CARDIORESPIRATORY CRISIS AT THE END OF PREGNANCY: A CASE OF PHEOCHROMOCYTOMA

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Abstract

Pheochromocytoma during pregnancy is extremely rare. Its clinical manifestation includes hypertension with various clinical presentations, possibly resembling those of pregnancy-induced hypertension. The real challenge for clinicians is differentiating pheochromocytoma from other causes of hypertension (preeclampsia, gestational hypertension, and pre-existing or essential hypertension), from other cause of pulmonary edema (preeclampsia, peripartum cardiomyopathy, stress or Takotsubo cardiomyopathy, pre-existing cardiac disease [mitral stenosis], and high doses betamimetics), and from other causes of cardiovascular collapse (pulmonary embolism, and amniotic fluid embolism). Although, several cases of pheochromocytoma during pregnancy have been published, fetal and maternal mortalities due to undiagnosed cases are still reported. We report a case of a patient whose delivery by cesarean section was complicated by severe hemodynamic instability resulting in a cardiac arrest. Later on, pheochromocytoma was suspected based on computed tomography (CT) scan findings. Diagnosis was confirmed with special biochemical investigations that showed markedly elevated catecholamines in urine and metanephrines in serum, and later by histopathology of the excised left adrenal mass. This case illustrates the difficulty of diagnosing pheochromocytoma in pregnancy and raises the awareness to when this rare disease should be suspected.

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**Introduction**

Pheochromocytoma is a rare catecholamine-secreting tumor and extremely rare in pregnancy. The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor that may precipitate life-threatening cardiovascular complications. Diagnosis is often difficult and can be easily missed, as pheochromocytoma may present a broad spectrum of clinical manifestations, particularly mimicking pre-eclampsia.

**Case presentation**

A 31-year-old gravida-8, para-6 + 1 woman at 42 weeks gestation presented to the emergency department with abdominal pain. At 16:30, she was admitted to the delivery ward as being in labor. All her previous pregnancies ended in a normal spontaneous vaginal delivery except the last one that ended in a cesarean section (CS). Her past medical, family and social histories were unremarkable. She was not on any medication, or known to have any allergy. On physical examination, she was afebrile. Her heart rate (HR) was 112 beats per minute (BPM), blood pressure (BP) was 107/80 mm Hg, respiratory rate (RR) was 20 breaths per minute, and her oxygen saturation (SpO2) was 98-100% while she was breathing room air. Her abdomen was gravid and not tender to palpation. Mild uterine contractions were noted (3 to 4 in 10 minutes) with mild to moderate pain (pain score 2 to 4). No edema was found on her lower extremities. On pelvic examination, her cervix was 4 to 5 cm dilated and 80% effaced, with the head at -3 station. Her initial blood analysis revealed a hemoglobin of 110 g/L, a white cell count of 8.8 × 10⁹/L, and a platelet count of 281 × 10⁹/L. All electrolyte levels were unremarkable, her serum creatinine was 46 μmol/L and uric acid 195 μmol/L. An intravenous cannula was inserted and infusion of a crystalloid solution at the rate of 125 mL/hours was commenced. Two doses of 100 mg of meperidine and 25 mg of promethazine, with 6 hours interval, were administered intramuscularly for pain control. Continuous cardiotocograph (CTG) monitoring showed normal fetal HR with acceleration and normal variability, and uterine hyperstimulation for which 2 doses of 0.25 mg of terbutaline, with 4 hours interval, were administered subcutaneously.

At 21:50 hours, she became moderately distressed, her BP was recorded at 152/119 mm Hg and her HR at 155 BPM. Distress, hypertension and tachycardia were attributed to anxiety, pain and the use of terbutaline. On obstetrician request and patient agreement for analgesia, an epidural catheter was sited at the L3-4 interspace. A bolus of 1 liter Lactated Ringer (LR) was administered as preparation for the epidural analgesia. A test dose (3 ml of lidocaine 1.5% with 1:200,000 epinephrine), followed by a 5-ml dose of 0.125 % bupivacaine were injected and provided adequate analgesia. During the following hour, her BP ranged 125-150/76-111 mm Hg, HR 80-163 BPM; however, both RR and SpO2 remained stable (20-22 and 98-100%, respectively).

