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Hypertension in pregnancy: Pathophysiology and treatment

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Abstract

Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality. Despite the differences in guidelines, there appears to be consensus that severe hypertension and non-severe hypertension with evidence of end-organ damage need to be controlled; yet the ideal target ranges below 160/110 mmHg remain a source of debate. This review outlines the definition, pathophysiology, goals of therapy, and treatment agents used in hypertensive disorders of pregnancy.

Keywords

Hypertension, pregnancy, gestational hypertension

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Introduction

The prevalence of hypertension in reproductive-aged women is estimated to be 7.7%.[1] Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality.[2] The terms, goals of therapy, and treatment agents have been long debated and remain controversial. We aimed to review the pathophysiology and treatment of hypertensive disorders of pregnancy.

Terminology

The definition of hypertension in pregnancy has not always been standardized, but following the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy" recommendation is currently a systolic blood pressure (SBP) $\geq$ 140 mmHg and/or a diastolic blood pressure (DBP) $\geq$ 90 mmHg (Table 1).[11] The diagnosis generally requires two separate measurements.[12] The severity of hypertension is as follows:

- *Non-severe hypertension.* Any values between SBP 140–159 mmHg and DBP 90–109 mmHg. Sometimes this category as a whole is termed "mild," or it is further broken down into mild (140–149/90–99 mmHg) and moderate (150–159/100–109 mmHg).[13]
- *Severe hypertension.* SBP $\geq$ 160 mmHg and/or DBP $\geq$ 110 mmHg.[14] Severe hypertension in pregnancy has lower thresholds than in non-pregnant adults because pregnant women are known to develop hypertensive encephalopathy at lower blood pressures.[15]

Of note, the American College of Obstetricians and Gynecologists (ACOG) acknowledged in the newly released recommendations[3,12] that its hypertension definitions conflict with the recently changed diagnostic criteria of the American College of Cardiology (ACC) and American Heart Association (AHA) (stage I hypertension 130–139/80–89 mmHg; stage 2 $\geq$ 140/90 mmHg),[16] but have not yet redefined their diagnostic criteria.[12] Both the European Society of Cardiology (ESC) and Hypertension Canada, whose task forces also published guidelines for the management of cardiovascular diseases during pregnancy since the AHA/ACC recommendations changed in 2017, have also not changed their diagnostic criteria.[4,5]

Specific hypertensive disorders of pregnancy are named based on the context in which the hypertension is first identified (Table 1). Accepted across international guidelines are the following four categories:[3–10]

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Table 1. Hypertension categories in pregnancy.

	American College of Obstetricians and Gynecologists (ACOG)[3] 2019	Hypertension Canada[4] 2018	European Society of Cardiology (ESC)[5] 2018	Society of Obstetricians and Gynaecologists of Canada (SOGC)[6] 2014	International Society for the Study of Hypertension in Pregnancy (ISSHP)[7,8] 2018	Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[9] 2014	Royal College of Obstetricians and Gynaecologists (RCOG)[10] 2011
Categories	Chronic Hypertension Preeclampsia-eclampsia Chronic hypertension with superimposed preeclampsia Gestational hypertension	Chronic hypertension Gestational hypertension Preeclampsia (includes non-severe preeclampsia, severe preeclampsia, HELLP syndrome, eclampsia)	Pre-existing hypertension Gestational hypertension Preeclampsia Pre-existing hypertension plus superimposed gestational hypertension with proteinuria Antenatally unclassifiable hypertension	Pre-existing (chronic) hypertension - With comorbid condition(s) - With evidence of preeclampsia Gestational hypertension - With comorbid condition(s) - With evidence of preeclampsia Preeclampsia Other hypertensive effects - Transient hypertensive effect - White-coat hypertensive effect - Masked hypertensive effect	Chronic hypertension - Essential - Secondary White-coat hypertension Masked hypertension Gestational hypertension Transient gestational hypertension Preeclampsia – de novo or superimposed on chronic hypertension	Preeclampsia - eclampsia Gestational hypertension Chronic hypertension - Essential - Secondary White Coat Preeclampsia superimposed on chronic hypertension	Chronic hypertension Gestational hypertension Preeclampsia Severe preeclampsia Eclampsia HELLP
Definitions	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, measured at least 4 h apart Severe: SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg, measured at least 4 h apart	Hypertension: BP ⩾ 140/90 mmHg Severe: BP ⩾ 160/110 mmHg	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg Mild: BP 140–159/90–109 mmHg Severe: SBP ⩾ 160 mmHg or DBP ⩾ 110 mmHg Emergent: SBP ⩾ 170 mmHg or DBP ⩾ 110 mmHg	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, measured at least 15 min apart Severe: SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, confirmed over a few hours Severe: SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg, confirmed within 15 min	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg measured several hours apart Severe: SBP ⩾ 160 mmHg or DBP ⩾ 110 mmHg	Hypertension: SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg Mild: BP 140–149/90–99 mmHg Moderate: BP 150–159/100–109 mmHg Severe: SBP ⩾ 160/110 mmHg

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HELLP: hemolysis, elevated liver enzymes, low platelet count.

- *Chronic/pre-existing hypertension.* Hypertension discovered preconception or prior to 20 weeks' gestation.
- *Gestational hypertension.* Hypertension that appears de novo after 20 weeks' gestation and normalizes after pregnancy.
- *Preeclampsia-eclampsia.* De novo hypertension after 20 weeks' gestation accompanied by at least one of the following:
  - Proteinuria;
  - Other features of maternal organ dysfunction, including acute kidney injury (creatinine $\geqslant$90 μmol/L; 1 mg/dL), liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), and hematological complications (decreased platelet count <150,000/μL, disseminated intravascular coagulation, hemolysis);
  - Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth).

- *Chronic/pre-existing hypertension with superimposed preeclampsia-eclampsia.* Chronic hypertension as defined above, that develops signs and symptoms of preeclampsia or eclampsia after 20 weeks' gestation.

