Hypercalcemia in pregnancy – a multifaceted challenge: case reports and literature review

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Key Clinical Message
Hypercalcemia in pregnancy is an uncommon event that can cause major maternal morbidity and/or fetal or neonatal morbidity and mortality. Management is a challenge for the clinicians, especially as regards to investigations in pregnancy, surgery, and the use of cinacalcet and bisphosphonates. We present three case reports and discuss management.

Keywords
Bisphosphonates, cinacalcet, fibroma, hypercalcemia, hyperparathyroidism, pregnancy

Introduction
Hypercalcemia is a rare pathology in pregnancy, but an important one to recognize in the effort to reduce fetal and neonatal morbidity and mortality. The difficulty arises from the nonspecific presentation of hypercalcemia. Symptoms may be confused with nausea and other discomforts frequently observed in pregnancy, and total calcium levels are modified by decreased albumin values. Further, physicians involved in pregnancy management are often reluctant to use radiological imaging for investigations and therapeutic options appear limited. We will present three cases of hypercalcemia to illustrate some of these challenges and discuss optimal management. For convenience, we have included calcium conversion and correction factors (Table 1).

Case Histories

Patient 1
A 40-year-old woman on her fourth pregnancy and one live birth (G4P1) was admitted at 33 weeks’ pregnancy with known sickle-cell disease, bone pain, and polyuria. Prior to pregnancy, she had had several episodes of acute thoracic syndrome and multiple hospitalizations for bone pain, cholestasis, chronic articular pain, retinopathy, and a kidney infarct. The sickle-cell disease was being treated with erythrocytapheresis every 8 weeks and, since pregnancy, every 6 weeks. In the last year, the patient’s serum calcium levels had fluctuated from normal to high (maximum 2.73 mmol/L; normal range [NR]: 2.2–2.5 mmol/L), with no further investigations. During an admission for a sickle-cell crisis and hyponatremia at 28 weeks’
Corrected Ca (mmol/L) = Ca mmol/L + (0.02 x (40-albumin g/L))
Parathyroid hormone (PTH) pg/mL = PTH pmol/L x 0.1061
PTHrP pg/mL = PTHrP pmol/L x 1

Table 1. Correction and conversion to SI units.

| Calcium(Ca) mg/dL | Ca mmol/L x 4 |
|------------------|----------------|

gestation, hypercalcemia was noticed at 2.68 mmol/L (ionized calcium: 1.44 mmol/L; NR: 1.14–1.35 mmol/L). The parathyroid hormone (PTH) level was 7.8 pmol/L (NR: 1.3–6.8 pmol/L). A parathyroid adenoma was diagnosed on cervical ultrasound.

The medical team considered important to reduce the patient’s serum calcium levels because hypercalcemia was thought to be responsible for the polyuria, with ensuing dehydration and sickle-cell crisis. Despite aggressive saline infusion, followed by furosemide, and then administration of calcitonin at 10 IU/kg twice daily for 48 h, serum calcium levels remained unchanged. Surgery was not considered because of the advanced pregnancy and active sickle-cell disease. The patient had an in-depth discussion with the multidisciplinary team, and she agreed to receive cinacalcet 30 mg twice daily; three days later, it was increased to 60 mg twice daily, in spite of significant nausea requiring medication. Calcium levels dropped progressively to 2.04 mmol/L 10 days after starting treatment.

Cinacalcet was stopped prior to the patient’s scheduled erythroctapheresis, as the procedure usually induced symptomatic short-term hypocalcemia. Two days later, the calcium level was 2.26 mmol/L and labor was induced. The patient gave birth vaginally to a normal 2650-g boy at 35.6 weeks’ gestation. The newborn’s calcium levels were normal over the following 10 days. Cinacalcet and calcitonin were stopped after delivery. Five months postpartum, the mother had surgery to remove the parathyroid adenoma.

