Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy

Education

Éducation

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Abstract

Objective: To provide Canadian physicians with evidence-based guidelines for the pharmacologic treatment of hypertensive disorders in pregnancy.

Options: No medication, or treatment with antihypertensive or anticonvulsant drugs.

Outcomes: Prevention of maternal complications, and prevention of perinatal complications and death.

Evidence: Pertinent articles published from 1962 to September 1996 retrieved from the Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews and from MEDLINE; additional articles retrieved through a manual search of bibliographies; and expert opinion. Recommendations were graded according to levels of evidence.

Values: Maternal and fetal well-being were equally valued, with the belief that treatment side effects should be minimized.

Benefits, harms and costs: Reduction in the rate of adverse perinatal outcomes, including death. Potential side effects of antihypertensive drugs include placental hypoperfusion, intrauterine growth retardation and long-term effects on the infant.

Recommendations: A systolic blood pressure greater than 169 mm Hg or a diastolic pressure greater than 109 mm Hg in a pregnant woman should be considered an emergency and pharmacologic treatment with hydralazine, labetalol or nifedipine started. Otherwise, the thresholds at which to start antihypertensive treatment are a systolic pressure of 140 mm Hg or a diastolic pressure of 90 mm Hg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks' gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions or target-organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. The thresholds in other circumstances are a systolic pressure of 150 mm Hg or a diastolic pressure of 95 mm Hg. For nonsevere hypertension, methyldopa is the first-line drug; labetalol, pindolol, oxprenolol and nifedipine are second-line drugs. Fetal distress attributed to placental hypoperfusion is rare, and long-term effects on the infant are unknown. Magnesium sulfate is recommended for the prevention and treatment of seizures.

Validation: The guidelines are more precise but compatible with those from the US and Australia.

Sponsor: Preparation of the guidelines was funded by the Canadian Hypertension Society. The guidelines are endorsed by the Canadian Hypertension Society, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens-gynécologues du Québec.

Résumé

Objectif : Formuler des lignes directrices définitives à l'intention des médecins canadiens qui fournissent des soins prénataux pour le traitement pharmacologique des problèmes hypertensifs de la grossesse.

Option : Aucun médicament ou traitement aux agents hypotenseurs ou anticonvulsivants.

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This article has been peer reviewed.

This is the final article in a series that began in the Sept. 15, 1997, issue of CMAJ*; part 2 appeared in the Oct. 1 issue.*

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Résultats : Prévention des complications chez la mère et prévention des complications et de la mortalité périnatales.

Preuves : Articles pertinents publiés entre 1962 et septembre 1996 tirés du module «Pregnancy and Childbirth» de la Cochrane Database of Systematic Reviews et de MEDLINE; articles supplémentaires trouvés par une recherche manuelle de bibliographies; opinions d'experts. Classement des recommandations selon le niveau de preuve.

Valeurs : Importance égale attribuée au bien-être de la mère et du fœtus, les effets secondaires du traitement étant minimisés.

Avantages, préjudices et coûts : Réduction du taux de morbidité et de mortalité périnatales. Les effets secondaires possibles des agents hypotenseurs comprennent une hypoperfusion placentaire, un retard de croissance intrautérin et des répercussions à long terme sur le nourrisson.

Recommandations : Chez une femme enceinte, une tension artérielle systolique supérieure à 169 mm Hg ou une tension diastolique supérieure à 109 mm Hg doivent être considérée comme une situation d'urgence et nécessite un traitement pharmacologique par administration d'hydralazine, de labetalol ou de nifédipine. Dans les autres cas, un traitement pharmacologique s'impose si la tension artérielle systolique atteint le seuil de 140 mm Hg et la tension diastolique, 90 mm Hg avant 28 semaines de grossesse chez les femmes atteintes d'hypertension induite par la grossesse sans protéinurie, et d'hypertension avant la grossesse. Il faut aussi traiter quel que soit le moment de la grossesse celles qui sont atteintes d'hypertension induite par la grossesse en présence de protéinurie, celles qui sont atteintes d'hypertension avant la grossesse et de maladies sous-jacentes ou de dommages aux organes cibles, et celles qui sont atteintes d'hypertension avant la grossesse compliquée d'une hypertension induite par la grossesse. Dans les autres cas, les seuils sont une tension artérielle systolique de 150 mm Hg ou une tension diastolique de 95 mm Hg. Pour l'hypertension non sévère, le méthyldopa est le médicament de première intention, tandis que le labetatol, le pindolol, l'oxprenolol et la nifédipine devraient être employés en second lieu. La souffrance foetale par hypoperfusion placentaire est rare et les effets à long terme sur le nourrisson sont inconnus. On recommande le sulfate de magnésium pour la prévention et le traitement des crises convulsives.

