

Evaluation and Management of chronic Hypertension in Pregnancy

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Abstract

Chronic hypertension is present in 1-2% of pregnant women. Women with chronic hypertension are at an increased risk of maternal and perinatal complications when compared with normotensive women. It is not uncommon for the women with chronic hypertension to present first time during pregnancy and obstetricians are the first one to encounter them during antenatal checkup. Secondary hypertension is often unrecognised and misdiagnosed thus leading to improper treatment with significant risk to the mother and fetus. It is potentially treatable and timely recognition leads to excellent pregnancy outcome. It is important to look into the causes of chronic hypertension in pregnancy and do individualised management for best outcome.

Keywords: Chronic hypertension; Secondary hypertension, Pregnancy

Introduction

Hypertension is a major health issue in pregnancy contributing to significant maternal and neonatal morbidity and mortality. Hypertensive disorders of pregnancy can be classified as chronic hypertension, gestational hypertension and preeclampsia. Chronic hypertension is present in 1-2% of pregnant women [1,2]. Prevalence of chronic hypertension increases with advancing maternal age and obesity. Chronic hypertension during pregnancy is defined as hypertension (blood pressure of more than 140/90 mmHg on 2 occasions 4 hours apart) present before pregnancy or 20 weeks of gestation or hypertension diagnosed during pregnancy that does not resolve in postpartum period after 12 weeks [3].

Chronic hypertension is associated with an increased risk of superimposed preeclampsia. The treatment of hypertension in pregnancy is independent of the cause. However, the patients with chronic hypertension must be fished out from the collective of patients with pregnancy-induced hypertension and preeclampsia, as they require treatment after the end of the postpartum period. It is classified as severe if blood pressure is $\geq 160/110$ mm Hg.

Chronic hypertension is essential in 90% of cases. It can also be secondary due to various endocrine, renal or

immunological causes in 10% of cases, which amounts to the significant proportion of women and thus should not be overlooked [1]. Women with high blood pressure should be screened for underlying secondary causes, such as chronic kidney disease, autosomal dominant polycystic kidney disease, pheochromocytoma, renovascular hypertension, takayasu arteritis, primary aldosteronism, Cushing's syndrome, coarctation of the aorta, etc. The presence of resistant hypertension, hypokalaemia (potassium levels <3.0 mEq/l), elevated serum creatinine level (>1.1 mg/dl) and family history of kidney disease are important suggestive findings of secondary hypertension. A detailed workup will help to check for secondary hypertension and end organ damage. Timely recognition and appropriate management helps in reducing the number and extent of poor outcome.

Risks Associated with Chronic Hypertension in Pregnancy

There is increased risk of maternal and perinatal morbidity and mortality in women with chronic hypertension. A systematic review of 55 studies including 795,221 pregnancies concluded that women with chronic hypertension have high rates of superimposed preeclampsia (26%), preterm delivery (28%), caesarean delivery (41%), low birthweight (17%), perinatal death

(4%), and neonatal intensive care unit (NICU) admission (21%) [4].

Superimposed preeclampsia is difficult to differentiate from severe hypertension and new-onset proteinuria or any indication of maternal end-organ or fetoplacental involvement points toward its diagnosis. Untreated chronic hypertension increases the risk of cardiovascular defects in the fetus [5,6]. Chronic hypertension is associated with increased risk of gestational diabetes which may be due to common risk factors for both [7,8]. Risk of cerebrovascular accident, pulmonary edema, renal failure, and postpartum hemorrhage is higher than in the normotensive women [9,10]. This risk is further increased in those women with secondary hypertension, end organ disease, severe hypertension and superimposed preeclampsia.

Secondary Hypertension

The presence of secondary hypertension can significantly increase the risk of maternal and fetal morbidity and mortality. It is suspected when hypertension presents at young age with no family history of hypertension and is resistant to treatment. The causes of secondary hypertension in pregnancy include chronic kidney disease, renovascular hypertension (fibromuscular hyperplasia of the renal arteries and Takayasu's arteritis), pheochromocytoma, primary aldosteronism and Cushing's syndrome, thyroid disease, systemic lupus erythematosus, connective tissue diseases, coarctation of aorta. Suggestive clinical features of these conditions are given in Table 1.

Many symptoms associated with these can be attributable to normal pregnancy (e.g., dizziness, palpitations, edema, fatigue, and frequent urination) and thus there are chances of missing the accurate diagnosis. It is important to diagnose and treat them in the context of pregnancy for favorable perinatal outcome. A thorough history, physical examination and relevant investigations is the key to detect rare causes of secondary hypertension.