**Patient 2**

A 30-year-old woman (G1) was transferred to our center at 36 weeks’ gestation for symptomatic urolithiasis, acute renal insufficiency, and hypercalcemia. She had had multiple episodes of nephrolithiasis in the previous year, but investigations were postponed when she became pregnant. The patient’s bloodwork revealed a creatinine level of 1002 μmol/L (NR: 80–120 μmol/L), elevated calcium levels (total calcium: 2.97 mmol/L; corrected calcium: 3.33 mmol/L; measured ionized calcium: 1.68 mmol/L). The patient was taking prenatal vitamins daily, vitamin D tablets (1000 IU), and calcium carbonate tablets as needed.

Aggressive intravenous hydration with isotonic saline was started, along with calcitonin 4 IU/kg twice daily.

Table 1. Correction and conversion to SI units.

| Calcium(Ca) mg/dL | Ca mmol/L x 4 |
|------------------|----------------|

Over the next few days, the pain decreased and creatinine and calcium levels improved to 89 μmol/L and 2.43 mmol/L, respectively. However, the patient developed diabetes insipidus and calcium levels again increased to 2.82 mmol/L, despite a doubling of the calcitonin dose. PTH was measured at 29.3 pmol/L, vitamin D levels were normal, and bilateral nephrocalcinosis was detected, along with a large renal staghorn calculus without hydronephrosis. A diagnosis of primary hyperparathyroidism was made.

Considering that the pregnancy was at 37.5 weeks and that calcitonin has a timed-limited efficacy, labor was induced. The patient gave birth vaginally, with no complications, to a healthy 2496-g girl. The baby’s calcium levels were normal over the next 10 days. Immediately after delivery, the mother’s calcitonin was stopped and she received 60 mg of intravenous pamidronate as there was uncertainty about the timing of an eventual surgery. A sestamibi parathyroid scan showed a single parathyroid adenoma. Finally, the woman had resection of the adenoma on postpartum day 7. Thereafter, serum calcium levels remained normal and the creatinine returned to prepregnancy values.

**Patient 3**

A 26-year-old woman (G1) was admitted at 14 weeks’ gestation for nausea and vomiting. She had no medical problems except for a fibroma discovered at 8 weeks’ gestation.

On admission, the patient complained of nausea, vomiting, constipation, weight loss, and severe arthralgia in the wrists, hands, knees, and back. Initial bloodwork revealed normocytic anemia (hemoglobin: 81 g/L; NR: 120–160 g/L) and elevated calcium levels (total calcium: 3.64 mmol/L; measured ionized calcium: 2.05 mmol/L). Parathyroid hormone was undetectable, but parathyroid hormone-related peptide (PTHrP) was elevated at 46 pg/L (NR < 15 pg/L). Vitamin D concentrations were slightly elevated at 388.4 pmol/L (NR: 63–228 pmol/L). The angiotensin-converting enzyme level was normal. Bone marrow aspirate, breast ultrasound, bone series, and thoracic magnetic resonance imaging (MRI) were normal. A pelvic ultrasound and abdominal MRI showed a 9-cm fibroma and bilateral nephromegaly, with a hyperechoic cortex and diminished corticomedullary differentiation.

On admission, the patient was administered intravenous saline with electrolyte replacement and calcitonin (8 IU/kg four times a day), followed by furosemide, ondansetron, dimenhydrinate, and hydromorphone. We then discussed the possible use of cinacalcet with the patient and after reflection, she agreed to start cinacalcet 30 mg daily which was increased to twice daily 2 days
later, but without clinical or biochemical improvement (serum calcium: 3.76 mmol/L). In view of the persistent hypercalcemia and symptoms, the source of the PTHrP was thought to be either the placenta or fibroma and we opted, after discussion with the patient, to terminate the pregnancy. The patient underwent curettage and immediately after she developed mild symptomatic pancreatitis which resolved over the next week. Intravenous pamidronate 90 mg was administered and calcium levels and PTHrP normalized 2 days after. Calcitonin and cinacalcet therapy were stopped. Her clinical status improved, with the exception of persistent arthralgia. A positron emission tomography (PET) scan showed increased uptake at the knees, elbows, ulnocarpal joints, fingers, and kidneys in a nondiagnostic pattern. The histopathological study of the placenta showed trophoblastic and stromal cells with strong immunohistochemical reactivity for PTHrP.

