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Review article

Disorders of bone and mineral metabolism in pregnancy and lactation: A case based clinical review

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ABSTRACT

Bone and mineral metabolism in the human body undergoes significant adaptations during pregnancy and lactation to meet the physiological demands of both the mother and fetus. The growing fetus requires approximately 30 g of calcium, with 80% of this transferred from the mother during the third trimester. These adaptations involve complex hormonal changes, such as increased parathyroid hormone-related peptide (PTHrP) and 1,25-dihydroxyvitamin D, ensuring the mother maintains calcium balance despite fetal demands. However, these changes can also exacerbate pre-existing metabolic bone disorders, presenting unique challenges during pregnancy. This narrative review, framed around illustrative case examples, focuses on the management of metabolic bone disorders in pregnancy. Relevant case studies of hypercalcemia, hypocalcemia, hypophosphatemia, and osteoporosis and chronic kidney disease mineral bone disorder are reviewed to illustrate the biochemical changes, clinical implications, and therapeutic strategies available during pregnancy and lactation. We analyze literature from case reports and existing guidelines to provide practical clinical recommendations. The review highlights critical pregnancy-related metabolic adaptations, such as increased intestinal calcium absorption and skeletal resorption. Disorders like primary hyperparathyroidism (PHPT) and familial hypocalciuric hypercalcemia present significant maternal and fetal risks, including miscarriage, growth restriction, and neonatal complications. Early identification and tailored treatment, including hydration, parathyroidectomy, and vitamin D supplementation, mitigate these risks, with surgical interventions in PHPT improving pregnancy outcomes compared to conservative management. Management of metabolic bone disorders during pregnancy and lactation requires a nuanced approach to meet the dual needs of the mother and fetus.

1. Introduction

Bone mineral homeostasis that is maintained in the non-pregnant state via the intricate relationship between the various components of the calcium-parathyroid hormone-vitamin D axis, undergoes significant changes to adapt to the physiological needs of pregnancy. The adaptations that occur may also impact on preexisting disorders of bone and mineral metabolism that the woman may have.

During pregnancy, the growing fetus depends on maternal calcium and minerals for skeletal development. Throughout the course of pregnancy, the fetus accretes approximately 30 g calcium, 20 g phosphorus and 0.8 g magnesium [1]. Eighty percent of this accretion occurs during the third trimester [1]. This requirement is met through placental transfer from the mother. Several mechanisms allow maternal adaptation to meet this demand. Many hormones including parathyroid hormone-related peptide (PTHrP), estradiol, prolactin, and placental lactogen rise during pregnancy. Increased 1α-hydroxylation of 25(OH)D in the kidneys, results in an elevation of 1,25(OH)D levels. The rise in maternal 1,25(OH)D levels subsequently stimulates increased intestinal absorption of calcium reaching almost 400 mg/day by the third trimester. This is two-fold that of a non-pregnant woman. Secondly, there is also an increase in maternal skeletal resorption during pregnancy. These adaptations allow maternal calcium levels to remain stable despite the increased fetal demands. Though total serum calcium level decreases, due to a fall in serum albumin secondary to hemodilution, the physiologically important fraction, namely ionised calcium, remains stable.

Serum phosphate and magnesium concentrations remain normal

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throughout pregnancy. Serum parathyroid hormone (PTH) concentrations are low particularly in the first trimester, and subsequently increase to the mid-normal range by term. On the other hand, PTHrP, which is produced by breast and placental tissue, rises during pregnancy and lactation. Serum 1,25(OH)D concentrations rise 2 to 5-fold in early pregnancy and remain elevated till delivery. Urinary calcium levels increase secondary to absorptive hypercalciuria, and the 24-h urinary calcium creatinine ratio (UCCR) often exceeds the normal range. This has implications on the use of fractional excretion of calcium for the diagnosis of certain conditions such as familial hypocalciuric hypercalcemia (FHH) in pregnancy. Table 1 summarises the physiologic changes in calcium and mineral metabolism that occur during pregnancy and lactation.

Fetal calcium homeostasis relies heavily on maternal calcium supply. Fetal parathyroid development begins at the 6th week of gestation, but fetal PTH concentrations remain low. Instead, maternal PTHrP drives an active influx of maternal calcium via the placenta. Fetal calcium concentrations rise throughout pregnancy, reaching a peak of 2.5–2.75 mmol/L in the third trimester. Post-delivery, neonatal calcium levels fall, reaching a physiologic nadir at day two. This is accompanied by a rise in neonatal PTH, which then maintains calcium homeostasis in the newborn.

The management of mineral and bone metabolic problems in pregnancy poses a challenge to physicians. In this review, we aim to provide guidance on the management of these disorders in pregnancy. The cases presented in this review are not derived from actual patient records but are constructed based on the authors' clinical experience managing similar presentations. They are designed to illustrate key diagnostic and therapeutic considerations in a manner that aligns with real-world clinical practice.

