the two conditions may share some pathophysiology or risk factors.[19–22]

TABLE 21.1 Conditions contributing to pregnancy- and lactation-related osteoporosis

Hormonal and endocrine disorders
Excess PTHrP-mediated bone resorption during pregnancy
Excess PTHrP- and low-estradiol-mediated resorption during lactation
Primary hyperparathyroidism
Hyperthyroidism
Cushing's syndrome
Chronic oligoamenorrhea
Hypothalamic amenorrhea
Pituitary disorders leading to sex steroid deficiency
Premature ovarian failure
Prolonged lactation
Diabetes (type 1 and 2)
Hypophosphatemic rickets
Nutritional
Low dietary calcium intake
Dairy avoidance
Lactose intolerance
Low vitamin D intake/vitamin D deficiency
Anorexia nervosa
Mechanical
Petite frame
Low body weight
Low peak bone mass
Excess exercise
Increased weight-bearing of pregnancy
Lordotic posture of pregnancy
Bed rest
Carrying child
Prolonged lactation with insufficient skeletal recovery afterward
Pharmacological
GnRH analog treatment
Depo-Provera
Glucocorticoids
Calcineurin inhibitors
Proton pump inhibitors
Certain antiseizure medications (phenytoin, carbamazepine)
Cancer chemotherapy
Alcohol
High-dose thyroxine

Continued

TABLE 21.1 Conditions contributing to pregnancy- and lactation-related osteoporosis—cont'd

Cyclosporine
Heparin (long term)
Highly active antiretroviral therapy
Antidepressants (particularly selective serotonin reuptake inhibitors)
Excess vitamin A intake
Thiazolidinediones
Gastrointestinal
Celiac disease
Crohn's disease
Cystic fibrosis
Other malabsorptive disorders
Renal
Hypercalciuria/renal calcium leak
Chronic renal insufficiency
Renal tubular acidosis
Primary disorders of bone quality
Osteogenesis imperfecta
Osteopetrosis and other sclerosing bone disorders
LRP5-inactivating mutations
Hypophosphatasia
Hematologic disorders
Thalassemia
Sickle cell disease
Leukemia
Connective tissue disorders
Ehlers-Danlos syndrome
Marfan syndrome
Rheumatological disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Mastocytosis
Other nonspecified genetic disorders
Family history of osteoporosis or skeletal fragility
Idiopathic osteoporosis
Other
Hereditary hemochromatosis
Gaucher's disease
Malignancy: breast cancer

21.2.1.3 Investigations and Overall Management Considerations

Table 21.2 lists suggested investigations for women who present with low trauma fractures during pregnancy (or lactation), while Table 21.3 lists additional suggested investigations for women who present with multiple vertebral compression fractures.[4,7,8]

Because fragility fractures occur rarely during or after pregnancy, there are no randomized trials of management approaches. Sound clinical judgment must be used to balance the potential benefit and risks of treatments, which are delineated in Table 21.4. With both vertebral compression fractures and transient osteoporosis of the hip, spontaneous recovery of bone mass and strength typically occurs (even when there were fractures), so watchful waiting may be the first approach. Pharmacological therapy in the postpartum period and surgical intervention should be reserved for more severe or recalcitrant cases, such as those who experience multiple vertebral fractures or persistent disabling pain or who do not achieve a satisfactory spontaneous increase in BMD. The evidence regarding the safety and efficacy of drugs used during pregnancy is quite limited and mostly based on experience from case reports and series.[4,23]

21.2.1.4 Nonpharmacological Treatment

Calcium and vitamin D intake should be optimized for all women. For calcium, this is a total intake of 1200 mg/day elemental calcium from all sources, whereas for vitamin D, it is whatever intake is required to achieve a 25-hydroxyvitamin D (25OHD) level of at least >50–75 nmol/L (see the discussion of vitamin D replacement guidelines during pregnancy later in Section 21.2.7.4).[24] Reasonable weight-bearing physical activity should be encouraged, nutritional deficiencies should be corrected, and reversible causes of bone loss or fragility discovered during the workup should be treated wherever possible. Women who experienced compression fractures should avoid lifting heavy objects or other activities that may precipitate a fracture. A supportive corset may be helpful for short-term pain relief. Breastfeeding for the first few weeks postpartum may be allowed in order to optimize neonatal immunity through the transfer of maternal immunoglobulins. However, this must be balanced against the progressive loss in BMD and transient increase in fracture risk that may occur with prolonged breastfeeding, as explained in Chapter 5.

21.2.1.5 Pharmacological Therapy

It is tempting to prescribe antiosteoporosis medications immediately for women who fractured during pregnancy, but this enthusiasm should be tempered by the realization that BMD normally increases during the subsequent 6–12 months in women who fractured, without any interventions. Indeed, BMD by dual X-ray absorptiometry (DXA) or quantitative computed tomography (qCT) was shown to increase spontaneously by means of 20%–70% in such cases.[15,17,25–29] Furthermore, the common antiresorptive treatments lead to a secondary reduction in osteoblast activity, which raises the concern that such treatments could impair spontaneous skeletal recovery. Therefore, it would be prudent to delay the use of pharmacological therapy for 12–18 months until the extent of spontaneous recovery has been assessed.

Pharmacological therapy has been used in many women who presented with clinical fractures associated with pregnancy. This includes nasal calcitonin, bisphosphonates, denosumab, strontium ranelate, and teriparatide (see Refs. 1 and 4 for an extensive list of studies). The doses were typically the same as those for postmenopausal osteoporosis. Treatment duration varied between 6 months and 2–3 years, and can extend to as much as 10 years.[1,4,5,30–35] Breastfeeding was usually stopped during treatment, while subsequent pregnancies occurred as early as 3 months after pharmacological therapy ended. All these reports are observational and lacked controls to determine whether the BMD changes exceeded the substantial (20%–70%) increments that would have been observed with spontaneous recovery. These agents are generally not indicated for premenopausal women, so any use is off-label.[4,7,23] In postmenopausal women, there are concerns about potential long-term skeletal and nonskeletal adverse effects of bisphosphonates, denosumab, and strontium ranelate.[4] Calcitonin is available now only in injectable form for short-term use. Given the safety concerns, clinicians should carefully consider whether a young woman should be committed to long-term treatment and what the end point might be.

Additional concerns are that bisphosphonates cross the placenta and theoretically could interfere with fetal endochondral bone development. However, in a review of 78 patients in whom bisphosphonates were used during pregnancy, no obvious problems were reported in most cases, with the possible exception of transient hypocalcemia in the infant with bisphosphonate use during lactation.[23] The number of pregnancies involving bisphosphonate use is too small to be completely reassured about its safety. Denosumab should be avoided because it crosses the placenta and caused an osteopetrotic-like disorder in cynomolgus monkeys and mice.[36,37] Teriparatide and abaloparatide are limited to 24 months of lifetime exposure, and their use might be best reserved for older people, when fracture risk can be expected to be substantially higher.

TABLE 21.2 Suggested initial investigations

Anthropometric
Height by stadiometer
Weight
Body mass index (BMI)
Comparison to best recalled height or prior documented height
Radiological
Areal BMD by DXA (preferred use of *z*-scores)
Plain radiographs of thoracic and lumbar spine to assess for compression fractures
Radiographs of both hips (when presenting with hip pain or fracture)
MRI of affected hips (when presenting with hip pain or fracture)
Dietary assessment for nutritional deficiencies
Calcium intake
Vitamin D intake
Other nutritional deficiencies
Hematological
Complete blood count
Erythrocyte sedimentation rate (ESR)
Serum protein electrophoresis/myeloma screen
Biochemical
Electrolytes
Epidermal growth factor receptor (EGFR)
Ionized calcium or albumin-corrected serum calcium
Serum phosphate
Serum magnesium
Alkaline phosphatase
25-Hydroxyvitamin D
TTG and antiendomesial antibodies
Hormonal
PTH
PTHrP
Thyroid-stimulating hormone (TSH)
Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (off hormonal contraceptives)
Prolactin
Urine
24-h urine calcium, creatinine, and sodium[a]

[a]*Note that 24-h urine calcium may be high (hypercalciuric) during pregnancy and low (hypocalciuric) during lactation; see Chapter 5.*

TABLE 21.3 Additional secondary investigations in severe cases

Radiological
Skeletal survey for evidence of sclerosing bone disorders
Radionuclide bone scan for evidence of myeloma or other pathology
Biochemical
Bone formation markers[a]—e.g., bone-specific alkaline phosphatase, P1NP, or osteocalcin
Bone resorption markers[a]—e.g., C-telopeptide (CTX), N-telopeptide (NTX), or deoxypyridinoline/creatinine
Ferritin or serum iron measurements
Tryptase, IgE levels
Glucocerebrosidase
Hormonal
Calcitriol
24-h urine-free cortisol
Late-night salivary cortisol
Other
Bone biopsy at hip fracture site
Tetracycline-labeled, transiliac bone biopsy
Genetic referral when family history of early or severe fragility present (low BMD and/or vertebral fracture, and/or multiple fractures) in the absence of secondary causes, constitutional leanness, and late puberty
Gastroenterology referral for small bowel biopsy in those who have abdominal symptoms but negative celiac antibodies

[a]*Note that there are confounding considerations if these are measured during pregnancy or lactation; see Chapter 5.*

21.2.1.6 Surgical Therapy

Vertebroplasty and kyphoplasty introduce cement into a crushed vertebral body to treat painful vertebral fractures during the postpartum period. The overall efficacy of these methods is uncertain, given that blind, randomized trials have found no superiority over sham surgery or medical approaches in older subjects.[38, 38a] Another concern is that the cement may increase mechanical strain on adjacent vertebrae, thereby predisposing to more crush fractures.

For transient osteoporosis of the hip, the main consideration is whether to rod the affected femur or femurs prophylactically or only to observe, expecting spontaneous recovery without fracture.

21.2.2 Primary Hyperparathyroidism

21.2.2.1 Incidence and Epidemiology

Hypercalcemia, which presumably and in large part represents primary hyperparathyroidism, has been found in 0.03% of routinely screened, reproductive age women, but how often it is present during pregnancy is uncertain.[1] There are at least several hundred cases in English-language medical journals, while the first author's advice has been sought for several cases each year by clinicians across North America. Two case series found that approximately 1% of all parathyroidectomies were done during pregnancy,[39,40] so the condition may not be as rare as previously thought. Similar to nonpregnant cases, single adenomas are the most common pathology, followed by four-gland hyperplasia.

The dilutional fall in serum albumin and calcium that occur during normal pregnancy (see Chapter 5) may mask hypercalcemia, delay the diagnosis, and contribute to it being underrecognized. The albumin-corrected calcium or ionized calcium should be used, combined with a nonsuppressed parathyroid hormone (PTH) level, to diagnose primary hyperparathyroidism during pregnancy.[1,41,42]

TABLE 21.4 Suggested treatment strategy

For all women
Optimize calcium and vitamin D intake
Early mobilization; avoid bed rest
Encourage weight-bearing and muscle-strengthening physical activity
Consider shortening the duration of lactation (with pregnancy fractures) or weaning the baby (with lactation fractures)
Avoid lifting heavy objects
Avoid high-risk activities that include flexion, twisting, sudden loads, or risk of falls
Supportive corset (temporary) for vertebral fracture pain
Cane or crutches for transient osteoporosis of the hip without fracture
Assess spontaneous recovery of vertebral BMD at 12–18 months and reassess
Assess spontaneous recovery of hip edema (MRI) and BMD (DXA) at 12–18 months
For severe cases (Recurrent fractures, disabling pain, insufficient spontaneous regain of vertebral BMD)
Analgesia
Paracetamol/Acetaminophen
NSAID
Opioids
Antineuropathic drugs
Bone-specific therapy[a]
Estrogen replacement for oligoamenorrheic women
Bisphosphonate (e.g., alendronate, risedronate, zoledronic acid)
Denosumab
Teriparatide
Parenteral calcitonin—only short-term use for vertebral fracture pain relief, if at all
Surgical treatment[a]
Kyphoplasty
Vertebroplasty
Spinal fusion
For transient osteoporosis of the hip
Analgesia
Paracetamol/acetaminophen
Nonsteroidal antiinflammatory drug (NSAID)
Opioids
Surgical treatment[a]
Hip replacement/arthroplasty for fracture
Consider prophylactic arthroplasty or rodding for opposite hip if radiological features indicate low BMD with increased water content

[a]*Drugs or surgical intervention should be considered only in severe refractory cases that do not improve with conservative measures because the safety and efficacy of these approaches is not well established in these conditions.*

On the other hand, pregnancy can also worsen primary hyperparathyroidism because the physiological changes of pregnancy have their own effects to increase intestinal calcium absorption, hypercalciuria, and bone resorption. Indeed, primary hyperparathyroidism during pregnancy is perceived to confer higher risks of severe hypercalcemia, pancreatitis, and kidney stones. On balance, the transfer of calcium across the placenta and into the developing fetus should protect somewhat against severe maternal hypercalcemia by creating an outflow for excess calcium. This likely explains why sudden hypercalcemic crises have occurred after delivery. Physical inactivity and bed rest during late pregnancy and the puerperium will also increase skeletal resorption, which in turn aggravates hypercalcemia.

Maternal hypercalcemia has been shown in animal models to increase the flow of calcium across the placenta and suppress the fetal parathyroids. Fetal hypercalcemia in turn causes increased renal water excretion and polyhydramnios.

21.2.2.2 Clinical Presentation

Maternal hypercalcemia causes nonspecific, constitutional symptoms (e.g., nausea, constipation, fatigue, weakness, and mental symptoms), which are difficult to distinguish from those of normal pregnancy. More severe hypercalcemia has been associated with hyperemesis, weight loss, seizures, and preeclampsia. Additional maternal signs may include nephrocalcinosis, nephrolithiasis, urinary tract infection, acute pancreatitis, bone loss, and fractures. It can rarely present as brown tumors of the jaw.[43] The serum calcium may be somewhat reduced initially due to the dilutional fall in serum albumin, but the calcium may rise higher under the influence of the pregnancy-related increase in intestinal calcium absorption. A hypercalcemic crisis can occur during the third trimester or puerperium.

Risks to the fetus and neonate include miscarriage, stillbirth, intrauterine growth retardation, premature birth, transient hypocalcemia, and rarely permanent hypoparathyroidism. These are discussed in Chapter 44.

21.2.2.3 Approach and Management

There have been four international consensus conferences on the management of primary hyperparathyroidism, but none have addressed pregnancy.[44]

Localizing an adenoma preoperatively is difficult because radioisotope-based parathyroid scans must be avoided, ultrasound has limited sensitivity, 10%–20% of cases may involve hyperplasia of all four glands, and ectopic parathyroids occur.