Six weeks after termination, an abdominal ultrasound showed normal kidneys and the persistence of a 9-cm fibroma. A myomectomy was performed by median laparotomy, without complications. The arthralgia that had persisted since pregnancy termination resolved within 24 h. The fibroma weighed 325 g, and no malignancy was detected. Immunohistochemical staining for PTHrP was positive on more than 50% of cells of the fibroma and showed strong nuclear and moderate cytoplasmic positivity. It was impossible to determine whether the site of maximal PTHrP secretion had been the placenta or the fibroma.

**Discussion**

**Description, etiology, diagnosis**

Hypercalcemia in pregnancy is uncommon, occurring in approximately 0.03% of women of reproductive age [1]. The condition is probably underdiagnosed due to its non-specific symptomatology and the physiological decrease in total calcium accompanying lower albumin levels. Pregnancy does not affect the level of measured ionized calcium, and PTH levels are also usually unchanged, although they may decrease in the third trimester [2]. Table 2 presents the changes in calcium homeostasis during pregnancy and lactation.

Symptoms of hypercalcemia are not dependent on pregnancy status; they are the same whether a woman is pregnant or not. Directly related to serum calcium levels, symptoms are reported in up to 67% of affected women.  

| Measured levels | Pregnant woman | Placenta | Fetus | Lactating woman |
|-----------------|----------------|----------|-------|-----------------|
| Serum Ca        | Total Ca ↓     | Active transfer | Higher than maternal levels; regulated by fetal PTHrP | Ionized Ca slightly ↑ Bone resorption ↑ |
|                 | Ionized Ca ↔   | dependent on PTHrP + passive transfer | | |
|                 | Intestinal absorption twofold ↑ | | | |
| Urinary Ca      | ↑              | No transfer | Unknown | ↑↑: secretion by breasts |
| PTH             | ↓↔             | No transfer; placental and amniotic secretion | Low | |
| PTHrP           | Progressively ↑ secretion by decidua and breasts | Higher than in mother Secretion by the umbilical cord and fetal parathyroid glands as early as 10 weeks | Low | |
| 25-vitamin D    | ↔              | Transfer; placental hydroxylation | Renal hydroxylation | ↔ |
| 1,25-dihydroxyvitamin D | Progressive ↑ by 100%; calbindin-D9k ↑ | No transfer | Low | ↔ |
| 1α-hydroxylase activity | ↑ Stimulated by estradiol, prolactin, placental lactogen, PTHrP | Present | Present in the kidney | ↔ |
| Calcitonin      | ↑ by 20% Secretion by thyroid and breasts | No transfer; placental secretion | ↑ in the first 6 weeks | |

Ca, calcium level; PTHrP, parathyroid hormone-related protein; calbindin-D9k, vitamin D-dependent calcium-binding protein.
↑, increased; ↔, unchanged; ↓, decreased.
Data derived from Kovacs et al. [2] and Thiede et al. [15].

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They are mostly nonspecific and overlap with the usual complaints of pregnancy: fatigue, nausea, vomiting, constipation, and difficulty concentrating [3]. Serious maternal complications of hypercalcemia in pregnancy include severe hypertension, pancreatitis, nephrolithiasis, and renal insufficiency [2, 4–6]. Fetal complications have declined over the last 20 years but may include intrauterine growth restriction, early or late demise (2%), neonatal death (2%), neonatal hypocalcemia with tetany (15%), and, rarely, permanent hypoparathyroidism [2, 7–9].

The main cause of hypercalcemia in pregnancy is primary hyperparathyroidism (PHPT) [1, 9]. Most of the data in the literature on hypercalcemia in pregnancy come from women with PHPT. Other causes are similar to those encountered in the nonpregnant population, namely hyperthyroidism, vitamin A or D toxicity, familial hypocalciuric hypercalcemia, acute or chronic renal failure, granulomatous diseases, milk–alkali syndrome, and malignancy. Various approaches have been proposed for determining the cause of hypercalcemia in the general population, and we consider that most of these are applicable to pregnant women [10]. It is noteworthy that parathyroid nuclear scintigraphy is relatively contraindicated in pregnancy. Even if parathyroid ultrasound is reported to have varying degrees of sensitivity, ultrasound remains the preferred imaging modality [11]. The possibility of malignancy should be suspected, even in pregnancy, in the presence of low serum PTH and elevated PTHrP. Breast, lung, ovarian and renal cell carcinomas, lymphoma, leukemia, and multiple myeloma are the most common malignancies associated with humoral hypercalcemia.

