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Management of severe and symptomatic primary hyperparathyroidism in the first trimester of unplanned pregnancy

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Summary

Primary hyperparathyroidism (PHP) is the most common aetiology for hypercalcaemia. The incidence of PHP in pregnant women is reported to be 8/100 000 population/year. It presents a threat to the health of both mother (hyperemesis, nephrolithiasis) and fetus (fetal death, congenital malformations, and neonatal severe hypocalcaemia-induced tetany). However, there is a lack of clear guidance on the management of primary hyperparathyroidism in pregnancy. In this study, we describe the case of a 26-year-old female patient who presented with severe hypercalcaemia secondary to PHP and underwent successful parathyroid adenectomy under local anaesthesia.

Learning points:

- Primary hyperparathyroidism is a rare complication in pregnancy, but the consequences for mother and fetus can be severe.
- A perceived risk of general anaesthesia to the fetus in the first trimester has resulted in a general consensus to delay parathyroid surgery to the second trimester when possible – although the increased risk of fetal loss may occur before planned surgery.
- If the patient presents with severe or symptomatic hypercalcaemia, minimally invasive surgery under local anaesthetic should be considered regardless of the gestational age of the pregnancy.

Background

Primary hyperparathyroidism (PHP) is the most common aetiology for hypercalcaemia. The incidence of PHP in pregnant women is reported to be 8/100 000 population/year (1). It presents a threat to the health of both mother (hyperemesis, nephrolithiasis) and fetus (fetal death, congenital malformations, and neonatal severe hypocalcaemia-induced tetany) (2). However, there is a lack of clear guidance on the management of primary hyperparathyroidism in pregnancy.

Case presentation

A 26-year-old female presented to the endocrinology clinic with hypercalcaemia (corrected calcium: 2.82 mmol/L), serum raised parathyroid hormone (PTH) (13.7 pmol/L), and normal serum vitamin D (53 nmol/L) (Table 1).

Investigation

Familial hypercalcaemic hypocalciuria was excluded with a normal calcium excretion study and a presumed diagnosis of primary hyperparathyroidism was made. An ultrasound scan did not detect a parathyroid adenoma. Upper body planar views were acquired with single-photon emission computed tomography (SPECT-CT) through the neck and upper thorax after administration of Tc-99m sestamibi which suggested the presence of a right-sided parathyroid adenoma to the right of the oesophagus posterior to the right lobe of the thyroid (Fig. 1). In view of the patient's young age, she was referred to the surgical team for

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parathyroid resection. Normal urine metanephrine sampling excluded a co-existing phaeochromocytoma.

Due to the COVID 19 pandemic, surgery was delayed and the patient represented to the endocrine department as she was 8 weeks pregnant, suffering from hyperemesis and severe dehydration. Blood tests revealed severe hypercalcaemia (3.48 mmol/L). An early pregnancy scan showed a viable *in utero* pregnancy. Despite aggressive i.v. rehydration for 13 days, her corrected calcium remained consistently above 3 mmol/L. Consequently, the patient could not be discharged from the hospital and it was felt that the risk of ongoing severe and symptomatic hypercalcaemia to mother and fetus (pancreatitis, renal stones, dehydration, cardiac arrhythmia, torsade de pointe, cardiac arrest, and risk of miscarriage (1, 2)) was outweighing the risks of attempting parathyroidectomy under local anaesthesia in the first trimester (3). Some data suggest a three- to five-fold increased risk of fetal loss associated with maternal primary hyperparathyroidism, largely in the second trimester of pregnancy and mostly when maternal calcium is above 2.85 mmol/L (4).

Treatment

While there is no clear international consensus on the management of primary hyperparathyroidism in pregnancy, historical consensus largely favours operating in the second trimester for patients where the calcium persists above 2.75 mmol/L (5, 6, 7). However, this approach is not evidence-based, and many of the complications and risks of severe hypercalcaemia may occur in the first trimester such as hyperemesis gravidarum, renal calculi, pancreatitis, and hypercalcaemic crisis (2, 8).

The consensus to delay surgery until the second trimester appears largely due to historical perceived risks of general anaesthesia in the first trimester (5). There have been concerns that exposure to general anaesthesia during organogenesis in the first trimester could result in increased rates of congenital malformation or fetal loss (6). However, a review on first-trimester anaesthesia exposure and fetal outcome published in 2007 suggests that the risks of surgery to the fetus during the first-trimester surgery are largely related to a combination of surgical manipulation of the pelvis and compromised uterine blood flow during surgery in addition to the sequelae of the condition that requires surgery rather than the exposure to anaesthetic agents. There is no evidence to suggest an increase in congenital anomalies at birth in women who underwent anaesthesia during pregnancy (9, 10).

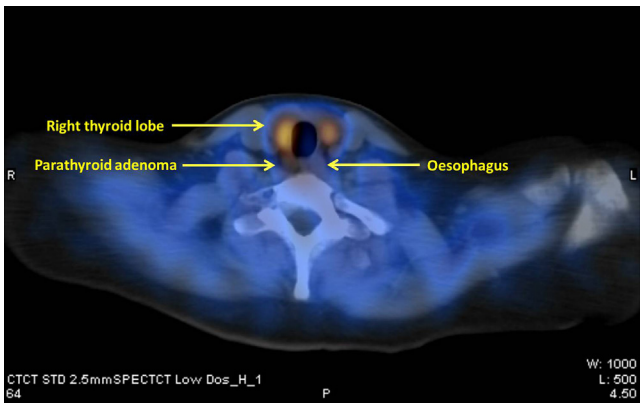

Figure 1
SPECT image indicating probable location of parathyroid adenoma.