Traditionally, parathyroidectomy has been done during the second trimester to avoid fetal and neonatal morbidity and mortality, as well as maternal hypercalcemic crisis during the third trimester or postpartum period. Due to the rarity of this condition, there are no randomized trials comparing medical vs surgical approaches. In a 1991 review of 109 cases, neonatal deaths and morbidity were lower in surgically treated mothers than medically treated mothers, but the analysis was confounded by the undeclared circumstances that led clinicians to choose a particular modality in each case.[40] If surgery is to be performed, the second trimester is preferred for the lower risks of anesthetic or surgical complications, precipitated delivery, and neonatal death, although other reports have defended the apparent safety of intervening during the third trimester.

Modern cases of primary hyperparathyroidism are, for the most part, milder than the older cases in the literature. This has led to the impression that the adverse effects of primary hyperparathyroidism may be lower for the mother and baby, and that surgery may be safely delayed until postpartum. Analysis of a database registry found 1057 reproductive-age women with primary hyperparathyroidism (60% had been pregnant before the diagnosis, while 15% had been pregnant after it) who were compared to 3171 age-matched women. The rate of cesarean sections was doubled in women with primary hyperparathyroidism, there was no difference in the incidence of spontaneous abortions, and no data were available on other pregnancy outcomes or neonatal complications.[45] In another study, 134 pregnancies in 74 women with primary hyperparathyroidism were compared to 431 pregnancies in 175 normocalcemic women.[41] There were no differences in the rates of spontaneous abortions or pregnancy-related complications; however, neonatal complications were not reported.[41]

Other recent cases appear to confirm lower rates of stillbirth, neonatal death, and neonatal tetany than shown in older research. Yet fetal death still occurred in 30 out of 62 medically managed cases (maternal serum calcium correlated with the risk), but in none of 15 cases that were operated on during the second trimester.[46] Mild primary hyperparathyroidism in the mother can still result in a third-trimester hypercalcemic crisis, neonatal hypocalcemia, and even permanent neonatal hypoparathyroidism.[1] The variability of outcomes is probably related to other maternal and fetal risk factors for adverse obstetrical outcomes, as emphasized by a twin pregnancy in which one neonate had hypocalcemic seizures while the other remained normocalcemic.[47]

Medical management includes the first-line approach of hydration and correction of electrolyte abnormalities. Pharmacotherapy has not been systematically studied in pregnancy, but available medications have been used in individual case reports, with the same doses as those administered in nonpregnant women. Calcitonin is a Category B medication for

pregnancy because it does not cross the placenta, and it has been used safely (4–8 IU/kg every 12 h) to suppress bone resorption and promote urine calcium excretion in pregnant women. Oral phosphate is Category C, with modest efficacy to bind calcium, but its use is limited by diarrhea, hypokalemia, and the potential risk of ectopic calcifications. Furosemide is a Category C medication that promotes renal calcium excretion. As mentioned previously, bisphosphonates (also Category C) cross the placenta, but no overt adverse skeletal effects have been seen; there may be an increased risk of neonatal hypocalcemia. Denosumab should be avoided because its transplacental passage has led to an osteopetrotic-like disorder in monkeys and mice.[36,37]

Cinacalcet is Category C, but it has been used during pregnancy in several cases, in doses ranging from 30 to 360 mg/day.[1] It suppresses PTH synthesis and release and stimulates calcitonin through its actions on the calcium receptor in the parathyroids and C-cells, respectively. The calcium receptor is also expressed in placenta, fetal parathyroids, and C-cells, which raises the concern that the drug may suppress the fetal parathyroids, stimulate fetal calcitonin, and alter placental calcium transfer. High-dose magnesium can be useful because it binds to the calcium receptor and lowers PTH and calcium. Heparin-free hemodialysis has been used to lower serum calcium before surgery.[48]

The relative benefits and risks of each option are uncertain, given that the data come from case reports and follow-up on the children has been very brief. Given that these women are young, genetic disorders that cause hypercalcemia should be ruled out through selective mutation analysis.

21.2.2.4 Conclusion: Surgical vs Medical Management?

Overall, maternal and fetal complications appear less likely to occur with the milder forms of primary hyperparathyroidism that are encountered in the modern era; however, risks are not completely absent.[1] Surgery is still preferred; ideally, it should be carried out during the second trimester if medical management fails or symptoms worsen. There is some consensus that a serum calcium level that persists at >2.80 mmol/L (11.1 mg/dL), or an ionized calcium >1.4 mmol/L (5.6 mg/dL), are indications for surgery.[49,50] A bilateral approach is often warranted because of the lack of preoperative imaging to localize the adenoma. If medical observation is undertaken for seemingly mild hypercalcemia, the clinician must beware of the potential for a hypercalcemic crisis to occur during the third trimester, and even more abruptly after delivery. Newborns must be watched for neonatal hypocalcemia that may have an immediate or delayed presentation.

21.2.3 Familial Hypocalciuric Hypercalcemia

Autosomal-dominant, inactivating mutations of the calcium receptor gene (*CASR*) account for the majority of cases of FHH. It is characterized by hypercalcemia, hypocalciuria [with a calcium/creatinine (Ca/Cr) clearance ratio of <0.01], and nonsuppressed PTH.[51] It is asymptomatic, probably because its origin in utero[52] results in full adaptation of the brain and other tissues to hypercalcemia, while the hypocalciuria protects against nephrocalcinosis and stones.

A pregnant woman with known FHH will have persistent hypercalcemia with nonsuppressed PTH; the serum calcium may rise even higher during the second and third trimesters. Importantly, the normal diagnostic criteria of FHH cannot be used because the pregnancy-related increase in intestinal calcium absorption results in absorptive hypercalciuria and a Ca/Cr clearance of well over 0.01.[53,54] Consequently, FHH presenting during pregnancy can be easily mistaken for primary hyperparathyroidism.

FHH does not pose any maternal risks; however, the fetal parathyroids can become suppressed by even mild maternal hypercalcemia. Consequently, women have been diagnosed with FHH in the puerperium after their newborns presented with neonatal hypocalcemia or seizures. With the mother having FHH, neonates are also at increased risk not only for inheriting FHH, but also for developing neonatal severe hypercalcemia (see Chapter 44).

21.2.3.1 Clinical Management

The key approach to FHH is to consider the diagnosis whenever a woman presents with hypercalcemia during pregnancy, and also to be wary that fractional urine calcium excretion will not be suppressed. A genetic test may be needed to confirm the diagnosis. Above all else, FHH must not be mistaken for primary hyperparathyroidism. Surgery is never indicated for FHH; moreover, a seemingly normal serum calcium level will be experienced as symptomatic hypocalcemia by someone with FHH. Unfortunately, at least one woman with FHH underwent a three-and-a-half-gland parathyroidectomy during the second trimester when she presented with marked hypercalcemia and hypercalciuria in pregnancy. FHH was only considered and recognized after maternal hypercalcemia persisted and her neonate developed hypercalcemia.[53] When pregnant women were recognized to have FHH, the serum calcium was not treated; however, close monitoring of the neonate for hypocalcemia is recommended.

21.2.4 Hypoparathyroidism

Studies in genetic and surgical animal models of hypoparathyroidism have shown that maternal hypocalcemia is hazardous for the fetus, with increased likelihood of the development of secondary hyperparathyroidism, skeletal demineralization, and fragility fractures occurring in utero or during and after delivery.[1] These adverse outcomes do not occur if the mother is normocalcemic or has mild hypocalcemia. Moreover, these models also have shown that maternal hypocalcemia can spontaneously improve during pregnancy, whereas it worsens in other models.[1] A physiological increase in calcitriol synthesis and intestinal calcium absorption still occur during pregnancy without PTH, but with varying effectiveness.[1]

The same divergent outcomes have been documented in women in whom hypoparathyroidism was known to be present prior to pregnancy. But longstanding hypoparathyroidism can also be asymptomatic, and some affected women have not been diagnosed until their newborns presented with severe secondary hyperparathyroidism, hypercalcemia, increased bone resorption, and fractures. As in the animal models, maternal hypocalcemia can have serious effects on the fetus and neonate (see Chapter 44).

Multiple published cases have shown that hypoparathyroidism can improve during pregnancy, as seen by fewer hypocalcemic symptoms and reduced need for supplemental calcium or treatment with calcitriol, 1α-cholecalciferol, or vitamin D.[1] In a well-documented case, calcitriol was stopped and the woman required only 1.2 g of calcium intake daily during the third trimester.[55] In a group of 10 cases of hypoparathyroidism, serum calcium declined due to the pregnancy-related fall in serum albumin, but the ionized calcium remained normal during pregnancy, with no need for calcitriol.[56] The author is aware of other unpublished cases in which hypoparathyroidism improved during pregnancy, and the dose of calcitriol was significantly decreased or stopped. When hypoparathyroidism improves during pregnancy, that may imply that upregulation of calcitriol synthesis, intestinal calcium absorption, or both have occurred without PTH, but they may possibly be due to PTHrP, consistent with what has been seen in rodent models.[1] However, in 1 case where maternal symptoms were subjectively improved but serum calcium measurements were not taken, the fetus had secondary hyperparathyroidism, which suggests that maternal hypocalcemia must have been present.[57]

Other reports have documented no change in serum calcium during pregnancy while on stable replacement doses of calcium and calcitriol/vitamin D; however, in some of these cases, serum calcium even increased in the last week or two before delivery.[1] In all these cases, serum calcium was not adjusted for the declining serum albumin, so the lack of a drop in unadjusted serum calcium during pregnancy may imply that ionized calcium had increased. Two reports on hypoparathyroid women found that ionized calcium did not change during pregnancy,[58,59] but in one case, the ionized calcium abruptly fell during labor, perhaps due to hyperventilation-induced alkalosis.[58]

However, other reports have found significant worsening of calcium metabolism during pregnancy. The evidence for this includes a decline in serum calcium, hypocalcemic symptoms that may increase, and increases in the prescribed doses of supplemental calcium and vitamin D, 1α-cholecalciferol, or calcitriol.[1] In most cases, calcitriol levels were not done or cannot be interpreted because of concurrent treatment with calcitriol or 1α-cholecalciferol (endogenous and exogenous calcitriol are indistinguishable).

However, in some of the reports in which hypoparathyroidism appeared to worsen during pregnancy, the normal dilutional decrease in serum calcium during pregnancy appears to have prompted an increase in the prescribed doses of calcium, vitamin D, or calcitriol.[1] In other words, the artifactual decline in total serum calcium, which is physiologically irrelevant, was misinterpreted to mean that an intervention was required. For example, in 1 case, the serum albumin had fallen from 4.2 to 2.0 g/dL, and the resulting change in serum calcium prompted increases in the doses of calcium and calcitriol.[60] But when the data in that report are reviewed, it is clear that the albumin-corrected serum calcium rose from 9.5 mg/dL (normal) in early pregnancy to 10.2 mg/dL (also normal) by 2 weeks before delivery; it had not decreased. Similarly, treatment of the albumin-related drop in unadjusted serum calcium resulted in women becoming hypercalcemic,[61,62] which confers fetal risks, as described earlier. In another case, an increase in urine calcium excretion was misinterpreted as worsening hypoparathyroidism when it represented the consequence of the pregnancy-related physiological increase in intestinal calcium absorption.[63] In yet another case, hypoparathyroidism did objectively worsen during pregnancy, but it was in a woman who took high-dose prednisone and azathioprine for a kidney transplant;[64] the high-dose prednisone would have reduced intestinal calcium absorption and likely played a role in what occurred during that pregnancy.

In summary, the available evidence indicates that many hypoparathyroid women have improvements in calcium metabolism during pregnancy, whereas some have objective evidence of worsening. In still other cases, the artifactual fall in total serum calcium or the physiological increase in urine calcium excretion was misinterpreted as evidence of worsening of hypoparathyroidism. A recent study of 10 cases by one group of investigators similarly found that some pregnant hypoparathyroid women improved, while others worsened.[65]

Why does hypoparathyroidism improve during pregnancy in some women and yet appear to worsen in others? It may be due to variability in the adaptive responses to pregnancy or in the achieved concentrations of hormones that stimulate intestinal calcium absorption or calcitriol synthesis. For example, high estradiol concentrations occur in pregnancy and have somewhat opposing effects of suppressing bone turnover and stimulating Cyp27b1 activity to synthesize calcitriol. If the greatest effect is on stimulating Cyp27b1, that may lead to overall improvements in pregnancy, as opposed to a potential worsening in women in whom the suppression of bone turnover may be more dominant. There also may be variations in how much PTHrP is released from the breasts and placenta, or in the increases in other pregnancy hormones (placental lactogen, oxytocin, etc.) that are thought to contribute to maternal mineral homeostasis during pregnancy. Calcium intake is critical, with Institute of Medicine guidelines suggesting a daily requirement of 1200 mg of calcium during pregnancy.[24] Yet in half of the reports in which hypoparathyroidism appeared to worsen during pregnancy, either no supplemental calcium or at most 300 mg/day was consumed, and the dietary intake of calcium was not determined.[1] Lack of adequate calcium intake in the first half of pregnancy will prevent the net positive calcium balance that is normally achieved, and it also may increase the likelihood of inadequate calcium delivery to the fetus in the third trimester.

21.2.4.1 Clinical Management

The available animal and human data, summarized previously, indicate two polar opposite extremes can occur when hypoparathyroid women become pregnant: there may be substantial improvement (normalization of serum calcium and phosphorus with reduced need for supplemental calcium and calcitriol) or worsening (more marked hypocalcemia requiring significant increases in supplemental calcium and calcitriol). There also will be women who exhibit no significant changes during pregnancy. These differences reflect such factors as variability in the adaptive response to increase intestinal calcium absorption during pregnancy despite the absence of PTH, as well as in the baseline calcium intake.

The ionized calcium or albumin-corrected calcium must be followed every 2–4 weeks during pregnancy, while changes in the unadjusted serum calcium should not be acted on. The prescribed doses of calcium and calcitriol (or other vitamin D analogs) need to be adjusted according to each individual's response to pregnancy. The doses will need to decrease in some women, others will require progressive increases, and still others may require no changes. PTH analogs are generally too expensive to use for physiological replacement and have not been formally studied during pregnancy, but a continuous infusion of teriparatide normalized calcium homeostasis during 1 pregnancy.[66]

In nonpregnant adults treated with calcium and calcitriol, the goal is to maintain the albumin-adjusted calcium or ionized calcium at or just below the lower end of normal. This minimizes hypocalcemic symptoms, while protecting the kidneys from an increased filtered load of calcium. However, during the 9 months of pregnancy, the ionized or albumin-corrected calcium should be preferably maintained within the normal range, in order to minimize the risk of fetal and neonatal complications from maternal hypocalcemia. Hypercalcemia also must be avoided because of the adverse effects that it has on fetal development. Thiazides are commonly used in the management of hypoparathyroidism, but they should be discontinued during pregnancy, as they are Category C medications.

