



CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Stroke in Pregnancy

*A Consensus Statement by the Canadian Stroke Best Practices
Stroke in Pregnancy Writing Group.*

Part One: Prevention of Recurrent Stroke in Pregnant Women and Women Planning a Pregnancy.

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Canadian Stroke Best Practice Recommendations
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Canadian Stroke Best Practice Recommendations

Stroke in Pregnancy~ Sixth Edition (November 2017)

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STROKE IN PREGNANCY: A Consensus Statement by the Canadian Stroke Best Practice Stroke in Pregnancy Writing Group.

Part One: Prevention of Recurrent Stroke in Pregnant Women and Women Planning a Pregnancy.

Overall introduction to stroke in pregnancy consensus statements

Stroke, the sudden loss of neurological function due to neuronal injury of a vascular cause, is a leading cause of disability in adults and when stroke occurs as a complication of pregnancy, the impact on the mother, child and families can be devastating. A recent systematic review and meta-analysis showed that stroke affects 30/100,000 pregnancies [Swartz, Cayley, Foley et al, 2017], roughly 3 times that seen in the general population of young adults [Singhal et al, Neurology, 2013]. Several aspects of pregnancy can increase the risk of stroke including: hypertensive disorders of pregnancy [Leffert et al., Obstetrics and Gynecology, 2015] (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 hemoconcentration; and changes to cerebral vasculature (for example, reversible cerebral vasoconstriction syndrome (RCVS), arteriovenous malformations). Given this etiological variability, the practical limitations to clinical trials research in pregnant patients with stroke, 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 get pregnant, or women who develop a stroke during or after a pregnancy. Thus, there is a need for a rational approach to management decisions, based on the best available literature and guided by expert consensus.

Goal: to provide guidance on the management of stroke in pregnancy based on a critical appraisal of current research evidence on obstetrical and stroke management and expert review and appraisal.

Scope: This document represents a consensus statement based on the process above, focused on the unique aspects of pregnancy-related stroke. Many consensus statements 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.

A full list of existing best practice recommendations for stroke and obstetrical care are comprehensively covered elsewhere, such as:

- A) acute stroke treatments and vascular risk reduction in non-pregnant women (www.strokebestpractices.ca (see specific recommendations for acute treatment [Casaubon et al., IJS 2016 Feb;11(2):239-52], secondary prevention [Coutts et al., IJS 2015 Apr;10(3):282-91] and rehabilitation[Hebert et al., IJS 2016 Jun;11(4):459-84]); www.professional.heart.org; www.nice.org.uk),
- B) routine obstetrical management and management of vascular risk factors like diabetes or hypertension in non-stroke obstetrical patients (www.acog.org; www.sogc.org; www.nice.org.uk, [Diabetes Canada](http://DiabetesCanada.ca)),
- C) general teratogenicity of medications in pregnancy (DART database)

<https://toxnet.nlm.nih.gov/newtoxnet/dart.htm>) or in breast feeding (Lactmed <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>), Motherisk www.motherisk.org/women/drugs.jsp; <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>). Rather, this set of guidelines seeks to organize an approach and apply existing evidence to this specific subset of stroke patients (those pregnant) and this specific subset of pregnant patients (those with acute or previous stroke).

This is a medical consensus statement based on existing literature and expert consensus; it is not intended to be an evidence-based guideline, especially given the relative paucity of evidence 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.

Current state of research evidence: The majority of research evidence and clinical trials in this area are derived from either general stroke or general pregnancy cohorts. Pregnancy has been an exclusion from virtually all stroke acute and prevention trials. There are case reports, single institution retrospective chart reviews and population-based registry data to inform estimates of incidence of first stroke in a pregnancy [Swartz et al., IJS 2017], but minimal evidence surrounding recurrence rates in subsequent (post-stroke) pregnancies (<300 post-stroke pregnancies across 4 studies) [Lamy Neurology 2000;55:269; Coppage Am J Obst Gynecol 2004; 190:1331; Crovetto Arch Gynecol Obstet 2012;286:599; Soriano Acta Obstet Gynecol Scand 2002;81:204]. Our consensus statement will be reviewed at least every three years and updated as warranted by the publication of new evidence.

