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CASE REPORT

Primary hyperparathyroidism in pregnancy: a case of successful parathyroidectomy in the third trimester

Ivan Brychta[1], Alexander Mayer[1], Michal Gergel[1], Marián Vidiščák[1], Karol Plank[2]

1 1st Surgical Clinic, Slovak Medical University and University Hospital Bratislava, Slovakia
2 1st Clinic of Gynecology and Obstetrics, Slovak Medical University and University Hospital Bratislava, Slovakia

Correspondence to: MUDr. Michal Gergel, PhD.
Chirurgická klinika, Limbova 5, 83101, Bratislava, Slovakia
tel: +421259544496, e-mail: chirurgia.sekretariat@kr.unb.sk

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Abstract

Primary hyperparathyroidism (PHPT) in pregnancy is rare and may be associated with increased maternal and fetal morbidity and mortality. The ideal timing for parathyroidectomy is during the second trimester, and parathyroidectomy in the third trimester is extremely rare. We present a case of a 32-year-old woman who was admitted to our hospital with severe hypercalcemia in the 36th week of her first pregnancy. Conventional bilateral neck exploration was performed and parathyroid adenoma was removed. The surgical procedure was tolerated well by the mother, and she delivered a healthy girl 10 days after surgery. The newborn had mild hypocalcemia that required minimal substitution postnatally; however, no tetany occurred. This case demonstrates that parathyroidectomy in the third trimester followed by spontaneous delivery may be performed safely.

Abbreviations:
PHPT - primary hyperparathyroidism
PTH - parathyroid hormone

BACKGROUND

Primary hyperparathyroidism (PHPT) is a parathyroid gland abnormality where one or more of the four parathyroid glands enlarge and secrete excess parathyroid hormone (PTH). PTH normally regulates calcium and bone metabolism, and it's excess production results in high blood calcium levels. PHPT is most often a result of a solitary parathyroid adenoma (90%), but it can also be associated with multiglandular disease (10%) and, rarely, with parathyroid carcinoma (< 1%) (Yeh *et al.* 2013). The most common cause of PHPT in pregnancy appears to be a solitary adenoma, as well. The incidence of primary hyperparathyroidism in the general population is 4/100,000 per year, occurring mostly in patients older than 45 years old with a female:male ratio of 3–4:1. (Pessah-Pollack & Jovanovič, 2011, Bilezikian, 2018). Among women of childbearing age, the incidence is approximately 8/100,000, while among women above the age of 60, the incidence is 188/100,000 (Heath *et al.* 1980). PHPT in pregnancy is uncommon, and approximately 200 cases have been published in medical literature since the first case was reported in 1932 (Vera *et al.* 2016). The disease usually causes very mild elevations in serum calcium and requires no intervention; however, when associated with moderate to severe hypercalcemia, the disorder carries substantial maternal and fetal risks (Rubin & Silverberg, 2017). The ideal timing for surgical intervention is

during the second trimester. Parathyroidectomy in the third trimester is extremely rare. Schnatz *et al.* reviewed the literature published up to 2005 and identified only 16 cases of PHPT treated surgically after 27 weeks of gestation (Schnatz & Thaxton, 2005).

