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Drug Treatment of Hypertension in Pregnancy

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Abstract

Hypertensive disorders represent major causes of pregnancy related maternal mortality worldwide. 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 [1]. 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 and 2005 [2]. In low-income and middle-income countries, preeclampsia and its convulsive form, eclampsia, are associated with 10–15% of direct maternal deaths [3]. The optimal timing and choice of therapy for hypertensive pregnancy disorders involves carefully weighing the risk-versus-benefit ratio for each individual patient, with an overall goal of improving maternal and fetal outcomes. In this review we have compared and contrasted the recommendations in different treatment guidelines and we have outlined some newer perspectives on management. We have aimed to provide a clinically orientated guide to the drug treatment of hypertension in pregnancy.

Introduction

Hypertension in pregnancy includes a range of conditions, most notably preeclampsia, a form of hypertension unique to pregnancy that occurs de novo or may be superimposed on chronic hypertension. The other forms, chronic and gestational hypertension, usually have more benign courses [1]. Preeclampsia, a pregnancy-specific disorder characterized by hypertension (≥140/90 mm Hg) and proteinuria (≥300 mg in a 24-hour urine), affects 3–4% of all pregnancies worldwide. However, recent obstetric literature questions the importance of kidney injury (as demonstrated by proteinuria) in the diagnosis of preeclampsia, suggesting that a subclass of “non-proteinuric preeclampsia” should be added [4] or that detection of proteinuria should not be mandatory for a preeclampsia diagnosis [5]. Risk factors include primiparity, previous preeclampsia, increased maternal body mass index (BMI) before pregnancy, ethnicity (black women are more at risk), multiple gestations, and underlying medical conditions such as renal disease and diabetes mellitus [6]. Preeclampsia is a condition that involves numerous and constant interactions among the placental, immunologic, and cardiovascular systems [7]. It is a syndrome associated with impaired early placentation and dysfunctional trophoblast development, defective placental

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angiogenesis, and an exaggerated maternal systemic inflammatory response [8–11]. Risks to the fetus include premature delivery, growth retardation, and death. Treatment of severe hypertension is necessary to prevent cerebrovascular, cardiac, and renal complications in the mother.

In the US the National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure in Pregnancy was first presented in 1990 and was most recently updated in 2000 [1]. The definition and treatment recommendations for hypertension in pregnancy, unlike those for hypertension in the general population, have not similarly evolved and vary among different organizations that provide guidance in this area. Blood pressure levels requiring therapy in pregnancy, although somewhat different among various groups and professional societies, have been set, in general, at higher systolic and diastolic levels compared to the general population [12]. There are several reasons for this. First, there was (and still is) a relative paucity of well-designed clinical trials establishing the benefit of treatment of mild chronic hypertension during pregnancy, typically defined in the relevant literature as a SBP 140–160 mm Hg and/or DBP 90–100 mm Hg. As a result, the current 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 risk for cardiovascular disease, neither during the pregnancy nor later in life. However, there is increasing evidence that hypertension in pregnancy is an under recognized risk factor for future cardiovascular disease (CVD). Compared with women who have had normotensive pregnancies, those who are hypertensive during pregnancy are at greater risk of cardiovascular and cerebrovascular events years after their pregnancy [13–15].

There is the concern that decreased BP in the mother may compromise uteroplacental unit perfusion and fetal circulation. With respect to antihypertensive therapy, the choice has been limited to those that have proven to be relatively safe, have long been in clinical use, and have a side-effect profile that most obstetricians have found to be acceptable [12].

Throughout the article, where available, we have ranked the level of evidence in support for the measurement and treatment of hypertension in pregnancy. A full explanation of the ranking systems used is available in the appendices.

Measuring blood pressure in pregnancy

The guidelines for measuring blood pressure in pregnancy are outlined in table 1.Throughout this paper we will refer to blood pressure levels that are based on clinic blood pressure measurements. There has been much discussion on using ambulatory blood pressure monitoring (ABPM) in pregnancy but international guidelines currently base diagnosis and treatment interventions on clinic measurements.

Classification of hypertension in pregnancy and treatment guidelines

According to NHBPEP and The American College of Obstetricians and Gynecologists (ACOG) practice bulletins, hypertension in pregnancy is classified as chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed upon chronic hypertension and gestational hypertension [1, 21, 17]. Chronic hypertension is defined as BP ≥140/90mm Hg

before pregnancy or <20th week of gestation or use of antihypertensive medication before pregnancy. Preeclampsia-eclampsia is a pregnancy-specific disorder that occurs after 20 weeks gestation. Eclampsia is the convulsive form of preeclampsia and affects 0.1% of all pregnancies. Preeclampsia can also occur superimposed upon chronic hypertension. Gestational hypertension is defined as new onset BP ≥140 mmHg systolic or 90 mmHg diastolic on at least two occasions, at least 6 h 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.

The NHBPEP guidelines state that in pregnancy normal or acceptable blood pressure is SBP≤140 and DBP≤90 mmHg, mild hypertension SBP 140 to 150 or DBP 90 to 109 mmHg and severe hypertension ≥ 160 systolic or ≥110 diastolic mmHg[1].

