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CLINICAL CARDIOLOGY

CASE REPORT: HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

Pheochromocytoma

Secondary Hypertension in Pregnancy

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ABSTRACT

Secondary hypertension can occur from a variety of renal and endocrine disorders. Pheochromocytoma, a rare catecholamine-secreting neuroendocrine tumor, is associated with adverse maternal and fetal outcomes in the absence of a timely diagnosis and a coordinated multidisciplinary approach. Clues to diagnosis include resistant hypertension or an adrenal mass on imaging. (J Am Coll Cardiol Case Rep 2024;29:102217) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 29-year-old female patient, G5P1213, presented to an outside institution at 10 weeks' gestation with substernal chest pain, abdominal pain, blood pressure of 180/94 mm Hg, and a heart rate of 94 beats/min. Her high-sensitivity troponin level was elevated at 4,369 pg/mL (**Table 1**), but cardiac catheterization did not show coronary disease consistent with myocardial infarction nonobstructive coronary disease (MINOCA). The symptoms were attributed to a hypertensive emergency. She was subsequently referred to our cardio-obstetrics group for definitive management in the second trimester.

LEARNING OBJECTIVES

- To recognize clues to the presence of secondary hypertension in pregnancy.
- To differentiate pheochromocytoma from preeclampsia and other hypertensive disorders of pregnancy.
- To develop a team approach to timely diagnosis of pheochromocytoma in pregnancy.

Her past medical history included preeclampsia complicated by hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) in 2 earlier completed pregnancies and cesarean delivery. She had a history of nephrolithiasis and pyelonephritis. Outside of pregnancy, she denied a history of preexisting hypertension, smoking, or diabetes. However, she noted a family history of coronary artery disease.

QUESTION 1: HOW DO YOU DEFINE HYPERTENSION IN PREGNANCY?

Hypertension that develops before 20 weeks' gestation or that persists for 12 or more weeks post partum is considered chronic. Although the American College of Cardiology/American Heart Association hypertension clinical practice guidelines lowered the

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ABBREVIATIONS AND ACRONYMS

HELLP = hemolysis, elevated liver enzymes, and low platelets

LV = left ventricular

MRI = magnetic resonance imaging

RAAS = renin-angiotensin-aldosterone system

threshold for the diagnosis of stage 1 hypertension to 130/80 mm Hg, most global guidelines define hypertension in pregnancy as blood pressure ≥140/90 mm Hg. However, the diagnosis can be missed because of the physiological decreases in systolic and diastolic blood pressure that occur in early gestation. These decreases typically reach a nadir between 16 and 20 weeks' gestation and gradually rise to prepregnancy levels by term. Systolic blood pressure ≥160/90 mm Hg is considered severe. Gestational hypertension refers to new onset hypertension that develops after 20 weeks' gestation without proteinuria. In contrast, preeclampsia typically occurs after 20 weeks and is often associated with proteinuria and/or end-organ dysfunction.[1] Pregnancy-associated hypertensive disorders are major contributors to maternal and fetal morbidity and mortality.[2] Although indications for initiation of therapy and goal blood pressures are evolving, appropriate therapy may reduce maternal complications without increasing fetal risk.

QUESTION 2: WHAT IS THE DIFFERENTIAL DIAGNOSIS OF HYPERTENSION IN PREGNANCY?

The differential diagnosis of hypertension in pregnancy includes essential hypertension and secondary hypertension related to other disorders such as obstructive sleep apnea, thyroid disease, chronic kidney disease, primary aldosteronism, renal artery stenosis, Cushing syndrome, and pheochromocytoma, or it can be caused by the pregnancy itself. Initially, her early gestational age suggested chronic hypertension.