21.2.5 Pseudohypoparathyroidism

Resistance to the actions of PTH is termed *pseudohypoparathyroidism*. This condition results not from absence of the PTH receptor, but from postreceptor defects in Gs-α that create end-organ resistance. Affected individuals have hypocalcemia, hyperphosphatemia, blunted phosphaturic response to PTH, and increased circulating concentrations of PTH. There are two main subtypes: Type I has blunted PTH-induced phosphaturia and renal production of cyclic adenosine monophosphate (cAMP), while Type II has just blunting of PTH-induced phosphaturia. They are managed similarly to hypoparathyroidism, with calcium, vitamin D, and calcitriol (or other analogs).

Type I pseudohypoparathyroidism improved during four pregnancies in women who maintained 1 g/day of supplemental calcium intake. Hypocalcemic symptoms lessened, normocalcemia was achieved, PTH levels lowered to near normal, endogenous calcitriol increased threefold to fourfold, urinary excretion of calcium normalized, and supplemental vitamin D, calcitriol, or analogs were no longer required.[67] Hypocalcemia and the need for supplemental calcium and calcitriol recurred within 3 weeks after delivery (none of the women breastfed). These reports are consistent with PTH-independent increases in intestinal calcium absorption and calcitriol synthesis occurring during pregnancy. In contrast, seven other pregnancies in women with Types I and II pseudohypoparathyroidism (described in detail in Ref. 1) resulted in subjective worsening of hypocalcemia-like symptoms or the need to increase the prescribed doses of calcium, calcitriol, or 1α-cholecalciferol.[1]

Overall, the clinical experience with pseudohypoparathyroidism appears to be similar to that of hypoparathyroidism, ranging from improvement to worsening, as described in Section 21.2.5. PTH-independent upregulation of calcitriol synthesis and intestinal calcium absorption could explain improved mineral metabolism in women with pseudohypoparathyroidism during pregnancy. Indeed, there is evidence of this from several pregnancies. Serum calcitriol doubled during the second and third trimesters in 2 women in whom supplemental calcitriol was discontinued. Another woman had increases in endogenous serum calcitriol during the first two trimesters, accompanied by stable serum calcium, but then serum calcitriol declined to the prepregnancy value in the third trimester, accompanied by reemergence of hypocalcemia. These changes in serum calcitriol among these women may indicate that a sustained increase in endogenous serum calcitriol during the third trimester predicts whether pseudohypoparathyroidism remains improved by pregnancy.

Placental production of calcitriol has previously been touted as a possible explanation for improvements in pseudohypoparathyroidism during pregnancy, but this is unlikely because the placenta contributes little calcitriol to the maternal circulation.[1] Analysis of placentas from 4 pseudohypoparathyroid women also confirmed that calcitriol production was no different than in placentas from normal women.[1]

As noted in Chapter 5, as well as in Section 21.2.4, evidence from animal models indicates that independent of PTH, other hormones of pregnancy may stimulate intestinal calcium absorption and the activity of Cyp27b1 to produce calcitriol. These considerations also apply to pseudohypoparathyroidism. It is also possible that hormonal changes during pregnancy (such as 100-fold higher estradiol) could improve postreceptor PTH signaling.

The intake of calcium is an important consideration. In four pregnancies in which pseudohypoparathyroidism objectively improved, the women took 1 g daily of supplemental calcium throughout.[67] In contrast, in pregnancies where pseudohypoparathyroidism appears to worsen, either no supplemental calcium was consumed, or at most 250–500 mg/day.[1] In none of these pregnancies was dietary intake of calcium assessed.

An intake of 1200 mg/day of calcium, combined with the doubling of efficiency of intestinal calcium absorption that occurs during normal pregnancy, should be more than sufficient to meet the combined needs of mother and fetus during a normal pregnancy. But if calcium intake is below this amount, then secondary hyperparathyroidism will be invoked to provide additional mineral from the mother's skeleton. Consequently, pseudohypoparathyroidism can be expected to worsen during pregnancy if oral calcium intake is insufficient.

21.2.5.1 Clinical Management

As is the case with hypoparathyroidism, women with pseudohypoparathyroidism can have polar opposite outcomes during pregnancy: an improved or worsened condition, as well as unchanged. Furthermore, the dilutional drop in total serum calcium that occurs during normal pregnancy—and which is physiologically unimportant—can be mistaken for evidence of clinical worsening.

Dietary calcium intake should be formally assessed and adjusted with supplements as needed to provide a total intake of 1200 mg/day. If dietary intake cannot be assessed, then a 1-g supplement may reasonably be prescribed to meet the combined maternal and fetal requirements. Variability in the responses of women with pseudohypoparathyroidism to the demands of pregnancy may be due to relative contributions of pregnancy-related hormones to regulating maternal mineral homeostasis, genetic or ethnic differences that influence these pregnancy-related adaptations, and the phenotypes of Type 1 or 2 pseudohypoparathyroidism. The progressive rise of PTHrP in the maternal circulation may have effects on maternal mineral metabolism, but this should not increase renal Cyp27b1 activity in women with pseudohypoparathyroidism because of the absence of Gs-α activity in the proximal tubules.

The goal of management should be to monitor and maintain normal ionized or albumin-corrected serum calcium in pregnant women with pseudohypoparathyroidism, thereby minimizing the risk of fetal and neonatal complications from maternal hypocalcemia or hypercalcemia. As with hypoparathyroidism, this means expectant management with adjustments to oral calcium and calcitriol doses as required during pregnancy. It should be anticipated that some women will require decreases in their doses to avoid hypercalcemia, while others will need increases to avoid hypocalcemia.

21.2.6 Pseudohyperparathyroidism

The breasts and placenta are sources of PTHrP in the maternal circulation during pregnancy.[1] It appears as if this increase in PTHrP results from autonomous production, or at least through mechanisms that are not responsive to maternal serum calcium. The production of PTHrP by the breasts during pregnancy may correlate with the amount of mammary tissue.

Pseudohyperparathyroidism is the condition of PTHrP-mediated hypercalcemia that occurs for physiological reasons, as opposed to hypercalcemia of malignancy, in which PTHrP is overproduced due to production by a tumor.

The development of this condition during pregnancy confirms that production of PTHrP by the breasts and placenta can alter the regulation of maternal mineral homeostasis. While this section discusses the onset of hypercalcemia as a result of PTHrP production during pregnancy, it is likely that the systemic release of PTHrP during normal pregnancy plays a role in maternal calcium and bone metabolism.

Hypercalcemia has developed as a consequence of very high circulating concentrations of PTHrP that have arisen from the breasts or placenta. The culprit is evident after reviewing the clinical course: hypercalcemia and PTHrP production persist after delivery, when the breasts are the source of PTHrP, whereas the serum calcium and PTHrP concentration plummet within a few hours when the placenta is the source.[1]

The breasts have been implicated in several cases of PTHrP-mediated hypercalcemia, including women with massive mammary hyperplasia (pregnant or nonpregnant), as well as in pregnant women with normal-sized breasts.[1] In several cases of hypercalcemia during pregnancy, serum PTH was undetectable, PTHrP circulated at a high concentration or its expression was markedly increased in breast tissue, and the hypercalcemia resolved only after weaning, bilateral mastectomy, or use of a dopamine agonist (bromocriptine or cabergoline). When PTHrP-mediated hypercalcemia persists after delivery, it confirms that breasts are the source of PTHrP because placental PTHrP should disappear from the circulation within minutes of the afterbirth. In a woman with marked hypercalcemia and an elevated PTHrP of 34.9 pmol/L during pregnancy, and who did not breastfeed, the hypercalcemia resolved slowly, while the elevated circulating PTHrP concentration persisted for 3 months.[68] This was evidently due to sustained production of PTHrP in the breasts, despite refraining from breastfeeding.

Release of PTHrP from the breasts occurs physiologically during lactation and partially or completely normalizes mineral homeostasis in women with hypoparathyroidism; this was discussed in Section 21.2.4. Pseudohyperparathyroidism also occurs from overproduction of PTHrP by the placenta. A clear-cut case involved a woman with normal-sized breasts who had severe hypercalcemia (21 mg/dL or 5.25 mmol/L), undetectable PTH, and a serum PTHrP of 21 pmol/L in the third trimester.[69] So, 6 h after an urgent cesarean section, she was profoundly hypocalcemic, with undetectable PTHrP and elevated PTH. The rapid reversal toward low PTHrP, high PTH, and hypocalcemia can be explained only by the abrupt loss of placental-derived PTHrP.

21.2.6.1 Clinical Management

It will be difficult to be certain of the source of excess PTHrP until after delivery. When the placenta is the cause, the hypercalcemia should self-correct within hours after delivery, whereas overproduction of PTHrP by the breasts is more likely to lead to hypercalcemia that persists and may worsen after delivery due to loss of the placental efflux of calcium and the onset of lactation. Prior to delivery, hypercalcemia may be addressed with fluid resuscitation and correction of electrolyte abnormalities, and the measures discussed previously with respect to primary hyperparathyroidism (loop diuretic, calcitonin, and bisphosphonate; denosumab should be avoided due to a transplacental passage). A more specific treatment that addresses the cause is bromocriptine or cabergoline, which can be expected to suppress both placental and mammary production of PTHrP.[70] A reduction mammoplasty is also a consideration if it is clear that the breasts are the cause, such as in massive mammary hyperplasia.

21.2.7 Vitamin D Deficiency, Genetic Vitamin D Resistance, and 24-Hydroxylase Deficiency

21.2.7.1 Animal Data: Vitamin D Deficiency and Genetic Vitamin D Resistance

Calcitriol's role in reproductive physiology has been examined through several approaches, including studying severely vitamin D-deficient rats, *Cyp27b1*-null mice that cannot make calcitriol, and *Vdr*-null mice that lack the receptor for calcitriol.[1] In all these instances, females conceive less frequently and bear fewer pups per litter. However, fertility is unaffected in *Cyp27b1*-null (Hannover) pigs, which bear only singletons or twins. In the rodent examples, both the reduced fertility and smaller litter sizes are fully treated by providing a high-calcium diet that is also enriched in lactose to enhance calcium absorption.[1] Therefore, it is not lack of calcitriol, but calcium itself, that causes these fertility problems.

Studies have also been carried out in severely vitamin D-deficient rats, *Cyp27b1*-null pigs, *Cyp27b1*-null mice, and *Vdr*-null mice, to determine if loss of calcitriol or its receptor causes any disruption of normal pregnancy.[1,71] In each study, occasional sudden deaths, presumably from hypocalcemia, occurred during late pregnancy in response to anesthesia or exposure to colder temperatures. This may indicate that rapid transfer of calcium across the placenta, which is at its highest rate during late pregnancy, can overwhelm maternal regulation of the ionized calcium. But as noted in Chapter 44, the fetuses of each of these models exhibit normal mineral homeostasis and skeletal development. This includes that *Vdr*-null fetuses and their WT littermates, and *Cyp27b1*-null fetuses and their WT littermates, which were indistinguishable from

each other when born of their respective heterozygous-deleted mothers. However, all offspring of *Vdr*-null females were proportionately smaller than offspring of their WT and $Vdr^{+/-}$ sisters, a difference that was not seen between fetuses born of vitamin D-deficient and replete rats, or born of *Cyp27b1*-null vs WT mice.[72] The smaller sizes of offspring of *Vdr*-null mothers may indicate that maternal expression of VDR affects offspring growth, independent of the fetal genotypes and calcitriol.

Pregnancy in severely vitamin D-deficient rats, *Vdr*-null mice, and *Cyp27b1*-null mice results in increases in maternal serum calcium and phosphorus, suppression of secondary hyperparathyroidism, increased mineralization of osteoid, and significant gains in skeletal mineral content.[1,71] These improvements result from a calcitriol-independent increase in intestinal calcium absorption that has been confirmed in severely vitamin D-deficient rats and *Vdr*-null mice, and inferred to be present in *Cyp27b1*-null mice.[71] In these studies, it was the onset of pregnancy that invoked improvements in intestinal calcium absorption and mineral homeostasis, without requiring vitamin D, calcitriol, and VDR. What factors regulate the increase in intestinal calcium absorption during pregnancy in the absence of calcitriol remain unknown.[1] The apical calcium channels (Trpv6, Trpv5), the Ca2+-ATPase, and the sodium-calcium exchanger Ncx1, are upregulated within the enterocytes of normal mice during pregnancy,[1] whereas in *Vdr*-null mice, a further upregulation of Trpv6 and PTHrP has been seen compared to normal pregnant, related controls.[73,74]

Vitamin D/calcitriol has been proposed to play diverse, nonskeletal roles during pregnancy, but these have not been extensively examined in these animal studies. Pregnant vitamin D-deficient mice had higher systolic and diastolic blood pressure and upregulation of renal expression of renin and angiotensin II receptor messenger ribonucleic acid (mRNA) compared to pregnant vitamin D-sufficient mice.[75] These data are consistent with the possibility that vitamin D deficiency could increase the risk of pregnancy-induced hypertension.

21.2.7.2 Animal Data: 24-Hydroxylase Deficiency

Mice with 24-hydroxylase deficiency are fertile. During the last 5 days of gestation, they develop a marked elevation in calcitriol, severe hypercalcemia, and hypercalciuria.[76]

21.2.7.3 Human Data: Vitamin D Deficiency and Genetic Vitamin D Resistance

Calcitriol-dependent active absorption of calcium represents about 20% of net calcium absorption, and this route of delivery is especially important when dietary intake of calcium is low. The remaining 80% of calcium is absorbed through passive, nonsaturable mechanisms, which are also stimulated in part by calcitriol. Because pregnancy represents a time of increased need for calcium delivery and many women do not meet the recommended daily intake for calcium, calcitriol's role in regulating intestinal calcium absorption should become critical during pregnancy. But the animal models described previously have displayed normal pregnancies and fetal development, which suggests that calcitriol is not required.

Therefore, is there any clinical evidence that vitamin D deficiency, or genetic disorders causing loss of calcitriol or VDR, will affect maternal mineral metabolism and obstetrical or fetal outcomes?