The ESC suggests that gestational hypertension should resolve within 42 days postpartum, which is the puerperal period, and that preexisting hypertension persists beyond this period;[5] however, many investigators support the concept that pregnancy hypertension may be termed chronic hypertension if it persists beyond 12 weeks after delivery.[17,18] ESC also includes a category "antenatally unclassifiable hypertension" as that which arises before 20 weeks, but has not yet been evaluated after 42 days postpartum for final classification.[5] There are a few other discrepancies across guidelines as well. Several societies include "White Coat Hypertension"[6–9] and the specific preeclampsia spectrum disorders (e.g. eclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP)).[4,10] The Society of Obstetricians and Gynaecologists of Canada also characterize their chronic and gestational hypertension as "with" or "without comorbidities."[6]

As noted previously, there remain terminology and definition discrepancies across international guidelines.[3–10] Hypertension itself has been defined over the years by diastolic or systolic readings alone, as well as by changes in pressures throughout pregnancy.[19] Cutoffs for what is considered severe hypertension have been different. Semantics have clinical implications, and systematic reviews often have to compare studies or populations, which are inferred to be the same, rather than standardized.[20] The International Society of the Study of Hypertension in Pregnancy (ISSHP) identified this as one of the factors for the range of controversies surrounding the treatment of hypertension during pregnancy and appointed a committee to address them beginning in 1998.[21] Reviewing various international guidelines, definitions are more standardized; however, there are still discrepancies in sphygmomanometer intervals that define hypertension, precise definitions of proteinuria, the terms used to characterize blood pressure in the non-severe range, and even terminology used to classify the hypertensive disorders themselves.[3–10] All of this reflects that the understanding of hypertensive disorders of pregnancy remains fluid and that further research is required before an universal consensus is reached on how to treat these disorders.

One important aspect of diagnosing and managing hypertension in pregnancy is ruling out secondary causes. These can add to both the maternal and fetal morbidity and mortality. Data from the Nationwide Inpatient Sample (NIS) of hospitalizations for delivery between 1995 and 2008 showed that of the patients with chronic hypertension (1.15% of the sampled population), 11.2% had secondary causes. Secondary hypertension had higher odds of adverse maternal and fetal outcomes when compared to essential hypertension (odds ratio (OR), 11.92 vs 10.18 for preeclampsia, 51.07 vs 13.14 for acute renal failure, 4.36 vs 2.89 for spontaneous delivery < 37 weeks).[22] Examples of secondary forms of hypertension are chronic kidney disease (most common cause), hyperaldosteronism, renovascular disease, obstructive sleep apnea, Cushing's syndrome, pheochromocytoma, thyroid disease, rheumatologic diseases (e.g. scleroderma or mixed connective tissue disease), and coarctation of the aorta; lack of understanding on how to diagnose and treat these conditions during pregnancy may lead to a higher morbidity and mortality.[23] While the diagnosis and treatment of each of these individual causes is outside of the scope of this article, it should be noted that many of the disorders have overlapping features with preeclampsia. The hormonal disorders often have different thresholds for diagnosis in pregnant patients, and if indicated, surgical interventions often need to be planned around gestational age.[23]

Cardiovascular physiology

The hormonal changes of pregnancy induce significant adaptations in the cardiovascular physiology of the mother.[24] Beginning early in the first trimester, there are surges of estrogen, progesterone, and relaxin (hormone that, like progesterone, mediates nitric oxide release), leading to systemic vasodilation.[25–27] Concurrently, the renin–angiotensin–aldosterone system (RAAS) is augmented to engender salt and water retention, leading to an expansion in plasma volume.[28] This, combined with an increased ventricular wall mass, leads to an increased stroke volume.[29] The expansion in plasma blood volume also results in a physiologic anemia, as the rate of increase

is faster than that of the increase in red blood cell mass.[30] In order to compensate for the aforementioned systemic vasodilation and physiologic anemia, heart rate raises.[29] The combination of elevated stroke volume and tachycardia leads to an increase in cardiac output during pregnancy, which compensates for the decline in vascular resistance in order to maintain blood pressure at high enough levels for maternal and placental perfusion.[29] A meta-analysis of 39 studies (1479 women) reviewing cardiac output data for healthy singleton pregnancies demonstrated that average increases in cardiac output, heart rate, and stroke volumes were 31%, 24%, and 13% of non-pregnant values at their peaks, while systemic vascular resistance at its nadir was 30% below that of non-pregnant patients.[31] Peaks for cardiac output and heart rate, as well as the nadir for systemic vascular resistance, were early in the third trimester, whereas the peak for stroke volume was early in the second trimester, with trends toward pre-pregnancy values as they got closer to term.[31] As expected, due to incomplete compensation of cardiac output for the amount of systemic vasodilation perfusion,[29] the mean arterial blood pressure was generally lower than pre-pregnancy pressure, with its nadir at an average of 8 mmHg (9%) below baseline during the second trimester.[31] As such, it is plausible that women with hypertension preconception may naturally fall out of the indicated treatment range during pregnancy.

