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Treating Hypertension in Women of Child-Bearing Age and during Pregnancy

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Abstract

Hypertension is found among 1 to 6% of young women. Treatment aims to decrease cardiovascular risk, the magnitude of which is less dependent on the absolute level of blood pressure (BP) than on associated cardiovascular risk factors, hypertension-related target organ damage and/or concomitant disease. Lifestyle modifications are recommended for all hypertensive individuals. The threshold of

BP at which antihypertensive therapy should be initiated is based on absolute cardiovascular risk. Most young women are at low risk and not in need of antihypertensive therapy. All antihypertensive agents appear to be equally efficacious; choice depends on personal preference, social circumstances and an agent's effect on cardiovascular risk factors, target organ damage and/or concomitant disease.

Although most agents are appropriate for, and tolerated well by, young women, another consideration remains that of pregnancy, 50% of which are unplanned. A clinician must be aware of a woman's method of contraception and the potential of an antihypertensive agent to cause birth defects following inadvertent exposure in early pregnancy. Conversely, if an oral contraceptive is effective and well tolerated, but the woman's BP becomes mildly elevated, continuing the contraceptive and initiating antihypertensive treatment may not be contraindicated, especially if the ability to plan pregnancy is important (e.g. in type 1 diabetes mellitus). No commonly used antihypertensive is known to be teratogenic, although ACE inhibitors and angiotensin receptor antagonists should be discontinued, and any antihypertensive drugs should be continued in pregnancy only if anticipated benefits outweigh potential reproductive risk(s).

The hypertensive disorders of pregnancy complicate 5 to 10% of pregnancies and are a leading cause of maternal and perinatal mortality and morbidity. Treatment aims to improve pregnancy outcome. There is consensus that severe maternal hypertension (systolic BP ≥170mm Hg and/or diastolic BP ≥110mm Hg) should be treated immediately to avoid maternal stroke, death and, possibly, eclampsia. Parenteral hydralazine may be associated with a higher risk of maternal hypotension, and intravenous labetalol with neonatal bradycardia. There is no consensus as to whether mild-to-moderate hypertension in pregnancy should be treated: the risks of transient severe hypertension, antenatal hospitalisation, proteinuria at delivery and neonatal respiratory distress syndrome may be decreased by therapy, but intrauterine fetal growth may also be impaired, particularly by atenolol. Methyldopa and other β-blockers have been used most extensively. Reporting bias and the uncertainty of outcomes as defined warrant cautious interpretation of these findings and preclude treatment recommendations.

This article reviews the definitions of hypertension and its management both for women of childbearing age and for pregnant women, as 50% of pregnancies are unplanned. It is meant to provide an overview of the area, with references intended to provide the reader with a more in-depth review of the data.

1. Prepregnancy Hypertension and the Woman of Child-Bearing Age

1.1 Definition and Measurement

Hypertension is arbitrarily defined as a sustained blood pressure (BP) of ≥140/90mm Hg, regardless of gender or pregnancy status. BP measurement should be standardised,[1] with the patient seated in a chair, the back and arm supported (at the level of the heart), the bladder of the cuff encircling ≥80% of the circumference of the arm, and the use of mercury sphygmomanometry. Phase V (disappearance of the Korotkoff sounds) should be used to define diastolic BP (DBP), as it is more reliable than phase IV. If BP is elevated, another reading should be obtained after at least 2 minutes and the average taken as that visit's value; more measurements are required if readings differ by more than 5mm Hg.

The measurement of BP in the clinic setting re-

mains the gold standard, given the clear epidemiological association between elevated clinic BP and adverse cardiovascular outcomes. There is currently a lack of adequate prospective data on prognosis as it relates to home or ambulatory BP measurements, which cannot be recommended as a matter of routine in all hypertensive individuals.[2] However, many clinicians and patients find such information useful, especially if it may affect commitment to lifestyle modifications and/or antihypertensive therapy. Ambulatory BP monitoring is recommended when 'white coat' hypertension is suspected (e.g. variability in office BP or hypertension that is resistant to treatment) or when symptoms suggest postural hypotension.[3]

In the absence of a hypertensive crisis, BP should be elevated on at least 3 visits to diagnose hypertension, to avoid incorrectly classifying the 7 to 24% of patients with 'white coat' hypertension.[2] The frequency of visits should depend on the presence/absence of concomitant disease (especially diabetes mellitus) and/or hypertension-related target organ damage (i.e. heart disease, stroke or transient ischaemic attack, nephropathy, peripheral arterial disease or retinopathy). In the absence of these, recommendations advise confirmation of an elevated BP by repeat measurement within 2[1] to 6[2] months.

1.2 Importance of Hypertension as a Cardiovascular Risk Factor

Hypertension, when defined as DBP ≥90mm Hg, is present among 1 to 6% of women aged 18 to 44 years.[4] However, there is a great deal of ethnic variation, with hypertension being more prevalent among certain ethnic groups, such as American Blacks. A diagnostic cut-off at a DBP of 90mm Hg is arbitrary, as there is a continuous relationship between higher BP and elevated cardiovascular risk. Although hypertension is a major risk factor for adverse cardiovascular outcomes (such as stroke and renal failure), factors other than the absolute level of BP are actually more important determinants of absolute cardiovascular risk.[5] These factors include smoking, dyslipidaemia, diabetes mellitus, age >60 years, gender (men and postmenopausal women) and a family history of premature cardiovascular disease, as well as hypertension-related target organ damage (i.e. heart disease, stroke or transient ischaemic attack, nephropathy, peripheral arterial disease or retinopathy), and/or other illnesses. Indeed, given identical BP measurements, risks for cardiovascular disease can vary by more than 10-fold depending on the presence of other cardiovascular risk factors.[6]

1.3 Treatment – General Principles

Hypertensive emergencies are rare and require immediate reduction of BP, although not necessarily to normal levels. Emergencies include hypertensive encephalopathy or haemorrhage, unstable coronary syndromes, and in pregnancy, eclampsia. The objective of BP reduction is prevention or limitation of target organ damage. Hypertensive emergencies are treated with parenteral agents to decrease the risk of imminent target organ damage. Parenteral agents are used initially to lower mean arterial BP by 25% over minutes to hours, and then to further lower BP to 160/100mm Hg over subsequent hours.[1] It is important to avoid inducing hypotension, which may cause ischaemia, particularly since the cerebral vasculature may lose its autoregulatory ability at the levels of BP being treated. A wide variety of agents are available, including parenteral labetalol, sublingual captopril and direct vasodilators such as sodium nitroprusside (section 3).

