Obstetrical and Pediatric Anesthesia

Pheochromocytoma and pregnancy: a case report and review of anesthetic management

[*Phéochromocytome et grossesse. Exposé d'un cas et revue de la démarche anesthésique*]

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Purpose: To describe a patient diagnosed with pheochromocytoma in the third trimester of pregnancy and discuss the perioperative and anesthetic management.

Clinical features: A 32-yr-old previously healthy woman (gravida 4, para 2) presented to our tertiary care obstetrical hospital at 34 weeks five days gestation with a history of labile blood pressure and severe hypertension. A week prior to admission she began having episodes of severe headache, dizziness, sweating and nausea. On a routine obstetric visit she was noted to be severely hypertensive with a blood pressure of 200/120 mmHg. Biochemical investigations confirmed the diagnosis of pheochromocytoma and magnetic resonance imaging demonstrated a 3 cm × 3 cm right adrenal mass. The patient was invasively monitored in the intensive care unit and treated with alpha- followed by beta-blockade with phenoxylbenzamine and metoprolol. A multidisciplinary conference was organized involving endocrinology, anesthesiology, general surgery and obstetrics to determine the most appropriate management of the patient. An uncomplicated laparoscopic adrenalectomy was performed following a period of recovery after an uneventful elective Cesarean delivery.

Conclusions: The primary goals in the management of pheochromocytoma in pregnancy are early diagnosis, avoidance of a hypertensive crisis during delivery and definitive surgical treatment. Timing of surgical resection will depend on the gestational age at which diagnosis is made. Cesarean section is the preferred mode of delivery when the tumour is still present. This case illustrates that with antenatal diagnosis, advanced methods of tumour localization, adequate preoperative adrenergic blockade and team planning, pheochromocytoma in pregnancy can be treated successfully.

Objectif : Présenter une patiente chez qui on a découvert un phéochromocytome au troisième trimestre de la grossesse, et son traitement périopératoire et anesthésique.

Éléments cliniques : Une femme de 32 ans, antérieurement en bonne santé (G4, P2) s'est présentée à notre hôpital obstétrical de soins tertiaires à 34 semaines et cinq jours de grossesse. Elle avait une histoire de tension artérielle labile et de sévère hypertension. Une semaine avant l'hospitalisation, elle a eu des épisodes de céphalées sévères, étourdissements, transpiration et nausées. Lors d'une visite obstétricale de routine, une tension artérielle de 200/120 mmHg avait indiqué une hypertension importante. Les examens biochimiques ont confirmé le diagnostic de phéochromocytome et l'imagerie par résonance magnétique a montré une masse surrénalienne droite de 3 cm × 3 cm. La patiente, sous monitoring effusif à l'unité des soins intensifs, a reçu des alpha-bloqueurs, puis des bêta-bloqueurs combinés à de la phénoxybenzamine et à du métoprolol. Une réunion des endocrinologue, anesthésiologiste, chirurgien général et obstétricien a permis de déterminer le traitement le plus approprié. Une surrénalectomie laparoscopique sans complications a été exécutée après que la patiente a été remise de la césarienne sans incident réalisée auparavant.

Conclusions : Le traitement d'un phéochromocytome pendant la grossesse visent à établir un diagnostic précoce, à empêcher une crise hypertensive pendant l'accouchement et à procéder à l'intervention chirurgicale définitive. Le moment choisi pour la résection dépend de l'âge gestationnel au moment du diagnostic. La césarienne est le mode d'accouchement privilégié lorsque la tumeur est toujours présente. Le cas présent montre que le diagnostic prénatal, des méthodes perfectionnées de localisation de la tumeur, un bloc adrénergique préopératoire adéquat et une planification multidisciplinaire permettent de traiter avec succès un phéochromocytome pendant la grossesse.

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PHEOCHROMOCYTOMA in pregnancy is rare (reported incidence less than 0.2 per 10,000 pregnancies)¹ but important due to potentially devastating consequences for both mother and fetus. Early recognition and treatment is paramount prior to delivery of the fetus and tumour excision. Pheochromocytoma should be considered when severe hypertension occurs before 20 weeks gestation and blood pressure (BP) is labile or associated with headaches, palpitations and diaphoresis.² Detecting elevated levels of catecholamines and their metabolites in plasma and urine establishes the diagnosis. In pregnancy, ultrasonography and magnetic resonance imaging (MRI) are the most acceptable modalities of tumour localization for cases in which the fetus must be protected.³ Medical treatment of pheochromocytoma consists of alpha-adrenergic blockade to control hypertension followed by beta-adrenergic blockade to treat tachycardia and cardiac dysrhythmias. Surgical excision of the tumour is the definitive treatment for pheochromocytoma.

