HYPERTENSION IN PREGNANCY: DIAGNOSIS, BLOOD PRESSURE GOALS, AND PHARMACOTHERAPY

A Scientific Statement from the American Heart Foundation

AUTHORS

Vesna D. Garovic, MD, PhD, Chair; Ralf Dechend, MD; Thomas Easterling, MD; S. Ananth Karumanchi, MD; Suzanne McMurtry Baird, DNP, RN; Laura A. Magee, MD, FRCPC; Sarosh Rana, MD, MPH; Jane V. Vermunt, MBChB, MSc; Phyllis August, MD, MPH, Vice Chair.

On behalf of the American Heart Association Council on Hypertension, Council on the Kidney in Cardiovascular Disease Science Subcommittee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Lifestyle and Cardiometabolic Health, Council on Peripheral Vascular Disease, and Stroke Council

Slides prepared by members of the writing group
Contact: Dr Vesna D. Garovic
Professor and chair of Nephrology, Mayo Clinic, Rochester, Minnesota

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HYPERTENSIVE DISORDERS OF PREGNANCY

American College of Obstetricians and Gynecologists definitions for Hypertensive Disorders of Pregnancy

Hypertension in pregnancy	Systolic BP ≥140, or diastolic BP ≥ 90 mm Hg, or both measured on 2 occasions at least 4 hours apart
Severe-range hypertension	Systolic BP ≥160, or diastolic BP ≥110 mm Hg, or both measured on 2 occasions at least 4 hours apart (unless antihypertensive therapy initiated before this time)
Chronic hypertension	Hypertension diagnosed or present before pregnancy, or before 20 weeks of gestation; or hypertension that is diagnosed for the first-time during pregnancy and that does not resolve in the postpartum period
Gestational hypertension	Hypertension diagnosed after 20 weeks of gestation and a previously normal BP
Chronic hypertension with superimposed preeclampsia	Preeclampsia in a woman with a history of hypertension before pregnancy, or before 20 weeks of gestation
Preeclampsia	Hypertension in pregnancy >20 weeks of gestation and previously normal BP or severe range hypertension, in addition to at least 1 of the following: • Proteinuria (≥300 mg/24-hour urine, or PCR ≥0.3, or dipstick 2+ only if other quantitative methods not available) • Renal insufficiency (creatinine > 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease) • Thrombocytopenia (<100× 10^9/L) • Impaired liver function (ALT/AST ≥ 2x upper limit of normal) • Pulmonary edema • New-onset headache or visual disturbances (not due to alternative diagnoses)
Preeclampsia with severe features	• Severe range hypertension (Systolic BP ≥160, or diastolic BP ≥110 mm Hg, or both) • Renal insufficiency (creatinine > 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease) • Thrombocytopenia (<100× 10^9/L) • Impaired liver function (ALT/AST ≥ 2x upper limit of normal) • Severe persistent right upper quadrant or epigastric pain unresponsive to medications • Pulmonary edema • New-onset headache or visual disturbances (not due to alternative diagnoses)