2. Hypercalcemia in pregnancy

2.1. Case example

A 36-year-old lady (G3P1) was referred for hypercalcemia (serum calcium 3.01 mmol/L, reference 2.06–2.46 mmol/L) at 14 weeks' gestation. An ultrasound performed as part of a health screening package three years ago had shown medullary nephrocalcinosis. Work-up then had revealed a PTH-dependent hypercalcemia with serum adjusted for albumin calcium 2.61 mmol/L (Normal Reference (NR):2.15–2.58 mmol/L) and intact PTH (iPTH) 9.9 pmol/L (NR: 0.8–6.8 pmol/L). Urine calcium creatinine clearance ratio was 0.0203. A diagnosis of PHPT had been made. A parathyroid sestamibi scan done at that time had reported subtle delayed tracer washout over the inferior poles of the bilateral thyroid beds and a concurrent ultrasound had reported hypoechoic extrathyroidal lesions posterior to the inferior poles of both thyroid lobes. She however had declined surgery at that point as she was asymptomatic and calcium levels were stable.

At current consultation, she reported constipation but was otherwise asymptomatic. She revealed that she had suffered a miscarriage 2 years ago when she was 10 weeks pregnant. There was no family history of calcium disorders or any endocrinopathy. Physical examination was unremarkable. Serum ionised calcium was 1.62 mmol/L (NR: 1.18–1.37 mmol/L) and iPTH 8.6 pmol/L (NR: 0.9–6.2 pmol/L). A repeat neck ultrasound was not able to visualize the bilateral inferior parathyroid adenomas reported on the earlier scan. Genetic testing was recommended, but the patient declined.

Table 1
Physiologic maternal changes in calcium and mineral metabolism in pregnancy and lactation.

	Pregnancy	Lactation
Total serum calcium	↓	↔
Ionised calcium	↔	↔
Parathyroid hormone (PTH)	First trimester: ↓ Third trimester: ↔	↓
Parathyroid hormone-related peptide (PTHrP)	↑	↑
1,25(OH)D	↑	↔
Serum Phosphate	↔	↔
Serum Magnesium	↔	↔

↑: increase; ↔: remain the same; ↓: decrease.

2.2. Clinical questions

1. What are the maternal and fetal consequences of hypercalcemia during pregnancy?
2. How should hypercalcemia in pregnancy be evaluated?
3. What are the management options for primary hyperparathyroidism in pregnancy, including pharmacological options, and what do we know about the safety and optimum timing of parathyroidectomy in pregnancy?

2.3. Discussion

2.3.1. Primary hyperparathyroidism

The maternal adaptations in calcium metabolism, such as increased intestinal calcium absorption and increased skeletal resorption, may lead to worsening hypercalcemia in pregnancy. Factors such as physical inactivity and bedrest in late pregnancy also contribute to increased skeletal resorption, further aggravating hypercalcemia.

A large primary hyperparathyroidism (PHPT) database reported by Pal et al. [2] described that out of 386 women with PHPT, 8 had gestational PHPT (2.1%). Other smaller available series describe an incidence of $< 1\%$ [3,4]. However, the true incidence of hypercalcemia in pregnancy is likely to be underestimated, for several reasons. Firstly, calcium levels are not measured in routine or even complicated pregnancies. Moreover, hypercalcemia may be missed if only total serum calcium levels are checked, due to the fall in serum albumin concentrations. Symptoms of hypercalcemia such as nausea, constipation, polyuria and fatigue are non-specific and difficult to distinguish from those of normal pregnancy. In fact, some studies suggest that the majority of cases of primary hyperparathyroidism in pregnancy may go undiagnosed, with miscarriage occurring even before the diagnosis is made [5].

Gestational hypercalcemia is associated with significant maternal and fetal morbidity and mortality. Pregnancy can exacerbate existing hypercalcemia, resulting in severe hypercalcemia or even precipitate a hypercalcemic crisis. Mothers are also at higher risk of complications such as hyperemesis, nephrolithiasis, pancreatitis, and fractures. The risk of pregnancy-related complications such as pre-eclampsia and eclampsia are also increased. In the fetus, hypercalcemia is associated with an increased risk of miscarriage, growth restriction and premature birth [6]. Post-delivery, neonatal hypocalcemia can occur due to failure of neonatal parathyroid glands to upregulate following prolonged suppression in-utero. This can be associated with severe neonatal complications such as arrhythmias, laryngospasm, seizures, and even death [7]. While most cases of neonatal hypocalcemia are transient and resolve by 3–5 months, cases of permanent hypoparathyroidism have also been reported [7,8].

