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Hypertensive disorders in pregnancy: diagnosis, target blood pressure levels and pharmacotherapy

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This review article discusses current and controversial data related to questions about the prevalence, diagnosis, and treatment of hypertensive disorders of pregnancy (HDP). Current data on the definition, classification, and pathophysiology of HDP, including the pathophysiology of uterine and placental pre-eclampsia, are presented. The issues of stratification and risk prediction of pre-eclampsia development using modern laboratory and instrumental examination methods are discussed. Much attention is paid to modern, clinically based approaches to HDP, improvement of outcomes and prevention of maternal and fetal complications in HDP. Special attention is paid to the management of severe arterial hypertension (AH), pre-eclampsia, including pre-eclampsia with severe manifestations. Data on the pathophysiology of development, treatment of postpartum AH, including breastfeeding, are presented. The main approaches to the diagnosis and treatment of pre-existing secondary AH in pregnancy are also presented.

Keywords: hypertensive disorders of pregnancy, gestational arterial hypertension, pre-eclampsia, risk stratification.

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Introduction

The prevalence of hypertensive disorders of pregnancy (HDP) is nearly 10% worldwide and is a major cause of maternal, fetal or neonatal morbidity and mortality [1]. On the maternal side, elevated blood pressure (BP) leads to increased risks of acute cerebral circulatory failure, pulmonary edema, placental abruption, disseminated intravascular coagulation

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and thromboembolic complications, as well as to the multiple organ failure. On the fetal side, HDP leads to the development of antenatal mortality, prematurity, delayed development, increased risks of preterm labor, and low birth weight [2]. The prevalence of HDP continues to increase due to the increasing incidence of obesity and other cardiometabolic factors in pregnant women, as well as the increasing age of pregnant women [3].

Definition and classification of hypertensive disorders in pregnancy

Most guidelines worldwide define the arterial hypertension (AH) during pregnancy as BP ⩾140/90 mmHg and classify AH as mild (140-159/90-109 mmHg) or severe (⩾160 mmHg/110 mmHg) [2, 4], in contrast to the commonly accepted three-stage classification of AH outside pregnancy.

The thresholds for diagnosis and treatment of AH for the general population have changed over the years. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines lowered the threshold for diagnosis of AH to 130/80 mmHg from 140/90 mmHg [5] based on observational studies and clinical trials demonstrating a reduced incidence of cardiovascular events when treated to lower BP levels.

Elevated systolic blood pressure (SBP) throughout pregnancy, even below the diagnostic threshold for AH, is associated with an increased risk of preterm labor, prematurity for gestational age, and low birth weight [6]. A cohort study including 137,389 pregnancies estimated the prevalence of AH among pregnant women using the lower ACC/AHA diagnostic threshold (SBP⩾130 mmHg or diastolic blood pressure (DBP) ⩾80 mmHg) instead of the American College of Obstetricians and Gynecologists (AGOG) threshold (SBP⩾160 mmHg or DBP ⩾105 mmHg). At the same time, the prevalence of AH increased from 10.3% to 28.1%, resulting in a net reclassification index of 20.8% for the detection of future preeclampsia and 3.8% for fetal/neonatal adverse events [7].

HDP are classified according to the timing of their occurrence during the pregnancy. The definition and classification of HDP [8] are summarized in Table 1.

BP measurements at the beginning of the second trimester in women who have not previously measured BP should be interpreted with caution because of the physiologic drop in BP in the second trimester. Women with hypertensive level of BP after 20 weeks and unknown BP before 20 weeks should be managed as women with gestational AH. In these women with unclassifiable pre-pregnancy AH, reassessment of BP 6 weeks after delivery will help distinguish pre-existing hypertension from gestational AH.

Among women with pre-existing hypertension, nearly 25% will develop pre-eclampsia [9]. This is usually associated with an abrupt or progressive

Table 1. **Classification of arterial hypertension in pregnancy**

<table>
<tr><td colspan="4">A. Pre-existing (chronic) AH.
AH that precedes pregnancy or develops before 20 weeks' gestation, usually persists for more than 42 days after delivery, and may be associated with proteinuria.</td></tr>
<tr><td>1. Primary AH</td><td>2. Secondary AH</td><td>White coat AH (elevated office BP and normal BP outside the office)</td><td>Masked AH (normal office and elevated out-of-office BP).</td></tr>
<tr><td colspan="4">B. Gestational AH.
AH develops after 20 weeks of pregnancy and usually resolves within 42 days of the delivery</td></tr>
<tr><td colspan="2">1. Transient gestational AH is detected in the clinic but then resolves with repeated BP measurements taken within a few hours, is associated with a 40% risk of developing true gestational AH or pre-eclampsia in the remainder of pregnancy</td><td colspan="2">2. Pre-eclampsia is gestational AH accompanied by one or more of the following conditions first occurring at or after 20 weeks of gestation:
- proteinuria (24-hour urinary albumin excretion >300 mg/day or albumin/creatinine ratio in a random urine sample >30 mg/g)
- acute kidney injury (serum creatinine ⩾90 μmol/l)
- liver damage (elevated alanine aminotransferase or aspartate aminotransferase levels >40 IU/l with or without right subcostal or epigastric pain)
- neurologic complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomas)
- hematologic complications (platelet count <150,000*109, disseminated intravascular coagulation syndrome, hemolysis)
- uteroplacental dysfunction (fetal growth retardation, abnormal umbilical artery Doppler analysis or stillbirth)</td></tr>
<tr><td colspan="4">C. Preexisting AH + pre-eclampsia.
Preexisting AH associated with any of the above-mentioned maternal organ dysfunction consistent with pre-eclampsia, or further BP elevation with first-onset proteinuria.</td></tr>
<tr><td colspan="4">D. Antenatally unclassifiable AH.
If elevated BP is first recorded after 20 weeks of gestation and AH is diagnosed, the reassessment 42 days after delivery is necessary. If AH resolves, it should be reclassified as gestational AH, whereas if AH persists, it should be reclassified as pre-existing AH.</td></tr>
</table>

increase in BP. Clinicians should always consider pre-eclampsia as a serious disease with rather unpredictable consequences.

