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Hypertension in Pregnancy: Is it time for a new approach to treatment?

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Abstract

Hypertensive disorders represent major causes of pregnancy-related maternal mortality worldwide. The current definition and treatment recommendations for elevated blood pressure during pregnancy in the US have remained unchanged for many years, unlike the recommendations for hypertension treatment in the general population. Clinical studies have provided convincing evidence that women with hypertensive pregnancy disorders are at both immediate and long-term risk for cardiovascular complications; these findings suggest that consideration be given to lowering the presently recommended blood pressure thresholds, both for the initiation of therapy and for therapeutic targets, and to simplifying the approach to the management of elevated blood pressure in pregnancy. This review focuses on the current treatment strategies for hypertensive pregnancy disorders, new developments in the field of hypertension, in general, and in pregnant patients, in particular, and their potential impact on contemporary blood pressure goals and the use of specific antihypertensive medications in pregnancy.

Keywords

hypertension in pregnancy; preeclampsia; antihypertensive therapy in pregnancy; cardiovascular complications

Historical aspects

Hypertension is the most common primary diagnosis in the US and has long been recognized as a major risk factor for cardiovascular and renal morbidity and mortality. Since 1977, the Joint National Committee (JNC) on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has taken a leading role in guiding the medical community in establishing criteria, both for the diagnosis and treatment of hypertension [1]. Through the years, and with the emergence of data from well-designed clinical trials demonstrating that antihypertensive therapy reduces the incidence of stroke, myocardial

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CONFLICT OF INTEREST

Dr. Garovic is the inventor of a patent for podocyturia technology as a diagnostic test for preeclampsia. The technology has been licensed to a commercial entity. Dr. Garovic and Mayo Clinic have contractual rights to receive royalties from the licensing of this technology.

infarction (MI), and heart failure (HF), even in patients with less severe hypertension, the blood pressure levels at which to begin treatment have been reduced. For example, the most recent JNC 7 report [2] defines a normal diastolic blood pressure (DBP) as ≤ 80 mm Hg, compared to ≤ 90 mm Hg in JNC I, and normal systolic blood pressure (SBP) as ≤120 mm Hg, compared to ≤140 mm Hg in JNC III [3]. JNC 7 introduced a new diagnostic category, termed "pre-hypertension" (SBP 120-139 or DBP 80-89 mm Hg) to identify a subset of patients at risk for developing hypertension. In all instances, hypertension is defined as a blood pressure (BP) of >140/90 mm Hg, which, if sustained, requires treatment. In certain subsets of patients with significant co-morbidities, treatment is indicated at lower values.

Similar to the non-pregnant population, hypertension is the most common medical disorder encountered during pregnancy and is estimated to occur in about 6-8% of pregnancies [4]. A recent report highlighted hypertensive disorders as one of the major causes of pregnancy-related maternal deaths in the United States, accounting for 579 of the 4693 (12.3%) maternal deaths that occurred between 1998-2005 [5]. The 1990 National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure in Pregnancy [6] expanded on the recommendations presented in JNC IV in 1988 [7]. These recommendations were subsequently updated in 2000 (Table 1) [4]. The definition and treatment recommendations for elevated BP in pregnancy, unlike those for hypertension in the general population, have not similarly evolved. In this review, we discuss new developments in the field of hypertension, in general, and in pregnant patients, in particular, and their potential impact on BP goals and antihypertensive medication use in pregnancy. We propose that consideration be given to reducing blood pressure to levels lower than presently advocated, both for the initiation of therapy and as therapeutic targets. A new simplified approach to the management of elevated BP in pregnancy is presented.

Current Guidelines and Practice

Due to gestational physiology, BP may decrease during the first trimester of pregnancy, reaching its nadir by mid-pregnancy. A normal BP of 110-120/70-80 mm Hg in a healthy woman of 20-30 years of age might decrease by 5-10 mm Hg during this interval, as compensatory increases in blood volume and vasodilatation occur. SBP is less affected than DBP because of the increased cardiac output that offsets the systemic vasodilation.

