Pheochromocytoma in a Pregnant Patient

Jeannette M. Potts, MD, and John Larrimer, MD
Cleveland and Columbus, Ohio

Pheochromocytoma accounts for only 0.1% of hypertension found in adults between 40 and 70 years of age. Although it is extremely rare in pregnancy, if it occurs and is unrecognized in pregnant women, pheochromocytoma can have catastrophic effects. For instance, maternal fatal hypertension can be precipitated by anesthesia, vaginal delivery, uterine contractions, or even vigorous fetal movements. Fetal growth retardation is often seen secondary to decreases in uteroplacental perfusion. Fetal hypoxia or death can also occur with maternal episodes of headache, palpitations, and diaphoresis related to tumor secretions. Because many of the signs and symptoms of pheochromocytoma are similar to more frequently encountered hypertensive syndromes related to pregnancy, the diagnosis of pheochromocytoma can be easily overlooked. The case report presented here illustrates the difficulties associated with the diagnosis of pheochromocytoma in a pregnant patient, highlights problems encountered by patients with the tumor, and reviews diagnostic and treatment approaches.

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Pheochromocytomas account only for 0.1% of hypertension found in adults between 40 and 70 years of age[1] and are extremely rare in pregnancy.[2] It is estimated to occur once in approximately 50,000 term pregnancies.[2]

Because this tumor is derived from neural crest tissue, it is capable of secreting a wide variety of neurotransmitters, which, in turn, cause the observed symptomology and can be fatal.[3] If unrecognized in pregnancy, pheochromocytomas can be catastrophic to both mother and infant. For instance, fatal hypertension can be precipitated by anesthesia, vaginal delivery, uterine contractions, or even vigorous fetal movements. Fetal growth retardation is often seen secondary to decreases in uteroplacental perfusion. Fetal hypoxia or death can also occur, with episodes of maternal headache, palpitations, and diaphoresis caused by tumor secretion.[2] In one case report, an infant died on the 21st day postpartum as a result of intractable heart failure and hypertension attributed to maternal pheochromocytoma.

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From the Family Practice Residency Program, Metro Health Medical Center, Cleveland (J.M.P.), and the Department of Medicine–Endocrinology, Grant Medical Center, Columbus, Ohio (J.L.). Dr Potts was formerly with the Family Practice Residency Program, Grant Medical Center. Requests for reprints should be addressed to Jeannette Potts, MD, 4903 Grace Rd, Cleveland, OH 44070.

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Studies show a 58% maternal and 56% fetal mortality rate in undiagnosed pheochromocytoma in pregnancy.[3] Since 1989, the maternal mortality rate has decreased from 17% to 0%, and the fetal mortality rate from 26% to 15%, when maternal pheochromocytoma is diagnosed before birth.[2]

Because many of the signs and symptoms of pheochromocytoma are similar to the more frequently encountered pregnancy-related hypertensive syndromes, the diagnosis of pheochromocytoma is easily overlooked. Moreover, pheochromocytoma can be missed because it often masquerades as preeclampsia.[4] Effective therapeutic intervention requires early diagnosis of this rare tumor. The following case report illustrates the difficulties associated with diagnosing pheochromocytoma in a pregnant patient and highlights problems experienced by patients with this tumor.

Case Report

A 32-year-old woman, G3P2002, presented at 37 weeks' estimated gestational age for what she described as "worsening attacks" that lasted approximately 10 minutes, occurred several times each day, and included elevated blood pressure, palpitations, severe headaches, and

diaphoresis. She also described vomiting even though she did not feel nauseated. Simple activities, such as sitting up and attending to the needs of her children, exacerbated her attacks. In retrospect, she noted that lying on her left side to relax or to read to her children worsened her symptoms. She had recently been hospitalized to receive intravenous fluid hydration because of hyperemesis.

The patient's medical history included pregnancy-induced hypertension, preeclampsia, cluster headaches, and recently diagnosed hypothyroidism, for which she was receiving levothyroxine sodium. Her family history revealed that her brother suffered from cluster headaches and that several aunts and cousins had cardiomyopathies of unknown cause. There was no family history of endocrinopathy.

