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Challenges in the management of hypercalcemia in pregnancy – Case report of two cases

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ABSTRACT

Hypercalcemia in pregnancy is rare and can pose a great diagnostic challenge due to its asymptomatic presentation. It is associated with maternal complications such as urolithiasis, pancreatitis, renal insufficiency and preeclampsia, fetal complications such as growth restriction and intrauterine fetal demise, and neonatal complications such as neonatal hypocalcemia, tetany and hypoparathyroidism. Prompt diagnosis and treatment of the underlying cause of hypercalcemia is important. Two cases of hypercalcemia in pregnancy were encountered over 12 months. Both presented asymptomatically in the first trimester and were associated with hyperparathyroidism and hypertensive disease in current and previous gestations. Genetic testing ruled out familial hypocalciuric hypercalcemia, and both women required surgical management in the second trimester for control of hypercalcemia. The literature on the diagnosis and management of hypercalcemia in pregnancy is reviewed, and the challenges and pitfalls are discussed. Hypercalcemia in pregnancy requires a high index of suspicion for early diagnosis, and young women with unexplained hypertension in early pregnancy should be investigated for secondary causes, including hypercalcemia and primary hyperparathyroidism. Management of hypercalcemia secondary to primary hyperparathyroidism requires multidisciplinary team management, and surgery should be considered if the patient has not responded to conservative measures, ideally in the second trimester.

1. Introduction

Hypercalcemia in pregnancy is rare, occurring in approximately 0.03% of women of reproductive age. [1] Hypercalcemia can pose a diagnostic challenge in pregnancy as symptoms can mimic those of normal pregnancy. It is frequently caused by hyperparathyroidism, which is most often secondary to parathyroid adenoma. Although uncommon, hypercalcemia in pregnancy must be recognized and treated early because of the potential complications for both mother and fetus. Hypercalcemia and hyperparathyroidism have been linked to hypertensive disease and preeclampsia with associated consequences in pregnancy.

This paper discusses two pregnant patients with hypercalcemia secondary to hyperparathyroidism. In both cases, the condition was promptly recognized and treated, and was associated with hypertensive disease in current and previous gestations. Both patients eventually required surgical intervention in the second trimester for control of the hypercalcemia. The possible mechanisms linking hypercalcemia, hyperparathyroidism and hypertension are examined, and the management of hypercalcemia secondary to primary hyperparathyroidism in pregnancy is discussed.

2. Case Presentations

2.1. Case 1

A 29-year-old woman presented in the first trimester for her booking visit. She had a history of intrauterine fetal demise 3 years earlier at 27 weeks of gestation due to pre-eclampsia. Adjusted serum calcium level was determined due to a history of asymptomatic hypercalcemia 3 years earlier and was found to be elevated at 3.1 mmol/l (2.1–2.55 mmol/l). Parathyroid hormone (PTH) was elevated at 13.1 pmol/l (0.9–6.2 pmol/

Abbreviations: CaCR, calcium:creatinine clearance ratio; FHH, familial hypocalciuric hypercalcemia; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

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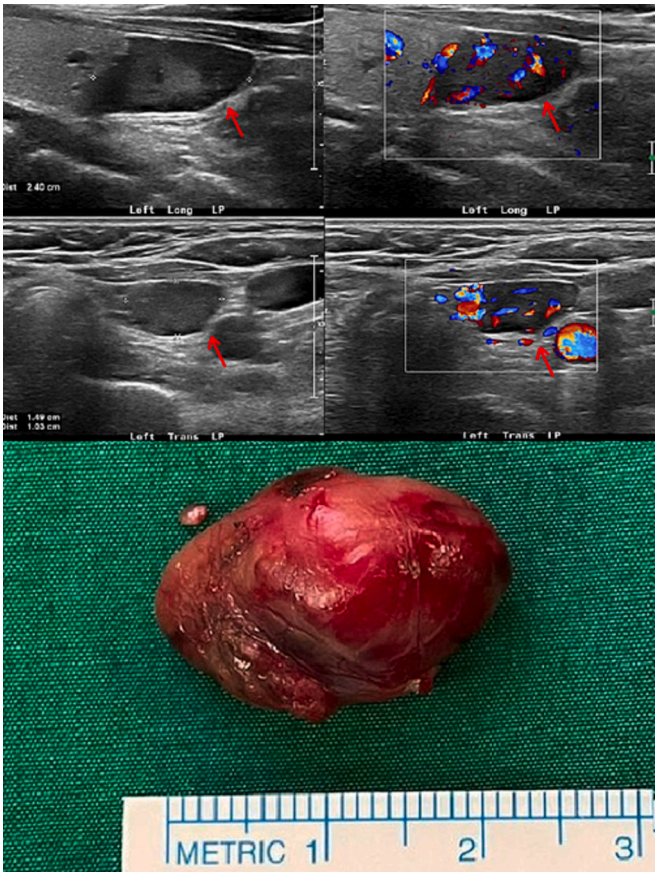