Secondary hypertension should be suspected in the setting of severe or resistant hypertension, sudden rises in previously stable patients, patients under age 30 years who are not obese in the absence of a family history, hypertension in the setting of electrolyte disorder, or age of onset before puberty.[3] A differential diagnosis scheme for secondary hypertension is shown in **Table 2**. Optimal management strategies vary by cause.[4-8] In nonpregnant patients, resistant hypertension should be considered when blood pressure remains elevated at maximum or maximally tolerated doses of 3 agents, typically including a long acting calcium-channel blocker, a renin-angiotensin system (RAAS) blocker, and a diuretic agent.[3] The diagnosis is more complicated in pregnancy because RAAS blockers are contraindicated and diuretic agents are not frequently used.

TABLE 1 Laboratory Findings

	Normal	Result
Plasma metanephrine	0-0.49 nmol/L	7.66 nmol/L
Plasma normetanephrine	0-0.89 nmol/L	1.52 nmol/L
Urine metanephrine (24-h)	36-229 μg/d	8,929 μg/d
Urine normetanephrine (24-h)	95-650 μg/d	1,290 μg/d
Renin activity	0.2-1.6 ng/mL/h	6.0 ng/mL/h
Urine aldosterone (24-h)	1.2-28.1 μg/d	72.9 μg/d
Urine cortisol (24-h)	<59 μg/d	58.5 μg/d
Aldosterone	<16.0 ng/dL	8.4 ng/dL
B-type natriuretic peptide	<100 pg/mL	11 pg/mL
High-sensitivity troponin	<15 ng/mL	4,369 ng/mL
Thyroid stimulating hormone	0.35-4.00 mIU/mL	1.52 mIU/mL
Urine toxicity screen	—	Negative

Laboratory testing was remarkable for an initial potassium level of 2.5 mEq/L, blood urea nitrogen of 10 mg/dL, creatinine of 0.63 mg/dL, glomerular filtration rate of 112 mL/min, and normal liver function. The initial work-up included the following: transthoracic echocardiography, revealing mild to moderate LV dysfunction with an ejection fraction of 40% to 45% and anterior and anteroseptal hypokinesis (Video 1); computed tomography for pulmonary embolism, which was negative; and electrocardiogram showing ST-segment and T-wave changes that were attributed to hypokalemia (**Figure 1**). She underwent cardiac catheterization, revealing normal coronary vasculature without evidence of dissection. Of note, a renal ultrasound scan at 6 weeks' gestation showed a round left suprarenal mass measuring 3.6 cm. Additional laboratory results, which demonstrated elevated urinary catecholamines, are shown in **Table 1**.

QUESTION 3: HOW DO THESE INVESTIGATIONS REFINE THE DIFFERENTIAL DIAGNOSIS?

Chronic kidney disease is the most common cause of resistant hypertension in pregnancy.[4] Normal kidney function in our patient eliminated this diagnosis. This patient did not have pre-existing hypertension, thus making treatment resistance or apparent resistance unlikely. Her thyroid function was normal. Negative toxicology screen results excluded a drug-induced hypertensive emergency. The mass noted on the initial ultrasound scan and subsequent abnormal urinary catecholamines were clues prompting further investigation. When pheochromocytoma is suspected, measurements of plasma or urinary free

