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Case Report
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Pheochromocytoma in Pregnancy: A Multidisciplinary Challenge and a Proposed Management Algorithm

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Abstract

Background: Pheochromocytoma [PHEO] in pregnancy is extremely rare. A late diagnosis, unplanned pregnancy course and delivery are related to a 40% to 50% maternal and fetal mortality risk. Conversely, early detection and treatment significantly reduces both to 5% to 15%. Based on a literature review and our implications for the present case report, we suggest a multidisciplinary diagnosis and management algorithm PHEO in pregnancy.

Case Report: A 35-year-old primigravida at 27+1 weeks of Gestation [GA] presented with headache and previously diagnosed chronic Hypertension [HTN] aggravation. Complete evaluation ruled out pregnancy related HTN. A high suspicion level for an alternative cause for HTN was raised. Appropriate imaging studies revealed a heterogenous mass adjacent to the left adrenal 8 cm × 7 cm in diameter, highly suspicious for adrenal tumor. Elevated urine catecholamines confirmed the diagnosis of PHEO. A multidisciplinary team was formed and a joint decision for disease control and delayed surgery until after delivery was taken. Blood pressure control was achieved by a combined alpha and beta-adrenergic blocker approach at levels of 135-140/80-90.

Antenatal steroids for fetal lung maturation were administered with concurrent 24 h BP Holter. Her condition remained stable and at 32+0 GA a planned cesarean section delivery using a minimal intraperitoneal handling technique under neuraxial anesthesia. A male newborn of 1,960 g was delivered, 1'/5' Apgar score 6/9. The medical therapy was continued with lower BP goals and a planned laparoscopic adrenalectomy performed after 2 weeks of postpartum recovery. The mother and child were discharged in good condition.

Conclusion: The maternal and fetal lethal consequences of PHEO during pregnancy may be prevented by a high index of suspicion for the diagnosis and following a multidisciplinary algorithm of management, adapted to the individual patient, mainly based on achievement of BP control and the gestational age.

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Case Presentation

35-year-old primigravida at 27+1 weeks of Gestation [GA], work immigrant from the Philippines, was referred to our center with a diagnosis of severe aggravation of chronic Hypertension [HTN].

Her medical history was positive for a HTN disease diagnosed four years prior to referral and diagnosed as essential; treated with TRITACE (5 mg/25 mg ramipril and hydrochlorothiazide 5 mg) tid. Her family history was positive for chronic HTN (mother and maternal grandmother). Additionally, she was diagnosed with Diabetes Mellitus type 2 [DM2] and treated with Metformin 850 mg/daily with no regular control of glucose levels.

Her pregnancy was spontaneously conceived while a HbA1C % level of 6.5%. Genetic screening consisted of nuchal translucency, biochemical 1st and 2nd trimester screening as well as fetal anatomy Ultrasound [US] evaluation; all reported within normal limits. During the 1st trimester she reported intractable headache and Blood Pressure [BP] values registered as high as 240/125. At the time the patient denied flushing, palpitations, and sweating. Labetalol 200 MG tid was then added.

She was referred to the emergency department at 27+1 GA because of headache. The initial examination the BP measured 198/119, with no skin or vasomotor changes. The laboratory workup was within normal limits; hemoglobin percentage 13.6 g %, platelet count 413K, normal liver function and Protein Creatinine Ration [PCR] of 0.14. The uterine fundal height corresponded to the GA and the fetal biophysical profile was 10/10. A diagnosis of aggravated chronic HTN