Pathophysiology of hypertension

Any hypertensive disorder of pregnancy can result in preeclampsia. It occurs in up to 35% of women with gestational hypertension[32] and up to 25% of those with chronic hypertension.[17,33] The underlying pathophysiology that upholds this transition to, or superposition of, preeclampsia is not well understood; however, it is thought to be related to a mechanism of reduced placental perfusion inducing systemic vascular endothelial dysfunction.[34] This arises due to a less effective cytotrophoblastic invasion of the uterine spiral arteries.[35] The resultant placental hypoxia induces a cascade of inflammatory events, disrupting the balance of angiogenic factors, and inducing platelet aggregation, all of which result in endothelial dysfunction manifested clinically as the preeclampsia syndrome.[35,36] Angiogenic imbalances associated with the development of preeclampsia include decreased concentrations of angiogenic factors such as the vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) and increased concentration of their antagonist, the placental soluble fms-like tyrosine kinase 1 (sFlt-1).[37,38] Impeding the binding of VEGF and PIGF to their receptors is a factor in the reduction of nitric oxide synthesis, a crucial factor in vascular remodeling and vasodilation, which may otherwise be able to ameliorate placental ischemia.[39] Early-onset preeclampsia (EOPE), occurring before 34 weeks of gestation, is thought to be primarily caused by the syncytiotrophoblast stress leading to poor placentation, whereas late-onset preeclampsia (LOPE), occurring at or after 34 weeks, is understood to be secondary to the placenta outgrowing its own circulation.[40] It is worth mentioning that EOPE is more frequently associated with fetal growth restriction than LOPE, due to a longer duration of placental dysfunction.[29]

During the postpartum period, up to 27.5% of the women may develop de novo hypertension. This is due to several factors, including mobilization of fluid from the interstitial to intravascular space, administration of fluids and vasoactive agents. The shift of fluids increases the stroke volume and cardiac output up to 80%, followed by a compensatory mechanism of diuresis and vasodilation, which softens the rise in blood pressure.[35]

The pathophysiology of hypertension in pregnancy becomes particularly relevant when reviewing the current state of adjunct therapies to antihypertensives that may help prevent preeclampsia.

Target blood pressure

There is no debate that blood pressure needs to be controlled to less than 160/110 mmHg.[3–10] As noted previously, pregnant women are at a higher risk of central nervous system complications from hypertension than non-pregnant women,[15] and a cross-sectional study of more than 81 million pregnancy hospitalizations found that hypertensive disorders of pregnancy increase the risk of stroke 5.2-fold.[41] In addition, a subgroup analysis of the Control of Hypertension in Pregnancy Study (CHIPS) confirmed that severe hypertension was associated with higher rates of maternal death, pregnancy loss or high-level neonatal care for >48 h, small-for-gestational age (SGA), preterm delivery, and a variety of other poor obstetric outcomes compared to those with non-severe hypertension. This was regardless of preeclampsia status.[42]

How aggressively to treat non-severe hypertension remains controversial. This is evident when reviewing various guidelines, which range from recommending treatment for all women with blood pressure ⩾ 140/90 mmHg[4] to allowing blood pressure to run as high as 160/110 mmHg before treating.[3,12] The British guidelines and the ACOG Bulletin endorse targeting diastolic pressure above 80 mmHg to maintain the uteroplacental blood flow.[3,10] Many endorse a stricter control in patients with evidence of end-organ damage, though there is no consensus as to just how tight it should be.[3,5,6,8,10]

The differences are due to the paucity of data that clearly delineate benefits and risks of different degrees of blood pressure control. The most recent Cochrane systematic review of antihypertensive medications for mild to moderate hypertension during pregnancy analyzed 31 trials (3485 women) comparing different antihypertensives to placebo or no treatment, and 29 trials (2774 women) comparing one antihypertensive to another. It concluded that the use of antihypertensives halves the number of women who develop severe hypertension and has minimal, if any, effects on baby death at any time up through the first 28 days, the development of preeclampsia, preterm delivery (<37 weeks), or

SGA. There was insufficient data on the effect on maternal outcomes. Unfortunately, most of the studies were small; there was variety in how mild, moderate, and severe hypertension were defined; there was heterogeneity in regard to whether studies recruited participants with chronic, gestational, proteinuric, and non-proteinuric hypertension; SGA was defined differently across protocols.[20] Other meta-analyses which stratified proteinuric hypertension and chronic hypertension also could not find significant differences in maternal-fetal outcomes when control was tighter and found similar study limitations to the aforementioned Cochrane review.[43,44] Furthermore, it is difficult to extrapolate the data to modern practice, as 45% of the participants studied received agents not routinely used anymore for managing hypertensive disorders of pregnancy (e.g. atenolol, acebutolol, oxprenolol, pindolol, bendroflumethiazide, hydrochlorothiazide, ketanserin). In addition, beta-blockers are no longer first-line agents to treat hypertension outside of pregnancy, and the dose of bendroflumethiazide used in the included study was higher (5–10 mg daily) than the 2.5 mg dose used today.[44]

The CHIPS, a randomized controlled, open, multicenter, international trial, was designed to prevent the deficits from prior studies. The study randomized approximately 1000 women with nonproteinuric, preexisting, or gestational hypertension (defined as DBP of 90–105 mmHg or 85–105 mmHg if on antihypertensive medications) to "less-tight-control" versus "tight-control" (target DBP 100 mmHg vs 85 mmHg, respectively). The composite primary outcome (pregnancy loss or high levels neonatal care for more than 48 h during the first 28 days) and secondary outcomes (serious maternal complication in the first 6 weeks postpartum) were similar in both arms. The only significant finding was that severe hypertension developed more in the "less-tight-control" group than in the "tight-control" group.[45] Experts continue to remain conflicted about how to apply these findings, though two subgroup analyses suggest that there is both maternal and perinatal benefit to preventing severe hypertension.[42,46]

The Chronic Hypertension and Pregnancy (CHAP) project, an even larger, multicenter randomized controlled trial, is currently underway in the United States. The study is recruiting pregnant women with chronic hypertension who are either untreated or on monotherapy, with blood pressure ranging between 140–159/90–104 mmHg. Patients are randomized to the "anti-hypertensive therapy" arm to control their blood pressure to <140/90 mmHg, or the "no antihypertensive or low dose therapy" arm, with the goal of maintaining a blood pressure <160/105 mmHg; antihypertensives are only given in small enough doses to maintain pressures just below this threshold. Primary outcomes will be composite adverse perinatal outcomes up to 2 weeks postpartum (fetal and neonatal death, preeclampsia with severe features, placental abruption, and preterm labor < 35 weeks gestation) and SGA (<10th percentile birth weight). The trial is expected to recruit 4700 participants, which is almost five times that of CHIPS.[47] Given that almost 75% of the participants included in the analysis of CHIPS had chronic hypertension,[45] the results of CHAP will likely be able to corroborate or contest those of CHIPS, despite a study design that is not identical. If the treatment arm of CHAP ends up proving non-inferior, or even beneficial, there will likely need to be follow-up analysis regarding the safety and benefits of controlling blood pressure in pregnancy at the lower pressures dictated in the updated 2017 AHA/ACC blood pressure control guidelines.

