REVIEW

Pheochromocytoma in pregnancy – a rare but dangerous diagnosis

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ABSTRACT

Pheochromocytoma is a rare cause of hypertension in pregnancy. Unrecognized, it carries a great risk for both mother and the foetus. The main reason for missing the diagnosis is the misconception that any hypertension occurring in pregnancy is gestational hypertension or pre (eclampsia). As many as 90% of patients report one or more pheochromocytoma-related symptoms antenatally, but the diagnosis is made in 75% of patients, meaning that 3 out of 10 patients are diagnosed after childbirth or post-mortem. The symptoms are similar to other more common causes of hypertension in pregnancy, which presents a major diagnostic challenge. The diagnosis is based on determination of metanephrines in plasma or 24-hour urine. Magnetic resonance imaging (MRI) and ultrasound (US) are used to localize the tumour. If the diagnosis is made before the 24th week of pregnancy, laparoscopic removal of the tumour in the second trimester is recommended. If diagnosed later, the tumour could be removed during or after delivery. Preoperative preparation with alpha blockers is required to stabilize blood pressure. The decision on the mode of delivery depends on several factors, so an experienced multidisciplinary team is needed to minimize maternal and foetal mortality.

Key words: hypertension, pheochromocytoma, preeclampsia

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INTRODUCTION AND EPIDEMIOLOGY

Pheochromocytomas are rare neuroendocrine tumours that arise from chromaffin cells of the adrenal medulla and secrete catecholamines. In 15–20% cases they arise from the sympathetic ganglia of the abdominal cavity, thorax, or neck, and are then called paragangliomas (1). The incidence of pheochromocytomas in pregnancy is 1/15 000 to 1/54 000 pregnant women (2). A retrospective study showed that hypertension as the most common sign was observed in 87% of patients with pheochromocytoma and 86% of patients with paraganglioma. (3). Hypertension occurs in 6–8% of pregnant women, and 88% are classified as essential hypertension. Pheochromocytoma is the cause of hypertension in 0.007%, but if not diagnosed in time, mortality reaches 40–50%. Seventy-three percent of cases get diagnosed in the antenatal period, 32% of which are diagnosed in the 2nd trimester and 42% in the 3rd trimester of pregnancy (4). The largest number of cases is diagnosed in the 3rd trimester due to pronounced symptoms as a result of uterine compression (5). If recognised in time, maternal mortality is about 5%, while foetal mortality is less than 15% (3). The main reason for missing diagnosis is the misconception that any hypertension occurring in pregnancy is gestational hypertension or preeclampsia. Ninety percent of patients report one or more pheochromocytoma-related symptoms antenatally, but the diagnosis is made in 75% of patients, meaning that 3 out of 10 patients are diagnosed after childbirth or post-mortem (1).

EFFECTS OF CATECHOLAMINES IN PREGNANCY

Norepinephrine and epinephrin are potent cardiac and vasoactive compounds that play a central role in adaptation and protection against stressful stimuli, including pregnancy and childbirth (1,4). Maternal catecholamines have difficulty crossing the placental barrier. Even in patients with pheochromocytoma, umbilical cord blood contains less than 10% of maternal catecholamine concentrations. That is due to the presence of norepinephrine transporters and enzymes that metabolise catecholamines (catechol-O-methyltransferase and monoamine oxidase) and thus interrupt their biological activity (1). However, exposure of the placenta to high levels of catecholamines can cause narrowing of the blood vessels in the uterus and uteroplacental insufficiency. That can lead to miscarriage, foetal growth retardation, foetal hypoxia and intrauterine death. In recent years, the foetal mortality rate has decreased from 55% to 7% if the diagnosis was made antenatally (4).

CLINICAL PRESENTATION

Symptoms occur as a result of hypersecretion of catecholamines, most commonly norepinephrine and epinephrine. The usual triad of symptoms includes headache, sweating and palpitations, while hypertension is the most important sign (2). Other symptoms include paleness, dizziness, dyspnoea, weight loss, and obstipation (6). The clinical picture in pregnant women does not differ significantly from other patients (1). Symptoms worsen as the end of pregnancy approaches (6). Hypertension is the main sign and occurs in 87% of pregnant women, and in one-third of the cases, it is paroxysmal hypertension (1,7). The main reason for missing the diagnosis is the misconception that any hypertension that occurs in pregnancy is gestational hypertension or preeclampsia, so it is very important to know how to recognise and distinguish those two diseases (Table 1). Pregnant women are at higher risk for developing a hypertensive crisis due to foetal movement, uterine growth and contractions or anaesthesia during a caesarean section (7). A rare but potentially fatal complication is the development of cardiomyopathy caused by excess catecholamine secretion, which manifests as acute heart failure, cardiogenic shock, or acute coronary syndrome (4). When a pregnant woman presents with one of the cardiovascular emergencies, even without previously known hypertension, the possibility of pheochromocytoma should be taken into consideration (1).