CASE REPORT

In a 32 year old female (gravida 2, para 1), severe hypercalcemia was detected by a gynecologist at 36 weeks of gestation. The total calcium level was 3,34 mmol/L (reference range 2,15-2,55 mmol/L) and the ionized calcium was 1,89 mmol/L (reference range 1,10-1,30 mmol/L). Calcium concentration was not measured as a part of a routine laboratory screening prior. She had no symptoms of hyperparathyroidism and no history of calcium disorders, kidney stones, fractures, or osteoporosis. The patient was sent to an endocrinologist and subsequently admitted to the gynecological clinic at our hospital at 38 weeks of gestation. Additional testing showed an elevated PTH level of 650 pg/mL (reference range, 15–65 pg/mL) and decreased phosphorus level of 0,36 mmol/l (reference range, 0.87-1,45 mmol/L) confirming a diagnosis of primary hyperparathyroidism. Other than a slightly elevated alkaline phosphatase of 2,02 μkat/l (reference range 0,58-1,75 μkat/l), the patient had normal blood biochemical parameters and normal renal function. A maternal neck ultrasound performed by the endocrinologist revealed an enlarged (25 × 10 x 10 mm) lower parathyroid gland located posterior to the right lobe of the thyroid gland. Obstetric ultrasound examination showed normal fetal growth and no pathology. No other investigations, such as scintigraphy for localization, were performed. In addition to oral fluid rehydration, intravenous saline was infused after admission, but this attempt at lowering serum calcium levels was met with limited success. Due to the severe hypercalcemia, surgical management was deemed necessary after consultation with an endocrinologist, gynecologist, and pediatrician. The decision was made to remove the parathyroid adenoma followed by delivery at full term. Conventional bilateral neck exploration with identification of all four parathyroid glands to exclude multiglandular disease was performed on the third day of hospital stay by a highly experienced endocrine surgeon. An adenoma, located with ultrasound, was completely removed. No abnormal parathyroid tissue was identified on the other three parathyroid glands. Intraoperative PTH was not monitored as all four glands were visualized. Histological findings confirmed parathyroid adenoma. The surgical procedure was tolerated well by the mother, and no pathological changes were observed in the closely monitored fetus. Serum calcium level decreased gradually, achieving physiological level on the fourth postoperative day, and serum phosphorus normalized on the third postoperative day. No hypocalcemia occurred, and no calcium substitution was required. The patient delivered a healthy girl with normal measurements spontaneously under epidural anaesthesia 10 days after surgery, and the newborn was followed at the neonatal intensive care unit. No tetany occurred, and the calcium level was slightly decreased requiring minimal substitution 2 days postnatally. Since being discharged from the hospital, both the patient and her child have not had any health problems.

EFFECT OF HYPERPARATHYROIDISM ON PREGNANCY

Normal pregnancy can be associated with many nonspecific symptoms, such as nausea, vomiting, constipation, weakness, fatigue, or mental changes, that can mask the symptoms of hypercalcemia, often leading to a delayed diagnosis of hyperparathyroidism. Additionally, approximately 20% of patients with PHPT are asymptomatic, therefore maternal PHPT may go undetected, presenting only as neonatal tetany after delivery (Pessah-Pollack & Jovanovič, 2011). Nausea with or without vomiting and abdominal pain are the most frequent symptoms of PHPT in pregnancy, followed by renal colic, muscular weakness, mental symptoms, skeletal pain, and weight loss (Kristoffersson *et al.* 1985). PHPT is also associated with an increased risk of pre-eclampsia. Nephrolithiasis and nephrocalcinosis are not uncommon during pregnancy, but PHPT is not the only cause of their formation, since both conditions are more likely to occur due to increased intestinal calcium absorption and hypercalciuria, which are typical in a normal pregnancy. Clinical signs of PHPT may also include urinary tract infections and skeletal resorption (Kristoffersson *et al.* 1985). Acute pancreatitis was described in up to 15% of cases, usually during the second or third trimester, but the potentially life-threatening acute necrotizing pancreatitis due to PHPT is rare and appears to be limited to isolated case reports (Yang *et al.* 2019, Krysiak *et al.* 2011). The risk of pancreatitis is approximately ten times higher in pregnant patients with PHPT when compared to non-pregnant patients with PHPT.

Severe hypercalcemia or hypercalcemic crisis presents a significant health risk and can occur during the third trimester or, more often, postpartum when the transplacental calcium shunt from the mother to the fetus is removed. Transfer of calcium across the placenta during the third trimester protects against maternal hypercalcemia. A hypercalcemic crisis presents with nausea, vomiting, weakness, changes in mental status, and can progress to uremia, coma, and even death (Hui *et al.* 2010).

EFFECT OF HYPERPARATHYROIDISM ON FETUS AND NEONATE

Persistent maternal hypercalcemia increases calcium transfer across the placenta leading to fetal hypercalcemia. High calcium levels in the fetal circulation

results in suppression of fetal parathyroid function or fetal parathyroid development (Hui *et al.* 2010), which may lead to intrauterine growth retardation, preterm delivery, fetal death, or stillbirth. Fetal growth retardation, most commonly a result of inadequate maternal-fetal circulation, might occur in PHPT as a result of the premature calcification of the placenta (Graham *et al.* 1998). Maternal calcium supply is no longer available to the neonate after birth, and due to suppression of the fetal parathyroid function or undeveloped parathyroid glands, hypocalcemia and tetany can occur soon after delivery. The most serious complication after delivery is neonatal death due to severe hypocalcemia. The neonate is at high risk of hypocalcemia and tetany for weeks after birth, with reported cases presenting as late as 2.5 months postpartum (Ip, 2003). Neonatal hypoparathyroidism generally subsides within 3 to 5 months, but permanent hypoparathyroidism may be present in some children because of underdeveloped or absent parathyroid glands. Absence of the parathyroid glands at autopsy in the neonate has been described in the literature (Johnstone *et al.* 1972).