TABLE 2 Secondary Hypertension in Pregnancy

Cause	Comments
Chronic kidney disease	Most common cause (0.9% pregnancies) May not be recognized before to pregnancy Diagnosed by elevated BUN/creatinine or reduced GFR
Obstructive sleep apnea	Consider in setting of obesity May predate pregnancy or begin during pregnancy Increasing prevalence over the pregnancy continuum May require special screening symptom tools or sleep study for diagnosis
Thyroid disease	Common cause of secondary hypertension in women aged 19-39 years, overlapping with the reproductive period Both hyperthyroidism and hypothyroidism can affect BP
Renovascular hypertension	In reproductive age group, frequently caused by fibromuscular dysplasia Consider in setting of abdominal or carotid bruit Consider with history of spontaneous coronary artery or peripheral (carotid, vertebral, renal) dissection
Primary aldosteronism	Most common form of the rarer treatable causes of secondary hypertension Consider in the setting of otherwise unexplained hypokalemia Suspect with adrenal mass Diagnosis challenging in pregnancy because of increased PRA in pregnancy; consider with PRA between 1 and 4 ng/nL/h Formal diagnosis often delayed until post partum
Pheochromocytoma	Classic triad of headache, sweating, and tachycardia Sustained or paroxysmal hypertension may present with MINOCA or Takutsubo Syndrome Consider with adrenal mass
Cushing syndrome	More likely derived from an adrenal source in pregnancy Suspect with classic physical finding such as proximal muscle weakness, supraclavicular or dorsocervical fat pads, facial plethora, purple striae, truncal obesity, diabetes or glucose intolerance, abnormal menstrual cycles before pregnancy, or adrenal incidentaloma Diagnosis confirmed with 24-h urine free cortisol or midnight salivary cortisol testing
Coarctation	May manifest with hypertension in pregnancy if coarctation severity is mild or if repair occurred late Suspect with radial femoral pulse delay, when upper extremity BP is greater than or equal to lower extremity BP, or in the setting of bicuspid aortic valve Diagnosis usually confirmed by echocardiography, magnetic resonance imaging, or CT scan

BP = blood pressure; BUN = blood urea nitrogen; CT = computed tomography; GFR = glomerular filtration rate; PRA = plasma renin activity.

fractionated metanephrines have the highest diagnostic accuracy.[8]

At 22 weeks' gestation, she was evaluated by a multidisciplinary team consisting of cardiology, maternal fetal medicine, endocrinology, urology, genetic counseling, and obstetric anesthesia. Repeat transthoracic echocardiography showed normalization of left ventricular (LV) function. Abdominal magnetic resonance imaging (MRI) showed a 4.3-cm left adrenal mass concerning for pheochromocytoma (**Figures 2A and 2B**). Magnetic resonance imaging is preferred to ultrasound for diagnosis.[8]

QUESTION 4: HOW DO YOU MANAGE PHEOCHROMOCYTOMA IN PREGNANCY?

Before definitive surgical management, alpha-blockade is critical to avoid perioperative hypertension and hypotension, but unlike in the nonpregnant state, orthostasis and heart rate control are more difficult to obtain because of the systemic adaptations of pregnancy. She was started on doxazosin for alpha-blockade followed by metoprolol for heart rate control.

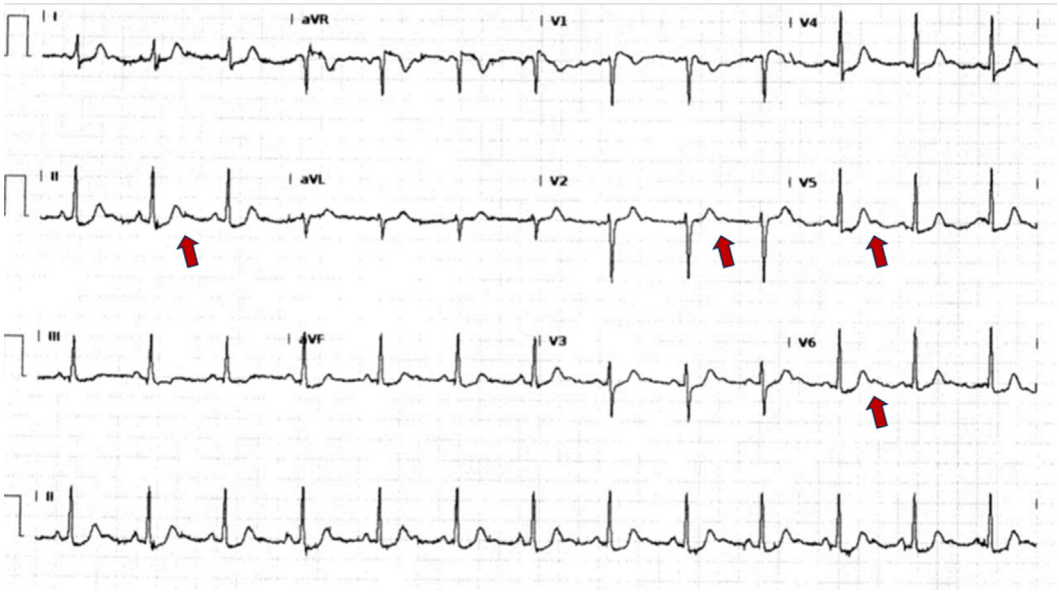
She underwent robotic-assisted left adrenalectomy without perioperative complication. The pathologic features were consistent with pheochromocytoma (**Figures 3A to 3C**). Surgical intervention is ideally performed before 24 weeks' gestation or at/after delivery.[8] Our case is one of few reported in the literature that used robotic-assisted adrenalectomy in pregnancy. Fetal monitoring should be considered if the fetus is viable.

