Primary hyperparathyroidism and pregnancy

Mousumi Som, DO, and Jeffrey S. Stroup, PharmD, BCPS

Primary hyperparathyroidism is the third most common endocrine disorder after diabetes and thyroid disease, and women are affected twice as often as men. Hyperparathyroidism in pregnancy was first reported in 1931. Maternal complications in patients with hyperparathyroidism can be as high as 67%. We present a case of a pregnant patient with chronic hypertension that was exacerbated throughout the course of her pregnancy with a concomitant diagnosis of primary hyperparathyroidism and its sequelae for both the mother and fetus.

Primary hyperparathyroidism (PHP) has a prevalence of 0.15%; however, when taking into account the undiscovered cases that are asymptomatic, some have estimated this rate to be as high as 1.4% (1). PHP is the third most common endocrine disorder after diabetes and thyroid disease, and women are affected twice as often as men (2, 3). Most patients suffering from PHP are older than 45 years, but 25% are diagnosed in their childbearing years.

Hunter and Turnbull documented the first case of hyperparathyroidism in pregnancy in 1931 (4, 5). It is theorized that the incidence of PHP in the pregnant patient is similar to that in the nonpregnant patient. PHP commonly goes unrecognized due to the physiological changes of pregnancy. Hypoalbuminemia, calcium transport across the placenta, and an increased glomerular filtration rate all contribute to the appearance of lower calcium levels in the pregnant patient. In addition, estrogen is thought to inhibit parathyroid hormone (PTH)–mediated bone resorption, causing a dose-related reduction in serum calcium in pregnancy (6). We present a case of a pregnant patient with chronic hypertension that was exacerbated throughout the course of her pregnancy with a concomitant diagnosis of PHP and its sequelae for both the mother and fetus.

CASE PRESENTATION

A 42-year-old Caucasian woman, gravida 3, para 0-2-0-0 at 29 weeks and 6 days, presented to labor and delivery after being seen in the obstetrics clinic for progressive hypertension and concern for preeclampsia. The patient was being followed by her obstetrician for chronic hypertension during her pregnancy, with elevated blood pressures occurring prior to 20 weeks of gestation. She denied any visual changes, headache, nausea, vomiting, vaginal bleeding, uterine contractions, loss of fluid, or right upper-quadrant pain. The patient was not on chronic bed rest at home.

Her past medical history was significant for asthma, migraines, anxiety, multiple miscarriages, diverticulitis, and hypercalcemia. Her past surgical history was significant for cholecystectomy, laparoscopic evaluation of endometriosis, colonoscopy, and dilatation and curettage. She denied tobacco use, illicit drug use, and alcohol use and was employed as a bus driver. Admission medications included methyldopa 500 mg twice daily, progesterone 200 mg at bedtime, prenatal vitamin daily, folic acid 0.8 mg daily, and butalbital/acetaminophen as needed for migraine headaches. Medication allergies included penicillin, levofloxacin, ibuprofen, and fluticasone/salmeterol.

Upon presentation to the hospital, her blood pressure was 160/87 mm Hg; heart rate, 64 beats per minute; respirations, 16 breaths per minute; and temperature, 98.3°F. Physical examination revealed 1 to 2+ pitting edema in the bilateral lower extremities and was otherwise without pertinent positive or negative findings. Admission laboratory tests revealed several abnormal findings: a serum potassium of 2.7 mEq/L (reference range, 3.5–5.0), magnesium 1.4 mg/dL (reference range, 1.6–2.1), albumin 3.3 g/dL (reference range, 3.5–5.0), adjusted calcium 11.2 mg/dL (reference range, 8.5–10.5), uric acid 6.1 mg/dL (reference range, 2.6–6.0), and hemoglobin 10.1 g/dL (reference range, 11.1–15.5). The 24-hour urine collection showed 408 mg of protein.

The patient continued to be hypertensive during her hospitalization and subsequently internal medicine was consulted. Initial review of her medications identified that the patient had been transitioned to nifedipine from methyldopa. Recommendations by internal medicine included the reinstitution of methyldopa, initiation of furosemide, addition of hydralazine for as-needed coverage of systolic blood pressures >160 mm Hg, and additional laboratory analysis that included PTH

From the Department of Medicine, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma.

Corresponding author: Jeffrey S. Stroup, PharmD, BCPS, Associate Professor of Medicine, Oklahoma State University Center for Health Sciences, 635 West 11th Street, Tulsa, Oklahoma 74127 (e-mail: Jeffrey.Stroup@okstate.edu).

level, phosphorus level, thyroid function tests, renin level, and aldosterone level. In addition, given her abnormal magnesium level, the patient received 2 g of magnesium intravenously.

