

Paroxysmal Hypertension, Pheochromocytoma, and Pregnancy

David J. Lyman, MD, MPH

Background: Hypertension is the most common medical complication of pregnancy. Pheochromocytoma in pregnancy is rare, and if unrecognized, can cause serious perinatal morbidity and mortality.

Methods: A patient with severe hypertension, postpartum pulmonary edema, and a recognized pheochromocytoma is described.

Results: Abdominal palpation after vaginal childbirth reproduced the diagnostic triad of hypertension, headaches, and palpitations. Magnetic resonance imaging established the correct diagnosis before biochemical confirmation of excess catecholamine production. The patient responded to α -adrenergic receptor blockade with control of her severe hypertension and clearing of pulmonary edema. The best time to diagnose a pheochromocytoma is before delivery because vaginal childbirth stimulates the release of lethal amounts of catecholamines.

Conclusions: The physician who delivers babies must distinguish between labile hypertension and paroxysmal hypertension. Most experts believe that a spontaneous vaginal delivery is contraindicated when the patient has a pheochromocytoma. Postpartum pulmonary edema associated with a pheochromocytoma is unusual. The profound pressor response elicited by palpation of the postpartum abdomen, the failure of medications usually effective in the treatment of a hypertensive crisis, and the use of magnetic resonance imaging to confirm a functioning adrenal adenoma are the features unique to this case. (J Am Board Fam Pract 2002;15:153–8.)

Pheochromocytoma during pregnancy is rare, with an estimated prevalence in full-term pregnancies of 1 in 50,000 to 54,000.^{1,2} Recent authors have reviewed the various clinical signs and symptoms, antenatal diagnostic features, and perioperative management of these rare endocrine tumors.^{1–6} Most patients have hypertension, either sustained or paroxysmal. The classic triad of headaches, palpitations, and excessive sweating is common, but less so in the pregnant than in the nonpregnant state.⁴ A wide variety of other signs and symptoms can also occur, including chest pain, dyspnea, visual disturbances, abdominal pain, nausea, vomiting, dizziness, dependent edema, postural hypotension, congestive heart failure, arrhythmias, seizures, and sudden death from hemorrhage into the tumor. Antenatal diagnosis is imperative to avoid maternal and fetal morbidity and mortality.

Before 1970 only 25% of cases were diagnosed during pregnancy. Since 1990, 85% of cases have

been diagnosed antenatally, suggesting an increased awareness of this rare but lethal condition.^{3,4} In the case report that follows, the diagnosis of a pheochromocytoma was not suspected until an examination of a postpartum patient's abdomen induced paroxysmal attacks of chest pain and hypertension. Magnetic resonance imaging (MRI) confirmed the diagnosis, and her hypertensive crisis and acute pulmonary edema responded to appropriate treatment.

Methods

A patient is reported who had severe hypertension, postpartum pulmonary edema, and a recognized pheochromocytoma. The literature was searched using the key words "hypertension," "pheochromocytoma," and "pregnancy."

Case Report

A 29-year-old, gravida 4, para 3, Hispanic woman whose previous childbirths were in Mexico approached her family physician while in early pregnancy with complaints of chronic hypertension and headaches. She spoke no English, which made an accurate medical history difficult to obtain. The patient was cared for in consultation with a perina-

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From the Department of Family Medicine, University of Tennessee, Jackson. Address reprint requests to David J. Lyman, MD, MPH, Family Practice Residency Program, UT/Jackson-Madison County General Hospital, 294 Summar Dr, Jackson, TN 38301.

tologist, and at 28 weeks' gestation, nifedipine was prescribed briefly. Serial sonograms showed adequate fetal growth and amniotic fluid, and twice weekly nonstress tests were reactive. At 36 weeks' gestation, the patient's hypertension worsened, nifedipine was again prescribed, and daily home nursing visits began.

One morning at 37 weeks' gestation, the patient awoke with a severe headache and blurred vision. When she was examined at Labor and Delivery, her blood pressure was 170/104 mm Hg. She had brisk deep tendon reflexes, proteinuria (2+), and a favorable cervix. Because of her chronic hypertension and preeclampsia, the perinatologist recommended immediate induction of labor. She had an amniotomy and was given oxytocin, magnesium sulfate, and supplemental intrapartum labetalol. She gave birth vaginally to a healthy female infant with Apgar scores of 8 at 1 minute and 9 at 5 minutes and a birth weight of 7 lb 13 oz. After the birth, intravenous magnesium sulfate was continued; intravenous labetalol had little effect on her extreme elevations in blood pressure. Chest pain, dyspnea, and hypoxemia occurred later in the day, and her blood pressure ranged from 140/80 to 240/140 mm Hg. A ventilation-perfusion scan was negative for pulmonary emboli.