No clinical study has measured intestinal calcium absorption during pregnancy in vitamin D-deficient compared to vitamin D-sufficient women, or in women with genetic disorders of vitamin D physiology. Consequently, it remains unknown whether a doubling of intestinal calcium absorption occurs during pregnancy when calcitriol or its receptor is absent.

Definitive evidence of calcitriol's role in human pregnancy (and fetal/neonatal development) would come from large, randomized, blind clinical trials that enrolled vitamin D-deficient women and randomized them to supplementation or placebo. Such studies would control for confounding, including any factors that led to the women being vitamin D deficient. However, no such large studies have been carried out for ethical and logistical considerations.

Instead, numerous small to modestly sized clinical trials of vitamin D supplementation have been done.[1] Only a few of these compared truly vitamin D-deficient to -sufficient women, while more recent larger studies have compared varying degrees of vitamin D sufficiency without having a group with clear-cut vitamin D deficiency.

The fetal and neonatal outcomes of these studies are described in Chapter 44, as well as in a comprehensive review article.[72] In brief, no changes in cord blood calcium, phosphorus, PTH, birth weight, or anthropometric measurements were observed when babies of vitamin D-supplemented mothers were compared to babies of placebo-treated mothers. However, the incidence of neonatal hypocalcemia after 48 h was reduced by vitamin D supplementation in several studies when the babies of placebo-treated mothers had cord blood 25OHD below 20 nmol/L.[72] This is consistent with the postnatal role that calcitriol has in the regulation of intestinal calcium absorption.

Due to considerations of space and limits on the reference list, all of the abovementioned studies cannot be described in detail. Instead, a recent comprehensive review can be consulted for more details and a review of many studies.[1] We will not discuss associational studies, as they are confounded by factors that predict a lower 25OHD level and the outcome analyzed,

including race/ethnicity, maternal overweight/obesity, lower socioeconomic status, poor nutrition, and others. For example, maternal overweight/obesity is well established to confer substantial risks of preterm delivery, cesarean sections, low birth weight, preeclampsia/pregnancy-induced hypertension, vaginal infections, and other adverse obstetrical outcomes.[77] Furthermore, associations do not prove causation; instead, they should suggest the need for large randomized controlled trials (RCTs) that compare vitamin D-deficient and -sufficient mothers to test the outcome of interest.

This chapter will focus on obstetrical outcomes from a few RCTs that included over 100 participants per study who were vitamin D deficient at entry, and some recent studies that gained press attention over the last few years but which did not include many vitamin D-deficient subjects (see Table 21.5). Fetal and neonatal outcomes from these studies are addressed in more detail in Chapter 44.

There were two trials each in Bangladesh, the United States, and the United Kingdom, and one each in New Zealand, Iran, and the United Arab Emirates.[78–86] The largest studies were in Bangladesh and the United Kingdom, with over 1000 participants.[85,86] Baseline maternal 25OHD levels were lowest (20–29 nmol/L) in the trials from Bangladesh, the United Kingdom, Iran, and UAE, and they were in the 40–60 nmol/L range in the others. The interventions consisted of placebo or low-dose (400 IU/day) or high-dose vitamin D (1000–5000 IU/day equivalent), which were started between the end of the first trimester and the mid-second trimester, and maintained until delivery. For almost all trials, the primary outcomes were simply maternal and neonatal-cord blood 25OHD and calcium (Table 21.5).

The most recent, and largest, study from Bangladesh administered prenatal vitamin D, and in one of the treatment arms, it was continued for 26 weeks postpartum, and prespecified infants' length for age *z*-scores at 1 year of age as the primary outcome.[86] In the remaining studies, offspring anthropometric parameters, bone mineral content (BMC), or both were prespecified in a limited number of studies.[82,84,85]

In all these studies, the administration of vitamin D increased maternal serum and cord blood 25OHD, while there was no overall effect on cord blood calcium. Maternal serum 25OHD reached a mean between 60 and 165 nmol/L at delivery, depending on the baseline level and the dose administered (Table 21.5). The largest difference achieved in a single study was 16 nmol/L (6.4 ng/mL) in the placebo-treated and 168 nmol/L (67 ng/mL) in vitamin D-supplemented mothers at term; however, there was no obstetrical benefit.[78] There was a benefit in reducing the incidence of neonatal hypocalcemia, which is discussed in Chapter 44.

In the recent study from Bangladesh, there was no significant difference in infant length, or any other clinical or anthropometric neonatal or maternal outcome, between treatment arms.[86] In one US-based study, there was no benefit to mode of delivery, gestational age at delivery, and preterm birth,[79] while in the other, there was no benefit in terms of mode of delivery, cesarean section rates, adverse events, hypertension, infection, gestational diabetes, stillbirth, gestational age at delivery, or combinations of these outcomes.[81]

The UK MAVIDOS trial reported no obstetrical benefit, and no benefit to any of the neonatal primary (neonatal bone area, BMC, and BMD within the first 10–14 days after birth) and secondary outcomes (anthropometric and body composition parameters within 48 h of birth). However, it was well publicized for a demonstrated increase in BMC and BMD in winter-born neonates of vitamin D-supplemented vs placebo-treated mothers.[85] Due to the normal rapid (100 mg/day) accumulation of skeletal mineral content after birth, this result may reflect improved intestinal mineral delivery over 14 days after birth, rather than a prenatal effect on skeletal mineralization. Curiously, autumn-born neonates of vitamin D-supplemented vs placebo-treated mothers showed an adverse trend of similar magnitude on BMC and BMD, which suggests possible harm from vitamin D supplementation. These results were based on significant findings from subgroup analyses of treatment by season interaction, which were not specified outcomes in the trial registries (ISRCTN 82927713 and EUDRACT 2007-001716-23). In the UK study that consisted mostly of vitamin D-deficient, subjects from India, there was a trend for a lower proportion of neonates being born small for gestational age (SGA) to mothers in the vitamin D-supplemented group (15% vs 28%, $0.05 < P < 0.1$), but the study was not powered for this outcome, which was also not prespecified.[78] In the studies from the UAE and Iran, there was also no benefit to obstetrical outcomes (variably, mode of delivery, cesarean section rates, adverse events, stillbirths, gestational age at delivery) or neonatal anthropometric measurements and bone mass measurements.[80,82,84]

The lack of any beneficial effect on maternal, immediate fetal/neonatal, and neonatal outcomes (anthropometrics and cord blood calcium), even in studies that included mothers with some of the lowest 25OHD levels,[78,82,84,86] may suggest that vitamin D supplementation during pregnancy confers no benefit to neonates. In contrast to almost all previous trials that were not sufficiently powered for obstetrical or neonatal outcomes, the most recent one was well powered to demonstrate a beneficial effect on infant length, but it still did not yield any significant results, despite low vitamin D levels in the mothers at the start of the study.[86]

Hollis and Wagner subsequently carried out multiple posthoc analyses of their two trials, including analyses in which selective data from both studies were pooled and analyses were done by achieved 25OHD level.[79,87–89] They reported

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range)	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range) 25OHD assay type	Prespecified outcomes as reported in paper and trial register	Results
Brooke et al. *BMJ* 1980 United Kingdom	*C* *N* = 67 23.7 ± 3.1 *I* *N* = 59 23.9 ± 4.8	Double-blind trial *Intervention:* *C:* No intervention *I:* Calciferol: 1000IU/day *Inclusion criteria:* • Pregnant Asian women • 28–32 weeks' gestation *Exclusion criteria:* • Preterm deliveries • Congenital malformations • Maternal illnesses likely to affect fetal growth (such as diabetes) *Ethnicity*: Asian (70% Indian)	*28*	20.1 ± 1.9 Competitive protein-binding	*Paper* *Outcomes:* • Maternal and infant calcium homoeostasis and fetal growth *Trial register not available*	*Maternal daily weight gain (g)* Mean ± SD: *C*: 46.4 ± 3.6 *I*: 63.3 ± 2.6 ($P < 0.001$) *Maternal 25OHD at delivery (nmol/L)* Mean ± SD: *C:* 16.2 ± 27 *I:* 168 ± 12.5 *Neonatal 25OHD at delivery (nmol/L)* Mean ± SD: *C:* 10.2 ± 2 *I:* 137.9 ± 10.8 *Maternal calcium at delivery (mmol/L)* Mean ± SD: *C*: 2.51 ± 0.01 *I:* 2.58 ± 0.02 ($P < 0.001$) *Maternal alkaline phosphatase at delivery (IU/l)* Mean ± SD: *C:* 136.1 ± 7.9 *I:* 114.3 ± 6.5 *Infant plasma calcium at day 6 (mmol/l)* Mean ± SD: *C:* 2.29 ± 0.02

Continued

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy—cont'd

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range)	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range) 25OHD assay type	Prespecified outcomes as reported in paper and trial register	Results
						I: 2.49 ± 0.04 ($P < 0.05$) Five infants developed symptomatic hypocalcemia in the control group and none in the treatment group *Neonatal fontanelle area measurement (cm^2):* Mean ± SD: *C:* 6.1 ± 0.7 *I:* 4.1 ± 0.4 ($P < 0.05$) Infants small for gestational age (%): *C:* 28.6% *I:* 15.3%, $0.05 < P < 0.1$
Hollis et al. *JBMR* 2011 United States	*C* *N* = 111 27.0 ± 5.6 *I1* *N* = 122 27.4 ± 5.7 *I2* *N* = 117 26.6 ± 5.4	Single-center, randomized, controlled, double-blind study *Intervention:* *C:* 400 IU vitamin D3/day *I1:* 2000 IU vitamin D3/day *I2:* 4000 IU vitamin D3/day *Inclusion criteria:* • Age ≥16 years • Confirmed singleton pregnancy • <16 completed weeks' gestation at the time of consent	*C* 12.5 ± 1.9 *I1* 12.6 ± 1.6 *I2* 12.4 ± 2.0	*C* 61.6 ± 27.1 *I1* 58.3 ± 22.3 *I2* 58.2 ± 21.8 Direct ultraviolet detection preceded by organic extraction and high-performance liquid chromatography	*Paper* *Primary outcomes:* • Maternal 25OHD[a] at delivery • Neonatal 25OHD at delivery *Secondary outcomes:* • 25OHD concentration of 80 nmol/L or greater achieved • 25OHD concentration required to achieve maximal $1,25OH_2D_3$ production	*Maternal 25OHD 1 month before delivery (nmol/L)* Mean ± SD: *C:* 79.4 ± 34.3 *I1:* 105.4 ± 35.7 *I2:* 118.5 ± 34.9 ($P < 0.0001$) *Maternal 25OHD at delivery (nmol/L)* *Mean ± SD:* *C:* 78.9 ± 36 *I1:* 98 ± 34 *I2:* 111 ± 40 ($P < 0.0001$)

		Exclusion criteria: • Preexisting calcium or parathyroid conditions • Chronic diuretic or cardiac medication therapy, including calcium channel blockers • Active thyroid disease (e.g., Grave's disease, Hashimoto's thyroiditis, or thyroiditis) *Ethnicity:* African American (28%–33%), Hispanic (44%–48%), Caucasian (37%–40%)			*Register/NCT00292591* Primary outcome measures: • 25OHD Concentration [Time frame: 7 months]. Circulating total 25OHD concentration measured in serum at visit 7, 1 month prior to delivery • BMD of both mother and infant 1.5 years[b]	*RR for achieving a 25OHD ≥80 nmol/L within 1 month of delivery* *RR (95% CI):* RR = 1.52 (95% CI 1.24–1.86) between *I1* and *I2* RR = 1.60 (95% CI 1.32–1.95) between *C* and *I2* *Maternal PTH 1 month prior to delivery (pmol/L)* Mean ± SD: *C:* 2.2 ± 1.3 *I1:* 2.1 ± 1.1 *I2:* 1.9 ± 1.1 PTH not significantly different by treatment groups; significance was obtained when PTH was stratified by race *Maternal circulating 25OHD required to achieve maximal 1,25OH$_2$D3 production during pregnancy (nmol/L):* At least 100 ($P < 0.0001$) *No effect on any obstetrical outcome:* • Preterm birth • Mode of delivery • Gestational age
Roth et al. *Nutrition Journal* 2013 Bangladesh	*C* *N* = 80 22.4 ± 3.4 *I* *N* = 80 22.4 ± 3.5	Double-blind, placebo-controlled, randomized trial *Intervention:* *C*: No intervention *I*: 35,000 IU vitamin D3/week	*C* 27.9 ± 1.0 *I* 27.6 ± 1.1	*C* 44.0 ± 20.9 *I* 45.4 ± 18.4	*Paper* *Primary outcomes:* • 25OHD in mother[a] and infant at delivery (primary biochemical efficacy outcome)	*Maternal 25OHD at delivery (nmol/L)* Mean ± SD: *C:* 38.4 ± 18.1 *I:* 134.4 ± 30.7 ($P < 0.001$)

Continued

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy—cont'd

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range)	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range) 25OHD assay type	Prespecified outcomes as reported in paper and trial register	Results
		Inclusion criteria: • Age 18 to <35 years • GA 26–30 weeks *Exclusion criteria:* • D supplement 400 IU/day within the month prior to enrolment • Refusal to stop supplemental vitamin D after enrollment • Current use of anticonvulsant or antimycobacterial drugs • Severe anemia (hemoglobin <70 g/L) • Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg • Proteinuria or glycosuria • Complicated medical or obstetric history • History of delivery of an infant with a major congenital anomaly • Birth asphyxia • Perinatal death *Ethnicity*: Not described		Chemiluminescent microparticle immune assay	Maternal serum calcium concentration at delivery (primary safety measure) *Register/NCT01126528* *Primary outcome measures:* • Serum 25OHD concentration [Time frame: Maternal: during third trimester; Neonatal (cord blood)]. Biomarker of vitamin D status *Secondary outcome measures:* • Serum calcium concentration [Time frame: Maternal: third trimester; cord blood] • Urine Ca:Cr ratio [Time frame: Maternal: third trimester] • Neonatal immune function [Time frame: cord blood]. Selected markers of innate and adaptive immunity • Infant growth [Time frame: Postnatal observational follow-up phase]. Infant growth parameters during postnatal follow-up, up to 12 months of age • Infant and maternal postnatal vitamin D status [Time frame: Postnatal observational follow-up phase] • Neonatal serum calcium [Time frame: First week postnatal].	*Neonatal 25OHD (nmol/L)* Mean ± SD: *C:* 39.0 ± 18.7 *I:* 102.8 ± 28.6 ($P < 0.001$) *Maternal serum calcium at delivery (mmol/L)* Mean ± SD: *C:* 2.31 ± 0.11 *I:* 2.32 ± 0.10 *Maternal albumin-adjusted calcium at delivery (mmol/L)* Mean ± SD: *C:* 2.40 ± 0.08 *I:* 2.43 ± 0.09 ($P < 0.05$) *Maternal urine Ca: Cr ratio at delivery (mmol/mmol)* Median (Range): *C:* 0.13 (0.0, 1.26) *I:* 0.20 (0.0, 2.26) *Maternal PTH at delivery (pmol/L)* *Median (Range):* *C:* 3.9 (0.3, 20.5) *I:* 2.3 (0.3, 9.8) ($P < 0.001$) There was no effect on obstetrical outcomes: • Mode of delivery