Hypertensive urgencies require BP reduction over a number of hours. Urgencies include isolated stage III hypertension (≥180mm Hg systolic, or ≥110mm Hg diastolic), as well as lesser elevations of blood pressure in the setting of less severe target organ damage than detailed under hypertension emergencies (e.g. optic disc oedema). Such urgencies are treated with either parenteral or oral agents (such as nifedipine or captopril) [section 3].

In the absence of a hypertensive urgency/emergency, hypertension is treated to maximally reduce the risk of long term cardiovascular disease. Antihypertensive treatment has both risks (adverse ef-

Table I. Absolute cardiovascular risk and the effects of treatment (reproduced from World Health Organization-International Society of Hypertension,[5] with permission)

Patient group	Absolute risk of CVD events over 10 years (%)	Absolute treatment effect (CVD events prevented per 1000 patient-years) with BP reduction of	
		10/5mm Hg	20/10mm Hg
Low risk	<15	<5	<9
Medium risk	15-20	5-7	8-11
High risk	20-30	7-10	11-17
Very high risk	>30	>10	>17

BP = blood pressure; **CVD** = cardiovascular disease.

fects) and benefits, and individuals with the highest cardiovascular risk benefit most.[7,8] Therefore, in determining the BP threshold at which antihypertensive treatment should be initiated, many guidelines now take into consideration both an individual's absolute cardiovascular disease risk over the next 10 years and the relative risk reductions in cardiovascular outcomes observed in clinical trials of about 5 years' duration (table I). Cardiovascular risk is defined as low (typically <15%), medium (15 to 20%), high (20 to 30%) and very high (≥30%)], based on (i) an individual's level of BP [classified as mild/grade 1 (140 to 159/90 to 99mm Hg), moderate/grade 2 (160 to 179/100 to 109mm Hg) or severe/grade 3 (≥180/110mm Hg)] and (ii) the presence of other cardiovascular risk factors, hypertension-related target organ damage, and/or associated clinical conditions (tables II and III).

Lifestyle measures are recommended for all individuals to address other cardiovascular risk factors (e.g. obesity) and, by lowering BP, to eliminate or decrease the need for antihypertensive therapy.[9] Although no clinical trial has confirmed their effectiveness, lifestyle measures are assumed to be worthwhile because they lower BP, and the effectiveness of antihypertensive medication is related to the BP reduction *per se* and not to the pharmacology of any one agent.[5] Most important among lifestyle modifications are smoking cessation, reduction of high salt intake, moderation of alcohol consumption, exercise and bodyweight reduction.

Antihypertensive therapy should be initiated immediately among patients at very high and high risk. Those at lower risk may have their BP monitored over weeks (if at medium risk) or over months to years (if at low risk), during which time investigations can be initiated, other cardiovascular risk factors addressed, and lifestyle modifications pursued. If, after 1 year, lifestyle modifications have been unsuccessful in lowering BP, antihypertensive therapy should be re-evaluated. Based on expert opinion, it has been recommended that investigations include the following: urinalysis, complete blood count, serum creatinine and electrolytes, fasting glucose, fasting cholesterol (total and both high and low density lipoprotein cholesterol), fasting triglycerides and a 12-lead electrocardiogram.[2]

For patients who need antihypertensive therapy, clinicians should base their choice on a number of considerations: cost, patient preference, history of adverse effects, potential interactions with other medications, and other disease states.[1,5] However, many guidelines[2,8] continue to recommend a diuretic or β-blocker as first-line therapy (especially in the presence of associated disease[3]) because of their proven favourable effect on long term cardiovascular outcomes.[10] Although the same may be true of newer agents, data are not yet available. At present, all classes of antihypertensives appear to be equally effective in lowering BP, and all have advantages and disadvantages related to adverse effects and/or effects on associated disease or other cardiovascular risk factors.[5] It is also important to recognise that compliance is enhanced when medication is well tolerated, leading to more effective treatment. The pharmacology and effects on pregnancy outcomes of the 6 antihypertensive drug classes are discussed in section 3.

Although most agents are appropriate for, and tolerated well by, women of child-bearing age, another consideration remains that of pregnancy. 50% of pregnancies are unplanned.[11] Therefore, before prescribing any medication to a fertile woman, it is important to have knowledge of her method of contraception and the potential teratogenicity of that medication. Only angiotensin ACE inhibitors (and, by association, angiotensin II receptor antagonists) are contraindicated for use in pregnancy (as discussed in section 3.6) and their use should be discontinued when pregnancy is diagnosed. Conversely, it is my opinion that if an oral contraceptive is effective and well tolerated by a woman, but her BP becomes mildly elevated, continuing the oral contraceptive and initiating antihypertensive treatment may not be contraindicated, especially if the ability to plan pregnancy has an important effect on pregnancy outcome. For example, this may be the case for a woman with type 1 or 2 diabetes mellitus, for whom excellent glycaemic control prior to conception can decrease her risk of having a baby with a major malformation to the baseline of 1 to 3%.[12]

