Pheochromocytoma in pregnancy: a case report and review of literature

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Summary: Hypertension is a common problem in pregnancy that can result in significant maternal and fetal morbidity and mortality. The common causes include pre-eclampsia, gestational hypertension and essential hypertension. Although phaeochromocytoma is a rare cause of hypertension in pregnancy, it can lead to potentially life-threatening cardiovascular complications for the mother and increased fetal mortality if left undiagnosed and untreated. The diagnosis can be confirmed by measurement of plasma and urinary catecholamines and their metabolites followed by radiological localization of the tumour. Surgical resection of the tumour after adequate pre-operative control of hypertension using sequential alpha- followed by beta-blockers is the definitive treatment. In pregnancy, depending on the gestation at which diagnosis is made, the optimal timing for surgery is during the late first or early second trimester. When the pregnancy is more advanced, medical management followed by combined caesarean section and tumour resection closer to term is preferred.

Keywords: hypertension, phaeochromocytoma, pregnancy

INTRODUCTION

Phaeochromocytomas are rare neuroendocrine tumours that secrete catecholamines and cause hypertension. Their occurrence in pregnancy is even more uncommon with approximately 200 cases reported in the literature. Antepartum diagnosis and management has reduced maternal mortality and fetal loss significantly. We describe a young woman who suffered a first trimester pregnancy loss associated with uncontrolled hypertension secondary to phaeochromocytoma.

CASE PRESENTATION

A 25-year-old woman was admitted to our hospital with acute onset of left-sided headache associated with vomiting but without aura, photophobia or neurological deficits. She had had recurrent headaches for the past two years that had been diagnosed as migraine. She did not report palpitations or diaphoresis. Clinical examination was unremarkable except for an elevated blood pressure of 180/110 mmHg. She was treated for migraine and hypertension with ibuprofen, metoclopramide and atenolol. When seen in the outpatient clinic four weeks later, she reported a missed period and was confirmed to be pregnant. Her blood pressure remained severely elevated at 200/110 mmHg. The 24-hour urinary vanillyl mandelic acid was noted to be elevated at 77.7 $\mu\text{mol/day}$. On account of her pregnancy and suspected phaeochromocytoma, atenolol was

stopped and switched to long-acting nifedipine. Further investigations were consistent with phaeochromocytoma (Table 1). She was started on phenoxybenzamine and later atenolol was added. At eight weeks gestation, ultrasound scan failed to detect any fetal heart activity. This was followed by spontaneous complete miscarriage three weeks later. The computerized tomography (CT) scan of the abdomen showed a $38 \times 36 \times 29 \text{ mm}^3$ heterogeneous enhancing mass arising from the right adrenal gland. Following adequate control of her blood pressure, laparoscopic right adrenalectomy was performed. Histopathology was consistent with adrenal phaeochromocytoma with no overt malignant features. Her blood pressure normalized postoperatively and antihypertensive medications were discontinued. The 24-hour urinary catecholamines and metanephrines done three months later were normal.

DISCUSSION

Phaeochromocytomas are rare catecholamine-secreting tumours arising from the chromaffin cells of the adrenal medulla or sympathetic ganglia (paraganglioma). The prevalence of phaeochromocytoma in patients with hypertension is 0.1–0.6% in the general outpatient setting.^{1,2} Its incidence in pregnancy is not known. There have been at least 200 cases reported in pregnancy and the prevalence is estimated at one in 54,000.^{3,4} It is important to suspect and diagnose these tumours because:

- Undiagnosed tumours have been associated with significant maternal and fetal mortality (up to 48% and 54.4%, respectively, in one early report);⁵

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Table 1 Results

Test	Preoperative	Postoperative
FBC		
• Hb	16.6 g/dL	12.1 g/dL
• Haematocrit	48.8%	35.4%
24-hour urinary		
• Vanillyl mandelic acid	77.7 µmol/day (0–34.3)	–
• Epinephrine	157 nmol/day (3–109)	10 nmol/day
• Norepinephrine	9577 nmol/day (89–473)	229 nmol/day
• Metanephrines	Not done	382 nmol/day
• Normetanephrines	22 253 nmol/day (600–1900)	1344 nmol/day
24-hour urinary free cortisol	216 nmol/day (59–413)	–
Plasma renin activity	11.75 µg/L/h (0.63–3.08)	–
Serum aldosterone	1119.2 pmol/L (97.3–834)	–

