

## Pheochromocytoma in the parturient

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### EPIDEMIOLOGY AND CLINICAL PRESENTATION

Pheochromocytoma (PCC) is a rare neuroendocrine tumor which may be characterized by a "rule of 10" - 10% familial, 10% extra-adrenal, 10% childhood onset, 10% malignant and 10% bilateral<sup>(1-3)</sup>. More specifically, PCC is a tumor affecting chromaffin cells in either the adrenal glands or in extra-adrenal sites<sup>(1)</sup>. It can occur sporadically (90% of cases), or it may occur in association with other familial disorders (10% of cases) including von-Hippel-Lindau disease (cerebellar hemangioblastomas, retinal angiomas, renal/pancreatic/epididymal cysts), MEN-IIa (medullary thyroid cancer, carcinoid syndrome, adrenal cortical adenoma, hyperparathyroidism, and pancreatic B-cell adenoma), MEN-IIb (mucocutaneous neuromas, medullary thyroid carcinoma, gangliomas of visceral autonomic ganglia, and PCC), and neurofibromatosis type 1 (*café au lait* spots, neurofibromas, CNS tumors)<sup>(3)</sup>. The pathophysiology of this tumor is primarily related to the systemic effects of norepinephrine and epinephrine secretion by the tumor. Signs and symptoms of the disease include hypertension (chronic or paroxysmal), orthostatic hypotension, sweating, palpitations, headache, flushing, nausea, anxiety, lethargy, weakness, neurologic symptoms, dyspnea, and abdominal pain. Interestingly, while more than 70% of patients present with hypertension, fewer than 25% demonstrate the classical paroxysmal hypertension<sup>(1)</sup>. The presence of headache, palpitations, and/or sweating in patients with hypertension is highly suggestive of PCC as these symptoms are found in approximately 40 - 80% of affected individuals<sup>(1)</sup>. Complications associated with PCC include myocardial infarction, cardiomyopathy, pulmonary edema, and cerebral hemorrhage; all of which can occur in the absence of obvious hypertension<sup>(4)</sup>.

The occurrence of PCC during pregnancy is rare (0.2/10,000)<sup>(5)</sup>, but it may be associated with considerable maternal and fetal risks. Reported maternal peripartum mortality has ranged from 4% to 40.3%, with improved outcomes

associated with earlier diagnosis<sup>(6)</sup>. For instance, prior to 1969 almost 40% of PCC in parturients was diagnosed at autopsy, and only 25% were diagnosed during pregnancy. In contrast, by 1997, approximately 80% were diagnosed during pregnancy and only 2% were diagnosed at autopsy<sup>(6)</sup>. PCC does **not** affect the fetus by directly exposing it to high catecholamine levels (as the placenta easily metabolizes catecholamines), but rather impacts the fetus by affecting uteroplacental blood flow through both through direct vasoconstrictive effects and paradoxically, with rebound episodes of hypotension<sup>(6)</sup>. The presence of both chronic and paroxysmal hypertension also predisposes to chronic and/or acute placental abruption. Fetal deaths and neonatal deaths, like maternal deaths, have also decreased with earlier diagnosis and treatment of PCC going from a high of 53% of all pregnancies with PCC to 11% in the 9 year period ending in 1997<sup>(6)</sup>. Pregnancy alone does not appear to accelerate the growth of a PCC.

### DIAGNOSIS – CLINICAL, LABORATORY, AND IMAGING

Diagnosis of PCC during pregnancy may be confusing due to an overlap of symptoms with pre-eclampsia. Symptoms of both can include headache, hypertension, abdominal pain, and visual disturbances. However, with PCC, the symptoms are commonly paroxysmal due to the intermittent nature of hormone secretion. Additionally, orthostatic hypotension is not seen with pre-eclampsia, but is a common feature of PCC<sup>(7)</sup>. Laboratory studies demonstrating proteinuria, hyperuricemia, and thrombocytopenia are more likely seen with pre-eclampsia as compared to PCC<sup>(2,5)</sup>. Other important differential diagnoses for PCC in pregnancy include cocaine/amphetamine intoxication and thyrotoxicosis<sup>(2)</sup>. The diagnosis during pregnancy begins with suspicion, and is confirmed by laboratory demonstration of increased catecholamine secretion. Increased catecholamine

