CASE REPORT

Primary hyperparathyroidism in pregnancy leading to hypercalcaemic crisis and uraemic encephalopathy

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SUMMARY

Primary hyperparathyroidism is rare during pregnancy. Recognition may be challenging as symptoms overlap with those of other common disorders of pregnancy. Furthermore, physiological changes of pregnancy affecting calcium homeostasis mean awareness of the condition and careful interpretation of results in the light of pregnancy are essential for diagnosis. Maternal complications of primary hyperparathyroidism include nephrolithiasis, pancreatitis, cardiac arrhythmias, hypertension and peptic ulcers. At its most severe, hypercalcaemic crisis may occur, presenting with acute neurological disturbance. Most commonly, the underlying aetiology is a solitary parathyroid adenoma whereby parathyroidectomy is the only cure. A 30-year-old Caucasian woman booked under Consultant care presented at 32 weeks gestation with vomiting and right-sided loin pain. Following presentation, she was diagnosed with renal calculi. She was delivered by caesarean section (CS) due to deterioration in renal function. Post-CS, she had a grand mal seizure. She was found to have hypercalcaemia with underlying hyperparathyroidism.

BACKGROUND

Primary hyperparathyroidism (pHPT) is rare during pregnancy, posing unique diagnostic and therapeutic challenges during pregnancy, as symptoms often overlap with those of a normal pregnancy. Furthermore, the physiological changes in calcium homeostasis that occur in pregnancy may mask the biochemical manifestations of HPT. The best outcomes are achieved where the condition is recognised prior to conception. At the extreme end, HPT can lead to catastrophic outcomes for both the mother and the baby.

We present a case of pHPT in pregnancy leading to hypercalcaemic crisis and uraemic encephalopathy post-caesarean section (CS). Our case demonstrates the extreme consequences that may occur with late recognition of HPT during pregnancy. Furthermore, it highlights the need for screening of calcium levels in pregnancy for at-risk women. Identifying risk factors for hypercalcaemia at booking, such as previous nephrolithiasis, may allow for early recognition and management. As far as we are aware, no other case of hypercalcaemic crisis due to HPT presenting with a grand mal seizure and uraemic encephalopathy post-CS has been reported in the literature.

CASE PRESENTATION

A 30-year-old woman booked under Consultant care presented at 32 weeks gestation with vomiting and right-sided loin pain. Her medical history was significant for right-sided nephrolithiasis and hydronephrosis. Her obstetric history consisted of two caesarean sections, a miscarriage, an ectopic pregnancy requiring right salpingectomy and one termination of pregnancy.

Following presentation, a renal tract ultrasound scan demonstrated right-sided nephrolithiasis. Her renal function showed creatinine 280 mmol/L and urea 9.5 mmol/L. Owing to pregnancy, a decision was made to insert a right-sided percutaneous nephrostomy in view of the renal calculi and deteriorating renal function. Immediately postnephrostomy, her pain settled and the urea and creatinine returned to normal. However, 1 week later, the pain reoccurred, her urine output decreased and her renal function deteriorated again (creatinine 220 mmol/L, urea 9.5 mmol/L). Her calcium level was noted to be high at this point (3.2 mmol/L) and she was started on intravenous fluids. However, owing to continued deterioration in renal function, she underwent an uncomplicated CS after steroid administration for fetal lung maturity at 33+3 weeks of gestation, delivering a healthy female infant weighing 2.185 kg and suffering no signs of neonatal hypocalcaemia and no further complications.

Post-CS over the next 4 h, she became thirsty and drowsy with evidence of twitching and neck stiffness. She was managed conservatively with fluids; however, she subsequently became hypotensive and her Glasgow Coma Scale (GCS) score deteriorated over a few hours (from 15 to 12 (E4 V3 M5)). She was given a loading dose of 4 g of magnesium sulfate as she became hyper-reflexive and starting twitching, in view of suspected eclampsia. She subsequently became responsive only to pain and suffered a grand mal seizure. She had no other signs of eclampsia (no proteinuria, no oedema). Hence she was intubated, ventilated and transferred to the intensive care unit (ICU) (GCS 3, E1 V1 M1). No definite cause was found at that stage for her condition.

INVESTIGATIONS

An arterial blood gas in the ICU demonstrated metabolic acidosis. Lumbar puncture and CT head were normal. Bloods demonstrated evidence of hypercalcaemia (corrected calcium 3.2 mmol/L (normal range 2.2–2.6 mmol/L)). While in the ICU, she was reviewed by the medical team who

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reviewed her parathyroid hormone (PTH) levels demonstrating elevated PTH (53 pmol/L (normal range 1–6.4 pmol/L)). Her serum urate was 448 μ mol/L.

