Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy

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Abstract
The Canadian Stroke Best Practice Consensus Statement: Secondary Stroke Prevention during Pregnancy, is the first of a two-part series devoted to stroke in pregnancy. This document focuses on unique aspects of secondary stroke prevention in a woman with a prior history of stroke or transient ischemic attack who is, or is planning to become, pregnant. Although stroke is relatively rare in this cohort, several aspects of pregnancy can increase stroke risk during or immediately after pregnancy. The rationale for the development of this consensus statement is based on the premise that stroke in this group requires a specifically-tailored management approach. No other broad-based, stroke-specific guidelines or consensus statements exist currently. Underpinning the development of this document was the concept that maternal health is vital for fetal wellbeing, therefore, management decisions should be based on the confluence of two clinical considerations: (a) decisions that would be made if the patient was not pregnant and (b) decisions that would be

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made if the patient had not had a stroke. While empirical research in this area is limited, this consensus document is based on the best available literature and guided by expert consensus. Issues addressed in this document include general management considerations for secondary stroke prevention, the use of antithrombotics, blood pressure management, lipid management, diabetes care, and management for specific ischemic stroke etiologies in pregnancy. The focus is on maternal and fetal health while minimizing risks of a recurrent stroke, through counseling, monitoring, and the safety of select pharmacotherapy. These statements are appropriate for health care professionals across all disciplines.

Keywords
Stroke, pregnancy, secondary prevention, antithrombotics, hypertension, statins

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Introduction

Stroke, the sudden loss of neurological function due to neuronal injury of a vascular cause, is a leading cause of disability in adults. When it occurs as a complication of pregnancy, the impact on the mother, child, and families can be devastating. A recent estimate suggests that stroke affects 30/100,000 pregnancies, roughly 3 times that seen in the general population of young adults. Several aspects of pregnancy can increase the risk of stroke, including: hypertensive disorders of pregnancy (chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia) and their complications; HELLP syndrome (hemolysis, elevated liver enzymes and low platelets syndrome); hematologic and prothrombotic changes in the third trimester and post-partum periods; hyperemesis resulting in hemococoncentration; and changes to cerebral vasculature (for example, reversible cerebral vasoconstriction syndrome (RCVS), arteriovenous malformations, or cervical artery dissection). Given this etiological variability, the practical limitations associated with conducting clinical trials research this population, and the rarity of events, it is not surprising that there is limited literature to guide important management decisions. Yet, stroke is sufficiently common that most specialists providing either obstetrical or stroke care encounter women with a past stroke wanting to become pregnant, or women who develop a stroke during or immediately after a pregnancy. Thus, there is a need for a rational approach to management decisions, based on the best available literature, guided by expert consensus.

This consensus statement was developed through an interprofessional collaborative effort among stroke and maternal-fetal medicine experts to provide guidance on the management of stroke in pregnancy based on current research evidence related to both obstetrical and stroke management, with expert interpretation. This consensus statement is appropriate for use by healthcare professionals across all disciplines that provide care to women planning a pregnancy who have a prior history of stroke or transient ischemic attack, or women who sustain a stroke during pregnancy.

This consensus statement is the first of a two-part Canadian Stroke Best Practice Recommendations (CSBPR) Stroke in Pregnancy series and focuses on the unique aspects of secondary stroke prevention in a woman with a prior history of stroke who is, or is planning to become, pregnant and addresses counseling, monitoring, and the safety of select pharmacotherapy on maternal and fetal health while minimizing risks of a recurrent stroke. The second part, which is in development, will focus on the acute management of a woman who experiences an acute stroke while pregnant, and address issues such as neuroimaging, acute thrombolysis and interventional treatments, blood pressure management, and pharmacotherapy. Many consensus statements within this document are applicable to both ischemic and hemorrhagic stroke. In cases where the statements are applicable to one type or the other, it will be explicitly noted.

Conceptual framework

Underlying these recommendations are several important concepts that guide the approach to complex and potentially high-risk scenarios involving pregnant women. First is the concept that maternal health is vital for fetal wellbeing. All decisions ultimately need to consider risks and benefits for both mother and fetus, but maternal health should be a prime consideration.

Second, management decisions should be based on the confluence of two clinical considerations: (a) what decisions would be made if the patient was not pregnant? and (b) what decisions would be made if the patient had not had a stroke? Existing guidelines and recommendations for standard of care treatments for both stroke and for pregnancy should be considered first and tailored as necessary to accommodate individual patient circumstances. Third, where possible, an interdisciplinary team approach is needed to address the complex care and management decisions and should involve those with stroke and obstetrical expertise, in addition to the patient and family. Finally,
decisions must be individualized based on the specific situation. A given management decision may be influenced by many factors. Some key factors include: the timing since stroke onset, severity of the stroke and residual deficits, bleeding risk associated with the stroke, pregnancy or delivery, etiology of the stroke and future stroke risk, timing within pregnancy, maternal age, medical comorbidities, obstetrical history, access to subspecialty services, and the goals and preferences of the individual woman/family.