secretion can be demonstrated by screening either urine or blood<sup>(8)</sup>. Measurement of 24 hr urinary vanillylmandelic acid has the lowest sensitivity (28 - 56%), but has a high specificity (98%). A 24 hr measurement of urinary metanephrine is more sensitive (71%) and has high specificity (99%). Combining 24 hr urinary metanephrines with urinary catecholamine results in a combined sensitivity and specificity of 88% and 99%, respectively. Measurement of both plasma metanephrine and normetanephrine results in a test with a 96% sensitivity and a 85% specificity. Plasma catecholamines can also be measured directly. Provocative testing (glucagon challenge) or suppression testing (with clonidine) should largely be avoided in parturients secondary to the possibility of profound hyper- or hypotension, either of which may have deleterious effects on the pregnancy<sup>(3,6)</sup>. Once biochemical evidence of a PCC is obtained, various imaging techniques can be used to provide anatomic localization<sup>(9)</sup>. Classically, these tests include abdominal ultrasonography (40% sensitivity), abdominal CT (76% sensitivity), abdominal MRI (95% sensitivity) and MIBG scintigraphy (95% sensitivity). Identification and localization of the tumor during pregnancy preferably involves ultrasound or MRI, so as to avoid exposure of the fetus to ionizing radiation.

### PRE-OPERATIVE CONSIDERATIONS

Following diagnosis of a PCC in a parturient, appropriate therapy must be initiated. Definitive therapy is surgical resection with medical therapy serving a temporizing role at best. Timing of the surgery represents the major medical decision in the management of PCC during pregnancy<sup>(6)</sup>. If the diagnosis is made prior to 24 weeks, it is believed that surgical resection should be undertaken as soon as possible with or without termination of the pregnancy as suggested by clinical circumstances. Operative resection of the PCC may be either be open or via laparoscopy. After 24 weeks, uterine size makes surgical access to the tumor difficult, and attempts are made to delay surgery until fetal maturity has occurred. This may entail prolonged therapy of the mother with  $\alpha$ -blockers + labetalol or even  $\beta$ -blockers (to control tachydysrhythmias) as needed. Upon either fetal maturity, or maternal/fetal compromise, surgical therapy is then undertaken. Both combined cesarean section/tumor resection procedures (open) and staged procedures with cesarean delivery, followed by a recovery period, and then by surgical resection of the PCC (open vs laparoscopic) have been performed. Vaginal delivery is relatively contra-indicated as the contracting uterus, bearing-down efforts by the mother, and perhaps even labor positioning may increase the pressure on the PCC; and thereby precipitate a hypertensive crisis<sup>(5)</sup>. As suggested by these considerations, parturients

with PCC undergoing vaginal delivery have been shown to have significantly greater mortality (31% vs 19%) than that in those undergoing cesarean section<sup>(10)</sup>.

