Chapter 15
Primary Hyperparathyroidism in Pregnancy

Haleigh James, Geoffrey B. Thompson, and Robert A. Wermers

Case Presentation

A 23-year-old pregnant woman was referred for management of primary hyperparathyroidism (PHPT) in the setting of multiple endocrine neoplasia type 1 (MEN1). Shortly after becoming pregnant, the patient's calcium was found to be 11.4 mg/dL. At the time of presentation, she was at 23-week gestation with the following laboratories: serum calcium, 10.2 mg/dL (nl, 8.9–10.1); phosphorus, 2.9 mg/dL (nl, 2.5–4.5); normal creatinine; and PTH, 45 pg/mL (nl, 15–65).

Her father and one of her three sisters also had MEN1, manifested by pancreatic neuroendocrine tumors, PHPT, and a pituitary tumor in her sister. She had been diagnosed with MEN1 by genetic testing (exon 10 Arg 527 stop) 6 years prior to pregnancy

H. James, MD • R.A. Wermers, MD (✉)
Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo College of Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: James.Haleigh@mayo.edu; wermers.robert@mayo.edu

G.B. Thompson, MD
Department of Surgery, Mayo College of Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: thompson.geoffrey@mayo.edu

A.E. Kearns, R.A. Wermers (eds.), *Hyperparathyroidism: A Clinical Casebook*, DOI 10.1007/978-3-319-25880-5_15,

and was found to have associated PHPT. At that time, her serum total calcium was 10.5 mg/dL (nl, 9.1–10.3), phosphorus was 3.1 mg/dL (nl, 2.5–4.5), parathyroid hormone (PTH) level was 40 pg/mL, and creatinine was 0.7 mg/dL. Nuclear parathyroid scan showed mild focal increased uptake at the lower pole of the left thyroid lobe and posterior to the right thyroid lobe, consistent with small parathyroid adenomas. She had normal bone mineral density and no history of nephrolithiasis and denied symptoms of hypercalcemia such as polydipsia, polyuria, nausea, anorexia, constipation, pain, and neuropsychiatric changes, so the decision was made to forego surgery and monitor her serum calcium every 6 months.

Other studies done at that time of her initial diagnosis of MEN1 included a magnetic resonance imaging (MRI) of the brain with and without contrast with inclusion of a sella protocol, which was normal. A computed tomography (CT) scan of her abdomen with biphasic imaging of the pancreas was also unremarkable. She had normal gastrin, chromogranin A, human pancreatic polypeptide (HPP), glucagon, insulin-like growth factor 1 (IGF1), and prolactin levels.

Assessment and Diagnosis

Neck ultrasound showed a $7 \times 3 \times 5$ mm hypoechoic oval nodule posterior to the right thyroid and a $4 \times 2 \times 3$ mm nodule inferior to the left thyroid lobe, suggestive of possible parathyroid adenomas. An obstetrical ultrasound was normal with an estimated gestational age of 20 weeks and 6 days. Maternal fetal medicine recommended fetal heart rate monitoring before and immediately after surgery. They also suggested she be positioned with left lateral tilt during surgery to avoid vena cava compression and possible compromise to uterine blood flow. Finally, they felt her risk of preterm labor was remote and hence, did not recommend delaying surgery for antenatal steroids for fetal lung maturity.

MEN1 is an autosomal dominant condition caused by mutations in the tumor suppressor gene *MEN1*, which classically predisposes affected patients to tumors involving the parathyroid glands, anterior pituitary, and pancreatic islet cells. Carcinoid, adrenal cortical tumors, facial angiofibromas, collagenomas, and lipomatous tumors can also develop in MEN1. PHPT due to parathyroid adenomas is the most common manifestation of MEN1, occurring in 90 % of patients [1]. Compared to patients with sporadic PHPT, patients with MEN1-associated hyperparathyroidism usually present at an earlier age (second to fourth decade vs. sixth decade), have an equal male-to-female ratio (1:1 vs. 1:3), and have lower bone mineral density [2]. Many of these patients are diagnosed after hypercalcemia is noted incidentally, but they may also present with vague symptoms of hypercalcemia (polydipsia, polyuria, malaise, constipation, neuropsychiatric changes) or with nephrolithiasis [1].

It is recommended that patients with MEN1 be screened for hyperparathyroidism yearly with serum calcium and PTH measurements. While preoperative imaging is often performed in patients with sporadic PHPT to determine if patients are candidates for minimally invasive surgery [3], it is of limited benefit in MEN1 patients because multiple glands are usually affected and bilateral neck exploration is required regardless of imaging results in patients who undergo surgery [1]. Nonetheless, some surgeons prefer preoperative localization to aid with surgical planning, even in MEN1 patients.

PHPT in pregnancy is associated with several risks to both the mother and fetus. Maternal complications include hyperemesis, nephrolithiasis, mental status changes, muscle weakness, and rarely pancreatitis. Neonatal hypoparathyroidism, hypocalcemia, and even tetany may result from fetal PTH suppression in the setting of maternal hypercalcemia because calcium is transported across the placenta to the fetus. Hence, in pregnancies complicated by PHPT, the neonate should have

monitoring of serum calcium, with awareness that hypoparathyroidism may not be present in the immediate postpartum period [4]. Also, formulas that are high in calcium and low in phosphate reduce the risk of hypocalcemia in these infants [5]. Low birth weight, preterm delivery, and miscarriage have also been associated with gestational PHPT, especially when hypercalcemia is pronounced [6, 7]. More recent data has shown that these complications are rare in the setting of mild maternal hypercalcemia (total serum calcium <11 mg/dL) [8].