Fig. 1. a (above): Case 1 – Parathyroid ultrasound scan showing hypoechoic nodule posterior and inferior to left thyroid gland measuring 2.40 × 1.49 × 1.03 cm. b (below): Case 1 – Parathyroid adenoma after surgical resection.

l). Her blood pressure was 132/95 mmHg. She was started on oral labetalol 100 mg twice daily for blood pressure control and aspirin for preeclampsia prophylaxis. Investigations at 16 weeks of gestation revealed that 24-h urine calcium was 6.56 mmol/day (0.65–6.24 mmol/day) and 24-h urine creatinine was 9.51 mmol/day (5.3–15.9 mmol/day). Fractional excretion of calcium was equivocal at 0.0115. A fractional excretion of calcium <0.01 can suggest a diagnosis of familial hypocalciuric hypercalcemia (FHH) [2], while a reading of >0.02 can suggest primary hyperparathyroidism (PHPT) [3]. Genetic testing for FHH was negative. An ultrasound scan showed a prominent hypoechoic nodule compatible with a parathyroid adenoma (Fig. 1a).

Conservative management was initiated with intravenous hydration and subcutaneous calcitonin (250 units 12-hourly) which resulted in a modest decrease in serum calcium from 3.12 mmol/l to 2.83 mmol/l. The decision was made to proceed with left parathyroidectomy at 18 weeks of gestation in view of persistent hypercalcemia. Intraoperatively, frozen section for a 2 cm left inferior parathyroid gland confirmed a diagnosis of parathyroid adenoma (Fig. 1b). Her serum PTH decreased from 20 to 2.2 pmol/l intraoperatively, and to <0.4 pmol/L 3 h post-operatively. On the second post-operative day, she was noted to have hypocalcemia (serum calcium 2.02 mmol/l), with symptoms of hand numbness and the Chvostek sign, requiring oral calcium replacement. Her serum calcium normalized to 2.19 mmol/l by 19 weeks of gestation.

Her pregnancy was later complicated by intrauterine growth restriction at 28 weeks of gestation, and preeclampsia at 30 weeks. She was delivered at 34 + 1 weeks via emergency cesarean section when umbilical artery Doppler scans revealed absent end diastolic flow that was indicative of placental insufficiency. The birth weight was 1.45 kg and Apgar scores were 9 and 9 at 1 and 5 min of life. The baby required admission to the neonatal intensive care unit and had transient borderline hypercalcemia but was discharged well at 3 weeks of life with normal growth parameters. The patient recovered well postnatally with normalization of blood pressure and discontinuation of antihypertensives 5 weeks postpartum.

2.2. Case 2

A 32-year-old woman with 2 previous cesarean sections and pre-existing hypertension booked for routine antenatal care at 7 weeks of gestation. Blood pressure at the booking visit was 141/94 mmHg. Two weeks later, her blood pressure was 166/101 mmHg despite administration of nifedipine LA 60 mg once daily. A hypertensive workup revealed hypercalcemia with a corrected calcium of 2.85 mmol/l and raised PTH of 6.7 pmol/l. Urine calcium/creatinine ratio was 0.0237, and genetic testing for FHH was negative. Thyroid ultrasound was normal.

The patient was placed on intravenous and oral hydration, which led to a modest decrease in serum calcium from 2.92 mmol/l to 2.65 mmol/l. After extensive multidisciplinary discussions, bilateral neck exploration was performed at 21 weeks of gestation. Intra-operatively, frozen section for a 0.9 cm left inferior parathyroid gland showed parathyroid tissue. Left inferior parathyroidectomy was performed, with serum PTH decreasing from 7.0 pmol/l to 1.3 pmol/l post-incision, and subsequent normalization of serum calcium. The pregnancy was complicated by the development of preeclampsia at 36 weeks of gestation, and the patient underwent a cesarean section at 37 weeks. She delivered a baby of birth weight 3.47 kg and Apgar scores of 9 and 9 at 1 and 5 min of life. Her baby was discharged well on day 3 of life.

3. Discussion

Hypercalcemia in pregnancy is rare, occurring in approximately 0.03% of women of reproductive age [1]. >90% of cases are caused by newly diagnosed primary hyperparathyroidism (PHPT) [4], and 4 out of 5 cases of PHPT are caused by parathyroid adenomas.