Primary hyperparathyroidism is the most common cause of hypercalcemia in pregnancy [9]. As in non-pregnant individuals, this is most commonly due to a single parathyroid adenoma. However, given the younger age of presentation, familial causes of primary hyperparathyroidism or parathyroid hyperplasia should be considered, including multiple endocrine neoplasia (MEN) 1, MEN-2A, and hyperparathyroidism jaw tumour syndrome [10]. Clinical evaluation for associated symptoms and significant family history should be undertaken.

Conventional imaging options for localisation of primary hyperparathyroidism in pregnancy are limited. ^{99m}Technetium-Sestamibi scintigraphy is not recommended, due to the potential radiation risk. Likewise, computed tomography and positron emission tomography

(PET) scans should be avoided [10]. Thus, parathyroid ultrasound remains the first-line imaging modality for pregnant women with primary hyperparathyroidism. While ultrasound is easily accessible and poses no radiation risk, its sensitivity is limited in cases of small adenomas, parathyroid hyperplasia, ectopic parathyroid glands, or concomitant thyroid disease [11]. It is also operator-dependent. Reported sensitivities range from 16% (for double adenomas) to 79% (for single adenomas) [12]. Another option that is feasible in pregnancy is needle aspiration for PTH, which has been described in case reports [13]. Lastly, genetic testing for the conditions previously described should also be considered, particularly in the following scenarios: young age, multi-gland disease, parathyroid cancer, clinical features of MEN syndrome or jaw-tumour syndrome, and if there is a positive family history [14].

Treatment of PHPT in pregnancy often presents a clinical conundrum. Most of the medications used for non-pregnant individuals with PHPT have safety concerns in pregnancy. Subcutaneous calcitonin is a category B medication in pregnancy: it does not cross the placenta and can be used safely to suppress bone resorption and promote urinary calcium excretion [15]. Cinacalcet, a calcimimetic, is a category C medication. While its use has been described anecdotally in case reports, a potential risk of neonatal hypocalcemia due to suppression of the fetal parathyroids exists [16,17]. Similarly, bisphosphonates are also category C medications. Since bisphosphonates are retained in the skeleton for a long time, the fetus may be exposed even if the use is stopped before pregnancy. A recent systematic review of 13 studies including 108 pregnancies of women exposed to bisphosphonates before or during pregnancy described cases of "spontaneous abortion (N = 6), congenital malformations (N = 4), hypocalcemia (N = 4), preterm birth (N = 3), and low birth weight (N = 3) [18]. However, due to the data being largely retrospective and the lack of control groups, a direct causal relationship between bisphosphonate use and adverse fetal outcomes cannot be ascertained from this review. There is also a lack of studies detailing the long-term consequences of in-utero bisphosphonate exposure on future skeletal health of offspring [19]. Denosumab is a category D medication and should not be used in pregnancy, as animal studies have described an increased risk of miscarriage and an osteopetrotic-like disorder in offspring [20]. Thus, hydration remains the only long-term therapeutic option for control of hypercalcemia in pregnancy.

Parathyroidectomy in pregnancy also has several challenges and considerations. Miscarriage risk with general anesthesia is highest during the first trimester [21]. Thus, the optimal timing for parathyroidectomy is during the early second trimester, with close control of hypercalcemia using hydration prior to surgery. Perioperatively, a multi-disciplinary team management for close maternal and fetal monitoring is required. In terms of surgical considerations, given the fact that options for pre-operative localisation imaging are limited, patients may require a bilateral neck exploration if a single adenoma was not confidently identified on imaging. In a case series of patients with PHPT in pregnancy, 13 of 15 patients who underwent parathyroidectomy in pregnancy required a bilateral neck exploration [22]. The two who underwent targeted surgery had sestamibi scans done prior to pregnancy. Intraoperative iPTH measurement is also important to ensure that the offending gland or glands have been removed [23]. Two large case series have reviewed the impact of surgical versus conservative treatment on pregnancy outcomes for gestational PHPT. The first, conducted by Norman et al. in a specialist parathyroid clinic, looked at 32 women with PHPT in pregnancy [9]. This included a total of 77 pregnancies (mean maternal calcium level 2.84 mmol/L), of which 62 were conservatively managed. Almost half of the pregnancies that were conservatively treated resulted in miscarriage, with a rate 3.5-fold higher than that of the general population. The risk of miscarriage correlated with the extent of maternal hypercalcemia. In patients with calcium levels $\geq$ 2.85 mmol/L, fetal death occurred more commonly than live birth. Pregnancy loss occurred between 7 and 23 weeks' gestation, with most miscarriages occurring from week 8–13. On the other hand, outcomes were better amongst the 15 patients who underwent parathyroidectomy in the second trimester. PHPT was cured, and all 15 had uneventful deliveries of healthy term infants. Thus, this study showed that amongst women with PHPT in pregnancy, higher maternal calcium levels were associated with greater risk of miscarriage, and that parathyroidectomy resulted in better outcomes compared to conservative treatment.

