Pheochromocytoma During Pregnancy: Two Cases and Management Review

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Abstract

Background: Unrecognized pheochromocytoma during pregnancy is associated with a high rate of maternal and fetal mortality.

Objective: To report 2 cases of pheochromocytoma managed during pregnancy and provide recommendations for clinicians based on the literature.

Case 1: A 21-year-old woman diagnosed at 16 Weeks of Gestation (WG) with high Blood Pressure (BP) and bilateral adrenal masses compatible with pheochromocytomas and von Hippel-Lindau syndrome. Bilateral adrenalectomy was performed with temporary normalization of BP. The patient later developed severe Pre-Eclampsia (PE) and delivered at 29 WG.

Case 2: A 24-year-old women was found to be pregnant after diagnosis of pheochromocytoma. Left adrenalectomy was performed at 17 WG. Labor was induced at 39 WG because of Pregnancy-Induced Hypertension (PIH).

Discussion: Uncontrolled high BP during early pregnancy caused by pheochromocytomas was likely responsible for the occurrence of PE/PIH, despite successful adrenalectomy in both patients. Preconception management and early pregnancy BP control is essential.

Introduction

Hypertensive disorders of pregnancy occur in 10% of pregnancies and are the leading causes of maternal and perinatal morbidity and mortality [1]. Pheochromocytoma, a rare cause of hypertension, can be mistaken for pre-eclampsia if presents during pregnancy [2] and is associated with a high mortality rate [3]. Early diagnosis and treatment of pheochromocytoma with timely tumor resection and aggressive Blood Pressure (BP) control can improve outcomes [2,4]. We report 2 cases of pheochromocytoma managed during pregnancy as well as a literature review and management recommendations for pheochromocytoma during pregnancy.

Case description

Case 1: A 21-year-old primiparous woman was diagnosed with high Blood Pressure (HBP) and bilateral adrenal masses at 16 Weeks of Gestation (WG). This adopted patient was not previously known to have HBP or diabetes mellitus. She was admitted to hospital with a BP attaining 190/130 mmHg and anti-hypertensive medication was introduced. She had no signs of pre-eclampsia, however Gestational Diabetes Mellitus (GDM) was diagnosed and insulin therapy was initiated. An Ultrasound (US) revealed 2 large adrenal masses, which were later confirmed on abdominal Magnetic Resonance Imaging (MRI) (left, 9.5 x 5.5 x 5.0 cm and right, 9.5 x 4.5 x 4.0 cm) (Figure 1). A complete work-up for secondary causes of HBP revealed high levels of urinary metanephrines, confirming the diagnosis of pheochromocytoma (Table 1). A low-dose dexamethasone suppression test was performed (despite known limitations of interpretation during pregnancy) and had a low result. Therefore not suggestive of Cushing syndrome [5]. Ophthalmologic examination revealed a retinal hemangioma on the left optic nerve highly suggestive of Von Hippel-Lindau (VHL) syndrome, a diagnosis later confirmed by genetic testing.

Prazosin, an alpha-blocker, was introduced and titrated up to 4 mg five times per day, targeting a systolic BP of 100-110 mmHg and a pulse of 70 bpm. Aggressive intravenous fluid hydration was started. Amlodipine 5 mg daily was added 14 days after optimal alpha-blockade. BP remained uncontrolled, with peak at 200/115 mmHg, therefore the patient was transferred to the Intensive Care Unit (ICU) and intravenous Labeletalol was added. Bilateral adrenalectomy was performed by laparotomy within 48 hours of ICU admission (at 18 WG) without complication. Intravenous hydrocortisone was given for the procedure (100 mg loading dose followed by 50 mg every 6 hours). Pathologic analysis confirmed 2 large pheochromocytomas with low mitotic index and without atypical mitosis. GDM resolved post-operatively. The patient was discharged at 19 WG with replacement doses of hydrocortisone (15 mg in the morning, 10 mg at noon and 5 mg in the evening), and fludrocortisone at 0.05 mg per day. Despite the bilateral adrenalectomy, at 27 WG, her BP rose and she developed proteinuria, with a protein-to-creatinine ratio (PCR) of 0.061 g/mmol (normal ≤ 0.04 g/mmol) without deterioration of kidney function. Fludrocortisone was stopped and hydrocortisone was slightly reduced to a total of 25 mg per day without signs or symptoms of adrenal insufficiency. Urinary collections for fractionated catecholamines and metanephrines at 19, 27 and 28 WG remained normal.