Target audience for consensus statement is the multidisciplinary group of health care professionals that manage both stroke and pregnancy including obstetricians, family physicians, maternal-fetal medicine specialists, obstetrical medicine specialists, obstetrical anesthetists, internists, neurologists and critical care specialists, emergency medicine, radiologists, nursing from neurological, obstetrical and critical care backgrounds, and stroke rehabilitation specialists.

Considerations: The following are the important overriding philosophies to the approach of these complex and potentially high-risk scenarios that were shared among the contributors to this consensus statement. (K. Rosene-Montella and E. Keely. Medical care of the pregnant patient. 2nd edition)

- 1) **Maternal health is vital for fetal wellbeing.** All decisions ultimately need to reflect the combination of benefits and risks to both mother and baby.
- 2) **What would I do if she wasn't pregnant AND what would I do if she hadn't had a stroke?** The initial question to be addressed should start with the best practices in stroke care (without pregnancy) and obstetrical care (without stroke). Existing guidelines and recommendations for standard of care treatment must be considered first, and nuanced only as needed. This is the basis of the approach to any medical issue in pregnancy – first what is the ideal investigation or treatment plan outside of pregnancy and then what needs to be modified due to pregnancy. Thus, these consensus statements will review common/important issues to consider that go beyond existing guidelines. Stroke prevention management decisions should be **individualized** to each woman's medical history, clinical considerations and personal goals and preferences.
- 3) **Where possible, an interdisciplinary team approach is needed** to address the complex care and management decisions, involving those with stroke expertise (neurologists, internists, and vascular specialists), those with obstetrical expertise (obstetricians, family physicians, maternal-fetal medicine specialists, anesthesiologists) and the patient and family. Collaboration and

communication are essential. The consensus panel was intentionally recruited to reflect the multidisciplinary nature of care of women with stroke and pregnancy.

- 4) **Decisions must be nuanced based on the specific situation.** There are multiple factors to consider that influence risk/benefit analyses in the setting of stroke and pregnancy (see Figures 1 and 2) including timing since stroke, severity of stroke/residual deficits; bleeding risk from stroke or treatment; etiology of stroke and risk for future events; timing within pregnancy; bleeding risk of pregnancy; delivery and treatment; maternal age; other medical comorbidities; access to subspecialty/multidisciplinary services; and the goals/preferences/philosophy of care of the individual woman.

Framework:

At the outset of this work, the expert writing group identified two pregnancy-related stroke scenarios as the focus of the consensus statements. These perspectives have been identified based on the timing of stroke relative to pregnancy, and the recognition of differences in decision-making and unique care requirements for each scenario.

These two scenarios include:

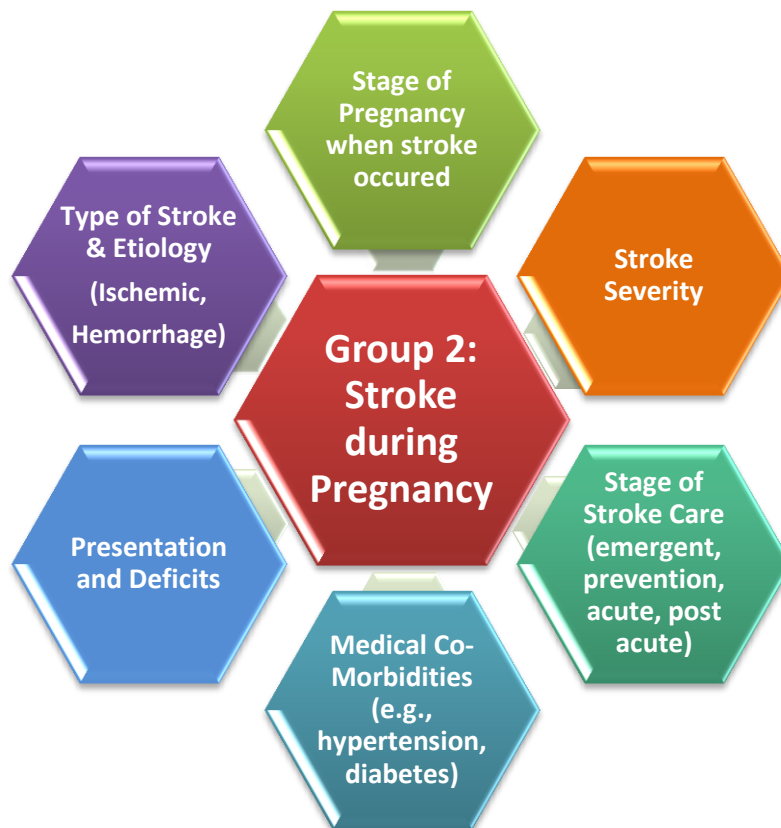
- 1) A woman *with a history of stroke who is planning to become pregnant* (or has had a stroke earlier in pregnancy), with a focus on issues of secondary prevention and management (Figure 1);
- 2) a woman *who is pregnant and experiences a sudden onset of neurological deficits* during pregnancy or immediate post-partum (first 6 weeks), with a focus on the acute stroke/TIA presentation and issues of emergency investigations, diagnosis, immediate management, and recovery (Figure 2).

The complexities and interdependencies that may arise in these patients require an individualized approach based on the timing of stroke to pregnancy. Several of the common and clinically important issues to consider are illustrated in Figures 1 and 2 below.

FIGURE 1: WOMEN WITH A HISTORY OF STROKE WHO ARE PLANNING OR BECOME PREGNANT



FIGURE 2: WOMEN WHO EXPERIENCE A STROKE DURING PREGNANCY



Consensus Statement Methodology:

The *Stroke in Pregnancy consensus statements* were developed by following the same 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 rigorous 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 http://www.strokebestpractices.ca/wp-content/uploads/2014/08/CSBPR2014_Overview_Methodology_ENG.pdf

1. Establish expert interprofessional writing group for module, including stroke survivors and/or caregivers;
2. Development of a framework to define the scope of the consensus statement and key elements for consideration and inclusion;
3. Systematic search, appraisal and update of research literature;
4. Systematic search and appraisal of external reference guidelines related to stroke, pregnancy and stroke in pregnancy;
5. Development of evidence summary tables;
6. Writing group review and discussion of evidence, development of proposed consensus statements, rationale and justification;
7. Submission of proposed statements to the Canadian Stroke Best Practices Advisory Committee for internal review and provision of feedback to writing group followed by completion of edits;
8. External review, and final edits based on feedback;
9. Final approvals, endorsement and translation of consensus statement documents;
10. Public release & dissemination of consensus statement documents;
11. Establish cycle for ongoing review and updates.

Conflicts of Interest: All potential participants in the development and review process are required to sign confidentiality agreements and to declare all actual and potential conflicts of interest in writing. Any conflicts of interest that are declared are reviewed by the Chairs of the Best Practices Advisory Committee and appropriate HSF staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant are not selected for advisory or writing group membership. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic, and if it is the chair, then another non-conflicted participant assumes the chair role for that discussion to ensure balanced discussions.

Assigning Evidence Levels: The writing group was provided with comprehensive evidence tables that include summaries of all high quality evidence identified through the literature searches. The writing group discussed and debates the value of the evidence and through consensus develops a final set of proposed statements.