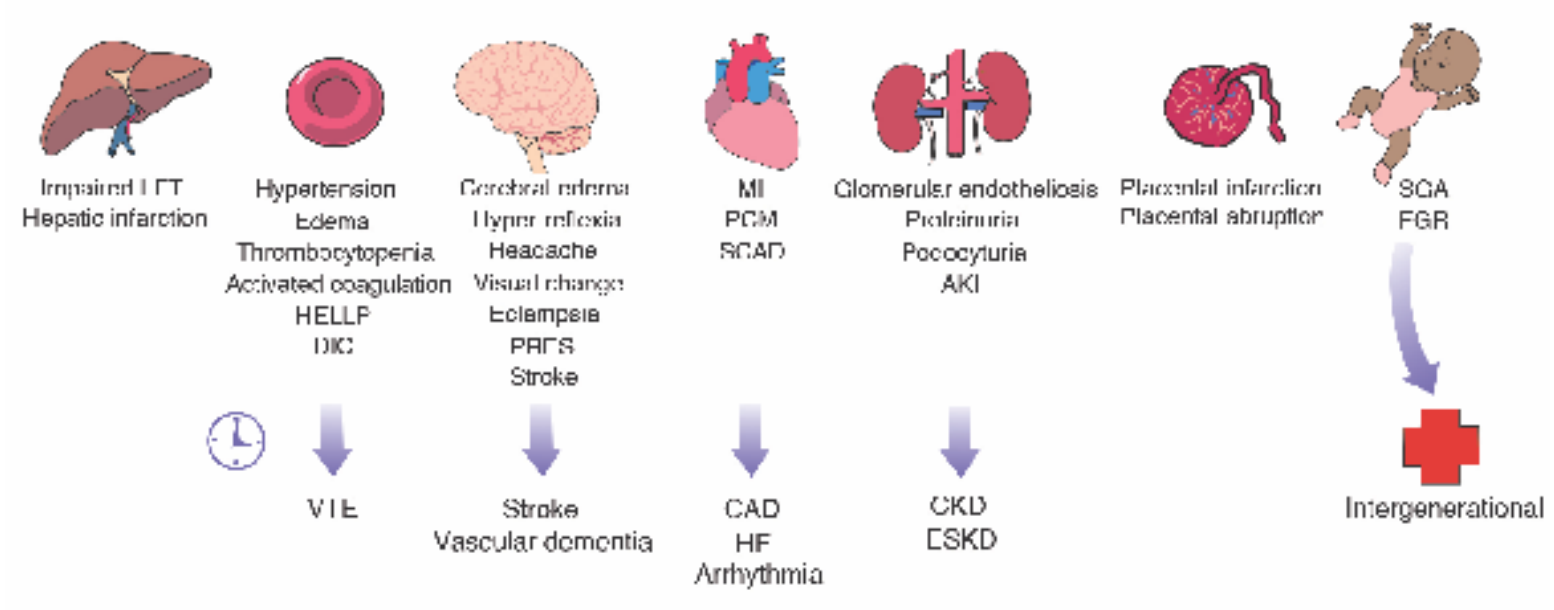
EPIDEMIOLOGY

EPIDEMIOLOGY

- Hypertensive disorders of pregnancy are the second leading cause of global maternal mortality (behind maternal hemorrhage).
- 15% of women will be affected by hypertensive disorders of pregnancy.
- Per-women incidence (15%) predicts the number of women at risk for future CVD based on their reproductive histories. Per-pregnancy incidence (7.5%), underestimates the number of women affected.

EPIDEMIOLOGY

- Hypertensive disorders of pregnancy are a significant cause of short and long term maternal and fetal complications



LFT = liver function tests, DIC = disseminated intravascular coagulation, VTE = venous thromboembolism, PRES = Posterior Reversible Encephalopathy Syndrome, MI = myocardial infarction, PCM = peripartum cardiomyopathy, SCAD = spontaneous coronary artery dissection, CAD = coronary artery disease, HF = heart failure, AKI = acute kidney injury, CKD = chronic kidney disease, ESRF = end stage renal failure, SGA = small for gestational age, FGR = fetal growth restriction

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FETAL OUTCOMES

SHORT TERM

- Small for gestational age (birth weight <10th centile)
- Still birth
- Preterm delivery (<37 weeks)
- Preterm delivery (<34 weeks)
- Placental abruption

LONG TERM

- Cardiovascular disease
- Stroke
- Increased BMI
- Hypertension (≥140/90 mm Hg)

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MATERNAL OUTCOMES

SHORT TERM

- Mortality
- Myocardial infarction
- Stroke
- Peripartum cardiomyopathy
- Spontaneous coronary artery dissection

LONG TERM

- Hypertension (≥140/90 mm Hg)
- Type 2 diabetes
- Hyperlipidemia
- Sub-clinical markers of vascular damage

- Cardiovascular disease
- Coronary heart disease
- Heart failure
- Atrial fibrillation
- Stroke
- Vascular dementia
- Chronic kidney disease
- End stage kidney disease
- Venous thromboembolism

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LONG TERM MATERNAL MORBIDITY

Hypertension

- Develops more frequently among women with a history of hypertensive disorders of pregnancy
- Develops faster; diagnosed up to 10 years earlier compared to women with normotensive pregnancies, though the precise timing requires further examination.