Home blood pressure monitoring

A diagnosis of hypertension in pregnancy warrants closer monitoring, particularly if it is diagnosed after 20 weeks' gestation.[3,12] Home blood pressure recording is being examined as a means of improving monitoring during this period and detecting white coat hypertension, masked hypertension, and sustained hypertension. The first role of home blood pressure monitoring is in confirming the diagnosis of hypertension. While the exact prevalence of white coat hypertension, elevated blood pressure in the office not present at home, is not known, the ACOG recommends ambulatory blood pressure monitoring for those patients in whom it is suspected.[12] Some studies suggest that the rates are not insignificant. A prospective observational study found that 32% of the 155 participants diagnosed with chronic hypertension after conception had white coat hypertension as confirmed by 24-h ambulatory blood pressure monitoring.[48] Another study found that approximately 60% of the 60 patients diagnosed with hypertension in the office during the second trimester had white coat hypertension.[49] One study using ambulatory blood pressure monitoring in 121 patients diagnosed with gestational hypertension or preeclampsia suggests that the prevalence of the white coat effect is significantly lower, with less than 5% of these patients having either systolic or diastolic white coat hypertension.[50] In addition, home blood pressure monitoring may identify masked hypertension, when blood pressure is normal in the clinic but elevated at home. A systematic review and individual patient data meta-analysis found masked hypertension in 3.2%, 1.6%, 2.9%, and 5.7% of self-monitoring patients at 5–14, 15–22, 23–32, and 33–42 weeks gestation, respectively.[51] The second role of blood pressure monitoring is in improving convenience for patients who need extra monitoring. One case–control study of 166 pregnant hypertensive women found that those who used home blood pressure monitoring had fewer outpatient visits than those who did not, without any change in outcomes.[52] For those at risk for adverse perinatal outcomes, home blood pressure monitoring may play a role in earlier diagnosis of hypertensive disorders of pregnancy. In one prospective cohort study, 200 pregnant women with risk factors for preeclampsia were asked to take two blood pressure readings twice daily three

times per week. Of those who self-monitored (74% compliant until 20 weeks' gestation and 66% until 36 weeks' gestation), 23 were diagnosed with gestational hypertension or preeclampsia, and 9 of those patients had elevated home blood pressure readings before they were found with an elevated blood pressure reading in the clinic.[53] Finally, the ambulatory blood pressure monitoring might predict fetal growth restriction better than the readings in the office.[54]

It is important to note that while home blood pressure monitoring may be important, the readings must be validated with those of the office sphygmomanometer. A systematic review of the accuracy of blood pressure devices in pregnancy noted that only some of the ambulatory monitoring devices pass validation protocols.[55] Another study comparing consecutive blood pressures by validated and non-validated automated blood pressure cuffs to sphygmomanometer readings in 127 pregnant patients showed that 69% of systolic and 77% of diastolic readings were within 5 mmHg of their manual standard and recommended that patients validate their home monitors in the office prior to use at home.[56]

Treatment of choice—severe hypertension

Historically, a variety of agents have been used to acutely lower blood pressure, including hydralazine, various calcium channel blockers, methyldopa, diazoxide, prostacyclin, ketanserin urapidil, prazosin, isosorbide, and even magnesium sulfate.[57] Most commonly used in recent years are intravenous hydralazine, intravenous labetalol, and calcium channel blockers (in particular short-acting oral nifedipine; Table 2).[58]

Hydralazine may fall out of favor, as two meta-analyses, one including 35 studies (3573 women) and another with 21 trials (893 women), have demonstrated that pregnant women taking calcium channel blockers were less likely to have persistent high blood pressure when compared to those treated with hydralazine.[57,59] One review also suggested that hydralazine was associated with an overall increase in adverse maternal hypotension, cesarean sections, placental abruption, oliguria, and more adverse effects on fetal heart rate and low 1-min Apgar scores compared to other antihypertensive medications.[59] Attempts have been made to compare oral nifedipine to IV labetalol, but the most recent meta-analysis of seven studies (363 mother–infant pairs) only found a statistically significant reduction in reported maternal side effects in those treated with nifedipine (relative risk (RR), 0.57; 95% confidence interval (CI), 0.35–0.94); there was no statistically significant difference in control of persistent hypertension, maternal morbidity or mortality, or fetal and neonatal outcomes.[58] As such, all three agents continue to be recommended by international guidelines,[3–7,9,10] and the ACOG currently has suggested protocols for all three agents in their 2019 practice bulletin (Table 3).[3] It is worth mentioning that a triple-blinded, placebo-controlled trial, in a small population (34 patients) diagnosed with severe preeclampsia and treated with magnesium sulfate, compared sublingual nifedipine to intravenous nitroglycerin. The study showed a greater and faster hypotensive response, with less variability in the nitroglycerin group, and no significant changes in fetal heart rate in response to the vasodilator therapy, with similar perinatal fetal-maternal adverse effects in both groups.[60]

Severe hypertension in pregnancy without end-organ complications is considered, as in the non-pregnant state, a medical "urgency." Blood pressure needs to be reduced to less than 160/110 mmHg, with an initial reduction of less than 25% in the first hours of treatment, and a more gradual decrease in the following hours. A more forceful reduction may place the fetus at risk for underperfusion, considering that the fetoplacental unit cannot autoregulate blood flow. In contrast, severe hypertension associated with end-organ complications such as pulmonary edema or acute kidney injury is considered an "emergency" and the blood pressure needs to be decreased much faster.[32]

There is insufficient evidence to support a specific blood pressure target in women with preeclampsia and cerebrovascular or renal complications. The degree of hypertension at which to institute therapy is the subject of many controversies. Most guidelines recommend starting therapy at a blood pressure level above 150/100 mmHg, while others recommend treatment only for blood pressure over 160/110 mmHg.[3,6,10] Failure to intensively treat SBP was associated with maternal deaths from cerebral hemorrhage and aortic dissection.[61] However, the risk of placental underperfusion is a real concern, especially with levels below 110/80 and such reduction in blood pressure should be avoided.

