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Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy

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Title: Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy

Short title: Management of Hypertension in Pregnancy

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Key Words: hypertension, high blood pressure, severe hypertension, guidelines, recommendations, adults, pregnancy, blood pressure management

BRIEF SUMMARY

Hypertension in pregnancy is common, affecting approximately 7% of pregnancies in Canada. In this first Hypertension Canada Guidelines for hypertension in pregnancy, seven recommendations are presented. For non-severe hypertension in pregnancy (systolic BP 140-159 and/or diastolic BP 90-109 mmHg), we provide guidance for the threshold for initiating antihypertensive therapy, blood pressure targets, as well as first- and second-line antihypertensive medications. Severe hypertension (systolic BP ≥ 160 and/or diastolic BP ≥ 110 mmHg) requires urgent antihypertensive therapy.

ABSTRACT

We present Hypertension Canada's inaugural evidence-based Canadian recommendations for the management of hypertension in pregnancy. Hypertension in pregnancy is common, affecting approximately 7% of pregnancies in Canada, and requires effective management in order to reduce maternal, fetal and newborn complications. Given this importance, these guidelines were developed in partnership with the Society of Obstetricians and Gynaecologists of Canada with the main common objective of improving the management of women with hypertension in pregnancy. Guidelines for the diagnosis, assessment, prevention and treatment of hypertension in adults and children are published separately.

In this first Hypertension Canada Guidelines for hypertension in pregnancy, seven recommendations for the management of non-severe and severe hypertension in pregnancy are presented. For non-severe hypertension in pregnancy (systolic blood pressure 140-159 mm Hg and/or diastolic blood pressure 80-109 mm Hg), we provide guidance for the threshold for initiation of antihypertensive therapy, blood pressure targets, as well as first- and second-line antihypertensive medications. Severe hypertension (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg) requires urgent antihypertensive therapy to reduce maternal, fetal and newborn adverse outcomes. The specific evidence and rationale underlying each of these guidelines are discussed.

Introduction

Hypertensive disorders of pregnancy (HDP) occur in approximately 7% of all pregnancies in Canada.¹ HDP represent a broad range of conditions including: chronic hypertension (i.e., pre-existing hypertension), gestational hypertension (i.e., hypertension that develops after 20 weeks gestation), and/or preeclampsia/eclampsia (gestational hypertension with proteinuria and/or other target organ involvement).² HDP have a major impact on maternal, fetal and newborn outcomes including: fetal growth restriction, preterm delivery and fetal and neonatal morbidity and mortality.² After pregnancy, emerging evidence demonstrates that women with HDP represent a high-risk population for the development of cardiovascular risk factors (hypertension, type 2 diabetes and obesity), chronic kidney disease, premature cardiovascular disease (cardiac, cerebrovascular, and peripheral arterial) and cardiovascular mortality.⁴⁻⁷ Notably, HDP are an independent risk factor for cardiovascular disease associated with gradually elevated risk of cardiovascular disease with increasing severity of HDP from 1.7 (adjusted hazard ratio [aHR]; 95% confidence interval [CI] 1.3 to 2.2) in women with gestational hypertension to 4.4 (aHR; 95% CI 2.4 to 7.9) in women with severe preeclampsia with fetal death.^{5,8}

As HDP are prevalent and have important short- and long-term health impacts, Hypertension Canada's target audience expressed a need for guidance on the management of hypertension in pregnancy. In response, a Pregnancy Subgroup was formed in 2014 to develop evidence-based blood pressure (BP) management guidelines for pregnancy. A formal partnership was then established between Hypertension Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) to ensure harmonization of guidelines through shared

guideline development as well as for broader reach of the guidelines through knowledge translation and dissemination strategies.

These inaugural Hypertension Canada Guidelines for hypertension in pregnancy are intended to provide a framework for evidence-based care of hypertension in pregnancy but should not replace clinical judgement. Practitioners are advised to consider patient preferences, values, and clinical circumstances when determining how to best apply these guidelines to individual patients.

Methods

The Hypertension Canada Guidelines are developed annually through a highly structured and systematic process designed to minimize bias. Hypertension Canada's guideline process has been externally reviewed and is in concordance with the **Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument** for guideline development (guidelines.hypertension.ca/about/overview-process).⁹ The Hypertension Canada Guidelines Committee (HCGC) is comprised of a multidisciplinary panel of both content and methodological experts divided into 16 subgroups distinct areas of hypertension (Supplemental Appendix S1 and S2 for list of members and conflicts of interest). The Pregnancy Subgroup consisted of eight members with a broad range of expertise, including internal medicine subspecialties as well as obstetrics (two members from the SOGC Maternal Fetal Medicine subcommittee).