The second study, conducted by Hirsch et al. [24], took place in a community setting. It reviewed data of women 20–40 years old with screening calcium levels done. This included 74 patients with PHPT in pregnancy, with 124 pregnancies during the study period. Outcomes were compared to a control group of pregnant women with normocalcemia. The extent of hypercalcemia in this cohort was mild, with a mean calcium level of 2.7 mmol/L, and only 19% with levels above 2.74 mmol/L. The majority of these patients were conservatively treated. There was no increased rate of pregnancy complications or miscarriage compared to controls. Thus, this study illustrated that there is a role for conservative treatment of PHPT in pregnancy in women with mild hypercalcemia.

Putting the findings of these studies together, it would be prudent to recommend that surgical management of PHPT be considered in women whose calcium levels are $\geq$ 2.85 mmol/L, or if they are $\geq$ 2.75 mmol/L with prior unexplained pregnancy loss. Parathyroidectomy should ideally be performed in the early second trimester, as most miscarriages occur at 10–15 weeks' gestation. On the other hand, there is a role for conservative treatment in women with mild hypercalcemia ie, $\leq$ 2.7 mmol/L [24]. Ultimately, treatment should be individualized based on the extent of hypercalcemia, overall pregnancy risk, and patient preference.

The challenges of management of PHPT in pregnancy emphasize the importance of pre-conception counselling in women of childbearing age with pre-existing PHPT. In Norman's study, 72% of the women had at least one pregnancy loss before entering the study [9]. Many in fact had known hypercalcemia, but it was not pursued until they became pregnant again. Thus, women with known PHPT who are planning for pregnancy should undergo pre-conception counselling, and definitive treatment should be considered prior to pregnancy.

2.3.2. *Familial hypocalciuric hypercalcemia*

Familial hypocalciuric hypercalcemia (FHH) is another important cause of hypercalcemia in pregnancy. FHH represents a group of autosomal dominant, heterozygous disorders, caused by dysfunction of the calcium sensing receptor and signalling proteins [25]. As in non-pregnant individuals, FHH in pregnancy is typically chronic and asymptomatic. However, a challenge may arise when it comes to differentiating FHH from PHPT in pregnancy. The absorptive hypercalciuria of pregnancy can lead to an increase in 24h urinary calcium creatinine ratios (UCCR) in patients with FHH, resulting in indeterminate levels ranging from 0.01 to 0.02 [26,27]. Thus, genetic testing should be considered early if UCCR is indeterminate and makes it difficult biochemically to differentiate FHH from PHPT.

No maternal adverse outcomes have been reported in women with FHH in pregnancy. However, fetal outcomes would depend on whether the fetus is genetically affected or not. If the fetus is genetically concordant (heterozygous), no adverse outcomes will be seen [28]. However, if the fetus is unaffected, the elevated maternal calcium levels may lead to suppression of fetal parathyroid glands in-utero, giving rise to neonatal hypocalcemia. The final rare scenario is if the fetus has a homozygous mutation. This would result in neonatal severe hyperparathyroidism, which can be fatal [29]. Thus, post-delivery, neonates require close monitoring of their calcium levels. Prenatal testing is not routinely required as FHH is a benign condition but should be considered if both parents have FHH in view of the risk of neonatal severe hyperparathyroidism described above.

3. Hypocalcemia in pregnancy

3.1. Case example

A 28-year-old primigravida presented at 28 weeks' gestation with contractions and impending pre-term delivery. She also reported intermittent tingling, cramps, and numbness in her fingers and peri-oral region. These symptoms were present prior to pregnancy but were mild and had worsened during her pregnancy. She had a history of a previous total thyroidectomy for Graves' disease three years ago, for which she was on levothyroxine 100 μg daily. Laboratory investigations showed hypocalcemia with a serum albumin adjusted calcium of 1.69 mmol/L (NR: 2.06–2.46 mmol/L), hyperphosphatemia (serum phosphate: 2 mmol/L, NR: 0.9–1.5 mmol/L), and hypoparathyroidism (iPTH: 0.5 pmol/L, NR: 1.0–6.3 pmol/L). Her electrocardiogram showed a prolonged QTc of 560 ms.

3.2. Clinical questions

1. What medications are safe in the treatment of hypocalcemia in pregnancy?
2. What is the target calcium level in pregnancy?
3. How should maternal and fetal calcium levels be monitored post-delivery?

3.3. Discussion

Adequate calcium during pregnancy is essential for the development of the endochondral skeleton [30]. PTHrP plays an important role in calcium metabolism during pregnancy. It stimulates the preferential transfer of calcium across the placenta, even in the presence of inadequate maternal calcium [30]. However, when maternal calcium levels are severely low, calcium levels will be insufficient to meet fetal requirements. This then leads to stimulation of the fetal parathyroid glands (secondary hyperparathyroidism), which causes demineralisation of the fetal skeleton, fractures, and low birth weight [31,32]. Hypocalcemia also poses a risk for miscarriage as it increases uterine irritability.