In preeclampsia associated with pulmonary edema, ESC recommends the use of nitroglycerin given as an intravenous infusion.[62] Blood pressure should be reduced at a rate of approximately 30 mmHg over 3–5 min, followed by a slower rate to a target blood pressure of approximately 140/90 mmHg.[63]

The postpartum care of women with preeclampsia includes strict monitoring of blood pressure and clinical conditions. Previous medications should be continued when blood pressure is elevated and withdrawn slowly over days when blood pressure normalizes. Blood pressure medications may need to be discontinued if BP $<$ 110/70 mmHg or patient is symptomatic.[8]

- Adjunct measures to the treatment of severe hypertension in preeclampsia.

In patients with preeclampsia with severe features (e.g. severe hypertension and proteinuria or hypertension and neurological complications), or eclampsia, it is recommended that magnesium sulfate be given for seizure prophylaxis.[3] This measure was established by the Magpie Trial, a randomized placebo-controlled trial, in which over 10,000 women were either given magnesium sulfate or placebo upon diagnosis of a blood pressure of $>$140/90 mmHg and proteinuria of at least 30 mg/dL, which showed a 58% reduced risk of eclampsia, and improved

Table 2. Hypertension treatment in pregnancy.

	American College of Obstetricians and Gynecologists (ACOG)[3] 2019	Hypertension Canada[4] 2018	European Society of Cardiology (ESC)[5] 2018	Society of Obstetricians and Gynaecologists of Canada (SOGC)[6] 2014	International Society for the Study of Hypertension in Pregnancy (ISSHP)[7,8] 2018	Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[9] 2014	Royal College of Obstetricians and Gynaecologists (RCOG)[10] 2011
Indications for treatment	Persistent SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg Comorbidities/end-organ damage: >140/90 mmHg (per 2013 guidelines)	Any BP ⩾ 140/90 mmHg Target to DBP 85 mmHg Urgent lowering: ⩾160/110 mmHg	Emergent: SBP ⩾ 170 mmHg or DBP ⩾ 110 mmHg Persistent elevation ⩾ 150/95 mmHg >140/90 mmHg in women with gestational hypertension, pre-existing hypertension with superimposed gestational hypertension, subclinical organ damage or symptoms	Severe: SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg Non-severe: *Without* comorbid conditions: 130–155/80–105 mmHg *With* comorbid conditions: <140/90 mmHg	Urgent lowering: SBP ⩾ 160 mmHg and/or DBP ⩾ 110 mmHg If SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg lowering to a target DBP 85 mmHg and a target SBP < 160 mmHg (optimal SBP 110–140 mmHg)	>140–160/90–100 mmHg Urgent lowering: SBP ⩾ 170 mmHg	Uncomplicated hypertension: ⩾ 150/100 mmHg Target-organ damage: ⩾140/90 mmHg
Recommended treatment for urgent/severe	IV Labetalol IV Hydralazine PO Nifedipine immediate-release (IR)	Does not comment on agents	1st line: IV Labetalol PO Methyldopa PO Nifedipine 2nd line: IV Hydralazine IV Urapidil 3rd line: IV Nitroprusside IV Nitroglycerin	1st line: IV Labetalol IV Hydralazine PO Nifedipine IR 2nd line: IV Nitroglycerin PO Methyldopa PO labetalol PO clonidine 3rd line: IV Nitroprusside	PO Nifedipine IR IV Labetalol IV Hydralazine	1st line IV Labetalol PO Nifedipine IV Hydralazine IV Diazoxide 2nd line: IV Nitroprusside IV Nitroglycerin	1st line: PO Labetalol In critical care: IV Labetalol IV Hydralazine PO Nifedipine IR
Recommended treatment for non-urgent/ outpatient (All formulations are oral)	1st line: Labetalol Nifedipine ER Methyldopa 2nd line: Hydrochlorothiazide Avoid atenolol and ACE inhibitors or ARBs	1st line: Labetalol Methyldopa Long-acting nifedipine Other beta-blockers (acebutolol, metoprolol, pindolol, propranolol) 2nd line: Clonidine Hydralazine Thiazide diuretics Avoid ACE inhibitors and ARBs	1st line: Methyldopa Beta-blockers (most data available on labetalol) Calcium channel blockers (most data available on nifedipine) Avoid ACE inhibitors, ARBs, and direct renin inhibitors Avoid diuretics unless oliguric	"Most commonly used": Methyldopa Labetalol Calcium channel blockers (nifedipine XL) Beta-blockers (acebutolol, metoprolol, pindolol, propranolol) Avoid ACE inhibitors and ARBs	1st line: Methyldopa Labetalol Oxprenolol Nifedipine Diltiazem 2nd or 3rd Line Hydralazine Prazosin	1st line: Methyldopa Labetalol Oxprenalol 2nd line: Hydralazine Nifedipine slow release Prazosin Avoid ACE inhibitors, ARBs, diuretics, and atenolol	1st line: Labetalol 2nd line: Methyldopa Nifedipine long acting Avoid ACE inhibitors, ARBs, and chlorothiazide

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; PO: Per Os; IV: intravenous; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers.