					Infant serum calcium during the first week postnatal Last three outcomes were added in the latest version of the protocol in Aug 2012	• Cesarean section rates • Adverse events • Stillbirths or gestational age at delivery • Neonatal anthropometry (birth weight, length at birth, head circumference)
Wagner et al. *AJOG* 2013 United States	*I1* *N*=130 24.5±5.3 *I2* *N*=127 25.4±5.0	Two-center, randomized, double-blind study *Intervention:* *I1:* 2000IU/day *I2:* 4000IU/day *Inclusion criteria:* • Age ≥16 years • Confirmed singleton pregnancy of <16 completed weeks' gestation *Exclusion criteria:* • Preexisting calcium or parathyroid conditions • Chronic diuretic or cardiac medication therapy including calcium channel blockers • Active thyroid disease (e.g., Graves, Hashimoto's thyroiditis) *Ethnicity:* African American (47%–50%), Caucasian (9%–10%), Hispanic (36%–42%), other (2%–4%)	12.4±1.8	56.6±24.2 Direct RIA developed in another laboratory	*Paper* *Coprimary outcomes:* • Change in circulating maternal 25OHD[a] concentration from baseline to the completion of pregnancy • Neonate's 25OHD concentration at birth *Register/NCT00412087* *Primary outcome measures:* • 25OHD at Visit 7 [Time frame: 7 months] 25OHD at Visit 7, 1 month prior to delivery *Secondary outcome measure:* • Parathyroid hormone at Visit 7 [Time frame: 7 months] Intact parathyroid hormone at Visit 7, 1 month prior to delivery V1 and V2 of trial register do not specify timing to measure outcomes, V3, 4, 5 specify 9 months, and V6 states 7 months and 1 month prior to delivery	*Maternal 25OHD at delivery (nmol/L)* Mean±SD: *I1:* 90±24 *I2:* 94±33 *Neonatal 25OHD at delivery (nmol/L)* Mean±SD: *I1:* 55±26 *I2:* 67±33 *Maternal iPTH 1 month prior to delivery (pg/ml)* Mean±SD: *I1:* 17.5±8.2 *I2:* 15.2±9.3 *Preterm labor* *N (%):* *I1:* 24 (28.9%) *I2:* 13 (16.7%) (*P*=0 .091) *Fenton weight percentile:* *I2* had 2.40 (95% CI 1.26–4.61) times the odds of having an infant in the 50th percentile, compared to *I1* *There was no effect on obstetrical outcomes:* • Mode of delivery • Cesarean section rates

Continued

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy—cont'd

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range) 25OHD assay type	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range)	Prespecified outcomes as reported in paper and trial register	Results
						• Adverse events • Hypertension • Infection • Stillbirths or gestational age at delivery
Dawodu et al. *JCEM* 2013 UAE	*I1* *N* = 64 27.5 ± 5.5 *I2* *N* = 65 27.3 ± 4.9 *I3* *N* = 63 25.6 ± 5.5	Randomized, controlled, double-blind study *Intervention:* *I1*: 400 IU vitamin D3/day *I2*: 2000 IU vitamin D3/day *I3*: 4000 IU vitamin D3/day *Inclusion criteria:* • 12–16 weeks' gestation • Singleton pregnancy *Exclusion criteria:* • Preexisting calcium and parathyroid conditions • Active thyroid disease, liver or kidney disease • Type 1 diabetes, which is likely to affect vitamin D and calcium status *Ethnicity:* Gulf Arab (92%–94%), non-Gulf Arab (6%–8%)	*I1:* 12.2 ± 0.9 *I2:* 12.5 ± 1.1 *I3:* 12.6 ± 1.1	*I1:* 21.5 ± 13.0 *I2:* 20.5 ± 11.9 *I3:* 19.6 ± 7.7 RIA (DiaSorin, Stillwater, MN)	*Paper* *Primary outcomes:* • Maternal serum 25OHD[a] concentrations at delivery *Secondary outcomes:* • Proportion of mothers who achieved serum 25OHD 32 ng/mL or greater (≥80 nmol/L) defined as vitamin D sufficiency at the time of delivery *Register/NCT00610688* *Primary outcome measures*: • Serum maternal and neonatal 25OHD measurement [Time frame: 29 weeks] Maternal serum 25OHD measurement at 12, 16, and 28 weeks during pregnancy and at delivery and cord blood or neonatal serum 25OHD measurement *Secondary outcome measures:*	*Maternal 25OHD at delivery (nmol/L)* Mean ± SD: *I1*: 48 *I2:* 65 *I1:* 90 ($P < 0.0001$) *Mothers achieving 25 (OH)D >80 (nmol/L)*(%): *I1*: 9.5% *I2*: 24.4% *I3*: 65.1% ($P < 0.0001$) *PTH concentration at delivery*: Reduced in high-dose group *Maternal serum calcium and urine calcium/creatinine:* No differences were detected *No effect on:* • Mean birth weight • Length • Head circumference

					• Growth of the newborn infant as measured by crown-heel length and head circumference at birth [Time frame: At delivery] • Birthweight of newborn infant [Time frame: Measured at birth] Growth of the newborn infant as measured by birth weight in gramsOnly V4 of trial register specifies all time points to measure the primary outcome	• Gestational age
Grant et al. *Pediatrics* 2014 New Zealand	*C* *N* = 87 28 ± 6 *I1* *N* = 87 27 ± 6 *I2* *N* = 86 26 ± 7	Randomized, double-blind, placebo-controlled trial *Intervention:* C: No intervention I1: 1000 IU vitamin D3/day I2: 2000 IU vitamin D3/day *Inclusion criteria:* • GA 26–30 weeks • Singleton pregnancy *Exclusion criteria:* • Vitamin D supplementation > 200 IU/day • History of renal stones or hypercalcemia • Any serious pregnancy complication at enrollment *Ethnicity:* 34% European, 24% Maori, 49% Pacific, and other 25%. Ethnicity was defined by the participants. More than 1 ethnic group could be identified; therefore, percentages do not add up to 100	*C:* 27 (26, 29) *I1:* 28 (26, 29) *I2:* 27 (26, 29)	*C:* 55 (32, 80) *I1:* 57 (40, 90) *I2:* 55 (32, 87) Isotope-dilution liquid chromatography–tandem mass spectrometry	*Paper* *Primary outcomes:* • The proportion of infants[a] achieving a serum 25OHD ≥ 75 nmol/L during the first 6 months of infancy • Number of mothers and infants with hypercalcemia at any measurement point *Register/ACTRN12610000483055* *Primary outcome:* • The proportion of infants achieving a serum 25OHD concentration >75 nmol/L at 6 months of age. • The number of mothers and infants with hypercalcemia at any measurement point *Secondary outcome:* • The proportion of mothers achieving a serum 25[OH] vitamin D concentration > 75 nmol/L at 36 weeks' gestation	*Maternal 25OHD at delivery (nmol/L)* *Mean (25th, 75th centile):* *C:* 50 (30, 75) *I1:* 97 (80, 115) *I2:* 102 (72, 125) (*P* < 0.001) *Maternal serum 25OHD concentration > 75 (nmol/L) at 36 wks gestation (%):* *C:* 27% *I1:* 79% *I2:* 71% (*P* < 0.001) *Maternal serum calcium Concentration at 36 wks gestation (mg/dL)* Mean ± SD: *C:* 10.31 ± 0.53 *I1:* 9.04 ± 0.37 *I2:* 9.02 ± 0.29 (*P* = 0.09) *Neonatal 25OHD at delivery (nmol/L)* *Mean (25th, 75th centile):* *C:* 32.4 (22.5, 44.9) *I1*:59.9 (44.9, 74.9) *I2:* 64.9 (44.9, 87.4) (*P* < 0.001) *Infant serum 25OHD*

Continued

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy—cont'd

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range)	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range) 25OHD assay type	Prespecified outcomes as reported in paper and trial register	Results
						concentration > 50 (nmol/L) at 6 months, (%): *C:* 74% *I1:*82% *I2:*89% ($P < 0.07$)
Vaziri et al. *Early Human Development* 2016 Iran	*C* *N* = 65 26.0 ± 4.34 *I* *N* = 62 26.8 ± 4.92	Randomized clinical trial *Intervention:* *C:* Placebo (no intervention) *I:* 2000 IU/day vitamin D3 *Inclusion criteria:* • Age >18 years • No history of mental illness and internal diseases such as hyperthyroidism/hypothyroidism • No addiction to any kind of narcotic drugs or alcohol • Not divorced or widowed • No pregnancy complications such as preeclampsia, gestational diabetes, ruptured membranes, and suspicion of preterm birth • No previous cesarean sections, with a live fetus singleton pregnancy • GA 26–28 weeks	26–28	*C*: 31.8 ± 20.9 *I*: 29 ± 13.9 CLIA	*Paper outcomes:* • Maternal 25OHD at delivery[a] • Infants' anthropometric measurements (at birth, 4th and 8th weeks postnatal) • Maternal and infant bone mass parameters were examined during first 2 months after birth *Register/IRCT2015040910327N13* *Primary outcomes* • Description: Blood cord vitamin D concentration Time point: After delivery • Description: Bone densitometry Time point: During first 2 months after birth • 3.Description: Antropometric	*Maternal 25OHD at delivery (nmol/L)* Mean ± SD: *C:* 30 ± 14.5 *I:* 45 ± 23.9 ($P < 0.001$) *No significant differences between C and I:* • Birth weight • Height • Head circumference *No significant differences between C and I:* Bone mass measurements of the mothers: • BMD • BMC • BA

		Exclusion criteria: • Unwillingness to cooperate during the study • Consumption of <8 weeks of vitamin D3 supplements Gross congenital malformations and chromosomal disorders in infants *Ethnicity:* Not described			measurments (height, weight, and head circumference) Time point: At birth and 4 and 8 weeks later *Secondary outcomes:* None described	*No significant differences between C and I:* Bone mass measurements of the infants at birth and 4th and 8th weeks after birth: • BMD • BMC • BA
Cooper et al. *Lancet Diabetes Endocrinol* 2016 United Kingdom	*C* *N*=569 30.5±5.2 *I* *N*=565 30.5±5.2	Multicenter, double-blind, randomized, placebo-controlled trial *Intervention:* *C:* No intervention *I:* 1000 IU/day cholecalciferol *Inclusion criteria:* • Age >18 years • Singleton pregnancy • GA <17 weeks *Exclusion criteria:* • Women with known metabolic bone disease • Renal stones • Hyperparathyroidism • Hypercalciuria • Diagnosis of cancer in the last 10 years • Unable to give informed consent or comply with the protocol • Taking medication known to interfere with fetal growth • Fetal anomalies on ultrasonography	14	*C:* 46±17 *I:* 47±18 Liaison RIA automated platform	*Paper* *Primary outcomes:* • Neonatal whole BMC[a], assessed within 2 weeks after birth by DXA *Secondary outcomes:* • Maternal 25OHD concentration at 34 weeks' gestation • Change in 25OHD between 14 and 34 weeks' gestation • Neonatal whole-body bone area and BMD within 2 weeks after birth • Neonatal bone indexes at the spine *Register/ISRCTN82927713* *Primary outcome measures:* • Neonatal whole-body bone area, BMC, and BMD assessed by DXA within 10 days of birth.	*Maternal 25OHD at 34 weeks' gestation (nmol/L)* Mean±SD: *C:* 43±22 *I:* 68±22 (P<0.001) *No significant differences between C and I:* Bone mass measurements of the infants: • BMD • BMC • BA • Lean mass • Median fat mass • Birth weight • Length • Head circumference • Abdominal circumference

Continued

TABLE 21.5 Summary of large RCTs of vitamin D supplementation during pregnancy—cont'd

Author Journal Year Country	*N* Age (years) Mean ± SD or median (range)	Study design	Gestational age (weeks) at entry Mean ± SD or median (range)	Baseline maternal 25OHD (nmol/L) Mean ± SD or median (range) 25OHD assay type	Prespecified outcomes as reported in paper and trial register	Results
		Women already using >400 IU/day vitamin D supplementation *Ethnicity:* White 94%			*Secondary outcome measures:* • Neonatal and childhood anthropometry and body composition (weight, length and skinfold thickness measurements), assessed within 48 h of birth. Women's attitude to pregnancy vitamin D supplementation (qualitative study; assessed in main study only). Methodology and time points of assessment not yet defined as of March 3, 2008 Childhood bone mass at 4 years	
Roth et al. *NEJM* 2018 Bangladesh	*C* *N* = 259 Median (range) 23 (18–38) *I1* *N* = 260 Median (range) 22.5 (18–40) *I2* *N* = 259 Median (range) 22 (18–35) *I3* *N* = 260 Median	Randomized, double-blind, placebo-controlled, dose-ranging trial *Intervention:* *C:* Placebo *I1:* 4200 IU vitamin D3/week *I2:*16,800 vitamin IU D3/week *I3:* 28,000 IU vitamin D3/week *I4:* 28,000 IU vitamin D3/week (prenatal and postpartum until week 26) *Inclusion criteria:* • Age ≥18 years • GA 17–24 weeks	*C* Median (range) 20.4 (17–24) *I1* Median (range) 20.1 (17–24) *I2* Median (range) 20.3 (17–24) *I3* Median (range) 20.4 (17–24)	*C* 27.7 ± 13.8 *I1* 27.4 ± 14.3 *I2* 28.7 ± 14.0 *I3* 27 ± 14.7 *I4* 26.6 ± 13.2 LC-MS/MS using an Aglient 1290 HPLC interfaced with an AB Sciex 5500 Q-Trap mass spectrometer	*Paper* *Primary outcomes:* • Length-for-age *z*-score at 1 year (364–420 days). *Secondary outcomes:* • Infant anthropometric variables • Preterm birth (<37 weeks' gestation) • Gestational hypertension • Delivery characteristics • Stillbirth • Mother and infant symptoms, clinical encounters, and hospitalizations • Deaths • Congenital anomalies	*No significant differences across groups:* Infants mean length-for-age *z*-scores Other anthropometric measures, birth outcomes, and morbidity did not differ significantly across groups. *Maternal 25OHD at or near delivery (nmol/L)* Mean ± SD: *C* 23.8 ± 13.9 *I1* 69.7 ± 19.5 *I2* 109 ± 23.6