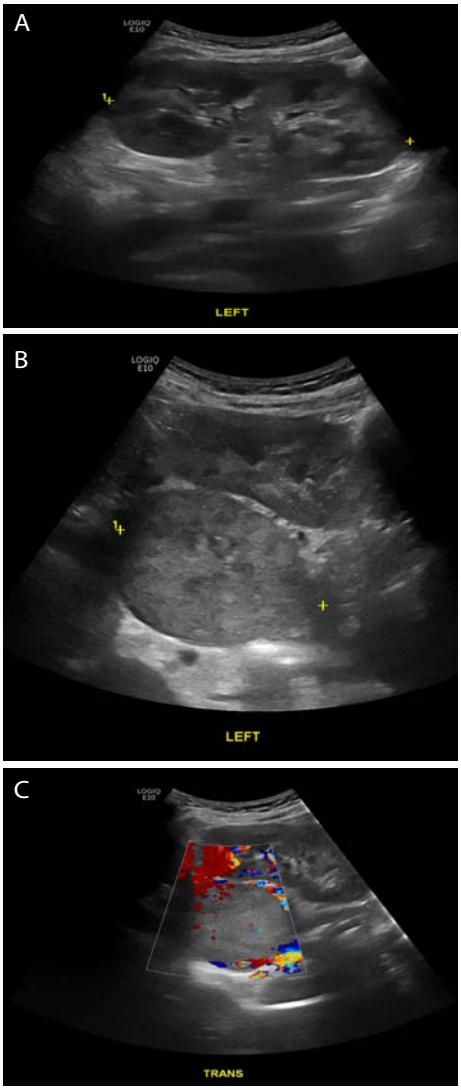

Figure 1: Abdominal ultrasound showing left adrenal tumor with a diameter of >8 cm **(A)**; mixed cystic-solid components **(B)** and Doppler vascular imaging confirms the presence of vascular flow **(C)**.

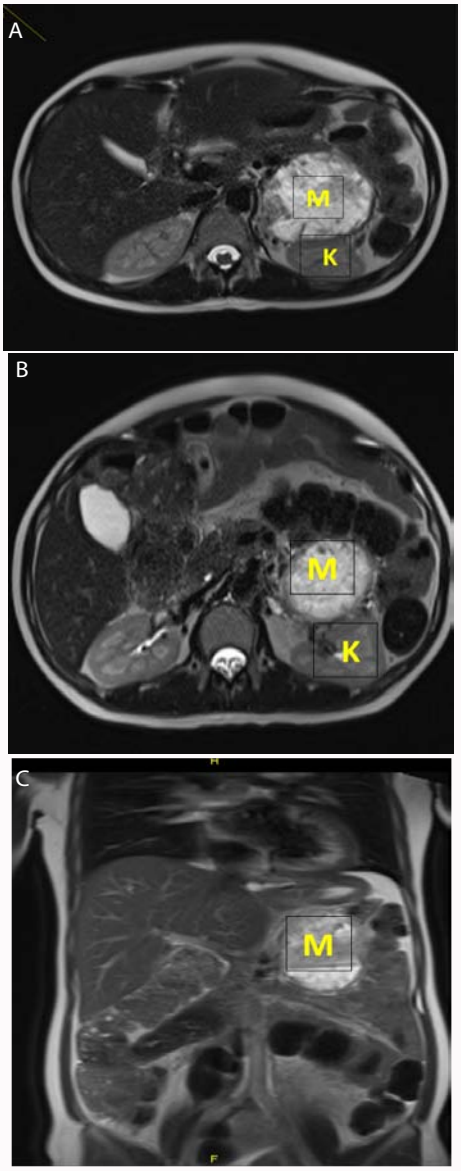

Figure 2: Magnetic Resonance Image [MRI] of the abdomen (axial and coronal planes) showing around heterogenous mass T2 hyperintensity measured 8.7 cm × 7 cm (M), the posterior part of it located near the left Kidney (K).

prompted treatment with intravenous hydralazine and magnesium sulfate and admission to the maternal fetal medicine ward.

Due to the sustained high BP the differential diagnosis was extended from superimposed Preeclampsia [PET] spectrum to other chronic HTN causes (endocrinopathies, renal artery stenosis etc.). Further examination included ophthalmologic examination, echocardiography, renal artery Doppler studies; all within normal range. Abdominal Sonography revealed a heterogenous mass adjacent to her left adrenal measured 8 cm × 7 cm (Figure 1). A subsequent Magnetic Resonance Imaging [MRI] showed a T2 hyperintensity space occupying lesion, without hyper vascularization and neither lymphadenopathy (Figure 2). A differential diagnosis of Pheochromocytoma [PHEO] versus Adreno-Cortico-Carcinoma [ACC] was raised. A 24 h urine with a metanephrine level of 94.9 mcg/24 h [range 39 to 256] nor-metanephrine 14777.7 mcg/24 h [range 92-604] confirmed a diagnosis of PHEO.