Measuring blood pressure during pregnancy

Manual auscultatory blood pressure measurement remains the gold standard, as automated devices tend to underestimate BP and are unreliable in severe preeclampsia. For clinical purposes, two BP elevations four hours apart are required to detect AH during pregnancy. Only devices approved specifically for pregnant women should be used [10]. 24-hour blood pressure monitoring (24HBPM) is superior to office BP measurement for predicting pregnancy outcome. 24HBPM helps to avoid unnecessary treatment in white coat AH.

Non-sustained arterial hypertension

White coat AH occurs in 25% of non-pregnant adults, its prevalence during pregnancy is less known and varies from 4% to 30% according to different data [11]. Based on 24-hour BP measurement, the white coat AH was diagnosed in 32% of women with AH [12]. A meta-analysis of studies on white coat AH showed an increased risk of pre-eclampsia and adverse fetal outcomes compared to women with normotension, but the risks were lower compared to women with sustained chronic or gestational AH [13]. Any category of non-sustained BP elevation during pregnancy can progress to persistent AH.

Pathophysiology of hypertensive disorders in pregnancy

During normal pregnancy, systemic vascular resistance decreases and plasma volume and cardiac output increase [15]. In women with pre-eclampsia, some studies have shown that plasma volume may decrease [16]. Renal blood flow and glomerular filtration rate (GFR) are increased by 50% in normal pregnancy, but about 30% lower in women with pre-eclampsia. Numerous studies in women with pre-eclampsia have shown suppression of plasma renin activity, high BP, decreased GFR, and frequent edema [9].

Cardiometabolic changes are more prominent in women who develop pre-eclampsia and include increased insulin resistance, total cholesterol, triglycerides, and low-density lipoprotein cholesterol [17]. Hypercoagulability, a feature of normal pregnancy, may be excessive in pre-eclampsia and is caused by increased thrombin formation, fibrinogen and activated protein C resistance, as well as due to decreased protein S and fibrinolysis [18].

Pathogenesis of placental and maternal pre-eclampsia syndrome

During normal pregnancy, the diameter of uterine spiral arteries increases significantly due to remodeling of the endothelium and vascular smooth muscle stimulated by the release of proteases from endovascular trophoblast and uterine natural killer cells. Failure to remodel the spiral artery (i.e., smooth muscle preservation) is a hallmark of pre-eclampsia and results in decreased uteroplacental perfusion, as demonstrated by non-invasive blood flow and perfusion studies using Doppler ultrasound (US) or magnetic resonance imaging (MRI) [19].

Placental pathology due to rheologic abnormalities includes changes in the architecture of the villi due to turbulent jets penetrating the intervillous space at a velocity of 1-2 m/s (10-20 times higher than normal), causing rupture of the entrapped villi and formation of echogenic cystic lesions visible during ultrasound [20]. In addition, preservation of vascular smooth muscle retains the ability to spontaneous vasoconstriction and leads to ischemia-reperfusion injury.

Abnormal placentation in early pregnancy leads to an increase in an antiangiogenic factor of placental origin: circulating soluble fms-like tyrosine kinase 1 (sFlt1), and a consequent neutralization and decrease in proangiogenic factors: placental growth factor (PlGF) and vascular endothelial growth factor, which contributes to glomerulopathy and increased BP [19]. Measurements of sFlt1, PlGF and their ratios have been included in risk stratification in several therapeutic trials for the prevention of pre-eclampsia, but are not commonly used to guide clinical care in most of the countries

An elevated sFlt1/PlGF ratio may be particularly prominent in women with early (less than 34 weeks' gestation) severe pre-eclampsia, which some refer to as placental pre-eclampsia because of the association between placental ischemia and adverse fetal outcomes [21].

Pre-eclampsia occurring later in pregnancy is associated with maternal vascular dysfunction prior to pregnancy (secondary to AH, diabetes mellitus, or

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obesity), less severe placental pathology, and fewer fetal complications [21]. The molecular and pathophysiologic mechanisms of pre-eclampsia are still not completely clear, but the etiology is likely a combination and interaction of both placental and maternal pathways. Regardless of the variant of pre-eclampsia, the diagnosis and treatment of HDP remains the basis for prevention of immediate maternal complications as well as of seizures treatment with magnesium sulfate.

Additional tests in pregnancy

In HDP, basic laboratory tests are recommended, including a general blood count, urinalysis, biochemical testing for liver enzymes, creatinine, and uric acid. Hyperuricemia in HDP is associated with an increased risk of adverse maternal and fetal outcomes [22].

Examination for 24-hour albuminuria, albumin-creatinine ratio can detect pre-existing renal disease in early pregnancy and pre-eclampsia in the second half of pregnancy. Proteinuria may also be a precursor to subsequent BP elevation in the natural course of pre-eclampsia, and the presence of proteinuria is no longer a necessary criterion for the diagnosis of pre-eclampsia [23].