Validation : Ces lignes directrices sont plus précises que celles d'instances américaines et australiennes, mais les rejoignent en général.

Commanditaires : Préparation des lignes directrices financée par la Société canadienne d'hypertension artérielle. Lignes directrices reconnues par la Société canadienne d'hypertension artérielle, la Société des obstétriciens et gynécologues du Canada et l'Association des obstétriciens-gynécologues du Québec.

*This is the final article in a 3-part series on hypertensive disorders in pregnancy. Part 1 describes the definitions, evaluation and classification of such disorders (*Can Med Assoc J *1997;157:715-25), and part 2 provides evidence-based guidelines for nonpharmacologic management and prevention (*Can Med Assoc J *1997;157:907-19).*

Hypertensive disorders in pregnancy pose serious risks for both mother and fetus. The pharmacologic treatment of them is a medical and obstetric challenge. There are currently no uniform guidelines in Canada for the management of hypertension in pregnancy because of a lack of good information about whether pharmacologic intervention is necessary and how to initiate it. This article provides evidence-based guidelines for Canadian physicians who provide care to pregnant women. Although US and Australian guidelines exist, ones specific to Canada are necessary because populations and health care systems are different.

Methods

The details of the consensus process are provided in part 1 of the series.[1] In brief, the Canadian Hypertension Society (CHS) decided in 1994 to develop a Canadian consensus on the diagnosis and management of hyperten-

sive disorders in pregnancy. The president of the society and cochair were charged to create panels to address the 3 parts of the project: definitions, evaluation and classification;[1] nonpharmacologic management and prevention;[2] and pharmacologic treatment.

The members of the panel addressing pharmacologic treatment were chosen for their expertise in obstetrics, internal medicine and clinical pharmacology. The work was distributed among the members, and one of them (E.R.) reviewed the literature and the prepared information. The panel members reviewed available evidence published from 1962 to September 1996 retrieved from various sources: articles retrieved through a MEDLINE search (English and French literature) using the terms "human pregnancy toxemia," "pre-eclampsia," "eclampsia," "complications [cardiovascular]" and "hypertension"; the bibliographies of retrieved reports, review articles and personal files of panel members; and the Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews. The levels of evidence were graded according to the methods of critical appraisal of research papers described by Sackett,[3] and the recommendations were graded according to the level of evidence supporting them (Appendix 1). The chair and cochair of the CHS at the time of the consensus project (Simon W. Rabkin and Robert F. Burrows) were involved as external reviewers. The initial recommendations were carried forward if approved by all of the panel members or were reached by a collective vote. In some areas, evidence-based recommendations were impossible, and therefore the opinions of experts were presented. The members of the panel revised the draft report several times. The final version of the recommendations, presented at a general consensus conference in Montreal in 1995, was endorsed by the CHS, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens-gynécologues du Québec.

Because the focus of pharmacologic treatment of hypertension in pregnancy should be on decreasing maternal and neonatal morbidity and mortality, the primary outcomes of interest were defined as follows: in cases of nonsevere hypertension, perinatal death (including death late in the second trimester), severe hypertension, superimposed gestational hypertension, preterm delivery and intrauterine growth retardation (IUGR); in cases of severe hypertension, perinatal death and preterm delivery; and in cases for which anticonvulsant therapy is required, seizures and perinatal death. Because these outcomes were not available from all trials reviewed, they were equally ranked. Despite the obvious importance of maternal death, there was insufficient data to include it as a primary outcome. The efficacy of a drug in decreasing blood pressure was defined as an intermediate outcome.