Table 3. Common antihypertensive medications used in pregnancy.

	Urgent BP lowering		Outpatient BP control	
Labetalol	Intravenous	10–20 mg, then 20–80 mg every 10–30 min, maximum 300 mg OR 1–2 mg/min infusion	Oral	200–2400 mg/day, divided into two to three doses
Hydralazine	Intravenous	5 mg, then 5–10 mg every 20–40 min, maximum 20 mg OR 0.5–10 mg/h infusion	Not commonly used first-line	
Nifedipine	Oral *Immediate release*	10–20 mg every 2–6 h*, maximum 180 mg/day *May repeat initial dose after 20 min if needed	Oral *Extended Release*	30–120 mg/day
Methyldopa	Not commonly used first-line		Oral	500–3000 mg/day, divided into two to four doses

Adapted from the American College of Obstetricians and Gynecologists Practice Bulletin Number 2019.[3,12]

maternal mortality in those who received magnesium sulfate.[64] This was confirmed in a study that demonstrated that women with severe preeclampsia had a lower incidence of seizure when given magnesium sulfate than those who were given nimodipine, a calcium channel blocker.[65] Of note, those who received magnesium were more likely to require hydralazine for blood pressure control.[65] The indications for using magnesium sulfate for seizure prophylaxis in patients with preeclampsia without severe features is more controversial and based on the number needed to treat in order to prevent a seizure.[3,8] As such, guidelines differ in their recommendations for using magnesium sulfate as seizure prophylaxis depending on resource setting and clinical scenario.[3,6,8]

There have been reports of exaggerated hypotension when nifedipine and magnesium sulfate have been combined.[66–68] However, a retrospective case–control study did not show that nifedipine increased the risk of magnesium-related side effects (e.g. neuromuscular weakness).[69] As such, the ACOG is comfortable with administering them simultaneously when indicated (ACOG task force 2013).

- Prevention of preeclampsia.

Several adjunct therapies are used to decrease the risk of developing preeclampsia.

Since 1979, aspirin has been shown to prevent preeclampsia.[70] Aspirin reverses the platelet aggregation induced by the imbalance of thromboxane A2/prostacyclin ratio mediated by the endothelial dysfunction.[36] The effect of aspirin has been validated by over 30 trials; most recently, by the Aspirin for Evidence-Based Preeclampsia Prevention trial, a multi-center, double-blinded, placebo-controlled trial comparing 150 mg aspirin to placebo in 798 women who were considered at risk for preeclampsia. The preterm preeclampsia occurred in 1.6% of the women on aspirin versus 4.3% of the ones in the placebo group (OR, 0.38; 95% CI, 0.20–0.74, $p = 0.004$).[71] Furthermore, a meta-analysis of 45 randomized studies (20,909 pregnant women) published in 2017 demonstrated that the effects of aspirin are dose dependent and also correlated with the gestational age at which the aspirin is initiated. When initiated at <16 weeks and at higher doses, aspirin was more effective at preventing preeclampsia, severe preeclampsia, and fetal growth restriction, whereas there was a smaller chance of preventing preeclampsia, and no effect on severe preeclampsia or fetal growth restriction seen if it was initiated after 16 weeks; there was also no dose effect when initiated later in the gestational period.[72] Aspirin is thus recommended for women at higher risk for preeclampsia (e.g. history of preeclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, age >35) by the British, American, and European professional societies.[3,5,10] Notably, the ACOG augmented their guidelines to expand their criteria at which to initiate aspirin therapy to include more maternal risk factors, and changed their suggestion from 60–80 mg of aspirin to 81 mg of aspirin.[2,3] With the updates to the ACOG recommendations, maternal risk factors guiding aspirin initiation are now similar across all three guidelines, though dosing recommendations for the aspirin remain varied; the ESC recommends 100–150 mg, and the National Institute for Health and Care Excellence (NICE) guidelines recommend 75 mg.[5,10]

As early as the 1950s, epidemiological studies showed an association between reduced rates of preeclampsia and eclampsia in populations whose diets were rich in calcium supplementation.[73,74] This observation has been confirmed by several randomized controlled trials. A meta-analysis of 27 of them (18,064 women) comparing calcium supplementation during pregnancy (at both high and low doses) with placebo or no calcium suggests that high-dose calcium supplementation ($\geqslant 1$ g/day) is associated with lower rates of preeclampsia, hypertension, and preterm birth. Similar reduction in rates of preeclampsia and hypertension are noticed with lower doses of calcium (<1 g/day); however, the evidence is more limited.[75] As such, the World Health Organization (WHO) recommends 1.5–2 g of oral calcium supplementation for those with low dietary calcium intake,[76]

a recommendation echoed by the ESC guidelines.[5] American guidelines acknowledge the above recommendations, but do not include them in their routine care,[3] as The Trial of Calcium for Preeclampsia Prevention, a large, multicenter, double-blinded randomized controlled trial of 2 g calcium supplementation versus placebo conducted across five American medical centers, did not show any effect on the rates of preeclampsia, pregnancy-associated hypertensive disorders, or blood pressure, which was attributed to the fact that study participants had adequate dietary calcium intake at baseline; results of other studies could thus not be extrapolated to care in the developed world.[77]

Currently under investigation is the role of statins to treat and prevent preeclampsia. The evidence from preclinical animal models suggests that their benefits are derived from their pleiotropic antioxidant, anti-inflammatory, and antithrombotic effects, helping to alleviate the endothelial dysfunction thought to be at the center of preeclampsia pathogenesis, with a specific focus on its effects on nitric oxide synthesis and antiangiogenic soluble Fms-like tyrosine kinase-1 expression.[78–81] A small case series of preeclamptic women treated with pravastatin demonstrated similar amelioration of endothelial dysfunction and decrease in antiangiogenic biomarkers when their placentas were analyzed; clinically, the patients' blood pressure, proteinuria, and uric acid levels were also stabilized.[82] Larger clinical trials are currently underway.

