Peripartum Hypertension from Pheochromocytoma: A Rare and Challenging Entity

Yehuda Kamari, Yehonatan Sharabi, Adi Leiba, Edna Peleg, Sara Apter, and Ehud Grossman

Background: Pheochromocytoma, a rare and usually curable cause of hypertension, is characterized by symptoms and signs related to increased catecholamine secretion. Pregnancy can elicit clinical manifestations of otherwise unrecognized pheochromocytoma.

Methods and Results: Four women, ranging in age from 27 to 37 years, were referred to the hypertension clinic with the following presentations: 1) a 35-year-old woman, diagnosed with gestational hypertension and headaches during the third trimester of her pregnancy and 5 months after delivery, was hospitalized with pulmonary edema. Echocardiography revealed severe dilated left ventricular (LV) dysfunction. Cardiac function was normalized after surgical resection of a pheochromocytoma from her left adrenal; 2) a 37-year-old woman suffered from preeclampsia, persistent hypertension and orthostatic hypotension after a cesarean section. A diagnostic work-up revealed a catecholamine-secreting paraganglioma in the retroperitoneum. The patient underwent a laparoscopic resection of the tumor; 3) a 27-year-old woman suffered from hypertension and episodes of palpitations, sweating, and dyspnea in the first trimester of her pregnancy. An ultrasound revealed a 5-cm mass in the left adrenal. She underwent a left adrenalectomy at the 17th week of pregnancy, which confirmed the diagnosis of pheochromocytoma; 4) a 34-year-old woman, at the 26th week of pregnancy, presented with an acute loss of vision and blood pressure of 230/140 mm Hg. Fundoscopy showed papilledema with soft exudates in both eyes. Chemical studies were positive and imaging revealed a left adrenal pheochromocytoma. Despite aggressive medical treatment, fetal distress mandated a laparotomy at the end of the 28th week of pregnancy. A healthy newborn was delivered and resection of the adrenal tumor confirmed the diagnosis of pheochromocytoma.

Conclusions: Although rare, pheochromocytoma can cause severe peripartum hypertension. Screening for pheochromocytoma, ideally with plasma-free metanephrines, should be considered in cases of peripartum hypertension.

Key Words: Pheochromocytoma, pregnancy, hypertension.

Pheochromocytoma is a rare cause of sustained and paroxysmal hypertension. Most cases of pheochromocytoma are sporadic; however, about 20% to 30% may be syndromic (multiple endocrine neoplasia [MEN] type 2a, MEN type 2b, von Hippel-Lindau disease, neurofibromatosis type 1) and due to a mutation of RET, VHL, SDHB, SDHD genes. In 15% to 24% of clinically sporadic pheochromocytoma a germ-line mutation may be found and in young people the risk for a germ-line mutation may be higher. The classic clinical findings of headaches, profuse sweating, palpitations, tachycardia, nervousness, pallor, and fever, accompanied by hypertension, are well known. Cardiovascular manifestations such as arrhythmias, angina pectoris, dilated cardiomyopathy, acute heart failure, and cardiogenic shock have also been reported. Although rare, pheochromocytoma is clinically important because it is usually curable but if unrecognized can cause arrhythmia, stroke, heart failure, and death.

Pregnancy-induced hypertension bares risks to both the mother and the fetus. There are several types of hypertension in pregnancy. Chronic hypertension can begin before...
and continue after delivery; transient hypertension usually resolves within 12 weeks postpartum; gestational hypertension, that is, hypertension occurring after week 20 without proteinuria; preeclampsia is associated with high blood pressure (BP) and proteinuria that usually appears after week 20 of gestation; and chronic hypertension with superimposed preeclampsia. Endocrine disorders rarely cause elevated BP during pregnancy. However, it is vital to have a high index of suspicion for pheochromocytoma as the risk for fetal and maternal morbidity and mortality is high. Endocrine disorders presenting as hypertension are primarily the result of autonomous production of renin, aldosterone, cortisol, or catecholamines.10 Among these conditions, pheochromocytoma is extremely rare, with an estimated prevalence in full-term pregnancies of 1 in 50,000 to 54,000.11 Diagnosing peripartum pheochromocytoma is challenging and extremely important, as it requires dealing with special issues in the clinical management such as specific treatments to lower BP, and determining the appropriate time and mode of delivery. We present four cases of pheochromocytoma diagnosed during pregnancy or early postpartum, illustrating the difficulty and importance of diagnosis and management.