DIAGNOSIS

The indications for biochemical testing are signs or symptoms that occur as a result of catecholamine secretion (especially if paroxysmal), unexpected blood pressure response to drugs or anaesthesia, inexplicable variability and difficulty in controlling blood pressure, incidentaloma, hereditary risk of pheochromocytoma, or any clinical manifestations of hereditary symptoms (9). Before biochemical testing, it is necessary to check which medicines the pregnant woman is taking to avoid the occurrence of false-positive results. Some of those include methyldopa or labetalol.

Table 1. Differential diagnosis between pheochromocytoma and preeclampsia

Variable	Pheochromocytoma	Preeclampsia
Hypertension (1,3,4)	It occurs at any stage of gestation, paroxysmal	Occurs after the 20th week of gestation, permanent
Orthostatic hypotension (1,4)	Occurs in 50 % of patients	Unusual
Related symptoms (4)	They occur paroxysmically - headache, sweating, tachycardia, palpitations, pallor, nausea	Headache, visual disturbances, altered mental status, nausea
Ankle oedema (1,4)	Unusual	Present
Proteinuria (1,4)	Unusual	Present (≥ 300 mg in 24 - hour urine)
Weight gain (4)	Unusual (catecholamines increase metabolism)	Sudden thickening (due to fluid retention)
Metanephrines in plasma or 24-hour urine (4,9)	Elevated (2 - 3 times higher than reference values)	Normal
Other laboratory findings (4)	Hyperglycaemia Glycosuria	Elevated serum uric acid levels Elevated serum creatinine > 97.26 µmol /L Elevated liver enzymes (> 2 times) Thrombocytopenia < 100,000 platelets /mm3
Personal and family history (4,8)	Presence of pheochromocytoma or paraganglioma Presence of pheochromocytoma-related syndrome features (MEN 2A, MEN 2B, VHL1, NF1, SDH mutations)	Presence of preeclampsia Maternal age > 40 or < 18 years Nullity Twin pregnancy Maternal diseases (chronic hypertension, pregestational diabetes mellitus, obesity before pregnancy (BMI > 30 kg/m2), antiphospholipid syndrome, systemic lupus erythematosus)

Catecholamine metabolism is unchanged during a healthy pregnancy and is only slightly elevated in patients with preeclampsia (4). Biochemical testing includes measuring plasma or 24-hour urinary metanephrine. In patients who had elevated levels of metanephrine, normetanephrine and 3-methoxytyramine prior to surgery, it is recommended that metanephrine and 3-methoxytyramine be tested annually in plasma or urine to determine whether there are local or metastatic recurrences or new tumours (10). Plasma samples should be taken in a supine position. When taking samples in a sitting position without prior rest, the values of catecholamine metabolites are 30% higher than in a supine position (1). Plasma metanephrine levels 2.5 times the reference value support pheochromocytoma (11). Moreover, 2-3 times higher urinary catecholamine levels are very likely to indicate pheochromocytoma (12). Provocation tests, such as the clonidine suppression test, should be avoided due to their low sensitivity and potentially severe side effects (3).

Ultrasound (US) and magnetic resonance imaging (MRI) are used to localise the tumour. The MRI is safe during pregnancy. There is a lack of strong evidence on the safety of gadolinium in pregnancy, so it is recommended to avoid it unless the benefits outweigh the potential risks (1,4). The MRI sensitivity is 90-100 %, while specificity is limited to 70-80%. Functional screening with 123I-meta-iodobenzylguanidine (MIBG) is contraindicated in pregnant women due to the passage of radioactive compounds through the placenta. A biopsy is also contraindicated because of the risk of hypertensive crisis.

Once the diagnosis is made, genetic counselling is required to decide if there is a need for genetic testing. It is useful because of the ability to identify patients who are at increased risk of multifocal, recurrent and metastatic disease. Forty percent of pregnant women with pheochromocytoma have a genetic mutation (1). The most common inherited syndromes occur due to mutations in the RET proto-oncogene and tumour suppressor genes VHL, NF1, SDHB and SDHD (Table 2) (1,13). Genetic testing is required if pheochromocytoma occurs at a younger age or is bilateral, and if there is a positive family history of pheochromocytoma or any of the listed clinical features of hereditary syndromes (14). Also, any hypertension that occurs before the age of 20 should raise the suspicion of pheochromocytoma (3).