Treatment of choice—non-severe hypertension

In cases of non-severe hypertension, the most commonly recommended first-line agents are methyldopa, labetalol, and nifedipine,[3–10] and the ACOG outlines their suggested doses in their 2019 practice bulletin (Tables 2 and 3).[3] Unsurprisingly, there is some variability in the specific recommendations,[3–7,9,10] driven by the uncertainty of which of these agents best prevent poor maternal and fetal outcomes.

- Methyldopa.

Methyldopa is recommended as a first-line agent for non-severe blood pressure control by American, Canadian, European and Australian/New Zealander guidelines.[3–5,9] It has been studied since the 1960s[20] and has long-term safety data in children whose mothers took it during pregnancy.[83] A prospective cohort study evaluating pregnancy outcomes in first trimester exposure found that it was not teratogenic; however, there was a higher rate of spontaneous abortions and preterm delivery.[84] Although recommended by the above guidelines, and noted to be most commonly used by the International Society for the Study of Hypertension in Pregnancy,[7,8] the most recent update from the Cochrane review of antihypertensive treatment for mild to moderate hypertension in pregnancy demonstrates that it is inferior to calcium channel blockers and beta-blockers in regard to preventing severe hypertension (RR, 0.70; 95% CI, 0.56–0.88, 11 trials, 638 women) and may be associated with more cesarean sections than other drugs (adjusted relative risk (aRR), 0.84; 95% CI, 0.84–0.95, 13 trials, 1330 women).[20] However, a subgroup analysis of the CHIPS trial found that those treated with methyldopa rather than labetalol post randomization had better primary and secondary outcomes, including birthweight, severe hypertension, preeclampsia, and preterm delivery.[85] Furthermore, a recent retrospective cohort study found that methyldopa was associated with fewer adverse infant outcomes, including respiratory distress, seizure, and sepsis, compared with oral labetalol.[86] Thus, methyldopa will likely not be removed from first-line agents until there is more definitive evidence against it.

- Oral labetalol.

Oral labetalol is considered a first-line agent for non-severe hypertension in pregnancy[3–7,9,10] and is in fact the only first-line agent recommended by the British guidelines.[10] In a prospective observational study, approximately 75% of women responded to oral labetalol as monotherapy.[87] Earlier randomized trials directly comparing it to methyldopa found equivalency in safety and efficacy,[88,89] and a more recent one showed borderline superiority of labetalol in preventing proteinuria, severe hypertension, and antenatal hospitalizations; labetalol was also independently associated with fewer maternal composite outcomes and perinatal composite outcomes.[90] However, there are also recent studies suggesting that labetalol is actually inferior to methyldopa in regard to preventing adverse maternal and perinatal outcomes.[85,86] Furthermore, an exploratory study comparing ambulatory blood pressure measurements of women taking oral labetalol to those taking modified release nifedipine showed that those on labetalol spent more time than their comparator below the diastolic target of 80 mmHg, indicating that they may be at higher risk of poor uteroplacental perfusion.[91]

- Other beta-blockers.

Beta-blockers other than labetalol are less well studied;[5] however, some are considered first-line agents in Canada (acebutolol, metoprolol, pindolol, propranolol).[4,6] Australia/New Zealand includes oxprenolol in its first-line treatments for non-severe hypertension in pregnancy.[10] There is some controversy regarding beta-blockers' teratogenicity and effect on birth weight. Atenolol is known to cause intrauterine growth retardation,[92] and the ACOG specifically recommends against its use.[3] In contrast, a study comparing oxprenolol to methyldopa found that outcomes and safety were equal.[93] A 2003 Cochrane review of oral beta-blockers to treat mild and moderate hypertension in pregnancy (12 trials, 1346 women) compared oral beta-blockers to no medication or placebo and found an increased risk of

SGA (RR, 1.36; 95% CI, 1.02–1.82).[94] This was supported by a cohort study, which found higher adjusted ORs of SGA < 10th percentile, <3rd percentile, preterm birth, and neonatal hospitalization for women with chronic hypertension taking beta-blockers compared to ones taking methyldopa.[95] However, a recent retrospective cohort study found that, after adjusting for maternal age, body mass index, and comorbidities, there was no association between beta-blockers and fetal cardiac anomalies.[96] Furthermore, an international cohort study which pooled over 15,000 women exposed to beta-blockers during the first trimester found no significant increase in the relative risk (RR, 1.07; 95% CI, 0.89–1.30) or risk difference per 1000 persons exposed (3.0; 95% CI, –6.6 to 12.6) for any major congenital malformation.[97] In contrast, a cohort study that examined more than 10,000 women exposed to beta-blockers late in pregnancy showed that both the risks of neonatal bradycardia and hypoglycemia were increased in those who were beta-blocker-exposed compared to those who were not; when looking at the three most commonly prescribed beta-blockers (labetalol, metoprolol, and atenolol), ORs were > 1 for both outcomes, except for the neonatal bradycardia in the metoprolol-exposed group (OR, 0.59; 95% CI, 0.32–1.09).[98]

- Calcium channel blockers.

Calcium channel blockers, in particular long-acting nifedipine, are preferred as first line in most guidelines.[3–7,9,10] A prospective cohort showed minimal teratogenicity when mothers are exposed to calcium channel blockers in the first trimester.[99] Furthermore, they have been shown superior to methyldopa in regard to controlling blood pressure[20] and are possibly safer than labetalol in regard to controlling blood pressure to a safely low diastolic pressure.[91] One randomized controlled clinical trial compared oral nifedipine and labetalol in pregnant women with chronic hypertension. A central aortic pressure drop of mean 7.4 mmHg was seen in the nifedipine arm, but peripheral blood pressures were effectively the same in both arms. There was a slight increase in neonatal intensive care unit (ICU) and neonatal adverse effects in the nifedipine arm.[100]

Data for amlodipine, another commonly prescribed dihydropyridine calcium channel blocker, appear to be very limited. Three case series concluded that amlodipine does not appear to be teratogenic,[101] and a small pilot study comparing amlodipine to aspirin and furosemide for the treatment of chronic hypertension revealed no differences between the two antihypertensives in maternal or perinatal outcomes.[102]

- Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin-receptor blockers (ARBs).