NHBPEP advises that antihypertensive medication might be safely withheld in women with a history of chronic hypertension, and recommend restarting treatment at > 150–160 mmHg SBP and/or 100–110 mmHg DBP, or in the presence of LVH or renal insufficiency [1]. In preeclampsia, antihypertensive therapy can be withheld unless there is persistent DBP 105–110 mmHg or higher (III-C). ACOG Practice Bulletins recommend that antihypertensive therapy be used for women with a history of chronic hypertension who develop severe hypertension in pregnancy, for maternal benefit and that treatment of uncomplicated mild hypertension is not beneficial [21, 17].

The American College of Obstetricians and Gynecologists (ACOG) recently convened a task force on hypertension in pregnancy and have provided an up to date statement with recommendations on treatment of hypertension in pregnancy [22]. They recommend that for women with mild gestational hypertension or preeclampsia (SBP < 160mmHg or DBP < 110 mmHg), antihypertensives are not recommended (the quality of this evidence is moderate and the strength of this recommendation is qualified). For women with preeclampsia and sustained SBP ≥ 160 mmHg or DBP ≥ 110 mmHg, antihypertensive therapy is recommended (the quality of this evidence is moderate and the strength of this recommendation is strong). In pregnant women with chronic hypertension and no end-organ damage, no antihypertensive therapy is needed if SBP <160 mmHg or DBP < 105 mmHg (the quality of this evidence is low and the strength of this recommendation is qualified). In pregnant women with chronic hypertension who are on antihypertensive therapy, BP should be maintained between 120/80 mmHg and 160/105 mmHg (the quality of this evidence is low and the strength of this recommendation is qualified).

Other international societies and organizations have different definitions and levels at which therapy should be initiated and these are also presented in table 2. These recommendations come from the Society of Obstetricians and Gynaecologists of Canada (SOGC), the European Society of Hypertension /European Society of Cardiology (ESH/ESC); the National Institute for Health and Clinical Excellence (NICE) UK and the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ).

Drug treatment of hypertension in pregnancy

According to NHBPEP methyldopa, labetalol, beta blockers (other than atenolol), slow release nifedipine, and a diuretic in pre-existing hypertension are considered as appropriate treatment [1]. If a woman's blood pressure is well controlled on an agent pre-pregnancy she may continue it during pregnancy, with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. If restarting drug therapy in women with chronic hypertension, methyldopa is recommended as first line therapy. For emergency treatment in preeclampsia, IV hydralazine, labetalol and oral nifedipine can be used [1]. The ACOG Practice Bulletins also recommend that methyldopa and labetalol are appropriate first-line agents and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended [21, 17].

In current practice, antihypertensive medications other than methyldopa and hydralazine are being used more often in pregnancy (Table 3), and particularly in patients for whom BP control cannot be achieved with these agents, or in the presence of intolerable side effects.

The drug treatments for severe acute hypertension in preeclampsia are highlighted in figure 1. [1]. Severe hypertension in preeclampsia being defined as ≥160 mm Hg systolic, ≥105 mm Hg diastolic, or both.

Profiles of recommended drug therapies

Centrally acting α_2-adrenergic agonists

Methyldopa is a centrally acting α_2-adrenergic receptor agonist. It inhibits vasoconstriction via a central mechanism by reducing catecholamine release [28]. It decreases central sympathetic outflow, decreasing systemic vascular resistance without decreasing cardiac output [27]. The side effects of methyldopa include fatigue, depression, poor sleep and decreased salivation. Dose independent adverse effects include elevated liver enzymes in up to 5% of women and some patients can develop a positive antinuclear antigen or antiglobulin (Coombs') test although a clinical haemolytic anaemia is rare [29, 27]. It has been suggested that methyldopa should be avoided in women with a prior history of depression, because of the possible increased risk of postnatal depression [30]. Methyldopa has a long history of use in pregnancy and does not appear teratogenic [27]. 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 [31]. 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 [32]. The doses of methyldopa recommended in pregnancy are similar to those used in non-pregnant patients [33].

Clonidine is a centrally acting adrenergic agonist. It works as an antihypertensive agent by stimulating α-$_2$ adrenergic receptors in the brainstem thereby decreasing central adrenergic output [34]. It acts on both peripheral and central α-$_2$ adrenergic receptors to decrease the cardiac output, systemic vascular resistance, systolic blood pressure and heart rate [35].

Clonidine is similar to methyldopa with regards to safety and efficacy [35]. It is generally used as a third-line agent for multidrug control of refractory hypertension [29].

According to the Food and Drug Administration (FDA) methyldopa is a Class B drug and clonidine is a Class C drug. According to either the World Health Organization and/or Thomson lactation ratings methyldopa is usually compatible with breast milk and clonidine has possible breast milk effects.

Peripherally acting adrenergic-receptor antagonists

Labetalol a non-selective β-blocking agent with vascular α-$_1$-receptor blocking capabilities is widely used in pregnancy [26]. Fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester [36], but not with other β-blocking agents, such as labetalol (an α and β-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 [37]. Side effects include fatigue, lethargy, exercise intolerance, sleep disturbance and bronchoconstriction have been reported [26]. β-blockers are not associated with teratogenicity [26].