A detailed history and examination of the patient's medical record indicated that her hypertensive symptoms were first noted in 1988 during the latter part of her first pregnancy. Because her blood pressure fluctuation was so significant at that time, blood pressure and urine checks were ordered three times per week. She was hospitalized for management of pregnancy-induced hypertension in the 37th week of pregnancy. Studies associated with that admission shed no light on her hypertensive status, and although she was not hypertensive at the time of delivery, her labor did not progress satisfactorily, resulting in the use of pitocin and, ultimately, vacuum extraction. She gave birth to a healthy 8-pound male infant at 40 weeks' gestation.

In 1989, the patient became pregnant a second time. At 20 weeks' gestation, she experienced palpitations, which increased in frequency throughout her pregnancy. In her 8th month, she developed severe right-sided headaches, which continued after the birth of her child. After an uncomplicated vaginal delivery of a viable male infant weighing 7 pounds 8 ounces, she was referred to a neurologist for management of her headaches. She was placed on home oxygen, β-blockers, Cafergot, and verapamil. Because the β-blockers caused significant exacerbation of her headaches, she discontinued these medications. Ultimately, the use of home oxygen and prednisone relieved her headaches. Her attacks of palpitations continued but were attributed to anxiety.

During the following year, the patient noted more frequent palpitations along with increasing fatigue. Laboratory studies revealed primary hypothyroidism, which was treated with thyroid replacement.

In August 1991, in her third pregnancy, the patient presented at 37 weeks' estimated gestation for evaluation of presumed pregnancy-induced hypertension. Her blood pressure was 200/102 mm Hg. Routine laboratory tests were within normal limits except for a mildly elevated alanine aminotransferase (ALT). The patient's history, particularly with respect to headache, diaphoresis, and palpitations, was typical of pheochromocytoma. That the paroxysms coincided with elevated blood pressure supported a possible diagnosis of pheochromocytoma. Further laboratory studies confirmed that diagnosis (Table 1). Abdominal ultrasonography demonstrated a left adrenal gland mass. While the patient was stabilized for surgery, other studies were performed to rule out multiple endocrine neoplasia. These tests were negative.

Table 1. Results of Laboratory Tests Performed in a Case of Pheochromocytoma

Laboratory Test	Preoperative Value, pg/mL	Normal Range, pg/mL	Postoperative Value, pg/mL
Serum norepinephrine	5811	70–750	41
Serum epinephrine	910	0–110	<10
Urine norepinephrine	484	15–80	15
Urine epinephrine	177	0–20	2.3
Vanillylmandelic acid	75	0–9	5.1
24-hour urine metanephrine	41	<3.1	0.2

Treatment

The critical first step in this patient's treatment was to stabilize her blood pressure and relieve the tachycardia. Incremental doses of phenoxybenzamine were administered, starting at 10 mg three times daily and increasing to 20 mg three times daily, when her blood pressure was adequately controlled. Four days following α-adrenergic blockade with phenoxybenzamine, β-adrenergic blockade was implemented to control tachycardia.

After 7 days of α-blockade and 3 days of β-blockade, the patient was taken for elective cesarean section and laparotomy for tumor resection. Swan-Ganz catheterization was performed preoperatively, and 2 minutes after general anesthesia, a viable male infant with an Apgar score of 7/9 was delivered. After uterine repair and hemostasis, the midline incision was extended superiorly and the retroperitoneum was explored. A mass measuring 7.5 cm × 7.0 cm × 5.0 cm and weighing 180 g was removed without incident. Blood pressure was controlled intraoperatively with esmolol, phentolamine, and nitroprusside. Sufentanil was also used following the delivery. The patient was extubated in the intensive care unit 4 hours postoperatively and transferred to the postpartum floor 1 day later. She was discharged from the hospital on the 7th postoperative day. Postoperative laboratory results are also listed in Table 1.

Table 2. Signs and Symptoms Associated with Pheochromocytoma

Severe hypertension
Fluctuating hypertension
Paroxysms*
Hypertension with abnormal glucose tolerance test or diabetes mellitus
Suspected thyrotoxicosis
Sudden collapse
Hypertension precipitated by anesthesia, trauma, antihypertensives
Onset of hypertension in first half of pregnancy

**Headache, palpitations, dizziness, diaphoresis, anxiety, nausea, vomiting, visual changes.*

Discussion

Clinical Symptoms

A high level of awareness is probably the most important factor in diagnosing a pheochromocytoma. The delay from onset of symptoms to diagnosis is typically 4.5 years.[5] This long delay illustrates the confusing presentation of pheochromocytoma even in the nonpregnant patient.