Women with known hypoparathyroidism have varying courses during pregnancy. This is postulated to be due to the variation in PTHrP levels and oral calcium intake. Some women may see a substantial improvement in hypoparathyroidism, due to the effects of PTHrP and increased intestinal absorption. On the other hand, some may develop worsening hypocalcemia due to the increased fetal demand. Lastly, some may have no change as the increased fetal demand is balanced by the increase in PTHrP. In view of the varying response, close monitoring is recommended in pregnancy. Ionised or albumin adjusted calcium levels should be monitored every 2–4 weeks [33]. Calcium in the low-normal range should be targeted, with careful avoidance of hypercalcemia [33]. Calcium, calcitriol, and vitamin D supplements are all safe in pregnancy. However, thiazides and recombinant PTH are category C medications during pregnancy [34]. In the post-partum period, close monitoring of maternal calcium is imperative, especially in the first few days after delivery. In the first two days post-partum, patients may have transient hypocalcemia due to sudden loss of placental PTHrP. Calcium levels then rise during lactation due to PTHrP production from lactating breasts; the extent of the rise in calcium levels depends on the intensity and exclusivity of breastfeeding [33]. During this period, it is important to monitor for hypercalcemia, and supplements may need to be reduced or stopped. Finally, during weaning, calcium levels may fall again, requiring further adjustment of medications. If there are no plans to nurse post-delivery, medications can be decreased to the pre-pregnancy doses [34].

4. Hypophosphatemia in pregnancy

4.1. Case example

A 30-year-old lady with X-linked hypophosphatemic rickets (XLH) consults regarding her desire to conceive. She was diagnosed at the age of 14 months and has been stable on supplemental phosphate (1 g of elemental phosphate in 3 divided doses), calcitriol 0.5 μg twice daily, and cholecalciferol 1000 unit daily. She has no other medical history. She enquires about the safety of her current medications in pregnancy, as well as the risk of her offspring inheriting XLH.

4.2. Clinical questions

1. How should hypophosphatemia in pregnancy be managed?
2. Which pharmacological options are safe in pregnancy?

4.3. Discussion

Phosphate levels typically remain stable in pregnancy and the causes of hypophosphatemia in pregnancy are similar to that in a non-pregnant individual. However, there are several pertinent conditions that call for attention amongst pregnant women.

In the first trimester, hypophosphatemia may be seen in women with hyperemesis gravidarum who are managed with parenteral supplementation and who develop refeeding syndrome, resulting in an intracellular shift of phosphate [35]. Cases of severe hypophosphatemia complicated by rhabdomyolysis and hemolysis have been reported in women with hyperemesis gravidarum [36,37]. Thus, close monitoring of phosphate levels is imperative in patients recovering from hyperemesis gravidarum.

An important cause of hypophosphatemia in pregnancy is XLH. As the most common congenital cause of hypophosphatemia, it is not infrequently encountered in women of childbearing age. It is caused by mutations in the phosphate regulating endopeptidase X-linked (PHEX) gene, which encodes a cell-surface-bound protein-cleavage enzyme predominantly expressed in osteoblasts, osteocytes, and teeth [38]. The loss of PHEX function results in enhanced secretion of the phosphaturic hormone fibroblast growth factor (FGF)-23 and a reduction in calcitriol levels, leading to renal phosphate wasting and hypophosphatemia [38]. Given the X-linked dominant inheritance pattern and X chromosome inactivation (lyonization) where one X chromosome is randomly turned off, females with XLH generally have been thought to exhibit a milder phenotype compared to males, with less pronounced skeletal complications [39] though this does not seem to have been confirmed in recent literature [40,41]. Nonetheless, close biochemical monitoring is required for women with XLH in pregnancy. Phosphate and calcitriol supplementation are safe in pregnancy, and doses may need to be increased [41]. Subcutaneous burosumab, a monoclonal antibody to FGF-23, has limited data in pregnancy. Reproductive toxicity has been demonstrated in animal studies, and thus its use is not recommended.

For offspring who inherit XLH, serum phosphate levels may be normal within the first 3–4 months after birth, but close monitoring is required, to allow for intervention before the development of inevitable rachitic skeletal abnormalities [42]. Offspring should also undergo PHEX mutation genetic testing since an affected female would pass the pathogenic variant to 50% of her offspring.

An important acquired cause of hypophosphatemia in pregnancy is that secondary to the use of Ferric carboxymaltose (FCM) injections. FCM increases circulating concentrations of bioactive FGF-23, leading to increased urinary excretion of phosphate, and a fall in serum phosphate levels. Two randomised controlled trials looked at the effects of FCM compared to iron isomaltoside on phosphate levels in iron deficiency anemia. Both studies demonstrated that FCM was associated with a much higher incidence of hypophosphatemia, occurring in up to 75% in the first 35 days, with a mean nadir phosphate level of 0.6 mmol/L 14

days after receiving the injection [43]. In contrast, the incidence of hypophosphatemia with iron isomaltoside was much lower, at 7%–8%. Although these studies excluded pregnant women, FCM has been used in pregnant women with iron deficiency anemia [44]. It is therefore important to be cognizant about the high incidence of hypophosphatemia with FCM, and to use it with caution in pregnant women.

