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# Identification and management of rare causes of chronic hypertension in pregnancy in a tertiary referral centre of North India

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## 1. Introduction

Hypertension in pregnancy is a major cause of maternal and perinatal morbidity and mortality. Chronic hypertension of various etiology may be brought to notice during pregnancy as it's the time when a woman may come in contact with a doctor first time in her life. Unusual causes of hypertension in pregnancy are often unrecognised and misdiagnosed as preeclampsia thus leading to improper treatment. The likelihood of adverse maternal and perinatal complications depends on the etiology and degree of hypertension and thus accurate diagnosis is important. Here, we report the causes of chronic hypertension detected first time during pregnancy and analysed the maternal and perinatal outcome in them. This highlights the need of looking into the causes of chronic hypertension in pregnancy and individualised management of pregnant women.

## 2. Methods

This is a retrospective analysis of pregnant women attending antenatal clinic of our hospital from July 2016 to June 2018 which is a tertiary care referral centre of northern India. Women were diagnosed to have chronic hypertension if blood pressure recorded to be higher than 140 mmHg systolic and 90 mmHg diastolic on two occasions four hours apart before 20 weeks of gestation. Apart from detailed history and examination as per a structured proforma, investigations were done to diagnose maternal disease which included renal function tests, urine examination, ultrasound and Doppler examination of abdomen including kidney. Investigation like Echocardiography and doppler of great vessels, serum and urinary metanephrines and Magnetic Resonance Imaging (MRI) were done only when clinically indicated. The eGFR in patients diagnosed with CKD was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation and the patients were classified according to their eGFR values (in mL/min/1.73 $m^2$) into five CKD stages as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines: normal or CKD stage 1 – eGFR $\geq$90; CKD stage 2 – eGFR 60–89; CKD stage 3 – eGFR 30–59; CKD stage 4 – eGFR 15–29; and CKD stage 5 – eGFR < 15 [1]. Appropriate genetic counselling was done when the maternal condition was found to be a single gene disorder and need for further follow up was explained.

## 3. Result

A total of 4625 pregnant women were seen during this period. Of the total pregnant women 354/4625 (7.6%) were diagnosed with preeclampsia and 67/4625 (1.4%) with chronic hypertension. Following investigations, cause of chronic hypertension could be delineated in 20/67 (29.9%) cases and rest 47/67 (70.1%) patients were diagnosed with essential hypertension. The causes of chronic hypertension in these cases were chronic kidney disease (CKD) in 9/20 (45%), Takayasu arteritis (TKA) in 6/20 (30%), autosomal dominant polycystic kidney disease (ADPKD) in 3/20 (15%) and one case each of phaeochromocytoma and coarctation of aorta (CoA). The cases and their pregnancy outcome are delineated in Table 1.

Chronic kidney disease which was not due to systemic disease was the commonest cause recognised in 9/20 (45%) cases. Of the women with chronic kidney disease, 4 patients had stage II and 5 had stage III of CKD. Termination of pregnancy was required before fetal survivability in one case due to superimposed severe preeclampsia in which blood pressure increased in the range of 170–180/110–120 mm Hg on maximum dose of labetalol and nifedipine apart from worsening biochemical parameters. Maternal complications like acceleration of blood pressure reaching to 160/110 mmHg, worsening of renal function was seen in 3/9(33%) cases which were all in stage III. Fetal complications like intra uterine growth restriction (IUGR), oligohydramnios was seen in 2/8(25%) cases one each in stage II and III disease. Apart from the 3 patients who developed superimposed preeclampsia, blood pressure was well controlled in the range of 120–130/80–90 mmHg on Labetalol alone or with nifedipine.