An EEG confirmed encephalopathy. In view of hypercalcaemia and elevated PTH levels, a diagnosis of pHPT with hypercalcaemic crisis leading to uraemic encephalopathy was made.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses included eclampsia, encephalitis, meningitis, dural venous sinus thrombosis and a space-occupying lesion.

TREATMENT

In the ICU, she was sedated due to persistent twitching and seizure activity. She was managed conservatively with active fluid hydration with a plan to start bisphosphonates if the calcium remained high or started to rise. Her condition improved with normalising calcium levels and renal function. She was discharged home on day 10 with outpatient follow-up arranged with the endocrinology team for further workup.

Four weeks postdischarge, serum calcium adjusted for albumin was again elevated. The calcium:creatinine clearance

ratio was greater than 0.01, ruling out familial hypocalciuric hypercalcaemia. Vitamin D was 10.3 nmol/L (normal value 50–75 nmol/L) and her urinary calcium was 3.9 mmol/day (normal value <6.2 mmol/day) (suspected to be an anomaly).

A sestamibi scan of the neck was performed for a suspected parathyroid adenoma. Ultrasound scan was requested as an adjunct for preoperative localisation of the adenoma. The sestamibi scan demonstrated increased uptake in the region of the left lobe of the thyroid consistent with a left superior parathyroid adenoma (figure 1). An ultrasound of the thyroid and parathyroid confirmed the presence of an 8 mm parathyroid adenoma (figure 2).

She underwent a total parathyroidectomy. Microscopy of the left parathyroid demonstrated a well circumscribed, cellular nodule composed predominantly of chief cells with mild variation in nuclear size and islands of oxyphilic cells consistent with the diagnosis of a parathyroid adenoma. Postoperatively, the corrected calcium was normal.

OUTCOME AND FOLLOW-UP

Postparathyroidectomy, she demonstrated no signs of transient hypocalcaemia. On follow-up several weeks postsurgery, she was

Figure 1 Sestamibi scan of the parathyroid consistent with a left-sided parathyroid adenoma.

Figure 2 Ultrasound scan of the thyroid and parathyroid demonstrating findings in keeping with a left-sided parathyroid adenoma.

asymptomatic, her calcium levels remained normal and she did not require calcium supplementation. Owing to low levels of vitamin D, she received 1 week of dekristol followed by a maintenance dose of fultium-D3 (colecalciferol).

DISCUSSION

This case highlights an important learning point in the management of obstetric patients with medical comorbidities. The importance of managing medical conditions has been highlighted by the most recent 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries' across the UK (MBRRACE) report. While the maternal mortality rate has halved in the last 10 years, the number linked to underlying medical conditions has remained static.¹ The identification of any underlying medical conditions during the pre-conceptional period or early in gestation will enable the most effective management of both pregnancy and medical disorders. In our patient, a workup for the history of nephrolithiasis at booking may have identified hypercalcaemia and HPT early in pregnancy enabling effective management of both the condition and the pregnancy. Our patient was seen twice during pregnancy and twice prior to pregnancy due to nephrolithiasis. An endocrinology review at this point may have identified the parathyroid adenoma allowing for earlier management and the prevention of complications. Owing to the late and acute presentation of her condition, delaying delivery in order to manage the underlying hypercalcaemia was an unfavourable option despite the risk of worsening hypercalcaemia postdelivery. Furthermore, all patients presenting with renal calculi should be screened for HPT and ideally be reviewed by an endocrinologist. This is particularly important for women in the reproductive age group due to the potentially serious complications of underlying HPT for both the mother and the baby.

Around 150 cases of HPT during pregnancy have been reported in the literature, mostly of parathyroid adenomas with a few reports of parathyroid malignancy.²⁻³ Only one case similar to ours has been reported of hypercalcaemia presenting with neurological signs postpartum along with nephrolithiasis.⁴ A further case of hypercalcaemic crisis presenting with nausea, vomiting and mild cognitive dysfunction has been published.⁵

pHPT has an incidence of around 6–8/100 000 per year in women of childbearing age.⁶ During pregnancy, total calcium is decreased while corrected/ionised calcium remains unchanged. Levels of PTH are low to normal during the first trimester of pregnancy and returning to normal by term. Overall, calcium demand increases, peaking during the third trimester. This is

met by increased intestinal calcium absorption. Postpartum, transfer of calcium across the placenta from the mother to the fetus ceases creating potential for maternal hypercalcaemia.⁶⁻⁷

