Case Report

Pheochromocytoma in a Pregnant Woman With Prior Traumatic Aortic Injury

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BACKGROUND: Pheochromocytoma, a catecholamine-producing tumor seldom encountered in pregnancy, is often heralded by nonspecific symptoms and undue mortality with delayed diagnosis. The presence of an aortic pseudoaneurysm poses a management challenge given the risk of aortic rupture amplified by hypertensive events.

CASE: A 30-year-old woman, gravida 3 para 1, presented at 23 6/7 weeks of gestation with vomiting, chest pain, and severe hypertension. Investigation revealed adrenal pheochromocytoma and pseudoaneurysm at the site of a previous aortic injury. Prazosin and phenoxybenzamine achieved α-blockade with subsequent addition of labetalol for β-blockade. Concerns for aortic dissection led to endovascular aortic repair at 30 2/7 weeks of gestation. A female neonate was delivered by urgent cesarean delivery for persistent postprocedure fetal bradycardia. An adrenalectomy followed with near-immediate symptom resolution. Mother and neonate remain well.

CONCLUSION: The case underscores the necessity of a meticulous approach to hypertension management and the pivotal role of diligent multidisciplinary collaboration to achieve a safe outcome.

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Pheochromocytoma is a rare catecholamine-producing tumor, seldom diagnosed in pregnancy, typically originating from chromaffin cells in the adrenal medulla\(^1\) and in the sympathetic ganglia in 10%\(^2\). Historically only one-fourth of pregnancy-associated cases were diagnosed antenatally; however, more recent reviews report antenatal diagnosis in greater than 80%\(^2,3\). Whereas older reports quote maternal mortality as high as 48% without treatment,\(^2\) contemporaneous series credit timely diagnosis and presurgical optimization with rates nearing 2%\(^3,4\).

**Teaching Points**

1. Measurement of urinary fractionated metanephrines has a similar sensitivity (95–100%) for the diagnosis of pheochromocytoma to that of plasma-free metanephrines and its assays are much more widely available than for the latter. However, both tests have false-positive rates of 10–15%, and imaging, preferably by magnetic resonance imaging, to localize the lesion is necessary.
2. Achievement of α-blockade is vital before introduction of β-blockers to avoid development of severe hypertension secondary to unopposed, catecholamine-induced α-adrenergic effects; the use of methyldopa (commonly used in perinatal hypertension management) may worsen symptoms.
3. Long-term follow-up is crucial after tumor removal, because recurrence can be observed up to 20 years later.

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**CASE**

A 30-year-old woman, gravida 3 para 1, presented at 23 6/7 weeks of gestation with excessive vomiting, chest pain, and elevated blood pressure (BP) of 220/110 mm Hg. Hypertension had been identified at 13 weeks of gestation, and metoprolol was initiated. The patient had a history of a traumatic aortic injury, requiring grafting of the descending thoracic aorta, 9 years before pregnancy. Chronic pain due to traumatic injuries led to opioid addiction managed with methadone. Blood work on presentation was normal aside from leukocytosis. A presumptive diagnosis of methadone withdrawal was made given intractable vomiting in the preceding days. With hydralazine (total 17.5 mg) and morphine (total 32.5 mg), BP decreased to 180/70 mm Hg.
Additional treatment with methyldopa, labetalol, and nifedipine over 24 hours proved suboptimal. An echocardiogram demonstrated left ventricular hypertrophy but no structural heart disease. The abdominal ultrasonogram showed a solid lesion in the right adrenal region (4.1 x 4.7 x 3.4 cm), suggestive of pheochromocytoma. Given this finding, methyldopa and labetalol were discontinued and prazosin was added. At 24 4/7 weeks of gestation, magnetic resonance imaging again suggested the presence of pheochromocytoma without evidence of para-aortic ganglioneuroma. Elective cesarean delivery was planned at 38 weeks of gestation with laparoscopic adrenalectomy 6 weeks postpartum, contingent on acceptable BP control. Inpatient management continued. At 24 5/7 weeks of gestation, concern over aortic dissection after reports of retrosternal chest pain led to another echocardiogram that suggested an abnormal appearance of the aorta and recommended a computed tomography angiogram, which identified a pseudoaneurysm at the proximal anastomosis of the aortic graft repair. Pheochromocytoma was confirmed after a 24-hour urine collection demonstrating free cortisol 652 nmol/24 hours (50–220 nmol/24 hours), daily epinephrine 1,996.0 nmol/24 hours (less than 60 nmol/24 hours), epinephrine:creatinine ratio 173.6 nmol/mmol (less than 7.0 nmol/mmol), daily norepinephrine 9,872 nmol/24 hours (less than 600 nmol/24 hours), norepinephrine:creatinine ratio 858.4 nmol/mmol (less than 70 nmol/mmol), daily metanephrines 45.4 micromoles/24 hours (less than 5.5 micromoles/24 hours), and metanephrine:creatinine ratio 3.95 micromoles/millimole (less than 0.6 micromoles/mmol).