Blood pressure then usually returns to preconception levels during the third trimester. Hypertension in pregnancy is defined as a BP of 140/90 mm Hg or higher in a previously normotensive patient, and when accompanied by significant proteinuria (≥ 300 mg/24 hours), fulfills the criteria for the diagnosis of preeclampsia. The NHBPEP recommendations state that antihypertensive therapy in preeclamptic patients is indicated for a diastolic blood pressure >105 mm Hg. The level of SBP at which therapeutic interventions are indicated was not defined [4]. For patients with chronic hypertension prior to becoming pregnant, antihypertensive medications are not recommended in these guidelines until higher levels are noted, i.e., SBP 150-160 mm Hg, or DBP 100-110 mm Hg. In the subset of pregnant patients with evidence of renal disease or other target organ damage, the institution of therapy in this population is suggested for a DBP ≥ 90 mm Hg.

Other international guidelines (Table 1), particularly the 2007 European Society of Hypertension/European Society of Cardiology ESH/ESC guidelines, support the premise of the initiation of drug treatment at lower blood pressure thresholds [8]. They recommend treatment for a BP ≥140/90 mm Hg in women with gestational hypertension (with or without proteinuria), pre-existing hypertension with superimposed gestational hypertension, or hypertension with subclinical organ damage or symptoms at any time during pregnancy. Despite these differences, the stated goals of treating hypertension during pregnancy among

the different guidelines are the same: prevention of maternal stroke, progressive renal or other target organ disease, and other cardiovascular complications.

With respect to the pharmacological treatment of hypertension in pregnancy, the choice of antihypertensive medications has been limited to those that have proven to be relatively safe, have long been in clinical use, and have side-effect profiles that most obstetricians have found to be acceptable. According to the Working Group Report of the NHBPEP [4], methyldopa and hydralazine, respectively, are recommended as initial oral or intravenous therapy. Of note, methyldopa has a record of safety in pregnancy, as established by follow-up studies in the 1980's of children exposed to the drug *in utero* [9]. More recent studies indicate that, in hypertensive pregnancy disorders, treatment with methyldopa does not affect the maternal uterine artery Doppler pulsatility and resistance indices, suggesting that it does not impair uteroplacental circulation and consequent fetal growth [10]. But is it the drug of choice in managing hypertension?

In current practice, antihypertensive medications other than methyldopa and hydralazine are being used more often in pregnancy (Table 2), and particularly in patients for whom BP control either cannot be achieved with these agents or because of intolerable side effects. Diuretics, beta-blockers, and calcium channel blockers (CCBs) are acceptable medications that can be continued in patients with pre-pregnancy hypertension. Diuretics are considered safe and have been not shown to increase adverse perinatal effects [4, 8, 11].

Beta-blockers appear to be more effective than methyldopa in avoiding episodes of severe hypertension in women with hypertensive disorders of pregnancy, including those with preconception hypertension and those with new-onset hypertension in pregnancy, with or without proteinuria [12]. However, at the same time, this review of antihypertensive drug therapy for mild to moderate hypertension during pregnancy showed no evidence of a difference in the risk of preeclampsia, neonatal death, preterm birth, or small-for-gestational-age babies.

Although only limited trials exist, nifedipine has been shown to decrease blood pressure without affecting the blood flow in the umbilical artery [13]. A temporary reduction in dosage may be necessary in patients who are being treated for hypertension prior to becoming pregnant due to the physiological reduction in blood pressure during the first trimester.

The NHBPEP guidelines suggest that preconception medications be continued in women with chronic hypertension who become pregnant, with the exception of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs), as both have been associated with adverse fetal effects [14].

There are several reasons why threshold BP levels requiring therapy have been set at higher systolic and diastolic levels in pregnant women compared to the general population. First, there was (and still is) a relative paucity of well-designed clinical trials establishing the benefit of treatment of a SBP 140-160 mm Hg and DBP 90-100 mm Hg. The contemporary treatment approach is based on the **assumption** that hypertension of 4-5 months duration in a young woman without other risk factors does not increase her overall lifetime risk for cardiovascular disease (CVD), or significantly increase the risk of a cerebral or cardiac event during pregnancy. In addition, there is the **concern** that decreased BP in the mother may compromise uteroplacental and fetal circulation. However, this has been demonstrated in relatively few studies, and the experimental methods utilized have been criticized [15]. Are there data to support or contradict this approach?