Chronic kidney disease is the most common cause of

secondary hypertension found in women with chronic hypertension [1]. The classification of chronic renal disease depends upon Glomerular Filtration Rate (GFR) as it relates with kidney function better than serum creatinine. There is stepwise increase in pregnancy-related risks for maternal-fetal and renal outcomes from CKD stage 1 to stage 5 [11]. Patient should be regularly monitored for blood pressure, renal function (serum creatinine and urea), midstream urine (for infection) and proteinuria to optimize perinatal outcome [12]. All the nephrotoxic drugs should be avoided. Careful fluid management should be done in peripartum haemorrhage as it can seriously threaten maternal renal function.

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 [13]. As the kidney cysts grow, hypertension and deterioration of kidney function develop. Diagnosis is carried out by USG imaging study of kidney. Diagnosis of ADPKD helps in identifying other affected members of family. Because of heritable nature of ADPKD there is risk of fetus getting affected and long term risk of end stage renal disease, thus proper counselling is warranted.

Pheochromocytoma is the most common adrenal tumor in pregnancy [14]. Maternal and perinatal outcome are poor with 40–50% mortality if condition is not identified and treated during pregnancy [15] and earlier detection helps in improved outcome. It is suspected when severe or intermittent hypertension is associated with paroxysmal symptoms of palpitation, headache and acute increase in blood pressure. 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.

Diagnosis is done with measurement of plasma and 24 h urinary metanephrine which are highly sensitive with a high negative predictive value [16]. Ultrasound and

Cause	Suggestive Clinical features
Renal disease	Edema, fatigue, frequent urination Elevated serum creatinine, Abnormal urinalysis
pheochromocytoma	Blood pressure lability, paroxysmal headache, palpitation, pallor, and dizziness
Takayasu arteritis	Pulselessness of unilateral and bilateral radial arteries, blood pressure discrepancies in bilateral arm
Primary aldosteronism	Muscle cramps, weakness Hypokalemia
Cushing's syndrome	Central obesity, facial rounding, easy bruisability, proximal muscle weakness
Coarctation of the aorta	delayed femoral pulse, low or unrecordable blood pressures in the legs

Table 1: Suggestive clinical features of these conditions causing of secondary hypertension in pregnancy.

MRI helps to localize the tumor. Appropriate medical management to control hypertension is essential to prevent catecholamine induced serious complications during surgery. Treatment is done with Alpha blocker (phenoxybenzamine, prazosin and doxazosin). 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. Definitive treatment is surgical resection of the tumour during the late first or early second trimester. When diagnosed in the late second or third trimester, it can be treated with medication and a combined caesarean section and tumor resection can be performed close to term.

Renovascular hypertension due to renal artery stenosis is commonly due to fibromuscular dysplasia. It is associated with severe uncontrolled hypertension, early superimposed preeclampsia, and adverse pregnancy outcomes [17]. Raised blood pressure and high plasma renin activity (>15 ng/ml/h) and raised peak systolic velocity on duplex Doppler ultrasonography are suggestive features of renovascular hypertension.

There is possible role of estrogen in pathogenesis and hence it is likely that pregnancy might aggravate the condition. If medical therapy fails in controlling BP, angioplasty might be considered for the treatment which has been successfully performed with appropriate shielding of fetus [17].

Takayasu arteritis (TKA) is the large vessel vasculitis causing narrowing, occlusion and aneurysm of systemic and pulmonary arteries especially aorta and its branches affecting predominantly women of reproductive age [18]. The clinical features are related to affected artery. Pulselessness of unilateral and bilateral radial arteries, vascular bruit, and 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. It has adverse implications on pregnancy like superimposed preeclampsia, abruptio, fetal growth restriction. Risk of fetal growth restriction is higher when bilateral renal involvement is present. Glucocorticoids are the drugs of first choice in pregnancy however resistant cases may require azathioprine.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multiorgan involvement characterized by periods of remission and relapse. Patients are treated with hydroxychloroquine, corticosteroids and immunosuppressants and therapy is dictated by both degree of disease activity and specific organ involvement. SLE patients have significantly increased risk of hypertension and preeclampsia [18]. Distinguishing a

lupus renal flare from preeclampsia is challenging. Laboratory and clinical evidence suggesting active disease support a diagnosis of a lupus flare, while preeclampsia is more often associated with stable SLE disease parameters and proteinuria with inactive urine sediment. Treatment requires well-coordinated, interdisciplinary care.

Hyperthyroidism and hypothyroidism can cause hypertension. Hyperthyroidism can cause systolic hypertension with a wide pulse pressure. Hypothyroidism often causes diastolic hypertension. Detailed clinical examination and thyroid function test will confirm the diagnosis. Appropriate pharmacologic management of the primary disease helps in the control of hypertension.