The CSBPR for the Secondary Prevention of Stroke were updated in parallel with the development of this consensus statement and appear in this issue of the journal (see www.strokebestpractices.ca). These stroke prevention recommendations, applicable for all individuals who have experienced a stroke, should be reviewed in conjunction with this statement, as should recommendations for management of pregnancy from the Society of Obstetricians and Gynecologists of Canada, available at https://sogc.org/clinical_practice_guidelines_eng/index.html.

Consensus statement development methodology

This is a medical consensus statement based on existing literature and expert opinion; it is not intended to be an evidence-based guideline, given the relative paucity of evidence directly specific to both stroke and pregnancy. Wherever possible, we have drawn on the respective stroke and pregnancy literature. Unless otherwise explicitly stated, the statements reflect agreement within our interprofessional panel of experts where research evidence is weak or not available.

The Canadian Stroke in Pregnancy consensus statements were developed by following the same rigorous process applied to the Canadian Stroke Best Practice Recommendations. The methodology for developing the consensus statements included several distinct steps to ensure a thorough and systematic process. The detailed methodology and explanations for each of these steps in the development and dissemination of the Canadian Stroke Best Practice Recommendations and consensus statements is available in the Canadian Stroke Best Practice Recommendations Overview and Methodology manual available on the Canadian stroke best practices website at: www.strokebestpractices.ca

An interprofessional group of experts from stroke, maternal-fetal medicine, obstetrics, gynecology, and obstetrical anesthesia disciplines was convened to review all available evidence, discuss a range of scenarios and current reasonable practices, then drafted and edited all consensus statements. Members with extensive experience across a range of relevant clinical areas who are considered leaders and experts in their field were selected to participate. Persons with experience in the review and appraisal of research evidence and individuals (or family members of individuals) who had experienced a stroke during or prior to pregnancy were also included either as group members or external reviewers in the development process.

A comprehensive systematic literature search was conducted to identify research evidence on the management of secondary stroke prevention during pregnancy. Due to limited randomized controlled clinical trial data directly applicable to this population, trials from stroke in general and from other obstetrical literature, as well as case-control and observational studies were considered. The evidence that has been referenced to develop stroke prevention guidelines outside of pregnancy and evidence included in development of pregnancy-related management outside of stroke were also reviewed and considered by the expert group.

The literature for this module was updated to August 2017. The writing group extensively reviewed and discussed the available evidence. Consensus was reached on all statements through a multi-round review and Modified Delphi voting process where 80% agreement was required to include a statement. Unlike our evidence-based Canadian Stroke Best Practice Recommendation guidelines, evidence levels were not assigned to each consensus statement. Most statements are based on the expert opinion of the writing group. In some cases where stronger evidence does exist, the wording of the statement is stronger (e.g. use of “should”) to indicate confidence in the evidence.

Secondary Stroke Prevention during Pregnancy Consensus Statements

The following sections provide detailed consensus statements associated with secondary stroke prevention and management practices during pregnancy. Primary prevention of stroke during pregnancy is beyond the scope of this consensus statement and can be found in existing stroke/pregnancy guidelines. Also, these recommendations pertain to patients with transient ischemic attack, ischemic or hemorrhagic stroke. Management of patients with suspected acute stroke that warrant hyperacute evaluation to determine eligibility for thrombolysis/endovascular therapy, will be addressed in a second part of this series.

This consensus statement is focused on the issues of stroke prevention encountered by a woman who has had a stroke in the past and is now planning to become pregnant, is currently pregnant, or who has had a stroke in pregnancy but is beyond the hyperacute phase. We first address general management considerations from preconception counseling to pregnancy and post-partum including breastfeeding (Part One).
We then review management considerations for commonly used secondary prevention strategies (Part Two), including antithrombotic medications (both antiplatelets and anticoagulants), blood pressure management, lipid management and diabetes care. Finally, we address some of the more common specific causes of stroke that affect young women of childbearing age and pregnancy (Part Three) including cardioembolic stroke, cerebral venous sinus thrombosis and cerebral artery dissection.

Part One: General management considerations prior to, during, and after pregnancy in a woman with stroke

During pregnancy, the risk of stroke varies depending on the stage, but is highest in the peripartum and early postpartum periods. There is minimal data with which to estimate the risk of stroke recurrence during subsequent pregnancies in women with a first stroke in pregnancy—4 cohorts with a total of <300 post-stroke pregnancies have been published to date.24–27 Ideally, women who have had a prior stroke would discuss plans to become pregnant with their healthcare providers in advance, but this is not always possible. Part One of this consensus statement addresses general stroke prevention strategies, including counseling to promote a healthy lifestyle, incorporating a balanced diet, exercise, weight control, reduction and avoidance of alcohol and tobacco. It also addresses additional screening tests that may be required for women at higher risk of stroke (e.g. diabetes, hypertension).

