REVIEW

Hypertensive disorders of pregnancy

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Abstract: Hypertension is a relatively common finding during pregnancy, complicating up to 10% of pregnancies and rank as the second most common cause of maternal death in developed countries. Hypertensive disorders of pregnancy represent an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia. The goal of blood pressure control in hypertensive pregnancy disorders is to reduce the risk of end-organ damage, the maternal and fetal morbidity and mortality. The aim of our study is to review the pathophysiology and management of hypertensive disorders of pregnancy, according to the current guidelines.
Keywords: hypertension, pregnancy, gestational hypertension, preeclampsia, eclampsia.

Rezumat: Hipertensiunea este o patologie întâlnită frecvent în sarcină, complicând până la 10% din sarcini, fiind a doua cauză de deces matern în țările dezvoltate. Tulburările hipertensive în sarcină reprezintă un termen umbrelă care include hipertensiunea preexistentă și hipertensiunea gestațională, preeclampsia și eclampsia. Scopul controlului tulburărilor hipertensive în sarcină este reducerea riscului afectării organelor țintă, dar și reducerea morbidității și mortalității materne și fetale. În acest studiu ne-am propus să prezentăm fiziopatologia și managementul terapeutic al tulburărilor hipertensive din sarcină, conform ghidurilor actuale.
Cuvinte cheie: hipertensiune, sarcină, hipertensiune gestațională, preeclampsie, eclampsie.

INTRODUCTION

Hypertensive disorders in pregnancy are the most common complications, affecting up to 10% of pregnancies. They represent a major cause of maternal and fetal morbidity and mortality worldwide, being associated with adverse maternal and fetal outcomes such as: placental abruption, stroke, multiple organ failure, and disseminated intravascular coagulation and also fetal high-risk of intrauterine growth retardation (25% of cases of preeclampsia), pre-maturity (27% of cases of pre-eclampsia), and intrauterine death (4% of cases of pre-eclampsia)[1,2].

DEFINITION AND CLASSIFICATION

The definition of hypertension in pregnancy has not always been standardized, but the most guidelines recommendations are currently a systolic blood pressure (SBP) ≥140mmHg and/or a diastolic blood pressure (DBP) ≥90mmHg, on two separate measurements (Table 1)[1,3-8]. According to the severity of hypertension, we may define two different categories:

- Non-severe hypertension: any values between SBP 140-159 mmHg and DBP 90-109 mmHg. Sometimes this category is further broken into mild (140-149/90-99 mmHg) and moderate (150-159/100-109 mmHg)[9].

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Table 1. Hypertension categories in pregnancy according to the current guidelines (adapted from 11)

	European Society of Cardiology (ESC)[1] 2018	American College of Obstetricians and Gynecologists (ACOG)[3] 2019	Hypertension Canada[4] 2018	International Society for the Study of Hypertension in Pregnancy (ISSHP)[6,7] 2018	Society of Obstetricians and Gynaecologists of Canada (SOGC)[5] 2014	Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)8 2014
Categories	Pre-existing hypertension Gestational hypertension Preeclampsia Pre-existing hypertension plus superimposed gestational hypertension with proteinuria Antenatally unclassifiable hypertension	Chronic Hypertension Preeclampsia-eclampsia Chronic hypertension with superimposed preeclampsia Gestational hypertension	Chronic hypertension Gestational hypertension Preeclampsia (includes non-severe preeclampsia, severe preeclampsia, HELLP syndrome, eclampsia)	Chronic hypertension - Essential - Secondary White-coat hypertension Masked hypertension Gestational hypertension Transient gestational hypertension Preeclampsia – *de novo* or superimposed on chronic hypertension	Pre-existing (chronic) hypertension - with comorbid condition(s) - with evidence of preeclampsia Gestational hypertension - with comorbid condition(s) - with evidence of preeclampsia Preeclampsia Other hypertensive effects - transient hypertensive effect - white-coat hypertensive effect - masked hypertensive effect	Preeclampsia - eclampsia Gestational hypertension Chronic hypertension - Essential - Secondary White Coat Preeclampsia superimposed on chronic hypertension
Definitions	**Hypertension:** SBP ≥140 mmHg and/or DBP ≥90 mmHg **Mild:** BP 140–159/90–109 mmHg **Severe:** SBP ≥160 mmHg or DBP ≥110 mmHg **Emergent:** SBP ≥170 mmHg or DBP ≥110 mmHg	**Hypertension:** SBP ≥140 mmHg and/or DBP ≥90 mmHg, measured at least 4h apart **Severe:** SBP ≥160 mmHg and/or DBP ≥110 mmHg, measured at least 4h apart	**Hypertension:** BP ≥140/90 mmHg **Severe:** BP ≥160/110 mmHg	**Hypertension:** SBP ≥140 mmHg and/or DBP ≥90 mmHg, confirmed over a few hours **Severe:** SBP ≥160 mmHg and/or DBP ≥110 mmHg, confirmed within 15min	**Hypertension:** SBP ≥140 mmHg and/or DBP ≥90 mmHg, measured at least 15min apart **Severe:** SBP ≥160 mmHg and/or DBP ≥110 mmHg	**Hypertension:** SBP ≥140 mmHg and/or DBP ≥90 mmHg measured several hours apart **Severe:** SBP ≥160 mmHg or DBP ≥110 mmHg

- Severe hypertension: SBP ≥160mmHg and/or DBP ≥110mmHg, which is associated with a high risk of hypertensive encephalopathy[10].