In nonpregnant patients, sustained or intermittent hypertension is the hallmark of pheochromocytoma,[3] which should be suspected in any patient manifesting any one of the signs or symptoms listed in Table 2.[2–4] Other diseases that have a strong association with pheochromocytoma and therefore should be considered include medullary carcinoma of thyroid, multiple endocrine neoplasia II and III, neurofibromatosis, and von Hippel-Lindau disease.

Paroxysmal symptoms of pheochromocytoma (Table 2) usually last less than 15 minutes. In nonpregnant patients, a triad of symptoms—diaphoresis, headache, and palpitations—has been found to be 91% sensitive when coupled with hypertension.[3,5] Postural hypotension is another characteristic, which is likely a result of volume contraction secondary to the elevated systemic vascular resistance.[4] Hypotension and tachycardia may also be the result of a primarily epinephrine-secreting tumor,[3] whereas a dopamine-secreting tumor may demonstrate no cardiovascular symptoms. An abnormal glucose tolerance test becomes more relevant in the absence of predisposing factors such as heredity and obesity.[5]

The pregnant patient presents additional diagnostic difficulties. The differential diagnosis includes essential hypertension, chronic renal disease, thyrotoxicosis, anxiety neurosis, epilepsy, renal artery stenosis, coarctation of the aorta, Conn's syndrome, and the spectrum of pregnancy-induced hypertension.[4,6] In essence, as a result of pregnancy, there are a large number of competing diagnoses not seen in the nonpregnant patient. Additionally, the classic symptoms of pheochromocytoma are less likely to manifest as such in the pregnant patient. The typical elevated blood pressure occurring in conjunction with the symptom triad (diaphoresis, headache, and palpitations) occurs less frequently in a pregnant woman with pheochromocytoma[2]; however, the incidence of headache occurs more often, as does the onset of hypertension, in the first half of pregnancy.[3]

Laboratory Studies

Tests to confirm the diagnosis of pheochromocytoma involve the measurement of catecholamines and their metabolites in the plasma and urine. Ideally, plasma sampling should occur at the time of a spell, as the half-life of catecholamines in the serum is 2 minutes.[7] Fortunately, urinary analysis can yield valuable results with less concern for test timing.

Two approaches can be employed. In the first, the patient should empty the bladder immediately following a paroxysm into a specially prepared receptacle. Within several hours, this sample should be tested for the presence of catecholamines.[5,7] Another, perhaps simpler, study is a 24-hour urine vanilmandelic acid (VMA) and metanephrine analysis. In one series, the second approach yielded a 98% sensitivity with VMA analysis and a 90% sensitivity with metanephrine analysis.[5] In one case report, however, the urinalysis was repeatedly negative, a result attributed to renal insufficiency related to the effects of long-term hypertension in the pheochromocytoma patient.[4]

Chemical induction (provocative testing) is not recommended in the patient with pheochromocytoma. If necessary, suppression testing utilizing clonidine can be used, but it remains highly controversial for pregnant patients and is not endorsed as part of an initial workup.[4,5,8]

There is impressive evidence to support analyzing platelets for catecholamines and other tumor markers. Because catecholamines are concentrated in platelets, the half-life is significantly longer than in serum, eliminating both false-positive and false-negative results associated with serum measurement. In a small sample of patients with pheochromocytoma, it proved to be just as sensitive as urinary metanephrine measurement.[5]

Imaging

Imaging studies are used primarily for tumor localization and should be employed only after chemical evidence for pheochromocytoma has been obtained. Commonly used imaging studies are computed tomography (CT), ultrasonography, magnetic resonance imaging, and metaiodo-

benzylguanidine (MIBG). Pregnant patients should be studied by ultrasonography first in spite of its limitations, such as the inability to detect small extra-adrenal tumors. Because of radiation risk, CT scanning is not a preferred approach during pregnancy. Magnetic resonance imaging is becoming an acceptable modality for the imaging of pheochromocytoma, as it has the capability of detecting extra-adrenal tumors equal to that of MIBG and CT combined,[5] and it eliminates the risk of radiation exposure to the mother and fetus.