TREATMENT

The tumour should be removed before 24 weeks of gestation. If diagnosed later, the tumour is removed during or after childbirth. The risk of miscarriage is lowest in the second trimester, while in the third trimester, the anatomical conditions are unfavourable for surgical removal and are, therefore, delayed. Laparoscopic removal of the tumour is preferred because it leads to less he-

Table 2. Hereditary syndromes associated with pheochromocytoma

Syndrome	Clinical features / frequency	Gene	Frequency (%) of genetic mutation in seemingly sporadic pheochromocytoma
Multiple endocrine neoplasia type 2A (MEN 2A) (1,15,20)	Medullary thyroid cancer / 95% Pheochromocytoma / 50% Hyperparathyroidism / 15 - 30%	RET	< 5
Multiple endocrine neoplasia type 2B (MEN 2B) (1,15,20)	Medullary thyroid cancer / 100 % Pheochromocytoma / 50 % Mucosal neuromas of the lips and tongue, ganglioneuromatosis of the gastrointestinal tract, marfanoid habitus	RET	< 5
Von Hippel Lindau syndrome (1,15,20)	Pheochromocytoma / 25 - 30% Hemangioblastomas of the central nervous system Tumours of the endolymphatic sac Epididymal cystadenomas Renal cell carcinomas Renal cysts Neuroendocrine tumours of the pancreas Pancreatic cysts	VHL	2 – 11
Neurofibromatosis type 1 (1,15,20)	Pheochromocytoma / 0.1 - 5.7 % Multiple fibroids on the skin and mucous membranes (> 2) Leather stains "Cafè au lait" (> 6)	NF1	Unknown
Familial paraganglioma type 4 (1,15,20)	Extra-adrenal paraganglioma Pheochromocytoma Renal cell carcinoma Gastrointestinal stromal tumours Pituitary adenomas	SDHB	3 – 10
Familial paraganglioma type 1 (1,15,20)	Multifocal paraganglioma of the head and neck Pheochromocytoma Renal cell carcinoma Gastrointestinal stromal tumours Pituitary adenoma	SDHD	4 – 7

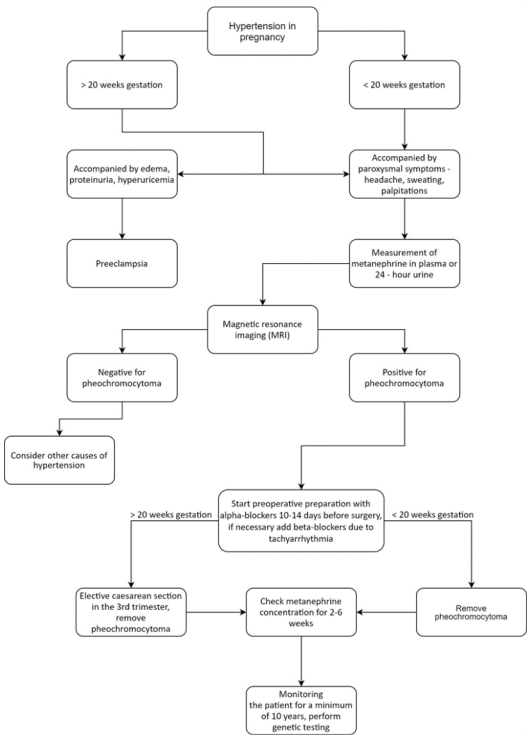

Figure 1. Algorithm for diagnosis and treatment of pheochromocytomas in pregnancy

modynamic instability, a shorter hospital stay, and less morbidity than open surgery (21,22). A transperitoneal approach is the most acceptable while the patient is in a lateral position (1). The left lateral position for the extirpation of the tumour located on the right side is well tolerated because there is no pressure on the inferior vena cava, while the right lateral position for the extirpation of tumours on the left adrenal gland can lead to compression of the inferior vena cava and increases the risk of uteroplacental hypoperfusion during surgery (3). Patients should be monitored 2 - 6 weeks after surgery, and plasma or 24-hour urinary metanephrine levels should be determined to confirm that the tumour has been completely removed. Long-term follow-up is required once a year for at least 10 years, while patients with gene mutations, extra-adrenal tumours and bilateral or large tumours should be followed for life due to the increased risk of disease recurrence (1).