Once antihypertensive treatment is initiated in a woman of child-bearing age who is not pregnant, close follow-up is mandatory. In the absence of special indications (e.g. diabetic nephropathy), BP should be lowered to 140/85mm Hg, as no benefits have been demonstrated for reductions much below this.[13] Patients should be seen not less frequently than every 6 months if BP is well controlled, and more frequently if not. Low doses of single agents are preferable. However, if BP control is not achieved, one may switch to another drug class or add a low dose of another agent (as increasing the dose of the first medication may increase the risk of adverse effects).[1]

It is not known whether pregnancy should be deferred in women with BP that is inadequately controlled before pregnancy. Given that BP usually falls in early pregnancy[14] (and this fall may be greater among women with chronic hypertension[15]), BP control may actually be achieved during preg-

Table II. Factors affecting absolute cardiovascular risk (reproduced from World Health Organization-International Society of Hypertension,[5] with permission)

Risk factors for cardiovascular diseases	Target organ damage[a]	Associated clinical conditions[b]
Used for risk stratification	Left ventricular hypertrophy (electrocardiogram, echocardiogram or radiogram)	Cerebrovascular disease
Levels of systolic and diastolic blood pressure (grades 1 to 3)		Ischaemic stroke, cerebral haemorrhage, transient ischaemic attack
Men >55 years	Proteinuria and/or slight elevation of plasma creatinine level (1.2-2.0 mg/dl)	**Heart disease**
Women >65 years		Myocardial infarction, angina, coronary revascularisation, congestive heart failure
Smoking	Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta)	**Renal disease**
Total cholesterol >6.5 mmol/L (250 mg/dl)		Diabetic nephropathy, renal failure (plasma creatinine level >2.0 mg/dl)
Diabetes mellitus	Generalised or focal narrowing of the retinal arteries	**Vascular disease**
Family history of premature cardiovascular disease		Dissecting aneurysm, symptomatic arterial disease
Other factors adversely influencing prognosis		**Advanced hypertensive retinopathy**
Reduced HDL-cholesterol		Haemorrhages or exudates, papilloedema
Raised LDL-cholesterol		
Microalbuminuria in diabetes mellitus		
Impaired glucose tolerance		
Obesity		
Sedentary lifestyle		
Raised fibrinogen		
High risk socioeconomic group		
High risk ethnic group		
High risk geographic region		

a Target organ damage corresponds to previous WHO stage 2 hypertension.

b Associated clinical conditions corresponds to previous WHO stage 3 hypertension.[9]

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **WHO** = World Health Organization.

Table III. Determination of cardiovascular risk (reproduced from World Health Organization-International Society of Hypertension,[5] with permission)

Other risk factors and disease history	Blood pressure (mm Hg)		
	grade 1 (mild hypertension) SBP 140-159 or DBP 90-99	grade 2 (moderate hypertension) SBP 160-179 or DBP 100-109	grade 3 (severe hypertension) SBP ≥180 or DBP ≥110
No other risk factors	Low risk	Medium risk	High risk
1 to 2 risk factors	Medium risk	Medium risk	Very high risk
3 or more risk factors or target organ damage or diabetes mellitus	High risk	High risk	Very high risk
Associated clinical conditions	Very high risk	Very high risk	Very high risk

DBP = diastolic blood pressure; **SBP** = systolic blood pressure.

nancy. Whether it is appropriate to take such a 'wait and see' approach is controversial. Although severe hypertension is associated with an increase in adverse pregnancy outcomes,[16] it is not known whether the hypertension itself causes the adverse outcomes or whether the hypertension is an effect of other deleterious maternal factors. Therefore, severe hypertension in early pregnancy that is brought under control is not necessarily an indication for elective termination of pregnancy.

The limitations of the current treatment guidelines must be acknowledged. First, using absolute cardiovascular risk to determine the need for antihypertensive treatment attempts to maximise the efficiency of antihypertensive treatment and arises from a public health perspective. This approach does not take into account the individual's perspective, which involves very personal considerations (such as self-perception of risk), as well as the ability to tolerate medication. Secondly, estimates of cardiovascular risk are based on data from the Framingham heart study, and therefore relate specifically to older men and women of Western populations; as such, they may not reflect risks among other ethnic groups or among young women. These estimates are also based on trials of typically 5 years' duration and may therefore underestimate risk reduction over longer periods of time.

2. Hypertensive Disorders of Pregnancy

2.1 Definitions and Measurement

Pregnancy hypertension refers to DBP ≥90mm Hg, with systolic BP (SBP) ≥170mm Hg and/or DBP ≥110mm Hg indicative of severe hypertension. Some professional societies have included SBP ≥140mm Hg in the definition of pregnancy hypertension.[17] A relative rise in DBP has not been widely endorsed, given its high false positive rate.[18] In early pregnancy, mean arterial BP falls by about 10mm Hg.[14] BP reaches its nadir at about 20 weeks' gestation and then rises towards prepregnancy levels by term. As in nonpregnancy, the measurement of pregnancy hypertension should be standardised and Korotkoff phase V used to designate DBP.[19] There are no guidelines for serial measurement of BP in pregnancy. However, repeat measurement seems to be advisable, given the results of 2 prospective studies showing that only 43 to 65% of women with clinic BP ≥140/90mm Hg remained hypertensive following serial measurements in obstetric day units.[20,21] These women with sustained elevation of BP also had more severe hypertension and perinatal complications, such as small for gestational age (SGA) infants.

There are 4 hypertensive disorders of pregnancy:

- chronic hypertension (diagnosed before pregnancy or in the first 20 weeks' gestation, and due to either essential or secondary causes);
- gestational hypertension (diagnosed after 20 weeks' gestation, and not associated with proteinuria);
- pre-eclampsia (diagnosed after 20 weeks' gestation – unless associated with gestational trophoblastic disease or hydrops – and associated with ≥0.3 g/24h of proteinuria);[22]

- pre-eclampsia superimposed on chronic hypertension.

