



Pheochromocytoma in Pregnancy: A Review of the Literature

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Abstract

Pheochromocytoma in pregnancy is a life-threatening condition. Although it is rare, if the diagnosis is missed or mismanaged, it has detrimental effect on both mother and fetus, with mortality up to 58%. Diagnosis of pheochromocytoma in pregnancy remains a huge challenge faced by clinicians due to its non-specific signs and symptoms and the fact that it mimics other conditions which occur much more commonly in pregnancy. On the other hand, early recognition, prompt diagnosis and appropriate treatment during pregnancy are associated with a significant reduction in maternal and fetal mortality. In this review, we provide a brief overview regarding the clinical features, diagnostic tests, and management of pheochromocytoma in pregnancy. We highlight that a delay or missed management is associated with adverse fetal and maternal outcome and that a multidisciplinary team approach is essential and each case considered individually to achieving the best outcome in both mother and fetus. This review should provide a guide for clinicians who come across the condition.

by multiple organ failures, severe blood pressure variability, high fever, encephalopathy, with resultant cardiometabolic sequelae [6,7].

Pheochromocytoma is malignant in approximately 10% of cases [8], and surgical resection may be curative [9]. Pheochromocytoma presenting in pregnancy is rare, it has an incidence of less than 0.2 per 10000 pregnancies (approximately 1 in 54000) [10], and diagnosis may be difficult as it may present with a wide range of non-specific signs and symptoms which mimic other common disorders of pregnancy [5]. All cases should be managed by a multidisciplinary team approach consisting of endocrinologist, obstetrician, paediatrician, endocrine surgeon, anaesthetist, and geneticist to ensure appropriate management plans are established for each patient. This review discusses the clinical features, diagnostic tests, and the management of Pheochromocytoma in pregnancy as a delay or missed diagnosis and/or treatment is associated with adverse fetal and maternal outcome.

Pregnancy and Pheochromocytoma

The majority of cases of pheochromocytoma in pregnancy are diagnosed prior to pregnancy [11]. However, diagnosis during pregnancy may be delayed as it may be difficult to distinguish the signs and symptoms from other common disorders of pregnancy such as hyperemesis, pregnancy-induced hypertension, preeclampsia, eclampsia, and gestational diabetes mellitus [12-14]. One fifth of cases were identified only in the peripartum period as a result of acute complications, and the minority of the cases were noted only after adverse fetal or maternal outcomes [11]. It is difficult to ascertain whether pre-existing Pheochromocytoma worsens in pregnancy or not. However, the literature suggests a possible role of oestrogen in acting as a growth factor, thus leading to tumour progression in pregnancy [15,16].

Presentation

Patients with pheochromocytoma can present with variety of symptoms. Those who have an unknown genetic predisposition can be asymptomatic, whereas at the other end of the spectrum, patients may present as a life-threatening emergency [15]. Symptoms of

Introduction

Pheochromocytoma is a neuroendocrine tumour of the chromaffin cells of the adrenal medulla that secrete catecholamines. Extra-adrenal pheochromocytomas-paragangliomas are less common (5-15%), and arise from the sympathetic ganglia [1]. Pheochromocytomas occur equally in both genders and are more frequent between the third and fifth decades of life [2]. The prevalence of pheochromocytoma ranges from 0.05% to approximately 0.2% [1]. Although the occurrence is sporadic in the majority of cases, up to 25% of cases may be syndrome-associated-von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN 2), and neurofibromatosis type 1 (NF1) [3]. Currently, there are up to nine genes that have been identified as sites of mutations leading to pheochromocytoma [4].

The catecholamine effects from the pheochromocytoma may lead to presentations with paroxysmal or sustained hypertension, episodic headache, sweating and tachycardia [5]. Symptoms may be severe, and patients may present with 'Pheochromocytoma crisis', characterised

Table 1: Summary of characteristic presentations, treatments, and outcomes of pregnant women with pheochromocytoma from the 10 most recent case reports.