After resection, doxazosin was discontinued, and she was tapered off metoprolol. Blood pressure remained normal. She had an uncomplicated antepartum course. The patient underwent scheduled repeat cesarean delivery and bilateral tubal ligation. She is currently not taking any antihypertensive medications and is doing well.

QUESTION 5: WHAT IF SURGICAL MANAGEMENT IS DEFERRED UNTIL POST PARTUM?

If surgical treatment is deferred until post partum, adequate adrenergic blockade should occur. Without blockade, excess circulating maternal catecholamines can lead to an increased risk of adverse cardiac outcomes such as hypertensive crisis mimicking preeclampsia, myocardial infarction, cerebrovascular vascular accidents, heart failure, and maternal death. Our patient had complications of hypertensive

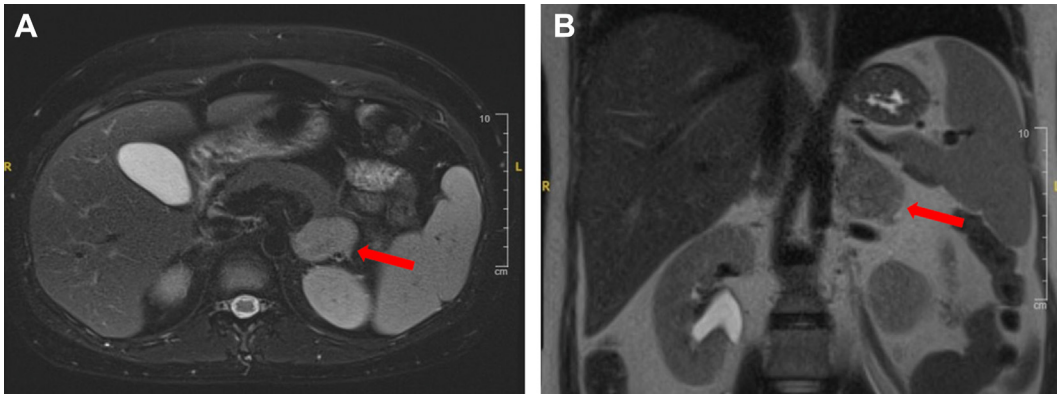
FIGURE 1 12-Lead Electrocardiogram at Initial Presentation



Electrocardiogram shows sinus rhythm with ST-segment depression and prominent U waves (arrows) in the precordial leads compatible with hypokalemia.