Primary Aldosteronism is characterized by increased secretion of aldosterone, low plasma renin activity, hypokalaemia and hypertension. Treatment requires medical therapy with appropriate antihypertensive agents in addition to potassium and magnesium replacement. If hypertension and hypokalaemia are resistant to treatment adrenalectomy can be performed in the late first or second trimester [19,20]

Cushing's syndrome in pregnancy can be due to adrenal or pituitary tumor. Poor maternal and fetal outcome can occur due to superimposed preeclampsia, eclampsia, and congestive heart failure. Fetal risk includes adrenal insufficiency and virilization apart from prematurity. The condition may be fatal to the mother or the fetus [21]. Diagnosis is made by 24-h urine free cortisol to detect hypercortisolism. Although normal pregnancy is associated with increases in urinary free cortisol, levels in pregnant patients with Cushing's syndrome are significantly higher than the physiologic (100–300 µg/24 h) increase found in normal pregnancy [21,22]. The loss of circadian fluctuation in serum cortisol, is pathognomonic. After exhausting all drug options to lower blood pressure, surgical management (adrenalectomy or pituitary adenomectomy) is required.

Coarctation of the aorta usually presents in young children but may be detected in adulthood for first time with severe hypertension. MRI will delineate the coarctation site and echocardiogram will help in the identification of bicuspid aortic valves (associated in up to 50% of all coarctations) as well as dilatation of the ascending aorta. In uncontrolled hypertension intervention with balloon dilatation may be required.

Management

Prepregnancy counseling

A woman with chronic hypertension should be evaluated before pregnancy to check for secondary hypertension and

end organ involvement, for optimization of blood pressure and to counsel regarding the risk of hypertension during pregnancy. Patient is counselled regarding modifiable risk factors. Weight loss in overweight and obese patients, increased exercise for sedentary individuals, and dietary changes are encouraged as nonpharmacologic means of reducing blood pressure and improving overall health and pregnancy outcome.

Review of medications and the need to stop certain agents before or as soon as pregnancy is confirmed is to be emphasized. There is risk of malformations (renal dysgenesis, calvarial hypoplasia) and fetal growth restriction with angiotensin converting enzyme inhibitors and angiotensin receptor blockers [23]. For the same reason it is better to avoid the use of these agents in the reproductive age group. If there is compelling reason to use it such as chronic renal disease for renoprotection, then it should be stopped as soon as pregnancy is confirmed.

Patients with raised serum creatinine and impaired creatinine clearance are at risk of worsening kidney functions during pregnancy. Women with long standing hypertension are likely to have hypertrophic cardiomyopathy and cardiomegaly and require evaluation for the same with electrocardiography and echocardiography. This is important for risk stratification and accordingly counselling and management during pregnancy and postpartum.

Management during pregnancy

Chronic hypertension is often diagnosed first time in pregnancy as this is the time when a woman comes in contact with the doctor. Baseline investigations which includes serum creatinine, electrolyte, uric acid, urine protein/creatinine ratio or 24-hour urine protein, liver transaminases (aspartate aminotransferase and alanine aminotransferase) platelet count and ocular fundoscopy should be done as it is useful if the patient exhibits signs/symptoms of preeclampsia later in pregnancy. Echocardiography and electrocardiogram is done in women with long-standing hypertension if not done before.

Administration of low dose aspirin preferably starting before 16 weeks until delivery is recommended in practice guidelines for women with chronic hypertension [24,25]. Monitoring of fetal growth by ultrasound is required due to the risk of fetal growth restriction in women with chronic hypertension and appropriate additional evaluation is done as needed [26]. Patient is educated regarding the symptoms of severe preeclampsia which include headache, visual disturbance or severe persistent right upper quadrant or epigastric pain.

Treatment of chronic hypertension during pregnancy

The decision of which women to treat and how to treat requires special consideration during pregnancy. There is still debate over the threshold blood pressure level above which treatment is required during pregnancy in women with chronic hypertension. Cochrane metaanalysis of 58 trials in 2018 concluded that treatment of mild to moderate hypertension reduced the risk of severe hypertension (RR-0.49) but there was little or no effect on development of superimposed preeclampsia, fetal growth restriction, preterm birth and perinatal outcome [27]. An international randomized controlled trial, 2015 Control of Hypertension In Pregnancy Study (CHIPS) compared the effect of tight control of blood pressure (target diastolic <85 mm Hg) to less tight control (target diastolic <100 mm Hg) on pregnancy outcomes. It concluded that tight control of hypertension reduced the incidence of severe hypertension (27.5% vs 40.6%; adjusted OR, 0.56; 95% CI ,0.42-0.74), although there was no reduction in perinatal morbidity and mortality (pregnancy loss or high-level neonatal care for >48 hours , birthweight <10th percentile and preterm birth) [28,29]. Importantly, 75% of the 987 women included in the trial had chronic hypertension.