In earlier reports, perinatal mortality has been reported to be as high as 25–31% with neonatal complication rates at 19–53%; however, the outcomes have improved over the past several decades (Hui *et al.* 2010). Stillbirth has declined from 13% to 2%, neonatal deaths have dropped from 8% to 2%, and neonatal tetany has decreased from 38% to 15% (Pessah-Pollack & Jovanovič, 2011).

DIAGNOSIS

Early diagnosis and appropriate management of PHPT in pregnancy is crucial to prevent maternal and fetal morbidity and mortality; however, calcium levels are not routinely measured during pregnancy in many countries. As a result, a number of cases of PHPT are undetected and, most commonly, the disease presents in the postpartum period with neonatal tetany. The diagnosis of PHPT is confirmed by hypercalcemia and raised or inappropriately normal parathormone (PTH). If the ionized (free) calcium or total calcium is increased with a detectable PTH level, the diagnosis of primary hyperparathyroidism is feasible. Ionized calcium reflects the exact calcium status of the patient, and many clinicians believe that serum albumin measurement is required in order to interpret total calcium concentrations. Many adjustment formulas based on simple linear regression models have been developed for this purpose, but their diagnostic accuracy is questionable and should be abandoned in clinical practice (Lian & Åsberg, 2018). Measurement of ionized calcium is now relatively inexpensive and is available in most hospitals and many outpatient settings, but in places where the measurement of ionized calcium is not available, total calcium should be assessed without the application of any correction formula.

It is important to note that the serum calcium level in a normal pregnancy is lowered through several mechanisms, such as increased glomerular filtration rate, calcium transport across the placenta for the developing fetus, and estrogen inhibition of PTH-mediated bone resorption, so a diagnosis of hyperparathyroidism can be obscured (Norman *et al.* 2009).

Once PHPT is biochemically confirmed, the patient is a surgical candidate and the accurate detection of the pathologic gland can help guide the surgeon and allow him to perform targeted surgery. The purpose of the imaging techniques is to precisely localize the abnormal parathyroid glands and to distinguish between uniglandular (solitary adenoma) and multiglandular disease. Precise preoperative imaging, however, is less critical when planning traditional bilateral neck exploration. The gold standard imaging techniques in the non-pregnant population includes ultrasound and Tc^{99m}-sestamibi. CT, MRI, ^{18}F-Fluorocholine PET/CT (FCH PET/CT), ^{11}C-choline PET/CT, and selective venous sampling of PTH levels are less frequently used.

Ultrasonography is the preferred and most appropriate imaging modality for localization of parathyroid lesions in pregnancy. ^{99m}Tc-sestamibi scan is traditionally avoided because of the radiation risk to the fetus (Rubin & Silverberg, 2017). The fetal health consequences can include pregnancy loss, malformation, developmental delay or retardation, and carcinogenesis, but it should be noted that the radiation exposure in fetuses and subsequent risk is mostly based on observations rather than on scientific research (Yoon & Slesinger 2021). Recent guidelines from the American College of Obstetricians and Gynecologists state that a ^{99m}Tc-MIBI scan represents a fetal exposure of <5 mGy, an exposure that is much lower than the exposure associated with fetal harm (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee Opinion No. 656, 2016). Thus, a parathyroid localization scan that does not exceed this level of exposure perhaps would not be unsafe during pregnancy (Rubin & Silverberg, 2017). Despite this, the majority of endocrinologists don't recommend this diagnostic test.

CT and MRI are, in general, relatively insensitive in the detection of parathyroid adenomas or hyperplasias and are usually used if an experienced endocrine surgeon is unable to locate the parathyroid glands intraoperatively. In these cases, there is a high probability that PHPT is caused by an adenoma located in the mediastinum. Based on our knowledge, there have been only two reported cases of negative neck explorations during pregnancy that have been described in the literature.