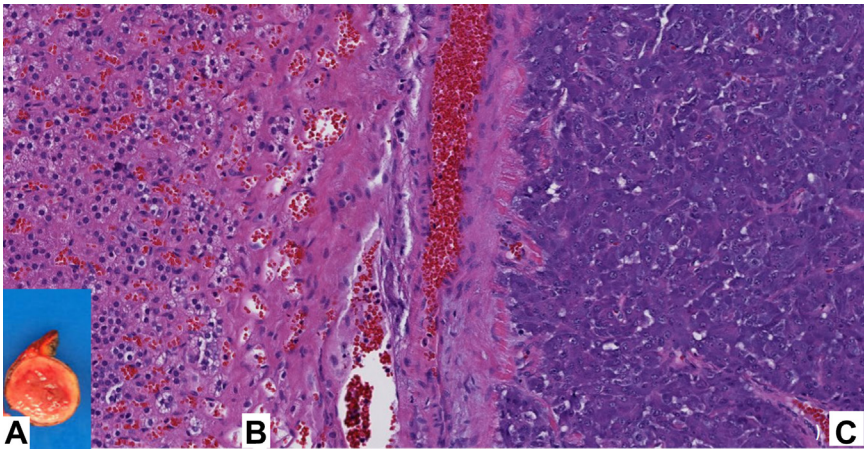
urgency, myocardial injury, and LV dysfunction before diagnosis that made her a suitable candidate for surgical resection. Although the optimal mode of delivery is uncertain because there are limited data on vaginal delivery in women who have not undergone surgical resection, our experience suggests that cesarean delivery should be reserved for the usual obstetric indications. Treatment goals should aim to maintain uteroplacental blood flow while avoiding severe hypertension.[8] Genetic screening should be offered because one-third of cases are familial and result from an identifiable pathogenic variant.[9] Of

FIGURE 2 Pheochromocytoma: Magnetic Resonance Imaging



(A) Axial T2-weighted image of an ovoid, mildly T2-hyperintense mass in the region of the left adrenal gland (arrow). (B) Coronal image of a left adrenal mass abutting adjacent kidney (arrow).

FIGURE 3 Pheochromocytoma: Pathologic Specimen



(A) The inset shows a gross specimen, with the lighter pink tissue rim of normal adrenal cortex and the darker tissue of the neuroendocrine-secreting tumor. (B) Normal adrenal tissue is present on the left portion of the microscopic section. (C) In contrast, the right portion shows typical polygonal and spindle-shaped cells arranged in nests (nests of Zellbalen) with prominent nucleoli and basophilic granular cytoplasm (original magnification 3B and 3C: 20x).

note, the results of our patient's genetic testing for hereditary paraganglioma and pheochromocytoma were negative.

Although maternal catecholamines do not cross the placental barrier easily, uncontrolled hypertension can lead to fetal adverse outcomes, including spontaneous abortion, fetal growth restriction, preterm birth, fetal distress, and fetal demise.[1,2]

QUESTION 6: HOW CAN YOU DIFFERENTIATE PHEOCHROMOCYTOMA FROM PREECLAMPSIA?

Pheochromocytoma is estimated to occur in only 0.2 per 10,000 pregnancies, but it should be suspected in the presence of new onset hypertension at <20 weeks' gestation, paroxysmal hypertension, paroxysmal headache, orthostatic hypotension, features of heredity syndromes, or suggestive symptoms such as sweating, palpitations, headache, weakness, or anxiety.[8] Pheochromocytoma is the most common cause of adrenal tumor in pregnancy.[8]

Differentiation of pheochromocytoma from preeclampsia may be challenging, but typically preeclampsia manifests later, is associated with proteinuria and edema, and may be associated with abnormal liver enzymes and a low platelet count (HELLP syndrome), whereas pheochromocytoma manifests earlier and with paroxysmal symptoms usually in the absence of end-organ dysfunction, as noted earlier.

PERSPECTIVES

Untreated pheochromocytoma is associated with adverse maternal fetal outcomes. Work-up for secondary hypertension should be considered in the setting of pregnancy when pre-existing or new onset resistant hypertension is present, or when the patient is unresponsive to the standard antihypertensive agents commonly used in pregnancy. Early screening and intervention are essential to prevent unwarranted preterm delivery for a false diagnosis of preeclampsia. Outcomes are improved when a multidisciplinary care team is involved.

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KEY WORDS **hypertensive disorder pregnancy, neuroendocrine tumor, resistant hypertension**

APPENDIX **For a supplemental video, please see the online version of this paper.**