At 22:55, the patient was transferred to the operating theatre for an emergency CS for failure to progress and persistent fetal tachycardia. Epidural anesthesia was extended using 11 ml of 2% lidocaine and 100 μg of fentanyl preceded by a bolus of 1 liter LR to prevent secondary hypotension. A male infant in poor condition was delivered with Apgar scores of 3 and 8 (at one and five minutes, respectively) and an umbilical arterial pH of 6.90. Oxytocin (10-units) was administered as a slow intravenous (IV) bolus on delivery of the baby. CS was uneventful and blood loss was estimated at 500 ml. However, her BP remained elevated ranging from 140 to 160/90 to 100 mm Hg with persistent sinus tachycardia at 130 to 163 BPM. Two 10-mg increments of esmolol were administered intravenously to control the HR; however, there was no significant response.

Suddenly, at the end of the CS and while she was breathing through a face mask with an FiO2 of 0.4, the SpO2 fell to 89% and sero-sanguinous fluid emerged from her mouth. Urgent intubation of the trachea was performed without administering any additional drug, and positive pressure ventilation was started. A large amount of pink frothy secretions were suctioned from the endotracheal tube, diagnosed as frank pulmonary edema. She remained hypoxic (SpO2 80-90%), tachycardic (150-170 BPM) and hypertensive (150-160/90-100 mm Hg). Labetalol 10 mg and amiodarone
150 mg were administered as slow IV bolus to control HR for a suspected atrial fibrillation (AF) with rapid ventricular response (irregular tachyarrhythmia). Shortly, the HR dropped to 30 BPM, the BP fell to 40/25 mm Hg and she became pulseless. Cardiopulmonary resuscitation (CPR), as per the Advanced Cardiac Life Support (ACLS) recommendations, was performed for 3 minutes and restored the BP to 130/80 mm Hg and the HR to 150 BPM. Pulmonary edema, secondary to the use of terbutaline and fluid shift, was considered to be the most likely etiology of the event. Sixty mg of furosemide was administered as IV bolus. The patient was transferred to the intensive care unit (ICU) at 00:10 of the next day.

On admission to the ICU, she was sedated, intubated and mechanically ventilated with an FiO2 of 1.0 and a lung protective strategy (respiratory rate 30 breaths/min, tidal volume 300 ml [6 mL/kg of predicted body weight], and PEEP of 16 cm H2O). She was severely hypoxemic with SpO2 around 60%. Arterial blood gas (ABG) analysis was pH 7.15, PaCO2 57.2 mm Hg, PaO2 41.1 mm Hg, HCO3-19.8 mmol/L, base excess -9.1 mmol/L and SaO2 63%. Chest X-ray showed pulmonary edema (Fig. 1). She was hemodynamically unstable with labile and rapidly fluctuating blood pressures. The systolic blood pressure (SBP) varied from 200 to 60 mm Hg and the HR from 140 to 170 BPM. Vasopressor infusions (norepinephrine, dopamine, phenylephrine, vasopressin and epinephrine) were used on and off according to the BP. Central and arterial cannula were inserted. Routine chest X-ray, following the central line insertion, confirmed the presence of pulmonary edema. The central venous pressure (CVP) was 20 mm Hg. A bolus of furosemide 60 mg IV was given followed by a continuous infusion at 10 mg per hour with poor response so a dialysis catheter was inserted for fluid removal. One hour after admission to the ICU, an episode of severe hypotension and bradycardia was followed by a pulseless electrical activity cardiac arrest. CPR for 42 minutes, epinephrine 5 mg (total), atropine 2 mg (total), vasopressin 40 units, 10% calcium chloride (20 ml) and 8.4% NaHCO3 (250 mmol) resulted in restoration of cardiac activity and hemodynamic stability.

As diagnosis was uncertain, a pulmonary artery catheter (PAC) was inserted, 3 hours after ICU admission, for hemodynamic assessment and monitoring. Cardiac index was at 2.2 to 2.8 L•min-1•m2 and the pulmonary capillary wedge pressure (PCWP) ranged from 6 mmHg to 9 mmHg. Transesophageal echocardiography (TEE) showed global hypokinesia of the left ventricle (LV) with ejection fraction (EF) of 25 to 30%. Supportive therapy was continued with full neurological, respiratory and hemodynamic recovery. However, her stay in the ICU was complicated with the development of fever and leukocytosis. A septic screen was performed and included a computerized tomography (CT) scan of the abdomen which showed a large (44 × 39 mm), heterogeneous, enhancing, left adrenal mass. A presumptive diagnosis of pheochromocytoma was confirmed with biochemical investigations that showed markedly elevated catecholamines in urine (Table 1) and metanephrines in serum (Table 2). The patient was treated with alpha-adrenergic blockade (phenoxybenzamine), with additional beta-blockade (metoprolol), and discharged home with the above medications. Two months after discharge, she underwent uneventful elective laparoscopic excision of the left adrenal mass. The histopathology described a nodular, encapsulated mass arising from the adrenal medulla measuring 2.5 × 2.3 × 1.5 cm, and confirmed the diagnosis of pheochromocytoma.
Fig. 2
Abdominal computed tomography (CT) scan showing a large (44 × 39 mm), heterogeneous, enhancing, left adrenal mass.