Hypertensive disorders in pregnancy were classified as pre-existing hypertension, gestational hypertension (with or without proteinuria) and unclassified hypertension, as defined in part 1 of the series.[1] Because there was no specific study on gestational hypertension superimposed on pre-existing hypertension, recommendations for gestational hypertension apply for this disorder.

The use of pharmacologic treatment does not exclude the use of nonpharmacologic therapy, reported in part 2.[2]

Deciding on when to treat

The recommendations on deciding when to treat hypertensive disorders in pregnancy are presented in Table 1.

There is general agreement that pregnant women with a systolic blood pressure greater than 169 mm Hg or a diastolic pressure greater than 109 mm Hg, or both, should receive pharmacologic treatment to prevent maternal intracerebral hemorrhage.[4,5] For lower readings, there was lack of consensus in the literature on what is appropriate management. There was no report that specifically addressed the critical blood pressure at which pharmacologic treatment should be initiated for the prevention of perinatal death and maternal complications.

Incidence rates of perinatal death and IUGR increase with elevation in blood pressure, with or without proteinuria.[6,7] An observational study involving 12 954 American women from 1959 to 1967 revealed that neonatal mortality increased when the mean arterial pressure was more than 89 mm Hg in the second trimester and more than 104 mm Hg in the third trimester.[6] (The mean arterial pressure is calculated as [systolic + (2 × diastolic)] ÷ 3; for example, a blood pressure of 120/75 mm Hg would give a mean arterial pressure of 90 and a blood pressure of 142/85 mm Hg would give a mean pressure of 104 mm Hg.) In another cohort of 50 806 American women, a diastolic blood pressure of 95 mm Hg in the absence of proteinuria and 85 mm Hg with proteinuria after 28 weeks' gestation was observed to be the threshold for an increase in the rate of perinatal death.[7] In cases of pre-existing hypertension, a diastolic blood pressure greater than 100 mm Hg before 20 weeks' gestation, left ventricular hypertrophy and a serum creatinine level of more than 88.4 μmol/L are risk factors for superimposed gestational hypertension and IUGR.[8] In a randomized controlled trial (RCT) of the effectiveness of methyldopa in decreasing perinatal mortality, the blood pressures used to include women in the study were 140/90 mm Hg before 28 weeks' gestation and 150/95 mm Hg thereafter.[9] In cases of nonsevere gestational hypertension, most of the RCTs reviewed had a criterion of 140/90 mm Hg as the blood pressure for inclusion.[10–15] Thus, from the little data available, it appears that different thresholds could be used depending on the presence of proteinuria and the gestational age.

No data were found to determine the optimal blood pressure to be attained with antihypertensive treatment. When specified in the trials, the aim of the treatment was to lower diastolic blood pressure to below 90 mm Hg.[14,16–18] The uncertainty is aggravated by the fact that there were no human data available on the autoregulation of the uteroplacental circulation. Antihypertensive drugs (when used at recommended dosages) do not seem to alter placental and fetal Doppler wave forms, which are used experimentally as a method to study uteroplacental vascular impedance.[19–24]

There is no established blood pressure threshold on which pharmacologic treatment may be started based on self-monitoring and automated 24-hour ambulatory monitoring.

Table 1: Recommended criteria for deciding when to admit women with hypertension in pregnancy to hospital and when to start antihypertensive therapy*

Admission to hospital (grade D)

Mandatory

- SBP > 169 mm Hg or DBP > 109 mm Hg or presenting with symptoms (epigastric pain, visual disturbance or severe headache)

Strongly recommended

- Gestational hypertension with proteinuria, unless special outpatient care program is available
- Pre-existing hypertension with superimposed gestational hypertension
- Gestational, pre-existing or unclassified hypertension without proteinuria in women with DBP > 99 mm Hg
- Pre-existing hypertension necessitating antihypertensive drug treatment and for which outpatient surveillance is impossible

