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REVIEW ARTICLE

Pharmacological treatment of acute severe hypertensives in Obstetrics: literature review

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Abstract

In obstetrics, hypertensive emergency is a critical state that merits the intervention of a multidisciplinary team that resolves the crisis, evaluates the well-being of the fetus, and performs adequate monitoring of the mother's organic function. This serious condition puts the binomial at vital risk, mortality and morbidity of both can be reduced if the appropriate use of antihypertensive drugs is used. This document reviews the pharmacological management of severe arterial hypertension at initial clinical presentation, generally in the emergency department and in intensive care.

Keywords: *Hypertensive emergency obstetrics. Severe hypertension. Anti-hypertensive treatment.*

Introduction

Hypertensive disorders of pregnancy (HDP) remain one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Affected women are also at increased risk for cardiovascular disease later in life, independently of traditional cardiovascular disease risks[1]. Affected women and newborns also have an increased risk of cardiovascular disease later in life, independent of traditional cardiovascular disease risks. Despite these risks, recommendations for optimal diagnosis and treatment have changed little in recent decades, probably due to fear of the fetal repercussions of decreased blood pressure (BP) and possible drug toxicity[2]. Gestational hypertension and pre-eclampsia without severe features can be managed with BP monitoring, laboratory testing for disease progression, antenatal testing for fetal well-being, and delivery at 37 weeks' gestation. The use of antihypertensive drugs to control non-severe hypertension in the setting of gestational hypertension and pre-eclampsia does not improve outcomes and is not recommended[3].

HDP can be classified into four groups depending on the onset of hypertension and the presence of target organ involvement: chronic hypertension, pre-eclampsia, gestational hypertension, and superimposed pre-eclampsia on chronic hypertension. Early diagnosis and proper treatment for pregnant women with hypertension remain a priority since this leads to improved maternal and fetal outcomes. Labetalol, nifedipine, methyldopa, and hydralazine are the preferred medications to treat hypertension during pregnancy[4].

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Despite major advances in the pharmacologic treatment of hypertension in the non-pregnant population, treatments for hypertension in pregnancy have remained largely unchanged over the years. There is recent evidence that a more adequate control of maternal BP is achieved when the first given antihypertensive drug is able to correct the underlying hemodynamic disorder of the mother besides normalizing the BP values[5]. In obstetrics, hypertensive emergency is defined as SBP BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg, confirmed 15 min apart[6].

Pregnant and postpartum women rarely need the involvement of intensivists in their care. When they do, it is crucial for their critical care physicians to be prepared to provide the best, most well-informed care by an interdisciplinary team including the obstetrician, maternal-fetal medicine specialist, anesthesiologist, and other relevant specialties. A fundamental knowledge of obstetric critical illness and specific aspects of maternal care and physiology is essential. This document reviews the pharmacological management of severe arterial hypertension at initial clinical presentation, generally in the emergency department and the intensive care unit.

Methods

The researchers met to organize the content of the manuscript to be discussed. The academic article was carried out including the keywords (Hyper tensive Emergency Obstetrics, Severe Hypertension, Anti-hypertensive treatment) were used with a time limit of 2014-2024. The PUBMED database returned 411 results, and the 34 most relevant that had a focus on were chosen, We eliminated results that contained topics unrelated to keywords and manuscript structure (treatment of hypertensive crisis according to the hemodynamic phenotype of pre-eclampsia or treatment goals according to the type of hypertensive emergency) The objective of the manuscript is not to carry out a systematic review, but to consult recent literature on the treatment of hypertensive emergency during pregnancy and the puerperium, giving the reader an overview of the ways to treat this very frequent clinical problem.

Definition

In pregnancy and the postpartum period, the diagnosis of hypertension is defined as SBP BP ≥ 140 mm Hg and/or a diastolic pressure ≥ 90 mm Hg in at least two readings more than 4 h apart. For non-obstetric providers in the urgent care and emergency setting, it is crucial for enhanced awareness of hypertension in pregnancy and the potential for late presentation in the postpartum setting[7].