	(range) 22 (18–38) *I4* *N* = 260 Median (range) 23 (18–38)	*Exclusion criteria:* • History of any medical condition or medications that may predispose to vitamin D sensitivity, altered vitamin D metabolism, and/or hypercalcemia (tuberculosis sarcoidosis, history of renal/ureteral stones, parathyroid disease, renal or liver failure, or current use of anticonvulsants) • High-risk pregnancy based on one or more of the following findings by point-of-care testing: • Severe anemia • Moderate-severe proteinuria • Hypertension • Multiple gestation • Major congenital anomaly • +Severe oligohydramnios • Unwillingness to stop taking nonstudy vitamin D or calcium supplements or a multivitamin containing calcium and/or vitamin D • Previous enrolment in the trial during a previous pregnancy *Ethnicity:* not described	*I4* Median (range) 20.1 (17–24)		• Infant neurologic disabilities • Infant rickets • Other secondary biochemical, anthropometric and clinical outcomes listed in the paper supplementary material) *Register/NCT01924013* *Primary outcomes:* • Infant length for age *z*-scores with prenatal supplementation • Infant length for age *z*-scores with postpartum supplementation *Secondary outcomes:* • Serum calcium In addition to outcomes listed under "*Other outcome measures*"	*I3* 110.7 ± 28 *I4* 113.6 ± 25.7 ($P < 0.001$)

[a]*Denotes the primary outcome on which the sample size was calculated in each trial, as reported in the paper.*
[b]*Outcome removed from the latest version of trial protocol in 2016.* P-*Values only reported when <0.1.*
*Primary and secondary outcomes as reported under "Methods" in the respective trial published papers and trial registers.*1,25OH_2D_3*: 1,25-dihydroxyvitamin D3;* 25OHD*: 25-hydroxyvitamin D;* BA*: bone area;* C*: control;* Ca*: calcium;* CLIA*: chemiluminescence immunoassay;* Crea*: creatinine;* I*: intervention;* iPTH*: intact parathyroid hormone;* NA*: Not available;* RIA*: direct radioimmunoassay;* RR*: relative risk;* SD*: standard deviation;* V*: version.*

that mothers with serum 25OHD reaching above 100 nmol/L had a 47% reduction in preterm birth; however, these results must be viewed with skepticism. The analyses suffer from being associational (thereby removing the protection against confounding achieved by randomization into groups), lack of adjustment for multiple comparisons, arbitrary grouping of outcomes, and arbitrary exclusion of some ethnicities from the analysis. Noteworthy, these were not prespecified analyses. Overall, therefore, it is unclear that these posthoc analyses provide meaningful data on the beneficial effect of vitamin D supplementation during pregnancy. A recent follow-up report on one of these trials revealed that there were no differences between groups in BMD or BMC of the spine and femoral neck at the gestational or postpartum measurements.[90]

We identified six recent systematic reviews that specifically assessed the effect of vitamin D supplementation during pregnancy.[91–96] The studies discussed in detail earlier in this chapter were sometimes included among these reviews. For example, data from the UK trial by Brooke et al., which had the largest achieved difference in 25OHD between placebo-treated and vitamin D-supplemented mothers, was included in four systematic reviews,[92,94–96] while data from the trial of Hollis et al. was included in three of them.[94,95] All the reviews assessed the effect of vitamin D supplementation on maternal and neonatal extraskeletal outcomes, but they differed in their methodology, inclusion/exclusion criteria, whether combined calcium and vitamin D data could be included, and whether the review was explicitly stated.

Among these six systematic reviews, vitamin D supplementation had no significant effect on preeclampsia in four,[92,94–96] and a positive effect in two reviews,[91,93] while combined vitamin D and calcium supplementation reduced the incidence of preeclampsia by 34%–53% in three systematic reviews.[91–93] No consistent effect was seen on other outcomes, such as preterm birth, low birth weight, SGA infants, infections, cesarean section rate, and newborn anthropometrics. Overall, available data are insufficient within these systematic reviews to conclude that vitamin D supplementation during pregnancy confers any proven obstetrical benefits.

In summary, the few large RCTs reported today do not provide evidence of a beneficial effect of high-dose vitamin D supplementation (1000–5000 IU/day), on maternal and neonatal outcomes. The most recent large trial seems to make it unlikely that vitamin D supplementation in deficient women would yield any beneficial effect on infant length.[86] The other studies were limited by low power, baseline maternal serum 25 OHD levels that were often not low, and lack of prespecification of obstetrical and neonatal outcomes. The potential protective effect of vitamin D on neonatal BMC in the MAVIDOS trial makes physiological sense because the intestines become the route of calcium delivery after birth, and this finding is consistent with the benefit observed in some RCTs of prenatal vitamin D supplementation reducing the incidence of neonatal hypocalcemia; these issues are discussed further in Chapter 44. Systematic reviews and meta-analyses of vitamin D RCTs suggest that combined calcium and vitamin D administration may reduce the risk of preeclampsia, but whether this is driven by the proven benefit of calcium alone is unknown. In contrast, there are suggestive but no consistent results among the meta-analyses as to whether vitamin D alone confers any obstetrical or neonatal benefits.

Any putative protective effects of vitamin D on maternal or neonatal outcomes are worthy of further study in adequately powered and designed trials, which also must enroll a significant number of women with low 25OHD. This is particularly relevant in view of their potential public health implications, especially in developing countries where some of the lowest maternal 25OHD levels are reported. However, ethical considerations (in particular, fear that vitamin D deficiency may be harmful to either mother or fetus) makes it difficult for such studies to be carried out.

With the genetic disorders of vitamin physiology, available data come from case reports and series. Pregnancies have been unremarkable in women with vitamin D-dependent rickets type 1 (VDDR-I) which is due to the absence of Cyp27b1, and in women with VDDR-II that is due to absence of functional VDRs.[97–99] In one published VDR-II case, pregnancy was unremarkable in a woman who maintained her prepregnancy intake of supplemental calcium (800 mg) and high-dose calcitriol.[98] The clinicians increased her calcitriol later in the pregnancy "because of the knowledge that the circulating 1,25-$(OH)_2$D concentration normally rises during pregnancy," but not because of any change in albumin-adjusted serum calcium.[98] Consequently, it is unclear that any change was needed. In pregnant women with VDDR-I, the dose of calcitriol was unchanged in one-third of pregnancies and increased 1.5-fold to twofold in others.[97]

Overall, and in summary, the previously discussed animal data (severe vitamin D deficiency and genetic loss of VDR or *Cyp27b1*) demonstrated that maternal mineral homeostasis and intestinal calcium absorption improve during pregnancy, resulting in normalization or near-normalization of mineral and bone metabolism. Such findings suggest that calcitriol is not required for the adaptations that are invoked during pregnancy or that unknown mechanisms compensate for its absence. Human data are less extensive or robust, but available clinical trials do not show a clear benefit of high-dose vitamin D supplementation on maternal mineral or skeletal homeostasis, or obstetrical and fetal outcomes. Many of the clinical trials did not enroll women who were truly vitamin D deficient and did not prespecify obstetrical and neonatal outcomes, and thus they had reduced power to be able to detect a benefit from vitamin D supplementation.

21.2.7.4 Clinical Management: Vitamin D Deficiency and Genetic Vitamin D Resistance

Pregnant women appear to require the same intake of vitamin D as nonpregnant women to maintain a certain 25OHD level. No data suggest that pregnant women need a higher 25OHD level than nonpregnant women.[24] Therefore, whatever intake maintains a sufficient level of 25OHD in an individual woman should be maintained during pregnancy.

The desirable 25OHD level in pregnant women is still a matter of debate. While the Institute of Medicine and the American College of Obstetricians and Gynecologists (ACOG) recommend a minimum of 50 nmol/L (20 ng/mL),[100,101] the Endocrine Society recommends ≥75 nmol/L (30 ng/mL).[102] The doses needed to reach such targets also vary, ranging from 600 to as much as 2000 IU/day.[100,102] The World Health Organization (WHO) does not recommend supplementation of pregnant women unless they are from poor countries, have a darker skin color, and come from populations with a high prevalence of hypovitaminosis D or inadequate exposure to sunshine.[103]

If a woman presents with vitamin D deficiency while pregnant, then supplementation should be prescribed immediately, with loading doses considered to replenish maternal vitamin D stores more rapidly. The preceding discussion of animal and human data revealed that vitamin D deficiency does not clearly have adverse effects on obstetrical outcomes, and so vitamin D insufficiency is even more unlikely to have adverse consequences.

The review of evidence is not intended to suggest that a woman should be left vitamin D deficient during pregnancy. Instead, these data should reassure the clinician that if a woman presents late in pregnancy with vitamin D deficiency, it is unlikely to be associated with adverse maternal or fetal outcomes unless there is global maternal (and, thereby, fetal) malnutrition. It is still prudent to correct and avoid a vitamin D-deficient state wherever possible.

In the genetic disorders, calcium and calcitriol or 1α-cholecalciferol should be adjusted as needed to maintain a normal level of ionized or albumin-corrected serum calcium. It is possible that the doses will remain the same or that they might need to increase, and this can be determined only on an individual basis.

21.2.7.5 Human Data: 24-Hydroxylase Deficiency

More recently, 24-hydroxylase deficiency has been identified as a cause of significant gestational hypercalcemia. Loss of the catabolic effects of 24-hydroxylase in nonpregnant adults leads to persistently high calcitriol and mild hypercalcemia that may be asymptomatic and go unnoticed.[104] But during pregnancy, the physiological increase in calcitriol is unopposed by catabolism and appears to lead to an exaggerated increase in calcitriol, with resulting symptomatic hypercalcemia. Presenting patients will have hypercalcemia (sometimes quite marked), suppressed or undetectable PTH, and calcitriol concentrations that exceed what is expected for pregnancy.[105–107] In addition to symptoms of hypercalcemia, complications have included nephrolithiasis and acute pancreatitis.[107,108]

21.2.7.6 Clinical Management: 24-Hydroxylase Deficiency

Treatment of the hypercalcemia is complicated by the pathophysiology of 24-hydroxylase deficiency and that all agents that could be used are not approved for pregnancy. The main mechanism for the hypercalcemia is likely through increased intestinal calcium absorption, and thus the use of increased hydration and a modestly restricted calcium diet, combined with phosphate supplementation to bind dietary calcium, is a relatively safe approach that addresses the mechanism of the hypercalcemia. If PTH rises above normal, that would suggest that the dietary calcium restriction is too severe and should be lessened to prevent maternal bone resorption and fetal secondary hyperparathyroidism. Other pharmacologic therapies should be reserved for the most severe cases and used with caution. Oral glucocorticoids (Category C or D) could conceivably be used to suppress intestinal calcium absorption, but at the lowest doses to minimize any adverse effects on maternal glucose, blood pressure, risk of avascular necrosis of the hip, and the fetus (prednisone is converted in the liver to prednisolone and crosses the placenta, where it gets converted back to prednisone). Additional options include the use of a loop diuretic to promote urinary calcium excretion and a bisphosphonate to reduce bone resorption. However, because the main action of calcitriol is on intestinal calcium absorption, a bisphosphonate would be of limited efficacy at best. Cinacalcet will not be useful because PTH will be suppressed due to the combined effects of pregnancy and hypercalcemia.

21.2.8 Calcitonin Deficiency

Calcitonin circulates at higher levels during pregnancy and has been theorized to protect the maternal skeleton from excessive resorption. *Ctcgrp*-null mice lack both calcitonin and calcitonin gene-related peptide-α, but they displayed no disturbance in calcium metabolism during pregnancy, nor was there any alteration in skeletal mineral content or structure by the end of pregnancy.[109,110] These studies indicate that calcitonin is not required during pregnancy in mice.

No women with genetic loss of calcitonin or its receptor have been identified or studied during pregnancy. The closest thing to subjects with an absence of calcitonin are totally thyroidectomized women, but it is not deficient during pregnancy due to the production of calcitonin by the breasts and placenta.[1] No studies have specifically examined whether thyroidectomized women have disturbances in calcium metabolism or BMD while pregnant. Several studies have examined whether total thyroidectomy increases BMD loss and fracture risk over the long term in both men and women, with just as many reporting adverse effects as those that reported no effects.[1]

Overall, the available evidence suggests that loss of calcitonin should have no adverse effects on maternal calcium and bone metabolism during pregnancy.

21.2.9 Low or High Calcium Intake

It is very clear from multiple animal studies that a calcium-restricted diet can lead to marked hypocalcemia and secondary hyperparathyroidism during pregnancy, with the potential for sudden hypocalcemic death near term.[1] Placental calcium transport must be impaired because a low-calcium diet also leads to secondary hyperparathyroidism and skeletal resorption in the fetus.[1] Conversely, high calcium intake prevents any resorption of the maternal skeleton by enabling all or most of the calcium transported to the fetus to come from the maternal diet.[1]

In women, pregnancy normally results in absorptive hypercalciuria with suppressed PTH, which implies that calcium intake and absorption exceed maternal requirements. But in women with low dietary calcium intake, or high intake of phytate that blocks calcium absorption, PTH does not fall and indeed actually may rise above normal, consistent with secondary hyperparathyroidism.[1] Intestinal calcium absorption may increase further in pregnant women with low calcium intake, as suggested by women who were estimated to be in a positive calcium balance during all three trimesters despite a total intake of <420 mg of calcium.[111] However, low calcium intake should be anticipated to provoke bone loss during pregnancy (especially the third trimester) and to increase the risk of osteoporosis.[1] If maternal hypocalcemia occurs, that reduces calcium delivery to the fetus, which may develop secondary hyperparathyroidism, skeletal demineralization, and fractures.[1] The lowest quintile of maternal calcium intake is also associated with increased risk of preeclampsia, whereas calcium supplementation reduces that risk.[1]

High calcium intake can have effects that are similar to primary hyperparathyroidism, including increased intestinal calcium absorption, maternal hypercalcemia, increased flow of calcium across the placenta to the fetus, and suppression of the fetal parathyroids. Cases of neonatal hypoparathyroidism have been reported in which women consumed 3–6 g of elemental calcium daily to treat nausea.[1]

Overall, it is clear that extremes of calcium intake should be avoided during pregnancy because both low and high calcium can have adverse effects on the mother and fetus.