Several laboratory markers have been tested for predicting pre-eclampsia in early pregnancy:

- Angiogenic factors [endoglin, PlGF, sFlt-1 and sFlt-1/PIGF ratio];
- Pregnancy-related plasma protein A in combination with clinical (e.g., BP, maternal risk factors - FR) and ultrasound characteristics (e.g., uterine artery Doppler) [24].

However, additional studies are desirable to clarify the role of the above-mentioned markers alone or in combination with clinical characteristics in predicting pre-eclampsia (24, 25).

If serum creatinine or any parameters in urinalysis are abnormal, renal ultrasound and uterine and umbilical artery duplex scanning (performed after 20 weeks of gestation) should be considered to identify those at higher risk of gestational AH, pre-eclampsia and fetal development delay.

Prevention of pre-eclampsia and adverse maternal and fetal outcomes

A meta-analysis of 44 randomized controlled trials demonstrated that diet correction reduces maternal weight gain during pregnancy and improves pregnancy outcomes [26].

In addition, in women with low calcium intake (i.e., < 600 mg/day), calcium supplementation at a dose of at least 1 g/day has been recommended to reduce the risk of pre-eclampsia [27]. Although there are no recommendations for salt restriction, it is important for women with pre-existing AH to continue on a sodium-restricted diet.

Physical exercise can reduce the risk of gestational AH and pre-eclampsia by about 30% and 40%, respectively [28]. The first Canadian guideline on physical activity during pregnancy, published in 2019, recommends physical activity for all women without contraindications [29]. If there are no contraindications, aerobic exercise (3–4 times a week for 30–60 minutes before delivery) should be recommended.

Drug therapy

Low-dose aspirin starting at 12-16 weeks of gestation reduces the risk of pre-eclampsia and related adverse outcomes by 10–20% in high-risk women. The classification of pre-eclampsia risk as high and moderate is based on the ACOG recommendations for aspirin therapy to prevent pre-eclampsia. Therapy is indicated in the presence of ⩾1 high or ⩾ 2 moderate risk factors [30].

The high risk of pre-eclampsia includes:

- Previous pre-eclampsia;
- Chronic AH (BP ⩾140/90 mmHg);
- Pre-gestational diabetes;
- Chronic kidney disease (CKD);
- Multiple pregnancy;
- Autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome.

The moderate risk of pre-eclampsia includes:

- History of adverse pregnancy outcomes (stillbirth, placental abruption);
- Age 35 years or older;
- Body mass index (BMI) of 30 kg/m^2 or more at the first visit;
- Aggravated family history (first degree relatives);
- Low socioeconomic status;
- Race (Negroid).

Other risk factors (RF) of pre-eclampsia development also include: chronic AH (BP 130-139/80-89 mmHg), white coat AH, BMI more than 25 kg/m2, ges-

tational diabetes, insulin resistance, history of acute kidney injury, hyperthyroidism, fetal trisomy-13, genetic predisposition, assisted reproductive technologies, oocyte donation, pregnancy interval more than 4 years.

If the risk of pre-eclampsia is high or moderate, 100–150 mg of acetylsalicylic acid is recommended from week 11 to 14 until the 36th week of pregnancy [31].

Antihypertensive therapy during pregnancy

The treatment of HDP includes the question of the benefit of treatment and normalization of BP in pregnant women combined with concerns about fetal well-being due to decreased uteroplacental perfusion and intrauterine exposure to antihypertensive drugs.

Mild pre-existing essential arterial hypertension

The decision about antihypertensive therapy use in the first and early second trimester may be individualized, based on pre-pregnancy BP levels in the absence of treatment, BP values in the first trimester, the presence of target organ damage, and BP values after possible short-term withdrawal of antihypertensive treatment in individual cases. It should be decided on a case-by-case basis whether the benefit of drug treatment during fetal organogenesis (up to week 16) exceeds the risk of fetal exposure, as any drug can be potentially harmful in the first trimester, including alpha-methyldopa [32].

All renin-angiotensin system (RAAS) blockers should be discontinued during the first trimester. In a large meta-analysis including 19 studies and 4,163,753 pregnant women, 13 studies reported an increased risk of at least one adverse pregnancy outcome in women who were exposed to RAAS blockers [33].

In the first trimester in women with office BP < 130/80 mmHg, antihypertensive therapy may be discontinued or de-escalated under careful BP monitoring until week 16. If BP rises >140/90 mmHg, antihypertensive therapy should be resumed at any gestational age.

It should be remembered that there may be a physiologic decrease in BP at the beginning of the second trimester, and that even mild antihypertensive therapy during this period can potentially lead to excessive BP reduction, which increases the risk of miscarriage.

In the large randomized multicenter CHIPS (The Control of Hypertension in Pregnancy Study) study [34], which included 987 women with HDP, of whom 74.6% had a history of AH, BP was 138.8 ± 0.5 mmHg among women in the less strictly controlled group versus 133.1 ± 0.5 mmHg in the strictly controlled group. Among women receiving antihypertensive therapy, labetalol was the most commonly used drug (68.9% and 68.8% in the two groups, respectively), with the remainder receiving methyldopa or nifedipine. In another large randomized CHAP (Chronic Hypertension and Pregnancy) study [35], which included 2806 women with chronic AH with less than 23 weeks' gestation, were assigned to receive antihypertensive drugs (labetalol or prolonged-acting nifedipine or other drugs such as amlodipine or methyldopa (active treatment group), or receive no treatment unless severe AH developed (control group).