Recommended

- Gestational hypertension without proteinuria or unclassified hypertension with DBP 90–99 mm Hg in order to:
  - Obtain serial blood pressure readings
  - Exclude conditions associated with poor outcome
  - Assess fetal well-being

Transfer to tertiary care facility should be considered according to locally available neonatal care

Initiation of antihypertensive drug treatment

Immediately

- SBP > 169 mm Hg or DBP > 109 mm Hg with symptoms (grade D)

After 1–2 hours of observation

- SBP > 169 mm Hg or DBP > 109 mm Hg without symptoms (grade D)

After 24–48 hours of observation

- SBP > 139 mm Hg or DBP > 89 mm Hg before 28 weeks' gestation in women with gestational hypertension without proteinuria (grade D) or in those with pre-existing hypertension (grade A)[9]
- SBP > 139 mm Hg or DBP > 89 mm Hg any time in pregnancy in women with
  - gestational hypertension with symptoms (grade D),
  - gestational hypertension with proteinuria (grade D),
  - pre-existing hypertension with underlying conditions (grade D),
  - pre-existing hypertension with target-organ damage (cardiovascular disease, renal impairment) (grade D), or
  - pre-existing hypertension with superimposed gestational hypertension (grade D)
- SBP > 149 mm Hg or DBP > 94 mm Hg in other circumstances (grade D)

*These recommendations do not apply to women in labour. See Appendix 1 for definitions of the grades of recommendations. SBP = systolic blood pressure, DBP = diastolic blood pressure.

Treatment of nonsevere hypertension

The recommendations about the treatment of nonsevere hypertension (blood pressure less than 170/110 mm Hg) are presented in Table 2 and Appendix 2.

There were few RCTs on the efficacy of different pharmacologic interventions for the treatment of nonsevere hypertension. Studies involving women with pre-existing hypertension in the first trimester were rare[36] because blood pressure normally decreases in the first half of pregnancy. In gestational hypertension the effects of the drugs are time-limited, because delivery is considered the ultimate treatment of this disorder. The more frequent methodological problems were the inclusion of a heterogeneous population (which made it difficult to distinguish between pre-existing and gestational hypertension),[9,17,18,25–27,31,37–40] the use of 2 drugs in the protocol[11,25,28,36,38] and the exclusion of an important number of women from the final analysis (which raises a concern about the potential for bias).[10,36,41]

Effect on maternal and perinatal outcomes

Perinatal death

Perinatal death is rare. The only 2 RCTs reporting a

Table 2: Recommended treatment of nonsevere hypertension in pregnancy

Treatment goal
DBP 80–90 mm Hg (grade D)
First-line drug
Methyldopa (grade A)[9,25]
Second-line drugs*
Labetalol (grade A/B)[12,14,26–28]
Pindolol (grade A/B)[29]
Oxprenolol (grade A/B)[17,18,28]
Nifedipine (grade A/B)[15,30]
Third-line drugs
Clonidine + hydralazine (grade A, but monotherapy preferable)[13]
Metoprolol + hydralazine (grade A, but monotherapy preferable)[11]
Clonidine (grade B)[31]
Methyldopa + a second-line drug or hydralazine (grade D)
Special indications (renal or cardiac diseases)
Diuretics (grade D)
Drugs to avoid
Angiotensin-converting enzyme inhibitors (grade C)[32–35]
Angiotensin II receptor antagonists (grade D)
Caution

- Neuromuscular function and blood pressure should be closely monitored when using nifedipine + magnesium sulfate (grade D)
- Fetuses and newborns of women taking atenolol, acebutolol or metoprolol should be observed for signs of ß-blockage (grade D)

*For second-line drugs, recommendations are grade A for the prevention of severe hypertension and grade B for the prevention of perinatal death.