Pre-eclampsia is caused by abnormal development of the placenta,[23] which, in later pregnancy, is thought to release factors that cause diffuse maternal endothelial cell dysfunction and multiorgan complications, including proteinuria.[24] Beyond an appropriate history, physical examination and urinalysis, further investigation into other causes of hypertension (e.g. glomerulonephritis, thyrotoxicosis or phaeochromocytoma) or organ dysfunction (e.g. microangiopathies that mimic pre-eclampsia[25]) should be guided by clinical suspicion. Pre-eclampsia may develop *de novo* or in approximately 20% of women with chronic hypertension.[26] Not infrequently, it is possible to classify hypertension with certainty only at 6 to 12 weeks postpartum.[18,27]

2.2 Importance of Hypertensive Disorders of Pregnancy: Effect on Pregnancy Outcome

According to population-based data, hypertensive disorders complicate 7.3 to 8.8% of pregnancies.[28] Approximately 1% is chronic hypertension, 5 to 6% gestational hypertension (proteinuria <2+ by urinary dipstick testing) and 1 to 4% pre-eclampsia.[26,29] Hypertensive disorders of pregnancy remain a leading cause of maternal and perinatal (defined as fetus at ≥20 weeks' gestation at birth or ≥500g in birthweight, or neonate during the first 28 days of life) mortality and morbidity worldwide.[30,31]

2.2.1 Risks During Gestation

Severe hypertension (SBP ≥170mm Hg and/or DBP ≥110mm Hg) in pregnancy accounts for much of the maternal risk associated with hypertensive disorders; formerly, most maternal deaths related to pregnancy hypertension were due to the complications of severe hypertension, particularly intracerebral haemorrhage.[32]

Mild-to-moderate hypertension (DBP 90 to 109mm Hg) in pregnancy is associated with lower maternal risk. Death and stroke are rare (with none reported among 22 trials enrolling 2552 women)[33] and eclampsia is unusual, occurring in 0.1% [95% confidence interval (CI) 0.01 to 0.6%] of women without proteinuria and 3.8% (95% CI 2.2 to 6.0%) of women with proteinuria.[34] In fact, just as in nonpregnancy, factors other than the level of BP are more important determinants of maternal risk in pregnancy. First, most hypertension-related maternal deaths in the UK are now due to nonhypertensive complications of pre-eclampsia such as hepatic failure or acute respiratory distress syndrome.[35] Secondly, 20% of eclampsia occurs in the absence of antenatal hypertension.[36] Antihypertensive treatment is not known to affect the risk of these complications.[36]

2.2.2 Perinatal Risks

It is difficult to ascertain the incidence of perinatal complications among women with hypertensive disorders of pregnancy because of methodological problems with the published studies:[37]

- the preponderance of, and bias associated with, data from tertiary care centres;
- variability in definitions of maternal hypertension, proteinuria and perinatal complications, including the definition of SGA infants (usually defined as birthweight <10th percentile for gestational age at delivery);
- failure to account for factors (including antihypertensive treatment) that may confound the relationship between maternal disease and perinatal outcome;
- outcomes in older studies may be worse because of outdated treatment.

Consequently, published estimates can be regarded only as approximations.

Chronic hypertension is associated with perinatal complication rates that are doubled for placental abruption and tripled for perinatal mortality, most likely because of hypoxia and complications of preterm delivery.[16,38-43] This is particularly true when there is progression, in approximately 20% of cases, to pre-eclampsia.

Women with gestational hypertension without proteinuria at presentation have perinatal complication rates similar to those of normotensive women.[44] However, among women who develop gestational hypertension at <34 weeks' gestation,

the risk of perinatal complications is assumed to be elevated, given that 36 to 42% of these women progress to frank pre-eclampsia.[45-47]

There is general agreement that pre-eclampsia is associated with the highest risk of perinatal complications.[37] This is especially true in the approximately 30% of women with associated fetal growth restriction[48] and/or the approximately 50% of women with preterm onset of disease, given that gestational age at delivery is the primary determinant of perinatal outcome.[49-61] It was previously thought that the SGA infant, who had most commonly been 'stressed' *in utero* by a decrease in substrate for growth, had fewer perinatal complications, including respiratory distress syndrome (RDS).[62] However, the converse appears to be true. Being SGA increases the risk of short term neonatal complications,[63-67] long term sequelae (although these are, most commonly, mild in severity)[68-71] and, possibly, cardiovascular complications in adulthood because of *in utero* metabolic adaptations that become permanent (the 'Barker hypothesis').[72-83]

There is also a continuum of risk between incremental increases in maternal BP and both perinatal mortality and intrauterine growth restriction.[84-86] Although women with pre-eclampsia tend to have higher BP, this association between BP and perinatal outcome appears to hold even in the absence of maternal proteinuria. This information has resulted in some recommendations to normalise BP in pregnancy.[87]

2.2.3 Threshold for Initiation of Antihypertensive Therapy

Severe Hypertension

There is consensus that maternal risk is decreased by antihypertensive therapy that acutely lowers severely elevated BP, and this has been borne out by a recent decrease in maternal death from severe pregnancy hypertension-related intracerebral haemorrhage in the UK.[31,87-89] Most women with severe hypertension will have pre-eclampsia, for which antihypertensive therapy is but one component of management. Decisions about timing and method of delivery are within the realm of obstetrics and beyond the scope of this article. Although delivery remains the only cure for pre-eclampsia, hypertension may take days to months to resolve, and postpartum antihypertensive treatment is often needed.

Mild-to-Moderate Hypertension

There is no consensus as to how mild-to-moderate pregnancy hypertension (regardless of type) should be managed to optimise pregnancy outcome.[17] What is contemplated is short term therapy over weeks to months. This is a time period over which nonpregnant women at low-to-medium risk would only be observed. This is also a time period over which there is no evidence that antihypertensive medication decreases long term cardiovascular risk. What is the evidence that antihypertensive therapy improves pregnancy outcome?