Studies have shown that compared with placebo, strict and less strict BP control on antihypertensive therapy were more beneficial and not harmful. In the CHIPS study [34], the effect of BP lowering was favorable for the primary outcome, i.e. severe pre-eclampsia, preterm delivery at less than 35 weeks of gestation, placental abruption or development of neonatal fetal death.

The BP values observed in the CHIPS (133/85 mmHg) and CHAP (129/79 mmHg) studies reduced pregnancy-related complications by 35% and 18%, respectively; both studies achieved a reduction in pre-eclampsia, including severe pre-eclampsia.

However, in the CHIPS study, there was a gestational age-insignificant increase in the incidence of adverse neonatal outcomes, while this was not found in the CHAP study, keeping the issue of excessive BP lowering and the associated risk of fetal hypoperfusion relevant.

Current epidemiologic and demographic trends indicate an increase in age at first pregnancy. In addition, fertility treatments facilitate pregnancy in women who have conditions associated with increased cardiovascular risk (e.g. diabetes mellitus, CKD, polycystic ovary syndrome). In high-income countries, chronic kidney and heart diseases are seen in 3% and 1–4% of pregnancies, respectively [36, 37], with more intensive treatment recommended for these women.

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It is widely accepted that initial antihypertensive therapy is monotherapy with a recognized first-line drug: methyldopa or labetalol. Some [38, 39] but not all scientific societies support the use of nifedipine as initial therapy. In countries where labetalol is not available (e.g. Germany), alternative beta-blockers such as metoprolol or oxprenolol can be considered. These therapeutic options are based on small individual studies and are supported by national and international clinical practice guidelines.

Based on a systematic review of randomized trials for all types of AH in pregnant women considered together, for all antihypertensive drugs considered together, or for beta-blockers (including labetalol) considered separately, there is no clear evidence that one drug is preferable to another [40].

However, in a separate network meta-analysis specifically focused on the treatment of chronic AH, atenolol was associated with fetal growth retardation [41], especially in long-term use.

Mild gestational arterial hypertension

Although the CHIPS study [34] included a limited number of women with gestational AH (25.4%), secondary analysis showed no differences in outcomes between women with gestational and pre-existing AH for both primary and secondary outcomes. Initiating treatment at BP values ≥140/90 mmHg seems reasonable, whereas lowering DBP to <80 mmHg is not recommended. The same medications recommended for pre-existing AH can be used in women with gestational AH.

Pre-eclampsia

Antihypertensive therapy for pre-eclampsia with mild or severe AH is not different from treatment of AH without pre-eclampsia, although evidence is limited. AH control can be achieved with labetalol (unless contraindicated) alone or with a combination of labetalol, prolonged-acting nifedipine, and/or alpha-methyldopa.

In pre-eclampsia with severe manifestations (AH of any degree with cardiovascular, neurological, hematologic complications, liver or renal dysfunction, severe AH), treatment with magnesium sulfate infusion is necessary to prevent eclampsia and remains also the method of choice for eclamptic seizures. Magnesium sulfate infusion is recommended within 24 hours after delivery and for prophylactic purposes [43].

Severe arterial hypertension

In severe AH, hospitalization is mandatory to ensure a gradual decrease in BP to <160/105 mmHg and to exclude pre-eclampsia. Continuous cardiotocographic monitoring is also mandatory [42]. The choice of antihypertensive drugs and route of administration depends on the initial diagnosis, expected time of labor and the presence/absence of pre-eclampsia, as well as the preferences and experience of the treating physicians.

A recent comprehensive network meta-analysis including 29 studies and 2521 women showed that nifedipine can be recommended as a BP control strategy in pregnant women with severe AH, while labetalol and hydralazine actually showed limited efficacy [44]. However, in cases of pre-eclampsia with severe manifestations, persistent severe AH, or recurrent severe AH despite oral medication, intravenous labetalol or urapidil should be used before, during, and often after delivery. In pre-eclampsia without severe manifestations or severe AH without pre-eclampsia, an effective and gradually escalating multidrug regimen should be used to lower BP to target levels [34], with hydralazine avoided before delivery because of its association with more adverse perinatal outcomes.

Hydralazine should be administered when labetalol or urapidil is unavailable, insufficient BP reduction, presence of grade II or III atrioventricular block, severe heart failure, asthma, bradycardia or severe postpartum AH.

If pre-eclampsia is accompanied by pulmonary edema, the drug of choice is nitroglycerin administered intravenously at a dose of 5 mg/min with gradual increases every 3–5 minutes to a maximum dose of 100 mg/min with careful BP control.

Sodium nitroprusside is recommended as a reserve drug in the treatment of severe AH because of the increased risk of fetal cyanide poisoning with prolonged use [45].

Pregnant women with severe AH living far away from the maternity hospital may be given 10 mg of short-acting nifedipine orally, and a second dose should be administered 1 hour later if severe AH persists. Short-acting nifedipine sublingually is contraindicated. Successful treatment of severe AH with oral preparations of labetalol, intermediate-acting nifedipine, and methyldopa has been clinically confirmed in resource-limited countries [46].