A multidisciplinary team of maternal-fetal medicine, neonatology, endocrinology, anesthesiologists, and general surgery was formed. The midpoint of the discussion was the balance upon the immediate surgical tumor removal in the presence of pregnancy induced cardiovascular changes and a 28 weeks uterus and subsequent delivery or deferral of the adrenal surgery until fetal maturity. After consideration of the data and previous surgical experience and a joint consult with the mother a decision was made for continuous hospitalization aimed towards the utmost conservative approach regarding the pregnancy. The aim was set for a Cesarean Delivery [CD] at 32 weeks to be followed by the adrenal surgery. A combined antihypertensive therapy was started consisting of Labetalol 400 mg tid, Amlodipine 10 mg tid and Doxazosin 7 mg bid; with a therapeutic goal of BP of 130/80; a dose of corticosteroids for fetal lung maturation under Holter monitoring of BP. Within a week of the medical therapy the BP goal was achieved. In parallel insulin therapy was started and glucose control reached. The fetal growth was appropriate and daily

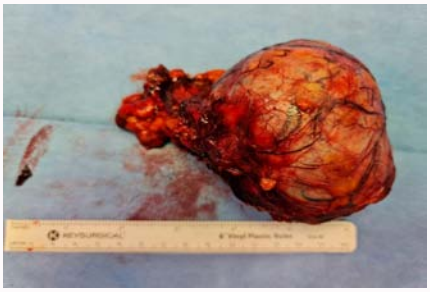

Figure 3: Left adrenalectomy surgical specimen.

fetal wellbeing assessment (US BPP and NST) were reassuring.

At 32+0 weeks of gestation the mother was prepared for a minimal intraperitoneal handling technique of cesarean delivery with neuraxial anesthesia.

Upon entering the surgical suite, the patient was connected to a non-invasive BP monitor, administrated Midazolam (1 mg) and Esmolol (10 mg); to meet the anxiety and related hypertension during the preparations. A radial arterial line was then placed (local anesthesia) towards a Combined Spinal Epidural anesthesia (CSE), the patient received a spinal shot of hyperbaric Bupivacaine (5 mg), Fentanyl (20 mcg) and Morphine (0.15 mg), followed by Lidocaine 2% (4 ml) injected into the epidural catheter, sensory T6 level block was diagnosed by pinprick.

A male newborn of 1,960 g was delivered, 1'/5' Apgar score 6/9, with the umbilical cord 3 times around neck and a true knot. The placenta was sent for pathological assessment and later reported to be normal and adequate to the GA. Intravenous oxytocin was during surgery continued with administered, a low dose of Oxytocin drip (1 unit/h) 24 h postoperative. The postoperative course was normal. The medical therapy was continued after the CD surgery for an additional two weeks in hospital. Thereafter, a planned for laparoscopic adrenalectomy under general anesthesia was preformed following a rigorous pharmaceutical preparation; a large highly vascular adrenal mass measured 8 cm in diameter was removed, no signs of macroscopic metastatic disease (Figure 3). The antihypertensive medication was limited to Labetalol 200 mg twice bid. The pathologic assessment of the adrenal mass confirmed the diagnosis of PHEO with intact capsule and no evidence of mitotic activity (Ki-67 proliferation index: 1%) or invasion.

Discussion

Pheochromocytoma [PHEO] a benign type catecholamine-secreting tumor, originating from chromaffin cells of medullary region of the adrenal gland or sympathetic ganglia, is an extremely rare cause of HTN disease; 0.2% to 0.4%, of all causes of hypertension. During pregnancy a scarce prevalence of 1 in 54,000 pregnancies has been reported [1,2].

The diagnosis of PHEO is based on a high level of suspicion facing related severe HTN crisis. The immediate medical interventions as aimed to limit the hazards related to extreme HTN while the definite therapy is surgical resection with the laparoscopic approach being