Parathyroid hormone-related peptide is a large and complex protein synthesized by many tissues, with chemical and functional properties overlapping those of PTH [12]. The aminoterminal portion of PTTHrP is homologous to PTH and activates common PTH receptors. This explains how PTTHrP promotes bone resorption and renal calcium reabsorption. Studies in mice have shown that the mid-region of PTTHrP was responsible for placental calcium transport [12, 13]. The placenta and mammary glands produce PTTHrP, and serum levels of PTTHrP are therefore higher during pregnancy and lactation. The myometrium may also synthesize PTTHrP, especially under the stimulation of estrogens [14, 15]. Excessive production of PTTHrP by the placenta, the amnion, or the mammary glands is a rare cause of hypercalcemia in pregnancy or lactation [16–18].

Occasionally, high levels of PTTHrP may be found in association with benign tumors. The literature reports a few cases associated with the presence of dermoid cysts, pheochromocytomas, and fibromas [16, 19–25]. We have identified six published cases of hypercalcemia secondary to benign uterine fibromas. Table 3 provides details on the two cases reported in pregnancy and Table 4 on the four cases reported in nonpregnant women. All patients showed significant symptoms and were cured following surgical removal of the fibroma. Two studies presented histological proof that fibromas were the source of the PTTHrP secretion [20, 24].

### Table 3. Summary of the literature on fibroma-associated hypercalcemia in pregnancy.

| Tamawa et al. [20] | Rahil et al. [21] |
|------------------|------------------|
| **Maternal age (years)** | 32 | 36 |
| **Gestational age at discovery** | 29 weeks | First month of pregnancy |
| **Clinical presentation** | Lethargy, nausea, vomiting, abdominal pain | Nausea, vomiting, abdominal pain, weight loss |
| **Clinical course** | 33 5/7 weeks | 34 weeks |
| | • Aspiration pneumonia, intubation | • PPROM, emergency cesarean section |
| | • Admission to intensive care unit | • Postoperative septic shock and hemorrhage |
| | • Spontaneous labor, vaginal delivery | • Slight neurological impairment secondary to diffuse ischemic changes and hypoxic insult |
| | • Postmyomectomy hemorrhage | |
| **Newborn** | IUGR, no postnatal complications | No complications |
| **Surgery** | Myomectomy immediately after delivery | Myomectomy with cesarean section |
| **Maximal Ca level (mmol/L)** | 5.2 (NR 2.1–2.63) | 4.8 (NR 2.1–2.6) |
| **PTH (pmol/L)** | Undetectable | 0.3 (NR 1.6–6.9) |
| **PTHrP (pmol/L)** | 22 (NR < 2) | N/A |
| **Treatment** | Hydration, furosemide, pamidronate 15 h after delivery, dialysis | Calcitonin, dialysis |
| **Fibroma characteristics** | 23 cm in diameter, benign pedunculated | 30 cm in diameter, calcifications, benign |
| | Histological proof of PTTHrP expression | |

Ca, calcium; IUGR, intrauterine growth restriction; N/A, not available; NR, normal range; PPROM, premature preterm rupture of membranes; PTH, parathyroid hormone; PTTHrP, parathyroid hormone-related protein.
Treatment of hypercalcemia in pregnancy

Most of the nonpharmacologic and pharmacologic approaches used in nonpregnant women apply to pregnant women as well. However, there is uncertainty concerning surgery and the use and safety of calcitonin, cinacalcet, and bisphosphonates.

An observational study reporting on 109 women with PHPT during pregnancy found that parathyroidectomy reduced fetal complications [7]. Some authors favor surgery early in the second trimester of pregnancy if calcium levels reach 2.85 mmol/L to prevent late fetal loss [9]. The second trimester is the ideal time for surgery but uneventful surgeries in the third trimester have been reported as well [10, 16, 26].