In a review of antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy, β-blockers appear to be more effective than methyldopa in limiting episodes of severe hypertension in women with hypertensive disorders of pregnancy [38]. However, at the same time, this review showed no evidence of a difference in the risks of preeclampsia, neonatal death, preterm birth, or small-for-gestational-age (SGA) babies.

Prazosin is an α_1-blocker that selectively blocks post-synaptic α_1-adrenoceptors, producing a decrease in total peripheral resistance (and a reflex increase in sympathetic tone) [27]. It is considered as a second-line agent by SOMANZ [19] but is not recommended by SOGC [16]. Prazosin has a useful role in chronic renal disease complicating pregnancy. It is associated with postural hypotension and palpitations.

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According to FDA labetalol is a Class C drug. It may be associated with a risk of fetal bradycardia and neonatal hypoglycemia. According to either the World Health Organization and/or Thomson lactation ratings methyldopa is usually compatible with breast milk. Atenolol is an FDA Class D drug. It is not recommended due to risk of IUGR and is not recommended if breast-feeding.

Calcium channel blockers

Oral nifedipine and verapamil are frequently seen as second line agents used for the treatment of hypertension in pregnancy. They do not appear to be teratogenic [39]. Calcium channel blockers (CCBs) inhibit the influx of calcium ions to vascular smooth muscle, resulting in arterial vasodilation; nifedipine act predominantly on the vasculature and verapamil acts primarily on the heart [27] [28]. Side effects of CCB use in the mother include tachycardia, palpitations, peripheral edema, headaches and facial flushing [40].

According to FDA nifedipine and verapamil are Class C drugs. With all CCBs, there is a risk of interactions with magnesium, resulting in profound hypotension. Nifedipine and verapamil are usually compatible with breast milk.

Direct vasodilators

Hydralazine is now predominantly used intravenously for the treatment of severe hypertension in pregnancy. Hydralazine selectively relaxes arteriolar smooth muscle. Adverse effects include headache, nausea, flushing, and palpitations. It does not appear teratogenic. There have been reports of neonatal thrombocytopenia, rare cases of a pyridoxine-responsive polyneuropathy with chronic use, and drug-induced lupus [41].

However, there is evidence that intravenous labetalol or oral nifedipine are preferable first-line agents compared to intravenous hydralazine in severe hypertension in pregnancy [37].

Sodium nitroprusside is rarely used in pregnancy and is reserved for life-threatening severe hypertension [42]. Adverse effects include cyanide and thiocyanate toxicity and also the risk of cardio-neurogenic syncope.

Hydralazine is an FDA Class C drug. It is usually compatible with breast-feeding.

Diuretics

The use of diuretic therapy during pregnancy remains controversial, primarily due to theoretical concerns about reduced plasma volume. 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 [43]. 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 [44]. The 2000 NHBPEP Working Group Report, however, recognized that the major concern for the use of diuretics in pregnancy is primarily theoretical, as supporting evidence for their deleterious effects is lacking.

Thiazides are FDA Class B drugs. They may cause volume contraction and electrolyte abnormalities but rare with small doses. Diuretics may reduce milk production [29]. Spironolactone is not recommended due to potential fetal antiandrogen effects.

Renin Angiotensin System drugs

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are contraindicated in pregnancy due to their association with adverse fetal effects [45]. ACE inhibitors are labelled FDA class C for the first trimester of pregnancy, and FDA class D for the second and third trimesters.

Current clinical practice

As discussed in earlier sections there are several guidelines and recommendations available to practitioners treating hypertension in pregnancy. These however may not always reflect clinical practice. Two recent reviews give us a reflection of actual drug therapy being used in hypertension in pregnancy. Table 4 summarizes drug therapy currently being used in clinical practise to treat very high blood pressure in pregnancy.

There is further evidence of the increasing use of antihypertensives in pregnancy. A review of outpatient antihypertensive medication use during pregnancy in a Medicaid population was performed from 2000 to 2006 [47]. They noted that the prevalence of antihypertensive use both in the first trimester and in pregnancy overall increased during this period by approximately 50%; by the end nearly 5% of all pregnancies were exposed to antihypertensive therapy [47]. The authors reported significant variation in the range of antihypertensive drugs used across all trimesters of pregnancy and in the approach to the management of patients entering pregnancy on antihypertensive medication. There were study limitations but a significant number of women taking antihypertensives prior to pregnancy were kept on their same drug and not switched to one of the preferred agents. Beta-blockers, thiazides, and calcium channel blockers were often used as first line agents.

Drugs used for the prevention of preeclampsia/eclampsia

Magnesium sulphate and other anticonvulsants for preeclampsia

In a Cochrane review of treatment of women with preeclampsia, magnesium sulphate more than halves the risk of eclampsia, and probably reduces maternal death [48]. In women with eclampsia, magnesium sulphate reduces the risk ratio of maternal death and of recurrence of seizures, compared with diazepam.