decrease in the rate of perinatal death (mainly in the second trimester) involved the administration of methyldopa after 12 weeks' gestation for women with pre-existing hypertension (level I evidence).[9,25] Studies of β-blockers, nifedipine and clonidine were too small to provide evidence about the effects of these drugs on perinatal death, even when considered collectively in a meta-analysis.[42–44] In a level II trial, in which methyldopa and labetalol were given from the first trimester, the effects of treatment on perinatal death were reported to be similar to those of placebo.[36] In other level II trials, labetalol, atenolol and oxprenolol were found to be similar to methyldopa in their effect on this outcome.[17,18,26,27] Diuretics were not found to decrease perinatal mortality among women with pre-existing hypertension or those with excessive weight gain (level II evidence).[37,45–47] A meta-analysis of the data from 9 trials of diuretics, involving a total of 7000 women, revealed that these drugs do not prevent perinatal death.[48]

Prevention of severe hypertension

This outcome was the most common one studied. In cases of pre-existing hypertension, methyldopa was shown to be effective in preventing severe hypertension (level I evidence).[9] In cases of gestational hypertension, level I trials demonstrated the effectiveness of the following drugs in preventing severe hypertension: atenolol,[10] labetalol,[12,14,49] nifedipine,[15,30] oxprenolol,[28] pindolol,[29] combined treatment with metoprolol and hydralazine,[11] and combined treatment with clonidine and hydralazine.[13] Propanolol,[39] clonidine[31] and acebutolol[26] were shown to be as effective as methyldopa in reducing the risk of severe hypertension (level II evidence). Diuretics were not found to be effective in preventing severe hypertension (level II evidence).[37,45–48]

Superimposed gestational hypertension

No antihypertensive drug was proven to be effective in preventing gestational hypertension with proteinuria in women with pre-existing hypertension, even when treatment was started in the first trimester (level II evidence).[9,25,36,41,42] One trial reported that diuretics were effective in preventing gestational hypertension (defined as edema and an increase in blood pressure) (level II evidence).[37] However, neither that study, nor a meta-analysis on diuretics,[48] demonstrated that they were effective in preventing proteinuria.

Preterm delivery

This outcome was poorly reported. Thus, there was insufficient evidence on which to draw any reliable conclusion about the effectiveness of drug treatment in preventing preterm delivery. The combination of oral antihypertensive drugs with bed rest and intensive antenatal fetal monitoring was reported in one study as prolonging gestation (but not beyond 37 weeks) in women with severe gestational hypertension with proteinuria (level II evidence).[50]

Intrauterine growth retardation

This outcome was not well reported and was expressed differently in the trials. Antihypertensive drugs did not seem to promote or compromise fetal growth (level II evidence),[9,42–44] with the possible exception of atenolol. One small RCT reported an increase in the incidence of IUGR with atenolol among women with pre-existing hypertension (mean duration of treatment 24 weeks),[41] whereas another, larger, RCT showed no effect on IUGR among women with gestational hypertension also given atenolol (mean duration of treatment 5 weeks; level II evidence).[10] In a case series, the birth weight was lower among newborns whose mothers had been given atenolol than among those whose mothers had been given pindolol (level V evidence).[51] Of 6 RCTs of labetalol,[12,14,26,27,36,49] only 1 reported an increase in the rate of IUGR among women with severe proteinuric hypertension with the use of labetalol.[12] A reduction in plasma volume was reported with the use of diuretics (level II evidence),[52] which could potentially interfere with fetal growth. An increase in the incidence of low birth weight (below the 25th percentile) was reported in one study in which diuretics were given to women with excessive weight gain (with no significant decrease in plasma volume)[47] but not in other studies.[37,45,46]

Safety

Teratogenicity: We found no fetal malformations attributable to methyldopa,[53] β-blockers or clonidine, but experience with these drugs in the first trimester was limited[36] or lacking. First-trimester use of diuretics is a questionable risk for congenital defects.[54] Digital or other limb defects were observed in animals exposed in utero to supratherapeutic doses of calcium-channel blockers.[55] Further studies attributed these problems to an important decrease in uteroplacental blood flow and observed the same problems with high doses of other antihypertensive drugs.[56] A recent prospective observational study suggested that calcium-channel blockers do not represent a major teratogenic risk.[57] Miscarriage, fetal death, fetal renal failure and malformation were observed with the use of angiotensin-converting enzyme (ACE) inhibitors.[32–35] There were no data on the use of angiotensin II receptor antagonists in humans, but adverse effects are likely to be similar to those with ACE inhibitors.