Review of evidence

In the absence of well-powered studies demonstrating reduction of obstetric complications with antihypertensive treatment, few clinical issues provoke more debate than the question of how, if at all, to treat mild to moderate hypertension in pregnancy. Central to this controversy is the concern that antihypertensive therapy may provide no significant maternal benefits while increasing fetal risks related to 1) intrauterine exposure to medications with potential adverse effects (Table 2), and 2) the effects of BP lowering on the uteroplacental blood flow that may ultimately lead to small-forgestational-age (SGA) infants. Consequently, some health care providers elect to discontinue antihypertensive medications in patients with preconception hypertension. The argument against this approach is provided by evidence from studies suggesting that chronic hypertension is indeed associated with increased maternal and fetal risks, such as perinatal mortality and placental abruption [16], and that treatment of chronic hypertension may prevent progression to severe hypertension [12, 17].

Concern regarding the potential adverse effects relates to certain classes of antihypertensive medications, such as ACEI and ARBs, due to their mechanisms of action that exert adverse effects on a growing fetus. One notable exception is beta-blockers, as fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester [18], but not with other beta-blocking agents, such as labetalol (an alpha and beta-blocker), which is used frequently for the treatment of severe acute hypertension during pregnancy, and has shown equivalent efficacy and better tolerability compared to hydralazine [19]. .

The use of diuretic therapy during pregnancy remains controversial, primarily due to theoretical concerns. In the 1970s, physicians were advised that diuretics may actually be contraindicated because of the potential deleterious effects on placental blood flow. This recommendation was based on a study that has not been replicated [20]. As noted, some experts have pointed out that the study was flawed and that dehydroisoandrosterone sulfate clearance, which was used to estimate the uterine blood flow, is not an acceptable test [15]. Subsequent studies have provided evidence supporting the use of diuretics for treatment of hypertension in pregnancy. In a randomized trial of women with chronic hypertension in pregnancy, the use of diuretics reduced plasma volume, but was not associated with adverse pregnancy outcomes [21]. At present, women on maintenance diuretic therapy prior to pregnancy can be continued on this regimen, unless they develop premonitory signs of preeclampsia, such as proteinuria. At that point, some physicians would opt to stop diuretic medications, due to the concern that, with the lower plasma volume characteristic of preeclampsia, the use of diuretics may further aggravate the hypovolemic state, stimulate the renin-angiotensin system, and worsen hypertension [22]. The 2000 NHBPEP Working Group Report, however, recognized that the major concern for use of diuretics in pregnancy is primarily theoretical, as supporting evidence for their deleterious effects is lacking.

Concerns regarding the possible relation between feto-placental growth and the use of oral antihypertensive medications to treat less severe hypertension, in the absence of well-designed and adequately powered studies, are primarily based on a meta-analysis that concluded that a 10 mm Hg decrease in **mean** arterial pressure (MAP) was associated with a 145 g decrease in neonatal birth weight [23]. However, only 16% of the variation in birth weight was accounted for by the change in BP, suggesting that several variables may have independently contributed to the impairment in fetal growth. Several authors [24] have argued that this meta-analysis was subject to selection bias; for example, a study showing that the use of nicardipine compared to metoprolol resulted in a greater decrease in BP, but a concurrent trend towards a higher mean birth weight, [25] was not included in the meta-

analysis. Subsequent studies have provided more data regarding the effects of specific antihypertensive agents on uteroplacental blood flow and fetal growth. The effects of clonidine on fetal growth have been shown to be mediated through the maternal hemodynamic response to medication: reduced fetal growth was noted in women who experienced a reduction in cardiac output, but not in those with reduced peripheral vascular resistance [26]. These results may support the use of vasodilatory antihypertensive medications, such as the dihydropyridine CCBs or diuretics, which do not significantly reduce cardiac output after an initial period of physiologic adjustment. Although the use of methyldopa and hydralazine results in vasodilatation, BP is often not lowered sufficiently with these agents, as therapeutic doses may lead to intolerable side effects (methyldopa) and significant fluctuations in BP (hydralazine), which may necessitate their discontinuation during pregnancy. In summary, the negative effects of antihypertensive therapy on birth weight have not been consistently demonstrated. There are also data showing that the presence of hypertension itself results in lower birth weights, regardless of the use of medication [27], further suggesting that factors other than the pharmacologic reduction in BP may play a role.