Antiplatelet agents and preeclampsia

A review of 59 trials, involving 37,560 women, found low doses of aspirin reduced the risk of preeclampsia by 17%, the risk of fetal or neonatal deaths by 14%, and the relative risk of preterm births by 8% [49]. Doses up to 75 mg appear to be safe. Guidelines from the ESH/ESC suggest that women at high risk of preeclampsia (from hypertension in a previous pregnancy, CKD, autoimmune disease such as systemic lupus erythematosus, or antiphospholipid syndrome, type 1 or 2 diabetes or chronic hypertension) or with more than one moderate risk factor for preeclampsia (first pregnancy, age >40 years, pregnancy interval of >10 years, BMI >35 kg/m2 at first visit, family history of preeclampsia and multiple pregnancy), may be advised to take 75mg of aspirin daily from 12 weeks until the birth of the baby, provided that they are at low risk of gastrointestinal haemorrhage [23]. Similarly the UK NICE guidelines advise woman to take aspirin 75 mg/day from 12 weeks

until birth if they have at least two moderate risk factors (as listed above) or at least one high risk factor (as listed above) for preeclampsia exists [25]. They state that this is an unlicensed indication and that informed consent should be taken. There is support for the use of low-dose aspirin before 16 weeks with investigators suggesting the possibility that because normally the transformation of uterine spiral arteries by trophoblasts is completed by 16–20 weeks and this is abnormal in preeclampsia; early use of aspirin may be beneficial [50] [51].

Antioxidants for preventing preeclampsia

It has been demonstrated that supplementation with vitamin C (at a dose of 1000 mg daily) and vitamin E (at a dose of 400 IU daily) do not reduce the rates of either serious adverse outcomes of pregnancy-associated hypertension or preeclampsia among low-risk, nulliparous women [52].

Calcium supplementation for preventing hypertensive disorders

A review of calcium supplementation during pregnancy for preventing hypertensive disorders concluded that calcium supplementation appears to approximately halve the risk of preeclampsia, reduce the risk of preterm birth, and the rare occurrence of the composite outcome: ‘death or serious morbidity’ [53]. Of note, most of the women in these trials had a low calcium diet and were supplemented with at least 1 g of calcium daily. However, the evidence for added calcium in the prevention of hypertensive disorders is conflicting [54].

Other agents

Fish oil supplementation and vitamin and nutrient supplements appear to have no benefit in the prevention of hypertensive disorders [55]. Other management options such as the use of corticosteroids, plasma volume expansion, or interventions such as rest or exercise, have not been validated [3]. Steroid therapy is recommended only for lung maturation [16, 19, 25].

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 trial [56], the Goal-directed Therapy in Pregnant Women at High Risk of Developing Preeclampsia trial (therapeutic intervention, nifedipine vs. labetalol), the Labetalol vs. Magnesium Sulfate (MgSO4) for the Prevention of Eclampsia Trial and the Antihypertensive Treatment in Stable Pregnant Women with Severe Preeclampsia. Results from these trials may further enhance our treatment therapies for hypertension in pregnancy.

Novel therapeutic targets and emerging treatments

Angiogenesis

Dysregulation of angiogenesis appears to play a key role in the pathogenesis of preeclampsia. Placental cystathionine γ-lyse (CSE) expression is reduced in preeclampsia, leading to reduced plasma levels of the pro-angiogenic gaseous vasodilator, hydrogen sulfide (H2S) and increased sFlt-1 [57]. Targeting CSE/H2S activity may be a potential therapy pending additional studies.

Aminopeptidases

Aminopeptidases, such as placental leucine aminopeptidase (P-LAP) and aminopeptidase A (APA) do not cross the placental barrier. In the pregnant, spontaneously hypertensive rat, APA acts as an antihypertensive agent, degrading vasoactive peptides, and as a result, normalizes blood pressure [58]. The role of aminopeptidases as potential therapeutic agents is being investigated.

Heme oxygenase 1

A recent study examined heme oxygenase 1 (HO-1) induction in a rat model of placental ischemia [59]. George et al, suggest two potential pathways through which HO-1 acts, namely, normalization of angiogenic balance in the placenta, and reduction in oxidative stress. Both pathways are potential targets for treatment in preeclampsia.

Marinobufagenin

Uddin et al, and others, have investigated the role of marinobufagenin (MBG), a cardiotonic steroid, and its antagonist resibufogenin (RBG), in experimental animal models of preeclampsia [60]. This group has demonstrated that in a rat model of preeclampsia, MBG inhibits first trimester cytotrophoblast cell function and that urinary excretion of MBG is elevated prior to the development of hypertension and proteinuria. MBG also causes hypoxia and ischemia leading to an imbalance of pro- and anti-angiogenic factors. RBG, when given early in pregnancy, prevented the development of hypertension, proteinuria, and intrauterine growth restriction.

G protein-coupled receptor (GPCR) targets

There is potential for investigation of novel GPCR-based therapies in preeclampsia, including calcitonin receptor-like receptor / receptor activity modifying protein 1 complexes, the angiotensin AT1, 2 and Mas receptors, and the relaxin receptor RXFP1 [61].

Inhibitors of the enzyme poly ADP ribose polymerase (PARP)

In states of increased oxidative stress, such as diabetes, overstimulation of PARP leads to endothelial dysfunction and PARP inhibitors have been shown to be of benefit [62]. A recent investigation has demonstrated a protective effect of a PARP inhibitor, preventing the development of both endothelial dysfunction and hypertension, in a rat model of preeclampsia [62].