3/20(15%) pregnant patients who presented with hypertension were found to have ADPKD on detailed evaluation. Detailed history and evaluation revealed other affected members in all three patients. Fetus was not found to be affected in any of the patients. Genetic counselling and prenatal diagnostic testing was offered. One woman developed

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**Table 1**
List of maternal and fetal outcome in cases of chronic hypertension.

| Case | POG at presentation (wk) | Maternal disease | Maternal/Fetal Complications | Anti-hypertensive used | GA at delivery | Neonatal outcome |
|---|---|---|---|---|---|---|
| 1 | 26 | CKD Stage II | IUGR*, oligohydramnios Superimposed preeclampsia | Labetalol | 33 weeks | SGA** weight-1.4 kg On CPAP for RDS |
| 2 | 16 | CKD Stage III | Severe preeclampsia at 22 weeks | Labetalol Nifedipine | Termination pregnancy | NA |
| 3 | 12 | CKD Stage III | Worsening renal function | Labetalol | 34 weeks | AGA***, weight = 2.0 kg, neonatal hyperbilirubinemia |
| 4 | 14 | CKD Stage III | IUGR | Labetalol | 35 weeks | SGA, Weight-1.6 kg late onset sepsis |
| 5 | 8 | CKD Stage III | Superimposed preeclampsia | Labetalol Nifedipine | 37 weeks | AGA, No complications |
| 6,7,8,9 | 7–18 | CKD Stage II | none | Labetalol | 37–38 weeks | 1 had transient tachypnoea of newborn |
| 10 | 14 | ADPKD | Superimposed preeclampsia, IUGR | Labetalol Nifedipine | 36 weeks | SGA-weight = 1.8 kg, RDS on CPAP |
| 11,12 | 18 ,19 | ADPKD | none | Labetalol | 38 weeks | AGA, no complication |
| 13 | 18 | TKA | IUGR and oligohydramnios | Labetalol | 33 weeks | SGA, weight = 1.1 kg, Had RDS |
| 14 | 16 | TKA | Uncontrolled hypertension | Methyldopa Labetalol Nifedipine | 36 weeks | AGA, weight = 2.5 kg |
| 15 | 16 | TKA | Severe preeclampsia, IUGR and deranged Doppler | Labetalol Nifedipine | 34 weeks | SGA, weight = 1.4 kg Neonatal jaundice |
| 16 | 20 | TKA | IUGR | Labetalol | 37 weeks | SGA, weight = 2.2 kg |
| 17,18 | 18,22 | TKA | None | Labetalol | 38 weeks | AGA, no complications |
| 19 | 32 | Phaeo with NF | oligohydramnios | Prazosin | 36 weeks | AGA, no complication |
| 20 | 20 | CoA | Severe uncontrolled hypertension | Labetalol, Nifedipine, Clonidine, Hydrochlorothiazide | 32 weeks | SGA-1.2 kg, RDS, on CPAP for 7 days, recovered |

POG: period of gestation, GA: gestational age, CKD: Chronic kidney disease, TKA: Takayasu arteritis, ADPKD: Autosomal polycystic kidney disease, RDS: Respiratory distress syndrome, CPAP: Continuous positive airway pressure.
* IUGR: intra uterine growth restriction.
** SGA: small for gestational age.
*** AGA: Appropriate for gestational age.

superimposed preeclampsia and fetal growth restriction and delivered at 36 weeks whereas rest two women delivered at term. Blood pressure was well controlled in the intrapartum and postpartum period on antihypertensives as depicted in Table 1.

Takayasu arteritis was diagnosed in 6/20(30%) patients. Hypertension with bilateral asymmetrical pulses helped in suspecting the diagnosis which was later confirmed by doppler ultrasound. Computed Tomography (CT) Angiography was postponed to be done after delivery to pinpoint the site of narrowing (Fig. 1). All women were put on oral steroid therapy (0.5–1 mg/kg body weight/day). Of the affected women, four (33%) women later developed gestational diabetes and equal number had maternal superimposed preeclampsia and/or fetal IUGR, oligohydramnios leading to preterm delivery in 3 of 6 (50%) patients. Two patients had worsening hypertension in pregnancy, one of whom required three antihypertensives. Her blood pressure remained high in the range of 160–180/100–110 mm Hg in the intrapartum and immediate postpartum period, however came back to prepregnancy range of 130–140/80–90 mmHg after 7 days postpartum.