The patient developed acute pulmonary edema and was transferred to the intensive care unit. A cardiology consultant found diastolic dysfunction with preserved systolic function on echocardiography. Early the next morning, intravenous labetalol was stopped when the patient developed intermittent junctional tachycardia. Intravenous nitroglycerin was begun, but her headaches worsened, and she continued to experience chest pain with poorly controlled episodes of severe hypertension. Because the patient spoke no English, and an interpreter was not always available, fear and cultural isolation were thought to contribute to what we believed was her labile hypertension.

During weekend rounds on the first postpartum morning, with little improvement in the patient's condition, the obstetric nursing staff fortuitously observed that routine uterine massage elevated the patient's blood pressure. Her abdomen, which was not tender, was carefully palpated, and an explosive pressor response was induced with recurrence of chest pain, suggesting the release of massive amounts of catecholamines. A magnetic resonance image (MRI) of the abdomen was ordered imme-

diately, which confirmed a 7-cm right adrenal mass. Nitrates were discontinued, and the patient was given phenoxybenzamine – an irreversible α -adren-
ergic receptor antagonist – which resulted in stabilization of her blood pressure. Her pulmonary edema cleared, and the patient was weaned from oxygen. Subsequent laboratory tests confirmed the diagnosis: urine vanillylmandelic acid was 134 mg/24 h (normal < 10 mg/24 h); urine catechol-
amine levels were markedly elevated, with norepinephrine = 12,529 μ g/24 h, epinephrine = 3773 μ g/24 h, and dopamine = 820 μ g/24 h. She was released from the hospital with prescriptions for doxazosin mesylate, 2 mg twice a day, and phenoxybenzamine, 10 mg daily.

The patient returned in 2 weeks and underwent a right adrenalectomy. There was no evidence of malignancy or extraadrenal involvement. She required intraoperative esmolol for hypertension, and despite preoperative fluid hydration, was hypotensive (90/60 mm Hg) in the immediate postoperative period. She was given large-volume fluid resuscitation, her blood pressure rapidly stabilized, and she was released from the hospital with normal blood pressure 5 days after surgery.

Discussion

Pheochromocytoma in pregnancy is rare, and we misread all the warning signals in our patient. Headaches, hypertension, hyperreflexia, edema, proteinuria, oliguria, hyperuricemia, and thrombocytopenia define preeclampsia, and our patient certainly had some of these features. Postural hypotension and hypertension worsening in the supine position suggest the diagnosis of pheochromocytoma, but these findings were not sought in our patient.^{3,4} Worsening headaches and labile hypertension were mistakenly attributed to stress, cultural isolation, and even medication (ie, nitroglycerin). In retrospect, our patient had paroxysmal hypertension, in which extreme elevations in blood pressure are unpredictable and not part of an anxiety or panic disorder.⁷

The maternal mortality rate is 2% to 4% if the tumor is diagnosed in the antenatal period, compared with 14% to 25% if it is diagnosed intrapartum or after delivery.^{4,6} Fatal hypertensive crises can be precipitated by anesthesia, mechanical effects of the gravid uterus, vaginal delivery, hemorrhage into the tumor, and vigorous fetal movements.^{2,4} Fetal mortality is 11% to 15% when

pheochromocytoma is diagnosed before delivery but approaches 55% if the diagnosis is delayed.^{1,4} In summary, high rates of both maternal and fetal morbidity and mortality are to be expected if the diagnosis of pheochromocytoma is missed during pregnancy.^{1,3,4}

Liu et al⁸ described the reproduction of classic signs and symptoms of a pheochromocytoma by abdominal massage in the postpartum period, but this finding has not been emphasized in recent obstetric reviews. The case described above reaffirms the value of this physical finding when hypertension in pregnancy has atypical features. In retrospect, this patient's initial signs and symptoms were classic. Had she not been pregnant, the symptom triad of headaches, sweating, and palpitations in a young patient with hypertension would have demanded an immediate evaluation for pheochromocytoma.^{9,10} In pregnancy, the diagnosis is often overlooked because it is rare and because the clinical picture often resembles preeclampsia. A brief review of the pathophysiologic characteristics and management of pheochromocytoma in pregnancy might help others from repeating our mistakes.