5. Osteoporosis in pregnancy and lactation

5.1. Case example

A 35-year-old lady presented with persistent lower back pain that had occurred spontaneously during the third trimester of her first pregnancy. It had been treated conservatively at the time. Her pregnancy and delivery had been uneventful, and she breastfed her child post-delivery. However, the lower back pain persisted for more than a year after delivery. There had been no preceding trauma or falls, and the pain was not associated with lower limb weakness or numbness. She had a medical history significant for mild asthma that was managed with beclomethasone (steroid) inhaler. She also had lactose intolerance and had a low dietary calcium intake of 229 mg per day. She was a non-smoker. There was no family history of osteoporosis or metabolic bone disorders. Biochemical investigations including calcium, phosphate, iPTH, 25(OH)D, kidney function, blood count and thyroid function test were normal. However, a lumbar spine x-ray revealed an L1 compression fracture. She was also found to have low bone mineral density with a Z-score of −3.2 at the lumbar spine, −2.9 at the neck of femur, and −2.3 at the total hip.

5.2. Clinical questions

1. What are the reasons for osteoporotic fractures in pregnancy?
2. What form of treatment is recommended and safe in pregnancy?
3. What are the risks of further osteoporotic fractures during subsequent pregnancies?

5.3. Discussion

There are several factors that may lead to a decrease in bone mineral density (BMD) during pregnancy and lactation. Firstly, there are increased fetal and neonatal calcium demands during pregnancy (with an average of 30 g of calcium accreted by the fetus during pregnancy) and lactation (daily loss of 280–400 mg of calcium) [1]. With these increasing demands, there may be insufficient dietary calcium or vitamin D intake in women who avoid dairy or are lactose intolerant. Secondly, the rise in PTHrP concentrations in pregnancy and lactation may be excessive in some women, thus worsening skeletal resorption [1]. Lastly, mechanical factors such as increased weight-bearing of pregnancy, lordotic posture, and carrying the child post-partum also place stress on the spine.

Other important pre-existing risk factors include low body mass index, conditions causing low estrogen levels (such as anorexia nervosa), endocrinological conditions (such as hyperthyroidism), malabsorptive gastrointestinal disorders, bone or connective tissue disorders, smoking, medications that may induce bone loss (such as glucocorticoids or anti-epileptics), and a family history of osteoporosis and the use of medications that may induce bone loss such as anti-epileptics and glucocorticoids [45,46]. A 27% increase in the relative risk of osteoporotic fractures has been found in patients using even inhalational corticosteroids long-term [47]. Women with these underlying risk factors therefore require closer monitoring and tailored management before, during, and after pregnancy to reduce the risk of further bone loss during pregnancy and lactation.

In view of radiation exposure concerns, very few studies have been conducted to estimate BMD changes during normal pregnancy. Most existing studies report a decline in BMD of about 5% during pregnancy, particularly in the lumbar spine [48–50]. During lactation, studies describe a fall in bone mineral content at trabecular sites by 3%–10% after 2–6 months of lactation, with smaller losses at cortical sites [51]. This rate of bone loss exceeds even that occurring right after menopause (1%–3%) [52]. These bone density losses of lactation are usually substantially reversed within 6 months of cessation of lactation. This is irrespective of how much bone density was lost initially, and parity and lactation do not appear to increase the long-term risk of osteoporosis or fractures [53].

Fragility fractures during pregnancy and lactation are rare, but if they do occur, vertebral fractures are the ones that most commonly do. Their incidence may be under-recognised and under-reported, given the frequency of back pain in pregnancy. Vertebral fractures typically occur during a first pregnancy, during the third trimester, or first few months in the post-partum period [54]. Most of these women do not have a previous history of bone or mineral metabolism disorders. At diagnosis, BMD is low, but this improves spontaneously 6–12 months after cessation of lactation. Previous case series described a low risk of recurrence with future pregnancies [55].

Another entity distinct from osteoporosis in pregnancy is that of the likely misnamed transient osteoporosis of the hip. This is a rare condition causing skeletal fragility localised to one or both hips but is not associated with systemic skeletal resorption [56]. Hip BMD is usually low and out of keeping with the lumbar spine measurement. Transient osteoporosis of the hip in pregnancy typically occurs in the third trimester and is postulated to be associated with risk factors such as femoral venous stasis, fetal pressure on the obturator nerve, reduced activity and bedrest. Women may present with hip pain, limping, or even hip fractures. Magnetic resonance imaging (MRI) of the hip reveals bone marrow edema of the femoral head and neck, commonly associated with a joint effusion [57]. The MRI and BMD changes typically resolve spontaneously within 3–12 months post-partum.