Fetal and neonatal β-blockage: Decreased blood pressure or heart rate, or both, in the fetus and the newborn were reported with the use of acebutolol, atenolol and metoprolol.[12,24,58]

Long-term infant development: Methyldopa was the only drug for which a longitudinal study, with a follow-up period of 7.5 years, showed adequate development of children exposed in utero.[59] Studies of the long-term safety of atenolol and labetalol were small and limited to follow-up periods of 1 year and 6 months after birth.[60,61] Data did not exist for other antihypertensive drugs.

Interaction with magnesium sulfate: A possible increase in the hypotensive effect of nifedipine and neuromuscular blockage were reported when nifedipine and magnesium sulfate were used concomitantly.[62–65]

Other drugs: There were insufficient data on prazosin, nicardipine, verapamil, isradipine and nisoldipine (currently not available in Canada) to provide reliable information on their efficacy and safety.

Treatment of severe hypertension

The recommendations about the treatment of severe hypertension are presented in Table 3 and Appendix 2.

The definition of severe hypertension in pregnancy differs from that used for nonpregnant individuals. In nonpregnant people, severe hypertension is usually defined as a diastolic blood pressure greater than 115–120 mm Hg. In pregnant women, severe hypertension is usually defined as a systolic blood pressure greater than 160 or 169 mm Hg or a diastolic blood pressure greater than 109 mm Hg, or both. These levels are chosen because a diastolic pressure of more than 109 mm Hg is associated with cerebral hemorrhage.[4,5]

There were no placebo-controlled trials examining the effect of treatment of severe hypertension in pregnant women, and none will likely be performed because of ethical considerations. It is accepted that, because the significant elevation of blood pressure is associated with poor outcome, treatment is necessary during pregnancy or post partum if the blood pressure is 170/110 mm Hg or higher.

There were few RCTs comparing the effectiveness of 2 drugs in preventing adverse outcomes that would validate the clinical impressions.[16,66–72] The samples were too small and inadequate to meet the criteria for level I evidence.

Methyldopa, hydralazine, labetalol and nifedipine were found to be effective in decreasing blood pressure in cases of severe hypertension (level II evidence).[16,66–72] Labetalol and nifedipine were also useful in decreasing the pressor response to tracheal intubation (level II evidence).[73,74] Fetal distress attributed to placental hypoperfusion was reported in some cases, usually when high doses were used, the blood pressure decreased rapidly or the goal diastolic pressure was too low.[72,75] Concomitant use of nifedipine and magnesium sulfate was shown to cause severe hypotension and fetal distress.[62,64] Placental hypoperfusion was not observed with sublingual use of nifedipine, but experience was limited.[72,76] Hydralazine and nifedipine may induce maternal tachycardia, which may limit their efficacy.

Diazoxide, even in low doses, was associated with significant hypotension,[77] arrested labour[78] and maternal and neonatal hyperglycemia.[77,78] Sodium nitroprusside was shown to be effective in cases of severe hypertension, but its use was infrequent.[79,80] Brief infusions of low-dose sodium nitroprusside were not found to result in toxic fetal cyanide levels in small observational studies.[79,80]

Table 3: Recommended treatment of severe hypertension in pregnancy

Treatment goal
DBP 90–100 mm Hg (grade D)

First-line drugs
Hydralazine (grade B)[66–68]
Labetalol (grade B)[66,69,70]
Nifedipine (grade B)[67,71,72]

Special indications (patient refractory to first-line drugs)
Diazoxide (grade D)
Sodium nitroprusside (grade D)

Caution
- Neuromuscular function and blood pressure should be closely monitored when using nifedipine + magnesium sulfate (grade D)
- Fetal heart rate should be monitored during acute treatment (grade D)

Treatment of postpartum hypertension

The recommendations about the treatment of postpartum hypertension are presented in Table 4.