There have been 22 published trials, including 2549 women with various hypertensive disorders of pregnancy, that compared the effect of differential control of BP on maternal and perinatal outcomes and have been subjected to meta-analysis.[90,91] Maternal hypertension was defined in these trials in such a way as to permit analysis according to 'chronic hypertension' (always mild) and 'late onset hypertension', defined as a mixed population of women with either chronic hypertension presenting for treatment only later in pregnancy, gestational hypertension or pre-eclampsia.

Among women randomised to receive antihypertensive therapy only when BP reached 160/100 to 110mm Hg, there was a trend toward a decrease in SGA infants [odds ratio (OR) 0.76, 95% CI 0.57 to 1.02; 16 trials]. Although this risk was not explained by the type of underlying hypertension (i.e. 'chronic' or 'late onset' as defined above) or type of antihypertensive (with the possible exception of a trial of atenolol *vs* placebo[92] that was a statistical outlier), risk of an SGA infant did appear to be increased by a greater antihypertensive-induced fall in mean arterial BP.[91,93] Among women whose BP was normalised (DBP goal <90mm Hg), there was a decrease in the risk of severe hypertension (BP >160/100 to 110mm Hg) [OR 0.34, 95% CI 0.26 to 0.45; 17 trials], maternal hospitalisation (OR 0.41,

95% CI 0.28 to 0.61; 5 trials) and 'proteinuria at delivery' (OR 0.71, 95% CI 0.57 to 0.90; 19 trials); this was true for both chronic hypertension and 'late onset' hypertension. In addition, there was a decrease in neonatal RDS (OR 0.27, 95% CI 0.13 to 0.54; 5 trials) which was reported only by 'late onset' hypertension trials.

In summary, no conclusions can be made about the relative maternal or perinatal benefits/risks of antihypertensive therapy for mild-to-moderate pregnancy hypertension, regardless of type. First, meta-analyses are retrospective in design and should be regarded only as hypothesis-generating. Secondly, clinical trials included in the aforementioned meta-analysis did not report all outcomes of interest, and defined certain outcomes in ways that may not be clinically relevant. For example, a BP of 160/100mm Hg is a poor surrogate marker for stroke, and 2 trials defined RDS as need for ventilation, which could have included neonates with transient tachypnoea of the newborn (which is not a serious neonatal outcome). Finally, it was not possible to adequately distinguish effectiveness by type of hypertension, as traditionally defined.

National societies differ in their recommendations for the BP at which antihypertensive therapy during pregnancy should be started. The Americans recommend starting therapy at a DBP ≥100mm Hg without specifying a DBP treatment goal.[88] The Canadian Hypertension Society recommends normalisation of BP for most hypertensive disorders of pregnancy, with a BP of 140 to 150/90 to 95mm Hg to be treated to achieve a DBP of 80 to 90mm Hg.[87] The Australasians recommend initiation of antihypertensive therapy at BP ≥160/90mm Hg, to reach a target BP of 110 to 140/80 to 90mm Hg.[17] All groups list methyldopa, labetalol and nifedipine as acceptable agents (section 3). Until more definitive data become available, it seems reasonable to choose a target DBP of 85 to 100mm Hg for pregnant women with mild-to-moderate hypertension, regardless of type.

Existing evidence does not support the effectiveness of hospitalisation and/or strict bedrest for women with any type of pregnancy hypertension.[90,94] These approaches also may increase the risk of thromboembolic events among pregnant women, who are already at increased risk.[95] All pregnant women, and not just those who are hypertensive, are recommended to stop their intake of cigarettes and alcohol. However, other lifestyle measures, such as bodyweight loss, restricted salt intake and initiation of a new exercise programme, are not recommended in pregnancy because of theoretical concerns.

A discussion of other interventions among women with hypertensive disorders of pregnancy is beyond the scope of this review. Briefly, there is currently no proven effective prophylaxis against pre-eclampsia, although antioxidant therapy holds promise,[96] and it may be premature to abandon hope that aspirin may benefit certain subgroups of women at high risk for pre-eclampsia.[97] The Eclampsia Trial established magnesium sulfate as the most effective therapy for eclampsia.[98] Although magnesium sulfate reduces the occurrence of eclampsia,[99,100] the efficiency of the therapy (in terms of number needed to treat) is unclear; magnesium sulfate is being evaluated in a large multicentre trial among women with pre-eclampsia, among whom seizure risk is highest.[101]

3. Which Antihypertensive Agent to Use?

For this review, the safety of drug use in early pregnancy was sought from case reports/series, record linkage studies, or controlled, observational studies of drug exposure in early human pregnancy. Data were reviewed for evidence of an absolute increase in the incidence of malformations and/or a specific pattern of malformations associated with drug exposure. Extrapolation of animal data to human pregnancy is very difficult and is not reviewed here. Narrative statements have been provided without regard to the US Food and Drug Administration classification,[102] given its inconsistencies and the recommendation that it be abandoned.[103]

This section briefly discusses the pharmacology and reproductive toxicology of each class of anti-

hypertensive agent. Special mention is made of the effect of each on pregnancy outcome; however, the reader should keep some general principles in mind.