One woman who was treated at primary health center as chronic hypertension with tablet Labetalol from 10 weeks of gestation was referred at 32 weeks because of uncontrolled hypertension in spite of being on maximum dose of labetalol. There was history of paroxysmal headache, palpitation and severe hypertension with blood pressure range of 200–240 mmHg systolic and 110–140 mmHg diastolic. On examination there were multiple café au lait spots and neurofibromas. Diagnosis of pheochromocytoma with neurofibromatosis was suspected and confirmed with markedly elevated 24 h Urine metanephrine and normetanephrine. Ultrasound and MRI showed mass in right suprarenal region (Fig. 2). Patient was started on alpha-blocker (Prazosin) therapy. After adequate alpha blockade her lower segment caesarean section followed by right adrenalectomy was done at 36 weeks. She delivered a live born female weighing 2600 gm and is doing well. In intraoperative period her blood pressure fluctuated between 220–90/140–60 mmHg

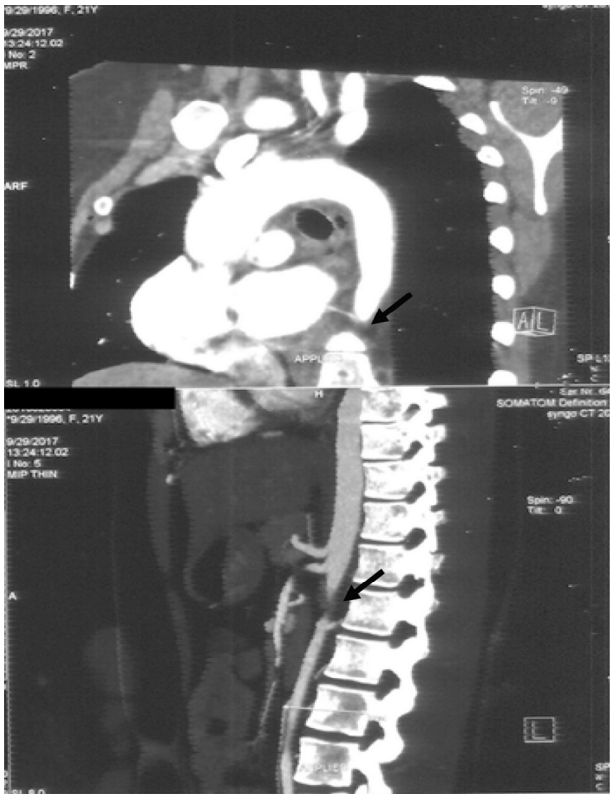

**Fig. 1.** Narrowing at multiple sites in aorta.

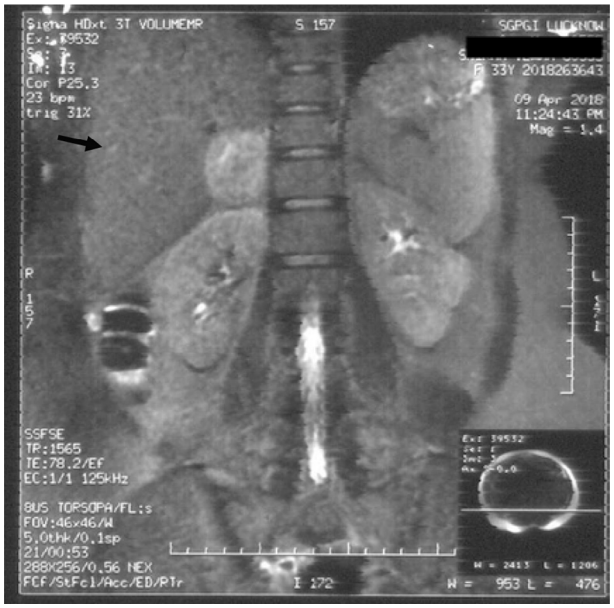


**Fig. 2.** Adrenal mass suggestive of pheochromocytoma.

and was managed by intravenous nitroglycerine (NTG) titration. Her blood pressure came down to normal at 48 h post-surgery and is normal at 6 months follow up.

