

Pheochromocytoma in pregnancy

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ABSTRACT

Pregnancy constitutes a unique clinical condition where several endocrine disorders may be more frequent and/or may have specific considerations

and challenges in terms of timely diagnosis and treatment. Although rare, adrenal disorders in pregnancy are may lead to severe complications, more so if they remain undiagnosed or are poorly managed. In this review pheochromocytoma in pregnancy is discussed.

Key Words: *Pheochromocytoma; Paraganglioma; Pregnancy; Catecholamines; Metanephrines*

INTRODUCTION

Although adaptation and stress response during pregnancy and childbirth involves adrenaline and noradrenaline, catecholamines are usually not significantly increased in a healthy pregnancy. Though mild increase is noted in conditions like preeclampsia and eclampsia, COMT produced by the placenta protects the fetus from the maternal catecholamines [1,2]. Neuroendocrine chromaffin cell tumors can arise from adrenal medulla (80%-85%) and are known as pheochromocytomas or from sympathetic ganglia (15%-20%) and are termed as paragangliomas (PPGLs) [3].

PHEOCHROMOCYTOMA

Pheochromocytoma is a rare syndrome with an incidence between 0.01% and 0.10% amongst the of newly diagnosed cases of hypertension [4]. Inclusion of autopsy diagnosed cases may increase the incidence to 0.1% [5]. This is attributed by possibility of missing the tumor during life due to the aspecific nature of the signs and symptoms associated with excess secretion of catecholamines. Mean age at detection is 43 years with no specific sex predilection [6,7]. It is exceedingly rare in pregnancy and carries an estimated incidence of 0.007% [8] PPGL during pregnancy has an estimated incidence of 1 in 15,000 to 54,000 [9,10].

In 90% of cases, pheochromocytoma is a unilateral catecholamine secreting adrenal lesion though bilaterality is noted in cases with strong family history. Association with genetic syndromes like Multiple Endocrine Neoplasia (MEN) is noted in 10%-20% of cases [6] In MEN type IIA and IIB pheochromocytoma is associated with medullary carcinoma of the thyroid and parathyroid adenoma (Sipple's syndrome). Type 1 neurofibromatosis (NF) and von Hippel-Lindau (VHL) syndrome have also been associated with pheochromocytoma in some cases. PPGLs are associated with pathogenic germline mutations in up to 40% of all patients and with higher incidence during pregnancy [11]. Most common being RET (Rearranged During Transfection), VHL (Von Hippel-Lindau), NF1 (Neurofibromatosis I), SDH (succinate dehydrogenase subunits SDHA, SDHB, SDHC, SDHD), FH (fumarate hydratase), TMEM127 (transmembrane domain protein 127), and MAX (MYC-associated factor X) [12]. Malignancy is noted in 10%-20% of pheochromocytomas but the incidence is higher in paragangliomas [13].

Pheochromocytoma and PPGL both are may lead to serious and even life threatening cardiovascular complications in pregnant woman and fetus, making the diagnosis during antepartum period a crucial step in prognosis [14]. Though earlier studies had mentioned very high mortality rates, with advances in detection and appropriate treatment, recent work shows the maternal and fetal mortality as 5% and 15% respectively [15-20]. Antenatal diagnosis improves prognosis and survival rates of the mother-baby dyad [19].

CLINICAL FEATURES

High suspicion is required for detection of pheochromocytoma or

PPGLs during pregnancy due to their varied presentation. Clue towards diagnosis can be obtained by thorough medical history (including recent medication), family history and physical examination. A previous or family history of PPGL, or associated conditions like MEN-2, VHL, NF, and familial paraganglioma syndromes may point towards further evaluation. Presentation of pheochromocytoma or PPGL during pregnancy can be with persistent hypertension, paroxysmal hypertension, or hypertensive paroxysms superadded on sustained hypertension. Blood pressure can be markedly labile in certain patients [21]. The classical triad of headache, sweating and tachycardia is uncommon in pregnancy [22]. Apart from hypertension, other clinical features include headache, sweating, nervousness, tremor, palpitations, weakness, abdominal pain, and warm flashes (Table 1). Less common symptoms include convulsions, syncope, blurring of vision, orthostatic hypotension, chest pain and weight loss. Evaluation may reveal high metabolic rate, arrhythmias, papilledema, hyperglycaemia, glucose intolerance and high erythrocyte sedimentation rates and even psychiatry disorders [22-24].

Differentiation from preeclampsia is an important aspect in management of pheochromocytoma and PPGLs. A past or family history of neuroendocrine disorder syndromes, gestational at onset (Preeclampsia rarely presents before 20 weeks), proteinuria, ankle edema and raised serum uric acid levels can provide an important diagnostic aid (Table 2). Also, paroxysmal hypertension and orthostatic hypotension are associated with PPGLs and not preeclampsia [1,25-27].