Patient Management

α-Adrenergic blockade to control hypertension is the primary objective in the management of pheochromocytoma. Phenoxybenzamine, an irreversible α-adrenergic receptor antagonist that protects against the effects of sudden catecholamine release from the tumor, is the drug of choice.[2,3] Because of its teratogenic potential, some have used labetolol until the 16th week of gestation and then initiated phenoxybenzamine.[6] Prazosin might be a better alternative, as it acts presynaptically to inhibit the release of norepinephrine and therefore decreases the degree of associated tachycardia. Effects of this drug on the fetus, however, are currently unknown.[9,10]

β-Blockade for the management of tachycardia and arrhythmias should not be initiated until adequate α-blockade has been achieved.[3,8] β-Blockade alone in the patient with pheochromocytoma can cause unopposed α-adrenergic stimulation, leading to extreme peripheral vascular constriction, which, in turn, could cause severe exacerbations of spells and even death. Although β-blockers are not known to be teratogenic, their use in pregnancy has been associated with intrauterine growth retardation, hypoglycemia, bradycardia, and respiratory depression.[8] β-Blockade as well as α-blockade may hinder the ability of the fetus to withstand brief hypoxic episodes that can occur during normal delivery.[4] For these reasons, the use of β-blockers should be accompanied by careful monitoring and be delayed as long as possible.

Cesarean section is undisputedly the safest means of delivery for both mother and infant in cases of maternal pheochromocytoma. Until 1989, there had been only 16 pregnant women with an antenatal diagnosis of pheochromocytoma, of which 15 underwent successful cesarean section delivery.[2] The first reported case of a pregnant woman with pheochromocytoma was in 1911, yet the first antenatal diagnosis was not made until 1955.[4] Infant and maternal mortality rates have been greatly reduced by means of improved antenatal diagnosis, management of the symptoms of pheochromocytoma, and subsequent surgical delivery of the infant.

Controversy remains with regard to the timing of tumor resection. Most early studies suggest immediate tumor resection if the patient is in the first or second trimester of pregnancy. Treatment with an α-blockade and subsequent postpartum resection were performed if the tumor was detected in the third trimester because of the technical difficulties of surgery during the latter stages of pregnancy and the relatively small period of drug exposure to the more mature fetus. One case report, however, demonstrated success with the use of an α-adrenergic blockade and atenolol in the first trimester of pregnancy with subsequent cesarean section delivery at 35 weeks' gestation.[1]

Until 1984, there were only 12 cases in the world literature in which tumor resection took place at the time of cesarean section.[10] In two cases reported in 1990, however, tumor resections were delayed for periods ranging from days to weeks postpartum to allow for further localization of the tumor.[6] This delay can be interpreted as a high index of suspicion for extra-adrenal tumors or malignancy or both and the fear of limited localization of tumors before and during surgery because of the advanced pregnancy. Another group supports the second postpartum procedure as a means of protecting the fetus and mother from high doses of prazosin and metoprolol that are necessary at the time of surgery. Another study cited fear of pressor response during tumor palpation for localization as a concern. In this instance, a CT localization was performed after cesarean section delivery, and final tumor resection was performed 18 days later.[9]

Long-term follow-up is necessary, as latency periods for recurrent or malignant pheochromocytomas may range from 2 to 12 years.[8] In 1989, 14 metastatic or recurrent pheochromocytomas were found among patients who had been diagnosed with this tumor during pregnancy.[2] Malignancy rates can range from 10% to 32% and can be defined only by location in more than one site or invasion to one given area. Histologically, the tumors always appear malignant and are defined as benign only when the borders remain encapsuled.[8,11] Theoretically, tumor spillage at the time of surgery can change its classification from benign to malignant.

Summary

Prenatal diagnosis of pheochromocytoma in pregnancy is necessary to significantly decrease infant and maternal morbidity and mortality in this rare disease. A thorough history for associated symptoms should be performed in the setting of hypertension in pregnancy, including a search for paroxysms that may confirm the presence of

this rare tumor. Medical as well as family history may demonstrate other disease processes that bear strong association with pheochromocytoma.

Twenty-four-hour urine analysis for VMA and metanephrines is considered a sensitive and practical first step in evaluating the patient in whom the diagnosis is considered. Imaging studies should follow laboratory confirmation of the disease. Medical stabilization, primarily by α-adrenergic blockade, is necessary before surgical intervention; however, the duration of medical therapy is dependent on the patient's condition and the gestational age of the fetus at the time of diagnosis. Timing of therapy will also depend on the experience and comfort level of the multidisciplinary team caring for the patient.

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