The usefulness of antihypertensive drug therapy in the immediate postpartum period is limited. Women with ges-

Table 4: Recommended treatment of postpartum hypertension

Indications
Severe hypertension (Table 3) (grade D)
Symptoms (grade D)
Gestational hypertension with DBP > 99 mm Hg 3 days after delivery and target-organ damage (grade D)

Drugs
Methyldopa (grade B)[81,82]
Nifedipine (grade B)[83]
Timolol (grade B)[81]

Treatment in presence of pre-existing hypertension
Same as treatment for nonpregnant people (grade D)

Table 5: Recommended treatment with anticonvulsant drugs

Indications
Prophylaxis for hypertension-related seizures: no data available to recommend when it should be used
Therapy for hypertension-related seizures (grade A)[85]

Drug
Magnesium sulfate (grade A)[85,86]

tational hypertension will often have a spontaneous decrease in blood pressure after delivery. Women with severe hypertension are usually managed as described previously.

Methyldopa, timolol and nifedipine were studied for their use in the postpartum period and were found to be effective in decreasing blood pressure (level II evidence).[81–83] These drugs are excreted in breast milk. No adverse effects were reported in nursing infants, but long-term exposure to these drugs has not been studied. These antihypertensive drugs are considered as being compatible with breast feeding by the American Academy of Pediatrics.[84]

Anticonvulsant therapy

The recommendations about anticonvulsant drug therapy are in Table 5.

Anticonvulsant drugs are used to prevent seizures and the recurrence of seizures in women with hypertensive disorders. Thus, the relevant clinical outcomes are the incidence of seizures and perinatal death. For both outcomes, there were few RCTs available, and except for 2 recent reports the number of women involved was small.[85–90]

Hypertension-related seizures are rare, and are more frequent in developing countries.[91,92] In a study in Hamilton, Ont., 1.4% of women with hypertensive disorders had seizures without preventive anticonvulsant therapy:[93] 0.6% of those with pre-existing hypertension, 0.1% with gestational hypertension without proteinuria, 4.3% with gestational hypertension with proteinuria, and 2.1% with superimposed gestational hypertension with proteinuria.

In the literature, prophylactic anticonvulsant therapy was recommended in all women with elevated blood pressure[94] or in those with gestational hypertension[95] or severe hypertension,[96] without firm data to support any of these statements.

We found 3 RCTs comparing magnesium sulfate and phenytoin in the prevention of hypertension-related seizures.[87–89] In 2 of them, involving women with severe gestational hypertension, no convulsions or perinatal deaths were reported in the treatment groups (level II evidence).[87,88] The third study involved 3534 hypertensive women treated either with magnesium sulfate (intramuscularly) or phenytoin (by intravenous bolus, then orally).[89] Seizures were reported to occur less frequently in the magnesium sulfate group (level I evidence); the incidence of perinatal deaths was similar in the 2 groups (level II evidence). However, this study used an extremely liberal approach to anticonvulsant therapy: it was given to all women with a blood pressure greater than 140/90 mm Hg. Eighteen percent of the study population had a result of +2 on a proteinuria dipstick test, and 4% received antihypertensive drug therapy. It is difficult to generalize the results of this study to Canadian practice.

Magnesium sulfate, phenytoin and diazepam have been studied in women with hypertension-related seizures.[85,86,90] The larger trial, a multicentre randomized study, involved 1680 women. In one group, magnesium sulfate was compared with phenytoin, and in another group it was com-

Table 6: Recommendations related to treatment of hypertension and seizures in pregnancy issued by the Canadian Hypertension Society (CHS) and other international bodies*

Category	CHS	NHBPEPWG[99]	ASSH[100]
Nonsevere hypertension			
BP readings at which to start treatment, mm Hg	SBP > 139 or 149 or DBP > 89 or 94	DBP > 99	SBP > 159 or DBP > 89
Treatment goal, mm Hg	DBP 80–90	–	SBP > 110
Drugs	Methyldopa, labetalol, pindolol, oxprenolol, nifedipine	Methyldopa	Methyldopa, labetalol, oxprenolol, clonidine
Drugs to avoid	ACE† inhibitors, angiotensin II receptor antagonists	ACE inhibitors	ACE inhibitors, diuretics
Severe hypertension			
BP readings at which to start treatment, mm Hg	SBP > 169 or DBP > 109	DBP > 104	SBP > 169 or DBP > 114
Drugs	Hydralazine, labetalol, nifedipine	Hydralazine	Hydralazine, labetalol nifedipine, diazoxide
Seizures			
Drugs for prophylaxis	Magnesium sulfate	Magnesium sulfate	Magnesium sulfate, phenytoin
Drugs for treatment	Magnesium sulfate	Magnesium sulfate	Diazepam intravenously