Gasotransmitters

Nitric oxide, a potent vasodilator that mediates endothelium-dependent relaxation, has been linked to endothelial dysfunction in preeclampsia [63]. Carbon monoxide, nitric oxide and hydrogen sulphide are endogenously generated gaseous transmitters known as, gasotransmitters. In preclinical animal models, the therapeutic use of CO gas and CO-releasing molecules demonstrated anti-inflammatory properties and cardiovascular protective effects [64]. These gaseous molecules may have a potential role in the therapeutics for several diseases, including cardiovascular disease and preeclampsia, although their instability and potential toxicity are significant drawbacks.

Podocytes

Derangements of podocytes and podocyte-specific proteins are implicated in preeclampsia. There is evidence of an association between dysregulated pro-angiogenic factors, hypertension, and podocyte injury. Further investigation focusing on the mechanism of podocyte injury and detachment may identify novel therapeutic targets.

These are only a few of the more recent potential therapeutic targets under investigation.

Perspectives in Management

Over the last decade, new evidence has emerged, both with respect to the pathophysiology of preeclampsia and the benefits of early hypertension treatment in the general population, which may affect the management of hypertensive pregnant patients. The notion that pregnant women with chronic hypertension are at low risk for cardiovascular complications within the short duration of pregnancy may be in question given the current trend towards advanced maternal age at first pregnancy. These women may have other cardiovascular risk factors, such as obesity or hyperlipidemia, and/or signs of target organ hypertensive damage. In addition, modern methods of assisted reproduction (such as *in vitro fertilization*) have enabled women with CVD risk factors that are associated with decreased fertility (such as diabetes mellitus and renal disease) to conceive. In these women, treatment of hypertension of even a short duration, may improve their cardiovascular risks, especially in view of recent studies in the general population showing an important correlation between the time taken to achieve goal BP and clinical outcomes, namely better outcome with earlier and more effective treatment [65, 66]. Finally, recent studies have indicated that cerebral vascular events in women with severe preeclampsia and eclampsia may occur when SBP exceeds 150 mm Hg, and called for a paradigm shift, by recommending antihypertensive therapy when the SBP reaches or exceeds 155–160 mm Hg [67]. Indeed, most investigators agree that antihypertensive therapy in the peripartum period should be initiated when the DBP approaches 100 mm Hg, or for a blood pressure ≥ 150/100 mm Hg [68]. As abrupt decreases in BP may adversely affect uteroplacental perfusion, treatment of hypertension mandates close maternal and fetal monitoring as the BP is lowered. The ultimate therapeutic goal is to prevent maternal complications without compromising fetal wellbeing.

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Appendices

Appendix 1

The NHBPEP Working Group Report on High Blood Pressure in Pregnancy reviewed and classified studies providing evidence supporting their recommendations. They used the following explanatory symbols and appended them to some of their references and to some of their citations [1].

M- Meta-analysis; an analysis of a compendium of experimental studies;

Ra- Randomized controlled studies

Re- Retrospective analyses; case-control studies

F- Prospective follow-up; cohort studies

X- Cross sectional population studies

Pr- Previous review or position statements

C- Clinical interventions (nonrandomized).

Appendix 2: ACOG evidence base

I: Evidence obtained from at least one properly randomized controlled trial

II-1: Evidence from well-designed controlled trials without randomization

II-2: Evidence from well-designed cohort or case-control studies, preferably from more than one centre or research group

II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Recommendations are provided and graded according to the following categories:

Level A. Recommendations are based on good and consistent scientific evidence

Level B. Recommendations are based on limited or inconsistent scientific evidence

Level C. Recommendations are based primarily on consensus and expert opinion.

Appendix 3

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment* Classification of Recommendations†

I: Evidence obtained from at least one properly randomized controlled trial

II-1: Evidence from well-designed controlled trials without randomization

II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group

II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

A. There is good evidence to recommend the clinical preventive action

B. There is fair evidence to recommend the clinical preventive action

C. The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making

D. There is fair evidence to recommend against the clinical preventive action

E. There is good evidence to recommend against the clinical preventive action

I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

Appendix 3

Explanation of the class of recommendations and levels of evidence used by the ESH/ESC, European Society of Hypertension /European Society of Cardiology

Classes of recommendations

Class I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. (Is recommended/is indicated).

Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.

Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy. (Should be considered).

Class IIb: *Usefulness/efficacy is less well* established by evidence/opinion. (May be considered).

Class III Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful. (Is not recommended).

Levels of Evidence

Level of evidence A- Data derived from multiple randomized clinical trials or meta-analyses.

Level of evidence B- Data derived from a single randomized clinical trial or large non-randomized studies.