Finally, increasing evidence supports the association between hypertensive pregnancy disorders and increased risks for cardiovascular disease (CVD) later in life (Table 3). This association is commonly explained by the fact that hypertensive disorders of pregnancy and CVD share several common risk factors, such as obesity and hyperlipidemia. Based on current data, it is particularly intriguing to hypothesize that hypertensive pregnancy disorders may result in metabolic and vascular changes [28] [29] that might increase the overall risk of CVD later in life. While the nature of this association remains to be determined, there is a growing awareness that women with a history of hypertensive pregnancy disorders are at risk for future CVD, and as such, should be monitored for traditional CVD risk factors and treated according to current guidelines [30]. Future studies designed to determine whether hypertensive disorders of pregnancy represent an independent risk for future CVD may have a major impact on the treatment of hypertension during pregnancy and primary prevention strategies in affected women.

Perspectives

Over the last decade, new evidence has emerged, primarily with respect to the pathophysiology of preeclampsia, and benefits of early treatment of hypertension in the general population, which **may affect** the management of hypertensive pregnant patients. However, it is of utmost importance to recognize that, at present, there are **too few data for definitive recommendations**.

Currently, several interventional trials for hypertension in pregnancy are in progress, with further information on these trials being available at ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. These include the Control of Hypertension in Pregnancy Study (CHIPS) trial [31], the Goal-directed Therapy in Pregnant Women at High Risk of Developing Preeclampsia trial (therapeutic intervention, nifedipine versus labetalol), the Labetalol Versus Magnesium Sulfate (MgSO4) for the Prevention of Eclampsia Trial (LAMPET), the Treatment Targets for Chronic Hypertension in Pregnancy (therapeutic intervention, methyldopa versus labetalol vs. nifedipine vs. clonidine) and the anti-Hypertensive Treatment In Stable Pregnant Women with Severe Pre-Eclampsia (Metildopape) METILDOPAPE. While awaiting the results from these trials, consideration needs to be given to a different approach for treating hypertension in pregnancy based on available evidence from clinical trials in both pregnant and non-pregnant individuals.

The epidemiology of chronic hypertension in pregnancy is an evolving field, due to a trend towards advanced age at first pregnancy, particularly in developed countries. The prevailing view that young women with chronic hypertension and absence of other CVD risks are at low risk for cardiovascular complications within the short duration of pregnancy may not be true, especially for women with advanced maternal age at the time of pregnancy, or even for some younger women with subclinical evidence of vascular damage that may not be detectable without special studies of vascular response. These women, in addition to having hypertension, may have other cardiovascular risk factors, such as obesity or hyperlipidemia, and/or signs of hypertensive target organ damage, which may only be detected by special studies. In addition, women who have undergone assisted reproduction (such as *in vitro fertilization*), may have additional CVD risk factors associated with decreased fertility, such as diabetes mellitus and renal disease. Therefore, treatment of hypertension of even a short duration, may decrease their cardiovascular risks, especially in view of recent studies showing an important correlation between achieving goal BP and clinical outcomes, i.e., better outcome with earlier and more effective treatment [32]. However, most studies showing an important correlation between the time taken to achieve goal BP and clinical outcomes are in high risk hypertensive patients [32,33]. As extrapolating these findings to hypertensive pregnant women is difficult, further clinical research is needed, focusing on immediate and long-term CVD outcomes as functions of BP control over the course of pregnancy.