*NHBEPWG = National High Blood Pressure Education Program Working Group (US), ASSH = Australasian Society for Study of Hypertension.
†ACE = angiotensin-converting enzyme.

pared with diazepam.[90] The women receiving the magnesium sulfate had a 52% lower risk of recurrent seizures than those receiving diazepam and a 67% lower risk than those receiving phenytoin (level I evidence); all 3 groups had similar rates of perinatal death (level II evidence).

Major maternal side effects of magnesium sulfate and phenytoin are unusual, and the rate of withdrawal is similar.[97] A number of minor adverse effects are attributed to the 2 drugs: for example, hot flushes and dyspnea with magnesium sulfate and transient burning at the intravenous site and ataxia with phenytoin. The major side effects of magnesium sulfate (respiratory depression and heart block) are due to overdose or renal insufficiency. Magnesium sulfate may cause hypotension or neuromuscular blockage when used with nifedipine or in women with myoneuronal disorders.[62–65] There have been no adverse neonatal effects documented with the short-term use of phenytoin. Magnesium sulfate may decrease short- and long-term fetal heart rate variability.[98]

Validation

The panel members reviewed the US and Australian consensus statements.[99,100] Certain discrepancies exist between the 2 statements (Table 6). Some of them are explained by the fact that the Australian recommendations were published later and based on data not available to the US group. In the Australian report, pharmacologic treatment of gestational hypertension is favoured because of the relative safety of the drugs and the potential benefit of reducing the risk of premature delivery. Our recommendations concerning the blood pressures at which to start treatment are more precise than those of the US and Australian panels, because we have taken into account the kind of hypertensive disorder and the gestational age as well as the presence of proteinuria and symptoms. As for the recommendations concerning which drugs to use, our recommendations are consistent with the US and Australian ones.

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Appendix 1: Levels of evidence used to rate studies of the treatment of hypertensive disorders in pregnancy and to grade recommendations*

Levels of evidence

I. Randomized controlled trial (RCT) that demonstrates statistically significant difference in at least 1 important outcome (e.g., survival or major illness)

   OR

   If difference is not statistically significant, an RCT with adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results

II. RCT that does not meet the level I criteria

III. Nonrandomized trial with contemporaneous control subjects selected by some systematic method (i.e., not selected by perceived suitability for one of the treatment options for individual patients)

   OR

   Subgroup analysis in an RCT

IV. Before–after study or case series (at least 10 patients) with historical control subjects drawn from other studies

V. Case series (at least 10 patients) without control subjects

VI. Case report (fewer than 10 patients)

Grading system for recommendations

A. The recommendation is based on 1 or more studies at level I

B. The best evidence available was at level II

C. The best evidence available was at level III

D. The best evidence available was lower than level III and included expert opinion

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Appendix 2: Recommended dosages of antihypertensive drugs (grade D)

Condition; drug	Dosage
Nonsevere hypertension	
Methyldopa	500 mg bid–qid
Labetalol	200–600 mg bid–tid
Oxprenolol	20–80 mg bid–tid
Pindolol	5–15 mg bid
Nifedipine	20–40 mg of long-acting formulation (PA) bid
Clonidine	0.05–0.2 mg bid–qid
Hydralazine	10–50 mg bid–qid
Severe hypertension	
Hydralazine	5–10 mg intravenously (IV) q 20 min or infusion of 0.5–10 mg/h
Labetalol	10–20 mg IV q 10 min up to 300 mg or infusion of 1–2 mg/min
Nifedipine	10 mg orally q 2–3 h