Level of evidence C- Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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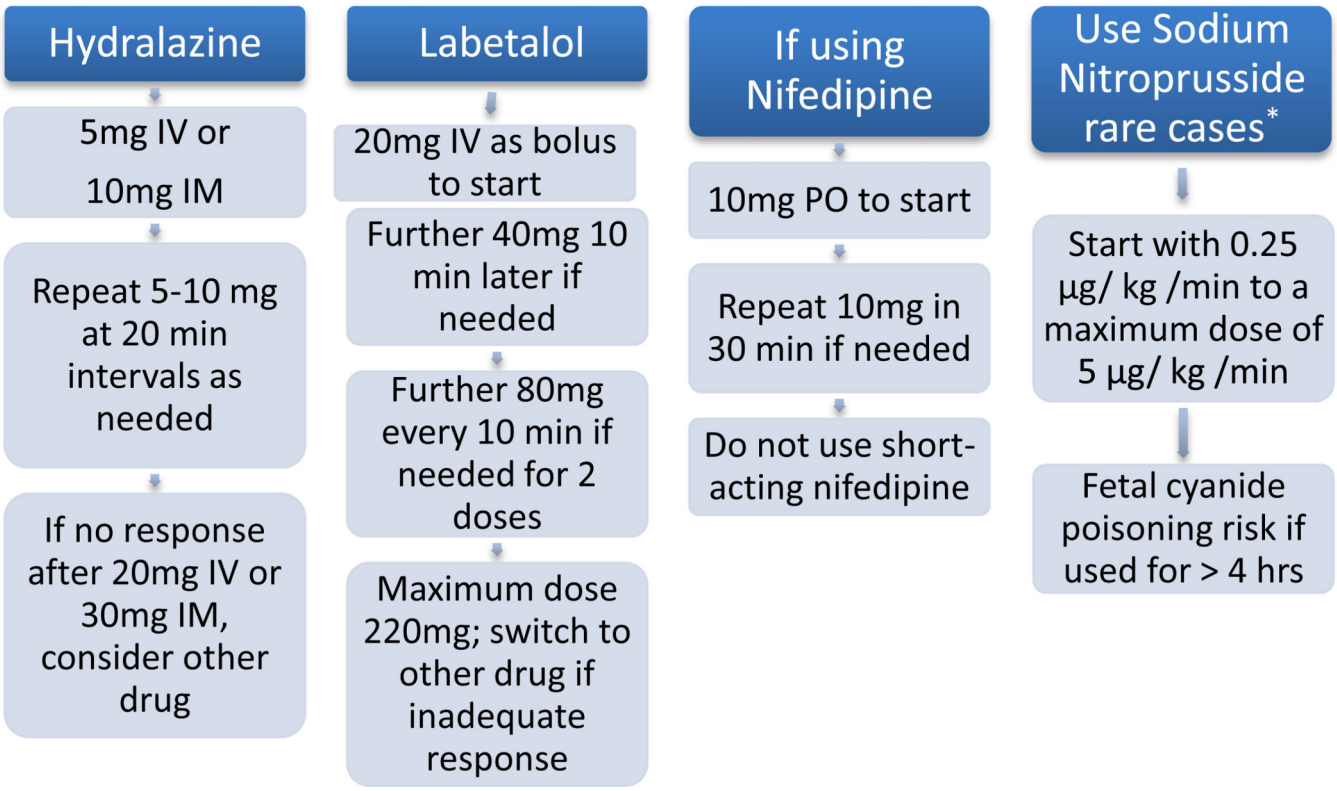

Figure 1.

Drug treatments and regimens for severe hypertension in preeclampsia [1]

* *The NHBPEP Working Group recommend the use of sodium nitroprusside in rare cases of hypertension not responding to the previously mentioned drugs, or clinical findings of hypertensive encephalopathy, or both*

Table 1

Guidelines for the measurement of blood pressure in pregnancy

Guideline	Measuring BP in pregnancy
SOGC [16]	Rest for 5 minutes. Measure BP in the sitting position with the arm at the level of the heart. (II-2A)
	Use an appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm). (II-2A)
	Korotkoff phase V should be used to designate DBP. (I–A)
	If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements. (III-B)
	BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device (validated for use in preeclampsia). (II-2A)
	Automated BP machines may underestimate BP in women with preeclampsia, and comparison of readings using mercury sphygmomanometry or an aneroid device is recommended. (II-2A)
	Ambulatory BP monitoring (by 24-hour or home measurement) may be useful to detect isolated office (white coat) hypertension. (II-2B)
	Patients should be instructed on proper BP measurement technique if they are to perform home BP monitoring. (III-B)
NHBPEP [1]	In gestational hypertension DBP is determined as the disappearance of sound (Korotkoff 5).
	Gestational blood pressure elevation should be defined on the basis of at least two determinations. The repeat blood pressure should be performed in a manner that will reduce the likelihood of artefact and/or patient anxiety. (Pr)
	In preeclampsia once BP starts to rise (this may be the first sign of developing preeclampsia); a repeat examination within 1 to 3 days is recommended.
	In selected patients, BP may be checked at home.
ACOG [17]	Rest for 10 minutes or longer
	Abstain from tobacco or caffeine use for 30 minutes before measurement (III)
	Take BP in upright position
	For patients in hospital BP can be taken sitting up or in left lateral recumbent position, patient's arm at level of heart (III)
	DBP is that pressure at which the sound disappears (Korotkoff phase 5) (III)
	Use correct cuff size (length 1.5 times upper arm circumference or a cuff with a bladder that encircles 80% or more of arm)
	Validated electronic devices can be used but mercury sphygmomanometer is the preferred as being most accurate (III)
NICE [18]	Remove tight clothing, ensure arm is relaxed and supported at heart level
	Use cuff of appropriate size
	Inflate cuff to 20–30 mmHg above palpated SBP lower column slowly, by 2 mmHg per second or per beat
	Read blood pressure to the nearest 2 mmHg
	Measure DBP as disappearance of sounds (phase V)
SOMANZ [19]	Sit comfortably, legs resting on flat surface
	Use correct cuff size; if arm circumference > 33cm use large cuff with inflatable bladder covering 80% of arm
	Measure BP in both arms at first visit*
	SBP is accepted as the first sound heard (K1) and the DBP the disappearance of sounds completely (K5). Where K5 is absent, K4 (muffling) should be accepted
	Mercury sphygmomanometers are gold standard but if using automated device validate against mercury sphygmomanometer
	Regular calibration of devices needed (ideally monthly)
	24 hour ABPM- Useful for the evaluation of early hypertension (<20 weeks gestation) where 1/3 of women will have "white coat" hypertension and half of these women will go on to have ABPM confirmed hypertension later in pregnancy
	ABPM less useful for screening for "white coat" hypertension in second half of pregnancy
ESH on ABPM [20]	ABPM particularly useful for detecting white-coat and nocturnal hypertension in pregnancy