Other cardio-metabolic risk factors (type 2 diabetes, hyperlipidemia, sub-clinical markers of vascular damage) and CVD events occur earlier.

Rates of chronic condition accumulation and multi-morbidity are higher.

- Supportive of the thesis of accelerated aging among women with a history of HDP

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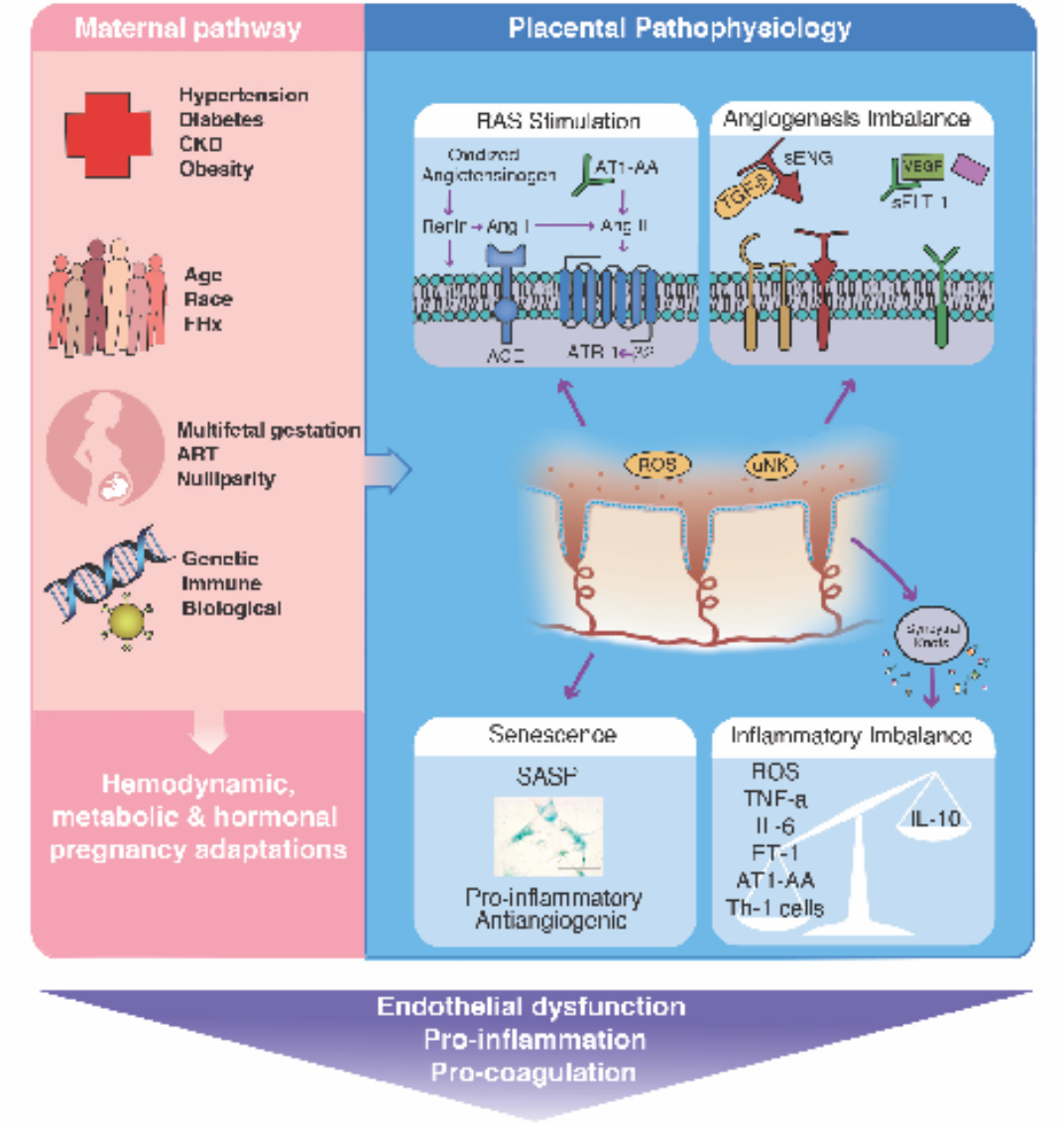
PATHOPHYSIOLOGY