- Hypertensive disorders of pregnancy are, themselves, associated with an increase in the risk of adverse pregnancy outcomes, such as intrauterine fetal growth restriction.
- There is a baseline risk of adverse pregnancy outcomes, including a risk of 1 to 3% for major malformations, regardless of drug therapy in pregnancy.
- All antihypertensive agents have been shown or should be assumed to cross the placenta and reach the fetal circulation.
- None of the commonly used classes of antihypertensive drugs has been shown to be teratogenic when taken in early pregnancy.
- ACE inhibitors and angiotensin receptor antagonists when taken later in pregnancy are associated with a characteristic fetopathy and are the only antihypertensive agents contraindicated in pregnancy.
- Atenolol is not recommended for use in pregnancy, given particular concerns about its potential to increase the risk of an SGA infant.
- The benefits and risks of using any antihypertensive agent in pregnancy have not been adequately defined; there are potential maternal benefits, and perinatal risks and benefits, and care should be individualised until definitive data become available.
- Because of a lack of sufficient information, no reliable conclusions can be drawn about the effect of antihypertensive agents on long term child development, even for methyldopa.
- For all antihypertensive agents, only large increases in reproductive risk (including major malformations) can be ruled out by existing data; therefore, 'no evidence of harm' cannot be regarded as equivalent to 'evidence of no harm', and the clinician must have clear therapeutic goals in mind when initiating treatment in pregnancy. Given that BP falls in early pregnancy, and that most young women have no other major cardiovascular risk factors, hypertension-related target organ damage or other relevant disease, clinicians should consider discontinuing antihypertensive therapy early in pregnancy.
- Orally administered antihypertensive agents should be used in standard doses in pregnancy (table IV); agents used for the acute severe hypertension of pre-eclampsia should be initiated at lower doses than in nonpregnant women, given that women with pre-eclampsia are intravascularly volume depleted and at increased risk of hypotension. Some protocols[17] recommend cautious use of intravenous volume restoration in this setting.
- All commonly used antihypertensive agents, including labetalol, oxprenolol, methyldopa, ni-

Table IV. Suggested dosages of the most commonly used antihypertensive medications in pregnancy[105,106]

Drug	Starting dosage	Maximum dosage
For severe hypertension[a]		
Short-acting nifedipine	5-10mg PO every 30 min	10mg PO every 30 min
Labetalol	5-20mg IV every 30 min *or* infusion of 1-2 mg/min	80mg IV every 30 min
Hydralazine	5-10mg IV/IM every 30 min *or* infusion of 0.5-1 mg/h	10mg IV/IM every 30 min
For mild-to-moderate hypertension		
Methyldopa	750mg PO loading dose, then 250-500mg PO bid	2000 mg/day in up to 4 doses
Labetalol	100-200mg PO bid	1200 mg/day in up to 4 doses
Hydralazine	10mg PO qid	200 mg/day in up to 4 doses
Long-acting nifedipine	20-30mg PO od	120 mg/day in 1 dose

a The starting dosages are lower than for nonpregnancy, given the greater potential to cause maternal hypotension and its important consequences for the fetus.

bid = twice daily; **IM** = intramuscularly; **IV** = intravenously; **od** = once daily; **PO** = orally; **qid** = 4 times daily.

fedipine and captopril, are considered to be compatible with breast feeding, based on their pharmacology and low detectable drug concentrations in breast milk.[106]

3.1 Diuretics

Among nonpregnant women, diuretics are among the most widely used of orally administered antihypertensives because of their low cost, availability and favourable effect on major cardiovascular events that has been proved in randomised controlled trials.[10] Most popular among these drugs are hydrochlorothiazide and potassium-sparing diuretics such as amiloride and triamterene. Diuretics lower BP by initially promoting natriuresis and a subtle decrease in intravascular volume; over time, they cause a persistent decrease in systemic vascular resistance, by complicated mechanisms ascribed to 'total body autoregulation'.[107] Diuretics are particularly effective among Black women and in combination with either a β-blocker or an ACE inhibitor. The adverse effects of diuretics, which include hypokalaemia and, possibly, impaired glucose tolerance,[108] can be minimised by using low doses (e.g. no more than 25mg of hydrochlorothiazide/day).

3.1.1 Effect on Pregnancy Outcome

Hydrochlorothiazide, triamterene and amiloride are not thought to be teratogenic, on the basis of a small number of case reports and a record linkage study.[109] Early studies raised concerns that thiazide diuretics may cause neonatal thrombocytopenia, but there was no increase in these events among diuretic-exposed neonates in clinical trials involving approximately 10 000 patients.[110] Although diuretics retard most of the plasma volume expansion of normal pregnancy,[111] this has not been proved to have a negative effect on fetal growth, as initially feared.[110]

3.2 Peripherally Acting Adrenergic Receptor Antagonists

3.2.1 β-Blockers

As with diuretics, β-blockers are inexpensive, widely available and favoured for treatment of nonpregnant women because of the wealth of trial data showing that they decrease the risk of major cardiovascular events.[10] β_1-Blockade decreases renal sympathetic output (and, for example, renin production and sodium excretion) and cardiac output, by decreasing heart rate and contractility. β_2-Blockade causes constriction of airway smooth muscle and increases systemic vascular resistance initially, although resistance falls with long term treatment, probably because of a persistent decrease in renin;[112] this may explain why β-blockers are less effective among patients of Black race, who tend to have low renin hypertension. β-Blockers differ in their affinity for β_1- and β_2-adrenoceptors (when prescribed at lower doses), lipid solubility and access to the central nervous system, and/or intrinsic sympathomimetic activity (partial agonist activity) mediated through stimulation of β_2-adrenoceptors and resulting in a lesser or no decrease in cardiac output. Atenolol is a very popular agent because it is cardioselective (i.e. blocks only β_1-receptors), hydrophilic and taken only once daily. β-Blockers are effective in combination with diuretics, dihydropyridine calcium antagonists (e.g. nifedipine) or α-blockers. The pharmacology of β-blockers largely predicts their adverse effects: lethargy and bronchospasm (through β_2 effects on skeletal muscle vasculature and small airways smooth muscle, respectively) and poor sleep and dreams (through use of lipid-soluble agents that traverse the blood-brain barrier).

Labetalol, a nonselective β-blocker with vascular α_1-blocking capabilities, has gained wide acceptance in pregnancy.