Case report

A 32-yr-old previously healthy woman (gravida 4, para 2) presented to our tertiary care obstetrical hospital at 34 weeks five days gestation with labile BP and severe hypertension. Her BP had been elevated throughout her pregnancy. She was initially assessed at 12 weeks gestation and underwent multiple investigations including 24-hr urine collection for protein and creatinine clearance. No specific cause for her hypertension was identified and she was started on methyldopa 500 mg bid. Her BP was well controlled until one week prior to hospital admission when she checked her BP at home and found it to be 200/113 mmHg. She had also developed nocturnal episodes of severe frontal headaches, dizziness, sweating and nausea. During a routine non-stress test (NST) her BP was recorded at 180 to 200/114 to 120 mmHg. The fetus was active with a normal NST and normal ultrasound [no intrauterine growth restriction (IUGR)] other than breech presentation. She was admitted to her local hospital and started on labetalol 200 mg bid in addition to the methyldopa. In hospital she had wide fluctuations in BP from 213/96 to 79/45 mmHg. Her physical examination was otherwise unremarkable. Blood work revealed normal coagulation, liver profile, hemoglobin, platelet count, electrolytes, urea and creatinine. Minimal proteinuria (270 mg·day⁻¹) was detected on urinalysis. An underlying pheochromocytoma was suspected and urinary investigation for catecholamines was arranged.

The patient had no history of diabetes, hypertension or cardiovascular disease. She was a non-smoker

and non-drinker, was not on any regular medications and had no reported allergies. There was no history of illicit drug use. She had two prior uncomplicated pregnancies with term vaginal deliveries and one miscarriage at 12 weeks gestation for which she had a dilatation and curettage. Family history was negative for multiple endocrine neoplasia (MEN) syndromes and pheochromocytoma.

The patient was admitted directly to our intensive care unit (ICU) with the presumptive diagnosis of pheochromocytoma. Continuous fetal heart rate monitoring and maternal electrocardiogram (EKG) were unremarkable. An arterial line and pulmonary artery catheter (PAC) were inserted for hemodynamic monitoring. Pulmonary artery (PA) pressures were 20 to 25/8 to 10 mmHg, cardiac index was within normal limits at 3.5 to 4.0 L·min⁻¹·m² and pulmonary capillary wedge pressure was 8 to 12 mmHg. The patient was given *iv* fluids and BP was controlled with phentolamine *iv* followed by phenoxybenzamine 30 mg tid to keep systolic BP 140 to 160 mmHg and diastolic BP < 90 mmHg. Metoprolol 50 mg bid was used to control maternal tachycardia. The patient received a total of 14 days of alpha-adrenergic blockade with phenoxybenzamine and ten days of beta-blockade with metoprolol preoperatively. Biochemical investigations showed markedly elevated 24-hr urine norepinephrine (740 nmol·day⁻¹), vanillylmandelic acid (63 µmol·day⁻¹), metanephrine (695 µmol·day⁻¹), and normetanephrine (8,878 µmol·day⁻¹) levels as well as elevated plasma norepinephrine (7,719 pmol·L⁻¹), confirming the diagnosis of pheochromocytoma. Subsequent MRI demonstrated a 3 cm × 3 cm right adrenal mass, normal left adrenal gland and no extra-adrenal tumours. A multidisciplinary conference involving endocrinology, anesthesiology, general surgery and obstetrics was held to determine the most appropriate management of this patient. As laparoscopic adrenalectomy would be technically difficult in the presence of a gravid uterus, it was decided that a Cesarean delivery would be performed first, followed by laparoscopic right adrenalectomy after a period of recovery. The patient was invasively monitored for seven days in the ICU until hemodynamically stable before being transferred to the antenatal unit until time of Cesarean delivery. The PAC and radial arterial line were removed upon discharge from the ICU.

Cesarean delivery occurred at 37 weeks gestation under general anesthesia. Intraoperative monitoring included a #20 gauge radial arterial line, PAC, 5-lead EKG and other routine monitors. Prior to induction, nitroprusside (0.5 µg·kg⁻¹·min⁻¹) and remifentanyl (0.1 µg·kg⁻¹·min⁻¹) infusions were started. Intermittent

boluses of esmolol 10 mg *iv* (total 30 mg) were also used to control BP (systolic BP 165 mmHg reduced to 120 mmHg pre-induction). The patient was positioned with left uterine displacement. A 5-mg defasciculating dose of rocuronium was administered and following three minutes of pre-oxygenation, a rapid sequence induction with 100 mg lidocaine, 280 mg thiopental and 120 mg succinylcholine was performed under cricoid pressure. A 7.0-mm endotracheal tube was easily inserted. The nitroprusside infusion ($0.5\text{--}1.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was used to control BP intraoperatively which ranged from 120 to 140/70 to 80 mmHg. PA pressures were within normal limits ($20\text{--}25/8\text{--}10$ mmHg). Anesthesia was maintained with 50% nitrous oxide and 0.4 to 0.8% isoflurane in oxygen. Following an uncomplicated Cesarean delivery, the patient returned to the ICU in stable condition for 48 hr of monitoring before transfer to our step-down unit. Postoperative pain was controlled with fentanyl patient-controlled analgesia. The reduction in intra-abdominal pressure and presumed decrease in mechanical stress on the adrenal tumour following delivery of the fetus did not lead to a reduction in anti-adrenergic drug requirement postoperatively and she remained hemodynamically stable. The neonate was transiently hypotensive postdelivery and required temporary inotropic support in the neonatal ICU.