There is limited randomized controlled research evidence available for stroke in pregnancy to guide decision-making; therefore this work was developed into consensus statements based on the collective expertise of the writing group and their colleagues informed by the existing research literature on stroke management and obstetrical care. Therefore evidence levels are not assigned to these statements. Most statements in this document would be considered 'C' level based on consensus and expert opinion. This level of evidence is used cautiously, and only when there is a lack of stronger evidence for topics considered important system drivers for patient care.

These consensus statements should be used as a general guide to inform clinical care and decision-making in patients with stroke before or during pregnancy.

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Citing the Secondary Prevention of Stroke during Pregnancy 2017 Module

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Comments

We invite comments, suggestions, and inquiries on the development and application of the *Canadian Stroke Best Practice Recommendations*. Please forward comments to the Heart and Stroke Foundation's Stroke Team at strokebestpractices@heartandstroke.ca.

Section Two: Introduction to Secondary Prevention of Stroke in Pregnancy

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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 1). We then review management considerations for commonly used secondary prevention strategies (Part 2), 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 3) including cardioembolic stroke, cerebral venous sinus thrombosis and cerebral artery dissection. Prevention of a first stroke in pregnancy is accomplished through general stroke primary risk reduction strategies and routine obstetrical care, especially management of hypertension in pregnancy (ref SOGC 2014 HTN guideline).

The management of a woman who experiences a stroke during pregnancy, including investigations and management, will be discussed in the second part of this Stroke in Pregnancy Consensus Statement series.

Stroke Prevention and Pregnancy Consensus Statement 2017:

Secondary Prevention of Stroke in Pregnancy

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

1A. Pre-Pregnancy Counseling for Women with a History of Stroke

- i. Discussions of pregnancy and implications for stroke recurrence should be included as a routine part of post-stroke management for all female stroke survivors of reproductive age.
- ii. Contraception should be addressed based upon the patients' fertility and pregnancy plans as well as the stroke mechanism and type.
 - a) In cases of ischemic and thrombo-embolic stroke, systemic estrogen-containing contraceptives or hormone replacement therapy that can increase the risk of thrombosis should be carefully considered and in most cases, should be avoided due to an increased risk of stroke.
 - b) Management alternatives, including progesterone-only oral contraceptives, progesterone-only or non-hormonal intrauterine devices, or barrier contraception can be considered. *Refer to CSBPR Prevention of Stroke Section 2 for more information.*
- iii. During pre-conception consultation with all female stroke survivors of reproductive age, stroke risk factor assessment and pharmacological management related to secondary stroke prevention in the context of pregnancy could be addressed. These include:
 - 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 safety 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 counselling 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 behaviours. *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 labour 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 2; Section A for more information.*

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)

- 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 labour 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) are indicated or already in use for stroke prevention, changing to low-dose acetylsalicylic acid (ASA) (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 as-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 guidelines²² 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 EAGeR²⁹ and ASPRE,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 acetylsalicylic acid is not excreted into breast milk and salicylate levels are low in women taking daily low-dose aspirin. Higher doses of daily acetylsalicylic acid 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 to 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.⁷
- 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 have not been established.

2B) Blood Pressure Management for Stroke Prevention in Pregnancy (ischemic and hemorrhagic)

- i. The non-pharmacological and pharmacological management of hypertension in pregnancy is reviewed in detail elsewhere:^{6, 18}
 - 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.
 - If they have been inadvertently taken, prompt referral to a regional centre for detailed fetal structural ultrasound and counselling is encouraged.
 - b. Commonly used first-line oral medications for blood pressure control in pregnancy are labetalol, methyldopa and long acting nifedipine.⁶ 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*⁶
 - 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.⁴⁴ 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

- 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

- 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

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 labour 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 labour 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 labour and delivery.*
 - 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 above for LMWH considerations and timing for labour and delivery.*
- iii. Evidence does not support routine Caesarean delivery in women with a prior cervical artery dissection. Caesarean delivery might still be considered, (e.g. for obstetrical indications, or if the dissection occurred during labour in a previous pregnancy some women have concerns about undergoing another labour). Individualized decision-making between the neurology and obstetrics teams is required.