Hypertensive emergency is a life-threatening pathology, characterized by a rapid increase in BP, exceeding the systolic value of 180 mmHg and/or diastolic value of 120 mmHg, associated with acute damage to one or more target organs[8]. Other situations with BP in severe ranges without damage to the target organ will be called episodes of severe acute uncontrolled hypertension[9]. Therefore, the elevation of BP alone (without the presence of damage to the target organ), does not define a hypertensive emergency; no matter how high the value of it may be[10]. There is consensus that a SBP BP ≥ 160 mmHg or a diastolic BP (DBP) ≥ 110 mmHg in an obstetric patient should be considered a hypertensive emergency and hospitalization is indicated[11], therefore the distinction between these two clinical entities is essential, due to the different approach and management. Hypertensive emergency will require immediate management and admission to the intensive care unit, while severe acute uncontrolled hypertension will generally not require admission and can be managed by initiating or intensifying previously prescribed antihypertensive treatment[12].

Initial approach

When we assist a hypertensive pregnant patient in the emergency department, it is important that the provider identify the disease process, presence of severe features, and initiate treatment to minimize symptoms and help prevent progression to eclampsia. It has been shown that prompt treatment within 30-60 min or as soon as reasonably possible can prevent serious fetal and maternal complications. Some organizations have recommended using SBP 140 mm Hg or DBP 90 mmHg as the threshold for initiation of antihypertensive medication. The degree to which the BP should be lowered is similarly debated, as there are mixed data regarding the BP level below which there may be a risk for placental hypoperfusion and growth restriction. First-line antihypertensive agents for the treatment of HDP are labetalol, nifedipine, hydralazine, and methyldopa[13].

The immediate therapeutic strategy for hypertensive emergency includes a brief history and physical examination, accompanied by paraclinical and cabinet studies, with early initiation of intravenous antihypertensive drugs being essential, respecting the goals of BP reduction and

the different specific treatment protocols for each etiology, to preserve organic perfusion; therefore, a personalized approach is justified to limit morbidity and mortality[14].

There are multiple routes for the administration of antihypertensive drugs; however, intravenous drugs are preferred due to their rapid onset of action and titration capacity (short half-life). A general objective could be the gradual and controlled reduction of BP by no more than 25% within the first 24 h, to avoid organic hypoperfusion, reaching normal BP levels between 24 and 48 h[15]. There are exceptions according to the type of injury to the target organ, sometimes requiring more or less aggressive approaches and management, such as hypertensive encephalopathy and pre-eclampsia; in which randomized trials have been carried out to arrive at a target BP, as well as for the choice of first-line drug, however, there are multiple factors that affect the combination of these results, such as the exclusion to a large extent of obstetric patients with extremely high BPs (systolic BP > 220 mmHg and/or diastolic BP > 110 mmHg), a situation of importance since taking the patient to the target BP goals established by most international obstetric protocols (systolic BP < 160 mmHg and/or diastolic BP < 110 mmHg), would be detrimental according to the theory of brain autoregulation. Therefore, a lot of emphasis should be placed on individualizing management according to the affected organic condition[16].

Antihypertensive treatment according to hemodynamic characteristics

The opinion on the mechanisms underlying the pathogenesis of pre-eclampsia still divides scientists and clinicians. This common complication of pregnancy has long been viewed as a disorder linked primarily to placental dysfunction, which is caused by abnormal trophoblast invasion, however, evidence from the previous two decades has triggered and supported a major shift in viewing pre-eclampsia as a condition that is caused by inherent maternal cardiovascular dysfunction, perhaps entirely independent of the placenta. In fact, abnormalities in the arterial and cardiac functions are evident from the early subclinical stages of pre-eclampsia and even before conception. Moving away from simply observing the peripheral BP changes, studies on the central hemodynamics reveal two different mechanisms of cardiovascular dysfunction thought to be reflective of the early-onset and late-onset phenotypes of pre-eclampsia. More recent evidence identified that the underlying cardiovascular dysfunction in these phenotypes can be categorized according to the presence of coexisting fetal growth restriction instead of according to the gestational period at onset, the former being far more common at early gestational ages[17]. Gestational hypertension and pre-eclampsia are the two main types of hypertensive disorders in pregnancy. Non-invasive maternal cardiovascular function assessment, which helps obtain information from all the components of circulation, has shown that venous hemodynamic dysfunction is a feature of pre-eclampsia but not of gestational hypertension. Venous congestion is a known cause of organ dysfunction, but its potential role in the pathophysiology of pre-eclampsia is currently poorly investigated. Body water volume expansion occurs in both gestational hypertension and pre-eclampsia, and this is associated with the common feature of new-onset hypertension after 20 weeks of gestation. BP, by definition, is the product of intravascular volume load and vascular resistance (Ohm's law). Fundamentally, hypertension may present as a spectrum of cardiovascular states varying between two extremes: one with a predominance of raised cardiac output and the other with a predominance of increased total peripheral resistance. In clinical practice, however, this bipolar nature of hypertension is rarely considered, despite the important implications for screening, prevention, management, and monitoring of disease[18].