Based on the context in which the hypertension is first identified, all the international guidelines accept the following categories: chronic (pre-dating pregnancy or diagnosed before 20 weeks of pregnancy) or *de novo* (either preeclampsia or gestational hypertension)[1,3-8] (Table 2).

The ESC Guidelines suggest that gestational hypertension should resolve within 42 days postpartum, while other studies support the concept that pregnancy hypertension may persist for up to 12 weeks after delivery[1,17,18].

PATHOPHYSIOLOGY OF HYPERTENSION

Women over the age of 35 years, those of black or latin descent, with preexisting hypertension or with diabetes have a higher risk of hypertensive disorders of pregnancy[12,13]. All pregnant women should undergo routine measurement of blood pressure and urinalysis at check-ups in the gestational and postpartum period, regardless of baseline risk profile. All the hypertensive disorders of pregnancy can result in preeclampsia and eclampsia, but the underlying pathophysiology that upholds this transition is not well understood. It is thought to be related to a mechanism of reduced placental perfusion inducing systemic vascular endothelial dysfunction[14,15]. The placental hypoxia will induce a cascade of inflammatory events, disrupting the balance of angiogenic factors, and inducing platelet aggregation, all of them resulting in endothelial dysfunction manifested clinically as the preeclampsia syndrome[15,16]. Preeclampsia occurs in up to 35% of women with gestational hypertension and up to 25% of those with chronic hypertension[17,18]. Women that have a high or moderate risk of pre-eclampsia (Table 3) should take a dose of 100-150 mg aspirin daily from week 12 to week 36-37, according to the current European Guideline[1,16].

Calcium supplementation (1.5-2 g daily, orally) is recommended by the European Guideline for the prevention of pre-eclampsia only in women with a low dietary intake of calcium (<600 mg/day)[1].

Pravastatin may be a promising therapeutic for preeclampsia, but his role is currently under investigation, also considering that statins are currently contraindicated in pregnancy. Only small case series of preeclamptic women treated with pravastatin demonstrated amelioration of endothelial dysfunction and decrease in antiangiogenic biomarkers in placentas, and this benefit derives from their pleiotropic antioxidant, anti-inflammatory and antithrombotic effect[19,20].

TARGET BLOOD PRESSURE

The goal of blood pressure control in hypertensive pregnancy disorders is to reduce the risk of end-organ damage, which is generally low in chronic and gestational hypertension. On the other hand, patients with

Table 2. Classification of hypertensive disorders affecting pregnancy

Hypertensive disorder	Diagnostic
Chronic hypertension	Hypertension present prior to pregnancy, before the 20th week of gestation, or persisting after the 42nd postpartum day.
Gestational hypertension	Hypertension that develops after the 20th week of gestation, may be present with or without proteinuria, but with the absence of other systemic features of preeclampsia, resolves by 6th postpartum week.
Preeclampsia	Hypertension presenting after the 20th week of gestation with evidence of proteinuria or one of other markers of end-organ damage. • Proteinuria diagnosed with 300 mg of protein per 24-h urine or a urinary protein to creatinine ratio of greater than 0.3. A urine dipstick with 1+ protein grade is suggestive, but confirmatory protein studies are recommended. • In the absence of proteinuria, one of the following: platelet count below 100 000/μl, serum creatinine concentration of 1.1 mg/dl, or doubling of the serum creatinine in the absence of other renal disease, liver transaminases elevated to twice the normal concentration, pulmonary edema, cerebral or visual symptoms
Eclampsia	The presence of seizures in a patient with preeclampsia. Associated with life-threatening complications including pulmonary edema, abruptio placentae, liver failure, disseminated intravascular coagulopathy, and HELLP (hemolysis, elevated liver enzymes, and low platelets).
Preeclampsia/eclampsia superimposed on chronic hypertension	Hypertension present prior to pregnancy with development of preeclampsia/eclampsia after 20th week of gestation.
Postpartum hypertension	Hypertension persisting after delivery, or new diagnosis of hypertension in the 2 week to 6-months postpartum period in previously normotensive patients.