The diagnosis of gestational PHPT is based on elevated serum calcium and PTH levels, just as in non-gestational PHPT. However, calcium is not routinely measured during pregnancy and gestational PHPT is often unrecognized [8]. Furthermore, several physiologic changes during pregnancy including hypoalbuminemia, increased glomerular filtration, transplacental transfer of calcium, and increased estrogen levels lower maternal serum calcium levels and may mask underlying PHPT [9]. PTH secretion is also suppressed during normal pregnancy due to increased intestinal calcium absorption and 1,25-dihydroxyvitamin D levels [10]. After biochemical confirmation, neck ultrasound is often utilized for preoperative localization in pregnant patients rather than nuclear or CT scans to eliminate risk to the fetus [7]. Thus, there would be no role for repeat nuclear parathyroid scan in this patient.

Management

The timing of parathyroid surgery in MEN1 patients with hyperparathyroidism is not well defined. Therefore, the indications for surgery (symptomatic or marked hypercalcemia, nephrolithiasis, osteoporosis, or renal insufficiency) used for patients with sporadic hyperparathyroidism [3] are often

applied to MEN1 patients. When surgery is elected, it should consist of open bilateral neck exploration with cervical thymectomy and subtotal parathyroidectomy (at least 3.5 glands removed) or total parathyroidectomy with autologous transplantation performed by an experienced endocrine surgeon (see Chap. 9) [1].

In this case, management was altered by the patient's pregnancy. While clear treatment guidelines for PHPT in pregnancy are lacking, surgery is often performed to prevent the maternal and fetal risks described above. If observation of PHPT during pregnancy is considered, then adequate hydration combined with measurement of serum calcium and regular biophysical profiles of the fetus with ultrasound are recommended, with consideration of parathyroidectomy postpartum [10]. If surgery is recommended, then parathyroidectomy during the second trimester is preferred because organogenesis is complete and the risk of anesthesia-induced preterm delivery is lower than in the third trimester [7, 11]. Surgery was opted for in this case rather than continued monitoring of calcium, given her earlier serum calcium during pregnancy of 11.4 mg/dL. The patient underwent cervical exploration and excision of three enlarged parathyroid glands with autotransplantation of the left inferior parathyroid gland to the left anterior chest wall as a precaution. A fourth parathyroid gland was not found. Intraoperative PTH decreased from 58.8 to 14.5 pg/mL. Most pregnancies complicated by sporadic PHPT are due to a single parathyroid adenoma (89 %), which is similar to what is seen in nongestational PHPT [12].

Outcome

Postoperative calcium normalized to 9.2 mg/dL. The patient had no complications from the surgery, and she continued with regular obstetric cares.

Clinical Pearls/Pitfalls

- Patients with MEN1 should have serum calcium and PTH measured yearly to screen for PHPT because its prevalence is 90 % in this population.
- PHPT during pregnancy is associated with several risks to the mother (hyperemesis, nephrolithiasis, mental status changes, muscle weakness, and rarely pancreatitis) and fetus (neonatal hypoparathyroidism, hypocalcemia, tetany, low birth weight, preterm delivery, and miscarriage), especially when maternal total serum calcium is >11 mg/dL.
- If parathyroidectomy is opted for in a patient with gestational hyperparathyroidism, it should be performed in the second trimester.
- In gestational PHPT, neonates should have monitoring of serum calcium with awareness that hypoparathyroidism may not be present in the immediate postpartum period.

Conflict of Interest All authors state that they have no conflicts of interest.

References

1. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011. Epub 2012/06/23.
2. Eller-Vainicher C, Chiodini I, Battista C, Viti R, Mascia ML, Massironi S, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. J Bone Miner Res: Off J Am Soc Bone Miner Res. 2009;24(8):1404–10. Epub 2009/03/25.

3. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9. Epub 2014/08/28.
4. Ip P. Neonatal convulsion revealing maternal hyperparathyroidism: an unusual case of late neonatal hypoparathyroidism. Arch Gynecol Obstet. 2003;268(3):227–9. Epub 2003/08/28.
5. Shangold MM, Dor N, Welt SI, Fleischman AR, Crenshaw Jr MC. Hyperparathyroidism and pregnancy: a review. Obstet Gynecol Surv. 1982;37(4):217–28. Epub 1982/04/01.
6. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. Clin Endocrinol (Oxf). 2009;71(1):104–9. Epub 2009/01/14.
7. Schnatz PF, Curry SL. Primary hyperparathyroidism in pregnancy: evidence-based management. Obstet Gynecol Surv. 2002;57(6):365–76. Epub 2002/07/26.
8. Hirsch D, Kopel V, Nadler V, Levy S, Toledano Y, Tsvetov G. Pregnancy outcomes in women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2015;100(5):2115–22. Epub 2015/03/10.
9. Som M, Stroup JS. Primary hyperparathyroidism and pregnancy. Proc (Baylor Univ Med Cent). 2011;24(3):220–3. Epub 2011/07/09.
10. Kovacs CS. Parathyroid function and disease during pregnancy, lactation, and fetal/neonatal development. In: Bilezikian JP, Marcus R, Levine M, Marcocci C, Potts J, Silverberg S, editors. The parathyroids. 3rd ed. San Diego: Academic Press/Elsevier; 2014. p. 877–902.
11. Truong MT, Lalakea ML, Robbins P, Friduss M. Primary hyperparathyroidism in pregnancy: a case series and review. Laryngoscope. 2008;118(11):1966–9. Epub 2008/09/02.
12. Kelly TR. Primary hyperparathyroidism during pregnancy. Surgery. 1991;110(6):1028–33; discussion 33–4. Epub 1991/12/01.