Part Two: Specific management considerations for secondary stroke prevention during pregnancy

2A. Antithrombotic Use in pregnancy (antiplatelets and anticoagulants) following ischemic stroke or transient ischemic attack (TIA)

While aspirin therapy for stroke prevention has been extensively studied and has been shown to reduce the risk of future vascular events, its use in pregnancy, especially in early pregnancy, has been less well studied. In pregnancy, outside of stroke, low-dose aspirin has been evaluated in randomized controlled trials for certain conditions, such as recurrent pregnancy loss, clotting disorders, or preeclampsia. The safety and potential benefit of pre-conception low-dose aspirin was examined in high-risk women with a history of one or two previous pregnancy losses in the EAGeR trial.29 Among women attempting to become pregnant, there was no significant reduction in the risk of pregnancy loss associated with 81 mg daily aspirin, compared with placebo (13% vs. 12%, RR = 1.06, 95% CI 0.77–1.46, p = 0.78), and there was no increase in adverse fetal outcomes. The authors of a meta-analysis including the results of 13 studies, reported that low-dose aspirin (60–100 mg) use was associated with a 24% reduction in preeclampsia (RR = 0.76, 95% CI 0.62–0.95), when initiated from 12 to 16 weeks gestation.30 More recently, the results from the ASPRE Trial31 suggested that low-dose aspirin (150 mg per day), initiated from 11 to 14 weeks of gestation until 36 weeks of gestation, reduced the risk of delivery with...
a. Counseling on healthy diet, regular exercise, achievement of normal range body mass index, smoking cessation, alcohol use, and other lifestyle factors that may increase recurrent stroke risk during pregnancy. Note: routine considerations for all women considering pregnancies are addressed elsewhere: e.g. Health Canada Healthy Pregnancy Recommendations at https://www.canada.ca/en/public-health/services/pregnancy/guide-healthy-pregnancy.html.

b. A review of investigations to ensure stroke etiological workup has been undertaken and appropriate secondary prevention strategies are in place. Refer to CSBPR Prevention of Stroke Section 2 for more information.

c. A review of current medications to evaluate for potential teratogenicity using available reference databases (e.g. Developmental and Reproductive Toxicology (DART) Database – https://toxnet.nlm.nih.gov/newtoxnet/dart.htm; Reprotox – reprotox.org); and the development of an individualized management plan for stroke risk reduction throughout conception, pregnancy, delivery and post-partum. Where possible, consider preconception use of medications with reasonable data throughout pregnancy (from pre-conception to breast feeding) to minimize the need for multiple medication switches throughout the pregnancy periods.

d. Communication between health professionals with stroke expertise and those with obstetrical expertise is encouraged in the pre-pregnancy counseling stages.

e. A discussion of the risk of recurrent stroke in future pregnancy.

Note: addressing fertility treatment in a woman who has previously experienced a stroke is beyond the scope of this consensus statement and should be dealt with on an individual basis in collaboration with Reproductive Endocrinology and Infertility consultants.

1B. Antenatal and intrapartum risk factor screening for women with a history of stroke

i. Initial obstetrical work-up for pregnant women with a history of stroke should include screening for and assessment of vascular risk factors, and counseling for healthy lifestyle behaviors. Refer to CSBPR Secondary Prevention of Stroke module for further information. (http://www.strokebestpractices.ca/prevention-of-stroke/)

ii. Individualized stroke prevention management plans based on each woman’s medical history, stage of pregnancy, type/etiology of stroke, stroke recurrence risk, and personal goals and preferences may be made at this time. This collaborative plan should include considerations for labor and delivery. Refer to the subsequent sections below for management of specific risk factors and co-morbidities during pregnancy.

Refer to Part Two of this Stroke in Pregnancy series for guidance on managing a woman with an acute stroke during antenatal, intrapartum or postpartum periods.