With respect to preeclampsia, there is an ongoing debate as to whether hypertension plays an important, if any, role in the pathogenesis of progression of preeclampsia to its convulsive form, eclampsia, as eclamptic seizure activity may occur in patients without severe elevations in BP. With respect to treating preeclampsia, it is widely recognized that the treatment of mild to moderate hypertension does not seem to result in a large reduction in the risk of preeclampsia, although a moderate reduction in risk may be possible [12]. Current NHBPEP guidelines advise BP therapy for a DBP >105 mm Hg for patients with sudden escalating hypertension, or imminent or frank eclampsia. The elevations in SBP in preeclamptic patients at which pharmacotherapy is indicated, however, have not been defined. A study of 29 women who sustained a stroke in association with severe preeclampsia and eclampsia called for **a paradigm shift**, and antihypertensive therapy for these patients when the SBP reaches or exceeds 155-160 mm Hg) [34]. Of note, BP measurements before the stroke were available in 24 patients from this group and the SBP was ≥160 mm Hg in 23 of 24 (95.5%), and ≥155 mm Hg in all women. In contrast, the DBP was ≥105 mm Hg in only 5 of 24 women (20.8%). In addition, posterior reversible encephalopathy syndrome (PRES), defined as the presence of neurological symptoms and signs, coupled with the radiologic findings of vasogenic cerebral edema, seems to occur at lower peak SBP readings in pregnant [35,36] compared to non-pregnant patients with hypertensive encephalopathy [36,37]. One possible explanation is that pregnancy itself may decrease the threshold at which an elevation in BP may lead to cerebral hyper-perfusion and brain edema [38]. Taken together, these findings provide evidence that supports medical treatment for a SBP reaching or exceeding 150 mm Hg in women who develop elevated BP during pregnancy, and also emphasizes the importance of maintaining patients with chronic hypertension on adequate therapy. These goals would be consistent with the most recent guidelines coming from the UK National Institute for Health and Clinical Excellence (NICE) in 2010 [39]. In patients with PRES, adequate BP control may prevent progression from vasogenic to cytotoxic edema and infarction, with resultant permanent neurologic deficits. As abrupt decreases in BP may adversely affect uteroplacental perfusion and fetal circulation, treatment of hypertension mandates close maternal and fetal monitoring as BP is lowered. Doses and the effective medications available, i.e. CCBs, beta blockers or diuretics, as well as methyldopa, can usually be titrated safely with a gradual decrease in BP.

Current and Future Considerations

A recent position paper from the American Society of Hypertension [40] clearly states that, "gestation is permitted to continue as long as BP is controlled" (without overt signs of life-threatening maternal or fetal complications). The recommendations for medical treatment of BP are similar to those of previous NHBPEP [4]. At present, the question can be posed – should we not treat hypertension in pregnant women before BP rises to very high levels, when we advocate the treatment of any BP >140/90 mm Hg in the general population? When BP rises to levels of ≥140/90 mm Hg in pregnant women, regardless of the presence of proteinuria or other signs of preeclampsia, treatment may prevent progression to severe hypertension, maternal complications (such as a cerebrovascular hemorrhage and heart failure), improve fetal maturity by permitting prolongation of pregnancy, and may prevent permanent vascular injury that may translate into CVD risk after pregnancy. Several methods are available that can be used to monitor clinically fetal well-being and safety during both the introduction and titration of antihypertensive medications.

Proposals

1. Patients with chronic hypertension which is adequately controlled on medications that are safe for pregnancy should continue this regimen throughout pregnancy.

Most physicians would agree with this recommendation, but a significant number still discontinue antihypertensive drugs, especially diuretics. As most guidelines use the level of BP as a major indication for delivery, keeping this controlled should allow for continuation of pregnancy in many cases. On the other hand, during the first trimester, these women may require a decrease in the dose of antihypertensive medications as their BP gradually decreases.

2 If BP in a previously normotensive woman rises above 140/90 mm Hg, we suggest that treatment with small doses of beta-blockers, a diuretic, or CCBs, should be considered, in addition to methyldopa and hydralazine, as necessary.

One or a combination of these therapies will usually prove to be effective. Treatment will prevent further increases in BP, and possibly prevent some of the physiological abnormalities that can occur in the pregnant woman, even over a short period of time. Certainly, this approach may help to prevent the unusual, but definite occurrence of some of the complications discussed earlier. One of the authors (MM) has suggested a simple approach to therapy and a simplification of the definitions of hypertension in pregnancy (Table 4) [41]. In conjunction with this approach, close monitoring for signs of preeclampsia and/or fetal distress are crucial during therapy. In addition, as preeclampsia has a different pathophysiology, treatment options such as magnesium sulphate for prevention of seizures are available, as well as the need for possible early delivery.