At 25 2/7 weeks of gestation, phenoxybenzamine was initiated and prazosin was discontinued. Once α-blockade was achieved, labetalol was reintroduced to mitigate iatrogenic tachycardia. Genetic testing for other conditions associated with pheochromocytoma such as neurofibromatosis type 1, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease was negative. By 29 3/7 weeks of gestation, BP remained labile, ranging from 130/80 to 160/90 mm Hg at rest to 264/98 mm Hg with ambulation. Preeclampsia was excluded with normal laboratory parameters, lack of typical symptoms, and absence of proteinuria. Fetal monitoring with weekly ultrasonograms and daily nonstress tests was reassuring throughout.

Concerns over ongoing hemodynamic stress on the abnormal aorta prompted thought of earlier intervention. After a multidisciplinary meeting involving maternal–fetal medicine, obstetric medicine, cardiology, and vascular surgery, three options were proposed: 1) expectant course until fetal maturity followed by delivery with concomitant graft placement; 2) repeat thoracotomy with operative revision of stent graft; or 3) endovascular aortic repair of the pseudoaneurysm. The patient elected to proceed with endovascular aneurysm repair, which was planned for 30 2/7 weeks of gestation. The need for subsequent adrenalectomy was discussed, and an interval approach was chosen. Betamethasone for fetal lung maturity was administered. Because BP control was increasingly more difficult, intensive care unit transfer was organized and magnesium sulfate was initiated while awaiting endovascular aneurysm repair.

Given that the procedure was primarily for maternal benefit, an intervention for fetal distress detected in the midst of it would have been impossible because interruption of the endovascular aneurysm repair would have carried a high risk of maternal cardiovascular compromise. The patient thus made the difficult decision to forego intraoperative fetal assessment, accepting the possibility of fetal loss should significant maternal hemodynamic instability occur. However, immediate postprocedure fetal assessment and intervention on fetal behalf were highly desired, provided maternal stability was assured. The obstetric and neonatology teams were in attendance in anticipation of that possibility. The patient was placed in the supine position with leftward tilt to prevent aortocaval compression. General anesthesia was used. Intraoperatively, BP was labile, with systolic BP up to 300 mm Hg. The graft was deployed successfully (Fig. 1), and a small right common femoral artery tear was repaired. Bedside fetal ultrasonography after graft placement revealed persistent fetal bradycardia, leading to an urgent cesarean delivery, resulting in the birth of a female neonate weighing 1,555 g (50th centile) with Apgar scores of 1 at 1 minute and 9 at 5 minutes and cord arterial pH of 7.19 with base deficit of 4.2. Given the intraoperative BP instability and presence of a midline laparotomy, adrenalectomy was proposed. Consent was obtained from the patient’s husband, who was well-informed regarding the clinical context and recommendations, having attended all prior meetings. An uncomplicated adrenalectomy ensued, and BP immediately after surgery decreased to 140/60 mm Hg without need for antihypertensives. A chest computed tomography scan on postoperative day 7 verified the endovascular aortic stent in the proper position in the proximal descending thoracic aorta with no evidence of an endoleak, which refers to continued blood flow within the aneurysm around the conduit provided by endovascular aneurysm repair and is a common complication of the procedure. Urine catecholamine levels 1 week postoperatively were normal. The patient was discharged home on postoperative day 9, and the neonate was transferred to a local neonatal unit the same day, given clinical stability and a need to remain in the neonatal unit only to gain maturity. Obstetric and vascular follow-up at 7 weeks postpartum were uneventful, with complete symptom resolution. The patient remains without recurrence and her daughter is developing normally. Annual follow-up is ongoing.