The comprehensive literature search was performed by a highly-trained medical librarian based upon key words and terms provided by the subgroup. The initial literature search was performed in June 2015 and updated in June 2016 (details of search strategies and retrieved

articles are available upon request). The literature was reviewed and graded using the standardized method developed by Hypertension Canada (Supplemental Table S1) and according to the Hypertension Canada Guidelines established process.¹⁰

The proposed pregnancy guidelines were then reviewed and modified by the Central Review Committee, unbiased experts in clinical epidemiology, to ensure that the guidelines reflected the evidence and verify proposed grading. The draft guidelines and supporting evidence were presented to the HCGC in Toronto, on October 12, 2017. Following the discussions, the guidelines were further revised and finalized for an electronic vote by all 81 members of the HCGC, with greater than 70% support required for approval of each new/revised guideline.

Challenges in pregnancy research

There are several methodologic challenges in the obstetrical research related to BP that were taken into consideration during the Hypertension in Pregnancy Guidelines development process (**Table 1**). First, the definition of hypertension in pregnancy has changed over time.¹¹ Older studies included pregnant women with a DBP ≥ 90 mm Hg, whereas more recent studies have included women with a SBP ≥ 140 mm Hg or a DBP ≥ 90 mm Hg. Similarly, the definition of severe hypertension in pregnancy was reduced from $\geq 170/110$ mmHg to $\geq 160/110$ mm Hg after the association of stroke in pregnancy with a lower BP level.¹² Second, as outlined above, the HDP represent a broad range of conditions with differing underlying pathophysiologies. Thus, the clinical outcomes (e.g., the neonate's birth weight) may be a result of the underlying process (i.e., maternal endothelial dysfunction) and not solely the maternal BP values. Further, there is a lack of consensus on the definition of preeclampsia ranging from a restrictive definition (gestational hypertension plus proteinuria) to a broader definition (gestational hypertension plus

either proteinuria or ≥ 1 relevant **target** organ complication).¹¹ This heterogeneity may influence clinical outcomes and as such it was taken into consideration when examining the findings of the studies. Third, the duration of antihypertensive treatment in pregnancy is relatively short (often a few weeks to months) when compared with studies of hypertension in non-pregnant population. Fourth, the clinical outcomes in studies of hypertension in pregnancy are generally not hard cardiovascular outcomes (i.e., cardiovascular events or cardiovascular mortality) which are associated with higher grades in the Hypertension Canada grading system (Supplemental Table S1).¹⁰ Studies of hypertension in pregnancy use other clinical outcomes (e.g., severe hypertension $\geq 160/110$ mm Hg, preterm birth, etc.). While severe hypertension is considered a validated surrogate outcome due to its relationship with adverse maternal, fetal and newborn outcomes, it is associated with a lower grade of evidence.¹³ Finally, the sample size of studies of hypertension in pregnancy are generally small and, therefore, this limits accurate assessment of rates of adverse events associated with individual antihypertensive medications.

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Measurement and diagnosis. Accurate BP measurement is essential to appropriately recognize and treat HDP. Detailed information on BP measurement as well as the classification and definitions of the HDP, are presented in SOGC's 2014 Guideline "Diagnosis, evaluation and management of the hypertensive disorders of pregnancy".² In brief, women should have their BP measured using a standardized protocol after a period of rest in a quiet environment, be in sitting position with their arm at the level of the heart using an appropriately sized cuff (i.e., length 1.5 times the circumference of the arm).² The arm with higher BP values should be used for hypertension diagnosis and BP monitoring.² Non-severe elevated BP should be re-measured

again at the same visit, with at least a gap of 15 minutes from the first measurement. Over 50% of women with a first BP reading of $\geq 140/90$ mm Hg have white coat effect.¹⁴⁻¹⁶ Hypertension in pregnancy is defined as a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) ≥ 90 mm Hg (average of at least 2 measurements taken at least 15 minutes apart). Severity of hypertension in pregnancy is considered based upon *both* the presence of **target** organ involvement (i.e., maternal or the fetus itself) as well as the actual BP level. BP levels between 140/90 mm Hg and $<160/110$ mm Hg are considered as non-severe hypertension in pregnancy. A BP level of $\geq 160/110$ mm Hg is associated with increased risk of maternal stroke in pregnancy and is therefore considered the diagnostic threshold of severe hypertension in pregnancy.^{2, 17}

Classification of HDP are summarized in Figure 1.