In summary, hypertensive pregnancy disorders remain leading causes of both maternal and fetal morbidity and mortality worldwide. The overall risk of ischemic stroke or intracerebral hemorrhage during pregnancy and in the first 6 weeks postpartum is estimated to be 2.4 times greater than for non-pregnant women of similar age and race [42]. A recent study of trends in pregnancy hospitalizations in the United States reported that the number of pregnancy-related stroke hospitalizations grew by 54%, increasing from 4085 in 1994/1995 to 6293 in 2006/2007, and identified hypertensive disorders as a leading cause of stroke [43]. Questions, such as whether pregnancy outcomes may be improved with earlier and better BP control, and what should be the optimal BP treatment targets, are complicated by the lack of prospective trials. This underscores the need for prospective, randomized, and likely, multi-center trials that will be adequately powered to compare the effects of different BP targets on maternal and fetal outcomes [31], as previously discussed on page 12.

While awaiting the results of these trials, a different approach to managing elevated BP in pregnancy should be considered, one that should protect the mother from the complications of hypertension and possible long term CVD consequences post pregnancy. There is little to no substantial evidence at present that this approach is harmful to the fetus. Follow-up studies now suggest that short-term elevations of BP during pregnancy are accompanied by vascular abnormalities post-partum [44]. Blood pressures >140/90 mm Hg, which are clearly recognized as abnormal for a pregnant woman, should be treated with antihypertensive medication, i.e., CCBs, diuretics, beta-blockers, in addition to methyldopa and hydralazine, if necessary. The optimal timing and choice of therapy, in conjunction with judicious timing of delivery, must remain a matter of carefully weighing the risk-versus-benefit ratio for each individual patient, with an overall goal of improving maternal and fetal outcomes.

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Table 1

Guidelines for Diagnosis and Treatment of Hypertensive Pregnancy Disorders

Guideline	Classification of Hypertension	BP treatment levels
NHBPEP/ACOG [6, 45]	**Chronic hypertension-** BP ≥140/90 mm Hg before pregnancy or < 20th week of gestation. **Preeclampsia-eclampsia-** a pregnancy-specific disorder, BP ≥140/±90 mm Hg on at least 2 occasions, at least 6 hours apart, and proteinuria ≥ 300 mg in a 24-hr urine; after 20 weeks gestation. Eclampsia is the convulsive form of preeclampsia and affects 0.1% of all pregnancies. **Preeclampsia superimposed upon chronic hypertension** **Gestational hypertension-** new onset BP ≥140/±90 mm Hg, on at least two occasions, at least 6 hours apart, after 20 weeks gestation, in the absence of proteinuria. This category encompasses women with preeclampsia who have not yet developed proteinuria, those with transient hypertension-if BP returns to normal by 12 weeks postpartum- and women with chronic hypertension, if BP elevation persists after 12 weeks	In chronic hypertension, restart treatment at SBP greater than 150–160 mm Hg and/or DBP of 100–110 mm Hg, or in the presence of left ventricular hypertrophy or renal insufficiency; start therapy for a DBP > 90 mm Hg. In preeclampsia, antihypertensive therapy can be withheld, unless there is persistent DBP of 105–110 mm Hg or higher.
SOGC [46]	**Pre-existing hypertension (before pregnancy or < 20 wks)** • with comorbid conditions • with preeclampsia (hypertension, proteinuria, and adverse conditions, >20 weeks gestation) **Gestational hypertension (≥ 20 wks)** • with comorbid conditions • with preeclampsia (hypertension, proteinuria, and adverse conditions)	In chronic hypertension and gestational hypertension, severe hypertension (>160/≥110 mm Hg), blood pressure should be lowered to <160 mm Hg SBP and <110 mm Hg DBP Non-severe hypertension (140–159/90–109 mm Hg), BP should be lowered to 130–155 mm Hg SBP and 80–105 mm Hg DBP, when there are no comorbid conditions For women with comorbidities, SBP should be lowered to 130–139 mm Hg, and DBP to 80–89 mm Hg
ESH/ESC [8]	**Pre-existing hypertension** **Preeclampsia-gestational hypertension with significant proteinuria** **Gestational hypertension** **Pre-existing hypertension plus superimposed gestational hypertension with proteinuria** **Antenatally unclassifiable hypertension-** post partum re-classified • gestational hypertension with or without proteinuria • pre-existing hypertension	Drug treatment indicated when SBP ≥150 mm Hg or DBP ≥ 95 mm Hg In the presence of gestational hypertension and preeclampsia, pre-existing hypertension with superimposed gestational hypertension, or hypertension with subclinical organ damage, antihypertensives are indicated for blood pressures ≥140/90 mm Hg. SBP ≥170 mm Hg or DBP ≥110 mm Hg requires emergency treatment
NICE [39]	**Primary or Secondary chronic hypertension** < 20 weeks gestation or on antihypertensive meds before referral to maternity service **Preeclampsia-** new hypertension > 20 weeks with significant proteinuria: mild, moderate, severe hypertension, or eclampsia (convulsive condition). **Gestational hypertension-** new hypertension >20 weeks without significant proteinuria: mild, moderate, or severe hypertension	In pregnant women with uncomplicated chronic hypertension, aim to keep BP lower than 150/100 mmHg. Do not lower diastolic BP below 80 mm Hg. Offer pregnant women with target-organ damage secondary to chronic hypertension (for example, kidney disease) treatment, with the aim of keeping BP lower than 140/90 mm Hg. In preeclampsia and gestational hypertension, treat only if BP ≥ 150/100 mm Hg
SOMANZ [47]	**Chronic hypertension:** essential, secondary, or white coat **Preeclampsia-eclampsia** **Gestational hypertension** **Preeclampsia superimposed upon chronic hypertension**	Antihypertensive treatment should be commenced in all women with SBP ≥170 mm Hg or DBP ≥110 mm Hg Treatment for mild to moderate hypertension of 140–160/90–100 mm Hg is optional and will reflect local practice