PATHOPHYSIOLOGY OF HYPERTENSIVE DISORDERS OF PREGNANCY



ETIOLOGY

- Likely a combination of, and interaction between, factors from both maternal and placental pathways. Variable contributions of these pathways result in the heterogeneous phenotypes of hypertensive disorders of pregnancy.

- The subsequent widespread endovascular damage and dysfunction may be long-lasting with a possible intergenerational effect.

CKD, chronic kidney disease; FHx, family history; RAS, renin angiotensin system; AT1-AA, angiotensin II receptor 1 autoantibodies; Ang I, Angiotensin I; Ang II, Angiotensin II; ACE, Angiotensin converting enzyme; ATR1, Angiotensin II type 1 receptor; TGF-β, transforming growth factor beta; sENG, soluble endoglin; VEGF, vascular endothelial growth factor; sFlt1, soluble fms-like tyrosine kinase 1; ROS, reactive oxygen species; uNK, uterine natural killer cell; SASP, senescence-associated secretory phenotype; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; ET-1, endothelin-1; AT1-AA, Angiotensin II type 1-Receptor Autoantibody ; Th-1, Type 1 T helper cell; Th-1, Type 1 T helper cell; IL-10, Interleukin 10.

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PREVENTION

LONG TERM MATERNAL MORBIDITY

PRECONCEPTION

- Health education to improve cardiometabolic profile

DURING PREGNANCY

- Dietary interventions to reduce maternal gestational weight gain
- Exercise
- Low dose aspirin
- ? Metformin
- ? Statins

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BLOOD PRESSURE MEASUREMENTS

BLOOD PRESSURE MEASUREMENT IN PREGNANCY

- While most guidelines recommend hypertension management be based on office blood pressures in pregnancy, for the general population, out of office measurements are widely endorsed as more accurate and a better predictor of cardiovascular morbidity and mortality.

- Available information does not demonstrate a systematic difference between self and office measurements in pregnancy, which suggests appropriate treatment and diagnostic thresholds for self-monitoring during pregnancy may be equivalent to standard clinic thresholds.

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TYPES OF HYPERTENSION

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NON-SUSTAINED HYPERTENSION

- White coat hypertension
  - Not extensively studied
  - Meta-analysis reports increased risks of preeclampsia and adverse fetal outcomes compared to women with normotension

- Self-measured BP is important for diagnosing non-sustained BP elevations, including masked hypertension and white coat hypertension which occur prior to 20 weeks of gestation

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TYPES OF HYPERTENSION

BLOOD PRESSURE VARIATION

- Limited small studies of gestational short-term and visit-to-visit blood pressure variation suggest that greater variation is associated with adverse maternal and perinatal outcomes.

- There is a need for consensus regarding the methodology for the measurement of BP variability in pregnancy.

- Standard gestational age-specific blood pressures and centiles can assist in clinical interpretation of blood pressure changes from expected levels.