**DISCUSSION**

Pheochromocytoma is typified by excess release of catecholamines (norepinephrine, epinephrine, dopamine) and their metabolites (normetanephrine, metanephrine, vanillylmandelic acid), producing paroxysmal hypertension and the classic triad of palpitations, diaphoresis, and headaches, although up to 15% of
patients remain normotensive.\(^1\) Other symptoms include chest pain, heart failure, arrhythmias, anxiety, visual disturbances, seizures, and abdominal pain.\(^1\) Orthostatic changes secondary to pheochromocytoma-related relative hypovolemia may be accentuated by pregnancy,\(^2,4\) although the entity may remain unidentified, because symptoms often mimic preeclampsia.\(^1\)

Fetal risks are ascribed to maternal catecholamine excess. Although catecholamines are metabolized by the placenta, never reaching the fetus,\(^3,6,7\) they invoke vasoconstriction in uteroplacental circulation with potential induction of fetal hypoxia, growth restriction, and abortion.\(^1,3,8\) Serial fetal ultrasonograms and regular nonstress tests starting at periviability provide a reasonable approach to monitoring of fetal growth and well-being.

Case series of undiagnosed pheochromocytoma noted fetal mortality of 26–55\%, contrasting with rates of 11–15\% with early diagnosis.\(^3,7,8\) Current diagnostic and treatment options allow earlier detection and cure in more than 90\% of patients.\(^9\) Biochemical testing remains possible, because catecholamine levels are unaffected by pregnancy.\(^10\) Although plasma-free metanephrines have a sensitivity of 95–100\%,\(^11\) urinary fractionated metanephrines provide a similar sensitivity\(^12,13\) but more widely available assays.\(^11\) Both have false-positive rates of 10–15\%.\(^11\) Although no studies establish their diagnostic value in pregnancy, no physiologic basis suggests that reference ranges would differ.\(^11\)

Imaging is required to localize the lesion.\(^9\) An abdominal ultrasonogram may be used, but uterine enlargement hampers visualization.\(^2\) Although computed tomography with contrast identifies 95\% of adrenal lesions 1 cm or greater and 90\% of extraglandular lesions greater than 2 cm,\(^14\) magnetic resonance imaging is more sensitive and specific\(^15\) and more suited to pregnancy, lacking contrast requirements and avoiding radiation exposure.\(^13\) \(^1\)-metaiodobenzylguanidine uptake occurs in 81–85\%\(^9\) but is avoided in pregnancy to limit radiation exposure.\(^4,14\) One-fourth of pheochromocytomas are genetic in origin,\(^1,16\) 33\% owing to mutations in the SDH-B, SDH-C, and SDH-D genes.\(^16\) Familial syndromes (von Hippel-Lindau disease and multiple endocrine neoplasia) also exist.\(^16\)

Antenatally, prevention of hypertensive crisis is the primary goal,\(^4\) because suboptimal control often results in adverse outcomes.\(^1\) The gravest complication is aortic dissection and vulnerability highest with aortic disease such as aortopathy owing to bicuspid aortic valve, connective tissue disorders (ie, Ehlers-Danlos or Marfan), or aortic coarctation.\(^17,18\) Because a significant number of dissections in young women occur antenatally, pregnancy has been labeled an independent risk factor for dissection, most commonly of the proximal aorta.\(^19,20\)

Suggested antihypertensives are presented in Table 1. Prompt initiation of \(\alpha\)-adrenergic blockade\(^11,14,21\) is linked with lower maternal and fetal mortality.\(^22\) Prazosin, doxazosin, and phenoxybenzamine are comparably efficacious in attaining BP and plasma volume control.\(^23\) Once \(\alpha\)-blockade is achieved, \(\beta\)-blockers are added to treat iatrogenic tachycardia.\(^21\) Maintaining this sequence is imperative, because instituting \(\beta\)-blockers as sole, or first-line, agents may result in severe hypertension secondary to unopposed, catecholamine-induced \(\alpha\)-adrenergic effects.\(^21\) Although magnesium sulfate is not used as an antihypertensive agent in hypertensive disorders of pregnancy, its pharmacodynamics make it uniquely suited to treatment of hypertension in pheochromocytoma. Not only does magnesium sulfate block catecholamine release, but it directly inhibits the sensitivity of catecholamine receptors themselves and acts as a direct vasodilator.\(^24,26\) Conversely,
methyldopa is contraindicated, because it may worsen symptoms.\(^2,4\) Beyond minimizing risks of intraoperative catecholamine surges, medical therapy permits advancement of gestation, allowing greater fetal maturity before delivery.