The overall treatment strategy for osteoporosis in pregnancy and lactation is that of watchful waiting, as spontaneous recovery of BMD does occur even in women who have suffered fractures [58]. However, several supportive measures are important. Nutrition, calcium, and vitamin D intake should be optimised, with a recommend a dietary intake of 1200 mg/day of calcium. While the role of vitamin D in calcium metabolism and bone health is well-documented, the association between this micronutrient and pregnancy outcomes is still debated and the desirable 25(OH)D levels that should be maintained during pregnancy are still unclear. An intake of 600 IU/day of vitamin D as recommended by the WHO appears to be prudent [59,60].

What impact osteoporosis during pregnancy has on fetal, neonatal and childhood bone health has not been studied. A meta-analysis of three trials suggests moderate-to high-dose vitamin D supplementation in pregnancy might increase offspring BMD in early childhood, but further trials are required to confirm this finding [61].

Pharmacologic therapy of pregnancy and lactation associated osteoporosis should be reserved for severe or recalcitrant cases and should be delayed for 12–18 months until the extent of spontaneous recovery has been determined. Case series have described the successful use of bisphosphonate treatment, with improvements of BMD at the spine (by 10.2%–23.0%) and femoral neck (by 2.6%–7.5%) at 1–3 years [55,62]. However, the concern about bisphosphonates is its accumulation in bone, possibly leading to fetal exposure in subsequent pregnancies [63]. The optimal duration of treatment is also unknown.

Denosumab therapy for osteoporosis of pregnancy and lactation is limited to case reports. Its use during pregnancy is not recommended due to limited data in humans. Reproductive toxicity including increased mortality and growth impairment have been described in animal studies [20]. Available case reports describe its use in the early post-partum period, with an improvement of BMD at the spine (16.5%–32%) at 12–18 months [64–66]. However, duration of therapy and an appropriate exit strategy need to be carefully planned given the risk of rebound vertebral fractures upon cessation of therapy [67].

Teriparatide therapy for patients with pregnancy and lactation-associated osteoporosis has been described in retrospective cohort studies and case reports. A multi-center retrospective cohort study comparing women treated with teriparatide with calcium and vitamin D (N = 19) versus those with calcium and vitamin D only (N = 8) reported that those in the teriparatide treatment arm achieved a greater increase in lumbar spine BMD at 24 months (32.9 ± 13.4% vs 12.2 ± 4.2%) [68]. These findings were similarly reflected in other cohort studies and case reports [69]. Importantly, another study described that the use of sequential therapy with anti-resorptives after Teriparatide treatment for women with pregnancy and lactation-associated osteoporosis did not affect BMD gains [70]. Thus, Teriparatide is a promising option for the treatment of pregnancy and lactation-associated osteoporosis. However, further randomised controlled data would be required to determine its efficacy and safety in this population.

Table 2 summarises the current evidence, benefits, and risks of osteoporosis pharmacotherapy for osteoporosis in pregnancy and lactation.

In addition to the above strategies, the duration of breastfeeding post-partum should be balanced against the risk of progressive BMD loss and fracture risk.

6. Chronic kidney disease-mineral bone disorders (CKD-MBD) in pregnancy

6.1. Case example

A 32-year-old woman (G2P1) with stage 3a chronic kidney disease (CKD) due to IgA nephropathy presents at 10 weeks' gestation for prenatal care. She was diagnosed 5 years ago and has been followed by a nephrologist for mild proteinuria (800 mg/day) and stable kidney function (eGFR ~50 mL/min/1.73 m^2 pre-pregnancy). She has a history of secondary hyperparathyroidism (SHPT) with chronically elevated PTH and mild hyperphosphatemia.

She was on calcitriol 0.5 μg daily and calcium carbonate 1g three times a day before pregnancy to maintain calcium homeostasis. Due to persistent hyperphosphatemia, sevelamer 800 mg three times a day had been started six months prior but was discontinued after confirmation of pregnancy on her nephrologist's advice. She had also been on a low-phosphate diet.

At her first prenatal visit, she reports fatigue and occasional muscle cramps. She has no history of fractures. She is concerned about the effects of her kidney disease on her pregnancy and her baby's skeletal development.

Laboratory Investigations at 10 weeks' gestation showed serum calcium of 2.06 mmol/L (NR: 2.06–2.46 mmol/L), serum phosphate 1.89 mmol/L (NR: 0.9–1.51 mmol/L), PTH 24.8 pmol/L (NR: 1.0–6.3 pmol/L), 25(OH)D 22 ng/mL, Serum creatinine 123 mmol/L (eGFR: 49 mL/min/1.73 m^2, and urinary protein/creatinine ratio 850 mg/g. She is currently taking prenatal vitamins with 800 IU vitamin D3 daily, along with calcium carbonate and calcitriol under nephrology guidance.