Delivery and perinatal care

The patient was re-hospitalized at 28 WG because of severe PE and fetal Intrauterine Growth Restriction (IUGR). An urgent cesarean section was performed under intravenous hydrocortisone coverage due to breech presentation and suspicion of fetal distress. A 1.08 kg baby girl was delivered at 29 6/7 WG with an Apgar score of 6, 8 and 9. The placenta showed congested vessels with advanced villous maturation and focal chorangiomaticous transformation. The newborn died at 25 days of life from necrotizing enterocolitis.

Long-term follow-up

BP normalized over the first year postpartum and all anti-hypertensives were stopped. Urinary collection and MRI (Table 1) showed no pheochromocytoma recurrence. Detailed work-up did not show any other stigmata of VHL syndrome. Genetic testing demonstrated an intragenic mutation in the VHL gene (c.499C>T). Genetic counseling was offered to her only known living relative.

Long-term follow-up

Case 2: A 24-year-old obese (BMI 40 kg/m²) and hypertensive women, was referred for management of a left pheochromocytoma (Table 1). The diagnosis was made after discovering a left adrenal incidentaloma identified on a scan performed for unexplained anemia. She was known to have had HBP for the past 4 years. However, HBP was mild at 130-140/80 mm Hg and pulse at 100 bpm at first evaluation without medication. MRI showed a left adrenal mass of 3.7 cm. Prazosin was introduced and increased progressively to 1 mg 3 times per day. An unplanned pregnancy as well as GDM were diagnosed at 7 WG when she presented to the emergency room with nausea and vomiting less than 3 months after initial investigations. The patient underwent a successful left adrenalectomy by laparoscopy at 17 WG after medical optimization of BP with prazosin and bisoprolol. Post-operatively, BP and pulse normalized. Pathology reports confirmed presence of a pheochromocytoma with rare presence of mitosis and no necrosis.

Delivery and perinatal care

The rest of the pregnancy in this primiparous women was uneventful with resolution of HBP and GDM. At 21 WG, BP gradually rose but stayed under 140/90 without medication and negative PE work-up until delivery. Labor was induced at 39 WG because of high BP (170/84) without PE. A healthy baby boy of 2.8 kg was delivered vaginally with Apgar score of 9-9-9.

Long-term follow-up

BP normalized postpartum. BP and urinary catecholamine and metanephrine levels remained normal over five years of follow-up (Table 1). MRI showed no recurrence of adrenal mass at the surgical site. Search for known germline genetic mutations (VHL, SDHB, SDHD and RET genes) did not show any mutations. No further pregnancy is desired.
Table 1: Biochemical testing in our subjects.

<table>
<thead>
<tr>
<th>Endocrine tests</th>
<th>Case 1 Before surgery (16WG)</th>
<th>1 week after surgery</th>
<th>2.5 years after surgery</th>
<th>Case 2 Before surgery and pregnancy</th>
<th>10 months after surgery</th>
<th>5 years after surgery</th>
</tr>
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<tbody>
<tr>
<td>24 hour urinary fractionated catecholamines and metanephrines (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Norepinephrine normal &lt; 440</td>
<td>13 916</td>
<td>319</td>
<td>69</td>
<td>2707</td>
<td>118</td>
<td>197</td>
</tr>
<tr>
<td>Epinephrine normal &lt; 110</td>
<td>32</td>
<td>83</td>
<td>&lt; 10</td>
<td>61</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>Normetanephrine normal &lt; 240</td>
<td>18 620</td>
<td>251</td>
<td>88</td>
<td>1883</td>
<td>78</td>
<td>143</td>
</tr>
<tr>
<td>Metanephrine normal &lt; 275</td>
<td>229</td>
<td>109</td>
<td>&lt; 30</td>
<td>238</td>
<td>&lt; 30</td>
<td>121</td>
</tr>
<tr>
<td>Dopamine normal &lt; 2579</td>
<td>1671</td>
<td>1581</td>
<td>1025</td>
<td>1771</td>
<td>1897</td>
<td>1856</td>
</tr>
<tr>
<td>24 hour urinary cortisol (nmol) normal &lt; 330</td>
<td>137</td>
<td>NA</td>
<td>NA</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Morning cortisol after dexamethasone 1 mg suppression test (nmol/L)</td>
<td>92*</td>
<td>NA</td>
<td>NA</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Discussion

Pheochromocytoma is an adrenal tumor originating from chromaffin cells, and accounts for 0.2% of hypertension cases. It has an estimated incidence of 1 in 50,000 pregnancies [6]. Approximately 25 to 35% of all pheochromocytomas and paragangliomas are associated with a hereditary syndrome such as VHL syndrome [7,8].