Nausea, vomiting and hyperemesis are frequently reported as the presenting symptoms of hypercalcaemia secondary to HPT, and thus many authors have advocated routine screening of calcium levels in these patients due to the non-specific presentation and potential for complications.⁸ Often, there may be difficulty in identifying pHPT in pregnancy as symptoms present in a similar manner to normal/other disorders of pregnancy also, including thirst, fatigue, headaches and hypertension.⁶

Maternal complications of HPT include nephrolithiasis, pancreatitis, osteopenia, cardiac arrhythmias, hypertension and peptic ulcers. Hypercalcaemic crisis may lead to uraemia, coma and death. Complications specific to pregnancy include pre-eclampsia, miscarriage and polyhydramnios.⁶

There are several published cases of neonatal hypocalcaemia as a result of maternal HPT including that of a neonate presenting with seizures 21 days postdelivery due to suppression of fetal parathyroid gland development.⁹⁻¹⁰ Fetal complications also include intrauterine growth restriction, low birth weight, preterm delivery and stillbirth. It is therefore critically important that infants born to hyperparathyroid mothers are closely monitored postdelivery.^{3-6,11-12}

The most common underlying aetiology is a solitary parathyroid adenoma but other causes such as parathyroid hyperplasia, multiple parathyroid adenomas and parathyroid malignancy must be excluded. Hereditary causes of hypercalcaemia must be excluded. These include multiple endocrine neoplasia, jaw-tumour syndrome, familial isolated HPT and familial hypocalcaemic hypercalcaemia.^{6,12-13}

The key biochemical finding is persistently elevated serum calcium with normal or elevated PTH in the presence of an increased urinary calcium/creatinine clearance ratio. Serum phosphate, magnesium and bicarbonate may be decreased and chloride and citrate may be raised. The chloride:phosphate ratio is usually elevated. Urinalysis may demonstrate hypercalciuria and elevated hydroxyproline levels.⁷

During pregnancy, exposure to radiation and nuclear material means that ultrasound scan is the safest method for parathyroid imaging. However, outside of pregnancy, sestamibi scintigraphy combined with sestamibi single photon emission CT (SPECT) is the preferred imaging method for preoperative localisation as it has the highest positive predictive value of all available imaging techniques.¹⁴⁻¹⁶ Sestamibi scanning may be complemented by ultrasound as an adjunct for localisation of a parathyroid adenoma; however, sensitivity is very much dependent on the sonographer.¹⁷⁻¹⁸ CT and positron emission tomography (PET) should be avoided during pregnancy due to the risk of radiation to the mother and fetus. MRI has little evidence base for diagnostic use.^{6,12-19}

Conservative management of pHPT in pregnancy includes hydration, low calcium intake, vitamin D supplementation and forced diuresis.^{6,12}

A couple of cases report on the medical management of hypercalcaemia during pregnancy and postpartum.⁸ Medical management with calcitonin risks tachyphylaxis. Bisphosphonates can cause fetal bone malformation and are limited to life-threatening hypercalcaemia. Cinaclet has been used only in two pregnant women with good results in the current literature.²⁰⁻²¹

Parathyroidectomy is the only cure, as per the National Institute of Health criteria for Parathyroidectomy.¹¹⁻²² Most case reports recommended surgical excision of parathyroid adenoma regardless of gestation to avoid the complications of pHPT. Cases are published on parathyroidectomy in all three

trimesters of pregnancy.^{3 23–26} Concurrent parathyroidectomy and CS has been reported with successful maternal and fetal outcomes after presentation of pHPT, hypercalcaemia and evidence of HELLP syndrome.²⁷

Learning points

- ▶ The effect of physiological changes of pregnancy must be considered on all medical conditions.
- ▶ We would like to raise awareness about the importance of preconception care, in particular for workup of primary hyperparathyroidism (HPT) whereby definitive management, including that of parathyroidectomy in cases of an underlying parathyroid adenoma, should be undertaken prior to pregnancy in view of the implications for mother and baby during pregnancy and immediately postdelivery.
- ▶ Every physician involved in the management of pregnancy and HPT should be aware of the potential neonatal hypocalcaemia in the newborn due to parathyroid hormone suppression that may put the newborn at risk of symptoms and potential cardiac arrhythmias requiring neonatologist/cardiologist input.
- ▶ Diagnosis of hypercalcaemia and HPT may prove challenging in pregnancy due to overlap with symptoms attributable to a normal pregnancy and other disorders of pregnancy.
- ▶ Every patient presenting with renal stones should be investigated for HPT and be reviewed by an endocrinologist.

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