Pregnancy and lactation cause changes in calcium homeostasis but do not usually greatly alter maternal serum levels of ionized calcium due to active transport of calcium ions from the mother to the fetus, causing the fetus to be relatively hypercalcemic [5,6]. Serum calcium is increased when PTH-related peptide is released by the placenta and breasts in response to estradiol, placenta lactogen and prolactin. This is potentiated by increased 1–25 vitamin D production and intestinal calcium absorption, which leads to increased mobilization of calcium [7].

The interplay between calcium disorders, parathyroid disease and hypertension has been documented in literature. An epidemiological study of 5560 participants in Korea found that there was a positive correlation between plasma calcium and hypertension (HR 1.24) [8]. Preeclampsia is also a known complication of hyperparathyroidism in pregnancy. Hultin et al. found that parathyroid adenoma was significantly associated with preeclampsia, with an odds ratio of 6.89 ($P < 0.001$) [9]. The possible causative relationship between hyperparathyroidism and preeclampsia has been proposed to be related to the interaction of PTH with the renin-aldosterone system, the sympathetic nervous system and the vascular endothelium [10]. A study in rats concluded that the presence of PTH plays a permissive role for the hypertensive action of hypercalcemia, and significant hypercalcemia induces an elevation of blood pressure [11]. The literature suggests there may be both direct and indirect associations between hypercalcemia and hypertensive disease in pregnancy.

Making a diagnosis of hypercalcemia in pregnancy is often challenging as the symptoms can overlap with symptoms commonly experienced in normal pregnancy, such as lethargy, nausea, vomiting and difficulty concentrating [12]. Serum calcium is not routinely tested as part of antenatal screening; hence most cases of hypercalcemia are detected incidentally or as part of a hypertensive workup. When

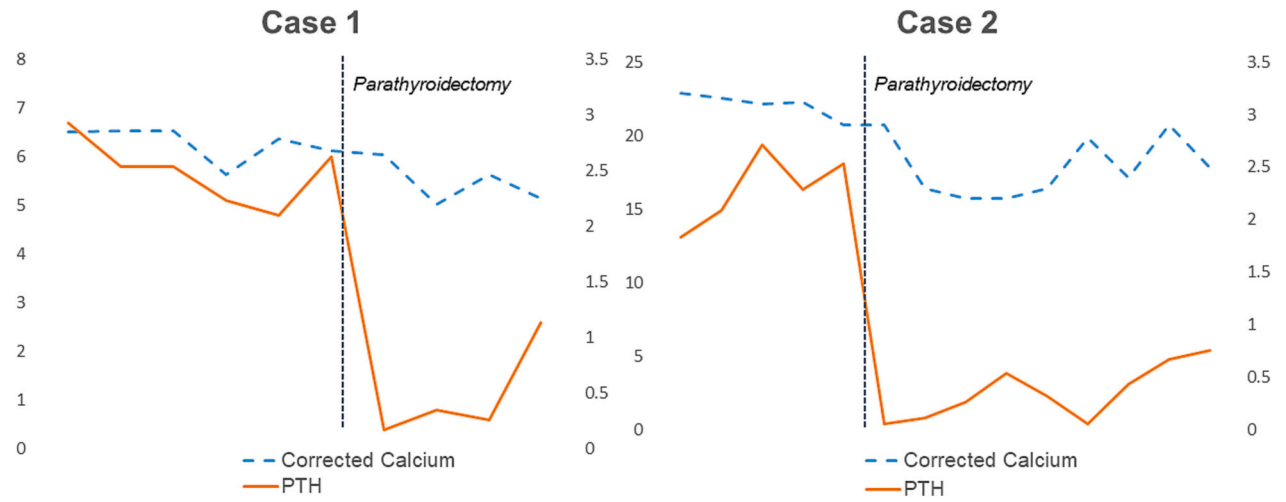

Fig. 2. Trend of serum parathyroid hormone and serum corrected calcium levels after parathyroidectomy for cases 1 and 2.

investigating the cause, it is imperative to first differentiate PHPT and familial hypocalciuric hypercalcemia (FHH), as treatment of these two conditions differs significantly. FHH is an autosomal dominant genetic condition which results in a loss-of-function mutation in the calcium-sensing receptor gene (CASR) that leads to decreased receptor activity, in turn leading to mild and asymptomatic hypercalcemia and hypocalciuria; patients can have normal or raised PTH levels [13]. Failure to diagnose FHH can lead to unnecessary surgical intervention in pregnancy. It has been proposed that PHPT can be differentiated from FHH on the basis of symptomatology, age of diagnosis, family history, and serum calcium levels in family members. Another area of differentiation is the calcium:creatinine clearance ratio (CaCR), although there can be significant overlaps in the range of values associated with the two disorders [14]. Physiologically increased calcium absorption in pregnancy results in up to a 46% increase in urinary calcium excretion in the third trimester, which can hinder interpretation of the CaCR, making it a less reliable way to distinguish the two conditions in pregnancy [15]. Definitive diagnosis of FHH requires genetic testing, although only two-thirds of FHH cases had a mutation detected in one study [16]. A combination of biochemical testing, family history, genetic testing, and testing of serum and urine calcium in relatives is required to distinguish between FHH and PHPT in pregnancy [17].