The key medical organizations (International Society for the study of hypertension in pregnancy, Royal College of Obstetrics and Gynaecology, Society of Maternal and Fetal Medicine, American College of Obstetrics and Gynaecology) have provided varying recommendations regarding blood pressure management for pregnant women with chronic hypertension. Based on the results of CHIPS trial practice guidelines of Canada, United Kingdom, and the International Society for the Study of Hypertension in Pregnancy (ISSHP) now endorse tight BP control for hypertension in pregnancy [25]. Due to the absence of evidence of benefit of tight control of hypertension in improving serious maternal complications or perinatal morbidity and mortality, ACOG recommends the initiation of antihypertensive therapy for chronic hypertension when systolic BP is \geq 160 mm Hg, diastolic BP is \geq 110 mm Hg or both, however in the setting of comorbidities (such as left ventricular hypertrophy or impaired renal function) treatment at lower threshold is appropriate to reduce the progression of underlying kidney or cardiovascular disease as outside pregnancy [30]. It also recommends to maintain BP between 160-120/110-80 mm Hg due to concerns of compromise in uteroplacental blood flow with aggressive BP control and insufficient data of improved maternal and perinatal outcome with tight BP control.

For the treatment of chronic hypertension in pregnancy labetalol, methyldopa or nifedipine are the preferred agents. Labetalol is combined alpha and beta blocker

(nonselective) and should be used with caution in mild to moderate asthma and avoided in severe asthma. Nifedipine is a dihydropyridine calcium channel blocker that acts on vascular smooth muscle to produce vasodilation. Side effects include reflex tachycardia, flushing, headache, and peripheral edema in high doses. Methyldopa is a centrally acting alpha receptor antagonist that decreases sympathetic tone and reduces peripheral vascular resistance. It is considered the first-line therapy for pregnancy antihypertensive treatment with the largest quantity of data regarding fetal safety. It can cause central nervous system side effects (drowsiness, depression). β -blockers are more effective than methyldopa in preventing episodes of severe hypertension but there is no evidence of difference in the risks of preeclampsia, preterm birth, small-for-gestational-age (SGA) or neonatal death [27]. Fetal growth restriction and low placental weight in patients have been associated with the use of atenolol during the second trimester [31] but not with other β -blocking agents, such as labetalol (an alpha and beta blocker), which is used frequently for the treatment of hypertension during pregnancy. Additional antihypertensive drugs from a different class should be used if target BP levels are not achieved with one drug .

Acute onset severe hypertension in pregnancy may be due to worsening chronic hypertension or superimposed preeclampsia and requires timely management. Oral Nifedipine, Intravenous (IV) Labetalol and IV hydralazine are used for the management of severe hypertension. There are no specific recommendations regarding choice of antihypertensive agent and is guided by clinician's experience and familiarity with the drug. Urapidil is a post-synaptic alpha 1 adrenoceptor antagonist, which is used to control hypertensive crises unrelated to pregnancy. There are very few studies of use of urapidil for control of severe hypertension in pregnancy and has not been included as first line by various governing bodies. A systematic review of antihypertensive therapy for acute severe hypertension in pregnancy concluded that there was insufficient evidence regarding comparative effectiveness and safety of any one agent over other [32]. The general principle is to gradually lower blood pressure from severely elevated range into the mildly elevated range, thereby avoiding sudden hypotension and reduced flow in the uterine arteries.

Delivery

The timing of birth for women with chronic hypertension varies widely and there is insufficient data available to assess the impact of planned delivery at term. For women with chronic hypertension and no maternal or fetal complications delivery before 38 weeks is not recommended. Clinician judgment on case by case basis, with consideration of factors such as trends in blood pressure, fetal growth and amniotic fluid volume is

required for appropriate management. For those women with superimposed preeclampsia with and without severe features expectant management till 34 weeks and 37 weeks respectively is recommended [33].

Postpartum management

Women with chronic hypertension will usually need treatment in postpartum period. Since there are no fetal considerations in the postpartum period the goal of therapy is lower blood pressure range of less than 150/100 mmHg [34,35]. When treatment is initiated postpartum, the initial goal is to maintain blood pressure below 140/90 mm. Both Labetalol and nifedipine have been found to be effective [36]. Methyldopa should be avoided as it may increase the risk of postpartum depression [37]. ACE inhibitors may be prescribed after delivery as the drug levels in breast milk are low. If blood pressure levels are poorly controlled, the patient may need to be weaned to optimize blood pressure medication.

Conclusion

If a woman is diagnosed with chronic hypertension in pregnancy, proper workup should be done if not done before pregnancy in order to rule out secondary causes of hypertension, evaluate baseline cardiovascular risk, and basic workup is to be done to be used for later comparison when superimposed preeclampsia is suspected.

Conflict of Interest

None to declare for any of the authors.

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