Due to the severity of maternal hypercalcaemia and associated neonatal risks (increased rate of fetal loss), a decision was made to perform a parathyroidectomy at 10 weeks of gestation. To avoid the perceived risk of general anaesthesia, the parathyroidectomy was performed under local anaesthesia.

The patient was lightly sedated and an appropriate skin crease was marked for incision. Bilateral superficial cervical plexus block and local field block at the incision site were performed with 10 mL of 0.5% bupivacaine and 10 mL of 1% lignocaine with 1:200 000 adrenaline. Surgery involved the use of Focus Harmonic Scalpel™ (Ethicon Endo-Surgery Inc. Cincinnatti, Ohio, USA). The skin was incised and subplatysmal flaps were raised. Strap muscles were divided in the midline, and the right thyroid lobe was mobilised to identify a right parathyroid adenoma deep to thyroid in the paraoesophageal region and deep to the recurrent laryngeal nerve which was protected throughout. In response to minor discomfort during the procedure, 5 mL of 0.5% bupivacaine with 10 mL of 1% lignocaine with 1:200 000 adrenaline was used. Haemostasis was confirmed and a drain was not used. Closure involved the use of 3/0 vicryl to the strap muscles and platysma, and 4/0 monocryl was used for subcuticular closure. Opsite spray dressing was applied. The patient tolerated the procedure very well and was pleased to have avoided general anaesthesia. No intra-operative PTH measurement was undertaken as this was not part of the routine practice of the centre and not recommended by NICE guidance for first-time parathyroid surgery due to increased expenditure, operating time, and risk to patients otherwise suitable for minimally invasive parathyroidectomy (11, 12).

Post-operative (24 h) PTH was undetectable (<0.3 pmol/L), corrected calcium was normalised (2.43 mmol/L), and the patient's symptoms of hypercalcaemia resolved.

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Table 1 Patient's data at baseline.

Parameters	Values
Age, years	26
Corrected calcium, mmol/L	2.82
PTH, pmol/L	13.7
Vitamin D, nmol/L	53
24 h urine collection for metanephrines and normetanephrines	Normal
Sestamibi/SPECT-CT scan	Right-sided parathyroid adenoma
Parathyroid ultrasound scan	No adenoma detected

Outcome and follow-up

A 12- and 20-week scan showed no fetal abnormality and the calcium levels remained in the normal range into the third trimester and post-delivery. The patient recovered well postoperatively with minimal analgesic requirement and no complications of surgery. The remainder of the pregnancy was unremarkable until 34 weeks when reduced fetal movements and an abnormal cardiotocograph tracing resulted in delivery at 34 weeks and 3 days. The baby weighed 2.01 kg and did not suffer from neonatal hypocalcaemia (a recognised complication of maternal primary hyperparathyroidism (neonatal calcium was 2.61 mmol/L)).

Discussion

Primary hyperparathyroidism may be under-recognised in pregnancy. The diagnosis of primary hyperparathyroidism during pregnancy may be delayed due to the cumulative effects of pregnancy-related haemodilution, hypalbuminaemia, increased transplacental calcium transport, relative hypercalciuria caused by increased glomerular filtration, inhibition of PTH-mediated bone resorption, and calcium-lowering effects of oestrogen (13). Maternal complication rates related to PHP during pregnancy have been reported to be as high as 67%, and fetal complications are reported to occur in up to 80% of cases (7, 14). Early management of PHP in pregnancy is purported to reduce fetal, neonatal, and maternal morbidity and mortality.

Initial management of PHP in pregnancy prioritises medical and supportive treatment with i.v. fluids. There are insufficient safety data to recommend bisphosphonates or calcium mimetics during pregnancy. Consensus guidance (15, 16, 17) suggests that if the maternal calcium can be maintained below 2.75 mmol/L (>0.25 mmol/L of upper limit of normal), conservative management should be maintained, but above these levels of maternal calcium, parathyroid surgery should be considered in the second trimester.

While historical dogma suggests that parathyroid surgery should be delayed until the second trimester, due to the perceived risk of general anaesthesia during the first trimester, there are little data to support this. Furthermore, delaying parathyroidectomy to the second trimester in patients with severe refractory hypercalcaemia above 3 mmol/L may increase the risk of miscarriage that appears to be three to five times increased if left untreated (4).

Parathyroidectomies can be performed under regional or local anaesthesia, particularly if an adenoma is clearly identified by prior imaging. As there are no reported concerns regarding local anaesthesia in the first trimester of pregnancy, performing parathyroidectomy by this method should be considered early in the pregnancy to negate some of the later pregnancy complications including miscarriage. In patients where surgery cannot be considered, focal ablative therapy done with ultrasound-guided percutaneous radiofrequency ablation has been reported in a patient in her second trimester of pregnancy (18, 19). However, careful consideration would be required for either of the aforementioned surgical approaches in patients where radiology had not identified a 'target' parathyroid gland and bilateral neck exploration might be required.

Our case highlights the importance of timely recognition and effective management of PHP in pregnancy challenging the historical consensus of management and providing a potential pathway to reduce the severe fetal complications reported with this condition.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

Adele Beck and Duncan Browne summarised the case report and wrote the paper. Venkat Reddy discussed surgical approach under local anaesthesia. Tom Sulkin described the ultrasound scan and SPECT-CT + Sestamibi Tc99m results. All authors were involved in reviewing the final manuscript and replying to the decision letter.

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