21.2.10 Hypercalcemia of Malignancy

More than a dozen cases have been published of hypercalcemia of malignancy during pregnancy.[1] It is often (but not always) a terminal condition. Treatment options include surgery, hydration, diuresis, pharmacotherapy for the hypercalcemia (calcitonin, bisphosphonates, or denosumab), and chemotherapy. The potential teratogenic effects and other concerns about pharmacotherapy were discussed in Section 21.2.2. At the earliest opportunity, a decision needs to be made about whether to terminate or continue the pregnancy, as well as whether chemotherapy will be administered during pregnancy or deferred until the baby is born. In some cases, chemotherapy was given during pregnancy regardless of its potential teratogenic effects. The fetus can be expected to have hypercalcemia with suppression of the parathyroids and a high risk for neonatal hypocalcemia. In over half the reported cases, the fate of the baby wasn't mentioned.[1]

21.2.11 Fibroblast Growth Factor 23 (FGF23)-Related Disorders

The most common disorder of fibroblast growth factor 23 (FGF23) is X-linked hypophosphatemic rickets, in which inactivating mutations in the *PHEX* gene lead to high circulating levels of FGF23, hypophosphatemia, and rickets or osteomalacia. In a mouse model of XLH, pregnancies were uneventful. In particular, despite very high circulating levels of FGF23, which normally downregulate calcitriol synthesis and increase its catabolism, maternal serum calcitriol increased to the high levels normally seen during pregnancy.[112,113] In turn, this rise in calcitriol should improve intestinal calcium and phosphorus absorption.

Several case reports of women with XLH reported persistent hypophosphatemia during pregnancy, without obvious adverse outcomes.[114,115] It is advisable to maintain calcitriol and phosphorus supplementation as need to keep the serum phosphorus close to normal throughout pregnancy.

Hyperphosphatemic disorders due to loss of FGF23 action have not been studied during pregnancy. In the animal models, the conditions are lethal prior to reproductive maturity. There have been no case reports of pregnancies in women with hyperphosphatemic disorders caused by deficiency of FGF23 or its coreceptor. Animal and human data from renal insufficiency or failure, which cause hyperphosphatemia, indicate increased obstetrical risks of gestational hypertension, preeclampsia, eclampsia, and maternal mortality. However, the extent to which the hyperphosphatemia contributes to these risks, beyond that of the renal failure, is unknown.

21.2.12 Tocolytic Therapy with Magnesium Sulfate

Magnesium sulfate infusions are typically used for 24–72 h to treat preterm labor, preeclampsia, and eclampsia. Magnesium is a natural ligand for the calcium-sensing receptor; therefore, prolonged tocolytic therapy can suppress PTH and cause hypocalcemia.[116–118] PTH drops within the first hour, and the total and ionized serum calcium levels remain suppressed several hours later.[117,118] These findings are in keeping with hypoparathyroidism induced by the magnesium acting on the calcium receptor. Most cases are asymptomatic, but symptomatic hypocalcemia has been reported with positive Chvostek and Trousseau signs, and even tetany.[119]

If the magnesium infusion is maintained for several weeks, PTH can rise above normal. This is probably secondary hyperparathyroidism in response to the hypocalcemia, which increases the loss of calcium in the urine.[120] In a series of 20 women treated for weeks with magnesium for premature labor, serum magnesium and phosphorus increased, serum calcium decreased, serum PTH increased, and urinary excretion of magnesium and calcium increased twofold-to-threefold.[120] This will contribute to loss of BMC and strength, and it explains why prolonged magnesium infusions have been associated with postpartum loss of BMD and calcaneal stress fractures.[120–122] There are also potential effects on the fetus and neonate, which are discussed in Chapter 44.

21.2.12.1 Clinical Management

Maternal serum and cord blood magnesium are usually not monitored during tocolytic therapy. However, this should be done if the infusion is given for 2 or more days because hypermagnesemia can cause hypotonia, respiratory depression, and bone abnormalities.[116,123–125] Fetal movements should also be assessed by ultrasound to detect evidence of hypotonia.

21.3 DISORDERS OF BONE AND MINERAL METABOLISM DURING LACTATION

21.3.1 Osteoporosis of Lactation

Osteoporotic fractures occur rarely in breastfeeding women, but more often than during pregnancy.[4] These are most often vertebral compression fractures, with many reports describing extreme cases of women who experienced 6–10 crush fractures within a short interval.

As noted in Section 21.2.1, skeletal fragility may precede pregnancy and multiple factors can contribute to bone loss during pregnancy and lactation (Table 21.1). All these causes need to be considered in a woman who presents with fragility fractures while breastfeeding. Lactation introduces an added physiological cause of bone resorption that is stimulated by PTHrP (produced by the breasts) and systemic low estradiol concentrations.

As described in Chapter 5, lumbar spine BMD normally declines 5%–10% during lactation and can reach values well below normal for healthy women, including z-scores of −3 or lower. In addition, it is conceivable that in some women, release of PTHrP by the breasts may be more excessive than normal, or there may be increased sensitivity to high PTHrP or low estradiol, each of which could contribute to enhanced bone loss. The idea that excess PTHrP-mediated bone resorption can cause fragility fractures has been suggested by several published cases in which women presented with hypercalcemia, increased plasma PTHrP, and vertebral compression fractures.[1] After weaning, serum calcium and plasma PTHrP normalized.

21.3.1.1 Clinical Management

Diagnostic and management strategies are summarized in Tables 21.2–21.4.

If a woman is known to have skeletal fragility or very low bone mass, it may be reasonable to advise against breastfeeding or limit its duration because the progressive physiological bone loss that occurs over the first 6 months of lactation

may lead to structural compromise of that woman's skeleton.[4] This must be balanced against other benefits of breastfeeding, including bonding and immune function. Furthermore, whenever fractures occur during lactation, it may also be reasonable to advise that breastfeeding stop in order to prevent further bone loss and initiate postweaning skeletal recovery.

Case series have shown that bone density spontaneously increases by 20%–70% in women who fractured while breastfeeding.[43] Therefore, as with pregnancy-associated fractures (as discussed previously), it may be prudent to withhold pharmacological therapy for 12–18 months to allow spontaneous recovery to occur, and then assess the need for additional treatment.[4] It is also a concern that antiremodeling agents such as a bisphosphonate or denosumab might blunt the spontaneous bone recovery that is expected during the postweaning interval.

Furthermore, all of the issues discussed earlier about pharmacotherapy (safety of individual agents, end-point to treatment) apply to breastfeeding women. Although individual case reports have described marked increases in bone mass associated with a variety of osteoporosis therapies, in each of these cases, the observed increase in bone mass was within the expected range that occurs with spontaneous postweaning recovery. Consequently, it is unclear that the use of pharmacotherapy in these studies achieved an added benefit. It is also unresolved as to whether an agent with a 2-year lifetime restriction on duration of use (i.e., teriparatide) should be used at a reproductive age when fracture risk should be inherently lower than it will be at older and postmenopausal ages, when pharmacotherapy might be more acutely needed.

21.3.2 Primary Hyperparathyroidism

If primary hyperparathyroidism was monitored rather than surgically treated during pregnancy, the postpartum period may remain uneventful. However, severe hypercalcemia from a parathyroid crisis can occur during the puerperium. This results from a combination of factors: Calcium is no longer being lost across the placenta, physiological bone resorption will occur from physical inactivity and bed rest, the onset of milk production will induce marked bone resorption (stimulated by low estradiol and increased PTHrP), and the systemic low estradiol levels of lactation will enhance skeletal responsiveness to the high circulating concentration of PTH. Consequently, significant worsening of hypercalcemia can occur in women with primary hyperparathyroidism who choose to breastfeed. However, a parathyroid crisis is not inevitable. In one published case, breastfeeding lessened hypercalcemia,[126] likely because production of breast milk also represents a new route for excess calcium to be drained from the circulation, thereby reducing the risk of severe hypercalcemia.

21.3.2.1 Clinical Management

Primary hyperparathyroidism can worsen significantly during the postpartum interval, with potential for more marked hypercalcemia in women who breastfeed. The clinician should reevaluate whether parathyroidectomy or medical therapy with cinacalcet is warranted at this time. Because the physiological hypercalciuria of pregnancy will have obscured the diagnosis of FHH, the possibility of this diagnosis should be reconsidered during the postpartum period. However, the physiological hypocalciuria of lactation will continue to make the calcium/creatinine clearance in urine to be invalid for diagnostic purposes. According to consensus guidelines for management of asymptomatic primary hyperparathyroidism, age <50 is an indication for surgery.[44] Therefore, postpartum women with primary hyperparathyroidism should be candidates for parathyroidectomy.

21.3.3 Familial Hypocalciuric Hypercalcemia

The calcium receptor not only controls the release of PTH by the parathyroids, but also the production of PTHrP by mammary tissue and the calcium content of milk.[1] When the *Casr* gene is ablated globally in mice, or selectively in mammary tissue, the consequences include reduced milk calcium content, increased mammary expression of PTHrP, greater bone loss during lactation, and urinary calcium excretion that exceeds that in normal controls.[127] Conversely, treatment with a calcimimetic drug such as cinacalcet results in increased milk calcium content and reduced mammary PTHrP production.[128,129]

These animal data predict that women with FHH will produce milk with reduced calcium content, accompanied by increased PTHrP, greater lactational bone loss, and increased renal calcium excretion. However, no such studies in lactating women with FHH have been done.

21.3.3.1 Clinical Management

FHH requires no management, apart from making certain that the affected women are not mistaken for having primary hyperparathyroidism and vice versa. During pregnancy, there is physiological hypercalciuria that can obscure the diagnosis of FHH, while during lactation, the resulting physiological hypocalciuria can obscure the diagnosis of primary hyperparathyroidism.[43] These considerations may require biochemical and genetic testing of relatives to determine if a mutation in *CASR* or other relevant genes are present, or waiting until the postweaning interval to determine if the biochemical picture is more in keeping with FHH vs primary hyperparathyroidism.

21.3.4 Hypoparathyroidism

For decades, hypoparathyroidism has been appreciated to improve during lactation, such that supplemental calcium and vitamin D analogs often are no longer required.[1] Some women with autoimmune hypoparathyroidism have been diagnosed when hypocalcemia abruptly occurs after weaning. The time of onset is consistent with a postpartum onset (typical of autoimmune endocrinopathies), but with a delay in clinical manifestation because of the effects that normal lactation has on bone and mineral metabolism. These observations led to the astute deduction that lactating breasts must produce a PTH-like hormone, which later proved to be PTHrP.

Animal studies have confirmed the physiological role that PTHrP plays in altering mineral and bone homeostasis during lactation, and that lactation can reverse the abnormalities created by absence of PTH.[1] In women, PTHrP has been confirmed to be expressed at high levels in lactating mammary tissue and milk, as well as being detectable in the circulation. PTHrP reaches the maternal circulation from the breasts, stimulates bone turnover, enhances renal tubular calcium reabsorption, and stimulates production of calcitriol.[60,130,131] Calcitriol increases in hypoparathyroid women from low levels, but it does not increase above normal, likely because PTHrP is less potent than PTH at stimulating the enzyme Cyp27b1 to produce calcitriol. The high prolactin and low estradiol of lactation may also alter the activity of Cyp27b1.[1]

Occasionally during the first 2 days postpartum, hypoparathyroid women have experienced transient hypocalcemia, presumably from the sudden loss of placental PTHrP.[55] This will resolve as lactation forces increased production of PTHrP by the breasts. In most cases, there has been no worsening in the early postpartum period. Instead, there has been a progressive lowering of the requirement for supplemental calcium and calcitriol as milk production upregulates. If this physiological response to lactation is not anticipated or recognized, the consequences have included severe hypercalcemia and even vertebral compression fractures.[28,60,131–135] In some women, all supplements need to be stopped, whereas in others, reduced doses are still required.

The rise and subsequent decline in plasma PTHrP has been shown to correspond to the rise and decline in serum calcium, calcitriol, and bone turnover markers in hypoparathyroid women.[28,60,130] In these cases, the improvement in mineral homeostasis correlates with the increasing intensity of lactation, while the subsequent decline correlates with reduced breastfeeding, and especially weaning. The less intensive or exclusive the breastfeeding, the more likely it is that hypoparathyroid women require some supplemental calcium and calcitriol to be maintained.

The rapidity with which the influence of PTHrP declines will vary, with some women requiring supplemental calcium and calcitriol to be restored before weaning, while others have not required this for weeks or months after weaning. In the latter cases, it is inferred that PTHrP production by the breasts has continued autonomously for months after weaning, which has been demonstrated in some women.[136] In one case described in the essay by Krista Rideout that introduces this textbook, a hypoparathyroid woman previously dependent on supplemental calcium and calcitriol has not required either for more than 6 years after weaning her child.

21.3.4.1 Clinical Management

The clinician should anticipate that lactation will cause normalization or near-normalization of mineral and skeletal homeostasis in hypoparathyroid women. Calcium monitoring should be done once or twice within 1 week after delivery in women who breastfeed, and every 2–4 weeks thereafter. The doses of supplemental calcium and calcitriol will need to be decreased as lactation becomes fully established, guided by measurements of the albumin-adjusted calcium or ionized calcium over the first several postpartum weeks. This should be followed by an interval of stability. But as lactation lessens, and especially after weaning, the need for supplemental calcium and calcitriol will gradually (or even abruptly) revert to prepregnancy levels.

21.3.5 Pseudohypoparathyroidism

The effect of breastfeeding on women with pseudohypoparathyroidism has not been described, and no animal model has been studied during lactation. Lactation can be anticipated to lead to an overall improvement in bone and mineral homeostasis due to the release of PTHrP from the breasts, akin to the clinical course of hypoparathyroidism. There is renal but not skeletal resistance to PTH in pseudohypoparathyroidism, and so it is possible that skeletal resorption may even be greater than normal during lactation, as the high levels of PTH and PTHrP combine to affect bone turnover.

21.3.5.1 Clinical Management

In the absence of any data to indicate otherwise, clinicians should consider that pseudohypoparathyroidism may improve during lactation (as does hypoparathyroidism), resulting in the need for decreased doses of calcium and calcitriol during lactation. If this occurs, it will be followed by a return of the need for the prior doses during or after weaning.

