CASE REPORT

Two cases of primary hyperparathyroidism in pregnancy

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Paul Hession, hession200@
gmail.com**SUMMARY**

Two women suffering from primary hyperparathyroidism in pregnancy are presented. Patient 1 with a history of four miscarriages, an ectopic pregnancy and a sixth pregnancy complicated by severe early onset preeclampsia. She was found to have high serum Ca^{2+} levels after delivery and parathyroid adenoma was diagnosed by ultrasound. A right inferior parathyroidectomy was performed. Patient 2 with a history of high serum Ca^{2+} and generalised symptoms of hypercalcaemia. Ultrasound did not reveal adenoma but an elective neck exploration was performed in light of the abnormal blood results. The right inferior parathyroid gland was excised and histology confirmed the presence of adenoma. These cases help highlight the different ways in which primary hyperparathyroidism can present and the barriers to diagnosis in pregnancy. Various potential complications (including miscarriage and preeclampsia) are explored and the appropriateness of surgical treatment during pregnancy is emphasised.

BACKGROUND

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder. It affects approximately 0.3% of the general population.¹ It is much less common in women of childbearing age, with the reported incidence of approximately 8/100 000.² It is argued, however, that this is not an accurate representation of the true number of cases.³ Approximately 80% cases of PHPT are caused by single adenomas, as was present in both of these cases. The majority of other cases are primary hyperplasia of all glands (15%) or double adenoma (3%), with carcinoma being a very rare cause.^{1,4}

The parathyroid glands regulate calcium homeostasis. Put simply, they respond to reduced serum calcium levels by producing parathyroid hormone (PTH). This stimulates increased renal tubular reabsorption and intestinal absorption of calcium, 1,25-dihydroxyvitamin D production and the release of bony calcium stores.⁵ In normal pregnancy, there is an overall slight drop in total serum calcium levels. Furthermore, intact PTH (iPTH) levels are in the 'low-normal' range in early pregnancy. This physiological reduction in the normal levels can obscure the presence of PHPT in pregnancy, with the degree of increase in iPTH perhaps being underestimated.

The authors hope that the presented cases will go some way towards highlighting the difficulties experienced with regard to diagnosis of PHPT in pregnancy. An increased awareness of PHPT will

benefit health professionals, with earlier diagnosis and treatment potentially leading to better outcomes for the mother and child.

CASE PRESENTATION**Case 1**

Patient 1 is a 33-year-old woman, para 1+5. She had a history of four first trimester spontaneous miscarriages and one ectopic pregnancy. During her most recent pregnancy, she developed renal calculi during week 17 for which she was admitted to hospital. This resolved during week 21. She also had a history of renal stones. The patient subsequently developed severe early onset preeclampsia and was again admitted during week 28. Despite treatment with labetalol and nifedipine, her hypertension and proteinuria remained high. Fetal well-being was monitored regularly and intermittent absent end diastolic flow was noted on umbilical artery Doppler assessment for two separate days. As a result, a decision was made to perform an emergency lower segment caesarean section at 30⁺6 weeks of gestation. The newborn was transferred to the neonatal intensive care unit (NICU). He suffered from Respiratory Distress Syndrome (RDS) of the Newborn and developed neonatal jaundice, but made a full recovery and was discharged after a number of weeks. Following delivery, it was noticed that the patient had high adjusted serum calcium levels, and that they dated back at least 2 years (figure 1).

A 24 h urine Ca^{2+} collection was performed and reported at 2.04 mmol/day (normal=2.5–7.5). This was suggestive of familial hypocalciuric hypercalcaemia. However, a subsequent collection was shown to be 6.01 mmol/day. The first result was, perhaps, an anomaly. iPTH was found to be 111.4 ng/L (normal=15–65). Parathyroid ultrasound was performed, which was highly suggestive of parathyroid adenoma.

Case 2

Patient 2 is a 29-year-old African woman, para 1 +0, who is currently pregnant. During her first pregnancy, 4 years ago, she reported of headache and vomiting, and was found to have an incidental adjusted serum calcium level of 2.91 mmol/L. PHPT was suspected. Three years later, the patient presented to endocrinology clinic with high Ca^{2+} and iPTH, as well as bone pains, irritability and lethargy. She had also recently suffered from renal calculi. During her current pregnancy, at 9⁺0 weeks of gestation, she attended the endocrinology clinic

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Figure 1 Summary of adjusted serum calcium for patient 1. The results are from 2 years predelivery, between 1 week predelivery and 10 days postdelivery (preparathyroidectomy) and postparathyroidectomy. Normal range is given for reference (2.17–2.51 mmol/L).

reporting migraines, irritability and constipation. Her serum calcium and iPTH remained high.