Pathophysiology

Pheochromocytomas are adrenal medullary tumors that secrete the amines epinephrine, norepinephrine, and dopamine. They can produce other vasoactive peptides, including somatostatin, substance P, vasoactive intestinal peptide, serotonin, gastrin, calcitonin, and adrenocorticotropic hormone. This complex hormonal milieu explains the wide variety of symptoms and signs that obscure the correct diagnosis.^{5,10} A rare epinephrine-secreting tumor can even cause hypotension and shock from peripheral vasodilatation.¹¹

Pheochromocytomas occur sporadically in 90% of cases, and they are inherited in 10%. They are associated with the following familial conditions: multiple endocrine neoplasia (MEN) syndromes MEN-IIA (medullary carcinoma of the thyroid, hyperparathyroidism) and MEN-IIIB (medullary thyroid cancer, mucosal neuromas, ganglioneuromatosis); von Hippel-Lindau disease (cerebellar hemangioblastoma, renal cysts, epididymal cystadenoma); and neurofibromatosis type 1 (café-au-lait spots, neurofibromas, central nervous system tumors). These tumors are often referred to as the 10% tumors: 10% are extra-adrenal in origin, 10%

in sporadic cases are bilateral, 10% are familial, 10% are multiple, and 10% are malignant.^{9,10} Histologic characteristics alone do not predict benign behavior, because 10% can develop recurrent (metastatic) lesions within an average of 12.6 years. Larger tumors and extra-adrenal tumors are more likely to exhibit malignant behavior.¹² In the familial syndromes, 50% of the adrenal tumors are bilateral.⁹

Diagnosis

Symptoms produced by the release of catecholamines can best be described as the four Hs: hypertension, headaches, hyperhidrosis, and heart palpitations. The triad of hypertension, headaches, and palpitations has a sensitivity of 89% but a specificity of only 67% in diagnosing this condition.¹³ There is no universal consensus as to the ideal screening test or combination of tests to diagnose a pheochromocytoma.¹⁰ Measurement of 24-hour urine metanephrine and normetanephrine excretion might be the best for screening, with a sensitivity of 67% to 91% and a specificity of 83% to 103%.^{9,13}

When a pheochromocytoma is strongly suspected, however, a 24-hour urine collection to test for epinephrine and norepinephrine is preferred.⁹ Measurement of urinary vanillylmandelic acid levels is the least sensitive of the tests, with a sensitivity of 28% to 56% and a specificity of 98% to 102%.¹³ Obtaining two 24-hour urine collections for metanephrine, fractionated catecholamines, and vanillylmandelic acid is a common practice.¹² Plasma metanephrine has a high sensitivity (ie, few false-negative results) and might have value as a screening test, but it cannot be recommended at this time.^{1,9} Normal levels of plasma and urine catecholamines obtained on at least two occasions exclude a pheochromocytoma.⁷ Certain medications must be avoided during the period of urine collection. The metabolites of labetalol falsely elevate urinary catecholamines for up to 3 days after being stopped.⁹

Numerous other conditions that increase catecholamines include anxiety, pain, bladder distention, trauma, and pressure on the tumor.¹³ Ingestion of certain foods containing tyramine (cheese, beer, wine) and drugs (clonidine, metoclopramide, tricyclic antidepressants, opiates) can also stimulate the release of catecholamines.¹³ A pheochromocytoma

toma might appear as myocarditis or cardiomyopathy, and cardiomyopathy as a complication of a pheochromocytoma in pregnancy has been reported.¹⁴ On the other hand, congestive heart failure is one of the many medical conditions that can mimic a pheochromocytoma, including increased plasma and urine metanephrine levels. Other conditions include alcohol withdrawal, cocaine use, clonidine withdrawal, anxiety or panic attacks, and acute myocardial infarction.^{7,14} Brain tumors and subarachnoid bleeding can also cause hypertension, headaches, and increased catecholamines.¹⁵

Because most pheochromocytomas involve the adrenal gland, the abdomen should be initially imaged, but only after the diagnosis has been confirmed biochemically.¹⁵ Computed tomography has 94% sensitivity for detecting the tumor and is the imaging modality of choice.^{10,13} MRI is the preferred imaging study during pregnancy.^{3,4,10} An additional advantage of MRI is that a pheochromocytoma often appears as a bright mass on a T2-weighted image, which allows the radiologist to distinguish a pheochromocytoma from the asymptomatic or incidental adrenal adenoma found on 5% of imaging studies.¹⁵ A review of the literature found no other case reports in which an MRI confirmed the diagnosis of pheochromocytoma in the immediate postpartum period and resulted in the use of life-saving treatment before establishing a diagnosis biochemically. A full discussion of other specific diagnostic methods, including a variety of pharmacologic or provocative tests and tumor imaging with radioactive scintigraphy, can be found in the medical literature.^{9–11,13,15} Provocative testing during pregnancy should be undertaken with caution, however, if at all.¹