Fig. 3
Photomicrograph of the lesion, showing a well demarcated mass (left) with a residual normal adrenal gland (right).

Fig. 4
The tumor cells are arranged in nests surrounded by a thin fibrovascular stroma, so called “Zellballen”. There is slight pleomorphism, but no atypia.
Table 1

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<thead>
<tr>
<th>Twenty-four hour urinary analysis</th>
<th>(catecholamines: HPLC) (u)</th>
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<tbody>
<tr>
<td>Epinephrine</td>
<td>475+ nmol/24 h N &lt;147</td>
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<tr>
<td>Epinephrine / Creatinine</td>
<td>145+ µg/g N &lt;25.0</td>
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<tr>
<td>Norepinephrine</td>
<td>2330 + nmol/24 h N &lt;573</td>
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<tr>
<td>Norepinephrine / Creatinine</td>
<td>657 + µg/g N &lt;115</td>
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<tr>
<td>Dopamine</td>
<td>2612 nmol/24h N &lt;3265</td>
</tr>
<tr>
<td>Dopamine / Creatinine</td>
<td>667 + µg/g N &lt;540</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.83- mmol/L N 2.48–19.2</td>
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</tbody>
</table>

N: normal

Table 2

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<thead>
<tr>
<th>Serum catecholamines (HPLC)</th>
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<tbody>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td>Norepinephrine</td>
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<tr>
<td>Dopamine</td>
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N: normal

Discussion

Pheochromocytomas are rare neuroendocrine, catecholamine-secreting tumors derived from the chromaffin cells of the adrenal medulla or extraadrenal paraganglia. Their incidence during pregnancy is even more infrequent with an estimated prevalence of 1 in 50,000 to 54,000 in full-term pregnancies. The maternal mortality rate is 2 to 4% if the tumor is diagnosed in the antenatal period, compared to 14 to 25% if it is diagnosed in the postpartum period.

There are limited case-reports in the literature. Bullough et al. reported a case of pheochromocytoma as an unusual cause of hypertension in pregnancy. Intravenous magnesium sulfate infusion proved successful in controlling hypertension in the postpartum period. Magnesium sulfate has also been used as the sole drug for control of hemodynamic disturbances during pheochromocytoma excision surgery. Dugas et al. described a patient who was diagnosed with pheochromocytoma in the third trimester of pregnancy and discussed the perioperative and anesthetic management. A fatal, undiagnosed pheochromocytoma mimicking severe preeclampsia in a pregnant woman at term was reported by Hudsmith et al. Post mortem examination of the patient revealed a 5.5-cm tumor of the right adrenal gland confirmed histologically as a pheochromocytoma. Pearson et al. reported a case of pheochromocytoma in an 18-year-old-woman. She presented with aproteinuric hypertension and intermittent panic attacks. Ultrasonography showed a structure obscuring the left adrenal gland. In the postpartum period, the tumor was resected and histologically arose from the sympathetic paraganglion cells; the left adrenal gland itself was normal. A pheochromocytoma was diagnosed following a crisis in late pregnancy (sudden onset of bitemporal headache and shortness of breath) in a 31-year-old-woman in the 37th week of pregnancy. In 2010, a case-report and literature review was published by George et al. The authors recommended evaluating for pheochromocytoma all patients with the typical triad of headache, sweating and palpitation in the presence of resistant or labile hypertension. Oliva et al. reviewed six cases of pheochromocytoma in pregnancy and concluded that pheochromocytoma was a rare but important cause of hypertension in pregnant women because of its high morbidity and mortality to both mother and fetus.

The excess release of catecholamines (norepinephrine, epinephrine and dopamine) accounts for the typical presentation of pheochromocytoma. Clinical manifestations can differ greatly, resembling several clinical conditions. Consequently, pheochromocytoma has often been referred to as the great mimic. However, the most common clinical feature is hypertension, associated with tachycardia and paroxysmal symptoms such as headache, sweating, nausea, tremor, palpitations and feelings of anxiety or panic. Although, hypertension is common and may be insidious or severe with hypertensive crises, there is growing number of normotensive and asymptomatic patients who are diagnosed with the disease. Consequent to an increased use of advanced imaging technology, nearly 25% of all pheochromocytomas are now diagnosed incidentally during imaging studies for distinct disorders.