Typical preoperative preparation of the patient with PCC involves  $\alpha$ -blockade in conjunction with intravascular volume repletion (as these patients are often severely volume constricted). The most commonly utilized  $\alpha$ -blocking agent is phenoxybenzamine<sup>(11)</sup>. Phenoxybenzamine is administered at a dose of 10 mg p.o. bid and is gradually titrated up to 40 to 50 mg bid to achieve well-recognized hemodynamic goals (vide infra). Prazosin (1 mg tid initially, titrated up to 2 - 5 mg tid or qid) and phentolamine (5 mg iv boluses to control paroxysms of hypertension) are other  $\alpha$ -blockers that have been used successfully<sup>(11)</sup>. Metyrosine, an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis has also been utilized in more refractory cases<sup>(11)</sup>. It is given as an initial bolus of 250 mg qid and titrated up by 250 - 500 mg per day to a maximum of 4 g/day). All of these agents are category 3 drugs (safety unproven during pregnancy), but have been utilized in parturients safely on a number of occasions. Labetalol has been used as a primary agent for blood pressure control (initial dose of 100 mg qid, titrated to a maximum of 800 - 1,600 mg/day), although some feel the use of labetalol should be limited to patients with a pre-existing  $\alpha$ -blockade as it has been reported to precipitate hypertensive crises in some patients<sup>(5,11,12)</sup>. Nicardipine has also been used to treat the hypertension associated with PCC<sup>(11,12)</sup>, but caution should be exercised in the parturient as calcium channel blockers may be associated with uterine relaxation/atrophy.  $\beta$ -blockade may be needed to control tachydysrhythmias, but should only be utilized after adequate  $\alpha$ -blockade has been established as paradoxical hypertension may occur secondary to unopposed  $\alpha$ -adrenergic activity<sup>(3,6,11)</sup>. Roizen has published well-accepted clinical criteria for demonstrating adequate  $\alpha$ -blockade<sup>(13)</sup>. These criteria are as follows:

1. Supine blood pressure should not exceed 165/90 for 48 hr prior to surgery
2. Orthostatic hypotension should be present, but not be below 80/45.
3. EKG should be free of ST-TW changes for at least 2 weeks.
4. No more than one PVC should be present every 5 minutes.

Despite the apparent general agreement regarding the need for pre-operative  $\alpha$ -blockade, not all feel this is necessary. Work emanating from the Cleveland Clinic has demonstrated that non-pregnant patients undergoing PCC resection may be safely managed intra-operatively with vasodilator therapy without undergoing preoperative  $\beta$ -blockade<sup>(14)</sup>. The appropriateness of this approach is unclear in

parturients, as experience with PCC management in this group is limited, and the demonstrated reductions in maternal and fetal mortality that have recently been observed (vide supra) may be simply due to earlier diagnosis and better antepartum and intra-operative care, rather than pre-operative  $\alpha$ -blockade *per se*.

## ANESTHETIC MANAGEMENT

Anesthesia for cesarean section, with either concurrent or staged PCC resection, has been successfully accomplished with general anesthesia, epidural anesthesia, or combined techniques employing both general and epidural anesthesia<sup>(2,12,15-17)</sup>. Adequate i.v. access should be obtained - at least two good i.v.s, one of which should be dedicated to the infusion of vasodilators and other vasoactive drugs. Careful attention should be given to prehydration especially if neuraxial anesthesia is being considered. Monitoring should include standard monitors, a foley catheter, and an arterial line<sup>(12)</sup>. Many would also advocate the use of either a pulmonary artery catheterization (PAC) or transesophageal echocardiography (TEE) to facilitate treatment of catecholamine-induced cardiomyopathy and/or assist in the diagnosis/treatment of intraoperative hypotension<sup>(5,17)</sup>. Use of PAC or TEE may be particularly important during combined cesarean section/PCC resection when rapid changes in circulating catecholamines may occur. General anesthesia should begin with pretreatment with i.v. fentanyl (2-3  $\mu$ g/kg) and lidocaine (1.5 mg/kg) to blunt laryngeal responses to intubation. A standard obstetric induction with either thiopental or etomidate along with succinylcholine may be given. Anesthesia is then maintained with O<sub>2</sub>/N<sub>2</sub>O/potent agent along with provision of an adequate narcotic base for intra-operative and early post-operative pain control. If neuraxial anesthesia is to be undertaken, epidural techniques are probably preferable to intrathecal techniques as they allow for more controlled induction of the block, thus minimizing possible hypotensive effects with development of a sympathectomy. Bupivacaine (0.5%) with 50 - 100  $\mu$ g of fentanyl is probably a particularly advantageous in this regard, allowing for a slow, smooth onset of sympathectomy. Phenylephrine should be used rather than ephedrine to treat symptomatic hypotension. Whether general or regional anesthesia is chosen for the patient, it should be emphasized to the obstetricians that both abdominal and uterine manipulation should be minimized by use of wide incisions and *in situ* repair of the uterus.