| Age (years) | Gestation at diagnosis (weeks) | Presentation | Diagnosis | Tumour location | Management | Outcome | Reference |
|-------------|---|--|---|--|---|--|-----------------------------------|
| 27 | 2 days postnatal after Caesarean section at term. | Headache, confusion, nausea and vomiting, shortness of breath, tachypnoea. Severe hypertension unresponsive to medical treatments. | Urine epinephrine. Urine norepinephrine. Urine metanephrine. Urine normetanephrine. Urine VMA. Abdominal CT. | Left adrenal mass measuring 58 mm × 50 mm × 30 mm. | α-adrenergic antagonist. β- antagonist. Surgical adrenalectomy. | Both mother and baby are well. | Naghshineh E, <i>et al.</i> [52] |
| 24 | 37 | Severe hypertension. | Urine metadrenaline. MIBG Iodine scan (postnatally). | Bilateral pheochromocytoma on the adrenal glands. | α-adrenergic antagonist. β- antagonist. Laparoscopic excision of tumours at 5 months postnatal. | Patient delivered by Caesarean section. Both mother and baby are well. | Weingarten M, <i>et al.</i> [53] |
| 32 | 12 | Right sided abdominal discomfort. | Urine metanephrine. Urine normetanephrine. Abdominal ultrasound. MRI. | Bilateral pheochromocytoma on the adrenal glands. (right side, 49 × 44 × 42 mm; left side, 73 × 61 × 75 mm). | α-adrenergic antagonist. Hydration. Exploratory laparotomy and bilateral adrenalectomy at 15 weeks gestation. | Pregnancy continued and uneventfully. Patient had normal vaginal delivery at 39 weeks gestation. Both mother and baby are well. | Kitayama K, <i>et al.</i> [54] |
| 34 | 9 | Palpitation, headache, sweating, nonspecific gastrointestinal disorders. Pressure on right renal area. Paroxysmal hypertension. | Urine catecholamine Urine VMA. Abdominal ultrasound. MRI. | Right adrenal tumour 10 cm in diameter. | α-adrenergic antagonist. β- antagonist. Surgical resection of tumour at 14 weeks gestation. | Baby was delivered uneventfully at the 36 weeks gestation. Both mother and baby are well. | Kiroplastis K, <i>et al.</i> [55] |
| 24 | 33 | Acute diffuse abdominal pain. Severe hypertensive crisis. Acute pulmonary oedema. | Urine noradrenaline. Plasma renin Serum noradrenaline Abdominal CT. MRI | Left adrenal mass measuring 56 x 49 mm. | α-adrenergic antagonist. β- antagonist. Calcium channel blockers. ACE1 inhibitor. Open left adrenalectomy 2 weeks later. | Had Caesarean section for fetal distress, baby died 2 weeks later. Mother is well. | Santos, <i>et al.</i> [1] |
| 34 | 13 | Severe hypertension unresponsive to medical treatments. | Urine VMA. MRI. | Right adrenal mass measuring 30 x 25 mm | α-adrenergic antagonist. β- antagonist. Open right adrenalectomy. Blood pressure was controlled with glyceryl-trinitrate and volatile agents intraoperatively. | She had uneventful pregnancy and delivered vaginally at term. Both mother and baby are well. | Memon, <i>et al.</i> [56] |
| 23 | 26 | Sweating, abdominal pain, palpitations. Severe hypertension unresponsive to medical treatments. | Abdominal CT | Right adrenal mass | β- antagonist. Hydralazine. Open adrenalectomy. | The pregnancy was terminated, baby died 2 days postnatal. The mother had good post-operative outcome. | Lalitha R, <i>et al.</i> [57] |
| 27 | 22 | Intermittent headache and epigastric pain. Severe hypertension unresponsive to medical treatments. | Urine norepinephrine. Plasma norepinephrine. Urine metanephrine. MRI. | Right adrenal mass measuring 40 x 40 mm. | α-adrenergic antagonist. Laparoscopic adrenalectomy at 25 weeks gestation. | Both mother and baby are well. | Doo AR, <i>et al.</i> [58] |
| 43 | Term | Patient had a background medical history of gestational diabetes mellitus. Sudden malignant hypertension with haemoptysis, sweating, and tachycardia during a planned Caesarean section. Baby was successfully resuscitated. The mother died after resistant cardiac arrest. | Autopsy and pathological analyses showed an acute pulmonary oedema and a necrotic left adrenal gland tumour, which was a pheochromocytoma | Left adrenal tumour | - | Mother died Baby survived. | Plu I, <i>et al.</i> [59] |
| 34 | Term | Hypertensive crises and a grand-mal seizure following elective caesarean section. Treatment for presumed eclamptic seizure was initiated followed by profound hypotensive episodes accompanied by severe biventricular failure and fluctuating systemic vascular resistance. | Abdominal ultrasound. Abdominal CT. Urinary assays. | Left suprarenal mass measuring 53mm. | α-adrenergic antagonist. β- antagonist. Surgical excision 6 weeks postnatal. | Both mother and baby are well. The cardiac function returned to normal and she has made a complete recovery. | Petrie J, <i>et al.</i> [60] |

Abbreviations: VMA: Vanillylmandelic Acid; CT: Computed Tomography; MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging.

pheochromocytoma tend to manifest more in the third trimester and are the result of catecholamine excess. Patients may present with headache, sweating, dizziness, dyspnoea, palpitations, nausea, vomiting, and abdominal pain [5,17]. Other symptoms include weight loss, constipation, and seizures. Signs include tachycardia, labile or uncontrolled hypertension, oedema and polyuria. Patients with neurofibromatosis may have signs such as café au lait spots, freckles, and fibromas [5,17].