3D) Antiphospholipid Antibody Syndrome

- i. Antiphospholipid antibody syndrome in a woman with a history of stroke is often treated with therapeutic anticoagulation alone, or in combination with low-dose ASA. These treatment options are reasonable in pregnancy considering the stage of pregnancy and the presence or absence of obstetric complications.

3E) Cryptogenic Stroke

- i. Antiplatelet agents are used for secondary stroke prevention after cryptogenic stroke. Refer to Part Two, Section A above for antiplatelet management.

Rationale

Stroke is a leading cause of adult neurological disability, death, and maternal morbidity and mortality in developed nations. Based on the pooled data in a recent meta-analysis (Swartz et al 2017) stroke affects 30/100,000 pregnancies. This is three times higher than rates for young adults overall (10/100,000 per year) and outcomes are dependent on rapid recognition and management. Stroke types are also more varied in pregnancy, with relatively more venous sinus thrombosis and intracranial hemorrhage. In addition, causes more commonly found in young adults (e.g. dissection, congenital cardiac complications), physiological adaptations to pregnancy (e.g., hypervolemia, increased clotting factors), and pregnancy specific disorders (e.g., HELLP, preeclampsia) combine to increase risk of stroke in pregnancy. 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.

System Implications

- Systems in place to enable women who become pregnant or are planning pregnancy to access appropriate antenatal care.
- Collaborative relationships established between obstetrical, maternal-fetal medicine experts and stroke specialists to optimize access and management for women who experience stroke before, during or immediately after pregnancy.
- Development of data collection systems to monitor women who experience stroke prior to, during or immediately after a pregnancy to improve knowledge of safety and efficacy of management approaches, drive quality improvement and systems change.
- Promote randomized controlled trials or large population-based observational studies where feasible to reduce knowledge gaps and increase the ability to move from a consensus statement to an evidence-based clinical practice guideline

Performance Measures

1. Proportion of women with a past history of stroke who experience a recurrent stroke during pregnancy or early postpartum.
2. Proportion of women with a past history of stroke who experience a change in neurological abilities (physical, cognitive or functional) during pregnancy or early postpartum (positive or negative).
3. Pregnancy-related maternal mortality in women with a past history of stroke.
4. Proportions and rates of adverse fetal and neonatal outcomes: congenital anomalies, preterm delivery, perinatal and intrapartum morbidity and mortality.

Implementation Resources and Knowledge Transfer Tools

For Professionals

- Acute stroke treatments and vascular risk reduction in non-pregnant women -

www.strokebestpractices.ca

- Secondary prevention and rehabilitation - www.strokebestpractices.ca, www.professional.heart.org; www.nice.org.uk
- The Society of Obstetricians and Gynecologists of Canada (SOGC)- www.sogc.org
- SOGC Hypertensive disorders of pregnancy guideline:
<https://sogc.org/wp-content/uploads/2014/05/gui307CPG1405Erev.pdf>
- Diabetes Canada. Clinical Practice Guidelines - <http://guidelines.diabetes.ca/>
- The American Congress of Obstetricians and Gynecologists - <https://www.acog.org/>
- Diabetes in pregnancy - <https://www.nice.org.uk/guidance/ng3>
- General teratogenicity of medications in pregnancy <https://toxnet.nlm.nih.gov/newtoxnet/dart.htm>; Reprotox – reprotox.org
- General teratogenicity of medications in breast feeding - Lactmed - <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>
- Prescribing medicine in pregnancy - <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>
- Motherisk - <http://www.motherisk.org/>

For Patients

- Public Health Canada – Guide to healthy pregnancy
<https://www.canada.ca/en/public-health/services/pregnancy/guide-healthy-pregnancy.html>
- Motherisk - <http://www.motherisk.org/>
- ACOG <https://www.acog.org/Patients>
- Stroke Best Practices patient and family resources including Your Stroke Journey and the Post Stroke checklist www.strokebestpractices.ca/resources