Treatment

Surgical excision of the tumor is the definitive treatment. The optimal timing of this surgery has not been determined.^{1–6} Although labor induction and delivery at 37 weeks' gestation was initially tolerated by our patient, the subsequent postpartum pulmonary edema was potentially life threatening. Had her diagnosis been suspected earlier, β -adrenergic blockade would have been delayed until α -adrenergic blockade had been established. The use of a β -blocker put our patient at risk for unopposed α -adrenergic stimulation, severe vaso-

constriction, and even death.^{1,4,11} Labetalol does not have adequate α -adrenergic blocking properties to justify its use when a catecholamine-secreting tumor is suspected.⁶ Ideally, patients should have 1 to 2 weeks of α -adrenergic blockade before adding a β -blocker to control tachycardia and tachyarrhythmias. The β -blocker – usually propranolol or atenolol – is given with an α -blocker for at least several days before attempting surgery.^{1,4} Combined α -adrenergic and β -adrenergic blockade can be used if surgery is to be delayed more than a few weeks.^{4,13}

Surgical management in early pregnancy is controversial. Keely⁶ cites a 44% risk of fetal death if surgery is performed before 24 weeks' gestation. His recommendation is to delay surgery until the fetus is mature. Other authorities quote fetal survival rates of more than 80% when the tumor is removed before 24 weeks' gestation.⁴ After 24 weeks, access to the tumor is limited by uterine size, unless the infant is first delivered. Experts concur, therefore, that a pheochromocytoma diagnosed in later pregnancy is best treated medically until the fetus is viable, unless maternal or fetal deterioration is noted.^{1,4,6} Long-term treatment with α -adrenergic receptor blocking agents has no adverse effects on the fetus, although the use of β -blockers could cause fetal growth restriction.⁴ Phenoxybenzamine is the preferred long-acting α -blocker. Prazosin – although less potent – causes less reflex tachycardia and could make the use of β -blockers unnecessary.⁹

Any decision to delay surgery might increase the risk of hemorrhage into the tumor, and patient informed consent is essential. In addition, pressure on the tumor from an enlarging uterus or an active fetus could precipitate a hypertensive crisis. Once the fetus is mature, tumor excision may be performed under adequate α -adrenergic and β -adrenergic blockade at the time of cesarean delivery. Intravenous propranolol or esmolol – as used in our patient – might be required to treat intraoperative tachyarrhythmias.⁹ In one study, a 31% maternal mortality rate was associated with tumor excision after vaginal delivery compared with a 19% maternal mortality rate after cesarean section.² Vaginal delivery is considered by most authors to be contraindicated. It is believed that vaginal delivery stimulates the massive release of catecholamines from the tumor.^{2–4} If vaginal delivery is attempted, invasive monitoring (Swan-Ganz, arterial lines) is

required to manage the extreme hemodynamic fluctuations known to occur. Conduction anesthesia is contraindicated, given the risk of sympathetic blockade, vasodilatation, and profound hypotension.¹

Prognosis

Catecholamine levels can remain elevated for several weeks after surgery. The first 24-hour urinary collection to test for catecholamine and metanephrine levels should be done 2 months after surgery. Recent studies suggest that annual urinary catecholamines should be measured for at least 5 years, even with benign lesions, as malignancy is impossible to define by histologic criteria alone.⁹ The likelihood of recurrence is higher in familial syndromes and those patients with a larger than average tumor mass.^{9,12} Gradually increasing urinary catecholamine or metanephrine levels strongly suggest recurrent disease.

Summary

The only way to diagnose a pheochromocytoma is first to think of it. The correct diagnosis was overlooked in our patient for 37 weeks and 36 frightening hours. The challenge is to differentiate preeclampsia from the hypertensive crisis of an unrecognized pheochromocytoma. Once the tumor is diagnosed, management with an appropriate α -adrenergic-receptor antagonist and delivery by cesarean section under the expert care of a perinatal team is ideal. If the tumor is not diagnosed antepartum, maternal and fetal morbidity is high.

Unique to this case was the use of MRI to diagnose pheochromocytoma and begin life-saving α -adrenergic blockade before establishing a biochemical diagnosis. Had the on-call physician awaited biochemical confirmation of a clinical suspicion – as suggested by current algorithms – the patient might have died. When the expected clinical course of hypertension in pregnancy has atypical features, the astute family physician must draw on previous training, clinical judgment, and wisdom. Paroxysmal (not labile) hypertension, failure of both labetalol and nitroglycerin to control hypertension, and numerous patient complaints – despite a language barrier – should prompt the family physician to reflect for just a moment on the missed possibilities, the unusual, the arcane. Step back and

reassess the critically ill patient. Watch the monitor as the nurse performs life-saving duties, and examine the abdomen as well as the heart and lungs in every hypertensive patient. Look for postural hypotension, labile hypertension, or an exaggerated pressor response in each hypertensive patient, pregnant or not.

If ever a colleague questions our role in the management of a critically ill patient under the care of a cardiologist and a perinatologist – think pheochromocytoma. The family physician's strength is in the breadth of shared experiences, not necessarily in the ability to perform a cesarean section or an adrenalectomy. If we fail to bring an open mind into each patient encounter – especially during childbirth – the next pheochromocytoma will be missed.

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