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Review Article

# Hypertension in Pregnancy

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**Abstract**

Hypertensive disorders are most important clinical problem in pregnancy. Hypertension is one of the most frequently observed medical diseases, which considerably affects maternal and fetal morbidity and mortality. There is a progressive increase in the incidence of hypertensive disorders in pregnancy worldwide. However, provision of blood pressure at a level sufficient to preserve maternal end organs plays key role in pregnancies progressing with high blood pressure. Here, we discuss types, risk factors, diagnosis, and management strategies of hypertensive disorders in pregnancies in the light of current guidelines. Moreover, we review hypertension-related preeclampsia and eclampsia.

## ABBREVIATIONS

ALT: Alanine AminoTransferase; AST: Aspartate Amino Transferase; SGA: Small for Gestational Age; ACE: Angiotensin Converting Enzyme; CBC: Complete Blood Count; BPP: Bio Physical Profile

## INTRODUCTION

Hypertension is a major risk factor for maternal ischemic and hemorrhagic stroke, myocardial infarction, heart failure and chronic renal diseases. In addition, it comprises a preventable cause of premature morbidity and mortality worldwide [1,2].

Hypertensive disorders in pregnancy are the second leading cause of maternal death in developed countries. Hypertension is most commonly encountered complication during pregnancy [3,4].

### Classification of Hypertension in Pregnancy

Hypertension in pregnancy is classified as chronic hypertension, gestational hypertension, preeclampsia superimposed chronic hypertension, preeclampsia and eclampsia [5,6]. Chronic hypertension is blood pressure elevation either diagnosed before gestational week 20 or known to be present before onset of pregnancy [7]. Gestational hypertension is defined as hypertension detected after gestational week 20 without proteinuria or one of the clinical features related to severe preeclampsia, which returns to normal at postpartum week 12.

Since proteinuria is lacking in 14% of patients with preeclampsia-eclampsia, the definition of preeclampsia is changed. Now, proteinuria is no longer a requirement for diagnosis of preeclampsia. Hypertension related to thrombocytopenia (platelet count<100,000 µ/L), hepatic dysfunction (AST or ALT elevation by 2-folds), new onset renal dysfunction (serum creatinine>1.1 or serum creatinine elevation by 2-folds in the absence of renal disease), pulmonary edema, new onset of clinical conditions such as cerebral or visual disorders regardless of proteinuria is defined as preeclampsia. If any of findings presented in (Table 1) is present in a preeclamptic patient, it is defined as severe preeclampsia [8]. Eclampsia is defined as presence of seizure accompanying to preeclampsia in the absence of any other reasons [6].

Preeclampsia-eclampsia superimposed upon chronic hypertension is further elevation of blood pressure with proteinuria (>300 mg/dL in 24 hours), thrombocytopenia or any systemic component of preeclampsia in a patient with chronic hypertension [9].

### Etiology and Risk Factors in Preeclampsia

Preeclampsia is a multi-systemic disease affecting both

| **Table 1:** Severe Features of Preeclampsia. |
|---|
| Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest |
| Thrombocytopenia (< 100,000/micro liter) |
| Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both |
| Progressive renal in-sufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentrat ion in the absence of other renal disease) |
| Pulmonary edema |
| New-onset cerebral or visual disturbances |
| **Adapted from:** Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, 2013. |

mother and fetus, in which many factors play role in the pathogenesis. The most remarkable factor is uteroplacental abnormality in the pathogenesis. A high-capacitance placental flow with low resistance occurs in normal pregnant woman as a result of invasion of spiral arterioles by trophoblasts. In preeclamptic patients, there is a failure in the invasion of spiral arterioles by fetal trophoblasts. This failure results in insufficient dilatation of placental bed; thus, decreased placental and fetal blood supply. The oxidative stress developed cause release of free radicals. Ischemic placenta impairs balance between angiogenic and anti-angiogenic factors. Hypoxia caused by defective placentation and resultant inflammation lead cytokine release into maternal circulation and neutrophil activation. In addition, systemic inflammation develops as a result of placental fragments and micro-particles, auto-antibodies and immunological factors, and inflammatory events such as lipid peroxidation in syncytiotrophoblasts. Besides, maternal medical complications such as chronic hypertension also predispose to placental vascular failure and cause preeclampsia during early gestation [10,11].

There are several risk factors thought to cause preeclampsia in pregnancy. Many conditions such as chronic hypertension, chronic renal disease or insulin dependent diabetes mellitus are risk factors for development of preeclampsia in pregnant women. (Table 2) Summarizes potential risk factors for preeclampsia in pregnancy [12].