Guideline	Measuring BP in pregnancy
	White-coat hypertension has a more favorable outcome than sustained hypertension diagnosed by ABPM
	Nocturnal hypertension is higher in women with preeclampsia than in those with gestational hypertension and is associated with more maternal and fetal complications
	The predictive accuracy of ABPM remains low; ambulatory pulse pressure and daytime DBP have been shown to be predictive of birth weight

* Variation in BP between upper limbs should be < 10 mmHg; 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; ABPM, ambulatory blood pressure monitor; ESH on ABPM, European Society of Hypertension position paper on Ambulatory Blood Pressure Monitoring; the National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure. The abbreviations/key codes in parentheses represent the ranking of evidence and grading of recommendations used by the SOGC, by NHBPEP Working Group Report on High Blood Pressure and ACOG. An explanation of these can be found in the appendices.

Table 2

Guidelines for diagnosis and treatment of Hypertensive Disorders of Pregnancy (*adapted from Moser M et al, 2012*)

Definitions and BP treatment levels	SOGC [16]	ESH/ESC [23, 24]	NICE [25]	SOMANZ [19]
Definitions of hypertension in pregnancy	A. Pre-existing hypertension (before pregnancy or < 20 wks.) (1) with co morbid conditions (2) with preeclampsia (hypertension, proteinuria, and adverse conditions, > 20 weeks' gestation) B. Gestational hypertension (≥20 wks.) (1) with co morbid conditions (2) with preeclampsia (hypertension, proteinuria, and adverse conditions)	A. Pre-existing hypertension B. Preeclampsia - gestational hypertension with significant proteinuria C. Gestational hypertension D. Pre-existing hypertension plus superimposed gestational hypertension with proteinuria E. Antenatally unclassifiable hypertension - postpartum re-classified as (1) gestational hypertension with or without proteinuria (2) pre-existing hypertension	A. Primary or Secondary chronic hypertension < 20 weeks' gestation or on antihypertensive meds before referral to maternity service B. Preeclampsia- new hypertension > 20 weeks with significant proteinuria (1) mild, (2) moderate, (3) severe hypertension Eclampsia (convulsive condition associated with preeclampsia) C. Gestational hypertension new hypertension > 20 weeks without significant proteinuria (1) mild, (2) moderate, (3) severe hypertension	A. Chronic hypertension (1) essential, (2) secondary, or (3) white coat B. Preeclampsia-eclampsia C. Gestational hypertension D. Preeclampsia superimposed upon chronic hypertension
Recommended BP treatment levels	Severe hypertension (>160/≥110 mm Hg), BP should be lowered to <160 mm Hg SBP and < 110 mm Hg DBP (II-2B) 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 co morbid conditions	Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. (IC)^ Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the	In pregnant women with uncomplicated chronic hypertension aim to keep blood pressure lower than 150/100 mmHg. Do not lower diastolic blood pressure below 80 mmHg. Offer pregnant women with target-organ damage secondary to chronic	Antihypertensive treatment 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

Definitions and BP treatment levels	SOGC [16]	ESH/ESC [23, 24]	NICE [25]	SOMANZ [19]
	(III-C) For women with comorbidities, SBP should be lowered to 130–139 mm Hg, and DBP to 80– 89 mm Hg (III-C)	presence of gestational hypertension, subclinical organ damage or symptoms. (IIbC)	hypertension (for example, kidney disease) treatment with the aim of keeping blood pressure lower than 140/90 mmHg. In preeclampsia and gestational hypertension, treat only if BP ≥ 150/100 mmHg	

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. The abbreviations/key codes in parentheses represent the ranking of evidence and grading of recommendations used by the SOGC and the ESH/ESC. An explanation of these can be found in the appendices.