Abnormal laboratory values from the additional testing showed an elevated PTH level of 146 pg/mL (reference range, 11–54 pg/mL) and phosphorus level of 2.4 mg/dL (reference range, 2.5–4.9 mg/dL). Review of her medical records identified an elevated PTH level of 242 pg/mL 6 months prior to the current hospitalization that was not given in the history.

It was felt that performing a nuclear medicine sestamibi scan during her pregnancy may have higher risk to the fetus than benefit. Given the fetus's gestational age, it was decided to treat her hyperparathyroidism conservatively. The patient continued to have elevated blood pressures despite continued titration of her antihypertensive medications. A discussion was held between the obstetrician and maternal fetal medicine specialist with a decision to deliver the baby at 32 weeks secondary to uncontrolled hypertension requiring polypharmacy. Of note, the patient also continued to have elevated calcium levels regardless of adequate hydration and administration of furosemide. Her serum calcium level on the day of delivery was 11.8 mg/dL. Approximately 36 hours subsequent to caesarean delivery, the neonate suffered from cardiopulmonary arrest and died. The patient received her nuclear medicine sestamibi scan prior to discharge, which showed a left parathyroid adenoma. Subsequent to delivery, her adjusted calcium levels continued to be elevated and reached a level as high as 12.8 mg/dL. She received one dose of pamidronate prior to discharge and was scheduled as an outpatient for adenoma removal. Histopathology from that surgery confirmed a large parathyroid adenoma.

DISCUSSION

Pathogenesis

Parathyroid glands secrete an 84-amino-acid single-chain polypeptide called PTH. The main function of PTH is to maintain calcium via the parathyroid calcium-negative feedback mechanism (1). Therefore, elevated calcium levels will inhibit further PTH release, and a decreased calcium level will trigger an almost instantaneous release of PTH. In addition to PTH, calcitonin also has a role in calcium homeostasis. Calcitonin receptors are structurally similar to PTH receptors, allowing them to have an antagonistic effect on PTH (1).

Fetal blood, as measured by cordocentesis, has a 0.5 to 1 mEq/L higher concentration of calcium. Elevated concentrations are required secondary to an increased demand by the fetus for adequate bone mineralization. Increased demand is met through active transport by the placenta via a maternal fetal gradient of 1:1.4 (7, 8). Elevated levels ultimately result in fetal PTH suppression. Maternal PHP results in an even further suppression of fetal PTH, which accounts for the hypocalcemic effects on the fetus at birth (7).

Etiologies for hyperparathyroidism are limited. There are a few case reports suggesting a link between irradiation or genetic abnormalities and hyperparathyroidism. Three major pathological conditions are associated with PHP: adenoma, hyperplasia, and carcinoma. Single adenomas account for approximately 89% of all adenomas, hyperplasia accounts for approximately 6% of all cases, and carcinoma occurs in 1% to 2% of PHP cases (9).

Clinical manifestations

Patients with PHP often have generalized nonspecific complaints that are consistent with their level of hypercalcemia. Symptoms associated with calcium levels of >12 mg/dL include fatigue, anorexia, nausea, vomiting, constipation, depression, and blurred vision. Once levels exceed 13 mg/dL, patients usually have more profound findings, including end organ calcification, which can manifest as renal impairment, mental status change, cardiac arrhythmias, renal calculi, osteopenia, peptic ulcer disease, pseudogout, and muscle atrophy. Levels of >14 or 15 mg/dL are rare but typically present as a medical emergency with hypercalcemic crisis that can result in uremia, coma, cardiac arrest, or death (1).

Symptoms secondary to hypercalcemia that occur in the nonpregnant patient can occur in the pregnant patient. However, >80% of PHP cases remain asymptomatic in both the pregnant and nonpregnant patient and are diagnosed incidentally by review of laboratory data (1, 3). Other findings that are specific to the pregnant patient include hyperemesis gravidum and a suspected link to preeclampsia (3).

Maternal complications can be as high as 67% and include nephrolithiasis (24%–36%), radiographic bone disease (13%–19%), pancreatitis (7%–13%), hyperemesis gravidum, muscle weakness, confusion, and hypercalcemic crisis. In addition, there is concern for further increase in calcium levels postpartum when fetal shunting is removed (1). Other clinical findings include maternal hypertension, although the association remains unknown (3).

A 25% incidence of preeclampsia has been observed in patients with PHP (4). A study published by Hultin and colleagues reviewed the impact of PHP on preeclampsia (5, 7, 10). The study demonstrated a significant association between parathyroid adenoma and subsequent preeclampsia (5, 7, 10). They theorized that the similarities in endothelial damage, insulin resistance, and cardiovascular disease shared between the two disease processes may support the hypothesis that a relationship exists between PHP and preeclampsia. In addition, it has been shown that maternal vitamin D deficiency has been associated with preeclampsia. This also supports the concept that the mechanisms that support calcium homeostasis affect blood pressure in the pregnant patient (10).