It is important to distinguish Pheochromocytoma in pregnancy from preeclampsia due to its non-specific presentation. Failure to do so may result in patients being initially treated for preeclampsia [12], and delay in diagnosis of Pheochromocytoma may be fatal. The supine position during pregnancy results in the gravid uterus compressing the tumour, thus causing paradoxical supine hypertension with normal blood pressure in the sitting or erect position. Episodes of hypertension in patients with preeclampsia tend to be uniform throughout the day whereas, in pheochromocytoma, the hypertension episodes may be paroxysmal and do not have a pattern of onset [18]. In addition, it is uncommon for preeclampsia to present with paroxysmal hypertension and to affect women before 20 weeks gestation. Moreover, the classical triad of pre-eclampsia which consists of hypertension, proteinuria, oedema, are often not suggestive of Pheochromocytoma, while postural hypotension is [12].

The excess catecholamine effects of Pheochromocytoma in pregnancy on the cardiovascular system may lead to hypertensive crisis and syncope, catecholamine-induced cardiomyopathy, presenting as acute coronary syndrome, arrhythmias, acute heart failure, cardiogenic shock, or acute coronary syndrome [6,7,19]. Acute cardiomyopathy may be seen during the peripartum period [20], but may also manifest as acute myocardial infarction during pregnancy [21]. Very rarely, patients with Pheochromocytoma may present with non-cardiac pulmonary oedema or aortic dissection [22], and stroke [15]. These effects are potentially reversible after tumour removal [23]. Therefore, Pheochromocytoma should be suspected in any pregnant patient who develops unexplained cardiomyopathy during pregnancy. Table 1 summarises the characteristic presentations, treatments, and outcomes of pregnant women with Pheochromocytoma from the 10 most recent case reports.

Diagnosis

When a diagnosis of Pheochromocytoma is suspected from medical history and physical examination, immediate biochemical testing should be performed to rule out or to confirm the diagnosis. Biochemical investigations for the diagnosis of Pheochromocytoma involve measurements of plasma, and 24-hour urinary fractionated metanephrines [5]. These tests are highly sensitive and yield a significant negative predictive value. Catecholamine levels in pregnant and non-pregnant woman are comparable [24]. Therefore, the sensitivity and specificity of laboratory testing is similar in pregnancy to that of the general population.

False positive findings as a result of interference with plasma or 24-hour urinary metanephrine and catecholamines may arise from medications such as methyl dopa, labetalol, tricyclic antidepressant, and other medical conditions such as acute myocardial infarction, congestive heart failure, alcohol or clonidine withdrawal, cocaine use, panic attacks, brain tumours, subarachnoid haemorrhage [10,25]. Additionally rare cases of elevation of plasma or urinary catecholamines in severe pre-eclampsia have been reported [26].

Magnetic Resonance Imaging (MRI) without gadolinium is the diagnostic imaging test of choice in pregnancy with suspected Pheochromocytoma as it provides good visualisation of abdomen, pelvis, neck, and mediastinum and does not involve the use of ionising radiation [5]. However, MRI is less reliable in visualising extra-adrenal tumours. MRI can also be used in emergency situations prior to biochemical testing in order to identify suspected cases in order to commence life-saving medical treatment [10].

Abdominal ultrasonography may be useful and has good sensitivity in the first trimester, however the sensitivity is reduced in

the second and third trimester of pregnancy as the enlarged uterus interferes with the visibility of the tumour [27]. Stimulation tests and diagnostic imaging such as computed tomography and scintigraphy with metaiodobenzylguanidine (MIBG) are the gold standard and highly sensitive in detecting underlying lesion(s) and diagnosing pheochromocytoma, but are not recommended in pregnancy due to potential undesirable effects on the fetus [11].

