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## CASE REPORT

# Anaesthetic management of a pregnant woman with carcinoid disease

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### ABSTRACT

Carcinoid tumours are neuroendocrine in origin and release vasoactive substances. Carcinoid tumours may be associated with carcinoid syndrome in 2–5% of patients and result in haemodynamic instability, bronchospasm, volume and electrolyte imbalance, and hyperglycaemia. We present the anaesthetic management of a 29-year-old parturient with metastatic carcinoid tumour. Although our patient did not ultimately develop carcinoid syndrome during the peripartum period, it was important that we used a multidisciplinary team approach, with close monitoring of her antenatal progress, and planned epidural analgesia for labour and delivery.

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### Introduction

Carcinoid tumours originate from enterochromaffin cells usually found in the gastrointestinal tract. Carcinoid syndrome occurs when these tumours secrete neuropeptides that have systemic effects including hypertension, hypotension, bronchospasm, flushing, hyperglycemia and diarrhoea. In pregnancy, the presence of metastatic disease, particularly with associated carcinoid syndrome, may be catastrophic as there is an increased likelihood of fetal demise.<sup>1</sup> There is no evidence of decreased fertility in patients with carcinoid tumours and there have been reports of symptomatic patients becoming pregnant. We present the rare case of a parturient with metastatic pancreatic carcinoid tumour and the management considerations for the peripartum period.

### Case report

A 29-year-old primiparous woman presented to the anaesthetic clinic at 32 weeks of gestation with a history

of primary pancreatic carcinoid tumour with liver metastases, not amenable to surgery. The tumour had been diagnosed six years previously during investigations for left upper flank pain. The patient received a course of octreotide injections over a 12-month period. This was followed by chemotherapy and radiolabeled octapeptide analogue, <sup>111</sup>Indium octreotide, to decrease the size of the tumour. For the year before her pregnancy, she had not received treatment and did not exhibit any signs or symptoms of carcinoid syndrome. She was regularly reviewed by her oncologist from the onset of her pregnancy with liver ultrasounds during each trimester, and monthly blood tests for liver enzymes and the tumour marker chromogranin A.

Examination revealed a well looking woman with no significant cardiorespiratory findings. She was 1.62 m tall and weighed 73 kg (body mass index 27.8 kg/m). Her blood pressure was 110/60 mmHg and her heart rate 88 beats/min and regular. Mallampati grade 1 was noted on airway examination. Blood results, including liver function tests, and echocardiogram were within normal limits.

After multidisciplinary discussion between the obstetrician, oncologist, anaesthesiologist, and pharmacologist it was decided to proceed with elective induction of labour at 38 weeks. It was felt that there was a possibility of the patient secreting neuropeptides during labour and the decision was made to control the whole course of labour and monitor her closely.

Repeat liver function tests and abdominal ultrasound scans showed no progression of her disease. Octreotide

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was made available in the delivery room. The protocol from the *Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumours of the gastroenteropancreatic system*<sup>2</sup> was our point of reference. If the patient had any evidence of a carcinoid crisis, she would be given a 500- $\mu$ g i.v. bolus of octreotide every 5 min until symptoms were relieved, and then she would be started on a continuous i.v. octreotide infusion of 100 units/h.

A radial arterial line and peripheral intravenous cannula were sited and, after a 500-mL i.v. fluid bolus of crystalloid solution, epidural analgesia was established with 15 mL of 0.1% ropivacaine plus fentanyl 2  $\mu$ g/mL, given in divided doses. A continuous epidural infusion was then started at 10 mL/h with the same ropivacaine/fentanyl solution. Use of epinephrine and ephedrine was avoided. Phenylephrine was available for treatment of hypotension, but was not required. The patient had a bilateral T8 block to ice within 10 min. Labour was then induced with artificial rupture of membranes and an oxytocin infusion. Prostaglandins were not used.

Blood pressure (120–135/60–80 mmHg) and heart rate (70–90 beats/min) remained stable throughout labour. The fetal heart rate was reactive with a baseline of 140 beats/min. The patient had a spontaneous vaginal delivery of a live, healthy male infant weighing 3155 g 12 h after induction of labour. Apgar scores were 6 and 9 at 1 and 5 min respectively. The patient was monitored post partum in the obstetric high-dependency unit, where she remained stable. She was discharged home two days after delivery and remained stable five weeks post partum when she was reviewed in the obstetrical clinic.

## Discussion

Carcinoid tumours are neuroendocrine in origin. They are rare, occurring in 2 per 100 000 and are found predominantly in the gastrointestinal tract. They frequently arise from the small intestine, or less often from organs derived from the embryonic foregut such as bronchus, stomach, pancreas and thyroid or from ovarian and testicular teratomas. Tumour metastases are often present at the time of clinical diagnosis.