By 19⁺6 weeks, the patient's Ca^{2+} level was still high and an ultrasound of the parathyroid glands was performed. This was reported normal, with no obvious adenomas. However, the patient was still symptomatic, most recently with 5 days of worsening xiphisternal pain. A 24 h urine Ca^{2+} collection showed high Ca^{2+} excretion at 15.15 mmol/day. Despite the normal scan result, a decision was made to perform an elective neck exploration in light of the consistently abnormal test results. A summary of these results is provided in figure 2. Just prior to this neck exploration, the patient presented to the emergency department reported a severe abdominal pain with vomiting.

TREATMENT

Case 1

A right inferior parathyroidectomy was performed. Histology from tissues removed confirmed the parathyroid adenoma, and the diagnosis of PHPT. The recovery in the patient's serum calcium levels to normal postoperatively is shown in figure 1.

Figure 2 Summary of adjusted serum calcium for patient 2 in the preparathyroidectomy and postparathyroidectomy phases. Normal range is given for reference (2.17–2.51 mmol/L).

Case 2

At neck exploration, the right inferior parathyroid gland was found to be enlarged, and was excised. The recovery of the adjusted serum Ca^{2+} and the iPTH postoperatively are shown in figures 2 and 3. The surgery was a success, with levels returning to the normal range very soon afterwards. The histology of tissue removed confirmed the diagnosis of PHPT due to adenoma of the parathyroid gland.

OUTCOME AND FOLLOW-UP

Patient 2 subsequently gave birth to a male child at term, with no complications.

DISCUSSION

Diagnosis

These cases demonstrate very clearly how the symptoms of PHPT can be difficult to appreciate. Patient 1 had no overt symptoms of hypercalcaemia despite a mean adjusted serum calcium level of 2.97 mmol/L, taken from 17 separate tests. However, the history of renal calculi, during the last pregnancy and in her medical history, is noteworthy. Seventy to eighty per cent of patients with hypercalcaemia are similarly asymptomatic, and only diagnosed incidentally.⁵ This presents a diagnostic challenge, especially as there are few clinical indications for checking serum calcium levels in pregnancy.⁶ When symptoms are present they are quite often non-specific, and could be confused with normal pregnancy. These include gastrointestinal (GI) symptoms such as abdominal pain, nausea and vomiting; fatigue; lethargy^{7 8} and neuropsychiatric symptoms, such as headaches, depression, confusion and irritability.⁵ More overt symptoms also present, including osteoporosis with related bone pain and fracture and, more commonly, symptoms of nephrolithiasis, which were present in the medical history of women. Patient 2 is interesting in that she had experienced many of the above signs and symptoms at some point, including renal calculi, bone pains, GI symptoms, headaches, irritability and fatigue. However, many of these symptoms occurred during pregnancy, and could have been attributed to this instead of her hypercalcaemia. If her hypercalcaemia had not been picked up incidentally in 2008, then it may have been more of a challenge detecting her parathyroid adenoma.

Diagnosis, as was shown in these cases, is by demonstrating high adjusted serum calcium, often in the presence of elevated iPTH levels. However, it is critical to realise that patients with PHPT may have normal iPTH. This is inappropriate if

Figure 3 Summary of intact parathyroid hormone levels for patient 2. Preoperative and postoperative samples were taken on the day of surgery. Normal range is given for reference (15–65 ng/L).

hypercalcaemia is present, and is also a diagnostic indicator.⁹ Imaging is also recommended preoperatively or for confirmation, with the gold standard being technetium-99m sestamibi and ultrasound. These have a combined sensitivity of 94.5%.¹⁰ Of course, in pregnancy, technetium-99m sestamibi is contraindicated, and ultrasound alone will suffice.⁹ This has a reported sensitivity between 57% and 69%.^{11 12} Therefore, in both cases, a high-resolution ultrasound was performed. This showed varying results. The parathyroid ultrasound of patient 1 demonstrated a hypoechoic nodule posterior to the inferior part of the right lobe of the thyroid gland, highly suggestive of parathyroid adenoma. This, combined with the very high levels of Ca^{2+} and iPTH, meant that parathyroidectomy was justified. The ultrasound for patient 2 did not show any irregularity. However, after no resolution in the patient's serum calcium levels despite strict oral hydration for further 6 days, a decision was made to proceed with the neck exploration. This was acceptable as the patient's hypercalcaemia and high iPTH were long-running. She also displayed various symptoms that may have been due to hypercalcaemia and, perhaps most importantly, there were established risks to the mother and fetus (which will be dealt with below). Overall, the negative ultrasound for patient 2 (despite the subsequent discovery of adenoma at neck exploration) helps support the theory of reduced sensitivity for this form of investigation, when used without added nuclear medicine imaging. This is a further potential barrier to diagnosis.