Management

Optimal medical therapy for pheochromocytoma in pregnancy is not clearly defined, since the published literature largely consists of case reports. The management of Pheochromocytoma in pregnancy involves blood pressure control and the avoidance of paroxysmal changes in blood pressure. It is important to correctly balance vasodilatation and vasoconstriction to optimise uteroplacental circulation to prevent fetal demise and to avoid impaired fetal growth. Although surgery provides definitive treatment [28], medical preparation is essential. Phenoxybenzamine, a non-specific, long-lasting α -adrenergic antagonist is the drug of choice. Although phenoxybenzamine crosses the placenta [29], good neonatal outcomes after maternal phenoxybenzamine treatment have been reported [30]. Neonatal hypotension and respiratory depression have been reported in some babies whose mothers were treated with phenoxybenzamine, it is therefore suggested that newborns of mothers receiving phenoxybenzamine should be carefully monitored after delivery [31]. Maternal tachycardia may occur with phenoxybenzamine treatment due to noradrenaline release from presynaptic nerve. In addition, hypotension may occur due to its prolonged half-life irreversible blockade of α -adrenoceptors [29]. Alternatives to phenoxybenzamine include other alpha-adrenergic antagonists such as prazosin, and doxazosin [15]. These agents produce less tachycardia with shorter duration of action that facilitates dosage titrations and fewer occurrences of postoperative hypotension [3,15].

Methyldopa is an indirect-acting α -adrenergic antagonist that is widely used to treat hypertension during pregnancy. It is not recommended for the treatment of patients with pheochromocytoma, as it may worsen the symptoms of pheochromocytoma and blood pressure control [32]. Moreover, methyldopa may lead to falsely high levels of urinary metanephrines, as it may interfere with laboratory assays that use liquid chromatography with fluorescence detection [27]. Hence, methyldopa should be discontinued when pheochromocytoma is suspected.

Pregnant women with pheochromocytoma are at high risk of catecholamine excess or hypertensive crisis in the peripartum period. This may be due to factors such as abdominal palpation, labour and delivery, anaesthesia or the use of certain medications (e.g. metoclopramide or opioids). In order to manage acute catecholamine excess in emergencies during pregnancy, phentolamine a competitive α 1- and α 2-antagonist or phenoxybenzamine, a non-selective, irreversible α 1- and α 2-blocker, may be considered for the treatment of catecholamine-induced severe hypertension because of the quick onset of action [33,34].

After adequate α -receptor blockade is obtained, β antagonists may be considered. This is because β blockade on its own is associated with dramatic blood pressure elevations attributed to unopposed α -adrenergic effects by catecholamines, especially in patients with Pheochromocytoma [34]. Esmolol, a cardioselective β 1 receptor antagonist, and labetalol, a mixed α and β receptor antagonist can be easily titrated due to their rapid onset of action and short duration of action [35]. This makes esmolol and labetalol ideal candidates for the control of both hypertensive crises and tachyarrhythmias associated with acute catecholamine excess. β -blockers should, however be used cautiously in patients with catecholamine-induced cardiomyopathy, due to potential effects such as hypotension, bradycardia and pulmonary oedema [36]. Short-acting calcium channel blockers, such as nifedipine and clevidipine have also been used to treat Pheochromocytoma successfully [37]. Magnesium sulphate is beneficial in the management of severe pre-eclampsia in order to prevent progression to eclampsia. In Pheochromocytoma,

Table 2: Summary of recommended diagnostic tools, drugs and treatment procedure for pheochromocytoma in pregnancy [3,5,11,15,27-30,33-35,37-40].

| Diagnostic Tools | Drugs | Treatment Procedure |
|--|---|--|
| Biochemical investigations (all trimesters and postnatal period): Plasma free metanephrines or 24 hour urine fractionated metanephrines Imaging: 1st trimester Abdominal ultrasound (1 st trimester) MRI without gadolinium 2nd and 3rd trimester MRI without gadolinium Postnatal period CT MIBG Iodine | Pre-operative control of catecholamine excess: α-adrenergic antagonist Phenoxybenzamine Prazocin Doxazocin β-receptor antagonist Esmolol Labetolol Propranolol Metoprolol Atenolol Bisoprolol Short-acting calcium channel blockers Nicardipine Clevidipine Management of acute catecholamine excess: The above ± the following can be considered Magnesium Sulphate Other direct vasodilators Hydralazine Nitroglycerin Sodium Nitroprusside | Factors to be considered: Location of tumour Gestation age of pregnancy Adequacy of blood pressure control Multiple or malignant tumours Accessibility of the lesion to surgery Treatment Procedure: 1st trimester Surgery is associated with a higher incidence of miscarriage and only recommended for life-threatening situation unresponsive to medical treatments. 2nd trimester Surgical resection of the tumour (adrenalectomy). Laparoscopic approach is the treatment of choice. 3rd trimester Delivery is planned with concurrent or delayed adrenalectomy |

Abbreviations: CT: Computed Tomography; MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging.

magnesium sulphate has been shown to be safe and effective in treating hypertensive crisis in Pheochromocytoma in pregnancy as it inhibits catecholamine release from the tumour, blocks peripheral catecholamine receptors, and is a direct vasodilator [38,39]. Other medications such as vasodilators hydralazine, nitroglycerin, and sodium nitroprusside can also be effective in the treatment of hypertensive crises in patients affected by Pheochromocytoma [27].