NHBPEP National High Blood Pressure Education Program; **ACOG,** American College of Obstetricians and Gynecologists; **SOGC,** Society of Obstetricians and Gynaecologists of Canada; **ESH/ESC,** European Society of Hypertension /European Society of Cardiology; **NICE,** National Institute for Health and Clinical Excellence; **SOMANZ,** Society of Obstetric Medicine of Australia and New Zealand

Table 2

Antihypertensive medications and pregnancy*

		Benefits [48]	Concerns [48]
Central-acting agents			
Preferred	Methyldopa	Proven safety and efficacy	Depression, hepatic disturbances, hemolytic anemia-may not lower BP adequately
Alternative	Clonidine	Efficacy & safety similar to methyldopa	Limited data regarding fetal safety
Beta blockers			
Preferred	Labetalol (alpha-and beta-blocking agent)	Safety similar to methyldopa; may be more efficacious than methyldopa	Neonatal hypoglycemia with larger doses
Contraindicated	Atenolol	N/A	IUGR
Calcium channel blockers			
Alternative	Verapamil	Similar efficacy to other oral agents	Risk of interaction with magnesium - bradycardia
Direct vasodilators			
Preferred	Hydralazine	Efficacious intravenous agent ESH no longer recommends it	Maternal polyneuropathy, tachycardia, drug-induced lupus, neonatal lupus and thrombocytopenia Tachyphylaxis
Alternative	Nitroprusside	Only considered for life-threatening severe hypertension	Cyanide and thiocyanate toxicity, must be carefully monitored. Also risk of cardio-neurogenic syncope
Diuretics			
	Thiazide	Useful in chronic hypertension	Volume contraction, electrolyte abnormalities – rare with small doses
Contraindicated	Spironolactone	None	Possible fetal anti-androgen effects

IUGR, intrauterine growth restriction; ESH, European Society of Hypertension

*In general, the use of a diuretic, a calcium channel blocker or a beta-blocker may be more effective in lowering BP than methyldopa or hydralazine over a prolonged period. These agents may be used together, e.g., methyldopa and a diuretic, or a beta-blocker and diuretic.