1C. Post partum stroke prevention management for women with a history of stroke

i. Stroke risk is highest peripartum and in the first 6 weeks post-partum. In this time frame, women may be educated about the signs of stroke (e.g. FAST) and to call 911 for sudden onset of new neurological symptoms, severe headaches or changes in mental status/consciousness.

ii. Women with high-risk conditions or conditions requiring regular assessment (e.g. diabetes, hypertension, pre-eclampsia) may require closer postpartum monitoring.6,16

iii. If not previously involved, consider facilitating stroke prevention specialist assessment to review long-term stroke prevention management plan with consideration to breast-feeding:

a. A prior stroke is not a contraindication to breast-feeding.

b. Where available, allied health support (occupational therapy, breast feeding specialists) can be helpful to facilitate breast-feeding and support the mother in caring for the baby (e.g. in cases where women have residual cognitive or physical deficits from stroke, to address safety during feeding, transfers or bathing).

c. Stroke prevention medications can be evaluated for compatibility with breast-feeding using existing reference databases. Preference can be given to medications that could be continued in the event that future pregnancies are desired.22,28 Refer to Part Two; Section A for more information.
preeclampsia before 37 weeks of gestation, compared with placebo (OR = 0.38, 95% CI 0.20–0.74, \( p = 0.04 \)), and without an increased risk of adverse events. The safety of low-dose aspirin use in pregnancy and during lactation is well-established.\textsuperscript{32–34} The risks of congenital malformations such as neural-tube defects, cleft palate, or cardiac malformations associated with aspirin use have not been shown to be significantly increased. In one study, concerns were raised that the incidence of gastroschisis may be elevated in those exposed to aspirin during the first trimester (OR = 2.37, 95% CI 1.44–3.88, \( p = 0.0006 \))\textsuperscript{33} but these events have not been reported to be elevated in the EAGeR or ASPRE trials. There is a theoretical risk of Reye’s syndrome associated with aspirin use during breastfeeding, but no confirmed reports associated with low dose ASA exposure.

Certain conditions, including the presence of artificial heart valves, or conditions related to hypercoagulability, may require anticoagulation in pregnancy. The safest known anticoagulants associated with pregnancy are low molecular weight heparin (LMWH) and unfractionated heparin (UFH), neither of which crosses the placenta. Vitamin K antagonists (VKA) are classified by the FDA as a category X substance, therefore their risks and benefits must be closely weighed, as their use has been associated with an increased risk of miscarriage, teratogenic effects in the first trimester, and risk of bleeding to both fetus and mother. For high-risk women with mechanical heart valves, low-dose warfarin (≤5 mg/d) may be the preferred treatment for the prevention of thromboembolic events.\textsuperscript{35} Anticoagulants have also been examined for the prevention of pregnancy complications associated with thrombophilias, but were not found to be effective. Results from the TIPPS trial indicated that among pregnant women with thrombophilia at high risk of pregnancy complications, antepartum prophylactic dalteparin did not reduce the risk of venous thromboembolism and placenta-mediated pregnancy

\[ \text{2A. Antithrombotic Use in Pregnancy (Antiplatelets and Anticoagulants) Following Ischemic Stroke or Transient Ischemic Attack (TIA)} \]

i. Decision-making regarding antithrombotic use can be complex and a multidisciplinary review may be needed to assess maternal and fetal risk/benefit of the options.

a. Antithrombotic management decisions can be tailored on an individual basis and may be informed by many issues, such as:
   - stroke etiology and accompanying stroke recurrence risk outside of pregnancy (e.g. prosthetic heart valve vs. cryptogenic stroke);
   - the size and recency of the stroke (e.g. bleeding risk is higher with larger and more recent infarcts);
   - the stage of pregnancy (e.g. peripartum and post-partum stroke risk is higher than first and second trimester).

b. If considering anticoagulation, in addition to factors listed above, consider a woman’s medical and obstetrical history. For example, a woman with a history of preterm labor or rapid delivery can be at higher risk of an early or rapid delivery, making a planned cessation of LMWH more challenging.

ii. In some women with a prior ischemic stroke whose underlying mechanism of stroke has resolved and residual risk is presumed to be comparable to the general population and who are not already on antithrombotics, it is reasonable to consider not starting antithrombotic prophylaxis during pregnancy.

iii. If antiplatelet agents (clopidogrel, acetylsalicylic acid, combined acetylsalicylic acid and extended-release dipyridamole, or ticagrelor at any dose at any dose) are indicated or already in use for stroke prevention, changing to low-dose acetylsalicylic acid (81 mg daily) is preferred prior to pregnancy or once a pregnancy is confirmed.

a. There is insufficient evidence to support the safety of antiplatelet agents other than acetylsalicylic acid in pregnancy. However, there may be cases where other antiplatelet agents are clinically indicated and these situations should be addressed on a case-by-case basis (e.g. Clopidogrel in the setting of coronary stents).

b. In women for whom antiplatelet agents would be recommended for stroke prevention, low dose acetylsalicylic acid is reasonable pre-conception, first trimester and throughout the rest of pregnancy.