I. Management of non-severe hypertension (BP 140-159/90-109 mm Hg) in pregnancy

Background. HDP treatment of non-severe hypertension in pregnancy is important to reduce maternal, fetal and newborn complications including: pregnancy loss, need for high-level neonatal care, preterm birth, and low birth weight.^{13, 18} In a 2014 Cochrane Collaborative systematic review, antihypertensive medication use for non-severe hypertension in pregnancy (49 randomized trials; n=4,723)¹⁹ was associated with a halving in the risk of progression to severe hypertension (relative risk [RR], 0.49; 95% CI 0.40 to 0.60). The number needed to treat was 10 (95% CI 8 to 13). This finding was consistent across all HDP range of conditions.¹⁹ There was no consistent statistically significant reduction in other clinically important maternal, fetal or newborn outcomes.¹⁹ While this Cochrane systematic review was methodologically strong, the primary studies were relatively old (only 4 after 2001), had small sample sizes, and were of low methodologic quality.¹⁹

The international multicentre randomized controlled trial, **Control of Hypertension in Pregnancy Study (CHIPS)**, examined the effects of maternal BP targets on perinatal and maternal outcomes.¹⁸ Pregnant women with non-severe gestational hypertension or chronic hypertension were randomized to either less-tight BP control (target DBP of 100 mm Hg) or tight BP control (target DBP of 85 mm Hg).¹⁸ The CHIPS trial found an increase in the incidence of severe hypertension (defined as $\geq 160/110$ mm Hg) in the less-tight group (RR 1.8; 95% CI 1.34 to 2.28).¹⁸ In post-hoc analyses of the CHIPS trial, the occurrence of severe hypertension was associated with an increased risk of pregnancy loss, the need for high-level neonatal care >48 hours, low birth weight, and preterm delivery.¹³

In considering specific antihypertensive agents for the management of non-severe hypertension in pregnancy, the above Cochrane systematic review demonstrated a similar benefit in reduction of severe hypertension amongst the following oral agents: labetalol, methyldopa, long-acting nifedipine, or other β -blockers (**Table 2**).¹⁹ Additionally, a secondary analysis of the CHIPS trial showed no statistically significant difference in clinical outcomes between different anti-hypertensive medications used (i.e., labetalol, methyldopa, or others).²⁰ Other oral antihypertensive medications such as clonidine, hydralazine, and thiazide diuretics can be considered as second-line drugs as they have not been associated with congenital malformations or other evidence to suggest harms. Angiotensin converting enzyme (ACE) inhibitors have not been consistently associated with congenital malformations but are associated with fetotoxic adverse effects to the developing fetal renal system (i.e., acute kidney injury and oligohydramnios) and, as such, should be avoided in pregnancy.²¹ Similarly, angiotensin receptor blockers (ARBs) have limited published safety data in pregnancy and should be avoided in pregnancy due to similar fetotoxic mechanisms associated with ACE inhibitors.²

Overall, decisions regarding specific antihypertensive drug must consider the context of the patient and fetus, medication side-effect profile (including maternal hypotension), availability of medications, clinician experience and a woman's preference. Other components of the management of women with non-severe hypertension in pregnancy are beyond the scope of this guideline. The involvement of an interdisciplinary team of care providers (i.e., obstetrics, maternal fetal medicine and medical specialists as appropriate) is prudent to ensure the ongoing well-being of the mother and fetus through frequent assessments, monitoring, and delivery planning, as indicated (**Figure 2**).²

Guidelines

1. Antihypertensive therapy is recommended for average SBP measurements of ≥ 140 mm Hg or DBP measurements of ≥ 90 mm Hg in pregnant women with chronic hypertension, gestational hypertension or preeclampsia (Grade C).
2. A. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral β -blockers (acebutolol, metoprolol, pindolol, and propranolol) (Grade C).
2. B. Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics (Grade D).
2. C. ACE inhibitors (Grade C) and ARBs (Grade D) should not be used in women once pregnant.
3. A. A DBP of 85 mm Hg should be targeted for pregnant women on antihypertensive therapy with chronic hypertension or gestational hypertension (Grade B). A similar target could be considered for pregnant women with preeclampsia (Grade D).

3. B. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy (Grade C). Add-on drugs should be from a different drug class chosen from first-line or second-line options (Grade D).

II. Management of severe hypertension (BP \geq 160/110 mm Hg) in pregnancy

Background. In a secondary analysis of the CHIPS trial, BP \geq 160/110 mm Hg was associated with significantly worse maternal and perinatal outcomes, independent of the development of preeclampsia. These included: increased maternal hospital length of stay $>$ 10 days, pregnancy loss or need for high-level neonatal care $>$ 48 hours, increased risk of preterm birth at $<$ 34 and $<$ 37 weeks gestation, low birth weight (i.e., weight $<$ the 10th percentile), maternal platelets $<$ 100x 10⁹/L, and elevated maternal liver enzymes.¹³ The CHIPS trial did not find significant difference in the rate of stroke between study arms due to a low event rate (n=1; 0.2% in tight arm vs n=0 in less tight arm), as stroke in pregnancy and the immediate postpartum period is a relatively uncommon adverse outcome (30 per 100,000 pregnancies).^{18,22} Importantly, BP \geq 160/110 mm Hg and the presence of HDP are both considered risk factors for ischemic and hemorrhage stroke in pregnancy.^{12,22-23} Specifically, a large US population based study found that women with HDP were 5.2 times more likely to be hospitalized for stroke compared with pregnant women with normal BP.²³ In a case series of 28 women with HDP with stroke in pregnancy or early postpartum, immediately prior to the stroke, SBP was recorded as \geq 160 mm Hg in 95.8% (23/24) and DBP \geq 110 mm Hg in 12.5% (3/24) of women. While no trials included in a Cochrane systematic review of the management of severe hypertension in pregnancy directly examined the effect of immediate BP lowering on stroke, BP reduction below this threshold of