## Diagnosis

Hypertension in pregnancy is defined as systolic blood pressure≥140 mmHg and diastolic blood pressure ≥90 mmHg. However, the patient must have to rest before blood pressure measurement and blood pressure should be measured at upper arm by using appropriately sized cuff [13]. Systolic blood pressure>140 mmHg and diastolic blood pressure>90 mmHg during rest in at least 2 different occasions by 4-hours interval is diagnostic for hypertensive disorder in pregnancy. In addition, if systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥110 mmHg in 2 different measurements, it is accepted that there is severe hypertension in the patient [3].

## Clinical presentation

Maternal intra-cerebral hemorrhage and poor fetal outcomes are increased in chronic and gestational hypertension. Many women with chronic hypertension generally have an event-free pregnancy. However, such women carry increased risk for pregnancy-related complications when compared to general population [7]. Superimposed preeclampsia develops in one-fourth of cases with chronic hypertension [14]. Even preeclampsia doesn't develop; likelihood of preterm birth is increased by 5-folds. The risk of small for gestational age neonate (SGA) is increased by 50% in women with chronic hypertension [15]. Risk for incident diabetes mellitus is also increased in hypertensive patients during early gestation [16].

**Table 2:** Principal risk factors for preeclampsia.

| | |
|---|---|
| Pre existing hypertension | Previous preeclampsia |
| Age >40 years | Obesity |
| Family history of preeclampsia | Antiphospholipid syndrome |
| Multiple pregnancy | Insulin-dependent diabetes |
| Nulliparity | Relative risk of preeclampsia |

Although preeclampsia-like complications can be seen in women with gestational diabetes mellitus, better clinical outcomes are seen in general. Although gestational hypertension is temporary in pregnant women, it could be a premise for future hypertension in these patients and such patients should be monitored for hypertension [8].

Patients with preeclampsia can present with a wide spectrum of clinical findings ranging from mild clinical findings to life-threatening conditions. Similarly, fetus can be affected minimally but it is possible that fetus may be affected severely. Most women are asymptomatic at early course of preeclampsia [17]. Thus, patients should be closely monitored with frequent obstetric visits during late gestation. The preeclampsia symptoms include cerebral findings (headache, dizziness, tinnitus, drowsiness, respiration rate, tachycardia and fever), visual findings (diplopia, scotoma, blurred vision, amaurosis), gastrointestinal findings (nausea, vomiting, epigastric pain, hematemesis) and renal findings (oligouria, anuria, hematuria, hemoglobinuria) [8].

Acute and long-term complications of severe preeclampsia affect both mother and newborn [18-22]. Maternal complications of severe preeclampsia include pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, severe renal failure and retinal injury. These complications develop due to acute maternal organ dysfunction in patients with previously known medical diseases. Fetal and neonatal complications of severe preeclampsia can develop due to preterm birth, uteroplacental failure or both [8,21,22]. On the other hand studies show that increased rates of heartattack, acute stroke among women with a history of preeclampsia and increased thromboembolic events among women with previous severe pre-eclampsia [23]

Eclampsia is defined as preeclampsia complicated by generalized tonic-clonic convulsions, causing marked increase risk for both mother and fetus. Eclampsia can be seen at antepartum, intrapartum or postpartum period. It is most commonly seen in the third trimester and its frequency increases by progression to term. Decreased incidence of postpartum eclampsia in recent years is attributed to improved prenatal care, early recognition of preeclampsia and prophylactic use of magnesium sulphate [24].

## Emergent Therapy for Acute Onset and Severe Hypertension

It is defined as presence of severe systolic (≥160 mmHg) and/or diastolic (≥110 mmHg) hypertension. It can manifest as preeclampsia, gestational hypertension or HELLP syndrome when onset in the second half of gestation in patients with unrecognized chronic hypertension as well as superimposed preeclampsia in the grounds of uncontrolled chronic hypertension which deteriorated in an acute manner [25].

Acute onset severe hypertension is a hypertensive period (measured by standard techniques) which has acute onset

and continues longer than 15 minutes and is considered as a hypertensive emergency. It is known that severe hypertension can cause central nervous system injury and a patient with above-mention blood pressure values should be considered as a hypertensive emergency, prompting emergent therapy. In the treatment, the goal isn't to reduce blood pressure to normal level, because it will be harmful to decrease blood pressure to a level which disrupts cerebrovascular auto-regulation [25,26].