Timing of tumor removal depends on maternal risk, response to treatment, and gestational age at diagnosis.\(^5,7\) Failure to control BP or evidence of malignancy should prompt definitive surgical intervention, regardless of gestational age.\(^26\) Given the low risk of perioperative loss in the second trimester,\(^26\) tumor removal should be considered with diagnosis before 24 weeks of gestation.\(^7,21,30,31\) With later diagnosis, extended medical management is advocated for fetal benefit,\(^11,16\) yet becomes increasingly challenging, because pressure from the gravid uterus, fetal movements, or contractions can precipitate catecholamine release and exacerbate hypertensive crisis.\(^24\) When resection is planned, laparoscopic adrenalectomy is the procedure of choice,\(^28,32,33\) although in advanced gestations, laparotomy after cesarean delivery may be more feasible.\(^3,3,28,33\) With adequate medical treatment

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose</th>
<th>Mechanism of Action</th>
<th>Pharmacology</th>
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</thead>
<tbody>
<tr>
<td><strong>Step 1—selected choices for initiation of α-blockade</strong></td>
<td></td>
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<tr>
<td>Phenoxybenzamine</td>
<td>Initial: 10 mg orally twice a day Maintenance: 20–40 mg orally twice daily to three times daily</td>
<td>Noncompetitive α1- and α2-blockade</td>
<td>Half-life: 24 h</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Initial: 1 mg orally at bedtime Maintenance: 2–15 mg orally at bedtime</td>
<td>Competitive, peripherally acting α1-blockade (possibility of displacement by catecholamines)</td>
<td>Half-life: 2–3 h Peak: 3 h</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>2–8 mg/d</td>
<td>Competitive selective α1-blockade</td>
<td>Half-life: 24 h Peak: 4 h</td>
</tr>
</tbody>
</table>

| **Step 2—selected choices for initiation of β-blockade (once α-blockade achieved)** | | | |
| Labetalol | Initial: 100 mg twice daily Maintenance: 200–400 mg twice daily to three times daily | Selective α1- and nonselective β-blockade Paradoxical increase in BP if inadequate α-blockade* | Half-life: 6–8 h Peak: 1–2 h |
| Propranolol | 30–60 mg/d orally in divided doses | Nonselective β-blockade | Half-life: 3–6 h Peak: 1–4 h |
| Metoprolol | 100 mg/d orally divided every 12 h, not to exceed 450 mg/d | Selective β1-blockade | Half-life: 3–4 h Peak: 1.5–2 h |

| **Adjunctive agents** | | | |
| Nilidine (extended-release) | 30–60 mg/d orally, not to exceed 120 mg/d | Calcium channel blockade | Half-life: 3–5 Peak: 6 h |
| Magnesium sulfate | Bolus 4 g intravenously then infusion 1–2 mg/h | Blockade of catecholamine release, inhibition of catecholamine receptor sensitivity, direct vasodilator 99% eliminated by 24 h | |

| **Not recommended** | | | |
| Methyldopa | 250–1,000 mg/d divided every 6–12 h orally (maximum 3 g/d) | Aromatic amino acid decarboxylase inhibitor* | Half-life: 10 h Peak: 6–9 h |

BP: blood pressure.

* Causes fluorescence in urine samples at the same wavelengths as catecholamines and thus may lead to reports of falsely high levels of urinary catecholamines.
and vaginal delivery, postpartum interval laparoscopy is reasonable. Delaying tumor removal allows for reduced tumor site vascularity as the physiologic adaptations of pregnancy dissipate.

Guidance concerning optimal mode of delivery is based on case reports and lacks consensus. Relevant articles reference a two decades old account by Schenker and Granat, quoting maternal mortality of 31% with vaginal delivery compared with 19% with cesarean delivery. Although advocates of elective cesarean delivery cite ease of monitoring and potential for concurrent tumor removal, reports of successful vaginal deliveries in well-chosen patients exist. Similarly, vaginal delivery in the context of previous stent graft repair of a traumatic aortic transection has been described. If vaginal delivery is considered, adequate epidural analgesia should be used to decrease pain-related catecholamine release and instrumental assistance offered in the second stage of labor to effect delivery, eliminating the need for maternal Valsalva maneuver and minimizing changes in intraabdominal pressure.

After completion of pregnancy and tumor removal, the need for continued, long-term follow-up remains, owing to the possibility of incomplete resection and risk of recurrence, which persists for up to 20 years.

REFERENCES