FBC, full blood count; Hb, haemoglobin

- Hypertension is potentially curable with resection of the tumour;
- The cardiovascular complications are potentially lethal;
- At least 10% of these tumours are malignant; and
- A hereditary basis may be found in up to 24% of patients and detection of phaeochromocytoma in the proband may result in early diagnosis in other affected family members.^{6–8}

The most common clinical presentation of phaeochromocytoma includes headaches, palpitations, diaphoresis and hypertension. Other symptoms such as nausea, flushing and anxiety are non-specific and can be easily overlooked, especially in a pregnant woman. Frequent headaches in our patient had been misdiagnosed as migraine. Phaeochromocytoma should be suspected in patients with paroxysmal signs and symptoms, in those with treatment-resistant or labile hypertension and in those who demonstrate a paradoxical blood pressure response during surgery and anaesthesia. Elevated haemoglobin level and haematocrit have been observed in patients with phaeochromocytomas due to tumour-associated erythropoietin production. In our patient the haemoglobin and haematocrit normalized following volume expansion prior to surgery.

Raised plasma renin activity and aldosterone levels have been observed in patients with phaeochromocytoma secondary to the norepinephrine-induced renin release contributing to the hypertension in pheochromocytoma.^{9,10} Moreover, the renin-angiotensin aldosterone system is activated as a physiological response to pregnancy.

Early diagnosis and treatment has been shown to reduce morbidity and mortality for the mother and the fetus.^{4,11,12} In pregnancy, paroxysms can be precipitated by stress, increasing intra-abdominal pressure, medications such as metoclopramide, fetal movements and vaginal delivery. The ensuing hypertensive crisis can be detrimental to both mother and fetus. Adverse pregnancy outcomes include spontaneous abortion (which was the case in our patient), intrauterine growth restriction and fetal death.

Catecholamine production generally remains unchanged during pregnancy. The initial and essential step in diagnosing phaeochromocytoma is biochemical confirmation of excessive catecholamine production. The most sensitive tests are measurements of plasma free metanephrines or urinary fractionated metanephrines (normetanephrines and metanephrines) mainly because production of *O*-methylated metabolites from

Table 2 Sensitivity and specificity of biochemical tests for diagnosis of phaeochromocytoma¹²

Test	Sensitivity (%)	Specificity (%)
Plasma free metanephrines	99	89
Plasma catecholamines	84	81
Urinary catecholamines	86	88
Urinary fractionated metanephrines	97	69
Urinary total metanephrines	77	93
Urinary vanillyl mandelic acid	64	95

phaeochromocytomas is continuous and independent of the highly variable release of catecholamines (Table 2).^{13,14}

It is important to remember that various foods and drugs such as tricyclic antidepressants, clonidine, methyldopa, prochlorperazine, decongestants and alcohol can increase measured levels of catecholamines and metanephrines, giving rise to false-positive results. This can be differentiated from true-positive results by the magnitude of increase (much greater) in patients with phaeochromocytoma. The clonidine suppression test can also help to differentiate true-positive from false-positive results. This test, however, has not been validated in pregnancy.

Following biochemical confirmation, the next step in evaluation requires localization of the tumour. This can be done by ultrasound, computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen (mass with bright signal on T2-weighted image). Ultrasound scans are safe but less reliable. CT scan and MRI have similar sensitivities (90–100%) and specificities (70–80%). MRI is the preferred modality during pregnancy as it is free from ionizing radiation. Functional imaging with ¹²³I-metaiodobenzylguanidine is indicated mainly for those with extra-adrenal or large (>5 cm) adrenal tumours because of increased risk of malignant disease or in those with suspected multifocal disease. It should be avoided during pregnancy.