An additional drug that may be considered for resistant AH is furosemide [47]. It is noteworthy that diuretics, the mainstay of treatment for AH in non-pregnant women, are infrequently used in pregnant women. It is now recognized that in women with salt-sensitive, hyporeninemic forms of chronic AH or CKD and reduced GFR, diuretics can be safely used, although possibly at lower doses [48]. Recent studies suggest that they may be particularly effective in postpartum AH [49].

Pre-existing secondary arterial hypertension

The majority (about 90%) of women with chronic AH have primary AH. Secondary AH may occur in a small proportion of women and is associated with poorer maternal and fetal prognosis. Secondary AH should be excluded if AH is severe or persistent, there is no family history of AH, in the presence of hypokalemia, decreased GFR, or albuminuria in early pregnancy, and maternal age <35 years.

Table 2 summarizes the major causes of AH in pregnancy, diagnostic features, outcomes, and management options.

Women with pre-existing AH should receive counseling before conception, including exclusion of secondary causes of AH. Ultrasound renal Doppler ultrasonography should be performed in all women with AH planning pregnancy. In women diagnosed with fibromuscular dysplasia, further evaluation of other vascular basins, especially the cerebral basin, should be performed before pregnancy to rule out any additional arterial damage. Achieving optimal BP control and, if indicated, renal artery revascularization are recommended before conception [50].

In women with known hyperaldosteronism before conception or with clinical suspicion of this condition early in pregnancy, careful laboratory evaluation should be performed. After the second trimester of pregnancy, eplerenone in addition to conventional BP-lowering treatment may be considered for uncontrolled AH with or without hypokalemia. The fall in progesterone levels after delivery due to its competitive antagonism with aldosterone may increase BP and exacerbate hypokalemia [51].

For the purpose of management of women with kidney disease before pregnancy, it is important to know the degree of CKD, the level of estimated GFR, or the degree of proteinuria rather than the underlying cause. Women without significant proteinuria, normal BP in early pregnancy, and mild renal failure usually have an uncomplicated pregnancy. Women with moderate or more severe CKD are at increased risk for both fetal and maternal complications and worsening of already impaired renal function. Women with a GFR less than 40 ml/min/1.73 m^2 and protein-

Table 2. **Secondary causes of arterial hypertension in pregnancy**

Name	Clinical fetures	Laboratory investigations	Pregnancy outcomes	Treatment/management
CKD	Edema Nicturia	Proteinuria Hematuria Decrease in estimated GFR	Pre-eclampsia Preterm labor Delayed fetal development	Antihypertensive drugs Low-dose aspirin
Primary hyperaldosteronism	Exacerbation of postpartum AH, muscle cramps and weakness, frequent urination, thirst.	Suppression of hypokalemia by aldosterone antagonists Increase in aldosterone-renin ratio	Increased risk of pre-eclampsia	Calcium channel blockers Labetalol Thiazide diuretics Potassium supplements
Renovascular hypertension	Persistent AH. Murmur when auscultating the renal arteries.	Increased plasma renin activity level	Pre-eclampsia Preterm labor	Antihypertensive drugs Angioplasty in the second trimester
Pheochromocytoma	Persistent BP elevation, hypertensive crises, rhythm disturbances, increased nervousness	Elevated levels of metanephrines or catecholamines in plasma/urine.	Severe AH Fetal + maternal mortality	MRI without gadolinium contrast Alpha-blockers Calcium channel blockers Surgery in the second trimester
Cushing's disease	Gestational diabetes Abdominal striae	Free cortisol in urine Cortisol in saliva late at night High dose dexamethasone suppression test	Pre-eclampsia Preterm labor Delayed fetal development Fetal mortality	Metyrapone surgery
Obstructive sleep apnea	Apnea Fatigue Headaches Depression	Polysomnography abnormalities. Desaturation Increased level of glycated hemoglobin Elevated erythropoietin levels	Pre-eclampsia Preterm labor	Mandibular repositioning devices (CPAP therapy)

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uria greater than 1 g/day should be considered at very high risk for pregnancy and renal outcomes, including the need for renal replacement therapy [52, 53].

Pheochromocytoma in pregnancy is a disease that is very rare with a frequency of 0.002% of all pregnancies, while it is one of the most life-threatening conditions for mother and fetus [54]. The dominant sign is AH, the rest of the signs and symptoms are highly variable and unspecific. If pheochromocytoma is not detected, maternal and fetal mortality is about 50%. Timely detection and adequate therapy during pregnancy reduce maternal and neonatal mortality to < 5 and <15%, respectively. For biochemical diagnosis, the tests of choice are the determination of metanephrines in plasma or urine. For reliable diagnosis of pheochromocytoma localization, MRI is the most appropriate method with a sensitivity of more than 90%.

If pheochromocytoma is diagnosed during pregnancy, laparoscopic adrenalectomy should be performed in 10-14 days after preliminary medical preparation (alpha-adrenergic receptor blockade combined with beta-adrenergic receptor blockade) [54]. When pheochromocytoma is diagnosed in the third trimester, using the same treatment regimen as surgical preparation, the patient should preferably be managed until the fetus is viable. Since natural childbirth is associated with a higher mortality rate, cesarean section with tumor removal in one session or at a later stage is preferred (54).

Blood pressure in the postpartum period

The prevalence of postpartum AH can be as high as 8% in women without preterm AH (48 hours after delivery and up to 6 weeks after delivery) and up to 50% in women with a history of pre-eclampsia 6-12 weeks after delivery [55]. About 80% of maternal mortality occurs in the first week after delivery, and HDP remains one of its leading causes.