Labetalol and hydralazine are preferred as first-line therapy in the management of acute onset, severe hypertension in pregnancy. There are evidence, indicating that nifedipine can also be used [25,27,28]. The patients can respond either one or other drug. Magnesium sulphate isn't used as an alternative agent in hypertension. Instead, it is used as prophylaxis for seizures in severe preeclampsia and to control seizures in eclampsia [25,29].

Initially, labetalol is given at a dose of 20 mg via intravenous route. If no response after 10 minutes, labetalol is repeated at a dose of 40 mg via intravenous route. Blood pressure measurements are recorded by 10-minute intervals. If the patient doesn't respond, labetalol can be repeated at a dose of 80 mg. If blood pressure is still above threshold value, 10 mg hydralazine is given via intravenous route. If this is failed to reduce blood pressure below threshold value, the patient should be consulted to maternal-fetal medicine, internal medicine, anesthesia or critical care subspecialists [25].

If hydralazine is preferred as initial therapy, 5-10 mg hydralazine is given via intravenous route. Blood pressure is measured within 20 minutes. If blood pressure is still above threshold value, hydralazine is repeated at a dose of 10 mg via intravenous route. If this is failed to control blood pressure, labetalol is used as second-line therapy [25].

Nifedipine is given at a dose of 10 mg via oral route. If blood pressure measured after 20 is still above threshold value, nifedipine at a dose of 10 mg should be given via oral route. If blood pressure is still high after 20 minutes, nifedipine should be repeated at a dose of 20 mg via oral route. However, 40 mg labetalol via intravenous route should be given if blood pressure couldn't be controlled by total nifedipine dose of 50 mg. Labetalol or nicardipine infusion pump can be used if blood pressure is still above threshold value despite all interventions. Short-term intravenous nitroprusside should be used in extreme emergency [25,30]. Current emergent treatments modalities are summarized in (Figure 1).

In all 3 treatment modalities, blood pressure should be monitored as follows if blood pressure is successfully controlled: 10-minutes intervals within first hour, 15-minutes intervals during next one hour, by 30-minutes intervals during following one hour and 1-hour intervals during following 4 hours [25].

## Management of Chronic Hypertension

There is an ongoing debate about management of mild hypertension without end-organ injury. In a study on patients with mild-moderate hypertension, it was shown that therapy didn't reduce superimposed preeclampsia, preterm delivery, small for gestational age [SGA] neonate or perinatal mortality; however, it decreased progression to severe hypertension by 50% [6,19].

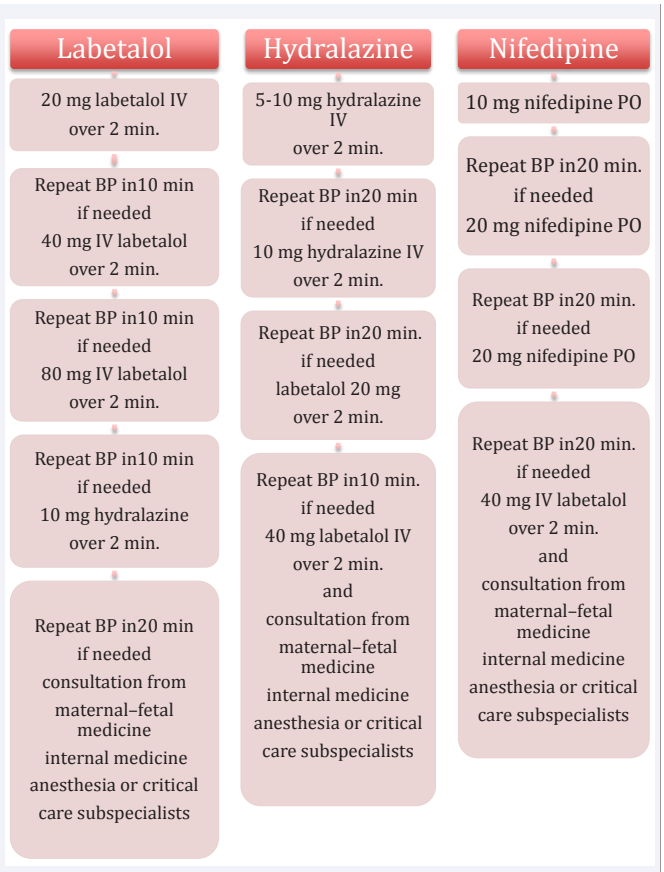


**Figure 1** Emergent Therapy for Acute-Onset and Severe Hypertension.

Superimposed preeclampsia or end-organ injury will not develop in majority of pregnant women. In such case, it will be appropriate not to start an anti-hypertensive agent to a patient who is normotensive at onset of pregnancy or not receiving any antihypertensive therapy. The treatment should be continued in hypertensive pregnant women in whom blood pressure is under control with antihypertensive therapy. Patients with blood pressure values below 140/90 mmHg can be monitored by stopping medical therapy.