**Case Presentations**

**Case 1**

A 35-year-old woman presented to the emergency department with pulmonary edema 5 months post cesarean section. During the third trimester of her last pregnancy she developed hypertension that was attributed to preeclampsia. She did not suffer headaches, palpitations, or sweating and her BP was normal after she gave birth. Physical examination on admission showed BP of 115/80 mm Hg, pulse rate 100 beats/min, and signs of left heart failure. Echocardiography revealed a dilated left ventricle with severe global left ventricular (LV) dysfunction (ejection fraction 25%). She developed shock, which required treatment with intravenous norepinephrine. It was suspected that she had a pulmonary embolism and therefore, she underwent a chest computerized tomographic (CT) angiography. The CT excluded pulmonary embolism, but unexpectedly revealed a left adrenal mass. Urinary catecholamines and metanephrines were elevated (Table 1); magnetic resonance imaging (MRI) (Fig. 1) and $^{123}\text{I}$-metaiodobenzylguanidine (MIBG) scan were suggestive of pheochromocytoma. She was treated with a loop diuretic, angiotensin-converting enzyme (ACE) inhibitor, aldosterone antagonist, and a selective $\beta_1$ blocker. Once pheochromocytoma was diagnosed, doxazosin was added to the regimen. A laparoscopic adrenalectomy confirmed the diagnosis of pheochromocytoma and the patient’s condition improved with a complete recovery of the LV function.
Case 2

A 37-year-old woman, with a history of hypertension that developed during the first trimester of her last pregnancy, was admitted to the hospital with severe hypertension that was controlled with nifedipine and \( \alpha \)-methyldopa. The hypertension persisted 2 months after a cesarean section and she complained of bouts of headaches with no palpitations or sweating. She had orthostatic hypotension with supine BP of 200/100 mm Hg and standing BP of 160/95 mm Hg. Echocardiography showed LV hypertrophy with diastolic dysfunction. Urinary catecholamines and metanephrines were elevated (Table 1). Plasma norepinephrine levels were elevated (5135 pg/mL; normal range 300 to 600 pg/mL) and were not suppressed 3 hours after 0.3 mg of clonidine (7618 pg/mL). An ultrasound study of the kidneys and adrenals was normal. An abdominal CT scan showed a retroperitoneal mass (Fig. 2) and \(^{123}\)I MIBG scan showed enhanced uptake in the retroperitoneal mass consistent with an extra-adrenal pheochromocytoma. The patient underwent a laparoscopic resection of the tumor with a complete recovery.

**FIG. 1.** Magnetic resonance imaging scan of a 35-year-old pregnant woman with hypertension and an adrenal pheochromocytoma: axial T2-weighted (A); T1-weighted (B); and gadolinium enhanced T1-weighted (C) images show a pheochromocytoma in the left adrenal gland (arrows). The tumor displays the typical features of pheochromocytoma with markedly high signal intensity on T2-weighted image (A) and intense enhancement on the contrast-enhanced image (C).

**FIG. 2.** Computed tomographic (CT) scan of a 37-year-old pregnant woman with hypertension and an extra-adrenal pheochromocytoma: unenhanced CT scan (A) shows a 3.0- by 3.4-cm mass in the retroperitoneum, located to the left of the abdominal aorta (black arrow) and contrast-enhanced CT scan (B) shows that the mass enhances markedly and has a small cystic component (white arrow).
Case 3

A 27-year-old woman, in the first trimester of her second pregnancy, was referred to our hypertension clinic due to high BP and episodes of palpitations, sweating, and dyspnea. Similar complaints were described during her previous pregnancy, but they disappeared after delivery. An abdominal CT scan performed after the first delivery revealed a 5-cm mass in the left adrenal gland. The initial diagnostic workup did not reveal the nature of this mass, and the patient did not pursue follow-up for further evaluation as she remained asymptomatic. When she came to our clinic her urinary catecholamine levels were elevated (Table 1). Treatment with labetalol was initiated with normalization of BP. Although the tumor was large (5 cm), it was accessible and resectable at this stage. Considering the risk of continuing the pregnancy with a large catecholamine-producing tumor and the ability to remove the whole tumor, we decided to remove the tumor before the 24th week of gestation. In the 17th week of her pregnancy she underwent a left adrenalectomy, which confirmed the diagnosis of pheochromocytoma. She completed a full-term pregnancy and a normal baby was delivered at 40th week of gestation.