Preoperative preparation

Preoperative preparation is necessary to stabilise blood pressure and reduce the risk of a paroxysmal rise in blood pressure. In pregnant

women with chronic hypertension, the goal is to achieve a pressure lower than 150/100 mmHg if there are no signs of damage to the target organs, or less than 140/90 mmHg if there is damage to the target organs.

The alpha-adrenergic blockade is started 10-14 days before surgery (4). Phenoxybenzamine and doxazosin, long-acting alpha-blockers, are most commonly used. Phenoxybenzamine is a non-competitive alpha 1- and alpha 2-adrenoreceptor blocker.

The initial dose is 10 mg twice a day, which is gradually increased from 20 mg to 1 mg/kg per day. The most prominent side effects of phenoxybenzamine include nasal congestion, orthostatic hypotension and tachycardia. Also, a long-lasting non-competitive alpha-receptor blockade leads to postoperative hypotension. Because of its passage through the placenta, the newborn is at risk of hypotension and respiratory depression. In the first 3 postnatal days, monitoring is recommended. Doxazosin is a competitive selective alpha-1 blocker. The initial dose is 2 mg per day, which is then increased to 16 mg or even 32 mg per day (1). It has fewer side effects than phenoxybenzamine and a lower incidence of reflex tachycardia and postoperative maternal hypotension (4). It can also pass through the placenta, but no adverse effects have been reported. It is recommended to use doxazosin as the drug of choice in pregnant women with pheochromocytoma. Both alpha-blockers can transfer into breast milk, but no adverse effects have been reported (1). Pregnant women with normal blood pressure should take lower doses to prevent paroxysmal spikes in blood pressure (4).

Following the introduction of an alpha-blocker, a beta-blocker is introduced as needed to treat or prevent tachyarrhythmias. In order to avoid alpha-adrenoreceptor-mediated vasoconstriction, beta-blockers should be introduced a few days after alpha-adrenergic receptor blockade. Propranolol 40 mg 3 times a day and atenolol 25-50 mg once a day are most commonly used (1). Labetalol, which has a combined effect on alpha and beta receptors, is not recommended in pregnancy due to its relatively weak alpha-receptor blockade, leading to paroxysmal hypertension. Methyldopa, the most commonly used drug to treat essential hypertension during pregnancy, is not recommended in pregnant patients with pheochromocytoma as it might aggravate hypertension. Beta-blockers are associated with intrauterine growth retardation, so their use should be short term only (4). In addition to medications, it is important to increase salt and fluid intake during preoperative preparation to reduce the risk of postoperative hypotension (1).

It is important to know which medications must be avoided in patients with pheochromocytoma. Some of them include corticosteroids, opioids (morphine), antiemetics (metoclopramide), muscle relaxants (mivacurium), anaesthetics (thiopental, ketamine, ephedrine) (4). Their use can lead to hypertensive crisis, hypertensive encephalopathy or ischemic heart disease. In that case, a short-acting calcium channel blocker such as nicardipine or a vasodilator magnesium sulphate used in the treatment of eclampsia may be administered intravenously. Magnesium sulphate induces vasodilation, inhibits catecholamine release, and decreases the sensitivity of adrenergic receptors to catecholamines, but its plasma concentration should be monitored if administered by continuous infusion (1).

CHILDBIRTH

Elective caesarean section has long been considered safer due to the recorded number of deaths that occurred during vaginal birth. Caesarean section can cause blood loss and catecholamine release due to peritoneal manipulation, and recent research shows success of vaginal delivery due to a good anaesthesiologic and obstetric treatment. Epidural anaesthesia reduces pain and stress during childbirth (4). Oxytocin and other uterotonics should be used with caution as they may lead to tachycardia and hypotension (3). The final decision depends on several factors, such as previous caesarean section, the success of preoperative preparation and the patient's personal preferences. In most cases, caesarean section remains the preferred method of delivery (1).

Hypertension occurs in 6-8 % of pregnant women. In rare cases, pheochromocytoma is the cause of hypertension, and it is important to know the indications for biochemical testing in order to make a diagnosis in time (Figure 1). As many as 90% of patients report one or more pheochromocytoma-related symptoms antenatally, but the diagnosis is made in 75% of patients, which me-

ans that 3 out of 10 patients are diagnosed after childbirth or post-mortem (1).

In conclusion, early diagnosis of pheochromocytoma significantly reduces the risk to mother and child and helps prevent potential complications.

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