Women with normotensive pregnancies may have an increase in BP in the first day after delivery, which is attributed to the use of vasoactive drugs to promote uterine contraction, blood transfusion, intravenous fluid administration, use of nonsteroidal anti-inflammatory drugs for postpartum analgesia, physiologic uterine "autotransfusion phenomenon" or excessive fluid intake, and mobilization of extravascular fluid. Women with pre-eclampsia have a decreased diuresis within 12-36 hours after delivery due to delayed fluid redistribution associated with a greater drop in colloid osmotic pressure compared with normal pregnancy [56].

The distinction between postpartum exacerbation of prenatal AH and de novo postpartum pre-eclampsia is unclear. The duration of AH varies from a few days to 3 months, which may lead to the development of both metabolic abnormalities in the mother, such as insulin resistance and weight gain, and serious complications, such as stroke, seizures, and cardiomyopathy. Further studies addressing the underlying mechanisms of such pathology are needed to improve outcomes [55].

The rate of increase in the prenatal sFlt1/PlGF ratio is an independent predictor of AH persisting after delivery [57]. In addition, it has been shown that pre-eclampsia-related endothelial dysfunction and altered cerebrovascular autoregulation persist in the postpartum period and may increase the risk of postpartum AH.

A recent randomized controlled clinical trial showed that postpartum use of furosemide in women with AH was associated with a 60% reduction in the incidence of persistent AH on day 7 of postpartum period [49].

Another unusual phenotype of postpartum AH is the so-called "late postpartum AH" phenotype, which appears 6 months after delivery and subsides within a few months. The pathogenesis of this condition is unknown, but one possibility is that the resumption of postpartum menstruation increases BP by redistribution of excess progesterone and activation of mineralocorticoid receptors [9].

All antihypertensive agents used during pregnancy can be used in the postpartum period to achieve BP control. However, the use of angiotensin-converting enzyme inhibitors in the postpartum period should be allowed in women with concomitant cardiorenal diseases [4].

Postpartum hypertension and breastfeeding

Antihypertensive drugs are excreted into breast milk mainly in very low concentrations. Nifedipine and verapamil are considered compatible with breastfeeding. Although diuretics are not contraindicated, they may lead to decreased milk production. Similarly, alpha-methyldopa is compatible with breastfeeding, although it is not the drug of first choice in the post-

partum period because it increases the risk of postpartum depression. Angiotensin-converting enzyme inhibitors are compatible with breastfeeding and can be used in women with concomitant cardiovascular diseases or CKD. Angiotensin II receptor blockers are not currently recommended in lactation due to limited safety evidence [4].

Long-term cardiovascular consequences of hypertensive disorders during pregnancy

Several registries have demonstrated that pregnant women with HDP are at increased cardiovascular risk, which also includes the risk of developing persistent AH in the future. A meta-analysis of cohort studies showed that pre-eclampsia with more severe manifestations was associated with a higher prevalence of future morbidity compared to pre-eclampsia with less severe manifestations [58]. A genome-wide genetic association study using Mendelian randomization provided evidence supporting an association between HDP and a higher risk of coronary heart disease and stroke, which is only partially mediated by cardiometabolic factors [59]. Lifestyle modification is indicated in women with HDP to reduce the risk of complications in subsequent pregnancies, as well as to reduce the risk of CVD in general.

Conclusion

To date, the superiority of any of the commonly used antihypertensive agents in the treatment of HDP has not been demonstrated. A personalized approach based on the nature of the AH, its degree, results of daily and ambulatory BP monitoring, heart rate, presence and nature of associated conditions, age, race, and patient preferences appears to be more effective in better controlling BP, protecting women from AH complications and possible CVD after pregnancy.

Evidence-based consensus is needed on diagnostic and treatment thresholds, BP targets, and long-term CVD risk assessment. Future guidelines should avoid integrating historical, unsubstantiated viewpoints that impede the improvement of women's health during pregnancy and the postpartum period.

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References

1. Thomopoulos C, Brguljan J, Cífková R, et al. Mild chronic hypertension in pregnancy: to treat or wait? Blood Press. 2022; 31:121–124. DOI: 10.1080/08037051.2022.2077698
2. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018; 39:3165–3241. DOI: 10.1093/eurheartj/ehy340
3. Ananth CV, Duzyj CM, Yadava S, et al. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. Hypertension. 2019; 74:1089–1095. DOI: 10.1161/HYPERTENSIONAHA.119.12968
4. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Journal of Hypertension. 2023. 41(12): 1874-2071. DOI: 10.1097/HJH.0000000000003480
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13–e115. DOI:10.1161/HYP.0000000000000065
6. Teng H, Wang Y, Han B, et al. Gestational systolic blood pressure trajectories and risk of adverse maternal and perinatal outcomes in Chinese women. BMC Pregnancy Childbirth. 2021;21:155. DOI:10.1186/s12884-021-03599-7
7. Bello NA, Zhou H, Cheetham TC, et al. Prevalence of hypertension among pregnant women when using the 2017 American College of Cardiology/American Heart Association blood pressure guidelines and association with maternal and fetal outcomes. Journal of the American Medical Association Network Open. 2021;4:e213808. DOI:10.1001/jamanetworkopen.2021.3808
8. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018; 13:291–310. DOI: 10.1016/j.preghy.2018.05.004
9. Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement From the American Heart Association. Hypertension. 2021; 79(2). DOI: 10.1161/HYP.0000000000000208
10. Stergiou GS, O'Brien E, Myers M, et al. STRIDE BP: an international initiative for accurate blood pressure measurement. J Hypertens. 2020; 38:395–399. DOI: 10.1097/HJH.0000000000002289