TREATMENT

Surgery is the first choice and is the only curative treatment in patients with symptomatic PHPT in the general population; however, no guidelines for the management

of PHPT in pregnancy currently exist. There are two options for the treatment of PHPT in pregnancy: conservative management or surgical intervention. Both approaches, however, are associated with risks (drug related side effects or surgery related side effects, respectively). Conservative management with oral or intravenous rehydration, a low-calcium diet, and vitamin D supplementation is safe; however, all of these methods only temporarily reduce serum calcium. Although cinacalcet therapy in pregnancy has been described in literature as useful in controlling serum calcium, there is a lack of safety data and should be avoided (Vera *et al.* 2016, Djokanovic *et al.* 2008). Bisphosphonates in the treatment of hypercalcemic crisis should also be avoided due to the risk of negative effects on fetal skeletal development (Djokanovic *et al.* 2008). The administration of calcitonin is limited by tachyphylaxis, and oral phosphates can lead to soft tissue calcifications or diarrhea (Pothiwala & Levine, 2009).

There is a wide spectrum of severity of PHPT, and it is likely that severe symptomatic disease has different maternal and fetal effects when compared to mild disease; however, serious fetal and neonatal complications have been reported even in cases of mild PHPT (Rubin & Silverberg, 2017). Mild hypercalcemia in symptom-free patients used to be treated conservatively leading to the postponement of parathyroidectomy until after delivery. Parathyroidectomy is absolutely recommended if the serum total calcium is above 3 mmol/l and ionized calcium is greater than 0.12 mmol/L above the upper limits of normal levels (Khan *et al.* 2017). In his investigation of 77 pregnancies in 32 women with PHPT, Norman *et al.* demonstrated that a mild elevation of calcium levels was associated with a 3 to 5 fold increase in pregnancy loss (Norman *et al.* 2009). Parathyroidectomy should therefore be performed during pregnancy for all PHPT patients regardless of calcium levels or symptoms, since delaying parathyroid surgery may result in a maternal hypercalcemic crisis postpartum.

There is a general consensus that the ideal timing for surgery is during the second trimester due to incomplete organogenesis in the first trimester and the risk of preterm delivery in the third trimester. In the event of a hypercalcemic crisis (serum calcium above 3,49 mmol/l), urgent parathyroidectomy after intravenous or orally administered rehydration is recommended regardless of the gestational age of the fetus. It remains unclear, however, whether parathyroidectomy should be performed in the third trimester before the delivery or simultaneously with Caesarean section.

The traditional approach to parathyroid surgery has been bilateral neck exploration with the identification of all four parathyroid glands in order to locate the pathological tissue. Significant improvements in preoperative imaging, together with intraoperative PTH monitoring that confirms the removal of the adenoma, have led to the implementation of a focused, minimally invasive surgical approach in non-pregnant individuals. As a result, the traditional bilateral neck exploration approach is no longer routinely performed in uniglandular disease.

The difference between the focused and bilateral approach is in the length of the neck incision and in the extent of dissection, since the focused approach limits the dissection to the abnormal parathyroid gland only. A smaller incision improves cosmesis, reduces surgical trauma leading to less postoperative pain, and has a potentially lower risk of complications compared to bilateral neck exploration where both sides of the neck are explored. Regarding the cure and complication rates, both approaches are comparable in the hands of an experienced surgeon. Improvements in surgical technique have also led to bilateral explorations that can be performed using shorter incisions when compared to the past. Currently practiced minimally invasive techniques include open minimally invasive parathyroidectomy (OMIP) and minimally invasive video-assisted parathyroidectomy (MIVAP). Fully endoscopic techniques using periareolar or an axillary approach in order to leave no scar in the neck cannot be considered minimally invasive as they require larger subcutaneous dissection than conventional open surgery. All of the aforementioned focused approaches require accurate preoperative localization of the diseased parathyroid gland and intraoperative PTH monitoring, thus their application in pregnancy is dubious. Ultrasonography alone may not be sufficiently accurate to confirm an enlarged parathyroid and intraoperative PTH monitoring increases operating time, therefore bilateral neck exploration seems to be more reasonable during pregnancy.

The cure rate of this procedure exceeds 95%.

CONCLUSION

The medical management of gestational PHPT is limited. Surgery is the only effective therapeutic option and should be performed during pregnancy regardless of calcium levels or symptoms. Delayed surgery may result in maternal hypercalcemic crisis after delivery, neonatal tetany, and an increased risk of pregnancy loss. The ideal timing for parathyroidectomy is during the second trimester, but it may safely be performed during the third trimester under the guidance of a multidisciplinary team. We consider the four-gland exploration performed by an experienced endocrine surgeon in a high-volume center to be the most suitable and safe approach to the management of PHPT in pregnancy.

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