There is currently no consensus or official guidelines on the management of hypercalcemia and hyperparathyroidism in pregnancy. Rehydration is usually adopted as the first-line treatment. Pharmacological methods can be used but are less favored due to concerns regarding efficacy and safety in pregnancy. Calcitonin inhibits osteoclast activity, inhibits bone resorption, and increases renal excretion of calcium. However, it is of limited effect and can be associated with tachyphylaxis [18]. Bisphosphonates are non-hydrolysable pyrophosphate analogs that decrease calcium release from bones, thereby decreasing serum calcium levels. They are known to cross the placenta, and can be associated with fetal skeletal abnormalities, reduced bone growth, reduced fetal weight, and neonatal hypocalcemia [19]. Cinacalcet decreases secretion of PTH by binding to the calcium-sensing receptor (CaSR) and enhancing reaction to extracellular calcium. The use of cinacalcet in pregnancy may alter placental function and induce fetal and neonatal hypocalcemia due to the presence of CaSR in the placenta. However, studies in pregnant rats and rabbits did not show embryonal or fetal toxicity [20]. Recommendation for its use in pregnancy is thus debatable.

Ultimately, surgical parathyroidectomy is the only definitive cure, and intervention in the second trimester of pregnancy is preferable as it reduces the risk of fetal complications [21]. In both of the reported cases there was a sharp decline in PTH and calcium levels after parathyroidectomy was performed (Fig. 2). Patient 1 developed symptomatic hypocalcemia requiring calcium replacement post-operatively, which is reflected in the slight increase in serum calcium trend after parathyroidectomy. In both cases, partial parathyroidectomy was performed, which is reflected in the mild increase in PTH later due to the function of the remaining parathyroid glands.

However, surgical parathyroidectomy is not without risks. A retrospective cross-sectional study by Kuy et al. in 2009 found that pregnancy increases the risk of surgical complications in thyroid and parathyroid surgery twofold; these complications include maternal hypoparathyroidism, hypocalcemia, tetany and recurrent laryngeal nerve injury. Absolute maternal and fetal complication rates were 4.5% and 5.5% respectively [22]. Fetal complications included miscarriage, preterm labor, fetal distress, intrauterine death, stillbirth, neonatal tetany, and neonatal hypoparathyroidism. The risks of surgery must therefore be balanced with the risks of conservative management, which include maternal complications such as urolithiasis, pancreatitis, renal insufficiency and preeclampsia, fetal complications such as growth restriction and intrauterine fetal demise, and neonatal complications such as neonatal hypocalcemia, tetany and hypoparathyroidism.

Awareness of the complications of hypercalcemia in pregnancy and therefore pre-pregnancy treatment can reduce negative outcomes. For example, pre-pregnancy counselling and optimization of the patient in case 1 in view of her known history of hypercalcemia three years earlier could have allowed for earlier investigation and treatment prior to conception. This would have then avoided the need for surgery during pregnancy and reduced the risk of preeclampsia and preterm delivery.

4. Conclusion

Hypercalcemia in pregnancy, although rare, is an important condition that should be investigated appropriately in view of its potential adverse effects on both the mother and fetus. It requires a high index of suspicion for diagnosis as its symptoms overlap with physiological symptoms in pregnancy, which can lead to a delay in diagnosis. Young women with unexplained hypertension in early pregnancy should be considered for workup to detect secondary causes of hypertension such as PHPT. The management of hypercalcemia and PHPT in pregnancy requires multidisciplinary management; surgical options can be explored if the condition is non-responsive to conservative measures, ideally in the second trimester of pregnancy.

Contributors

Shu Hui Lim contributed to the conception of the case report,

drafting of the manuscript, undertook the literature review, and revised the article critically for important intellectual content.

Weiying Lim contributed to patient care and revised the article critically for important intellectual content.

Serene Pei Ting Thain contributed to the conception of the case report, patient care and revised the article critically for important intellectual content.

All authors approved the final manuscript.

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Conflict of interest statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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