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TYPES OF HYPERTENSION

SECONDARY HYPERTENSION

- May occur in a small proportion of women and is associated with worse maternal and fetal outcomes
- Consider if:
  - Maternal age is <35 years
  - Hypertension is severe or resistant
  - There is no family history of hypertension
  - Suggestive laboratory features, such as hypokalemia, elevated creatinine, or albuminuria early in pregnancy

- Etiology
  - Chronic kidney disease
  - Primary Hyperaldosteronism
  - Renovascular hypertension
  - Pheochromocytoma
  - Cushing's Disease
  - Obstructive Sleep Apnea

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TYPES OF HYPERTENSION

POST PARTUM HYPERTENSION AND PREECLAMPSIA

- Increasing awareness of their significance. ~60% of all maternal deaths occur within the first year postpartum, and HDP remain one of the leading causes of maternal mortality.

- Prevalence of postpartum hypertension in women without antepartum hypertension may be as high as 8% (between 48 hours after delivery and up to 6 weeks postpartum), and up to 50% in women with a history of preeclampsia (6-12 weeks post-delivery).

- Intravenous fluids, mobilization of extravascular fluid and use of nonsteroidal anti-inflammatory drugs for postpartum analgesia may contribute to its occurrence.

- Postpartum hypertension offers an opportunity to use medications and achieve blood pressure goals without limitations related to their potential negative impacts on the fetus.

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BLOOD PRESSURE TREATMENT THRESHOLDS AND THERAPEUTIC TARGETS

CURRENT BLOOD PRESSURE GUIDELINES

NON-PREGNANT PATIENTS

- Stage 1 hypertension = 130/80 mm Hg, stage 2 hypertension = 140/90 mm Hg

PREGNANT PATIENTS

- For all hypertensive disorders of pregnancy, hypertension is internationally defined as ≥140/90 mm Hg, though treatment thresholds and therapeutic targets vary.
- Must balance prevention of maternal hypertensive complications and avoidance of fetal risks.
- The American College of Obstetricians and Gynecologists recommend antihypertensive therapy for women with:
  - Preeclampsia and a sustained systolic BP ≥160 mm Hg and/or diastolic BP ≥110 mm Hg
  - Chronic hypertension at a systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg
  - Treatment goal of 120-160/80-110 mm Hg.

- Internationally, most hypertension societies endorse a more aggressive approach for antihypertensive treatment, recommending therapy at ≥140/90 mm Hg. Therapeutic targets similar to the ACC/AHA target of 130/80 mm Hg are recommended by the International Society for the Study of Hypertension in Pregnancy, Hypertension Canada Guidelines, the United Kingdom National Institute for Health and Care Excellence, and the World Health Organisation.

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BLOOD PRESSURE GUIDELINES

Why are the blood pressure treatment thresholds and targets higher in the U.S. compared to those recommended for non-pregnant individuals and, in comparison to most international guidelines addressing HDP?

- Prevailing perspective, based on small studies, that there are no measurable immediate or long-term health benefits of more strict BP treatment during the relatively short length of pregnancy (4 to 9 months, depending on the type of disorder) in young women without other CVD risks.

- Concerns that lowering maternal blood pressure may compromise utero-placental circulation and negatively affect fetal well-being and growth.

- Therapeutic options are limited due to concerns regarding potential adverse fetal effects, particularly malformations from intrauterine exposure to antihypertensive medications.

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

ONE

- More aggressive treatment of hypertension in pregnancy prevents the development of severe hypertension, as demonstrated by both a systematic review of randomized trials and the Control of Hypertension In Pregnancy Study trial (CHIPS).

- The Chronic Hypertension and Pregnancy (CHAP) Project, a large randomized controlled trial, is nearing completion in the United States (ClinicalTrials.gov Identifier: NCT02299414) comparing outcomes between pregnant, chronically hypertensive women who are given antihypertensive treatment to maintain BP <140/90 mm Hg, to women given no treatment, unless BP is ≥160/105 mm Hg.

REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

TWO

- Pathophysiology of the neurologic manifestations of preeclampsia (headaches, visual disturbances, seizures) is similar to that of the posterior reversible leukoencephalopathy syndrome, but women with preeclampsia develop neurological complications at lower systolic blood pressure elevations compared to non-pregnant individuals

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

THREE

- Antihypertensive therapy for pregnancy hypertension of any type halves the incidence of severe hypertension. Whether there is a difference between women with chronic versus gestational hypertension, remains unknown.

- Maintaining non-severe hypertension in pregnancy, for example 140-155/90-109 mm Hg, may permit prolongation of pregnancy in women without other severe features of preeclampsia.

- When hypertensive disorders of pregnancy were reclassified using the lower ACC/AHA diagnostic threshold (≥130 mm Hg / DBP ≥80 mm Hg), the lower diagnostic threshold for hypertension better identified women at risk for developing preeclampsia and pregnancies at risk for adverse fetal/neonatal outcomes.

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

FOUR

- Lowering thresholds for treatment may allow for timely blood pressure control and avoidance of rushed deliveries that commonly lead to prematurity and related complications.

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

FIVE

- Current epidemiological and demographic trends towards advanced age at first pregnancy and higher cardiovascular risk challenges the classical view that young, hypertensive women without diagnosed cardiovascular risk factors are at low short term cardiovascular disease risk from untreated hypertension during the duration of pregnancy.

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

SIX

- It is estimated that approximately two thirds of the cardiovascular disease risk associated with hypertensive disorders of pregnancy is mediated via established risk factors, and the remainder likely explained by etiology specific to hypertensive disorders of pregnancy.

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REASONS TO CONSIDER A LOWER BLOOD PRESSURE TREATMENT THRESHOLD

We endorse informed decision making in partnership with the patient as to whether or not to treat non-severe hypertension during pregnancy to targets similar to those recommended in non-pregnant individuals.

Personalization of therapy, by giving special attention to other risk factors related to hypertension-related adverse outcomes (such as pre-existing heart or kidney disease; obesity and Black race) is a rational approach.

Whether treatment of non-severe hypertension is beneficial for preventing long term morbidity beyond pregnancy and the puerperium, remains to be demonstrated.

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ANTIHYPERTENSIVE MEDICATIONS

ANTIHYPERTENSIVE MEDICATIONS

- First line treatment – labetalol, or methyldopa; nifedipine is also indorsed by most societies.
- Treatment of acute, severe hypertension in pregnancy – a Cochrane review concluded that, short acting parenteral hydralazine, parenteral labetalol, and oral nifedipine (short, intermediate or long acting) were comparable with respect to safety and efficacy and recommended that providers choose based on experience and familiarity with a particular drug.
- In resource-poor countries – a report documented successful treatment of acute severe hypertension with oral preparations of labetalol, intermediate acting nifedipine, and methyldopa.
- For resistant hypertension – nicardipine, clonidine, and furosemide are additional agents that may be considered, although these are not extensively studied.
- Women with salt sensitive chronic hypertension, or chronic kidney disease and reduced GFR – diuretics may be used safely although perhaps at lower doses. Recent studies demonstrate that they may be particularly effective in postpartum hypertension.

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ANTIHYPERTENSIVE MEDICATION SAFETY

- Limitations of data regarding the safety of antihypertensives in pregnancy are highlighted by a systematic review of studies addressing in utero exposure to antihypertensive medications and adverse fetal outcomes.
  - Only 5 of 47 studies were considered high quality
  - Few studies reported increased odds of adverse effects in treated compared to normotensive untreated women, including congenital malformations.
  - Effects were not uniformly observed across different studies using the same medications.
  - Similar adverse events have been reported in untreated hypertensive women, leading to the conclusion that the evidence for teratogenicity of most antihypertensive agents is weak.
- No firm conclusions can be drawn regarding long-term offspring outcomes given the paucity of relevant high-quality studies. No adverse neurodevelopmental effects have been observed for methyldopa, nifedipine, or atenolol.
- Data regarding beta blockers and SGA/FGR are conflicting.
- All renin angiotensin system blockers should be avoided during pregnancy, blockade of the fetal renin angiotensin system clearly interferes with kidney development and function