One pregnant woman presented at 20 weeks with severe hypertension. On further workup she was diagnosed as coarctation of aorta with gradient of 46 mmHg. She was on Labetalol, dose of which was increased to maximum dose and antihypertensive drugs like calcium channel blocker (Nifedipine), diuretics (hydrochlothiazide), Clonidine were added to have optimum blood pressure control. Pregnancy was terminated at 32 weeks due to uncontrolled hypertension with blood pressure in the range of 180–200/110–120. Baby had respiratory distress syndrome, was on CPAP for 7 days and recovered. Following delivery her BP came down in the range of 140–160/100–110 and was still high. She was then planned for percutaneous intervention three months after delivery following which her BP became normal.

There was no neonatal mortality and none of the baby in this series required CPR in delivery room. All babies had Apgar score more than 5 at 5 min and cord blood pH more than 7

## 4. Discussion

Prevalence of chronic hypertension in women in reproductive age is 1–5% [2]. Many women often present for the first-time during pregnancy especially in developing countries like India and obstetricians are the first one to encounter them during antenatal check-up. Most common cause may be unidentifiable which is called essential hypertension and in 10% cases cause of hypertension may be delineated. In our series 29.9% patients of chronic hypertension were found to have secondary cause. Young women of less than 35 years, without a family history of hypertension and requiring two or more antihypertensive agents to control blood pressure should be considered to have secondary hypertension due to some underlying disease. Thorough evaluation should be done to search for the underlying cause of hypertension to guide therapy decisions.

Most common cause of secondary hypertension in reproductive age group is chronic kidney disease as found in our series also. The classification of chronic renal disease depends upon Glomerular Filtration Rate (GFR) since it relates better with kidney function than serum creatinine. Recent studies have confirmed a stepwise increase in pregnancy-related risks from stage 1 to stages 4–5 [3]. This was seen in our series also. The increase in risk is observed both for maternal-fetal outcomes, particularly prematurity, and for renal outcomes, including the development of hypertension, proteinuria, and shift toward a higher functional CKD stage or to dialysis [3]. In our series there was increased risk of superimposed preeclampsia, fetal growth restriction and preterm birth. Apart from regular monitoring of blood pressure, maternal renal function (serum creatinine and urea), midstream urine (for infection), proteinuria should be done to optimize perinatal outcome [4]. Addition of a prerenal insult, as peripartum haemorrhage or nephrotoxic drugs, can seriously threaten maternal renal function. In such circumstances, maternal circulation should be restored with careful fluid management.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic renal failure characterized by accumulation of fluid filled cyst in kidney and other organs [5]. As the kidney cysts grow, hypertension and deterioration of kidney function develop. Diagnosis is by USG imaging study of kidney. Hypertensive ADPKD women are at increased risk of worsening hypertension, superimposed preeclampsia, fetal growth restriction and preterm delivery [6]. All our patients were diagnosed as part of work up for chronic hypertension. In our patients correct diagnosis of ADPKD helped in identifying other family members and also the risk to the fetus could be ascertained which otherwise could not have been possible. Because of heritable nature of ADPKD and long term risk of end stage renal disease, proper counselling is warranted.

