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Management of high blood pressure during all-trimesters of pregnancy

Tratamiento de la hipertensión arterial durante todos los trimestres del embarazo

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ABSTRACT

High blood pressure (HBP) disorders of pregnancy are one of the leading causes of morbidity during pregnancy along with maternal-fetal mortality in developing countries. In this work, we discuss the physiopathology, diagnostic assessment, and treatment and prevention strategies focused on diminishing the burden of hypertensive disorders of pregnancy at all-care levels. Most of the current guidelines encourage to perform an adequate assessment in every woman living with chronic HBP prior to pregnancy. Preeclampsia stands for a multisystemic, multifactorial, dynamic, and progressive disease that could appear at any gestation week. Furthermore, an adequate assessment of any hypertensive disorder of pregnancy is needed to prevent acute and long-term complications related these diseases. Pharmacological management should be based on clinical manifestations at the moment of evaluation. All woman with hypertensive disorder during pregnancy had an increased cardiovascular risk, therefore, continuous follow-up management is highly recommended.

RESUMEN

Los trastornos de hipertensión arterial (HTA) en el embarazo son una de las principales causas de morbilidad durante el mismo, junto con la mortalidad materno-fetal en los países en desarrollo. En este trabajo se analiza la fisiopatología, la evaluación diagnóstica y las estrategias de tratamiento y prevención enfocadas a disminuir la carga de los trastornos hipertensivos del embarazo en todos los niveles asistenciales. La mayoría de las directrices actuales animan a realizar una evaluación adecuada en todas las mujeres que viven con HTA crónica antes del embarazo. La preeclampsia es una enfermedad multisistémica, multifactorial, dinámica y progresiva que puede aparecer en cualquier semana de gestación. Además, es necesario realizar una evaluación adecuada de cualquier trastorno hipertensivo del embarazo para prevenir las complicaciones agudas y a largo plazo relacionadas con estas enfermedades. El tratamiento farmacológico debe basarse en las manifestaciones clínicas en el momento de la evaluación. Todas las mujeres con trastorno hipertensivo durante el embarazo tienen un mayor riesgo cardiovascular, por lo que se recomienda un seguimiento continuo.

INTRODUCTION

High blood pressure (HBP) disorders of pregnancy are one of the leading causes of morbidity during pregnancy and maternal and fetal mortality in developing countries. Its estimated incidence during pregnancy is 7.5%, and it further increased up to 15.3% within women coursing its first pregnancy or with chronic health comorbidities, such as obesity, diabetes, and metabolic syndrome.[1,2] The European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American College of Ginecobsetry (ACOG) agreed that a standardized definition of HBP during pregnancy is a measured blood pressure ≥ 140/90 mmHg.[3-5] The proposed threshold is higher than the one proposed by the ACC and American Heart Association (AHA) to diagnose stage 1 HBP (≥ 130/80 mmHg), which has been demonstrated to be an optimal cut-off value to reduce the incidence of cardiovascular disease at long-term follow-up.[4] This work discusses the physiopathology, diagnostic assessment, and treatment and prevention strategies focused on diminishing the burden of hypertensive disorders of pregnancy at all-care levels.

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Physiopathology of hypertensive disorders of pregnancy

There have been described mixed physiological changes within the cardiovascular system during pregnancy, including a decrease in systemic vascular and increased plasmatic and cardiac volume output. Moreover, other physiological metabolic changes during pregnancy include increased insulin resistance, hypercoagulative state, and increased serum cholesterol and triglycerides production. Other changes that have been described related to the cardiovascular system include an increase in 50% renal and glomerular filtration rate. All these changes lead to a rise in blood pressure within each trimester of pregnancy and an augmented risk of hypertensive disorders of pregnancy.[1,2]

There has been a hypothesis to elucidate the real physiopathology of hypertensive disorders of pregnancy. The most accepted theories mention that an abnormal cytotrophoblast invasion within spiral arteries decreases utero-placenta blood perfusion. Thus, leading to an inflammatory cascade in a chain reaction, with a disrupted balance of angiogenic factors, plaquetary aggregation, and overall endothelial dysfunction.[1,6] Nevertheless, there are still unknown genetic, metabolic, and physiological pathways that need further study. Classification of hypertensive disorders of pregnancy are presented in *Table 1*.

Assessment of blood pressure during pregnancy

An adequate blood pressure assessment in the early stages of pregnancy is fundamental. Before the measurement is taken, the patient must be perfectly calmed and ideally situated in a comfortable chair. The sphygmomanometer must be certified and calibrated according to the user manual before any assessment. Therefore, the clinician or healthcare professional must proceed to assess the blood pressure. In case there are extreme measurements (systolic $\geq$ 160 or $\geq$ 110 mmHg diastolic), the whole procedure must be repeated after 15 minutes. Finally, all women should perform a self-measured blood pressure assessment within patients with previous HBP diagnoses or whether the patient had inadequate pregnancy control. Furthermore, self-monitory could mitigate the «white-coat» effect during clinical visits.