Presentation of pheochromocytoma during pregnancy often mimics PE [2,4]. Though rare, pheochromocytoma should be considered when severe HBP occurs before 20 WG or without proteinuria [2,4]. In our 2 cases, development of early GDM was another clue toward a diagnosis of pheochromocytoma, since elevated catecholamine levels are associated with hyperglycemia. A literature review was conducted and identified 56 other cases of early diagnosis of pheochromocytoma or paraganglioma in pregnancy (Figure 2), which are summarized below.

222 articles published between January 1st 2004 and February 28st 2018 were reviewed.

111 articles excluded
- Not written in French or English
- Review articles without new cases reported
- Not occurring and manage during pregnancy

111 articles were included for further analysis.

69 articles excluded
- Pheochromocytoma diagnosed ≥24 WG
- Insufficient information regarding management
- Review articles without new cases reported

242 articles (representing 56 cases) with pheochromocytoma diagnosed < 24 WG included.

9 cases of pregnancy termination excluded.

47 cases included for review

Figure 2: Algorithm for review- inclusion of cases.

Pubmed search terms included: « phaeochromocytoma » or « pheochromocytoma » or « paraganglioma » and « maternity » or « pregnancy » or « gestation » or « gravidity » or « pregnant women » or « gestational age » yielded 222 articles.
Management summary

Literature review and management

A systematic review in PubMed of articles published between the periods of January 1st 2004 and February 28th 2018 using search terms «pheochromocytoma» or «pheochromocyte» or «paraganglioma» and «pregnancy» or «maternity» or «gestation» or «gravida» or «pregnant women» or «gestational age» yielded 222 articles. Only articles written in English or French, presenting new cases of pheochromocytoma/paraganglioma managed during pregnancy were included for review. A total of 111 articles were identified with new cases of pheochromocytoma/paraganglioma occurring during pregnancy. Furthermore, eligible publications presenting women with pheochromocytoma/paraganglioma diagnosed prior to 24 WG and reported management and outcomes were analysed. A total of 69 articles were excluded because pheochromocytoma or paraganglioma was diagnosed at ≥ 24 WG, there was insufficient information concerning management or outcomes or they were review articles without presentation of new cases. Hence, 42 articles representing 56 cases were included.

Surgical management and outcomes

Among these cases, 9 (16%) underwent pregnancy termination with or without surgical resection of pheochromocytoma or paraganglioma and were not included in subsequent analysis [9-15]. Of the remaining, 32/47 cases (68%) underwent pheochromocytoma resection during the second trimester of pregnancy or up to 32 WG [4,12,13,16-40]. The majority of these women (25/32, 78%) had successful outcomes after surgery with early resolution of HBP, subsequent normal pregnancy with near-term delivery of healthy infants. There were two cases of preterm birth with elective cesarean being performed at 36 WG [4,27] and two cases of preterm birth with cesarean performed during bilateral adrenalectomy at 32 WG [17,35]. There were 3 cases of post-operative persistent HBP with subsequent adverse fetal outcome (jaundice) [32] including 2 cases of fetal death (1 IUFD [34], 1 neonatal death [21] (2/28, or 7%).

Medical management and outcomes

Fifteen patients (32%) were managed conservatively during pregnancy with alpha-blockade and other anti-hypertensive drugs, mainly beta-blockers and calcium blockers [4,17,40-49]. Maternal and fetal outcomes were less favorable with medical management compared to the surgical approach. With medical management alone there were 7 cases (50%) of preterm delivery [27,28,32,34,35,36 and 36 WG] [17,34,42,44,45,47,49] and 3 cases of unfavorable maternal outcomes (hypertensive crisis [44], hypertensive encephalopathy with disseminated intravascular coagulation and acute renal failure [4] and adrenal hemorrhage [46]) with 2 cases resulting in fetal death (2/12, or 16.7%) [4,44,46].