Calcitonin decreases hypercalcemia by inhibiting osteoclast activity (which in turn inhibits bone resorption) and enhancing renal excretion of calcium. Calcitonin is usually well tolerated and acts rapidly (4–6 h), but it has limited effect (maximum calcium decrease of 0.3–0.5 mmol/L) and is associated with tachyphylaxis after 48 h of use [27]. Calcitonin does not cross the placenta and is considered safe for the mother and fetus [2].

Cinacalcet is a calcimimetic agent that binds to the calcium-sensing receptor (CaSR), activating CaSR to react to the extracellular calcium concentration and decrease PTH secretion. Cinacalcet is effective in all forms of hyperparathyroidism but is mainly used for the treatment of parathyroid carcinoma and secondary hyperparathyroidism [28]. One study reported its efficacy in decreasing humoral hypercalcemia related to PTHrP in mice [29]. The use of this medication is limited by its delayed onset of action (30–40 h) and the lack of data on the fetus and neonate. As CaSRs are present in the placenta, cinacalcet may alter placental function and potentially induce fetal and neonatal hypocalcemia. Animal studies in pregnant rats and rabbits did not show embryonal or fetal toxicity [30]. Its use has been reported in two women during pregnancy: The first case was in a woman with primary hyperparathyroidism who received cinacalcet for 2 weeks before delivery at 34 week, and the second case was a woman with metastatic parathyroid carcinoma who used it in the second and third trimester in one pregnancy and throughout a second pregnancy [30, 31]. No adverse fetal effects occurred, and in the latter case, the children at 4 and 2 years of age were well with normal growth [31]. The authors hypothesized that when the suppressive effects of high maternal calcium levels were alleviated, parathyroid function in the offspring was likely to recover faster, especially in the postnatal period [31]. Moreover, because the half-life of cinacalcet is about 30 h, the medication is unlikely to induce a prolonged period of neonatal hypocalcemia [32]. There is also indirect evidence that CaSR is not pivotal in the regulation of placental transport, from a case describing an individual with autosomal-dominant hypocalcemia and a gain-of-function mutation of CaSR [30].

Bisphosphonates are commonly used in the treatment of osteoporosis, hypercalcemia, and other conditions characterized by excessive bone resorption. They are synthetic nonhydrolysable pyrophosphate analogues [33]. By binding to bone hydroxyapatite, they inhibit bone resorption, decrease calcium release and thereby serum levels of calcium, increase bone mineral density, and improve bone quality. Bisphosphonates are retained in the skeleton for a long time and do cross the placenta [33, 34]. Thus, even

| Table 4. Summary of the literature on fibroma-associated hypercalcemia in nonpregnant women. |
|---------------------------------------------------------------|
| **Bilici et al. [22]** | **Dagdelen et al. [23]** | **Herring et al. [24]** | **Garcha et al. [25]** |
| **Age (years)** | 45 | 48 | 49 | 79 |
| **Clinical presentation** | Anorexia, nausea, vomiting, constipation | Uncontrolled type 2 diabetes mellitus, inquinal pain, menometrorrhagia | Lethargy | Altered mental status, falls, acute renal failure |
| **Discovery of fibroma** | Gynecologic examination + CT scan | CT scan | Ultrasound + CT scan | CT scan |
| **Surgery** | TAH-BSO | TAH-BSO | TAH-BSO | TAH-BSO |
| **Maximal Ca level (mmol/L)** | 4 (NR 2.1–2.63) | 3 (NR N/A) | 3.37 (NR 2.1–2.6) | 4.25 (NR N/A) |
| **PTH (pmol/L)** | Undetectable | Undetectable | 0.3 (NR 0.7–5.7) | 1.4 (NR 1.6–6.9) |
| **PTHrP (pmol/L)** | 1.4 (NR < 1.3) | 2.5 (NR < 1.3) | 4.6 (NR < 1.8) | 40 (NR 14–27) |
| **Treatment** | Hydration, calcitonin, furosemide, pamidronate | Hydration, furosemide | Hydration, furosemide | Zoledronic acid |
| **Fibroma characteristics** | 6 cm, intramural | 6.9 cm, intramural | 7.5 cm, uncertain malignant potential, histological proof of PTHrP expression | Small and multiple |