Oral agents are preferred in the management of chronic hypertension in pregnant women [31]. There are randomized-clinical trials with labetalol and methyldopa [8,32,33]. Labetalol is a non-selective beta blocker with alpha blockade effects on vessel wall. It is commonly used as antihypertensive agent with good tolerability and safety in the management of hypertension in pregnancy. Recommended daily dose is 200-2400 mg divided into 2-3 doses. It should not be used in patients with asthma or cardiac failure [8].

Methyldopa is a centrally acting alpha-2 adrenergic agonist. It has been long introduced for therapeutic purposes and is considered to be safe in pregnancy. Recommended daily dose is 0.5-3 g divided in 2-3 doses. However, its use is limited by adverse effects such as nausea or dry mouth [6,8].

Although there is limited experience with long-acting

calcium canal blockers when compared to labetalol, they seem to be safe in pregnancy [7]. It has been thought that diuretics are contraindicated in pregnancy as they cause volume depletion; however, there are publications on patients treated with diuretics, supporting their safety in pregnancy [8,33,34]. ACE inhibitors are contraindicated in pregnancy [35,36].

## MANAGEMENT OF PREECLAMPSIA

### Management of Mild Gestational Hypertension or Preeclampsia

At diagnosis, CBC, serum creatinine and hepatic enzymes should be measured and urinary protein should be assessed. Urinary protein can be assessed either by 24-hours urine collection or estimated urinary protein/creatine ratio. Estimated fetal weight and amniotic fluid index are measured by sonography. Hospitalization and delivery is indicated in patients with gestational age≥37 0/7 weeks and those with suspected abruptio placenta in this assessment. The patients with gestational age 34 0/7-37 0/7 should be hospitalized if membrane rupture is present or labor is progressing, or if there is fetal weight<5th percentile), oligohydramnios (persistent amniotic fluid index<5 cm), persistent BPP≤6/10 and delivery should be planned. In case of maternal and fetal stability and no indication for delivery, patients should be followed by assessing once or twice in a week based on severity of disease. Hospitalization is indicated in patients with new signs or symptoms suggesting severe preeclampsia, fetal growth retardation, elevated hepatic enzymes and thrombocytopenia during follow-up [8].

Progression to severe gestation hypertension or preeclampsia within 1-3 weeks is frequently seen in patients with mild gestational hypertension. Clinical picture can progress to severe preeclampsia within days in patients without characteristics of severe preeclampsia [8,37].

It is failed to show benefits of using an antihypertensive agent in mild gestational hypertension or preeclampsia. Antihypertensive therapy can reduce progression to severe hypertension; however, it is associated to impairment of fetal growth [8,38,39].

### Management of Severe Preeclampsia

In severe preeclampsia, delivery is recommended in pregnancies with gestational age ≥34 0/7 weeks. Delaying birth can cause maternal or fetal complications. In pregnancies with gestational age≤37 0/7 weeks, delivery should be performed promptly after maternal stabilization if pulmonary edema, renal failure, abruptio placentae, severe thrombocytopenia, disseminated intravascular coagulation, persistent cerebral symptoms, non-reassuring fetal testing or fetal demise is present [8,20,21].

In severe preeclampsia, treatment discussed in the section "Emergent Therapy for Acute Onset and Severe Hypertension" should be promptly initiated in patients with systolic blood pressure>160 mmHg and diastolic pressure>110 mmHg in order to prevent maternal end-organ injury [40].

### Management of Eclampsia

Eclampsia is occurrence of grand-mal seizure in a preeclamptic patient without previous history of seizure. Blood pressure can be either normal, or mildly or severely elevated in these patients. In eclampsia, delivery is performed after stabilization of patient. Emergent anti-hypertensive therapy should be promptly initiated in patients with systolic blood pressure>160 mmHg and diastolic pressure>110 mmHg in order to prevent maternal end-organ injury [8,41].

In conclusion, hypertension is most frequently encountered complication in pregnancy. It can be fatal for mother and it can cause severe morbidity and mortality in infant as well, if it is failed to provide appropriate therapy. Thus, early diagnosis, treatment and knowledge of conditions with hazardous potential will play an important role in reducing maternal and fetal morbidity and mortality.

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