Note: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been linked to premature closure of the ductus arteriosus when used in the third trimester and may impair fetal renal function. Low-dose ASA, while an NSAID, has not been reported to increase the risk of premature closure of the ductus arteriosus in clinical trials, and increases in fetal renal impairment have not been reported. Other guidelines acknowledge case control studies that associated increased risk of fetal gastroschisis with ASA taken before the eleventh week of pregnancy. Results from more recent RCTs including EAGeR\textsuperscript{29} and ASPRE,\textsuperscript{31} using
low-dose ASA pre-conception (81 mg) or after 11 weeks (150 mg) to reduce the risks of pregnancy loss or the development of preeclampsia, have not been associated with increased risk of major adverse events when used throughout pregnancy.

c. Low-dose ASA can be considered during breastfeeding since there is evidence that aspirin is not excreted into breast milk and salicylate levels are low in women taking daily low-dose aspirin. Higher dose of daily aspirin may have additional risks, with possible risks of metabolic acidosis and theoretical risks of Reye’s syndrome in infants exposed to high doses of salicylic acid.39–41

iv. Warfarin is potentially teratogenic and should be avoided, especially between 6 and 12 weeks gestational age. When anticoagulation is considered, low molecular weight heparin (LMWH) is preferred throughout pregnancy.

a. In certain rare situations with very strong indications for warfarin (e.g. women with a mechanical cardiac valve), collaboration with thrombosis experts may be required. In these situations, switching to an alternative to warfarin may be considered as soon as pregnancy is discovered, and could consider restarting warfarin after the twelfth week of pregnancy until closer to delivery. Multidisciplinary management of these situations is preferred.

v. There are insufficient data on the safety of direct oral anticoagulants (DOAC) (apixaban, dabigatran, edoxaban, rivaroxaban) in pregnancy. Switching to LMWH is encouraged as soon as a pregnancy is identified or if pregnancy is planned.

vi. In certain circumstances, therapeutic doses of LMWH can be considered a reasonable alternative to ASA or prophylactic doses could be considered with or without low-dose ASA. For example:

a. A woman considered at high stroke/thrombotic risk (e.g. with multiple strokes),

b. A woman with known hypercoagulability (e.g. anti-phospholipid antibody syndrome).

vii. Low-dose LMWH should be stopped at least 12 hours prior to administration of regional anesthesia, and full-dose LMWH should be stopped at least 24 hours in advance of regional anesthesia or planned induction.7

viii. Intravenous unfractionated heparin could be considered in a hospitalized woman in place of LMWH, using standardized local protocols, especially if there is concern about need for urgent delivery or invasive procedures.

a. When using IV unfractionated heparin, a low dose, acute coronary syndrome nomogram, without bolus, is preferred in stroke patients, and would also be preferred in pregnancy.

ix. LMWH or unfractionated heparin can be restarted at least 4 to 6 hours after the removal of the neuraxial catheter if bleeding is well controlled and there are no neuraxial concerns, and continued for 6–12 weeks post-delivery.

x. After 6 to 12 weeks post-delivery, consider the choice of antithrombotic that was recommended outside of pregnancy, taking into account issues regarding breastfeeding (see section C above for links), and future pregnancy planning.

a. If anticoagulation is required, low molecular weight heparin and warfarin are both considered safe options during breastfeeding. The safety of direct oral anticoagulants in breastfeeding has not been established.

complications.36 There was also no significant difference among three treatment groups (LMWH, ASA, or both combined) in the percentage of live births in the HABENOX Trial.37

2B. Blood pressure management for stroke prevention in pregnancy (ischemic and hemorrhagic)

Women with hypertensive-disorders of pregnancy are at greater risk for stroke, especially those with traditional risk factors,3 therefore, treatment of moderate to severe hypertension is key. A limited number of agents, including methyldopa, labetalol, and nifedipine, are known to be safe and effective during pregnancy. The potential benefit of a tight versus less tight regimen among women with moderate diastolic hypertension (90–105 mm Hg) was evaluated in the Control of Hypertension In Pregnancy Study (CHIPS).42 Although the frequency of severe hypertension was significantly higher among women in the less-tight control group, there was no significant reduction in the frequency of any of the individual components of the primary outcome (miscarriage, ectopic pregnancy, elective termination, perinatal death, still birth or high-level neonatal care) associated with more-tight control. In a Cochrane review43 including 48 RCTs, while the risk of severe hypertension was significantly reduced in the active treatment group (≥1 antihypertensive agent), compared with women who received no treatment or placebo, the risks of pre-eclampsia/proteinuria, fetal or neonatal death, pre-term birth or small-for-gestational age, were not. In a sub-group analysis of beta blockers, the risk of developing proteinuria/pre-eclampsia was significantly reduced (RR = 0.73, 95% CI 0.57–0.94). The risks were not significantly reduced for women taking other antihypertensive treatments. In contrast, the importance of blood pressure reduction for secondary prevention after stroke has been well established. Thus, for pregnant women with a history of stroke, blood pressure reduction is undertaken as part of an overall secondary stroke prevention strategy.
2B. Blood pressure management for stroke prevention in pregnancy (ischemic and hemorrhagic)

i. The nonpharmacological and pharmacological management of hypertension in pregnancy is reviewed in detail elsewhere. 

a. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB’s) – two common classes of medications used in stroke prevention – carry an increased risk of fetal complications (kidney injury) and low amniotic fluid, especially if used after the first trimester. These medications should be discontinued prior to pregnancy or as soon as a pregnancy is recognized.

i. If they have been inadvertently taken, prompt referral to a regional center for detailed fetal structural ultrasound and counseling is encouraged.

b. Commonly used first-line oral medications for blood pressure control in pregnancy are labetalol, methyldopa, and long-acting nifedipine. Selection of specific antihypertensives should consider side-effect profiles for the woman, fetus or newborn baby.

ii. All women who develop hypertension during pregnancy require prompt investigations and review by an expert in the management of hypertension in pregnancy. After 20 weeks gestational age, the differential diagnosis should always include preeclampsia, which must be identified for appropriate obstetric and fetal management.

iii. In pregnancy, women with a previous stroke should have a blood pressure target of consistently lower than 140 mmHg systolic and consistently lower than 90 mmHg diastolic. Refer to CSBPR Secondary Prevention of Stroke module for Management of Hypertension after Stroke and SOGC guidelines for Management of Hypertension in Pregnancy 2014.

a. Monitoring is warranted to ensure targets are achieved, to detect early rises in blood pressure or urinary protein suggestive of preeclampsia, and to avoid severe hypoperfusion.

iv. Gestational hypertension and preeclampsia are dynamic pregnancy-related disorders that often require inpatient management, maternal and fetal monitoring, repeat laboratory investigations, frequent medication adjustment, and may affect the timing of delivery.

v. Preeclampsia is a risk factor for long-term cardiovascular disease. For all women with preeclampsia or gestational hypertension, long-term follow-up for blood pressure management is reasonable as the risk of hypertension, coronary, cerebrovascular or peripheral artery disease is increased. In the situation specifically considered here (pregnant women with a prior history of stroke), long-term blood pressure control should be optimized to standard secondary prevention of stroke targets. Refer to CSBPR Secondary Prevention of Stroke module for Management of Hypertension following Stroke.

2C. Statins for ischemic stroke prevention in pregnancy

While the benefits of statin use for secondary prevention are well-established, statin treatment is usually not warranted during pregnancy, as lipid dysregulation is a physiologic adaptation of pregnancy. The development of certain cells (e.g. myelin) and the accumulation of fat mass in the fetus are dependent upon lipid metabolism. Statin medications have been classified in pregnancy as Category X, and are contraindicated given their potential teratogenicity. Most of the evidence regarding statin use during pregnancy originates from studies comparing the pregnancy outcomes of women accidentally exposed to statins during pregnancy with those of women not exposed. The results are ambiguous with some studies suggesting adverse fetal and maternal outcomes associated with statin use, particularly during the first trimester. In the largest cohort study, statin use was associated with a significantly increased risk in the incidence of birth defects in unadjusted analysis (RR = 1.79, 95% CI 1.43–2.23), but was no longer evident in an analysis using propensity scores, adjusting for age, diabetes, and other confounding factors (RR = 1.07, 95% CI 0.85–1.37). Zarek and Koren pooled the results from 6 controlled studies and reported that the use of statins during pregnancy did not increase the risk of birth defects, although there was a significant increase in risk of miscarriage (RR = 1.35, 95% CI 1.04–1.75). In a case-control study, the frequency of major birth defects was non-significantly higher in the statin-exposed group (4.1% vs. 2.7%, OR = 1.5, 95% CI 0.5–4.5, p = 0.43), while the frequencies of pre-term delivery, miscarriage or fetal death were significantly higher in the statin-exposed group. Most recently, Karalis et al. reviewed the results of 16 case series, cohort studies, meta-analyses and an RCT, and concluded there was no clear evidence of a relationship linking congenital anomalies with statin use in pregnancy, suggesting they were probably not teratogenic, while at the same time, cautioning that their use should be avoided. Given that the benefits of statins for secondary stroke
prevention accrue over many years, a temporary interruption during pregnancy is unlikely to expose the pregnant woman to short-term harm.