Table 3

Hypertensive pregnancy disorders and future cardiovascular events

Author, Year, Country	Study design	Study group	Outcomes: study vs. control group[1]
Jonsdottir, [49] 1995, Iceland	Retrospective review, the maternity records 1931-1947 and IHD death	2.PE 3.HTN in pregnancy	1.IHD death RR 2.61 (1.11-6.12) 2.IHD death RR 1.90 (1.02-3.52) 3.IHD death RR 1.47 (1.05-2.02)
Hannaford, [50] 1997, UK	Retrospective analysis, a subgroup of women from the RCGP Oral Contraceptive Study who never used contraceptives	Women with history of toxemia[2]	HTN RR 2.35 (2.08-2.65) Acute MI RR 2.24 (1.42-3.53) Venous thromboembolism RR 1.62 (1.09-2.41)
Irgens, [51] 2001, Norway	Population-based study, the Norwegian medical birth registry, 1967-1992.	PE, either term or preterm deliveries[3]	All-cause death HR 1.2 (1.02-1.37) CV death for term PE, HR 1.65 (1.01-2.70) CV death for preterm PE, HR 8.12 (4.31-15.33)
Smith, [52] 2001, Scotland	Population-based study, the Scottish Morbidity Record System, 1981-1985.	PE	IHD HR 2.0 (1.5-2.5)
Kestenbaum, [46] 2003, USA	Population-based study, the Washington State Birth Event Record Data Base, 1987-1998.	1.Gestational HTN 2.Mild PE 3.Severe PE	1.Acute CVD event HR 2.8 (1.6-4.8) 2.Acute CVD event HR 2.2 (1.3-3.6) 3.Acute CVD event HR 3.3 (1.7-6.5)
Arnadottir, [53] 2005, Iceland	Case-control study, University Hospital Reykjavik, 1931-1947	Gestational HTN, PE, eclampsia	IHD death RR 1.66 (1.27-2.17) CVA death RR 1.46 (0.94-2.28)
Funai, [54] 2005, Israel	Population-based study, the Jerusalem Perinatal Study, 1964-1976.	PE	All-cause death RR 2.13 (1.79-2.53) CVD death RR 3.07 (2.18-4.34)
Wikström, [55] 2005, Sweden	Cross-sectional population study, the Swedish Medical Birth Register, 1973-1982.	1.Gestational HTN 2.Mild PE 3.Severe PE	1.IHD IRR 1.6 (1.3-2.0) 2.IHD IRR 1.9 (1.6-2.2) 3.IHD IRR 2.8 (2.2-3.7)
Ray, [56] 2005, Canada	Population-based study, the Ontario Health Insurance Plan, 1990-2004.	1.MPS[4] 2.PE	1.CVD HR 2.0 (1.7-2.2) 2.CVD HR 2.1 (1.8-2.4)
Garovic,[57] 2010, USA	Retrospective analysis of 4782 women from the Family Blood Pressure Program study [58]	HTN in pregnancy	1.HTN HR 1.53 (1.25-1.87) 2.Stroke HR 1.86 (1.16-2.98)

IHD, ischemic heart disease; PE, preeclampsia; HTN, hypertension; RR, relative risk; RCGP, Royal College of General Practitioners; MI, myocardial infarction; HR, hazard ratio; OR, odds ratio; IRR, incidence rate ratio; CVD, cardiovascular disease; CVA, cerebrovascular accident

[1] Where numbered, the outcomes correspond to a difference between the respective study group (labeled with the same number) and its control. For all studies, the control group consisted of women with normotensive pregnancies, with the exception of the study by Jonsdottir, et al., in which the outcomes were compared to those from the general population.

[2] Toxemia, a synonym that was used in the 1960's for preeclampsia

[3] Term delivery: delivery at ≥ 37 gestational weeks; preterm delivery: delivery at 16-36 gestational weeks

[4] MPS, maternal placental syndromes: gestational HTN, preeclampsia, placental abruption, and placental infarction

Table 4

Suggested Simplified Approach to the Management of Hypertension in Pregnancy[a]

	Therapy	Comments
Chronic hypertension (pre-pregnancy)	Continue medication-diuretics, calcium channel blockers or beta-blockers, other than atenolol (stop ACEI or ARB)	Dosage should be carefully monitored and possibly reduced during first and mid-second trimesters: -- but if BP >140/90 mm Hg, therapy should be increased or restarted
De novo hypertension > 20 weeks; BP≥140/90 mm Hg[*]	Specific antihypertensive therapy: calcium channel blockers, diuretics, beta-blockers, methyldopa, hydralazine	Close follow up for development of superimposed preeclampsia; fetal monitoring

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker. Other measures that are currently used in treating preeclampsia and the use of intravenous therapy in eclampsia are clearly indicated.

[*] Caution to be exercised for diuretic use in patients with premonitory signs of preeclampsia

[a] This approach has not been approved by any national or society guideline committees. Adapted from Moser, M [41]