Pheochromocytoma-related signs and symptoms may occur for the first time during or in late pregnancy. Furthermore, the earliest clinical presentation may
develop at the end of pregnancy during vaginal delivery or cesarean section. Increased vascularity of the tumor, hemorrhage into the tumor, mechanical effects such as enlarging gravid uterus or vigorous fetal movements which can stimulate catecholamine secretion, vaginal delivery, anesthesia and cesarean section (CS) are precipitating factors for crisis or worsened condition. Our patient was completely asymptomatic before and during pregnancy; her first presentation was as a sudden cardiorespiratory crisis. One or more of the above mentioned factors may have contributed to her deterioration.

In pregnant patients, the diagnosis of pheochromocytoma is often missed since the classical signs and symptoms may mimic pre-existing essential hypertension and other forms of pregnancy-related hypertensive syndromes including gestational hypertension and preeclampsia. Usually, pre-existing, essential hypertension is diagnosed and treated prior to pregnancy while pre-eclampsia develops after 20 weeks gestation and includes proteinuria. Conversely, pheochromocytoma is rarely associated with proteinuria, and the hypertension may occur throughout the entire pregnancy. A differential diagnosis of pheochromocytoma in pregnancy includes beta-mimetic-induced pulmonary edema, cardiomyopathy (preeclampsia, peripartum, stress or Takotsubo), pre-existing cardiac diseases such as mitral stenosis, pulmonary embolism (PE), aspiration pneumonitis (Acute Respiratory Distress Syndrome: ARDS), sepsis-related acute lung injury (ALI), and amniotic fluid embolism. Thus, a high index of suspicion is required for early diagnosis.

A combination of alpha- and beta-adrenergic receptor blockers for the treatment of pheochromocytoma-induced hypertension must be directed by their pharmacodynamic effects and should follow a certain sequence. Commencement of nonselective beta blocker treatment without prior alpha blockade in a patient with pheochromocytoma may precipitate a hemodynamic crisis. Premature initiation of a nonselective beta blocker results in a loss of beta-2 receptor-mediated vasodilatation and the unopposed alpha-adrenergic receptor stimulation. This causes vasoconstriction, arterial hypertension and increased afterload, leading to myocardial dysfunction and pulmonary edema. Sibal et al. reported that the initiation of beta blockers in four patients with pheochromocytoma was associated with further deterioration in hemodynamic status, labile blood pressure and cardiac arrhythmias. They concluded that “unexplained cardiopulmonary dysfunction, particularly after the institution of beta blockers, should alert clinicians to the possibility of pheochromocytoma”. Our patient suffered exactly the same consequences following the administration of emolol (a beta1-cardioselective adrenergic receptor blocking agent) and later labetalol (both selective alpha1-adrenergic and nonselective beta-adrenergic receptor blocking agent) and amiodarone. Nonselective beta blockers should be initially avoided in patients with a suspected pheochromocytoma, but can be used only after adequate alpha blockade.

Although, patients with pheochromocytoma are hypertensive, their intravascular volume may be reduced. Initiation of fluid removal, by administering diuretics or instituting hemofiltration, may precipitate cardiovascular collapse, and should be avoided. This might explain why our patient deteriorated further (PEA cardiac arrest) after administration of furosemide and fluid removal by hemofiltration. Invasive hemodynamic monitoring with a PAC suggested a low intravascular volume (PCWP 6 to 9 mmHg) and excluded other possible diagnosis such as pregnancy induced cardiomyopathy, fluid overload, and beta-mimetic-induced pulmonary edema. Moreover, most reported cases of beta-mimetic-induced pulmonary edema occurred with higher doses (more than 30 mg) of these drugs especially when administered intravenously (our patient received only 0.5 mg SC), making this diagnosis to be unlikely.

In our patient, pheochromocytoma was suspected by the finding of an adrenal mass on CT scan of the abdomen as a work up for septic shock in ICU. It was confirmed by high level of catecholamine in serum and urine and by biopsy after surgical resection. Our case report represents an atypical presentation of pheochromocytoma, including acute respiratory failure followed by PEA arrest, in a pregnant patient.
Conclusions

Pregnant women with pheochromocytoma may remain asymptomatic until the end of pregnancy. The first clinical presentation may develop during vaginal delivery or cesarean section and may manifest as a severe cardiorespiratory crisis.

Pheochromocytoma should be considered in the differential diagnosis of hemodynamic crisis occurring during or at the end of pregnancy.

Cardiovascular collapse following the administration of a beta blocker should alert one to the possibility of pheochromocytoma.

In patients who are suspected to have pheochromocytoma, beta blockers should be avoided until adequate alpha blockade is established.

Careful fluid management is also essential.
References