Fetal complications in mothers who have been untreated for PHP are reported to be as high as 80% (1). In conservatively treated mothers, the rate is reported to be as high as 53%, and 27% to 31% of those complications are identified as neonatal death (1). Other complications include intrauterine growth restriction, low birth weight, preterm delivery, and intrauterine fetal demise (1, 7). Up to 50% of neonates experience postpartum hypocalcemia secondary to elevated maternal calcium levels that suppress the fetal parathyroid glands (1, 3). This can be rectified with appropriate calcium supplementation and is traditionally considered to be a transient phenomenon. However, cases

have been reported in which the neonatal hypoparathyroidism lasts up to several months or is permanent (1). This is theorized to be due to a teratogenic effect of hypercalcemia on the embryological effect of calcium on the third and fourth brachial clefts (3).

Lastly, PHP may lead to spontaneous abortion prior to awareness of the pregnancy (1). Hyperparathyroidism is associated with a three- to fivefold increased risk of miscarriage, primarily in the second trimester. Fetal loss is associated with levels >11.4 mg/dL. Seventy-two percent of pregnancy losses in a study conducted by Norman and colleagues occurred at or above this level (11).

Although the impact of PHP on the mother and neonate as reported by Norman and Hultin is staggering, caution must be exercised in interpreting the data, as few patients were included. In the Norman study, only 32 patients were observed, and in the Hultin study, only 52 patients were observed. In addition, the physiology of pregnancy affects albumin measurements. Calcium is often adjusted for albumin inconsistencies. In the Norman study, unadjusted calcium levels were utilized when determining correlation with fetal loss. Utilizing adjusted calcium levels may have changed the interpretation of these data.

Diagnosis

PHP is diagnosed with an elevated calcium and elevated or normal intact PTH level (3). When evaluating calcium, it may be prudent to draw an ionized calcium. During pregnancy there is an increase in extracellular volume and a decrease in albumin, which may result in a factitiously low calcium, whereas the ionized calcium is normal (5). Intact PTH represents the N-terminal fragment of PTH. This is the recommended level to draw given the C-terminal or standard PTH level can be falsely elevated in patients with renal impairment due to the extended half-life and may be mildly elevated in the elderly (1).

Once PHP is diagnosed, imaging should follow to determine the etiology. The gold standard for imaging is a technetium-99m sestamibi scan. However, this is contraindicated in pregnancy, and ultrasonography is the preferred imaging modality. Ultrasonography has a 69% sensitivity and a 94% specificity in diagnosing parathyroid adenoma (3).

It is recommended that surgeons locate and identify the parathyroid adenoma before proceeding with any surgical intervention; however, if the adenoma cannot be located with imaging, neck explorations have a 95% chance of curing the patient (1).

Treatment

The National Institutes of Health suggests parathyroidectomy for asymptomatic nonpregnant patients with calcium elevations >1 mg/dL above the upper limits of normal (or >11.5 mg/dL) (12). Calcium levels vary in the pregnant patient due to the physiological changes that occur. Carella and Gossain stated that calcium concentrations >10.1 mg/dL during the second or third trimester should prompt an evaluation of PHP (6). In a retrospective patient series in the Norman Parathyroid Clinic in Florida, investigators examined pregnant patients with fetal loss and PHP (11). They found that patients with calcium levels of 10.7 mg/dL were associated with pregnancy loss, but most pregnancies continued to term. Calcium levels >11.4 mg/dL were associated with higher levels of fetal loss, and 72% of fetal loss occurred at or above this level (11).

Surgery is the definitive treatment for PHP. However, since surgery for PHP has inherent potential risks for the pregnant patient, it is often viewed as the last resort. However, given the increasing evidence that supports a higher morbidity and mortality associated with calcium levels of >11.4 mg/dL, surgical intervention is recommended in patients with levels >11.0 mg/dL, particularly in patients with prior pregnancy loss (11, 13, 14).

Gestational age plays a role in determining surgical candidacy. Traditionally, surgery is reserved for patients in the second trimester, given the higher risk in the first and third trimesters. First-trimester surgery is avoided due to incomplete organogenesis, and third-trimester surgery has been discouraged because it is associated with a higher risk of preterm labor. In addition, there is a reported 58% fetal mortality associated with third-trimester parathyroidectomy (3, 7). This mortality rate includes all postoperative complications for the infant, such as premature delivery, intrauterine growth retardation, infant hypocalcemia, neonatal death, and stillbirth. It is impossible to differentiate surgical complications from complications of prolonged hypercalcemia related to the underlying disease process (7).