Effect on Pregnancy Outcome

β-Blockers act by receptor-mediated mechanisms; therefore, their effect on pregnancy outcome is discussed as a class. β-Blockers do not appear to be teratogenic, based on limited data in human pregnancy.[93,109] Whether oral β-blocker therapy for weeks to months in pregnancy is fetotoxic (i.e. increases the risk of intrauterine growth restriction and/or causes other neonatal adverse effects such as bradycardia), as suggested by earlier case reports, is controversial. The best available evidence comes

from clinical trials in which β-blocker therapy figured prominently.[113] As discussed previously, antihypertensive agents were not distinguishable in their perinatal effects and were found to be associated with both perinatal risk (increase in SGA infants associated with greater fall in mean arterial pressure) and maternal and perinatal benefits (decreased severe hypertension, hospital admission, 'proteinuria at delivery' and neonatal RDS).[90,91] The quality of the data and the retrospective nature of meta-analysis preclude firm conclusions. For oral β-blocker trials specifically, there was a demonstrable increase in neonatal bradycardia, but it was not clinically significant, in that the bradycardia was detectable only by close neonatal monitoring, and no child required intervention to raise heart rate.[90,93,114]

It should be mentioned that there is mounting evidence that atenolol, for reasons that are unclear, may be a particular problem in pregnancy.[115] One clinical trial of long term atenolol for chronic hypertension in pregnancy found a dramatic increase in SGA infants among the atenolol-treated pregnancies.[92] Observational data also suggest such an effect,[116,117] even among nonhypertensive women with high cardiac output who were given atenolol as pre-eclampsia prophylaxis.[118] Given the large number of other β-blockers available for use, atenolol use should be avoided in pregnancy.

For severe hypertension, β-blockers may be administered parenterally; labetalol has been most studied in this regard. In clinical trials of acute severe hypertension in pregnancy, labetalol was associated with less maternal hypotension than hydralazine. However, hypotension may be associated with any antihypertensive agent, particularly among women with pre-eclampsia who are intravascularly volume depleted.[119] Therefore, it is recommended that pregnant women be initially treated with doses of agents that are lower than those used in nonpregnant women (table IV). In the same clinical trials, parenteral labetalol also increased the risk of neonatal bradycardia, which required intervention in 1 of 6 neonates.[90] Neonatal bradycardia has also been reported with other shorter-acting agents, such as esmolol,[120] but it is impossible to interpret the magnitude of the risk. Therefore, obstetric anaesthesia and neonatology should be aware of this information and be informed about the use of parenteral β-blockers during labour, although the absolute risk of problems is probably low.

3.2.2 α-Adrenergic Antagonists

α_1-Blockers, such as prazosin, are well tolerated and effective in lowering BP, but their effect on long term cardiovascular outcomes is uncertain. These drugs selectively block postsynaptic α_1-adrenoceptors, producing a decrease in total peripheral resistance (and a reflex increase in sympathetic tone). They are not first-line agents in nonpregnancy or pregnancy, but can be used successfully in combination with other agents. They cause postural hypotension and palpitations, and their use has been largely replaced by other agents with more favourable adverse effect profiles.

Effect on Pregnancy Outcome

α_1-Blockers have also not been extensively used in pregnancy, particularly early pregnancy. It is impossible to determine the significance of 1 case report of multiple fetal anomalies following first trimester exposure to prazosin.[121] In later pregnancy, prazosin has been used more extensively and is considered a reasonable choice of antihypertensive, usually in combination with a β-blocker. It has also been used for phaeochromocytoma,[109] although phentolamine (another short-acting α-blocker) is the drug of choice for such patients prior to surgery or delivery.

3.3 Centrally Acting α_2-Adrenergic Agonists

Like peripheral α_1-blockers, use of drugs such as methyldopa and clonidine has been supplanted by use of agents with more favourable adverse effect profiles. However, methyldopa remains a drug of first choice for treatment of hypertension in pregnancy.[87] The metabolites of methyldopa and clonidine act at central α_2-adrenoceptors to decrease central sympathetic outflow, thereby decreasing systemic vascular resistance without decreasing cardiac output in young, otherwise healthy, wom-

en. In addition to adverse effects stemming from its pharmacology (e.g. fatigue, depression, poor sleep), methyldopa has dose-independent adverse effects that include elevated liver enzymes (in 5% of women) and a positive Coomb's test (which is rarely associated with clinical haemolytic anaemia).

3.3.1 Effect on Pregnancy Outcome

Methyldopa is not thought to be teratogenic, based on limited data and a long history of use in pregnancy.[109] No specific fetal or neonatal toxicity has been reported, although the relative benefits and risks of antihypertensive therapy for mild-to-moderate hypertension in pregnancy remain to be established.

3.4 Calcium Antagonists

Calcium antagonists are popular antihypertensive agents in nonpregnancy, and nifedipine has been used extensively in later pregnancy. Calcium antagonists produce direct arterial vasodilation, by inhibiting influx of Ca^{2+} through channels in smooth muscle; different agents have different affinity for channels in the arterial resistance vessels and cardiac myocytes and cells of the conducting system. Dihydropyridines such as nifedipine, the calcium antagonist used most extensively in pregnancy, act predominantly on the vasculature; verapamil acts primarily on the heart. Calcium antagonists also appear to have a natriuretic effect and do not lead to volume retention; their associated dependent oedema probably results from effects on the microvasculature. Dihydropyridines produce a reflex increase in sympathetic tone, and immediate release nifedipine has been associated with ischaemic events among individuals with coronary artery disease or diabetes mellitus; however, controlled trials have not suggested that this is true for delayed release preparations or longer-acting agents (e.g. amlodipine), which are still used in nonpregnant individuals.[122,123] These agents are effective in combination with ACE inhibitors, but less so with diuretics, probably because both have natriuretic effects.[124]

Nifedipine is available in 3 forms. The capsule is very short acting, with peak effect by 30 minutes, and is used for treatment of severe hypertension. One type of tablet has peak onset within hours and may be used for moderate to severe hypertension, depending on the urgency of the situation. The second type of tablet has a delayed release system ('GITS'), which releases nifedipine over 24 hours and allows once daily administration.