Following delivery, the patient had a metaiodobenzylguanidine (MIBG) scan which was negative despite the presence of a right adrenal pheochromocytoma. Two weeks postpartum, the patient underwent uneventful laparoscopic right adrenalectomy with a similar anesthetic technique provided by the same anesthesiologist. Postoperatively she was observed for 48 hr in the ICU and her BP remained normal ($110\text{--}120/70\text{--}80$ mmHg) off all anti-hypertensive medications. Follow-up 24-hr urinary catecholamine levels were normal. Serum calcium, calcitonin and parathyroid hormone levels were measured one month postoperatively and within normal limits, excluding MEN (2A/2B) syndrome. Final pathology report confirmed the right adrenal tumour was indeed a pheochromocytoma. Unfortunately, there is no definitive pathological way to determine the malignant potential of pheochromocytomas.

Discussion

Pheochromocytoma is a catecholamine-secreting tumour derived from chromaffin tissue. Signs and symptoms of pheochromocytoma include paroxysmal or sustained hypertension, headache, sweating, palpitations, nausea, tremor and anxiety. Although it can be difficult to distinguish between pre-eclampsia and

pheochromocytoma in pregnancy, it is important to maintain a high index of suspicion in patients with paroxysmal or sustained episodes of hypertension, severe headaches, sweating and palpitations. Symptoms may occur for the first time in pregnancy or be worsened by the pregnant state because of increased vascularity of the tumour and mechanical factors such as pressure from the enlarging uterus or fetal movements which can stimulate catecholamine secretion.⁴ An important distinction between pre-eclampsia and pheochromocytoma is that pre-eclampsia is associated with proteinuria and hypertension occurring after the 20th week of gestation while pheochromocytoma is rarely associated with proteinuria and may cause hypertension throughout the entire pregnancy.⁵ The most sensitive and specific diagnostic finding is an elevation of urinary and plasma catecholamines and their metabolites. Pregnancy does not increase urinary catecholamine levels into the diagnostic range for pheochromocytoma and thus will not confuse the diagnosis.³ Antenatal diagnosis of pheochromocytoma is essential to improve both maternal and fetal outcome. In a review of 42 cases, Harper *et al.*⁶ found an overall maternal mortality of 17% and a fetal loss of 26%. With antepartum diagnosis, maternal mortality was reduced to nearly 0% and fetal loss to 15%.^{6,7}

Unrecognized pheochromocytoma in pregnancy can result in potentially fatal hypertensive crises precipitated by general anesthesia, vaginal delivery or the mechanical effects of an enlarging uterus, uterine contractions or fetal movements.^{6,8} The primary goal in the management of pheochromocytoma is to avoid a hypertensive crisis which can lead to hemorrhage and infarction in vital organs, congestive heart failure, cardiac dysrhythmias and death. In pregnancy, such a crisis can lead to uteroplacental insufficiency with resultant IUGR, fetal hypoxia and death. Accurate diagnosis is imperative as delivery of the fetus will be beneficial in the treatment of pre-eclampsia but can be catastrophic in undiagnosed pheochromocytoma.⁷

Once a diagnosis has been confirmed biochemically, efforts should be made to localize the tumour. Ultrasonography and MRI are the safest modalities of tumour localization in pregnancy.³ Ultrasound had a reported sensitivity of 89 to 97% for adrenal masses and MRI avoids all radiation and allows sectional imaging to identify extra-adrenal tumours.^{3,6,9} MIBG scintigraphy can be used for tumour localization following delivery of the fetus but has a reported sensitivity of 77% resulting in a significant false negative rate.¹⁰

Timing of tumour excision will depend on the gestational age at which diagnosis is made, fetal development and the success of treatment of maternal symptoms.⁵ It

is recommended that if diagnosis is confirmed prior to 24 weeks gestation, the tumour should be excised immediately, with termination or continuation of the pregnancy dependent on clinical circumstances.¹¹ After 24 weeks, the uterine size precludes adequate surgical exploration and it is reasonable to allow the pregnancy to continue under adrenergic blockade until fetal maturity is reached, assuming mother and fetus are medically stable. Establishment of adequate alpha-adrenergic blockade generally requires 10 to 14 days of treatment. Persistence of tachycardia or the presence of cardiac dysrhythmias is an indication for beta blockade and usually responds following two to three days of treatment. Elective Cesarean section is the preferred mode of delivery when the tumour is still present.^{3,9,11} Mechanical pressure placed on the adrenal tumour from uterine contractions and maternal expulsive efforts during vaginal delivery can precipitate a potentially fatal hypertensive crisis.^{3,9} In a study by Shenker, it was found that vaginal delivery carried a higher maternal mortality (31%) than Cesarean delivery (19%).¹²