Multiple miscarriage

Recent research would support the hypothesis that patient 1 had an increased chance of miscarriage due to her parathyroid adenoma. It is reported that 48% of patients with untreated PHPT suffer fetal loss. The majority of these miscarriages occurred in the late first or early second trimesters.¹³ This was strongly related to average serum calcium levels, and is summarised in figure 4. As noted, patient 1 had an average adjusted serum calcium level of 2.97 mmol/L. This would place her at a risk of approximately 70% for miscarriage according to figure 4. Therefore, one could postulate that her surgical treatment may reduce her chances of miscarriage in future pregnancies. However, caution is advised as there may be other aetiological factors not known in her case. It should be noted that patient 2 had an average serum calcium of 2.86 mmol/L, also putting her at an increased miscarriage risk (>36%). However, she reported no history of miscarriage.

Figure 4 Summary of rate of pregnancy loss in patients with hyperparathyroidism and its relationship to average serum calcium. Patients undergoing surgical parathyroidectomy during pregnancy were excluded.¹³

Other complications

Similar to miscarriage and the general symptoms of hypercalcaemia aforementioned, pregnancy has the potential to contribute extra risks to fetus and the mother, in the antenatal and post-natal periods. Maternal complications have been reported in up to 67% of cases.³ As mentioned previously, nephrolithiasis can be one of the more common difficulties encountered. Again, it is worth reiterating that this was present in the medical history of both patients. For patient 1, it had occurred for the third time in the second trimester of her recent pregnancy. Unfortunately, this did not lead to a query of hypercalcaemia secondary to PHPT at that time. Hyperemesis gravidarum is also seen more often with hyperparathyroidism.^{8 14}

An interesting finding is the association of hyperparathyroidism with preeclampsia. A recent study supports this statistically significant increased risk, with women who had a previous diagnosis of parathyroid adenoma being up to six times more likely to develop preeclampsia.¹⁵ A suggested mechanism by which this occurs is that increased PTH leads to increased intracellular calcium which results in amplified smooth muscle contractility.¹⁶ Because preeclampsia is relatively common, potentially life-threatening and has a relatively unknown aetiology, these studies may be clinically relevant.¹⁵ Support for this could well be seen in the case of patient 1. She developed severe early onset preeclampsia, eventually leading to her emergency lower segment caesarian section (LSCS). The issue for patient 1 is that, despite a successful parathyroidectomy resulting in normal serum iPTH and calcium, she may continue to carry this increased risk of preeclampsia into subsequent pregnancies. It has been shown in studies that the relationship between preeclampsia and parathyroid adenoma treated more than 5 years before delivery is still statistically significant.¹⁵ Thus, patient 1 may still suffer from the same increased risk of preeclampsia that she had for her most recent pregnancy. Indeed, previous preeclampsia is one of the major independent risk factors for subsequent preeclampsia.¹⁷ Rates of preeclampsia in previously preeclamptic women are reported to be as high as 17.9% for moderate and 5.3% for severe preeclampsia.¹⁸ Therefore, all things considered, it is important that a high index of clinical suspicion for preeclampsia be entertained with patient 1 in subsequent pregnancies. Regardless, she will be seen as a person of high-risk pregnancy, due to her history of recurrent miscarriages.

Acute pancreatitis is reported to be a serious but rare presentation of PHPT in pregnancy.^{19–21} However, recent population-based studies have refuted this association.²²

Complications at delivery

One of the times where the mother and baby appear to be most vulnerable to complications is after delivery. While in utero, the fetus is exposed to maternal hypercalcaemia. This may reduce fetal parathyroid function or, in severe cases, lead to permanent hypoparathyroidism because of impaired parathyroid gland development. On delivery, the neonate cannot mobilise Ca^{2+} due to reduced PTH levels. The result is hypocalcaemia, which can cause tetany.²³ This most frequently occurs between days 2 and 14 postdelivery.¹⁴ Sometimes these neonatal seizures can be the first indication of a parathyroid adenoma in an otherwise asymptomatic mother.²⁴ These infants will require intravenous calcium supplementation during the first few days of life.¹³

A related complication, known as a hypercalcaemic crisis, occurs in the mother when adjusted serum calcium reaches dangerously high levels (3.5 mmol/L or above). The patient may present with anorexia, vomiting, dehydration, weakness, mental

state changes and a rapid progression to uraemia, coma and death.²⁵ This complication can occur at any time in the pregnancy, but is particularly likely postpartum. This is because the placenta is no longer shunting calcium to the fetus, leading to a potentially rapid rise in maternal serum calcium levels.³