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POST PARTUM SCREENING

POST PARTUM SCREENING

- International guidelines, including the American College of Obstetricians and gynecologists, the International Society for the Study of Hypertension in Pregnancy, the European Society of Cardiology and the American Heart Association, emphasize the need for appropriate postpartum screening and control of cardiovascular risk factors for women with a history of preeclampsia.

- Randomized trials are needed to evaluate potential long-term cardiovascular benefits of early initiation of statins, aspirin, or renin angiotensin system blockers in women with only a history of HDP as a risk factor. Lifestyle interventions addressing obesity, hypertension, and dyslipidemia are good clinical practices.

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MULTIDISCIPLINARY TEAM APPROACH

PATHOPHYSIOLOGY

- Management of hypertension in pregnancy requires collaboration among obstetricians, maternal fetal medicine specialists, neonatologists, nephrology and hypertension specialists, cardiologists, anesthesiologists, pharmacists, nurses and midwives – all of whom contribute to providing cohesive and safe preconception, ante-, peri- and postpartum care.

- During hospital admission, nursing recognition of maternal compromise using early warning scores, hypertension bundles and tool kits ensures timely communication with a physician or advanced practice nurse and has been shown to reduce maternal mortality from hypertensive disorders.

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RACIAL DISPARITIES

RACIAL DISPARITIES

- US Maternal mortality is among the highest of high-income countries. Maternal mortality ratio = 18 per 100,000 live births.
- Racial maternal health disparities are unacceptably large.

Race	Maternal Mortality Ratio per 100,000 live births
Overall	18
Black American	41
American Indian and Alaskan Native	30
Caucasian	13

- Hypertensive disorders of pregnancy disproportionally affect Black, and American Indian and Alaskan Native women, predominantly due to the overall higher prevalence of cardiovascular risk factors, but there is also evidence to suggest biological factors (e.g., specific genetic variants) may increase the risk of preeclampsia for Black women.

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SUMMARY & FUTURE DIRECTIVES

SUMMARY & FUTURE DIRECTIVES

- The U.S. has one of the highest hypertensive related maternal mortality of high-income countries, in addition maternal morbidity and mortality from cardiovascular conditions and cerebrovascular accidents is increasing.

- The view that mild to moderate hypertension of short duration during pregnancy is not harmful to the mother, may be partly addressed by the Chronic Hypertension and Pregnancy study, a clinical trial that will extend observations made in earlier trials of women with chronic hypertension which demonstrated that normalization of blood pressure with antihypertensive treatment did not adversely affect fetal growth or neurodevelopmental outcomes.

- Adequate levels of BP control in the postpartum period should be revisited given there are no longer concerns about antihypertensive therapy and fetal growth.

- Evidence-based consensus on diagnostic and treatment thresholds long-term CVD risk assessment and HDP terminology are needed to facilitate progression in the field and ensure all women worldwide receive optimal care, before, during and after pregnancy.

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SUMMARY & FUTURE DIRECTIVES

- The superiority of any of the widely used antihypertensive(s) has not been demonstrated. A more personalized approach, based on patient preferences, age, race, heart rate, BP variations measured at home or in clinic, or more detailed hemodynamic assessments, may be more effective in protecting women from complications of hypertensive pregnancies and possible post-pregnancy CVD consequences.

- Ongoing research addressing causative pathways has the potential to identify new biomarkers and novel therapeutics that target fundamental mechanisms of preeclampsia.

- Studies must include sufficient participants from all racial groups, especially Black women, to address maternal health disparities and inform policy and clinical practice. We endorse studies addressing prevention of shared risk factors for HDP and CVD, and those aiming to improve antenatal and postnatal outcomes.

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