$\geq 160/110$ mm Hg is considered to play an important role in the prevention of stroke in pregnancy and is recommended.^{22, 24} Accordingly, severe hypertension is considered an obstetrical emergency from maternal and fetal perspectives, which requires immediate in-hospital care and urgent antihypertensive therapy (**Figure 2**).¹⁹

The specific antihypertensive management of severe hypertension is beyond the scope of this guideline and requires the involvement of an interdisciplinary team of care providers (i.e., obstetrics, maternal fetal medicine and medical specialists as appropriate) in a hospital setting to ensure the ongoing well-being of the mother and fetus through frequent assessments, monitoring, and delivery planning, as indicated.²

Guidelines

1. Women with severe hypertension SBP ≥ 160 or DBP ≥ 110 mm Hg in pregnancy require urgent antihypertensive therapy as it is considered an obstetrical emergency (Grade D).

Summary/Future Directions

The present guidelines summarize the best available evidence to guide clinicians in the management of hypertension in pregnancy and represents three years of work by the Hypertension in Pregnancy subgroup with the support of the HCGC and the SOGC. The next update for Hypertension Canada's Guideline is planned for 2020 to allow for optimal dissemination of the 2018 Guidelines though literature searches will be continued on an annual basis. New evidence identified as being "practice changing" for clinicians (i.e., associated with strong reduction in cardiovascular events or mortality; or a substantial reduction in resource utilization) will be brought forward for an interim update to ensure timely implementation of

important evidence. Priorities identified for the development of new guidelines in 2020 for the Hypertension in Pregnancy subgroup include, among others, the development of evidence-based guidelines addressing the management of hypertension both in preconception and postpartum women.

Implementation

Implementation and dissemination of the guidelines is a priority for Hypertension Canada. Many strategies are employed to reach a variety of providers who care for patients with hypertension. Efforts include knowledge exchange forums, targeted educational materials for primary care providers and patients, “Train the Trainer” teaching sessions, as well as slide kits and summary documents which are freely available online in French and English (www.hypertension.ca). Hypertension Canada receives feedback from end-users to continually improve guideline processes and content. The Research and Evaluation Committee conducts hypertension surveillance studies, and reviews existing Canadian health surveys to identify gaps between current and best practices.

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Disclosures

Please see Supplemental Appendix S2 for a complete list of disclosures.

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Table 1. Hypertension in Pregnancy Research – Methodologic Challenges

1. Definitions of hypertensive disorders of pregnancy (HDP):
 - a. Change in definition of hypertension in pregnancy over time.
 - b. Variable definition of preeclampsia between studies:
Restrictive (GHTN \geq 140/90 mm Hg plus \geq 300 mg proteinuria in 24 hours).
Broad (GHTN \geq 140/90 mm Hg plus either \geq 300 mg proteinuria in 24 hours or other end-organ involvement).
2. Heterogeneity in types of HDP included may differentially impact clinical outcomes:
 - a. Variable severity of disease (ranging from GHTN to severe preeclampsia).
 - b. Represent different underlying pathophysiology.
3. Clinical outcomes not cardiovascular events or mortality.
 - a. Use of surrogate outcomes.
4. Small sample sizes.
5. Short duration of follow-up (hours to months).

Table 2. Antihypertensive medications commonly used in pregnancy

First Line Oral Drugs (Grade C)	Second Line Oral Drugs (Grade D)	Medications to Avoid
Labetalol	Clonidine	ACEi* (Grade C)
Methyldopa	Hydralazine	ARBs* (Grade D)
Long-acting oral nifedipine	Thiazide diuretics	*fetotoxicity of renal system
Other β -blockers (acebutolol, metoprolol, pindolol, & propranolol)		

ACEi=angiotension converting enzyme inhibitors

ARBs=angiotension receptor blockers

Figure 1. Simplified Classification of Hypertensive Disorders of Pregnancy

* Rule out: White coat hypertension and transient hypertension

SBP = systolic blood pressure, DBP = diastolic blood pressure

HELLP = hemolysis elevated liver enzymes and low platelets

Figure 2. Management of Hypertension in Pregnancy

*See SOGC 2014²

**See Table 2

BP=blood pressure, DBP=diastolic blood pressure

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