Familial phaeochromocytomas such as von Hippel Lindau syndrome, multiple endocrine neoplasia type 2, neurofibromatosis type I and familial paraganglioma occur rarely. Genetic testing should be considered in those with a positive family history, those who are young (<50 years of age), those with bilateral phaeochromocytomas or multifocal extra-adrenal disease or those with associated tumours.¹⁵

Definitive treatment requires surgical resection of the tumour. The optimal timing for surgery is during the late first trimester or early second trimester. When diagnosed in the late second or third trimester, phaeochromocytoma is best managed medically until close to term when combined caesarean section followed by tumour resection can be performed. Vaginal delivery should be avoided as it may trigger a hypertensive crisis. The laparoscopic approach is now the preferred technique (for tumours that are <6 cm in size) as it is associated with lower postoperative morbidity and shorter hospital stay compared with conventional laparotomy. The complication rate of laparoscopic adrenalectomy is less than 8% and operative mortality rate is less than 1% in experienced centres.¹⁵ Appropriate preoperative medical management to control hypertension is essential to prevent catecholamine-induced serious complications during surgery including hypertensive crises, cardiac arrhythmias, pulmonary oedema and cardiac ischaemia. Blood pressure should be normalized two weeks before surgery. Alpha-blockade with

drugs such as phenoxybenzamine, prazosin and doxazosin is started followed several days later by beta-blockers to minimize reflex tachycardia. Among the alpha-blocking agents, phenoxybenzamine is the most common drug used during pregnancy. Phenoxybenzamine has been shown to cross the placenta and neonatal hypotension has been reported in newborns of mothers treated with the drug prior to delivery.^{16,17} Prazosin has been used to treat maternal hypertension, although one randomized controlled study comparing nifedipine and prazosin as a second-line agent to treat severe early hypertension in pregnancy noted that there were more intrauterine deaths in the prazosin group.¹⁸ There have been no reports on the use of doxazosin in pregnancy. Beta-blockers may be added if tachyarrhythmia is present, but it should not be started before alpha-blockade as the unopposed alpha-adrenoceptor stimulation can precipitate a hypertensive crisis. Intravenous phentolamine (by bolus or continuous infusion) is the agent of choice to control hypertension intraoperatively. Labetalol (alpha- and beta-adrenergic antagonist) has been used for preoperative adrenergic blockade; however, it has a fixed alpha- to beta-adrenergic blocking effect (1:7), which may result in paradoxical hypertensive crisis.⁹ Anaesthetic agents that can trigger hypertensive crisis such as fentanyl, ketamine, halothane and desflurane should be avoided.

Following successful surgical resection, blood pressure normalizes, although hypertension may persist after surgery in nearly 50% of patients.¹⁹ Recurrent disease of 17% has been reported in those with extra-adrenal disease and with familial disease.²⁰ All patients should undergo yearly surveillance for at least 10 years after surgery. For those with familial phaeochromocytoma or extra-adrenal disease, follow-up should be indefinite because of the higher risk of recurrent disease.

SUMMARY

Early diagnosis of phaeochromocytoma requires a high index of suspicion. Patients with the typical triad of headache, sweating and palpitations in the presence of resistant or labile hypertension should be evaluated for phaeochromocytoma. The most sensitive tests are measurements of plasma free metanephrines or urinary fractionated metanephrines. MRI is the preferred imaging modality for radiological localization of the tumour during pregnancy. Alpha-adrenergic blockade using phenoxybenzamine should be used for preoperative management of hypertension. Neonates born to mothers receiving phenoxybenzamine prior to delivery should be closely monitored for hypotension. In pregnancy, depending on the gestation at which diagnosis is made, the optimal timing for surgery is during the late first or second trimester. When pregnancy is more advanced, medical management followed by combined

caesarean section and tumour resection closer to term is preferred. Multidisciplinary care involving the endocrinologist, obstetric physician, anaesthesiologist, obstetrician and surgeon is essential for an optimal outcome.

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