

HYPERTENSION IN PREGNANCY: RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT

Renata Cifková, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal and neonatal morbidity and mortality not only in less developed but, also, in the industrialized countries. Pregnant women with hypertension are at higher risk for severe complications such as abruptio placentae, cerebrovascular accident, organ failure, and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity, and intrauterine death.

Physiologically, blood pressure falls in the second trimester, reaching a mean of 15 mmHg lower than levels before pregnancy. In the third trimester, it returns to pre-pregnancy levels. This fluctuation occurs in both normotensive and chronically hypertensive women.

Definition of hypertension in pregnancy

The definition of hypertension in pregnancy is not uniform. It used to include an elevation in blood pressure during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition **based on absolute blood pressure values (systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg)** is now preferred.

Measurement of blood pressure

It is essential to confirm high blood pressure readings on two occasions. It is recommended that both Phase IV and V Korotkoff sounds be recorded. Phase IV should be used for initiating clinical investigation and management.

Classification of hypertension in pregnancy

Hypertension in pregnancy is not a single entity but comprises:

- *Pre-existing hypertension*, which complicates 1-5% of pregnancies and is defined as blood pressure \geq 140/90 mmHg that either predates pregnancy or develops before 20 weeks of gestation. Hypertension usually persists more than 42 days post partum. It may be associated with proteinuria.
- *Gestational hypertension*, which is pregnancy-induced hypertension with or without proteinuria. Gestational hypertension associated with significant proteinuria ($>$ 300 mg/l or $>$ 500 mg/24 h or dipstick 2+ or more) is known as *pre-eclampsia*. Hypertension develops after 20 weeks' gestation. In most cases, it resolves within 42 days post partum. Gestational hypertension is characterized by poor organ perfusion.
- *Pre-existing hypertension plus superimposed gestational hypertension with proteinuria*. Pre-existing hypertension is associated with further worsening of blood pressure and protein excretion \geq 3 g/day in 24-hour urine collection after 20 weeks' gestation; it corresponds to previous terminology "chronic hypertension with superimposed pre-eclampsia".
- *Antenatally unclassifiable hypertension* - hypertension with or without systemic manifestation, if blood pressure was first recorded after 20 weeks' gestation. Re-assessment is necessary at or after 42 days post partum. If hypertension is resolved by then, the condition should be re-classified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be re-classified as pre-existing hypertension.

Edema occurs in up to 60% of normal pregnancies, and is no longer used in the diagnosis of pre-eclampsia.

Recommended laboratory investigations. Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may produce changes in the hematologic, renal and hepatic profiles that may adversely affect prognosis and both neonatal and maternal outcomes.

Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in *Table 1*.

Table 1
Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy

Hemoglobin and hematocrit	Hemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of hemolysis.
Platelet count	Low levels $<$ 100,000 \times 10 ⁹ /L may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in post-partum period, especially for women with HELLP syndrome.*
Serum AST, ALT	Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity.
Serum LDH	Elevated levels are associated with hemolysis and hepatic involvement. May reflect severity and may predict potential for recovery post partum, especially for women with HELLP syndrome.
Proteinuria (24-h urine collection)	Standard to quantify proteinuria. If in excess of 2 g/day, very close monitoring is warranted. If an excess of 3 g/day, delivery should be considered.
Urinalysis	Dipstick test for proteinuria has significant false-positive and false-negative rates. If dipstick results are positive (\geq 1), 24-h urine collection is needed to confirm proteinuria. Negative dipstick results do not rule out proteinuria, especially if DBP \geq 90 mmHg.
Serum uric acid	Elevated levels aid in differential diagnosis of pre-eclampsia and may reflect severity.
Serum creatinine	Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-h creatinine clearance may be necessary.

*HELLP – Hemolysis, Elevated Liver enzyme levels and Low Platelet count

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140-179/90-109 mmHg), and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal prognosis; they are candidates for non-pharmacological therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome.

Non-pharmacological management and prevention of hypertension in pregnancy

Non-pharmacological management should be considered for pregnant women with SPB of 140-150 mm Hg or DBP of 90-99 mmHg or both, measured in a clinical setting. A short-term hospital stay may be required for diagnosis and for ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management, depending on BP, gestational age and presence of associated maternal and fetal risk factor, includes close supervision, limitation of activities, and some bed rest in the left lateral position. *A normal diet without salt restriction is advised.* Preventive interventions, aimed at reducing the incidence of gestational hypertension, especially pre-eclampsia, including calcium supplementation (2 g/d), fish oil supplementation and *low-dose acetylsalicylic acid therapy*, have failed to produce consistently the benefits initially expected, especially on the fetus. Low-dose aspirin is, however, used prophylactically in women who have a history of early onset (< 28 weeks) pre-eclampsia. Increased energy and protein intake are not beneficial in the prevention of gestational hypertension. Although *weight reduction* may be helpful in reducing BP in non-pregnant women, *it is not recommended during pregnancy* in obese women. Weight reduction can be associated with reduced neonatal weight and lower subsequent growth in infants of dieting obese mothers.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial, treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her blood pressure, lower pressure may impair uteroplacental perfusion and thereby jeopardize fetal development. Much of the uncertainty about the benefits of lowering blood pressure in pregnant women with mild pre-existing hypertension stems from published trials that are too small to detect a modest reduction in obstetrical complications.

Pharmacological management of hypertension in pregnancy

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus. SBP ≥ 170 or DBP ≥ 110 mmHg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential. Pharmacological treatment with intravenous labetalol, or oral methyldopa, or nifedipine is to be initiated. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs. Otherwise, the thresholds at which to start antihypertensive treatment are SBP of 140 mmHg or DBP of 90 mmHg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks' gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions of target organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. The thresholds in other circumstances are SBP of 150 mmHg and DBP of 95 mmHg. For non-severe hypertension,

methyldopa, labetalol, calcium antagonists and beta-blockers are drugs of choice. Beta-blockers appear to be less effective than calcium antagonists. Calcium-channel blockers are considered to be safe if they are not given concomitantly with magnesium sulfate (risk of hypotension due to potential synergism). ACE inhibitors and angiotensin II antagonists should not be used in pregnancy. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria. Magnesium sulfate intravenously is recommended for the prevention of eclampsia and the treatment of seizures.

Table 2. Antihypertensive drugs used in pregnancy

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors and angiotensin II antagonists. In women with pre-existing hypertension with DBP ≥ 100 mm Hg (lower when end-organ damage or underlying renal disease is present) and in women with acute hypertension (DBP ≥ 105 mmHg), the following agents are suggested:

Central alpha agonists	Methyldopa is the drug of choice.
Beta-blockers	Atenolol and metoprolol appear to be safe and effective in late pregnancy.
Alpha-/beta-blockers	Labetalol has comparable efficacy with methyldopa; in the case of severe hypertension, it could be given intravenously.
Calcium-channel blockers	Oral nifedipine or i.v. isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulfate may induce hypotension.
ACE inhibitors, angiotensin II antagonists	Fetal abnormalities including death can be caused and these drugs are contraindicated in pregnancy.
Diuretics	Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia.
Direct vasodilators	Hydralazine is no longer the parenteral drug of choice because of its perinatal adverse effects.

Delivery induction

Induction of delivery is appropriate in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities or fetal distress.

Hypertension and lactation

Breast-feeding does not increase BP in the nursing mother. Bromocriptin, which is used to suppress lactation, may induce hypertension. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine whose concentrations in breast milk are similar to those in maternal plasma.

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