Carcinoid tumours may secrete a variety of peptide hormones, monoamines and vasoactive substances, namely serotonin, substance P, histamine, prostaglandins, corticotrophin, and bradykinin. Carcinoid syndrome results from the release of these vasoactive mediators into the systemic circulation. The symptoms reflect the presence of metastases to the liver (in 91% of cases) or primary carcinoid tumours located outside the gastrointestinal tract.<sup>3,4</sup> There are no symptoms from products of the gastrointestinal tumours because they are inactivated in the liver via the portal venous circulation before reaching the systemic circulation. The incidence

of metastases with pancreatic carcinoid tumours is 72%, with an incidence of 20% of associated carcinoid syndrome.<sup>4</sup> Our patient had multiple liver metastases and so had a 20% risk of developing carcinoid syndrome.

The common signs and symptoms of carcinoid syndrome include episodic cutaneous flushing of the head and neck (74%), intestinal hypermobility resulting in diarrhoea (with associated dehydration and electrolyte imbalances) and abdominal pain (68%), bronchoconstriction (18%), hypotension or hypertension, hepatomegaly due to metastases, hyperglycaemia and hypoalbuminaemia. Cardiac involvement affects 14–41% at some time in the disease course and can include right-sided valvular heart lesions secondary to fibrosis, decreased myocardial compliance, supraventricular tachycardia and, less commonly, left-sided involvement with decreased ventricular compliance and fibrosis of the mitral or aortic valves.<sup>5</sup> Carcinoid heart disease also includes high cardiac output from vasodilator release, which in 80% of patients with heart disease, leads to heart failure.<sup>4</sup> Carcinoid crisis occurs when all the symptoms of carcinoid syndrome occur concurrently. Carcinoid crisis may occur spontaneously or it may be associated with stress, chemotherapy, or anaesthesia. The five-year survival rate for patients with carcinoid tumours from all stages is 68%.

Serotonin is the most common mediator secreted (over 90% of those who secrete) and is responsible for many of the syndrome manifestations. It is broken down and secreted in the urine as 5-hydroxyindolacetic acid (5-HIAA), whose levels are a good biological marker for tumour activity.<sup>4,6</sup> Serotonin may be responsible for vasoconstriction or vasodilatation, hypertension or hypotension, intestinal hypermobility, hypoproteinaemia and hyperglycaemia. It is the mediator thought to be most responsible for the development of carcinoid heart disease.<sup>3</sup>

High pre-operative urinary 5-HIAA and carcinoid heart disease are significant risk factors for perioperative complications including death.<sup>3,6</sup> The extent of multisystem involvement including cardiovascular instability, respiratory function including bronchial tone, volume depletion, electrolyte balance and sugar balance should all be evaluated.<sup>3</sup>

Durkin published a review of pregnant patients with carcinoid tumour in 1983.<sup>7</sup> Outlined were 18 patients with carcinoid tumours involving 25 pregnancies. Of those, four patients appear to have had carcinoid syndrome. Two of these four patients had successful pregnancies, with the other two resulting in fetal deaths. Durkin's own additional patient had liver metastases without carcinoid syndrome, and also suffered a fetal death. Management was not discussed in these cases. In the Polish literature, Szczurowicz et al. published a case report of elective caesarean section for carcinoid syndrome, with no mention of the anaesthetic technique.<sup>8</sup>

The management of a patient with carcinoid syndrome focuses on blocking the production, release and effect of the mediators and preventing the vasoactive and bronchoconstrictive manifestations of a crisis. Triggers for this may be stress, pain, and histamine-releasing drugs. Octreotide inhibits the release of peptides from the carcinoid tumour and inhibits peptic effects on receptor cells. Octreotide, a synthetic somatostatin analogue, is the most effective agent in treating flushing, hypotension, bronchospasm and diarrhoea in most patients. Previously thought to be unsafe in pregnancy, octreotide crosses the placenta by passive diffusion and clearance of the somatostatin analogue by the infant is prolonged. Treatment with octreotide may in theory increase the risk of fetal hypophysectomy and information about its safety during pregnancy is limited. However, there have been several reported cases where octreotide has been given for long periods during pregnancy, without any suggestion of abnormal postnatal development.<sup>9-12</sup>

It is recommended in the *Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumours of the gastroenteropancreatic system* that a 500–1000- $\mu\text{g}$  i.v. bolus be given 1–2 h before emergency surgery in patients with functional neuroendocrine tumours.<sup>2</sup> Treatment of intra-operative carcinoid crisis with hypotension is a 500- $\mu\text{g}$  i.v. bolus every 5 min until symptoms are controlled. Alternatively, following a 500- $\mu\text{g}$  i.v. bolus of octreotide, an infusion of 50–200  $\mu\text{g}/\text{h}$  may be given.

Serum chromogranin A concentration is elevated in 56–100% of patients with carcinoid tumours and the level correlates with tumour bulk.<sup>4</sup> Concentrations may increase during pregnancy and in patients experiencing significant stress, without an increase in tumour size. In our patient, the level remained stable.