2D. Pre-existing diabetes and gestational diabetes for stroke prevention in pregnancy

i. Women with diabetes in pregnancy (pre-existing type 1 or type 2 diabetes or gestational diabetes) require frequent, close follow-up by an interdisciplinary team (where available) to monitor for maternal and fetal complications. Glycemic monitoring, monitoring for other vascular risk factors, and glucose management throughout pregnancy and postpartum should follow established guidelines (Diabetes Canada 2013; www.diabetes.ca).16

ii. For women with a history of stroke, glucose tolerance tests can be considered earlier in pregnancy (e.g. at 20 weeks instead of 24–28 weeks) if considered at high-risk of gestational diabetes.6,16

iii. It is reasonable to counsel women with a history of stroke and who have gestational diabetes to ensure long-term follow-up through primary care, with the goal to facilitate lifestyle interventions to reduce the future risk of developing diabetes and stroke. For women who experience gestational diabetes, the 10-year risk of diabetes and cardiovascular disease is elevated.56

Part Three: Management considerations for specific ischemic stroke etiologies in pregnancy

Limited evidence exists related to the management of strokes that occur during pregnancy with specific etiologies including cardioembolic source, cerebral venous sinus thrombosis (CVST), cervical artery dissection, antiphospholipid antibody syndrome (AAS), and cryptogenic stroke. The evidence base is largely composed of case reports and case series. Regardless of the etiology, common practice includes treatment with either oral anticoagulants or antiplatelet agents (acetylsalicylic acid). Outside of pregnancy, cervical artery dissections are usually treated with either a vitamin K antagonist or antiplatelet (acetylsalicylic acid) for 3–6 months. Case reports of women treated for carotid and vertebral dissections occurring in both the antenatal and early post-partum period indicate the same management strategies are used57–60 without reported adverse effects for the mother or infant. Both aspirin and warfarin were used for secondary prevention among 68 women who had suffered a previous CVST prior to pregnancy.24

For pregnant women who present with patent foramen ovale, management usually includes acetylsalicylic acid and LMWH for the duration of the pregnancy. Percutaneous closure may be considered beyond the first trimester in some cases, although generally closure is not indicated since evidence of its safety and efficacy during pregnancy is lacking. Even when indicated outside of pregnancy, the procedure is associated with short-term risks and the potential benefits accrue only after many years.

2C. Statins for Ischemic Stroke Prevention in Pregnancy

i. Interpretation of lipid levels is unreliable in pregnancy due to the normal physiologic changes of pregnancy and should not be used to guide decisions about therapy. In addition, serum lipid levels should not be routinely measured during pregnancy. First-line management of dyslipidemia includes counseling for healthy diet and exercise.

ii. There is insufficient evidence regarding the safety of statins in pregnancy and lactation. It is reasonable to temporarily interrupt statin therapy preconception and throughout pregnancy.

iii. The timing for restarting, or newly prescribing, statins for secondary stroke prevention after delivery should be individualized based on specific clinical circumstances (e.g. presence of high-risk conditions such as recent MI, compatibility with breastfeeding plans).

2D. Pre-existing diabetes and gestational diabetes for stroke prevention in pregnancy

Women with gestational diabetes are at increased risk of antenatal stroke,49,50 and may be at risk for future stroke up to 7 years after delivery.51 In studies that have examined the relationship between gestational diabetes and future risk of cardiovascular diseases, including stroke, the strength of the relationship is attenuated after adjusting for age and subsequent diabetes or menopausal status.52–54 A low glycemic index diet has been shown to significantly reduce both fasting and 2-hour post-prandial blood glucose, compared with a control group consuming intermediate-high glycemic index foods among women with gestational diabetes, without a history of diabetes.55 Target 1-hour postprandial blood glucose of <7.8 mmol/L has been associated with good outcomes and has been suggested as a reasonable target for women with gestational diabetes.16
Summary
The 2017 Canadian Stroke Best Practice consensus statement on secondary stroke prevention during pregnancy provides clinicians with guiding principles to manage women with a history of stroke who are, or wish to become, pregnant. These women may require closer monitoring throughout pregnancy and the early postpartum period. The consensus statement emphasizes the need for coordinated shared care with an interprofessional team involving both stroke experts and obstetric specialists along with the patient and their family. The evidence base for this consensus statement

Part Three: Management considerations for specific ischemic stroke etiologies in pregnancy

Note: Hemorrhagic stroke is addressed in the acute stroke in pregnancy module.

3A. Cardioembolic stroke
i. For syndromes that require anticoagulation outside of pregnancy (e.g. artificial cardiac valve, intracardiac thrombus), anticoagulation should be continued throughout pregnancy but may need to be adapted for safety. Refer to Antithrombotic section 2A above for LMWH considerations and timing relative to labor and deliver.

ii. Patent foramen ovale closure during pregnancy is not recommended. Low-dose oral ASA daily is considered first line for medical prevention. Refer to CSBPR Secondary Prevention of Stroke Module for additional information.
   a. If a pregnant patient with a known PFO is at increased risk of venous thrombosis, prophylactic LMWH doses could be considered.