Case 4

A 34-year-old woman, in the 26th week of her pregnancy, was admitted to the hospital because of acute loss of vision (230/140 mm Hg in both arms). She did not recall having headaches, palpitations, or sweating. Fundoscopy showed papilledema and soft exudates in both eyes. Urinary catecholamine levels were elevated (Table 1). Abdominal ultrasound and MRI revealed a left adrenal mass, compatible with pheochromocytoma. Despite aggressive medical treatment, fetal distress was evident in preeclampsia. The last three cases represent hypertension occurring during pregnancy that suggested the possible diagnosis of pheochromocytoma.

Several mechanisms might explain pheochromocytoma becoming clinically overt only during and probably due to the pregnancy. It has been suggested that increased intra-abdominal pressure, fetal movement, uterine contraction, abdominal palpation, the process of delivery, and general anesthesia can induce a surge of catecholamines. The latter may initiate the classic symptoms or could induce the less common clinical manifestations such as arrhythmia, stroke, and heart failure.

The first patient in our series had severe cardiomyopathy and presented with circulatory shock. It is probable that this unusual presentation was entirely related to the cardiomyopathy due to excessive catecholamines released by the pheochromocytoma. Alternatively, it could be related to idiopathic postpartum cardiomyopathy coexisting with the pheochromocytoma. The unusual presentation of circulatory collapse was probably due to low cardiac output from catecholamine-induced cardiomyopathy.

The complete recovery after removal of the tumor suggests that the entire clinical presentation was due to pheochromocytoma. The chance of a complete recovery of LV function in idiopathic peripartum cardiomyopathy is less than 50%, whereas the chance of LV function recovery in pheochromocytoma is much higher. Cases of catecholamine-induced cardiomyopathy in pregnancy or during the peripartum period have been described. To our knowledge, this is the first case described in the English language literature of peripartum cardiomyopathy presenting with circulatory shock as the clinical manifestation of sporadic pheochromocytoma. One other case was reported in a pregnant woman with familial pheochromocytoma associated with von Hippel-Lindau disease.

The second patient had hypertension during pregnancy and was misdiagnosed as preeclampsia. Her hypertension persisted after delivery and was associated with orthostasis. About half the patients with hypertension due to pheochromocytoma have sustained hypertension. When hypertension is first diagnosed during pregnancy it is usually attributed to preeclampsia. This case illustrates the challenge of diagnosing pheochromocytoma during pregnancy. Postural hypotension served as the only clinical clue for suspecting pheochromocytoma after delivery. Measurement of BP both in the supine and standing positions during pregnancy could have led to an early diagnosis of pheochromocytoma in our patient. In addition, about 18% of catecholamine-secreting tumors are extra-adrenal and a simple ultrasound examination may miss the tumor, as was the case during pregnancy to prevent fetal and maternal morbidity and mortality, as specific treatment is required in the management of both hypertension and delivery.

The four patients with peripartum pheochromocytoma presented as summarized in Table 1. The first case represents a reversible form of peripartum catecholamine cardiomyopathy that is important to suspect as it may be curable. Table 1 presents the four patients with peripartum pheochromocytoma.
with our patient. Our patient completed a full-term pregnancy without any significant complications.

The third patient represented the classic clinical presentation of pheochromocytoma, which included paroxysmal attacks of hypertension accompanied by palpitations, sweating, dyspnea, and nausea. These symptoms appeared twice during pregnancy and disappeared after the first delivery. The diagnosis was delayed because she was asymptomatic between the pregnancies. In her case it appears that the pregnancy exacerbated her symptoms. Because she became symptomatic relatively early in the course of her pregnancy with a large tumor that seemed resectable, we were concerned of complications during the remainder of the pregnancy and therefore decided to resect the tumor.