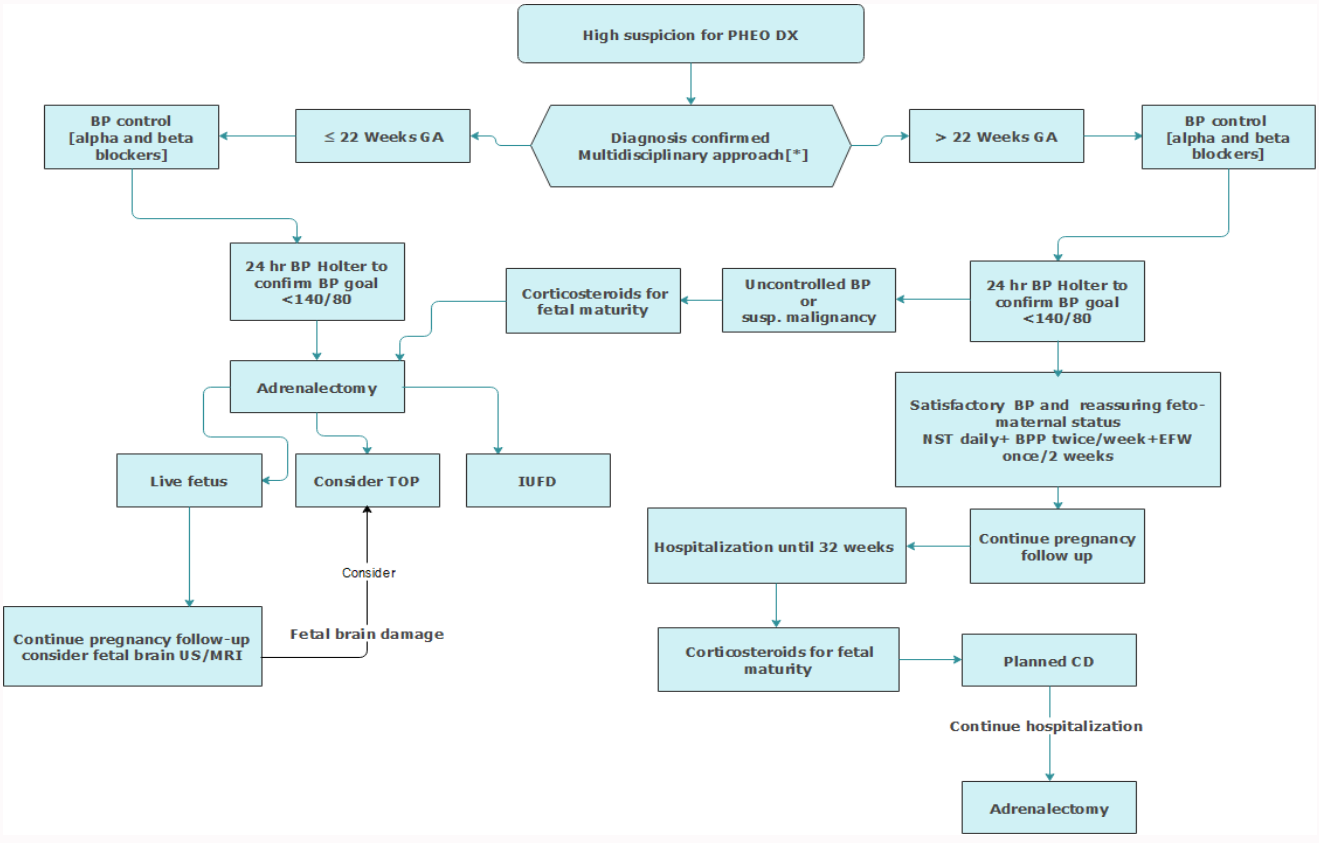

Figure 4: Multidisciplinary approach algorithm for management of PHEO during pregnancy [*]: Maternal-fetal medicine, neonatology, radiology, endocrinology, anesthesiologists, and general surgery.
GA: Gestational Age; BP: Blood Pressure; CD: Cesarean Delivery; TOP: Termination of Pregnancy; IUFD: Intrauterine Fetal Demise; NST: Non-Stress Test; BPP: Biophysical Profile; EFW: Estimated Fetal Weight

preferred [3]. The effect of a concomitant pregnancy presents an additional consideration of the PHEO related hazards in view of the maternal-fetal safety concerns. Previous reports show that the two thirds of PHEO cases during pregnancy were diagnosed antepartum and the rest postpartum [4].

The present case of PHEO during pregnancy is representative of all these challenges. We will focus on the PHEO-pregnancy related considerations and present a management algorithm (Figure 4) aimed to early antepartum diagnosis and therapy; both reported to decrease maternal mortality rates from 50% to less than 5% to 15% [5-8].

In PHEO, as in other surgical intervention during pregnancy, the second trimester of pregnancy is considered the optimal timing; due to the fetal organogenesis stage and in cases of intra-abdominal approaches, the gravid uterus does not impair the surgical view [9-14]. Earlier reports of the PHEO included cases diagnosed after adverse outcome of a delivery or uncontrolled BP, thus with a significant bias towards a recommendation of immediate medical therapy and PHEO removal, irrespective of gestational age or fetal maturity. We hereby raise the concerns of catecholamine excessive secretion when manipulating the tumor, prolonged exposure to general anesthesia agents, prolonged right decubitus position with subsequent profound maternal hypotension and fetal deterioration. We suggest that reviewing the later cases, adrenal surgery may be deferred until after delivery in the late prematurity period.