Summary of the Evidence

Secondary Prevention of Stroke in Pregnancy

Vascular Risk Reduction

This section is focused on issues of stroke prevention associated with women who have either had a stroke in the past and are now planning to become pregnant, or who have sustained a stroke during pregnancy, but who are beyond the hyperacute phase. Pregnancy is associated with an increased risk of stroke due to changes in hemodynamics and coagulation. The evidence associated with management for commonly used secondary prevention strategies, including antithrombotic medications (both antiplatelets and anticoagulants), blood pressure management, cholesterol management and diabetes care, is summarized.

Antithrombotics

While aspirin therapy has been shown to reduce the risk of future vascular events among high-risk individuals, its use for stroke prevention during pregnancy hasn't been specifically studied. Low-dose aspirin in pregnancy has been better studied for pregnancy-related conditions, such as recurrent pregnancy loss, clotting disorders or preeclampsia. The potential benefit of low-dose aspirin was

examined in high-risk women with a history of one to two previous pregnancy losses (EAGeR trial, Schisterman et al. 2014). The results of this trial indicated that among women attempting to become pregnant, there was no difference between groups (81 mg aspirin daily vs. placebo) in the number of pregnancy losses (13% vs. 12%, RR=1.06, 95% CI 0.77-1.46, p=0.78). In a meta-analysis including the results from 3 trials, low-dose aspirin was not associated with a reduction in the risk of preeclampsia, severe preeclampsia or pre-term birth (Roberge et al. 2016). More recently, the results from the ASPRE Trial (Rolnik et al. 2017) suggested that low-dose aspirin (150 mg per day), initiated from 11 to 14 weeks of gestation until 36 weeks of gestation, was associated with a reduced risk of delivery with preeclampsia before 37 weeks of gestation, compared with placebo (OR=0.38, 95% CI 0.20-0.74, p=0.04), without an increased risk of adverse events.

The safety of low-dose aspirin use in pregnancy is well-established. Nørgard et al. (2005) reported on the outcomes of 3,415 children with 4 congenital abnormalities, which were included in a national Congenital Abnormality Registry. Compared with a reference group that was composed of 19,428 children with other congenital abnormalities, exposure to aspirin was found not to significantly increase the odds of any of the 4 congenital abnormalities (including neural-tube defects, exomphalos/gastroschisis, cleft lip ± palate and posterior cleft palate). A meta-analysis including the results from 22 controlled studies yielded similar results (Kozer et al. 2002). Pooling the results from 8 and 6 studies, the overall odds of congenital malformations or cardiac malformations were not significantly higher in the aspirin-exposed group (OR=1.33, 95% CI 0.94-1.89, p=0.11 and OR=1.01, 95% CI 0.91-1.12, p=0.80, respectively). However, the incidence of gastroschisis was significantly higher in the aspirin-exposed group (OR=2.37, 95% CI 1.44-3.88, p=0.0006). There is a theoretical risk of Reye's syndrome associated with aspirin use during pregnancy, but no confirmed reports.

Certain conditions, including the presence of artificial heart valves, or conditions related to hypercoagulability require the continued need for thromboprophylaxis, or their initiation during pregnancy. The safest known anticoagulants associated with pregnancy are low molecular weight heparin (LHWH) 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. In a systematic review including 28 studies examining the use of oral anticoagulants among pregnant women with mechanical heart valves, Chan et al. (2000), reported that while their use was more effective for thromboembolic prophylaxis, the frequency of congenital abnormalities was 6.4%. In a more recent review, Xu et al. (2016) included the results of 51 studies (2,113 pregnancies) of women who received anticoagulation therapy related to management of mechanical heart valves. The frequency of congenital fetal anomalies associated with VKA use was 2.13% and 0.68% for low-dose VKA. There were no fetal abnormalities in the LMWH or UFH regimen groups. Maternal thromboembolic events (MTEs) and maternal deaths were lowest in the low-dose VKA subgroup (1.14% and 0.31%, respectively). The occurrences of MTEs and major antenatal hemorrhage events were highest in the UFH group (29.9% and 5.3%, respectively). Compared with low-dose VKA regimen, the incidences of spontaneous abortion and warfarin embryopathy were significantly higher compared with the high-dose VKA group.