Following preoperative optimization, definitive treatment of pheochromocytoma is surgical removal.^{1,3,5,9,10,13} A patient undergoing surgical excision of a pheochromocytoma is at greatest risk of hemodynamic instability during intubation of the trachea, tumour manipulation and following ligation of the tumour's venous drainage. The goal of anesthetic management is the avoidance of drugs or events that will result in stimulation of the sympathetic nervous system (SNS). Intraoperative monitoring is geared toward early detection of catecholamine-induced changes in cardiovascular performance and includes invasive arterial BP monitoring and PA catheterization. Use of transesophageal echocardiography to monitor myocardial performance and volume status has also been reported. Laryngoscopy and tracheal intubation can trigger abrupt catecholamine release and an acute hypertensive crisis resulting in uteroplacental insufficiency and fetal hypoxia.⁵ To minimize this, a surgical depth of anesthesia should be achieved (1.3 MAC) prior to any attempt at laryngoscopy and intubation.⁷ Administration of a bolus of *iv* lidocaine (1–2 mg·kg⁻¹) prior to intubation can attenuate catecholamine-induced responses including cardiac dysrhythmias. An *iv* opioid and short-acting vasodilator such as remifentanyl and nitroprusside respectively are useful adjuncts and were employed in our patient. All *iv* induction agents are reported to be safe except for ketamine which results in SNS stimulation. Intraoperative infusions of magnesium sulphate have been used successfully in the management of pheochromocytoma in pregnancy provided therapeutic

drug levels are attained.¹⁴ Its ability to inhibit catecholamine release from both the adrenal medulla and peripheral adrenergic nerve terminals, reduce the sensitivity of postsynaptic alpha-adrenergic receptors to catecholamines and act as a direct peripheral vasodilator make it an ideal agent. Non-depolarizing muscle relaxants with vagolytic or histamine-releasing properties are best avoided. Maintenance of anesthesia is most often achieved with the administration of a volatile anesthetic in combination with nitrous oxide and an opioid. Halothane is not recommended as it sensitizes the myocardium to circulating catecholamines. Desflurane should be avoided owing to catecholamine release associated with rapid administration of high concentrations. Isoflurane is the preferred agent because it does not sensitize the myocardium to catecholamines, is a vasodilator and provides good analgesia.¹⁵ Sevoflurane has also been used successfully. Following discussion of anesthetic options, a general anesthetic was administered for Cesarean delivery in keeping with both anesthesiologist and patient preference. Successful use of epidural anesthesia in patients antenatally diagnosed with pheochromocytoma has been reported.¹⁶

The transient hypotension seen in the neonate following Cesarean delivery may have resulted from placental transfer of phenoxybenzamine used to treat maternal hypertension. Santeiro *et al.*¹⁷ confirmed that placental transfer of phenoxybenzamine does occur in the third trimester of pregnancy and can accumulate in the fetal blood leading to perinatal depression and transient hypotension following Cesarean delivery. Placental transfer of remifentanyl does occur but has minimal neonatal effects secondary to rapid metabolism and redistribution.¹⁸

Laparoscopic adrenalectomy can be performed safely for excision of pheochromocytomas less than 7 cm in size.¹⁹ Previous concerns surrounding laparoscopy included the potential adverse hemodynamic effects associated with pneumoperitoneum. In a recent study, it was found that creation of a pneumoperitoneum for laparoscopic adrenalectomy did not have any significant effect on cardiac index or left ventricular work index when compared to a control group of patients undergoing open adrenalectomy for pheochromocytoma.¹⁹ Furthermore, serum catecholamine concentrations increased to a lesser extent with laparoscopic than with open adrenalectomy during tumour manipulation.¹⁰ Clinically, this translates into a lower incidence cardiovascular instability among patients undergoing laparoscopic tumour excision. Laparoscopy being a less invasive procedure also resulted in less postoperative pain and shorter hospital

stays.²⁰ Considering these benefits and the expertise of our consulting surgeon in laparoscopic surgery, it was the favoured technique.

This case report illustrates that with antenatal diagnosis, appropriate preoperative alpha-adrenergic blockade, multidisciplinary team planning, and administration of a carefully tailored anesthetic, patients with pheochromocytoma diagnosed in the third trimester of pregnancy can have a promising outcome.

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