Takayasu arteritis (TKA) is the large vessel vasculitis of unknown cause causing narrowing, occlusion and aneurysm of systemic and pulmonary arteries especially aorta and its branches affecting predominantly women during the reproductive years [7]. The clinical features are related to affected artery. Diagnosis is mainly based on clinical examination. Pulselessness of unilateral and bilateral radial arteries, vascular bruit, blood pressure discrepancies in bilateral arm helps in clinching diagnosis. Doppler ultrasound helps in confirming the diagnosis. Magnetic resonance angiography is the gold standard for delineating abnormal vessels. Pregnancy does not interfere with disease progression but TKA has several adverse implications on pregnancy like superimposed preeclampsia, abruption, fetal growth restriction [7,8]. Incidence of fetal growth restriction is high when bilateral renal involvement is present. The inflammatory reaction in TKA responds to glucocorticoids which are the drugs of first choice in pregnancy however resistant cases may require azathioprine. In our series all the patients were on steroid therapy. The higher rate of gestational diabetes in these patients emphasizes the need to look for steroid related complications in them.

Pheochromocytoma is catecholamine secreting endocrine tumor which is extremely rare in pregnancy [9]. Because of its rarity and overlap with features of pregnancy associated hypertension, diagnosis is often missed which happened with our patient. It is advisable to think of pheochromocytoma with severe or intermittent hypertension associated with paroxysmal symptoms as palpitation, headache and acute increase in blood pressure. Pheochromocytoma occurs in 1–2% of patients with neurofibromatosis [10]. Hypertension in these patients should raise the suspicion of underlying pheochromocytoma. In our patient café-au lait spots and fibromas helped in clinching the diagnosis. An unrecognized pheochromocytoma is particularly dangerous because potentially fatal hypertensive crisis may be precipitated by anesthesia, vaginal delivery, mechanical effects of gravid uterus and uterine contractions. When a diagnosis is suspected biochemical investigation should be done which involve measurement of plasma and 24 h urinary metanephrine which are highly sensitive and yield a significant negative predictive value [11]. Ultrasound and MRI are the imaging modalities of choice to localize the tumor. Maternal and perinatal outcome are poor with 40–50% mortality if condition is not identified and treated during pregnancy [12]. Appropriate preoperative medical management to control hypertension is essential to prevent catecholamine-induced serious complications during surgery. Alpha-blockade with drugs such as phenoxybenzamine, prazosin and doxazosin is started. Beta-blockers may be added if tachyarrhythmia is

present, but it should not be started before alpha-blockade as the unopposed alpha-adrenoceptor stimulation can precipitate a hypertensive crisis. Thus, it is very important to clinch the diagnosis so that adequate alpha blockade can be achieved before surgery. Definitive treatment is surgical resection of the tumour. The optimal timing for surgery is during the late first or early second trimester. When diagnosed in the late second or third trimester, pheochromocytoma is best managed medically until close to term when combined caesarean section followed by tumour resection can be performed as was done in our case.

Coarctation of aorta commonly presents early in life however occasionally it is diagnosed initially during pregnancy as in our case, when a cause for hypertension is sought. Systemic hypertension is related to the presence of a significant coarctation gradient. Our patient presented with severe uncontrollable hypertension and had significant gradient. Poorly controlled hypertension leads to adverse fetal (growth retardation, abruptio placentae and premature delivery) and maternal (renal failure, hypertensive crisis) outcomes [13]. Endocarditis is a source of concern at the time of delivery. There is 3% incidence of coarctation in the offspring and fetal echo at 20 weeks may be helpful [14]. Pregnancy increases the likelihood of aortic dissection which is a life threatening complication [15]. The role of percutaneous intervention in coarctation is evolving [16]. This was done in our case 3 months after delivery with good outcome.

## 5. Conclusion

An underlying cause of chronic hypertension may be found out in 29.9% cases when looked for. It is important to keep in mind secondary causes of hypertension which may include renal, vascular and endocrine causes. Recognition of the cause is helpful so as not to miss the possible window of opportunity to intervene at an early stage. Optimal maternal and fetal outcome depends upon the cause, early detection and careful individualized management. High rates of maternal and neonatal complications warrant close monitoring of these pregnancies in dedicated high risk pregnancy unit.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.07.004.

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