The fourth patient exhibited malignant hypertension with hypertensive encephaopathy and acute blindness. We previously described a case of a child with pheochromocytoma who presented with acute blindness.23 As far as we know this report is the first description of pheochromocytoma in pregnancy presenting with loss of vision. This case emphasizes the fact that extreme elevation in BP levels accompanied by visual symptoms should lead to the consideration of pheochromocytoma. The life-threatening hypertensive crisis in this case and the sequence of events in case 3 show that pheochromocytoma can be asymptomatic between pregnancies and cause a hypertensive crisis during the next pregnancy. Therefore, screening for pheochromocytoma should be made in cases with manifestations similar to the case reported.

Pheochromocytoma during pregnancy, as with other patients suspected of harboring this tumor, should first be diagnosed biochemically. This can be achieved with a 24-h secretion of urinary fractionated metanephrines. Plasma-free metanephrine and normetanephrine levels, which have very high diagnostic sensitivity (98% to 99%) can be helpful in excluding pheochromocytoma, were not available for use in our center at the time diagnoses were made in our patients. However, one must remember that plasma-free metanephrines in nonpregnant women may have a false-positive rate of 11% to 15%.24,25 There are no data regarding the sensitivity and specificity of plasma-free metanephrine and normetanephrine levels in pregnancy. Considering the significant rate of false positive in all the methods used for screening, we do not advocate that all pregnant hypertensive women should be screened for pheochromocytoma. Screening should be reserved for cases in which pheochromocytoma is considered based on clinical judgment. Larger prospective studies might be warranted to study this issue, taking into account the likelihood of the need to follow-up on false-positive results.

After establishing the diagnosis of pheochromocytoma in pregnant women, localization of the tumor should be performed with MRI. During pregnancy only imaging with MRI should be used for localizing pheochromocytoma, because it does not involve any radiation exposure, and provides good anatomical description.26 The MRI is also the preferred method for detection of extra-adrenal abdominal and pelvic tumors and familial adrenal pheochromocytoma.27 Functional imaging with 131I or 123I MIBG may be very helpful in detecting extra-adrenal pheochromocytoma because it scans the entire body,28 but it should be avoided during pregnancy. We have used MRI to detect extra-adrenal tumors during pregnancy. We have also used MIBG scintigraphy to detect pheochromocytomas postpartum. This approach maximized the ability to detect preeclampsia and preeclampsia extra-adrenal pheochromocytomas.

Treatment of pheochromocytoma requires aggressive medical control of BP and surgical removal of the tumor. Control of BP is the same in all patients with pheochromocytoma. Patients presenting with a hypertensive crisis may require temporary intravenous treatment, preferably with phentolamine, nitroglycerine, or nitroprusside to terminate the hypertensive crisis. In most cases, preoperative nonselective blockade of α-adrenergic receptors with phenoxybenzamine (10 to 30 mg twice daily), or selective blockade of α1 receptors with doxazosin (starting with 1 mg and increasing the dose gradually up to 8 mg daily if required and tolerated), or administration of calcium channel blockers, can usually control BP. The α1-blockade for 1 or more weeks before surgery will reverse hypervolemia, which is often present in patients with sustained hypertension due to pheochromocytoma.2 Preoperative β1-blockade may be required to control supraventricular arrhythmias and tachycardia or anginal syndrome. However, β-blockers should never be given before α-blockade, because β-blockade alone can cause marked hypertension in patients with epinephrine-secreting tumors. This is more apt to occur with nonselective β-blockers, because they inhibit any vasodilating effect of epinephrine by blocking β2-receptors and, thereby, enhancing vasoconstriction.27

α-Methylparatyrosine is an effective drug to control symptoms related to catecholamines excess. It is known to decrease serum catecholamines by inhibiting tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis. It has been reported to induce a decrease in the size of the tumor29 and was also reported to be effective and safe in patients with malignant pheochromocytomas.30 α-Methylparatyrosine has been reported to improve systolic function in patients with catecholamine-related cardiomyopathy31 and it has a particularly important role in the preoperative management as it decreases the surgical morbidity in patients with pheochromocytomas.32 We did not use α-methylparatyrosine because it is not available for routine use in our medical center and the patient improved with conventional treatment of heart failure.