However, there are identified various hemodynamic patterns dependent on gestational age at the time of diagnosis of pre-eclampsia, attributing a hemodynamic pattern with low cardiac output, increased peripheral vascular resistance, and a decrease in intravascular volume when the hypertensive state was diagnosed before 34 weeks of gestation (early-onset pre-eclampsia), and a hemodynamic pattern with increased cardiac output, decreased peripheral vascular resistance, and increased intravascular volume when the hypertensive state was diagnosed after 34 weeks of gestation (late-onset pre-eclampsia)[19].

However, in 2018 Tay et al. conducted a study including pregnant women diagnosed with pre-eclampsia between 24 and 40 weeks of gestation, adapting the hemodynamic patterns measured according to the gestational age of diagnosis of the hypertensive state, demonstrating that although early-onset and late-onset pre-eclampsia are considered different diseases, the hemodynamic characteristics of both were not related to gestational age, but these hemodynamic characteristics were strongly associated with the presence or

absence of fetal growth restriction (FHR), demonstrating a hemodynamic pattern with low cardiac output, increased peripheral vascular resistance and decreased intravascular volume in cases of pre-eclampsia associated with FHR and a hemodynamic pattern with increased cardiac output, decreased peripheral vascular resistance and increased intravascular volume in cases of pre-eclampsia without CRF, regardless of gestational age at diagnosis[20].

For this reason, it is essential to know not only the BP of the obstetric patient but also the cardiac output and systemic vascular resistance, parameters that can be obtained in real-time using a variety of non-invasive technological tools, such as Doppler ultrasound or impedance devices commonly used in operating rooms, emergency units, and critical care. Hemodynamic changes in women who eventually develop hypertensive complications are substantially different. Serial monitoring and plotting against developed normograms can identify women at risk and may allow timely intervention[21].

According Wang et al., Diltiazem is the most effective in reducing BP in pre-eclampsia patients; labetalol and nicardipine also had good effects. Diltiazem is preferred for the treatment of patients with severe hypertension[22].

According Bhat et al., oral calcium-channel blockers ranked highest for treatment success. Ketanserin achieved target BP fastest, warranting additional research[23].

Wu et al. demonstrated the superiority of oral nifedipine 50,60,90 mg, especially oral nifedipine 50 mg tablets, in the treatment of severe hypertension during pregnancy than IV labetalol 300 mg, while oral nifedipine 60,90 mg also showed superiority in the successful treatment rate of severe hypertension during pregnancy than IV hydralazine 15,25 mg[24]. Maternity care providers should feel comfortable initiating the management of severe hypertension in pregnancy using oral nifedipine, labetalol, and methyldopa[25,26].

Finally, the main goal of treatment in patients with hypertensive emergency in Obstetrics is to achieve hemodynamic stabilization of the patient, through BP reduction goals, but maintaining adequate organic perfusion, including placental perfusion, as well as preparing her for an eventual termination of pregnancy if she is still pregnant. Critically, ill patients during the postpartum period do not benefit from specific antihypertensive regimens. However, since the pregnant or postpartum patient can be critically complicated with organ dysfunctions at different levels, therapeutic options should also be taken into account according to the affected organ. Table 1 summarizes the treatments of choice for each situation.