Intra-operative blood pressure control may involve the use of nitroglycerine, sodium nitroprusside, nicardipine, phentolamine, and/or labetalol. The use of magnesium sulfate has been described in non-pregnant<sup>(12,18)</sup> and pregnant patients<sup>(2,5,15,16)</sup> for blood pressure control with both PCC

surgery and during hypertensive crises associated with PCC. In such cases, MgSO<sub>4</sub> boluses (3 - 4 g iv) are given pre-operatively, and continuous infusions (1 - 2 g/hr) are maintained during surgery in a manner analogous to the treatment of pre-eclampsia. MgSO<sub>4</sub> use during PCC management provides multiple advantages including: direct vasodilation<sup>(19)</sup>, inhibition of catecholamine release from the adrenal medulla<sup>(20)</sup>, decreased sensitivity of  $\alpha$ -receptors to catecholamines, and anti-arrhythmogenicity<sup>(21)</sup>.

## CASE REPORT

At the Cleveland Clinic, two siblings with multiple endocrine neoplasia IIa (MEN IIa - medullary thyroid carcinoma, hyperparathyroidism, and PCC), underwent elective primary cesarean sections in the presence of unresected PCCs. Neither patient was  $\alpha$ -blocked prior to delivery. A couple of months after their respective deliveries, both siblings underwent laparoscopic PCC resections, and had uneventful perioperative courses. We used intravenous magnesium sulfate (MgSO<sub>4</sub>) as a primary drug for blood pressure control in both parturients, and phenylephrine infusions prepared for use and readily available in the OR. The first sibling, a 24-yr old primiparous woman underwent a cesarean section at 38 weeks. Her past medical history was significant MEN IIa, with episodes of paroxysmal hypertension secondary to PCC (confirmed by elevated urinary metanephrines), a right adrenal mass, and a thyroidectomy. After placement of 2 large-bore i.v.s and a right radial arterial line, boluses of 3.6 g of MgSO<sub>4</sub> and 1,000 mL lactated Ringer's were given. A lumbar epidural catheter was placed and dosed with 0.5% bupivacaine containing 50  $\mu$ g of fentanyl to achieve a T3 level bilaterally. A MgSO<sub>4</sub> infusion of 2 g/hr was maintained throughout the cesarean section, with a documented post-operative magnesium level of 3.4 mg/dl. Nitroglycerin and nitroprusside infusions, as well as a phenylephrine infusion, were available for emergency blood pressure control. The cesarean section proceeded uneventfully under epidural anesthesia; with mean arterial blood pressures ranging from 80-120 mmHg. Uterine repair occurred *in situ* to limit stimulation of catecholamine secretion from organ manipulation. Intra-operative norepinephrine levels increased to 407 pg/ml (vs 295 pg/ml preoperatively). The increase in catecholamine secretion correlated to an elevated MAP prior to skin incision. Excellent blood pressure control was obtained for the remainder of the cesarean section after administration of two 5 mg i.v. boluses of labetalol. A female infant was delivered with Apgars of 9<sup>1</sup>/9<sup>5</sup>. Both mother and infant had an unremarkable postoperative course.

Her sibling, a 29-yr old primiparous woman with MEN IIa and a history of thyroidectomy, underwent elective cesarean section two months later. Again, a PCC was confirmed with

elevated urinary metanephrines. However, the anatomic location of the PCC was unknown. Perioperative management completely mirrored the previous patient's care. Intraoperative MAP ranged from 80-115 mmHg during her cesarean

section. A postoperative  $\text{MgSO}_4$  level of 3.4 mg/dl was determined. Intra-operative norepinephrine levels increased to 447 pg/ml (a 113% increase). Both mother and child were discharged on postoperative day three after an uneventful course.

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