11. ACOG Practice Bulletin No. 203: Chronic hypertension in pregnancy. Obstetrics & Gynecology. 2019;133:e26–e50. DOI: 10.1097/AOG.0000000000003020
12. Tucker KL, Bankhead C, Hodgkinson J. et al. How do home and clinic blood pressure readings compare in pregnancy? Hypertension. 2018;72:686–694. DOI: 10.1161/HYPERTENSIONAHA.118.10917
13. Johnson S, Liu B, Kalafat E, et al. Maternal and perinatal outcomes of white coat hypertension during pregnancy. Hypertension. 2020;76:157–166. DOI: 10.1161/HYPERTENSIONAHA.119.14627
14. Shen M, Tan H, Zhou S, et al. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: a functional data analysis approach. Sci. 2017;7:6227. DOI: 10.1038/s41598-017-06606-0
15. Sixtus Aguree and Alison D. Gernand Plasma volume expansion across healthy pregnancy: a systematic review and meta-analysis of longitudinal studies. BMC Pregnancy and Childbirth (2019) 19:508. DOI: 10.1186/s12884-019-2619-6
16. de Haas S, Ghossein-Doha C, van Kuijk SM, et al. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology. 2017;49:177–187. DOI: 10.1002/uog.17360
17. Thushari I., Heather J., Vincent W. Lee et al. Lipid profiling in maternal and fetal circulations in preeclampsia and fetal growth restriction-a prospective case control observational study. BMC Pregnancy and Childbirth (2020) 20:61 DOI: 10.1186/s12884-020-2753-1
18. Hellgren M. Hemostasis during normal pregnancy and puerperium. Seminars in Thrombosis and Hemostasis. 2003;29:125–130. DOI: 10.1055/s-2003-38897
19. Rana S, Lemoine E, Granger JP, et al. Preeclampsia: pathophysiology, challenges, and perspectives. Circulation Research. 2019;124:1094–1112. DOI: 10.1161/CIRCRESAHA.118.313276
20. Veronique Schiffer, Laura Evers, Sander de Haas, et al. Spiral artery blood flow during pregnancy: a systematic review and meta-analysis. BMC Pregnancy and Childbirth (2020) 20:680. DOI: 10.1186/s12884-020-03150-0
21. Staff AC, Benton SJ, von Dadelszen P, et al. Redefining preeclampsia using placenta-derived biomarkers. Hypertension. 2013;61:932–42. DOI: 10.1161/HYPERTENSIONAHA.111.00250
22. Schmella MJ, Clifton RG, Althouse AD, et al. Uric Acid Determination in Gestational Hypertension: Is it as Effective a Delineator of Risk as Proteinuria in High-Risk Women? Reprod Sci. 2015; 22:1212–1219. DOI: 10.1177/1933719115572477
23. Waugh J, Hooper R, Lamb E, et al. Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis. Health Technol Assess. 2017; 21:1–90. DOI: 10.3310/hta21610
24. O'Gorman N, Wright D, Poon LC, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound Obstet Gynecol. 2017; 49:756–760. DOI: 10.1002/uog.17455
25. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016; 374:13–22. DOI: 10.1056/NEJMoa1414838
26. Thangaratinam S, Rogozińska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. British Medical Journal. 2012;344:e2088. DOI: 10.1136/bmj.e2088
27. Hofmeyr GJ, Lawrie TA, Atallah AN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018; 10:CD001059. DOI: 10.1002/14651858.CD001059.pub5
28. Magro-Malosso ER, Saccone G, Di Tommaso M, et ak. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstetricia et Gynecologica Scandinavica. 2017;96:921–931. DOI: 10.1111/aogs.13151
29. Mottola MF, Davenport MH, Ruchat SM, et al. No. 367–2019 Canadian guideline for physical activity throughout pregnancy. Journal of Obstetrics and Gynaecology Canada. 2018;40:1528–1537. DOI: 10.1016/j.jogc.2018.07.001
30. ACOG Committee Opinion No. 743: Low-dose aspirin use during pregnancy. Obstetrics & Gynecology. 2018;132:e44–e52. DOI: 10.1097/AOG.0000000000002708
31. Garovic VD, Dechend R, Easterling T, et al. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. Hypertension (Dallas, Tex: 1979). 2022; 79:e21–e41. DOI: 10.1161/HYP.0000000000000208
32. Hoeltzenbein M, Beck E, Fietz AK, et al. Pregnancy outcome after first trimester use of methyldopa: a prospective cohort study. Hypertension (Dallas, Tex: 1979). 2017; 70:201–208. DOI: 10.1161/HYPERTENSIONAHA.117.09110
33. Buawangpong N, Teekachunhatean S, and Koonrungsesomboon N. Adverse pregnancy outcomes associated with first-trimester exposure to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: A systematic review and meta-analysis. Pharmacol Res Perspect. 2020;8:e00644. DOI: 10.1002/prp2.644
34. Magee LA, Singer J, von Dadelszen P, Group CS. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015; 372:2367–2368. DOI: 10.1056/NEJMoa1404595