Table 3

Recommended management options for treating hypertension in pregnancy

Drug Treatment	Dose[26, 27]	FDA Class	Safety	Side Effects	Breast feeding*
First line agents					
Methyldopa (F), (I–A) *Drug of choice according to all groups*	0.5–3 gm/day in 2divided doses	B	Proven safety and efficacy	Some concern with depression, hepatic disturbances, hemolytic anemia -may not lower BP adequately	Compatible with breast milk
Labetalol (M), (I–A)	200–1200 mg/day p.o. in 2–3 divided doses 20–40mg iv (max 220mg total)	C	Safety similar to methyldopa may be more efficacious than methyldopa;	May be associated with fetal growth restriction. Neonatal hypoglycemia with larger doses	Usually compatible with breast milk
Second-line agents					
Nifedipine Long-acting (Ra), (I–A)	10–30 mg p.o.	C	widely used	May inhibit labor; Rarely, profound hypotension if short-acting agent is used with magnesium	Usually compatible with breast milk
Verapamil	80mg tds p.o.	C	Similar efficacy to other oral agents	Risk of interaction with magnesium – bradycardia	Usually compatible with breast milk
Clonidine *Alternative option*	0.1–0.6 mg/day in 2 divided doses	C	Safety similar to methyldopa Limited data regarding fetal safety	Efficacy similar to methyldopa	Possible breast milk effects
Hydrochlorothiazide *Useful in chronic hypertension*	12.5–25 mg/day	B		Volume contraction, electrolyte abnormalities – rare with small doses	May reduce breast milk production

Drug Treatment	Dose[26, 27]	FDA Class	Safety	Side Effects	Breast feeding*
Hydralazine (F, Re) Not recommended by ESH [24, 23]	50–300 mg/d in 2–4 divided doses	D	Efficacious intraveno us agent	Possible maternal polyneuropathy, drug-induced lupus, neonatal lupus and thrombocytopenia; Tachyphylaxis	Usually compatible with breast milk
Atenolol	(Atenolol not recommended) (I–D) Atenolol has risk of growth restriction when started in first or second trimester and is not recommended if breast feeding				
Diazoxide	30–50 mg iv every 5–15 min; iv bolus for acute BP lowering in severe hypertension [19]				
Prazosin	0.5–5mg tds; consider as a second line agent by SOMANZ [19] Not recommended by SOGC[16] (I–D) Associated with postural hypotension and palpitations				
Oxprenolol (beta blocker with ISA)	20–160mg tds; a first line agent by SOMANZ[19] Contraindicated in heart block				
Nitroprusside	Only considered for life-threatening severe hypertension Cyanide and thiocyanate toxicity, must be carefully monitored. Also risk of cardio-neurogenic syncope				
Contraindicated[26]	ACE inhibitors, angiotensin II receptor blockers (Pr, Re), (II-2E), FDA Class D				
	Direct renin inhibitors				
	Spironolactone not recommended due to potential foetal antiandrogen effects				
Other Management Strategies					
Low dose aspirin	Use advised in women at high risk Used prophylactically in women with a history of preeclampsia at <28 Weeks				
Fish oil supplementation	Not recommended				
Calcium supplementation	May have role in decreasing incidence of preeclampsia Role in low calcium intake populations				
Vitamin C and E	Not recommended				
Steroid therapy	Only for fetal lung maturation				

*According to either the World Health Organization and/or Thomson lactation ratings. FDA, Food and Drug Administration; ISA, intrinsic sympathomimetic activity. The abbreviations in parentheses represent the types of studies that provided the evidence base for the recommendations from the NHBPEP. (M)- meta-analysis, an analysis of a compendium of experimental studies; (Ra)- randomized controlled trials; (Re)- retrospective analyses, also known as case-control studies; (F)- prospective follow-up, also known as cohort studies, including historical cohort studies and long-term follow-up; (Pr)- previous review or position statements; and the key codes from the evidence base used by the SOGC. An explanation of these can be found in the appendices.

Table 4

Drug therapy for the treatment of very high blood pressure in pregnancy

Author	Study design	Study group	Drugs compared	Side effects*
Duley L et al, Cochrane review [46]	Review of drugs used in pregnancy for the treatment of very high blood pressure, DBP ≥ 105 mmHg and/or SBP 160 mmHg	35 trials identified, 3573 women	labetalol vs. hydralazine; labetalol vs. CCBs; labetalol vs. methyldopa; labetalol vs. diazoxide; hydralazine vs. CCBs; hydralazine vs. diazoxide; hydralazine vs. prostacyclin; hydralazine vs. ketanserin; hydralazine vs. urapidil; methyldopa vs. atenolol; nifedipine vs. prazosin; nifedipine vs. chlorpromazine; nitrates vs. $MgSO_4$; nimodipine vs. $MgSO_4$; urapidil vs. CCBs	Hydralazine headache, flushing, light headedness, nausea and palpitations Labetalol flushing, light headedness, palpitations and scalp tingling Nifedipine flushing, nausea, vomiting Urapidil nausea and tinnitus $MgSO_4$ flushing Methyldopa somnolence.

* Few trials provided specific side effects. CCBs, calcium channel blockers; vs., versus; $MgSO_4$, magnesium sulphate