Invasive blood pressure monitoring was established before epidural placement, to aid in the early detection of sudden haemodynamic changes of a carcinoid crisis. Decreases in blood pressure were to be treated with phenylephrine, while epinephrine, norepinephrine and ephedrine were relatively contraindicated due to their ability to cause severe hypertension. In our case, the patient's blood pressure remained stable and no treatment was required. Epidural analgesia was instituted before induction of labour to minimize catecholamine release associated with the pain of labour. Careful titration was required to avoid hypotension and reflex sympathetic nervous system stimulation. We did not use a combined spinal-epidural technique in this case as there was no need to establish a regional block with any urgency. Epidural anaesthesia would also have been chosen in preference to spinal anaesthesia for caesarean section as this would have allowed gradual onset of surgical block, whilst maintaining haemodynamic stability. Small incremental doses of local anaesthetic would have been administered to establish surgical anaesthesia to the level of T4.

If general anaesthesia were required for surgical delivery, invasive blood pressure monitoring with an arterial line would be established and a rapid sequence induction and intubation with propofol and suxamethonium would be used. The general principles of obtunding the stress response to surgery were to be followed, with a careful choice of drugs and dosages so as to avoid the need for sympathomimetic agents to treat hypotension. Opioids, propofol, etomidate and volatile anaesthetics have all been used successfully with careful titration. Histamine-releasing drugs such as thiopental, meperidine, morphine, atracurium and mivacurium should be avoided. There is a theoretical risk of suxamethonium inducing compression of the carcinoid tumour with the onset of abdominal fasciculations. However, its safe use has previously been documented.<sup>3,6</sup>

In the event of a carcinoid crisis, other general management points include the use of pre-operative histamine blockade with corticosteroids or serotonin blockers such as ketanserin or cyproheptadine to counter gastrointestinal manifestations. Aprotinin has been used with variable success to treat flushing associated with bradykinin release.<sup>5,6</sup> Hypertension may be treated with labetalol, nitroglycerin or a serotonin antagonist. Pre-operative benzodiazepines may be useful in reducing stress-related catecholamine release.<sup>5</sup> Endocarditis prophylaxis is required in the presence of significant carcinoid-induced valvular heart disease. Ketamine is contraindicated due to the activation of the sympathetic nervous system causing the release of catecholamines and consequently kallikreins. The patient should be kept warm as hypothermia may trigger the release of peptides.<sup>5</sup> Hypercarbia is also avoided as it may increase catecholamine release.<sup>3</sup>

In summary, parturients with carcinoid disease with metastases have the potential to exhibit carcinoid syndrome, and also carcinoid crisis. We decided that a multidisciplinary approach, with careful assessment and close monitoring of this patient would provide us the best possible outcome in the event that a carcinoid crisis ensued. The use of epidural analgesia for labour and delivery ensured haemodynamic stability and also allowed for the management of any potential obstetric emergency.

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## References

1. Gough I R, Stitz R W. Metastatic carcinoid tumor: stability throughout pregnancy. *Aust NZ J Surg* 1991; 61: 960–2.
2. Oberg K, Kvols L, Caplin M et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine

- tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; 15: 966–73.
3. Graham G W, Unger B P, Coursin D B. Perioperative management of selected endocrine disorders. *Int Anesthesiol Clin* 2000; 38: 31–67.
  4. Jensen R T. Endocrine tumors of the gastrointestinal tract and pancreas. In: Fauci A S, Braunwald E, Kasper D L, Hauser S L, Longo D L, Jameson J L, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*, 17th Ed. New York: McGraw-Hill; 2008.
  5. Grant F. Anesthetic considerations in the multiple endocrine neoplasia syndromes. *Curr Opin Anaesthesiol* 2005; 18: 345–52.
  6. Kinney M A, Warner M E, Nagorney D M et al. Perianesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth* 2001; 87: 447–52.
  7. Durkin J W. Carcinoid tumor and pregnancy. *Am J Obstet Gynecol* 1983; 145: 757–61.
  8. Szczurowicz A, Wszelaki-Lass E, Debniak J, Wyda D. Carcinoid syndrome in a pregnant woman. Case report. *Ginekol Plo* 1995; 66: 59–60.
  9. Boulanger C, Vezzosi D, Bennet A, Lorenzini F, Fauvel J, Caron P. Normal pregnancy in a woman with nesidioblastosis treated with somatostatin analog octreotide. *J Endocrinol Invest* 2004; 27: 465–70.
  10. Mikhail N. Octreotide treatment of acromegaly during pregnancy. *Mayo Clin Proc* 2002; 77: 297–8.
  11. Caron P, Gerbeau C, Pradayrol L. Maternal-fetal transfer of octreotide. *N Engl J Med* 1995; 333: 601.
  12. Fassnacht M, Capeller B, Arlt W, Steck T, Allolio B. Octreotide LAR treatment throughout pregnancy in an acromegalic woman. *Clin Endocrinology* 2001; 55: 411–5.