Patient 1, patient 2 and their newborns were at risk for these complications. However, patient 1 did not exhibit any sharp increase in serum calcium post-LSCS (see figure 1) and patient 2 did not present with symptoms of hypercalcaemia after her previous delivery (no serum calcium level is available). The premature infant born to patient 1 had been getting regular blood tests, including adjusted serum calcium, prior to the discovery of his mother's parathyroid adenoma, as he was a patient in the NICU. This continued for the length of his admission. His calcium levels remained in the normal range throughout, and his iPTH was found to be normal prior to discharge. Both infants born to patient 2 did not display any signs of neonatal tetany.

Surgery during pregnancy

Because of the significant maternal, fetal and neonatal risks outlined, and the improved safety of general anaesthetic during pregnancy, surgical management is increasingly recommended.³ It is thought that the risks are outweighed by the benefits to reduce maternal serum calcium back to normal range. The preference for surgery over medical management (with oral phosphates, calcitonin, calcium wasting diuretics, etc) has been well established.¹⁴ It is supported by research indicating that neonatal complication rates are 37% after medical treatment and only 10% after surgical intervention.²⁶ This information supported the decision to undertake parathyroidectomy in both patients, and both surgical interventions were wholly justified according to the research.

As organogenesis is completed in the first trimester and there are associated risks of preterm labour with third trimester surgery, it has been recommended to undertake surgery in the second trimester.²⁷ This was the case for patient 2. Recent literature has supported early intervention, preferably as early in the second trimester as possible.¹³ This is due to the very high miscarriage rates aforementioned. While many of these occurred in the first trimester, fetal loss in the second trimester (30%) was still six times higher than expected.¹³ A further study would indicate that third trimester parathyroidectomy is much safer than previously suspected, with fetal complications as low as 5.9%.²⁸ Therefore, a widening of the recommended window for surgery has become apparent. Truong *et al*¹⁴ have recommended a treatment algorithm. They suggest surgery in the second trimester if the patient has an average serum calcium greater than 2.75 mmol/L or they are symptomatic. If the diagnosis is made in the third trimester, maternal and fetal factors should be weighed against possible risks of surgery (though these risks may be exaggerated).

PHPT was suspected in patient 2 during her first pregnancy in 2008. It may have been more appropriate to carry out a parathyroidectomy after delivery (regardless of symptoms) if it was known that she wished to have further children, as this is recommended in the most recent studies as the ideal scenario.¹³ Once she fell pregnant for a second time, ideally definitive diagnosis would have been established as soon as possible, with surgery planned for early in the second trimester to reduce the risk of miscarriage and other complications. However, her case was compounded by the normal result on ultrasound, ultimately delaying her surgery. Patient 1 did not receive her diagnosis until after delivery. However, if her adenoma *had* been discovered in the early third trimester then perhaps surgery would have been recommended. This is due to her very high calcium

levels and preeclampsia. A published case exists which almost mimics her exactly (early onset preeclampsia, emergency LSCS at 32 weeks, etc.) in which neonatal death occurred.²⁷ This is a dramatic reminder of the risk that her severe hypercalcaemia presented to her and her newborn.

Learning points

Both cases have helped demonstrate the following features of hyperparathyroidism occurring in pregnancy:

- Diagnosis can be difficult due to:
 - An under appreciation of the true number of affected women of childbearing age;
 - The large numbers of asymptomatic individuals;
 - The physiological reduction in intact parathyroid hormone and serum calcium in normal pregnancy;
 - The failure to follow-up on consistently high serum calcium results;
 - The similarity between some of the symptoms of hypercalcaemia and those of normal pregnancy;
 - The insensitivity of parathyroid ultrasound for adenomas.
- Severe complications can occur, and include increased miscarriage, preeclampsia, nephrolithiasis, bone disease and fractures, hyperemesis gravidarum, maternal hypercalcaemic crises and severe hypocalcaemia in the newborn.
- Surgical treatment is recommended preferably before a woman gets pregnant. Within pregnancy, it should be performed as early in the second trimester as possible, but is safe even into the third trimester where the benefits of parathyroidectomy are deemed to outweigh the risks of maternal hypercalcaemia.
- One is hopeful that patient 1 may be less likely to have miscarriages or complicated pregnancies in the future, and patient 2's current pregnancy was rendered safer due to the successful surgical intervention.

Contributors PH assimilated the information on both patients and wrote the draft case report while on obstetrics and gynaecology placement in medical school. The patients are under the care of GG and she contributed to the editing of the draft report with the help of JW, before it was submitted for publication.

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