The timing of the surgery is based on clinical judgement depending on the patient. Factors to be considered include the location of tumour, gestational age of the pregnancy, adequacy of blood pressure control, multiple or malignant tumours and accessibility of the lesion to surgery. Surgery in the first trimester is associated with a higher incidence of miscarriage. Adrenalectomy is generally recommended in the second trimester, with a laparoscopic approach considered to be the treatment of choice [40]. Although surgery during the second trimester is usually regarded as the best treatment option for early detected Pheochromocytoma, it has been reported that patients have been treated with long-term medical therapy throughout pregnancy despite an early diagnosis, with generally satisfactory maternal and fetal outcomes [41]. Nevertheless, the risk of fetoplacental exposure to medical treatment and catecholamine excess should be considered.

In cases where the Pheochromocytoma diagnosis is established after the second trimester, the laparoscopic approach may be hindered by the enlarged uterus. Therefore, medical treatment is commenced with observation until sufficient fetal maturity is achieved [11]. Delivery is then planned during final trimester, with concurrent or delayed adrenalectomy [27]. Caesarean section delivery is preferred as vaginal delivery in patients with Pheochromocytoma has been associated with high mortality rates for both mother and fetus. However, cases of safe vaginal delivery have been reported in the literature when timely diagnosis is made with institution of appropriate medical treatment [42]. Vaginal delivery may be considered in multiparous women, who are more likely to experience an uneventful labour and successful vaginal delivery [32]. In relation to the use of anaesthesia for patients with Pheochromocytoma having caesarean sections, epidural, spinal, general, and, or combined anaesthetic techniques have been used with good outcomes [43,44].

Caution should be exercised in the use of oxytocin treatment during labour and for active third stage of labour as it may cause adverse haemodynamic effects, such as tachycardia, and hypotension. A summary of recommended diagnostic tools, drugs and treatment procedure for Pheochromocytoma in pregnancy is shown in table 2.

After surgical resection, careful post-operative monitoring in a higher level of care is necessary as the removal of the tumour may lead to a sudden decrease in catecholamine levels and patients are at increased risk of hypovolemic shock [45]. Post-resection hypotension may depend on the presence of several factors such as, residual α-blockade, residual action of vasodilators, relative hypovolemia, acute catecholamine deficiency, and α-adrenoceptor down regulation [46,47]. Larger tumour size and high preoperative noradrenaline levels in blood and urine increase the risk of post-surgical hypotension [45,48]. In women experiencing post-operative hypotension, the initial management would be to replace the intravascular volume. In cases of refractory hypotension, noradrenaline and/or vasopressin has been used effectively. Another post-operative complication after surgical resection of Pheochromocytoma is hypoglycaemia. Akiba, *et al.* observed that in the case of pheochromocytoma, endogenous insulin secretion is suppressed by the increase levels of plasma catecholamines [49]. Hypoglycaemia arises when excessive rebound secretion of insulin after removal of a pheochromocytoma occurs. Thus careful monitoring of blood glucose levels is recommended after surgical resection of Pheochromocytoma [49].

Women with Pheochromocytoma successfully removed during pregnancy should be followed up in the long-term with biochemical testing and appropriate imaging in order to assess for recurrence or metastatic disease [50]. During follow-up study of over 25 years in non-pregnant Pheochromocytoma patients, Amar, *et al.* noted that the tumour recurrence rate has been estimated to be 14% in adrenal disease and 30% in extra-adrenal disease [51]. It has been recommended that all patients should have annual review for at least ten years after surgery. Due to high risk of recurrence, patients with extra-adrenal or familial pheochromocytoma should be followed up indefinitely [15]. Finally, young pregnant women who suffer from Pheochromocytoma should be offered genetic screening for

hereditary pheochromocytoma since about one-third of all patients has a hereditary predisposition [15].

Conclusion

Although the occurrence of Pheochromocytoma is a rare cause of hypertension in pregnancy, it should be considered in patients who present atypically or have resistant cases of hypertension despite treatment. A multidisciplinary team approach is important for the management of patients so that prompt diagnosis and management decisions can be established and ensure best pregnancy outcomes.

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