During pregnancy, most patients become progressively symptomatic with advancing gestation [25]. Although, some patients do not exhibit symptoms until they experience a major stress such as labour or caesarean section. Growing uterus, fetal movements, labour, Induction of anaesthesia, abdominal examination an even change in position can trigger the typical hypertensive crises which at times may progress to catastrophic conditions like acute coronary syndrome, arrhythmias, cardiomyopathy, stroke and even shock [26]. As compared to PPGLs, pheochromocytoma is associated

TABLE 1
Symptoms of pheochromocytoma in pregnancy

SYMPTOMS	CASES (%)
Hypertension	90
Headaches	70
Palpitations	40
Sweating	35
Anxiety	30
Blurred vision	20
Convulsions	10
Dyspnea	1

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with greater risk of hypertensive crises [27]. Irrespective of hypertension, in any woman during pregnancy or postpartum period presenting with acute cardiovascular emergency, an underlying PPGL should be ruled out [28]

During pregnancy, raised catecholamines and sustained hypertension can be associated with fetal growth retardation, fetal hypoxia and perinatal mortality [21]. On the other hand, paroxysmal episodes of hypertension may lead to placental abruption and rebound hypotensive episodes can cause severe intrauterine hypoxia and adverse fetal outcomes [26].

DIAGNOSIS

Once suspected, the first step is to undertake biochemical testing for catecholamine excess; the recommended test is a 24-hour urine collection for plasma free metanephrines or urinary fractionated metanephrines or combined [20]. An elevation in Vanillylmandelic Acid (VMA), catecholamines, or metanephrine in plasma and/or a 24-hour urine specimen is suggestive of the diagnosis, although levels may be slightly elevated in preeclampsia [14]. It is critical that all women are given written instructions on how to collect, store and deliver the 24-hour urine sample. Furthermore, the following medications can cause a false positive result and should be stopped: tricyclic antidepressants, reserpine, phenoxybenzamines, clonidine, levodopa, amphetamines, ethanol, most antipsychotics, decongestants, aminophylline and prochlorperazine [29]. False-positive elevations may also occur due to anxiety, strenuous exercise, increased intracranial pressure and hypoglycemia. Increased epinephrine excretion in excess of 50 µg/day is suggestive of an adrenal lesion [30].

For the biochemical diagnosis several tests are available with liquid chromatography and tandem mass spectrometry (LC-MS/MS) as the most accurate method of analysis [30]. Plasma levels of catecholamines should be measured particularly during a paroxysmal episode. It is recommended that the patient rest in the supine position in a quiet environment for 30 minutes before blood is drawn. Blood is obtained through an indwelling catheter. The plasma should be centrifuged, and the serum stored at temperatures lower than 4°C until assayed. Biochemical presence is to be followed by localising imaging. Both Computed Tomography (CT) of the abdomen and functional Metaiodobenzylguanidine (MIBG) scans deliver large doses of radiation; hence MRI is the imaging mode of choice for the adrenal gland in pregnancy [31]. Finally, obtaining a tissue specimen by tumor biopsy is contraindicated because of the risk of eliciting a hypertensive crisis [32].

Genetic testing is mainly indicated for 2 reasons:

- Identification of patients with specific mutations who have an increased risk of multifocal, recurrent or metastatic disease and who may benefit from personalized follow-up.
- Establishment of an earlier diagnosis and treatment of PPGLs and other syndromic manifestations in relatives of the proband who may also be willing to undergo genetic testing.

MANAGEMENT DURING PREGNANCY

Surgical management

Surgical resection is the treatment of choice. A multidisciplinary team including surgeons, maternal medicine specialist, obstetricians, endocrinologists and anaesthetists should deliver the care. However, the timing of resection should be planned carefully. Based on the available literature, the optimum timing of resection is before 24 weeks of gestation [2]. Beyond that, the anatomical changes of pregnancy are less favourable for surgical removal and the operation could be delayed until after delivery. Postpartum resection of the pheochromocytoma is not recommended due to the potential further release of catecholamines induced by uterine fundal massaging [33].

Table 2
Differentiating neuroendocrine tumors from preeclampsia

Symptoms where PGL is more likely than pregnancy-related hypertension	Symptoms possibly present in both	Symptoms where pregnancy-related hypertension more likely than PPGL
Presentation with hypertension <20 weeks	Nausea	Proteinuria
Paroxysmal hypertension or Orthostatic hypotension	Vomiting	Edema
Paroxysmal headache	Upper abdominal pain	Persistent headache
Syndromic features		HELLP

If diagnosed in the last trimester, it is preferred to commence medical treatment to protect the mother for catecholamine excess (see next paragraph) and to defer tumor removal until the fetus is viable, so until or after delivery. As this drug regimen is similar to that used for presurgical preparation of tumor removal, some centres choose for one combined surgical session of cesarean delivery and tumor removal [19]. The alternative strategy is to postpone surgery for several weeks after delivery. This has the potential advantage of allowing for functional imaging. The treatment of first choice in pregnant women is laparoscopic tumor removal, a transperitoneal approach, with the patient in the lateral decubitus position is preferred [19]. Follow-up at 2 to 6 weeks after surgery is required in all patients to ascertain complete tumor removal by measurements of plasma or urine metanephrines [1].