3.4.1 Effect on Pregnancy Outcome

Orally administered calcium antagonists, particularly nifedipine and verapamil, which have been best studied, do not appear to represent a major teratogenic risk.[125] Any antihypertensive agent may be associated with potential benefit and risk.[91] Administration of short-acting nifedipine for severe hypertension in pregnancy has, as with other antihypertensives, been associated with maternal hypotension (and fetal distress) which may be more likely with coadministration of magnesium sulfate.[126,127] Extrapolation of data from literature about patients with ischaemic heart disease or diabetes mellitus has resulted in withdrawal of nifedipine capsules from many pharmacies.[128] However, pregnant women represent a different patient population with different concerns (e.g. maternal hypotension and associated fetal distress). In clinical trials, hypotension was more common with parenteral hydralazine, which is discussed in detail in section 3.5.[90] One case report of neuromuscular blockade has also been associated with concomitant use of nifedipine and magnesium sulfate;[129] caution should be exercised when using these drugs concomitantly, although this is common practice in delivery suites, and the absolute risk of a problem is probably very low.

3.5 Direct Vasodilators

With the exception of hydralazine in later pregnancy, oral treatment of mild-to-moderate hypertension with direct vasodilators has largely been supplanted by use of other agents with more favourable adverse effect profiles. However, in nonpregnancy and pregnancy, these agents are still used parenterally for treatment of acute severe hypertension. These agents act directly on vascular smooth muscle by a number of actions; sodium nitropruss-

ide acts as a nitric oxide donor and diazoxide opens ATP-sensitive K^+ channels, whereas hydralazine acts by as yet unknown mechanisms.[105] Reflex sympathetic activation leads to tachycardia, palpitations, headache, flushing and fluid retention, among other adverse effects. Hydralazine rarely causes drug-induced lupus or polyneuropathy with long term treatment. Effective long term antihypertensive treatment with these agents requires combination therapy with either sympatholytic agents or diuretics. Nitroprusside is rarely used, and only in an intensive care unit or operating theatre setting; its use antenatally is not desirable given that its metabolism produces thiocyanate, which can produce maternal and/or fetal toxic effects after 24 hours of use (or sooner in the presence of renal dysfunction).

3.5.1 Effect on Pregnancy Outcome

Oral hydralazine is the direct vasodilator most likely to be administered during the first trimester of pregnancy. Limited data have not associated hydralazine with teratogenicity.[109] There are potential risks and benefits with use of any antihypertensive in pregnancy, as previously discussed.[91] Parenteral hydralazine (by bolus, intramuscular injection or intravenous infusion) is a drug of first choice for treatment of acute severe hypertension in pregnancy. However, data from trials indicate that hydralazine is more frequently associated with significant maternal hypotension (and Caesarean section and low Apgar scores) than is parenteral labetalol or short-acting (oral/sublingual) nifedipine.[90] Some specialised units report good experience with hydralazine when treatment is preceded by infusion of crystalloid or colloid; however, one must be aware that women with severe hypertension due to pre-eclampsia are at increased risk of pulmonary oedema, and it is not advised to infuse more than 1L without central monitoring. There is 1 reported case of maternal, and possibly neonatal, lupus following 6 days of parenteral hydralazine therapy for severe hypertension;[130] if this association were true, the magnitude of the risk would appear to be small, given the wide use of hydralazine in later pregnancy for this indication.

3.6 ACE Inhibitors and Angiotensin Receptor Antagonists

ACE inhibitors are effective, convenient to administer and well tolerated antihypertensive agents that have become widely used in women of childbearing age. These agents inhibit the enzyme that converts angiotensin I to angiotensin II, thereby decreasing production of angiotensin II and aldosterone, and ultimately producing vasodilation. Adverse effects of ACE inhibitors include a dry cough (that is due, at least in part, to accumulation of bradykinin), and this is the primary indication for a switch to be made to angiotensin receptor antagonists. ACE inhibitors may also cause renal failure in patients who depend on the selective renal efferent arteriolar vasoconstriction of angiotensin II to maintain glomerular filtration rate (e.g. with volume contraction or bilateral renal artery stenosis). A wide variety of ACE inhibitors (e.g. captopril, enalapril, fosinopril) and angiotensin receptor antagonists (e.g. losartan) are available.

3.6.1 Effect on Pregnancy Outcome

The available evidence on first trimester exposure to ACE inhibitors is not consistent with a high teratogenic risk, although a small risk cannot be ruled out.[131,132] Therefore, inadvertent drug exposure in early pregnancy is not normally considered an indication for elective termination of pregnancy. Use of ACE inhibitors in the second and third trimesters of pregnancy has been associated with a fetopathy characterised by both fetal problems (oligohydramnios, fetal distress and fetal death) and neonatal problems (renal failure, pulmonary hypoplasia, joint contractures, hypocalvaria and intrauterine growth restriction).[133] These effects are thought to be related to a direct pharmacological effect of the drugs on fetal physiology. The magnitude of the risk is not quantifiable because of the lack of prospective data, but risk appears to be increased by long term administration. ACE inhibitors (and angiotensin receptor antagonists, by association) should be discontinued in pregnancy.[134]

4. Conclusion

Whether pregnant or not, all women with severe hypertension should receive immediate antihypertensive therapy to decrease short term cerebrovascular events. Care should be taken to reduce BP only modestly, to avoid ischaemia of maternal organs (especially the brain) and/or the placenta and fetus.

Young women who are not pregnant, and have mild-to-moderate hypertension, do not necessarily need antihypertensive therapy, as they are usually at low cardiovascular risk. If indicated, all antihypertensive agents are appropriate choices given that none has been proven to be teratogenic when inadvertent exposure occurs in pregnancy. Only ACE inhibitors and angiotensin receptor antagonists are contraindicated for ongoing use in pregnancy.

Treating mild-to-moderate hypertension in pregnancy is controversial, as available data do not provide a clear picture of the relative maternal and perinatal benefits and risks. There is a wide choice of appropriate antihypertensive agents, although methyldopa and β-blockers (other than atenolol) enjoy the most support.

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