Severe hypertensive crisis during pregnancy according to most international guidelines limits its treatment options to labetalol, nifedipine, hydralazine, and methyldopa, probably in that order of priority[27]. Once in the puerperal stage, the treatment options are wider, since there is no concern about placental perfusion that affects fetal hemodynamics. Acute increases of BP values are common causes of patients' presentation to emergency departments, and their management represents a clinical challenge. They are usually described as "hypertensive crises," "hypertensive urgencies," terms that should be abandoned because they are misleading and inappropriate according to a recent task force of the European Society of Cardiology, which recommended to focus only on "hypertensive emergencies." The latter can be easily identified using the brain, arteries, retina, kidney, and/or heart strategy as herein described[28]. Hypertensive emergencies and hypertensive urgencies are a frequent cause of access to emergency departments, with hypertensive urgencies being significantly more common. BP levels alone do not reliably predict the presence acute hypertension-mediated organ damage, which should be suspected according to the presenting signs and symptoms[29]. Despite the general consensus on outpatient BP management, guidance on inpatient management of elevated BP without symptoms is lacking, which may contribute to variable practice patterns[30]. Table 2 summarizes each possible option according hemodynamics patterns in pregnancy patients.

In the expert consensus of the Pan American Health Organization, it is concluded that regarding the choice of an antihypertensive drug for severe hypertension during pregnancy and its route of administration, the evidence is limited. Hydralazine, methyldopa, β-blockers (including labetalol), and nifedipine appear to be reasonable options until more evidence is available. The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium nitroprusside should be avoided for their safety in women who are still pregnant[31].

One of the largest systematic reviews in existence published by Abalos et al., out of 63 trials, which evaluated the effects of antihypertensive therapy versus placebo in patients with mild to moderate hypertension during pregnancy, noted that treating pregnant women with mild to moderate hypertension did not reduce the incidence of complications such as the development

Table 1. Hypertensive emergencies blood pressure goals and treatment options

Category	BP goal (mm Hg)	Treatment option	Usual dose
Acute ischemic stroke: Lytic or endovascular candidate	< 185/110 before treatment < 180/105 post-treatment	Nicardipine Labetalol Clevidipine	Start with 5 mg/h, can be increased every 15 min to 2.5 mg/h, maximum up to 15 mg/h in continuous infusion. Start with 10-20 mg bolus, the dose can be doubled every 30 min up to a maximum of 80 mg per bolus, it can also be used in infusion 0.5-2 mg/min. Starting with an infusion of 1-2 mg/h, the dose can be adjusted every 5-10 min, up to a maximum of 20 mg/h.
Acute ischemic stroke: non-candidate	< 220/110	Nicardipine Labetalol Clevidipine	Same dose
Intracerebral hemorrhage	SBP < 160	Nicardipine Labetalol Clevidipine	Same dose
Hypertensive encephalopathy	Rapid MAP reduction of 25% (1st h), then gradual over 24 h	Nicardipine Labetalol Clevidipine Nitroprusside	Nitroprusside: should be started very slowly with doses of 0.1 mcg/kg/min and increased every 3-5 min by 0.1 mcg/kg/min, up to a maximum of 10 mcg/kg/min. Monitor for cyanide toxicity as a metabolite of nitroprusside
Aortic dissection	SBP < 120 and heart rate ≤ 60 bpm	Esmolol Labetalol Nicardipine Clevidipine Nitroprusside	Esmolol hydrochloride, 250 mcg per kg is administered as a bolus, later infusion at a dose of 50-300 mcg kg min, the bolus can be repeated 5 to 10 minutes after the first dose. Rest of drugs at previously mentioned doses.
Acute pulmonary edema	Rapid MAP reduction of 25% (1st h), then gradual over 24 h	Nitrates and loop diuretics, nicardipine, urapidil, or even nitroprusside	Furosemide bolus of 20-40 mg in patients who have not previously used diuretics, in users of this drug it can be administered at 0.5-2 mg per kg. Urapidil 50 mg administered intravenously in 20 minutes, the dose can be repeated after 5 minutes if necessary, infusion: 5-50 mg/hour. Rest of drugs at previously mentioned doses.
Acute coronary ischemia	MAP reduction of 15-20% (1st h), then gradual over 24 h	Nitroglycerin, labetalol or esmolol, morphine as adjuvant.	Same dose
Pheochromocytoma	MAP reduction of 25%, then gradual over 24 h	Phentolamine clevidipine nicardipine	Phentolamine: intravenous 1-15 mg is usually given every 5-15 min. Maximum 15 mg. Rest of drugs at previously mentioned doses.
Eclampsia, HELLP syndrome	Generally BP < 160/110 within 60-180 min	Labetalol, nifedipine, hydralazine, metildopa nicardipine, clevidipine	Labetalol same dose IV, nifedipine 10 mg oral every 20-30 min, max 40 mg, Hydralazine 5-10 mg every 10-20 min, max 20 mg, Metildopa 1 g oral dose.