The RAAS inhibitors have been universally contraindicated due to their association with oligohydramnios, intrauterine growth restriction, and a variety of renal and other congenital abnormalities when women are exposed during the second or third trimester of pregnancy.[2] These medications came under scrutiny after a cohort study of 30,000 infants born to non-diabetic mothers showed an increased risk of major congenital malformations in those exposed to ACE inhibitors during the first trimester compared to those who had no exposure to antihypertensives (RR, 2.71; 95% CI, 1.72–4.27).[103] However, the study did not explicitly control for maternal obesity, an independent risk factor for congenital anomalies.[104] In addition, the population studied was confounded by women with undiagnosed or diet controlled diabetes, another independent risk factor for birth defects.[105,106] A similar retrospective cohort study found an increased risk of congenital heart defects in those exposed to ACE inhibitors compared to normotensive controls (OR, 1.54; 95% CI, 0.90–2.62), though there was a similar OR found in those exposed to other antihypertensives (OR, 1.52; 95% CI, 1.04–2.21). Furthermore, compared to the hypertensive controls (those who were not medicated), there was no increased risk for the cardiac abnormalities (OR, 1.14; 95% CI, 0.65–1.98 and OR, 1.12; 95% CI, 0.76–1.64).[107] Several other studies, both prospective and retrospective, also debunk the risk of congenital malformations, specifically related to first-trimester exposure to both ACE inhibitors and ARBs.[108–110]

ACE inhibitors remain first-line agents in hypertension outside of pregnancy,[16,111,112] and along with ARBs, they are also indicated for prevention of microvascular complications of diabetes.[113] Because of the new lower thresholds for diagnosis of hypertension,[111] and increasing rates of diabetes in young people,[114] more women will qualify for ACE inhibitors and ARBs at reproductive age. Since approximately half of pregnancies are unplanned,[115] it is possible that many women on these agents will inadvertently expose their fetuses until they find out they are pregnant and have their antihypertensive switched. As such, it is particularly important to understand first trimester safety profile, as it will help direct the preconception management.

- Thiazide diuretics.

Thiazide diuretics are considered second-line therapy for non-severe hypertension per the ACOG and Hypertension Canada,[4,12] but are not recommended by the ESC, the Society of Obstetric Medicine of Australia and New Zealand, and the British NICE guidelines.[5,9,10] Thiazides were routinely prescribed prophylactically in the 1960s as it was thought that removing edema could prevent preeclampsia, regardless of hypertensive status.[116] This was driven by a trial with over 3000 patients randomized to thiazides or no thiazides, showing the thiazide group had less "toxemia" (the term then used for preeclampsia), perinatal mortality, and premature birth.[117] This practice dwindled as researchers started to believe that inadequate plasma blood volume expansion in pregnancy may be correlated with preeclampsia.[118] Further data did not support these concerns. A randomized prospective trial found

that there was a lower rate of plasma blood volume expansion in diuretic-treated women compared to those who were not; however, there was no difference in perinatal outcomes.[119] In regard to the effects on preeclampsia, one meta-analysis reviewed 9 trials (7000 women) and showed a decline in preeclampsia with the use of diuretics,[120] although a more recent Cochrane review (5 studies, 1836 women) did not show a significant difference in preeclampsia, pre-term births, or SGA in trials that compared thiazide diuretics to placebo or nothing.[116]

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of postpartum hypertension.

Hypertensive disorders of pregnancy can occur after parturition. One study of 151 women showed that 5.7% of them developed preeclampsia or eclampsia postpartum;[121] another study found that of 22 patients presenting to emergency department with preeclampsia up to 4 weeks after delivery, 55% were de novo.[122] The causes of postpartum hypertension are multifactorial; as the body attempts to return to prepregnant physiology, which includes mobilization of the extracellular fluid into the intracellular space, blood pressure may be further elevated by fluids and NSAIDs provided as part of supportive care.[123] NSAIDs came under scrutiny when a case series of six patients in Australia, some of whom had preeclampsia during pregnancy, developed hypertensive crises after being administered indomethacin or ibuprofen in the postpartum period.[124] Larger studies have conflicting evidence. One retrospective cohort study comparing 223 women with severe hypertensive disorders of pregnancy, 148 who had received NSAIDs and 75 who had not, showed that exposure was not associated with an elevation in mean arterial pressure postpartum.[125] Two randomized controlled trials comparing acetaminophen use to ibuprofen in women with severe preeclampsia in the postpartum period achieved conflicting results: one demonstrated significantly more hypertension in the ibuprofen arm,[126] and the other found that there was no difference in the duration of severe hypertension or mean arterial pressure.[127] As such, the ACOG does not advise against their use in the postpartum period.[3]

Conclusion

Despite the differences in guidelines, there appears to be consensus that severe hypertension and non-severe hypertension with evidence of end-organ damage need to be controlled; yet the ideal target ranges below 160/110 mmHg remain a source of debate. Intravenous hydralazine, immediate release nifedipine, and intravenous labetalol remain the drugs of choice for severe hypertension. Oral extended release nifedipine, oral labetalol, and methyldopa are the generally accepted first-line agents for non-severe hypertension. Beta-blockers and diuretics are acceptable, while RAAS inhibitors remain contraindicated.

In addition to needing more studies that compare various agents head-to-head, there also needs to be more research to create targeted management strategies to chronic versus gestational hypertension, as well as non-severe hypertension with evidence of end-organ damage.

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