Table 3. Factors associated with risk of pre-eclampsia

High risk of pre-eclamsia (any of the following)	Moderate risk of pre-eclampsia (more that one of the following)
• hypertensive disease during a previous pregnancy; • chronic kidney disease; • autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome; • type 1 or type 2 diabetes; • chronic hypertension.	• first pregnancy; • age 40 years or older; • pregnancy interval of more than 10 years; • BMI of ≥35 kg/m^2 at first visit; • family history of pre-eclampsia; • multiple pregnancy.

preeclampsia/HELLP/eclampsia, have a high risk of maternal and fetal health and treatment goal is to optimize the timing of delivery, for safe outcomes of mother and fetus. There is no debate that blood pressure needs to be controlled to less than 160/110 mmHg, but how aggressively to treat non-severe hypertension remains controversial[1,3-8] (Table 4).

For patients with chronic hypertension or gestational hypertension, blood pressure treatment goals are around 140 mmHg/90 mmHg once blood pressure reaches systolic 150-160 mmHg or diastolic pressure of 100-105 mmHg[21,22]. However, excessive blood pressure lowering may present fetal harm due to placental hypoperfusion and reduction of blood pressure below 110/80 mmHg should be avoided[23].

In patients with preeclampsia without severe features, twice weekly maternal and fetal testing should be carried out from diagnosis until delivery for screening of severe preeclampsia/eclampsia such as headache, vision changes, epigastric pain or shortness of breath. In these patients are also recommended weekly laboratory testing (24-hour urine protein or protein/creatinine ratio, liver transaminases, serum creatinine, and complete blood count)[11].

In patients with severe preeclampsia, continuation of pregnancy has significant risk for mother (disseminated intravascular coagulopathy, renal or liver failure, acute respiratory distress syndrome, myocardial infarction or stroke) and the fetus (uteroplacental insufficiency or preterm birth)[24,25]. When severe preeclampsia, HELLP or eclampsia is diagnosed at the 24th gestation week, before fetal viability, some guidelines recommend delivery of the fetus after maternal stabilization[3]. In patients with severe hypertension without end-organ damage, blood pressure needs to be reduced to less than 160/110 mmHg, with an initial reduction of less than 25% in the first hours of treatment, and a more gradual decrease in the following hours. If

Table 4. Indications for hypertensive treatment in pregnancy according to the current guidelines (adapted from 11)

	European Society of Cardiology (ESC)[5] 2018	American College of Obstetricians and Gynecologists (ACOG)[3] 2019	Hypertension Canada[4] 2018	International Society for the Study of Hypertension in Pregnancy (ISSHP)[7,8] 2018	Society of Obstetricians and Gynaecologists of Canada (SOGC)[6] 2014	Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[9] 2014
Indications for treatment	Emergent: SBP ≥170 mmHg or DBP ≥110 mmHg Persistent elevation ≥150/95 mmHg >140/90 mmHg in women with gestational hypertension, pre-existing hypertension with superimposed gestational hypertension, subclinical organ damage or symptoms	Persistent SBP ≥160 mmHg and/or DBP ≥110 mmHg Comorbidities/ end-organ damage: >140/90 mmHg (per 2013 guidelines)	Any BP ≥140/90 mmHg Target to DBP 85 mmHg Urgent lowering: ≥160/110 mmHg	Urgent lowering: SBP ≥160 mmHg and/or DBP ≥110 mmHg If SBP ≥140 mmHg and/or DBP ≥90 mmHg lowering to a target DBP 85 mmHg and a target SBP <160 mmHg (optimal SBP 110-140 mmHg)	Severe: SBP ≥160 mmHg and/or DBP ≥110 mmHg Non-severe: Without comorbid conditions: 130-155/80-105 mmHg With comorbid conditions: <140/90 mmHg	>140-160/90-100 mmHg Urgent lowering: SBP ≥170 mmHg

hypertension is associated with end-organ complications (pulmonary edema or acute kidney injury), the blood pressure needs to be decreased much faster[18].

Magnesium sulfate is recommended for seizure prophylaxis in patients with preeclampsia with severe features (proteinuria or neurological complications) or eclampsia[3].

TREATMENT OF CHOICE FOR URGENT/SEVERE HYPERTENSION IN PREGNANCY

There are only few randomized clinical trials of antihypertensive medications in pregnancy[26,27]. The aim of treating severe hypertension is to prevent congestive heart failure, ischemic or hemorrhagic stroke, myocardial infarction and renal injury, and literature data suggests that antihypertensive therapy should be administered as soon as possible, preferably within 30-60 minutes. The three agents most commonly used for urgent blood pressure control in pregnancy are intravenous hydralazine or labetalol and nifedipine with immediate release. (Table 5)

Of these, labetalol is often considered a first-line agent due to fewer adverse side effects[28]. Use of i.v. urapidil can also be considered, as second line treatment, according to the *European Society of Cardiology Guideline*[1]. Sodium nitroprusside should only be used as the drug of last choice since prolonged treatment is associated with an increased risk of fetal cyanide toxicity, especially in women with impaired renal function[1,29]. Nitroglycerin, given as an i.v. infusion of 5 µg/min, and gradually increased every 3-5 min to a maximum dose of 100 µg/min is the drug of choice for patients with pre-eclampsia and pulmonary edema[1].