Prevention of preeclampsia

It has been described that in women with a healthy lifestyle before pregnancy have a decreased risk of hypertensive disorders during pregnancy. Therefore, all women without evident contraindications should be encouraged to perform any type of exercise routine and be guided to change their diet patterns to achieve their ideal body weight composition even before pregnancy. Additionally, dietary recommendations include folic acid and calcium supplementation. Whether in women who have been already identified with preeclampsia or with two moderate risk factors, it is then recommended to prescribe a 100-1,500 mg acetylsalicylic acid dose during nights starting at the 12-16 week up to the 36 weeks of gestation.

Assessment on previous high blood pressure

Based on the current evidence, we encouraged that all women living with HBP needs to be submitted to a prompt medical evaluation with the objective to identify target-organ damage, need of additional clinical assessment, promote life-style changes, and give appropriate counseling about chronic HBP impairments during pregnancy. Additionally, this group need to be assessed regarding hazardous pharmacological regimes such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), renin-based and anti-aldosterone antihypertensives.[5,7] It is highly recommended that both a complete medical history and physical examination, along with target-organ assessment and biochemical evaluation should be made in every woman prior to pregnancy and at the diagnosis of pregnancy. Finally, for women with significant changes in blood pressure, or which arrived with signs of preeclampsia, it is mandatory to had a biochemical evaluation to exclude target-organ damage and a further evaluation on the fetal condition with an obstetric echocardiography with umbilical Doppler assessment.[2,5,8] Clinical risk factors are presented in *Table 2*.

Table 1: Classification of high blood pressure disorders.*

Disorder	Definition
Before pregnancy or < 20 weeks of gestation	
Chronic arterial high blood pressure	Detected high blood pressure before pregnancy or before 20 weeks of gestation
Essential	Arterial high blood pressure unknown cause
Secondary arterial high blood pressure	Arterial high blood pressure due to secondary cause
«White-coat» high blood pressure	SBP > 140 and/or DBP > 90 measured in the office/hospital, and pressure < 135/85 using ABPM or MPAC
Masked arterial high blood pressure	BP < 140/90 in the office/hospital and > 135/85 outside the office/hospital
≥ 20 weeks of gestation	
Gestational high blood pressure	*De novo* high blood pressure > 20 weeks' gestation in the absence of proteinuria and PE
Transient gestational high blood pressure	Arterial high blood pressure after 20 weeks of gestation, which disappears in subsequent shots of the BP
Pre-eclampsia *de novo*	PE *(de novo)* is gestational high blood pressure accompanied by one or more of the following conditions: — Proteinuria: protein/creatinine ratio (PrCr) in a urine sample > 30 mg/mmol, or albumin/creatinine (ACR) > 8 mg/mmol, or > 300 mg in 24-hour urine, or > 2+ in urine on dipstick if other tests are not available — Target organ dysfunction: • Neurological complications (eclampsia, headache, stroke, altered state of consciousness, scotomata) • Pulmonary edema • Hematological compromise: Hemolysis, platelets < 150,000) • Renal compromise: Creatinine > 1 mg/dL • Liver compromise (transaminases > 40 IU/L) with or without epigastric or right upper quadrant pain — Utero-placental dysfunction (abruption, fetal growth restriction, altered umbilical artery Doppler, fetal death
Pre-eclampsia with chronic high blood pressure	Women with chronic high blood pressure who develop proteinuria, maternal organ dysfunction or utero-placental dysfunction

*International Society for the Study of Hypertension in Pregnancy (ISSHP) classification.
SBP = systolic blood pressure, DBP = diastolic arterial pressure, ABPM = ambulatory blood pressure monitoring, HBPM = home blood pressure monitoring, PE = pre-eclampsia, BP = blood pressure.
Modified from: American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics.[7]

Management of high blood pressure during pregnancy

Management should be guided based on clinical and severity manifestations for any hypertensive disorders during pregnancy. It its highly recommended that all patients diagnosed with gestational HBP or with preeclampsia needs to be hospitalized. This recommendation guarantees a prompt evaluation of the fetal condition, an adequate stabilization of blood pressure and the creation of an appropriate follow-up clinical management.[2,5]

Different clinical societies have proposed different blood pressure thresholds to begin pharmacological treatment. The ACOG encourages to begin antihypertensive therapy whether clinicians identify persistent blood pressure over ≥ 160/110 mmHg. Moreover, the ACOG mentions that an ideal blood pressure goal is a systolic blood pressure between 120 to 160 mmHg while having a diastolic

blood pressure between 80 to 110 mmHg within coexistent comorbidities.[7] Conversely, diverse clinical societies, including the ESC have recommended to begin pharmacological management to every pregnant woman with blood pressure > 140/90 mmHg.[6,8,9] Furthermore, the same ESC encourages to treat every immediately every woman with the previously mentioned threshold and with gestational HBP, chronic HBP, preeclampsia or with evidence of target-organ damage. The accepted goals proposed by diverse societies is a blood pressure < 130/80 mmHg.[1,6,8-10] The International Society for the Study of Hypertension in Pregnancy (ISSHP) specifies that an ideal goal, regardless of systolic blood pressure, is a diastolic blood pressure < 85 mmHg.[11]