The present suggested multidisciplinary conservative approach is aimed towards all these concerns. Mainly, it consists of an initial alpha-blocker together with an optional beta-blocker therapy to obtain BP control at any GA [15]. Predelivery medical therapy is based α-blockers at least until up to 14 days before surgery, followed by β-blockers to prevent reflex tachycardia [16]. Among α adrenergic receptor blockers doxazosin rather phenoxybenzamine; although both category C drugs during pregnancy, the later was reported to be associated with neonatal cardiorespiratory complication [17,18]. We suggest that the BP therapeutic goals in pregnancy should be higher than in the non-pregnant state, especially if longer period until delivery is expected; hypoperfusion of the uteroplacental unit, intrauterine growth restriction and placental abruption may occur with excessive low BP [15].

Although the non-pregnant BP goal is considered less than 130/80 mmHg while seated and greater than 90 mmHg systolic while standing [19,20], we suggest, a BP goal of 140/90; all the more in cases of PHEO diagnosis in the late 2nd and 3rd trimester of pregnancy.

Gestational age, fetal status, patient's response to medical treatment, malignant characteristics of the tumor and the respectability of the tumor are the main factor to take into consideration in order to plan the surgical excision [21].

Before 24 weeks of pregnancy, the recommendation is that the delivery should be postponed after the surgical therapy, for full maternal benefit; and the mode determined by obstetric considerations. The 24 weeks limit has been derived from the fetal viability limits; however, we may suggest that since these limits are re-defined, 22 weeks of gestation seems a more reasonable bound. After fetal viability, additional considerations such as HTN crisis, placental abruption prior to or during adrenal surgery together with the difficult surgical field approach are to be taken in consideration [9,17,22]. Nevertheless, antihypertensive therapy and hemodynamic instability during adrenal surgery may be seriously detrimental to the fetus leading to severe brain hypoperfusion. We consider that the consult in the fetal pre-viability period should include the option of termination of pregnancy. In case surgical intervention is performed and the pregnancy is continued, careful targeted fetal brain imaging into the second part of the pregnancy is warranted.

In cases the PHEO is diagnosed after fetal viability, that the mainstay of the management should be aimed the achievement and maintenance of maternal BP response to medical therapy, under hospitalization in a center with multidisciplinary facilities. This first goal successful achievement is the indicator that allows postponing delivery and refraining from extreme prematurity, i.e., at least until 32 weeks gestation [11]. Although fetal movements have been postulated an ability to induce adrenal hypertensive crisis; we found no robust proof in the literature; including the present case. Antenatal steroids for fetal lung maturation are to be administered with concurrent 24 h BP Holter.

The delivery, either emergency or planned should be attended by a multidisciplinary team. Previous case reports suggested a higher maternal mortality rate after Vaginal Delivery [VD] in contrast with elective Cesarean Section [CS] [3]; CS is reported to lower the maternal and fetal mortality rate from 33% to 19% [23]. This might be the base that approximately 80% of the cases were delivered by CS; either planned or emergent [20,21].

The excess of maternal fetal hazards in the case of a vaginal delivery, has been explained by the maternal BP stress induced rapid changes, elevation of the intra-abdominal pressure during labor and the labor and the related pain which can result in excessive catecholamine's secretion. We consider that independent of the BP control, in view of a planned premature delivery with an expected low cervical Bishop score, a planned CS is the preferred mode of delivery. Importantly, the pain management is critical in either delivery situation [24-26].

The anesthetic management goal for the CS is preoperative anxiety limitation and BP stability and monitoring; in addition to ASA standard monitoring, a radial arterial line is warranted.

Neuraxial anesthesia should be considered for PHEO Caesarean sections [26]. This type of anesthesia may prevent the swift rise in BP often observed during intubation and reduce pain-related hypertension *via* use of intrathecal morphine. However, neuraxial anesthesia (namely spinal anesthesia) often results in sympathectomy, causing an associated decline in BP. In the present case a Combined Spinal Epidural anesthesia (CSE) approach was elected, as it allows the use of reduced doses of intrathecal Bupivacaine and reduced subsequent hemodynamic effects, with additional epidural doses, if needed.

Conclusion

In cases of concomitant PHEO and pregnancy, timed diagnosis, a multidisciplinary approach (Figure 4) with planned delivery will benefit the mother and the fetus with a favorable outcome.

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