21.3.6 Pseudohyperparathyroidism

As noted earlier in Chapter 5, the physiological release of PTHrP from the breasts will contribute to a small increase in serum calcium and phosphorus, suppression of PTH, increased bone resorption, and reduced renal calcium excretion. This is a silent aspect of lactational physiology that most women are unaware of unless they have hypoparathyroidism and find that they no longer need supplemental calcium and calcitriol while breastfeeding.

However, the effects of breast-derived PTHrP occasionally cause symptomatic hypercalcemia in otherwise-normal breastfeeding women. Such PTHrP-mediated hypercalcemia is called *pseudohyperparathyroidism* because it mimics primary hyperparathyroidism but is not due to PTH. It can develop during normal lactation, in women who deliver but are unable to breastfeed, and in nonlactating women with unduly large breasts.[1] The main pathophysiology is that high levels of PTHrP induce skeletal resorption accompanied by increased renal reabsorption of calcium. If PTHrP also causes increased calcitriol, then intestinal calcium absorption may be increased. Vertebral compression fractures have occurred in some women.

The published cases have emphasized extremes in which women developed symptomatic hypercalcemia while breastfeeding. Some cases may not be recognized because the symptoms of hypercalcemia are nonspecific and not readily distinguishable from the constitutional symptoms that any woman may experience when she is feeding a baby on demand. Furthermore, considering that serum calcium and ionized calcium rise modestly during normal lactation,[1] it is possible that asymptomatic hypercalcemia is more common during lactation than the case reports would suggest.

21.3.6.1 Clinical Management

If severe hypercalcemia occurs, the condition can be reversed rapidly by weaning the baby, combined with judicious use of breast binders and dopaminergic medications (cabergoline or bromocriptine) to suppress prolactin and shut off the production of PTHrP. This is likely a safer approach than using other drugs in the presence of continued breastfeeding. Indeed, there is limited evidence that bisphosphonates likely do not enter breast milk, but this has not been determined for denosumab.

Excess production of PTHrP has occasionally persisted long after weaning and has rarely required reduction mammoplasty or bilateral mastectomy to correct the disorder.[137]

21.3.7 Vitamin D Deficiency, Genetic Vitamin D Resistance, and 24-Hydroxylase Deficiency

21.3.7.1 Vitamin D Deficiency and Genetic Vitamin D Resistance

The effect of disrupted vitamin D physiology on lactation has been studied in *Vdr*-null and *Cyp27b1*-null mice, and vitamin D-deficient mice and rats.[1] The findings have been generally consistent among the various models, including that the calcium content of milk is normal, mineral metabolism improves to normalize the serum calcium, intestinal calcium absorption increases, lactational bone loss occurs that may be equal to or greater than normal, and during postweaning, there is increased bone formation with complete or near-complete recovery of skeletal microarchitecture and bone mass.[1] Occasional deaths occur during lactation, which are presumed to result from hypocalcemia, precipitated by milk production overwhelming the mother's ability to maintain her blood calcium. The overall findings suggest that calcitriol is not required for lactation to proceed normally or for the skeleton to restore itself after weaning.

Clinical data come from observational cohort studies and randomized interventional trials of vitamin D supplementation.[1] These have not shown any effect of higher 25OHD concentrations or vitamin D intake on maternal mineral or skeletal homeostasis in otherwise-healthy, lactating women. Vitamin D supplementation increases maternal 25OHD levels with similar efficacy as in nonpregnant or nonlactating women.

No studies have directly compared severely vitamin D-deficient and -sufficient women. However, the data discussed next support the proposition that vitamin D deficiency, VDDR-I, and VDDR-II are unlikely to affect lactation or milk production adversely.

Milk normally contains little vitamin D or 25OHD (approximately 30–40 IU/L combined), with very low to undetectable amounts of calcitriol. Consequently, milk production does not drain maternal vitamin D stores, and maternal 25OHD remains unchanged during lactation unless there are changes in dietary intake of vitamin D or exposure to sunlight. Randomized interventional studies have found that maternal vitamin D doses of 400–1000 IU/day do not consistently increase the breast milk content of vitamin D or 25OHD, whereas with doses of 2000 IU/day or higher, the milk content of vitamin D and 25OHD demonstrably improve and lead to an increase in neonatal 25OHD.[138–145]

The calcium content of breast milk calcium is unaffected by maternal 25OHD concentrations ranging from low [25 nmol/L (10 ng/mL)] to high [160 nmol/L (64 ng/mL)].[145,146] These data come from cohort studies[146] and randomized interventions that administered up to 6400 IU/day of vitamin D.[138,143,145] However, there have been a few cases from India in which milk calcium content was low in mothers with severe vitamin D deficiency [mean 25OHD of 6 nmol/L (2.5 ng/mL)]; they also had severe hypocalcemia, hypophosphatemia, and markedly elevated PTH.[147] Overall, these results indicate that calcitriol does not play a substantial role in stimulating calcium to enter milk. But in very severe vitamin D-deficient women, it may be the marked hypocalcemia, rather than a direct effect of loss of calcitriol, that leads to reduced milk calcium content.

In regions where severe vitamin D-deficiency rickets is endemic, such as India, affected neonates have been treated with breast milk as their only form of nutrition, while their mothers were receiving the equivalent of 1800 IU of vitamin D per day.[147,148] Mothers and babies were protected from sun exposure and had negligible amounts of vitamin D in the diet, and so the maternal supplement was the principal source of vitamin D for both. The mean 25OHD rose from 6 nmol/L (2 ng/mL) or below in mothers and babies to approximately 50 nmol/L (20 ng/mL) in the mothers and 40 nmol/L (16 ng/mL) in their babies. This finding indicates that more vitamin D enters breast milk than has been appreciated by the previously cited studies. Moreover, the normal calcium content of breast milk is very relevant because providing sufficient calcium alone will heal rickets due to vitamin D deficiency or VDDR-II.[72]

No clinical studies have explicitly examined whether vitamin D deficiency, VDDR-I, or VDDR-II affects the ability of the skeleton to acutely recover bone mass and architecture after weaning. As discussed in Chapter 5, dozens of large epidemiological studies have found neutral or protective associations of lactation on BMD and fracture risk in the long term, with many of the women in those studies being vitamin D insufficient or deficient by modern criteria.[1] Despite the limitations of associational studies, these consistent findings suggest that skeletal recovery after weaning is not impaired by vitamin D insufficiency either.

21.3.7.2 24-Hydroxylase Deficiency

As noted earlier, hereditary absence of Cyp24a1 reduces calcitriol catabolism and can lead to marked maternal hypercalcemia during pregnancy, accompanied by very high calcitriol concentrations. But calcitriol production falls to nonpregnant levels during normal lactation, and the same should be true in women with 24-hydroxylase deficiency. Consistent with this, in one affected woman who breastfed, hypercalcemia was milder compared to pregnancy and serum calcitriol was normal.[105]

21.3.7.3 Clinical Management: Vitamin D Deficiency and Genetic Vitamin D Resistance

Animal data consistently indicate that milk calcium content, skeletal resorption during lactation, and postweaning skeletal recovery may be unaffected by extremes of vitamin D physiology, including absence of VDR, calcitriol, and vitamin D. The more limited clinical data are similar, indicating that maternal vitamin D stores are not adversely affected by lactation, milk calcium content is unaffected by vitamin D deficiency (unless significant hypocalcemia is present), and lactational bone loss and recovery also may be unaffected by the absence of calcitriol's actions. There is no evidence that the requirement for vitamin D increases during lactation to meet maternal or neonatal needs.

Nevertheless, it remains prudent to correct vitamin D deficiency promptly whenever it is recognized. The available data suggest that the amount of vitamin D intake required to replenish total body stores and maintain a set level of 25OHD should be unaffected by lactation. Similarly, management of VDDR-I and VDDR-II should be unaffected by lactation.

Because milk normally contains low amounts of vitamin D or 25OHD, high-dose vitamin D supplementation has the possible benefit of enabling all of a baby's nutrition to come from breast milk rather than requiring that oral vitamin D supplements be given to breastfed babies. However, the high doses used in the studies cited previously are not needed if the goal is a 25OHD level of 50 nmol/L, as the Institute of Medicine and pediatric societies have suggested.[24]

21.3.7.4 Clinical Management: 24-Hydroxylase Deficiency

Lactation could conceivably worsen hypercalcemia in women with 24-hydroxylase deficiency by introducing the physiological bone resorption stimulated by PTHrP and low estradiol. However, because calcitriol production is normal during lactation, hypercalcemia is much less likely to occur than during pregnancy, and breastfeeding can be encouraged.

21.3.8 Calcitonin Deficiency

Calcitonin has been theorized to protect the maternal skeleton against excessive resorption during lactation. Earlier studies in thyroidectomized rats and goats yielded inconsistent results, likely because it is now recognized that lactating mammary tissue produces substantial calcitonin. Consequently, a thyroidectomized animal is not calcitonin deficient while lactating.[1] More recent studies examined *Ctcgrp*-null mice, which lack calcitonin and calcitonin gene-related peptide-α but retain calcitonin gene-related peptide-B.[149] This global calcitonin deficiency resulted in lactating mice losing twice the bone mass as their normal sisters during lactation—an effect that was prevented by treating with calcitonin injections at the onset of lactation.[110] The lactating calcitonin-ablated mice have increased expression of PTHrP, a doubling of milk calcium content, doubling of osteoclast numbers and surface, and half the osteoblast numbers and surface compared to normal sister mice.[109,110,150] Remarkably, the skeleton recovers from these marked deficits within 18 days of weaning, accompanied by a substantial fall in osteoclast numbers and a surge in osteoblast numbers and activity.[110,150] Overall, the *Ctcgrp*-null model confirms that calcitonin protects the rodent skeleton from excessive resorption during lactation, but whether the same is true for women has not been determined.

No clinical studies have specifically tested whether calcitonin deficiency causes increased bone loss during lactation. This is mainly because inactivating mutations of calcitonin or its receptor have not been identified in humans. A thyroidectomized woman nursing twins experienced multiple vertebral compression fractures and had marked bone loss confirmed by DXA; the authors speculated that calcitonin deficiency was to blame.[28] But thyroidectomized women are not expected to be calcitonin deficient while breastfeeding because lactating breast tissue produces normal circulating calcitonin levels.[1]

21.3.8.1 Clinical Management

There are no human data on clinical management, and so firm recommendations cannot be offered. However, the available animal data suggest that lactation leads to excessive skeletal losses, and so it may be prudent to recommend against breastfeeding in lactating women. Treatment with calcitonin conceivably could prevent excessive bone loss and allow lactation to continue, but there are no reports to validate this speculation.

21.3.9 Low or High Calcium Intake

Lactating rodents have a proportionately very high demand for calcium, given their large litter sizes (8–12 pups) and short duration of lactation (3 weeks). They rely on the combined effects of increased intestinal calcium absorption, skeletal resorption, and renal tubal calcium reabsorption. The rodent is capable to some extent of extracting more calcium from the skeleton when the diet is deficient, or more from the diet when the skeleton cannot be resorbed. Consequently, a calcium-restricted diet increases skeletal losses but also can lead to hypocalcemia and sudden death from tetany; conversely, a high-calcium diet reduces skeletal losses.[1] During postweaning, a low calcium intake impairs skeletal recovery in rats, but full recovery in the same rats was achieved when a normal-calcium diet was administered later.[151]

In contrast to the animal data, the calcium content of human milk appears to be largely derived from skeletal resorption. Consequently, low calcium intake does not reduce breast-milk calcium, nor does it cause increased skeletal resorption.[146,152–156] Conversely, high calcium intake neither increases breast-milk calcium nor reduces the amount of skeletal resorption that occurs during lactation.[153–161] These data come from well-designed randomized clinical trials and cohort studies and indicate that maternal calcium intake may be irrelevant during lactation because skeletal resorption is hormonally programmed to supply the needed amount of calcium. There is no evidence that women require a higher intake of calcium while breastfeeding.

No clinical studies have examined calcium intake during postweaning, which may be a more critical time to ensure adequate calcium intake. However, adolescents recovering from lactation experienced a substantial increment in bone mass despite a habitual intake of <500 mg/day of calcium.[162] Randomization to a 1-g calcium supplement daily resulted in a small gain in bone mass gain during 6 months of recovery.[159]

21.3.9.1 Clinical Management

The available data indicate that women do not require increased calcium intake during lactation or postweaning recovery. Instead, for all women, the recommended calcium intake remains the same as that of nonpregnant women, which is 1200 mg/day of calcium.[24]

21.3.10 FGF23-Related Disorders

Phex$^{+/-}$ females are the murine equivalent of XLH. The affected mice remain hypophosphatemic during lactation; produce milk with normal phosphorus, calcium, and protein content; and have pups that grow normally.[163] Hyperphosphatemic disorders due to loss of FGF23 of its coreceptor Klotho have not been studied during lactation because the mice die before reaching reproductive maturity.

In one case report, serum phosphorus normalized during lactation in a woman with XLH, whereas it was low during pregnancy and equivalent to expected nonpregnant values.[114] Serum phosphorus likely normalizes because of the increased skeletal resorption during lactation, which brings calcium and phosphorus into the circulation. However, despite normalization of serum phosphorus in the mother during lactation, the phosphorus content of expressed milk was reduced to 50% of normal in two cases, whereas the calcium content was modestly reduced in one but normal in the other.[114,115] It is unclear why milk from women with XLH had low phosphorus, while the content was normal in the animal model. Oral phosphorus supplementation normalized the milk composition.[114] In both cases, the babies inherited XLH, so the development of hypophosphatemia and rickets was likely due to the combined effects of the mutation and the low phosphorus content of milk.[114,115]

No studies have examined lactation in hyperphosphatemic disorders from the loss of FGF23 or its coreceptor, but it is conceivable that phosphorus content of milk will be increased.

21.3.10.1 Clinical Management

Women with XLH may require phosphorus supplementation to maintain normal phosphorus content in milk. If the calcium content is also reduced, this cannot be fixed by oral calcium supplementation. If a baby born of a woman with XLH develops hypophosphatemia, this could indicate that milk is deficient in phosphorus or that the baby inherited the mutation.

21.4 CONCLUSIONS

Doubling of intestinal calcium and phosphorus absorption during pregnancy meets the fetal demand for these minerals, while an increase in skeletal resorption provides the required mineral content of milk during lactation. These adaptations during pregnancy and lactation have important effects on preexisting disorders of bone and mineral metabolism. The symptoms, signs, diagnostic indexes, and treatment strategies may be altered. This is best exemplified by how lactation can normalize mineral homeostasis in hypoparathyroid women, but when this is overlooked, it has led to iatrogenic and life-threatening hypercalcemia.

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