SBP: systolic blood pressure; MAP: mean arterial pressure.

of PE, pre-term birth or maternal and fetal mortality, however, a decrease in the occurrence of severe hypertension was observed in the treated patients[32].

Finally, most guidelines and consensus recommend the use of β blockers and calcium channel blockers as first-line agents for the treatment of hypertension.

Labetalol, thanks to its mixed α and β-adrenergic blocking effect, is the most commonly used and has been shown to be safe. Pindolol and metoprolol are less studied but their use is considered acceptable as an alternative. Atenolol should be avoided during pregnancy as it is associated with fetal growth restriction and low birth weight.

Nifedipine extended-release has the advantage of acting faster and being easier to administer than labetalol.

Table 2. Summarizes the hemodynamic patterns that have been identified and the most beneficial treatment for these circulatory characteristics

Cardiovascular parameter	Low cardiac output and high vascular resistance phenotype	High cardiac output and low vascular resistance phenotype
Maternal heart rate	< 70 bpm Calcium channel blockers (e.g., nifedipine) Nitric Oxide (NO) donors and fluids.	90 bpm α- and β-blockers (e.g., α methyldopa, labetalol) preferred
Cardiac output	< 5 L/min Calcium channel blockers (e.g., nifedipine), NO donors, and fluids. (early-onset pre-eclampsia).	> 8 L/min α- and β-blockers (e.g., α methyldopa, labetalol) (late-onset pre-eclampsia)
Systemic vascular resistance	> 1400 dynes.s.cm 5 Calcium channel blockers (e.g., nifedipine), NO donors, and fluids (early-onset pre-eclampsia)	< 900 dynes.s.cm 5 α- and β-blockers (e.g., α methyldopa, labetalol) (late-onset pre-eclampsia)

Alpha-methyldopa has been widely used in pregnant women and with a safety record in follow-up for decades.

The second line of treatment includes thiazide diuretics and hydralazine. The use of thiazide diuretics may be associated with a significant decrease in volume, so close monitoring is recommended as it could affect amniotic fluid volume and fetal growth.

Hydralazine may cause associated side effects, including hypotension, headache, tremors, and edema. In addition, it can cause episodes of extreme hypotension, which could lead to adverse effects, both maternal and fetal[33].

Other agents, such as clonidine, are considered third-line. The use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists are contraindicated in pregnancy due to teratogenic effects, fetal renal abnormalities and failure, fetal growth restriction, malformations, and death, but can be used relatively safely during the postpartum period. In women with chronic salt-sensitive hypertension or chronic kidney disease and reduced glomerular filtration rate, diuretics can be used safely, although perhaps in lower doses, recent studies show that they can be very useful and effective in postpartum hypertension[34].

Conclusion

Hypertensive emergency should be evaluated conscientiously, taking into consideration the hemodynamic phenotype, as well as the type of organic emergency. Several trials and systematic reviews have shown that treating mild to moderate hypertension does not benefit the mother or the gestational product in morbidity or mortality; however, it reduces the occurrence of severe hypertension, which is ultimately beneficial. In pregnant patients, treatment options are generally limited to labetalol, nifedipine, hydralazine, and methyldopa, with the first two options being the first-line options, however, once pregnancy is over, it can be treated with the same options as non-obstetric patients. Reliably assessing the hemodynamic phenotype of a patient with hypertensive emergency will be limited to access to certain material and personnel resources in health care units.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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