The treatment of our patients was tailored to address their unique clinical challenges. The patient who presented with left heart failure was treated with a loop diuretic, ACE inhibitor, aldosterone antagonist, and a selective β1-blocker. At that time pheochromocytoma was not suspected, and she had primarily heart failure and did not
receive α-blockers. Once the diagnosis of pheochromocytoma was made she received doxazosin (2 mg daily). The second patient was initially treated postpartum with amlopidine, disothiazide, and a selective β1-blocker. Once pheochromocytoma was diagnosed doxazosin was added. The dose was increased progressively to keep systolic BP levels around 120 mm Hg. The fourth patient was initially treated with intravenous labetalol, which paradoxically induced a slight increase in BP. This led us to suspect the diagnosis of pheochromocytoma. Treatment with intravenous phentolamine simultaneously with an oral α1-blocker (doxazosin) was initiated and led to a dramatic decrease in BP with improvement of her vision. This case illustrates that labetalol should not be used to control hypertension if pheochromocytoma is considered because it may cause paradoxical hypertension. Preoperative sedation with diazepam, secobarbital, or meperidine should be avoided because they may release catecholamines, and atropine should be avoided because it may accelerate tachycardia. A muscle relaxant administered before endotracheal intubation minimizes a hypertensive response, and isoflurane is an excellent anesthetic. Arterial pressure, electrocardiogram, and blood gasses should be monitored at all times. Prompt administration of phentolamine, nitroglycerine, or nitroprusside can control hypertensive episodes and esmolol or lidocaine can control arrhythmias. Because hypovolemia is often present in patients with sustained hypertension due to pheochromocytoma, all of our patients received volume replacement during the operation to prevent postoperative hypotension.

The timing of surgical removal of the tumor after the diagnosis of pheochromocytoma during pregnancy, as in cases 3 and 4, is a challenging and a controversial issue. The timing may depend on the gestational age, the clinical response to medical treatment, the accessibility of the tumor, and the presence or absence of signs of fetal distress. Because it is more difficult to remove the tumor after 24 weeks of pregnancy, some investigators have recommended surgical removal of the tumor early in pregnancy, after adequate medical treatment. Other researchers have reported better results when fetal maturity is attained, with surgical removal of the tumor after an elective caesarean delivery. In the case of our third patient, diagnosis at an early stage of pregnancy, prominent symptoms, and the large size of the tumor, suggested the possibility of a devastating and catastrophic life-threatening hypertensive crisis with progression of the pregnancy. We therefore chose to remove the tumor at an early stage, to permit a safe delivery. The fourth patient, who presented with acute loss of vision, was initially managed conservatively, but the appearance of fetal distress mandated prompt delivery of the baby and resection of the tumor. Ideally, delivery of the fetus should be postponed until fetal maturity is attained. Once patients become symptomatic, medical treatment to control BP should be initiated. If medical treatment controls BP, careful monitoring of the baby for signs of fetal distress should be performed and the delivery should be withheld. If fetal distress appears despite medical treatment, a prompt cesarean delivery of the baby should be performed, as was done in our fourth patient.

Despite the clinical presentations of our patients all babies were born with normal cardiovascular systems. Patients with pheochromocytoma should be screened for medullary carcinoma of the thyroid, von Hippel-Lindau disease, and hyperparathyroidism. If familial disease is established, first-degree relatives should be evaluated for genetic mutations. Those with identified genetic mutations should be screened periodically for pheochromocytoma with appropriate biochemical tests. A detailed medical history of our patients and their families did not suggest a familial but rather a sporadic pheochromocytoma. We did not test for genetic mutations in our patients. However, as clinically sporadic pheochromocytoma can be due to germ-line mutations, the children should be followed in the future and evaluation for pheochromocytoma should be considered.

To conclude, the diagnosis of pheochromocytoma should be considered in all pregnant patients who develop hypertension. The diagnosis and treatment of pheochromocytoma during pregnancy is a great challenge. It requires collaboration of a hypertension specialist, obstetrician, anesthesiologist experienced in the operative management of pheochromocytomas, and a surgeon with experience in removing pheochromocytomas to insure the best outcome for both mother and baby. The increasing availability for routine measurement of plasma-free metanephrines and normetanephrine will provide a highly sensitive screening test for pheochromocytoma during pregnancy.

References