Management summary

Overall, including our 2 cases, 69% were managed surgically. No case of maternal mortality was reported and, 5/46 (11%) fetal deaths were noted. Among women treated with surgical resection of pheochromocytoma, there were two reports of PE complicating the course of pregnancy (case 1 above, [18]).

The most reliable diagnostic test for pheochromocytoma is plasma free or 24-hour urinary fractionated metanephrines measurement [50,51]. Results should not be altered during pregnancy and are only slightly elevated in patients with PE, making this a dependable method for diagnosis of pheochromocytoma in pregnancy [52]. However, it should be noted that no studies specifically examined the diagnostic accuracy of these tests in pregnant women. CT scan, the preferred imaging modality for adrenal masses, is not recommended in pregnancy and functional imaging with MIBG scintigraphy is contraindicated. MRI and US are the recommended imaging procedures during pregnancy, with MRI favored, due to higher sensitivity [3,4,50].

Aggressive treatment for rapid control of HBP is recommended to prevent maternal and fetal complications [1]. Alpha-blockers such as Phenoxybenzamine, Prazosin, Doxazosin and Terazosin are the preferred initial drugs for management of pheochromocytoma in pregnancy. Although class C medications [3,4,50], the benefits outweigh the potential fetal harm. Addition of beta-blockers and Calcium Channel Blockers (CCB) may be necessary after maximal alpha-blockade [52]. Magnesium sulfate may be added to inhibit catecholamine release and cause vasodilation [2,4,53].

It was demonstrated in our review of the literature that antenatal diagnosis and proper management of pheochromocytoma, particularly surgical resection in the second trimester of pregnancy, greatly reduced maternal and fetal mortality. Mannelli and Bemporad reported a maternal mortality reduction from 19% to 1%, and a fetal mortality reduction from 25% to 12% when the diagnosis was done antepartum compared to postpartum [6].

The vasoconstrictive effect of high catecholamine levels as well as uncontrolled HBP early in pregnancy may cause pathological changes to the uteroplacental circulation and abnormal placental development, leading to subsequent PE and IUGR despite removal of pheochromocytoma [1]. The risk for PE in subsequent pregnancies in case 1 was difficult to establish. Her pre-pregnancy BMI, early GDM and a new partner were risk factors for development of PE in her second pregnancy [1]. The occurrence of PE in a first pregnancy significantly increases risk of recurrence in a second pregnancy up to sevenfold, however this cannot be applied to our patient since uncontrolled HTN due to occurrence of pheochromocytoma probably explained the development of pre-eclampsia during the first pregnancy [54]. There are reports of repeated PE during subsequent pregnancies after pheochromocytoma removal without evidence of pheochromocytoma recurrence, although it is not known if these patients remained chronically hypertensive after surgical resection of pheochromocytoma [2]. Prevention of PE with low-dose aspirin and prophylactic LMWH was discussed with the patient to reduce the risk of placental complication in her pregnancy. Finally, her second pregnancy progressed favorably and has ended without occurrence of PE.

Suggested follow-up for pheochromocytoma diagnosed during pregnancy (Table 2).
During preconception care, patients with a pheochromocytoma-associated syndrome, should be screened for pheochromocytoma which should be resected if found. If pheochromocytoma is resected during pregnancy, plasma or urinary fractionated metanephrines should be monitored 1-2 weeks post-operatively to ensure complete resection [50]. Follow-up during pregnancy should be done at minimum once per trimester and include serial metanephrines testing, evaluation of glucocorticoid and mineralocorticoid dose (for patients who have previously undergone bilateral adrenalectomy) with assessment of volume status, blood pressure and serum electrolytes [55]. During labor, adequate hydration and stress doses of intravenous hydrocortisone could be required (25-50mg every 6 to 8 hours).