TREATMENT OF CHOICE FOR NON-SEVERE HYPERTENSION IN PREGNANCY

The most commonly used as first-line oral medication for the management of non-severe hypertension in pregnancy are methyldopa, labetalol and nifedipine. (Table 6) The central adrenergic inhibitor methyldopa has commonly used as first-line treatment. Because it has been associated with worsening of postpartum depression, some guidelines recommend discontinuation of the drug in the postpartum period[31,32]. Labetalol is a nonselective β-blocker with vascular α-receptor blocking

Table 5. The most commonly used antihypertensive drugs for urgent hypertension in pregnancy[3,30]

Drug	Dose	Comments	Onset of action
Labetalol	10-20 mg IV, then 20-80 mg every 10-30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1-2 mg/min IV	Tachycardia is less common and fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1-2 minutes
Hydralazine	5 mg IV or IM, then 5-10 mg IV every 20-40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5-10 mg/h	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings.	10-20 minutes
Nifedipine (immediate release)	10-20 mg orally, repeat in 20 minutes if needed; then 10-20 mg every 2-6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5-10 minutes

Table 6. Oral antihypertensive medications for non-severe hypertension in pregnancy[1,30]

Drug	Dose	Comments
Methyldopa	500–3,000 mg/day orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily.	May not be as effective for severe hypertension. Safety data up to 7.5 years post in utero exposure. Use limited by side effect profile (sedation, depression, dizziness).
Labetalol	200-2,400 mg/day orally in two to three divided doses. Commonly initiated at 100-200 mg twice daily.	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
Nifedipine (extended-release)	30–120 mg/day orally of an extended-release preparation. Commonly initiated at 30-60 mg once daily.	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia.
Hydrochlorothiazide	12.5-50 mg daily	Second-line or third-line agent. May cause intravascular volume depletion, use with caution.

ability, but some data suggest that it may be associated with small for gestation age infants[33]. Nifedipine is the most commonly used calcium channel blocker in pregnancy, with no adverse perinatal effects. Hydralazine and hydrochlorothiazide may also be used but as second line treatment for patients with non-severe hypertension, but only per ACOG and *Hypertension Canada Guidelines,* because they may worsen the hypovolemic state, leading to placental hypoperfusion[3,4]. Thiazide diuretics are not recommended by the other guidelines. Hydralazine may be also associated with hypospadias in the first trimester of pregnancy as well as thrombocytopenia and neonatal lupus-like syndrome in third trimester exposure. It may be considered to be co-administrated with a sympatholytic agent such as methyldopa or a beta-blocker[34,35].

All the guidelines contraindicate angiotensin-converting enzyme inhibitors and angiotensin receptor blockers throughout pregnancy due to risks of oligohydramnios, intrauterine growth restriction, hypocalvaria, renal dysplasia, anuria and neonatal death[36].

PROGNOSIS

About 29-57% of hypertensive disorders of pregnancy resolve within three days of delivery, 50-85% resolve by seven days of delivery and all pregnancy-associated hypertension, by definition, should resolve by the 42nd postpartum day (six weeks)[31,37]. In case that hypertension persists beyond the 6th postpartum week, workup for secondary hypertension and renovascular disease may be indicated.

Postpartum hypertension is common in the first week and methyldopa should be avoided because of the risk of depression. Most of the antihypertensive drugs are present at very low concentrations into breast milk, but drugs such as propranolol and nifedipine have breast milk concentrations similar to those in maternal plasma[1,38].

The occurrence of a hypertensive condition during pregnancy has implications for the woman in subsequent pregnancies and confers a higher lifetime risk of hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus[39,40]. In order to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk, lifestyle modifications, annual visits to a primary care physician to check blood pressure and metabolic factors are primarily recommended. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy[1].

CONCLUSIONS

Hypertensive disorders of pregnancy affect up to 10% pregnancies and have implications on maternal and fetal health. Despite the differences in current guidelines, there appears to be consensus that severe hypertension and non-severe hypertension with evidence of end-organ damage need to be controlled, and intravenous hydralazine, labetalol and immediate release nifedipine remain the drugs of choice. Methyldopa, labetalol and nifedipine (extended-release) are the most commonly accepted first-line agents for non-severe hypertension, while renin-angiotensin-aldosterone system inhibitors remain contraindicated. Management of hypertensive disorders in pregnancy requires increased surveillance and optimization of the timing of delivery, in order to reduce maternal and fetal complications.

Conflict of interest: none declared.

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