6.2. Clinical questions

1. What are the maternal and fetal risks associated with CKD-MBD in pregnancy?
2. How should secondary hyperparathyroidism and mineral imbalances be managed in pregnant women with CKD?
3. Which phosphate binders and vitamin D analogs are safe during pregnancy?
4. How should maternal and fetal bone health be monitored in CKD-MBD?

6.3. Discussion

Women with pre-existing CKD face increased maternal and fetal risks in pregnancy, with the risk increasing with increasing degrees of kidney dysfunction [71]. Pregnancy results in several alterations to renal physiology, such as changes in glomerular and tubular function. This can lead to declining renal function during pregnancy, especially in women with moderate to severe CKD, or concomitant hypertension and/or diabetes [71]. These changes in renal physiology during pregnancy may negatively impact maternal calcium and phosphate balance. Maternal risks include worsening kidney function due to increased glomerular filtration during pregnancy, hyperphosphatemia-related vascular calcification and cardiovascular risks, exacerbation of secondary hyperparathyroidism (SHPT), potentially leading to bone resorption and increased fracture risks, hypertension, and preeclampsia. Fetal risks include impaired skeletal mineralization due to maternal hyperphosphatemia and elevated PTH, increased risk of intrauterine growth restriction (IUGR), neonatal hypocalcemia due to prolonged fetal PTH suppression in utero and preterm delivery. Poorly controlled CKD-MBD leading to neonatal complications, including transient neonatal hyperparathyroidism or neonatal fractures, has also been reported.

There is scanty data on the appropriate management of women with CKD-MBD in pregnancy and these patients require a collaborative multidisciplinary approach involving the nephrologist, obstetrician, and endocrinologist to manage the bone mineral abnormalities that occur in them. Pre-conception counselling and planning is essential to ensure that kidney function, blood pressure, and other comorbidities are optimised before pregnancy. During pregnancy, the Nephrologist should ensure intensive hypertension control, suppression of proteinuria, and adjustment of dialysis/immunosuppression in women with end-stage kidney disease (ESKD) or kidney transplant respectively. Close fetal and placental surveillance should be performed by the obstetrician.

Management of mineral metabolism during pregnancy depends

Table 2
Current evidence and risks of osteoporosis pharmacotherapy in pregnancy and lactation.

Medication	Evidence	Benefits	Risks
Bisphosphonates	Case series	• Improvement of BMD at the spine (10.2%–23.0%) and femoral neck (2.6%–7.5%) at 1–3 years.	• Fetal exposure in subsequent pregnancies due to accumulation in bone. • Reports of spontaneous abortion, congenital malformations, neonatal hypocalcemia; although no clear association described. • Long-term consequences on growth and skeletal development unknown.
Denosumab	Case reports	• Improvement of BMD at spine (16.5%–32%) at 12–18 months.	• Maternal: drop in spine BMD and risk of rebound vertebral fractures following cessation of therapy. • Fetal: unknown effects; increased mortality and impaired growth reported in animal studies.
Teriparatide	Retrospective cohort studies and case reports	• Improvement of BMD at the spine (7.4%–36%) at 18 months.	• None reported; but lack of long-term and randomised data.

largely on the severity of CKD-MBD and whether the woman has pre-existing secondary or tertiary hyperparathyroidism. Calcium, phosphate, and iPTH levels should be assessed regularly, targeting calcium and phosphate levels within the normal range. Calcium-based binders are safe in pregnancy and lactation, but non-calcium-based binders such as sevelamer and lanthanum should be stopped pre-conception as animal studies have reported reduced or irregular ossification [71]. Calcimimetics such as cinacalcet are category C in pregnancy with animal data suggesting low risk and can be continued in women with poorly controlled hypercalcemia. Women with secondary hyperparathyroidism should also be continued on 1,25(OH)D supplementation. Women on dialysis should also have the dialysate composition of calcium and phosphate modified based on individual needs [72].

7. Conclusions

Management of metabolic bone disorders during pregnancy and lactation requires careful balance due to the dual needs of the mother and fetus. Early diagnosis, close monitoring, and individualized treatment, particularly in cases of hyper and hypocalcemia, hypophosphatemia and osteoporosis are essential to prevent adverse maternal and fetal outcomes. Optimal timing of interventions, such as parathyroidectomy, and the cautious use of pharmacological treatments, can significantly improve both maternal health and fetal development outcomes. A multi-disciplinary approach is paramount especially in women with complex pre-existing medical disorders such as CKD-MBD.

CRediT author statement

Manju Chandran: Conceptualization, Writing – original draft, Writing – review & editing. **Sarah Ying Tse Tan:** Writing – original draft.

Conflicts of interest

The authors declare no competing interests.

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