Some clinical clues for an underlying genetic syndrome include: Multifocal disease, young age at presentation (<30), family history of pheochromocytoma or syndrome-specific manifestations. However, it is currently recommended to discuss genetic testing with all patients diagnosed with pheochromocytoma or paraganglioma [50]. Furthermore, patients with pheochromocytoma in the course of syndromes can present with other manifestations: Neurofibroma, café au lait patches and axillae and inguinal freckling (Neurofibromatosis type 1 syndrome), medullary thyroid cancer, hyperparathyroidism and/or marfanoid body habitus (Multiple Endocrine Neoplasia type 2), multiple paragangliomas (familial paraganglioma-pheochromocytoma syndrome). Among the 56 cases reviewed, only 31 mentioned a search for germline mutations and genetic syndromes were diagnosed in 15 cases (48%). However, among the remaining cases without genetic testing there were total of 17 cases that were suspicious of genetic causes: bilateral pheochromocytomas, large ≥6 cm unilateral adrenal masses, paraganglioma, concomitant pheochromocytoma and paraganglioma, unilateral pheochromocytoma with ganglioneuroma [9,18,20,24,26,28,32,37-40,45,46]. Since genetic syndromes are frequently found among women diagnosed with pheochromocytoma during pregnancy (48% in our review) it should be mandatory to search for germline mutations in this population [17]. This is particularly important for appropriate screening during follow-up of the patient and their family, as well as for prenatal counseling for subsequent pregnancies. Finally, excluding presence or recurrence of pheochromocytoma is an impor-
taint component of pregnancy planning in patients with familiar syndromes.

Annual follow-up for patients with diagnosed VHL includes a complete physical examination by a specialist physician, plasma or urinary metanephrines measurement, retinal examination by an ophthalmologist and abdominal MRI. Biennial cerebral and spinal MRI, and aural testing by an audiologist should also be performed [56]. Prenatal screening by amniocentesis or chorionic villus sampling should be discussed for pregnant patients with VHL, and, for patients planning pregnancy, pre-implantation genetic diagnosis may also be an option. Follow-up during pregnancy should include serial ophthalmologic exams and testing for plasma or urinary metanephrines in each trimester and a cerebral and spinal MRI at 4 months gestation. The patient should also be counseled on symptoms and signs of growing cerebral and spinal hemangioblastoma and pheochromocytoma. If the woman has retinal, cerebral or spinal hemangioblastoma, vaginal delivery may be contraindicated [56]. In addition, for patients who have previously undergone bilateral adrenalectomy, glucocorticosteroid replacement is aimed at reproducing physiological requirements during pregnancy, with often similar doses to non-pregnant state in first and second trimesters and a slight dose increase required during the third trimester. Adequate hydration with serial administration of stress doses of intravenous hydrocortisone are required during labor (25 mg every 6 to 8 hours) with increasing doses of hydrocortisone if labor is prolonged (50 mg every 6 to 8 hours). Mineralocorticoid replacement are often stable during pregnancy, though the dosage can be slightly reduced during the third trimester. Some women with primary adrenal insufficiency even follow normal evolution during pregnancy without mineralocorticoid replacement. Serial assessment of volume status, blood pressure and electrolytes balance are necessary (minimum once per trimester) to assure proper mineralocorticoid replacement. In case 1, increasing blood pressure prompted the discontinuation of fludrocortisone without sequelae.

**Conclusion**

We examined 2 cases of pheochromocytoma managed during pregnancy with different outcomes. These cases demonstrate that rapid management of pheochromocytoma in pregnancy with aggressive BP control is essential to minimize maternal and fetal morbidity. GDM screening at pheochromocytoma diagnosis is important as there is an elevated risk of hyperglycemia. Surgery appears to be safe when done in the second trimester, with improved maternal and fetal outcomes, compared, in the literature, to medical management alone. Postoperative BP needs to be followed closely until the end of pregnancy, as there is an elevated risk of PE or late gestational hypertension even after pheochromocytoma removal. Preconception and prenatal care, as well as genetic counseling, are of primary importance for women in reproductive age with a past history of, or newly diagnosed pheochromocytoma.

**Declaration of Interest**

For all authors, there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Authors contribution**

All authors critically revised the manuscript and approved the final version to be published. Moreover, R.B. and THLN wrote the manuscript, researched data, reviewed the literature and contributed to discussion. F.W. and MJB reviewed/edited the manuscript. M.M. and I.B. researched data, contributed to discussion and reviewed/edited the manuscript. A.G. wrote the manuscript, reviewed the literature, contributed to discussion and reviewed/edited the manuscript.

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**References**