3B. Cerebral venous sinus thrombosis (CVST)

i. For acute CVST occurring during pregnancy, consider treatment with therapeutic doses of anticoagulation (unfractionated heparin or LMWH) for the remainder of pregnancy and for at least 6 weeks post-partum or until a post-partum switch to oral anticoagulation is feasible.

ii. A woman with a remote history of spontaneous CVST, not currently anticoagulated, can be considered for LMWH prophylaxis, during pregnancy and at least 6 weeks post-partum. See antithrombotics above for LMWH considerations and timing for labor and delivery.

3C. Cervicocephalic artery dissection

i. Antithrombotic therapy for stroke prevention is recommended for individuals with a diagnosis of an extracranial carotid or vertebral artery dissection.
   a. There is uncertainty about the comparative efficacy of antiplatelet therapy vs. anticoagulation even outside of pregnancy. Either treatment is considered reasonable, and decisions should be based on individual risk/benefit analysis. If anticoagulation is chosen, LMWH is preferred. Refer to Antithrombotic section 2A above for LMWH considerations and timing relative to labor and deliver.
   b. There is a lack of evidence regarding the optimal duration of antithrombotic therapy and the role of repeat vascular imaging in decision-making. Decisions may be based on individual clinical factors. Refer to CSBPR Secondary Prevention of Stroke module for additional information.

ii. In pregnancy, treatment options for cervicocephalic dissection include monitoring only (i.e. no treatment), low-dose ASA, or anticoagulation.
   a. Low-dose ASA is often considered for women with recent dissections without thrombus, or chronic dissections with complex morphology (e.g. residual flap, pseudoaneurysms).
   b. For women with a history of stroke caused by dissection who have stopped their ASA, restarting during pregnancy and post-partum could be considered.
   c. LMWH is a reasonable option in some cases (e.g. in women with dissection in the highest thrombotic risk stages (peri-partum to 6 weeks post-partum), or women with intra-arterial thrombus). See antithrombotics section above for LMWH considerations and timing for labor and delivery.

iii. Evidence does not support routine Cesarean delivery in women with a prior cervical artery dissection. Cesarean delivery might still be considered, (e.g. for obstetrical indications, or if the dissection occurred during labor in a previous pregnancy
varies in its scope and strength, reflecting the practical challenges in conducting randomized controlled trials with this specific sub-population. We have drawn upon stronger evidence from both maternal-fetal medicine and stroke literatures to develop these statements. We urge clinicians to collect and share data on management of women with stroke prior to pregnancy, documenting and reporting care and outcomes for large cohorts to help build a stronger knowledge base. This consensus statement continues to be a work in progress and will be regularly updated every 3–5 years to integrate newly released data to help ensure optimal patient care and outcomes.

**Author contributions**

Richard H Swartz (Co-First Author) and Noor Ladhani, (Co-First Author) co-chaired the Secondary Prevention expert writing group and are lead authors contributing to all aspects of the development, evidence reviews, analysis, writing, editing and final approval of this manuscript; M Patrice Lindsay is corresponding author, and senior editor contributing to all aspects of the development, evidence reviews, analysis, writing, editing and final approval of this manuscript; Norine Foley and Sanjit Bhogal conducted the evidence searches and article reviews, completed the evidence tables and evidence summaries supporting the development of this consensus statement, and contributed to the writing and editing of this manuscript; Jon Barrett; Cheryl Bushnell, Wee-Shian Chan, Radha Chari, Shital Gandhi, Michael D Hill, Andra James, Thomas Jeerakathil, Albert Jin, Adam Kirton, Sylvinant Lanthier, Andrea Lausman, Lisa Leffert, Jennifer Mandzia, Bijoy Menon, Kara Nerenberg, Aleksandra Pikula, Alexandre Poppe, Jayson Potts, Meryem El Amrani, Joel Ray, Gustavo Saposnik, Mukul Sharma, Simerpreet Bal, are all members of the Secondary Stroke Prevention during Pregnancy expert writing group and contributed by reviewing, analyzing and discussing the evidence and collectively finalizing the wording of all the consensus statements; Eric Smith is chair of the Canadian Stroke Best Practices Advisory Committee, and a member of the writing group, and contributed significantly to the methodology and consensus statement development and provided review and edits to this manuscript; Dariush Dowlatshahi and Gord Gubitz are senior advisors to the writing group and contributed significantly to the methodology and consensus statement development and provided review and edits to this manuscript. Elisabeth Smitko provided coordination and meeting support to the writing group and contributed to the development of supplementary materials.

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References


43. Abalos E, Duley L and Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014; Cd002252.


56. Retnakaran R and Shah BR. Role of type 2 diabetes in determining retinal, renal, and cardiovascular outcomes.