Ca, calcium; N/A, not available; NR, normal range; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.
if their use is stopped before pregnancy, the fetus may be exposed. In animals, high doses of bisphosphonates are associated with fetal skeletal abnormalities, reduced bone growth and fetal weight, and hypocalcemia at birth [34]. Published data on women exposed to bisphosphonates during pregnancy are very few. Stathopoulos et al. identified 78 fetuses where the mother took bisphosphonates before or during the pregnancy (69 live births) [34]. None of the newborns presented serious adverse events. The same study also reported on four pregnant women who received bisphosphonates only after 28 weeks’ gestation, for malignancy-associated hypercalcemia. Two neonates presented transient hypocalcemia after delivery. Three other studies reported on a total of 91 newborns whose mothers took bisphosphonates before or during the pregnancy [35–37]. No increase in major birth defects or skeletal abnormalities was observed. In long-term follow-up, only two infants exposed in utero to bisphosphonates were tested; they were shown to have normal bone density at five and six years of age, respectively [38]. In contrast, Losada et al. observed a 20% rate of congenital malformations in children of patients with autoimmune rheumatic diseases taking bisphosphonates combined with other medications [33]. Chronic use of bisphosphonates during lactation is safe according to Stathopoulos et al. [34].

Case Outcomes – Perspectives

Our cases illustrate the complexities of diagnosis and management in hypercalcemia in pregnancy. Of the three pregnancies, one had to be terminated and one was complicated by intrauterine growth restriction.

In the first case, hypercalcemia preceded pregnancy but was unnoticed for some time. It was masked by the erythrocytapheresis used to treat sickle-cell disease and could have contributed directly to the bone pain. A similar situation has been reported in a child [39]. Even though the hypercalcemia was mild, it may have played a part in the polyuria, dehydration, and recurrence of sickle-cell crises. Because surgery was not an option and the pregnancy was only at 33 weeks’ gestation, we opted to add cinacalcet to calcitonin, even if the use of this medication in pregnancy is uncommonly reported and its effects poorly documented. The combination was effective but was associated with significant nausea, necessitating medication and precluding an increase in dosage.

In the second case, the woman was symptomatic before pregnancy, and earlier treatment could potentially have prevented the renal insufficiency and problems during pregnancy. Surgery was clearly indicated for her.

The third patient presented an uncommon situation with excessive production of PTHrP. Parathyroid hormone-related peptide levels were clearly above the physiological threshold reported in pregnancy [14]. There was no response to the usual treatment as well as to cinacalcet, possibly because of the humoral form of hypercalcemia. Based on the case reports previously published, both the placenta and the fibroma could have been responsible for the excess production of PTHrP and, effectively, both showed histological proof of excessive secretion [16, 17, 20, 21]. As the level of PTHrP was undetectable in the early postpartum, the placenta was probably the major source of secretion. However, considering the improvement of the woman’s arthralgia only after the removal of the fibroma and knowing that secretion of PTHrP by the fibroma could be enhanced by estrogens and by human placental lactogen [14, 15, 40], it is reasonable to think that the fibroma played an active part in the hypercalcemia. We therefore hope that following removal of the fibroma, the risk of recurrence of hypercalcemia in future pregnancies will be low.

On the basis of the studies described above, one may wonder if bisphosphonates should have been used instead of terminating the pregnancy. Even if there are no case reports or studies showing any side effect on the fetus, there are no substantial long-term data describing consequences on the growth and structure of the infant’s bones. We considered that continuing the pregnancy on bisphosphonates was not an option.

Conclusions

Hypercalcemia in pregnancy may be the cause of serious maternal, fetal, and neonatal complications. Appropriate investigation of hypercalcemia is crucial in pregnancy, as early detection is a key to preventing complications. In PHPT, surgery should be strongly considered, especially in the second trimester. When faced with an unusual case, it may be necessary to consider treatments not studied in pregnancy, so as to mitigate harm to both mother and fetus.

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Conflict of Interest

None declared.
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