It has been reported that non-severe presentations of hypertensive disorders during pregnancy could be treated with first line oral pharmacological approaches, such as labetalol, nifedipine and methyldopa.[2,11,12] Conversely, women with urgent hypertensive crisis (defines as systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg) should be immediately treated and maintained with intravenous antihypertensives enlisted in *Table 3*.[5,8,11] The optimal goal within urgent hypertensive crisis is grounded on a blood pressure < 150/100 mmHg without triggering secondary hypotension or compromising utero-placenta blood perfusion. Finally, the ESC has recommended the use of use of nitroglycerin in cases with secondary edema due to preeclampsia, and in a last resourse, the use of sodium nitroprusside. Nevertheless, it should be monitored given the risk of fetal cyanuric intoxication.[2]

A cost-benefit should be performed between the risk of preterm labor and the maternal integrity to continue with pregnancy. It has been mentioned that within cases below the 34th gestational week, delivery should be guided in a close in-hospital surveillance setting to implement corticosteroids to accelerate fetal lung maturation along with an integral medical evaluation. The same recommendations are encouraged within cases between the 34th-37th gestational week.[5,6,12] Finally, immediate labor should be started in cases with severe neurological manifestations, uncontrolled HBP with ≥ 3 antihypertensives, incident pulmonary edema, progressive thrombocytopenia, transfusion requirements, abnormal creatinine, increased liver enzymes, or a severe fetal compromise.[11]

Management at delivery

All women should be advised regarding signs and symptoms of preeclampsia. Additionally,

Table 2: Clinical risk factors for PE.

	High risk factors	Moderate risk factor
Previous history	Previous preeclampsia	Placental abruption fetal growth restriction fetal death family history of PE (first degree)
Demography	BMI before pregnancy > 30 kg/m^2	Maternal age > 35 years Black race Low socioeconomic status
Previous medical conditions	Chronic high blood pressure Mellitus diabetes Chronic kidney disease Antiphospholipid syndrome	
Current gestation	Assisted reproductive therapy Multiple pregnancy	Nulliparity

PE = preeclampsia, BMI = body mass index, SLE = systemic lupus erythematosus.
Modified from: Braunthal S et al.[1] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics.[7]

Table 3: Antihypertensive treatment for urgent control in severe arterial hypertension.

Medication	Dose	Comment	Onset of action (minutes)
Labetalol	10-20 mg IV, followed by 20-80 mg every 10-30 minutes to a maximum cumulative dose of 300 mg, or 1-2 mg/min IV infusion	Avoid in women with asthma, myocardial disease, decompensated heart failure, advanced heart block, and bradycardia	1-2
Hydralazine	5 mg IV or IM, then 5-10 mg IV every 20-40 minutes up to a maximum cumulative dose of 20 mg, or infusion of 0.5-10 mg/hour	Higher or more frequent doses are associated with maternal hypotension, headache, and abnormal fetal heart rate tracing	10-20
Oral nifedipine (immediate release)	10-20 mg PO, repeat in 20 minutes, if necessary, then 10-20 mg every 2-6 hours, maximum daily dose 180 mg	Reflex tachycardia and headache as secondary effects	5-10

IM = intramuscular; IV = intravenous; PO = orally.

women living with hypertensive disorders during pregnancy and with uncontrolled blood pressure require close surveillance between 3-7 days. During the postpartum period, contraindicated medications like AICE inhibitors could be restarted. Advise of adverse effects of antihypertensives during lactation should be warranted. Finally, methyldopa should be avoided at postpartum due to the risk of depression and sedation.[3,11,12]

Follow-up and cardiovascular risk: fourth trimester (lifetime)

After childbirth, a «fourth trimester» begins. This term refers to the rest of the woman's life after pregnancy.[13] Women with a history of hypertensive disorders during pregnancy have 4% increased risk of gestational HBP or at least 15% more risk of preeclampsia in future pregnancies. The ISSHP recommends:

1. Three months after delivery, all women should be assessed with blood pressure measurements, urinalysis, and biochemical evaluation.
2. Six months after delivery, all women should also be reassessed whether possible.
3. Continuous assessment of cardiovascular risk throughout all life should be made in all women.
4. After any hypertensive disorders of pregnancy, all women and their children should adopt healthy lifestyles. These includes a healthy diet, regular exercise, ideal weight, no exposure to tobacco or smoke, and a blood pressure < 120/80 mmHg.[11]

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