Conservative medical therapy should be utilized in the asymptomatic patient with a calcium level of <11 mg/dL (11). The patient should be adequately hydrated with or without forced diuresis with a loop diuretic (15). In addition, patients should be started on a low-calcium diet. Phosphate therapy has been considered a modality of treatment in the past, but given the substantial risk of calcium phosphate precipitation it is not often recommended (1). Subcutaneous calcitonin is also utilized and has a category C rating. Calcitonin is somewhat limited in efficacy due to tachyphylaxis. Cinacalcet has also been used in conjunction with calcitonin and has demonstrated a highly effective reduction in PTH levels (15). Cinacalcet has a category C rating, but studies remain lacking to evaluate effects on mother and fetus/neonate (15).

CONCLUSION

Clinical evidence for the treatment of PHP in pregnant patients is limited, but most studies have determined the treatment modality based on the severity of disease. Severity of disease is classified by calcium level, symptoms at the time of presentation, and gestational age. Most evidence supports utilizing conservative measures for treatment during the first and third trimesters unless there are compelling reasons to perform surgery.

In the patient described in this case report, there appears to have been a correlation between the patient's aggravated hypertension and her PHP. Given her need for polypharmacy to achieve moderate hypertension control and given her history

of miscarriage, the question remains on whether parathyroidectomy should have been performed during her third trimester.

It appears that with higher awareness of this disease process and its impact on maternal and fetal morbidity and mortality, there may be more evidence to support parathyroidectomy regardless of gestational age, particularly for patients in the third trimester. This case would support this concept, and it is clear that further investigation is needed to refine guidelines on parathyroidectomy during pregnancy.

1. Schnatz PF, Curry SL. Primary hyperparathyroidism in pregnancy: evidence-based management. *Obstet Gynecol Surv* 2002;57(6):365–376.
2. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ 3rd. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. *J Bone Miner Res* 2006;21(1):171–177.
3. Kokrdova Z. Pregnancy and primary hyperparathyroidism. *J Obstet Gynaecol* 2010;30(1):57–59.
4. Schnatz PF, Thaxton S. Parathyroidectomy in the third trimester of pregnancy. *Obstet Gynecol Surv* 2005;60(10):672–682.
5. Pothiwala P, Levine SN. Parathyroid surgery in pregnancy: review of the literature and localization by aspiration for parathyroid hormone levels. *J Perinatol* 2009;29(12):779–784.
6. Breslau NA, Zerwekh JE. Relationship of estrogen and pregnancy to calcium homeostasis in pseudohypoparathyroidism. *J Clin Endocrinol Metab* 1986;61(1):45–51.
7. Truong MT, Lalakea ML, Robbins P, Friduss M. Primary hyperparathyroidism in pregnancy: a case series and review. *Laryngoscope* 2008;118(11):1966–1969.
8. Amaya García M, Acosta Feria M, Soto Moreno A, Dios Fuentes E, Navarro González E, Quijada Thong D, Del Valle A, Acosta Delgado D, Astorga Jiménez R. Primary hyperparathyroidism in pregnancy. *Gynecol Endocrinol* 2004;19(2):111–114.
9. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005;132(3):359–372.
10. Hultin H, Hellman P, Lundgren E, Olovsson M, Ekbom A, Rastad J, Montgomery SM. Association of parathyroid adenoma and pregnancy with preeclampsia. *J Clin Endocrinol Metab* 2009;94(9):3394–3399.
11. 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):104–109.
12. Eigelberger MS, Cheah WK, Ituarte PH, Streja L, Duh QY, Clark OH. The NIH criteria for parathyroidectomy in asymptomatic primary hyperparathyroidism: are they too limited? *Ann Surg* 2004;239(4):528–535.
13. Perin E, Cacciaguerra G, Lapenna R, Catena C, Sechi LA, Marchesoni D. Primary hyperparathyroidism in pregnancy. *Fertil Steril* 2008;90(5):2014.e13–e15.
14. McMullen TP, Learoyd DL, Williams DC, Sywak MS, Sidhu SB, Delbridge LW. Hyperparathyroidism in pregnancy: options for localization and surgical therapy. *World J Surg* 2010;34(8):1811–1816.
15. Horjus C, Groot I, Telting D, van Setten P, van Sorge A, Kovacs CS, Hermus A, de Boer H. Cinacalcet for hyperparathyroidism in pregnancy and puerperium. *J Pediatr Endocrinol Metab* 2009;22(8):741–749.