Long-term annual follow-up after surgery for several months is mandatory in all patients for at least 10 years and should include measurements of blood pressure and plasma or urinary metanephrines. Thereafter, annual follow-up should be continued lifelong only in young patients, those with a germline mutation, and those with an extra-adrenal or large tumor, as they have an increased risk for recurrent disease [1].

Medical management

Medical therapy is required at all times, regardless of the timing of surgery. Treatment with α-adrenergic receptor blockers can counteract the effects of catecholamines on the uteroplacental blood flow; nonetheless, it can induce hypotension, which can itself compromise this blood flow. The aim of the treatment is therefore to alleviate the effects of catecholamines and avoid hypotension. The 2 most widely used long-acting α-adrenoceptor blockers are phenoxybenzamine and doxazosine. Phenoxybenzamine is a non-competitive α1- and α2-adrenoceptor blocker whereas doxazosine is a competitive selective α1-adrenoceptor blocker. Phenoxybenzamine is most commonly used and is safe in pregnancy [25]. It can be started at 10 mg/day; the dose can be increased by 10 mg every 2-3 days until blood pressure and other symptoms are controlled. Although the dose may need to be adjusted because it has a half-life of about 24 hours and hence is cumulative, the usual dose of phenoxybenzamine is 40 mg/day-80 mg/day in divided doses. The blocking dose of phenoxybenzamine is 1 mg/kg/day. Phenoxybenzamine use can lead to nasal congestion, orthostatic hypotension and reflex tachycardia, while doxazocin has fewer side effects. It can cross the placenta; phenoxybenzamine has been associated with neonatal hypotension and respiratory depression; hence neonatal monitoring for first 3 days is required. Doxazosin is started at 2 mg per day with increasing the dose to 16 mg or even 32 mg per day [2], but no adverse effects have been so far reported. No adverse effects in lactation have been reported for both the drugs. A second kind of blockade in selected patients with a PPGL is β-adrenoceptor blockade with the aim to treat or to prevent tachyarrhythmias. To circumvent unopposed α-adrenoceptor-mediated vasoconstriction, a β-adrenoceptor blocking drug should only be started after some days of appropriate α-adrenergic blockade. Most commonly used drugs for this purpose are propranolol (40 mg 3 times daily) and atenolol (25 mg-50 mg once daily) [2,25,31]. Beta-blockers can also be added to reduce orthostatic hypotension and reflex tachycardia. Betablockers, including labetalol, can induce a hypertensive crisis if used without alpha-blockers. Hypertensive crises can be treated with intravenous phentolamine. If more agents are needed to control the blood pressure, calcium channel blockers may be added. All women should be advised to increase salt and fluid intake. It is important to note that the long-term effects of these agents are not known; nonetheless, the maternal and fetal benefits outweigh these risks. The catecholamine synthesis inhibitor α-methylparatyrosine (metyrosine) is used at some centres as an adjunct to phenoxybenzamine, but this drug is contraindicated in pregnant women. Despite the need to attain adequate α-adrenoceptor blockade in these patients, it may be prudent to target a blood pressure level of 140/90 mm Hg for presurgical preparation and in pregnancy to prevent uteroplacental poor perfusion.

Mode of delivery

The ultimate decision in elective cases about which mode of delivery to choose depends on several factors, such as parity, previous cesarean delivery, success of pre-treatment, and the personal preference of the patient [34]. In most cases, caesarean delivery remains the preferred way of safe delivery. Epidural, general, or combined anaesthetic techniques have been used successfully for cesarean delivery. Delivery can be associated with acute haemodynamic instability, so requires careful planning and timing. In addition, neonates are at risk of hypotension and respiratory depression. Besides, agents like syntocinon can cause adverse haemodynamic effects, such as hypotension and tachycardia. Nonetheless, vaginal delivery combined with epidural analgesia has been successful [35]. The attending physician should be prepared to manage any hypertensive crises that can occur during labour.

The three agents of choice are intravenous nitroprusside, phentolamine or nicardipine. Sodium nitroprusside is a rapid-acting vasodilator and is the treatment of choice; phentolamine is a non-selective α -blocker, while nicardipine is a calcium channel blocker. Hypertensive crisis can be life threatening and can be associated with hypertensive encephalopathy, or cardiac ischemia [36]. It is important to keep in mind that such PPGL crisis may be invoked by different kinds of frequently used drugs, in particular during peripartum period. These include metoclopramide, steroids, and sympathomimetics [37].

CONCLUSION

The outcome of pregnancy in patients with a PPGL has considerably improved over the last decades. Obviously, more refined surgical and anesthesiologic techniques have contributed pivotally to this progress. In addition, the increase in proportion of patients in whom the diagnosis is made antenatally and thus treated in a timely manner has made a crucial contribution. However, this proportion seems to plateau now on about 70% to 75% of all patients, indicating that the diagnosis is still missed antenatally 1 out of every 3 to 4 patients. Because the antenatal diagnosis followed by proper treatment provides the best chance for successful outcome of pregnancy for mother and child, early awareness and recognition of the potential presence of a PPGL in a pregnant patient with hypertension is key for preventing premature loss of life. Once the diagnosis of a PPGL is confirmed, this specific group of patients should be managed by an experienced and dedicated multidisciplinary team.

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