35. Tita AT, Szychowski JM, Boggess K, et al. Treatment for Mild Chronic Hypertension during Pregnancy. N Engl J Med. 2022; 386:1781–1792. DOI: 10.1056/NEJMoa2201295.
36. Elkayam U, Goland S, Pieper PG et al. High-risk cardiac disease in pregnancy: part I. Journal of the American College of Cardiology. 2016;68:396–410. DOI: 10.1016/j.jacc.2016.05.048
37. Ramlakhan, K.P., Johnson, M.R. & Roos-Hesselink, J.W. Pregnancy and cardiovascular disease. Nat Rev Cardiol 17, 718–731 (2020). DOI: 10.1038/s41569-020-0390-z
38. WHO Guidelines approved by the Guidelines Review Committee WHO recommendations on drug treatment for non-severe hypertension in pregnancy Geneva: World Health Organization; © World Health Organization 2020.
39. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management NICE guideline [NG133] 2019; 2019. Accessed, July 29, 2019.
40. Abalos E, Duley L, Steyn DW et al. C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews. 2018;10:CD002252. DOI: 10.1002/14651858.CD002252.pub4
41. Bellos I, Pergialiotis V, Papapanagiotou A, et al. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network meta-analysis. American Journal of Obstetrics & Gynecology. 2020;223:525–537. DOI: 10.1016/j.ajog.2020.03.016
42. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018; 13:291–310. DOI: 10.1161/HYPERTENSIONAHA.117.10803
43. Vigil-DeGracia P, Ludmir J, Ng J, et al. Is there benefit to continue magnesium sulphate postpartum in women receiving magnesium sulphate before delivery? A randomised controlled study. Bjog. 2018; 125:1304–1311. DOI: 10.1111/1471-0528.15320
44. Deng NJ, Xian-Yu CY, Han RZ, et al. Pharmaceutical administration for severe hypertension during pregnancy: Network meta-analysis. Front Pharmacol. 2022; 13:1092501. DOI: 10.3389/fphar.2022.1092501
45. Cifkova R, Johnson MR, Kahan T, et al. Peripartum management of hypertension: a position paper of the ESC Council on Hypertension and the European Society of Hypertension. Eur Heart J Cardiovasc Pharmacother. 2020; 6:384–393. DOI: 10.1093/ehjcvp/pvz082 DOI: 10.1093/ehjcvp/pvz082
46. Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. The Lancet. 2019;394:1011–1021. DOI: 10.1016/S0140-6736(19)31282-6
47. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: A randomized controlled trial. Hypertension in Pregnancy. 2017;36:84–89. DOI: 10.1080/10641955.2016.1239735
48. ACOG Practice Bulletin No. 203: Chronic hypertension in pregnancy. Obstetrics & Gynecology. 2019;133:e26–e50. DOI: 10.1097/AOG.0000000000003020
49. Lopes PJ, Lewey J, Hirshberg A, et al. Furosemide for accelerated recovery of blood pressure postpartum in women with a hypertensive disorder of pregnancy: a randomized controlled trial. Hypertension. 2021:Hypertensionaha12016133. DOI: 10.1161/HYPERTENSIONAHA.120.16133
50. Pappaccogli M, Prejbisz A, Ciurică S, et al. Pregnancy-Related Complications in Patients With Fibromuscular Dysplasia: A Report From the European/International Fibromuscular Dysplasia Registry. Hypertension (Dallas, Tex: 1979) 2020; 76:545–553. DOI: 10.1161/HYPERTENSIONAHA.120.15349
51. Landau E, Amar L. Primary aldosteronism and pregnancy. Ann Endocrinol (Paris) 2016; 77:148–160. DOI: 10.1016/j.ando.2016.04.009
52. Wiles K, Chappell L, Clark K. et al. Clinical practice guideline on pregnancy and renal disease. BMC Nephrology (2019) 20:401. DOI: 10.1186/s12882-019-1560-2
53. National Institute for Health and Care Excellence. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period [NG3]. Available at: https://www.nice.org.uk/ guidance/ng3 (Accessed 22 May 2019).
54. Lenders JW. Pheochromocytoma and pregnancy: a deceptive connection. Eur J Endocrinol. 2012; 166:143–150. DOI: 10.1530/EJE-11-0528
55. Ditisheim A, Wuerzner G, Ponte B, et al. Prevalence of hypertensive phenotypes after preeclampsia: a prospective cohort study. Hypertension. 2018;71:103–109. DOI: 10.1161/HYPERTENSIONAHA.117.09799
56. Rutgers University Press, Thomopoulos C, Makris T. Iatrogenic Aspects of Hypertension in Pregnancy. 2018. DOI: 10.1007/5584_2016_150
57. Lopes Perdigao J, Chinthala S, Mueller A, et al. Angiogenic Factor Estimation as a Warning Sign of Preeclampsia-Related Peripartum Morbidity Among Hospitalized Patients. Hypertension. 2019;73:868–877. DOI: 10.1161/HYPERTENSIONAHA.118.12205
58. Honigberg MC, Natarajan P. Women's cardiovascular health after hypertensive pregnancy: The long view from labor and delivery becomes clearer. Journal of the American College of Cardiology. 2020;75:2335–2337. DOI: 10.1016/j.jacc.2020.01.064
59. Rayes B, Ardissino M, Slob EAW, et al. Association of Hypertensive Disorders of Pregnancy With Future Cardiovascular Disease. JAMA Network Open. 2023; 6:e230034–e1230034. DOI: 10.1001/jamanetworkopen.2023.003