Anticoagulants have also been examined for the prevention of pregnancy complications associated with thrombophilias, but were not found to be effective. Results from the Thrombophilia in Pregnancy Prophylaxis Study (TIPPS) 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 complications (Rodger et al. 2014). In this trial, 292

pregnant women were randomized to receive 5,000 IU dalteparin once daily from randomization to 20 weeks' gestation and then the same dose twice daily until 37 weeks of gestation vs. no dalteparin. The primary outcome, a composite including any of proximal deep vein thrombosis, pulmonary embolism, or sudden maternal death, severe or early onset preeclampsia, oliguria, pulmonary edema, coagulopathy, birth of small-for-gestational-age SGA infant, or pregnancy loss, was not significantly reduced in the dalteparin group (risk difference of -1.8%, 95% CI -10.6%-7.1%, $p=0.70$). There was also no significant difference among three treatment groups (LMWH, ASA or both combined) in the percentage of live births in the Low Molecular Weight Heparin and/or Aspirin in Prevention of Habitual Abortion (HABENOX) Trial (Visser et al. 2011).

Hypertension

Women with hypertensive-disorders of pregnancy are at greater risk for stroke, especially those with traditional risk factors (Leffert et al. 2015), therefore, treatment of moderate to severe hypertension is critical to achieving a favourable outcome. 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) study (Magee et al. 2015). Although the frequency of severe hypertension was significantly higher among women in the less-tight control group, there was no significant difference between groups in the frequency of any of individual components of the primary outcome (miscarriage, ectopic pregnancy, elective termination, perinatal death, still birth or high-level neonatal care). The frequency of serious maternal complications was not significantly lower among women in the tight-control group (2.0% vs. 3.7%, adj OR=1.74, 95% CI 0.79-3.84). There was a single stroke/TIA in the tight-control group vs. none in the less-tight control group. A Cochrane review (Abalos et al. 2013) including 48 RCTs (4,723 women) evaluated antihypertensive drug treatment for mild to moderate hypertension during pregnancy, defined as SBP 140-169 mmHg and DBP 90-109 mmHg. Treatment contrasts compared ≥ 1 antihypertensive drug vs. either placebo or no antihypertensive drug ($n=29$), and one antihypertensive drug vs. another ($n=22$), with a duration of treatment of at least 7 days. Compared with women who received no treatment, the risk of severe hypertension was significantly reduced in the active treatment group. While the risk of pre-eclampsia/proteinuria was not significantly reduced in the active treatment group (RR= 0.93, 95% CI 0.80-1.08, $p=0.34$), in the sub group examination of beta blockers, the risk of developing proteinuria/pre-eclampsia was significantly reduced (RR=0.73, 95% CI 0.57-0.94). The risks of fetal or neonatal death, pre-term birth or small-for-gestational age were not significantly reduced for women taking antihypertensive treatment. In terms of treatment for the prevention of hypertension during pregnancy, a Cochrane review including 13 RCTs in women without hypertension examined the effectiveness of calcium supplementation to reduce the risk of hypertensive disorders of pregnancy (Hofmeyr et al. 2014). Women were randomized to receive either high-dose (≥ 1 g/day) or low-dose (< 1 g/day) calcium supplement or placebo, until delivery. High-dose calcium supplementation was associated with significantly reduced risks of high blood pressure (RR= 0.65, 95% CI 0.53-0.81, $p<0.0001$) and pre-eclampsia (RR= 0.45, 95% CI 0.31-0.65, $p<0.0001$). Low-dose supplementation was also associated with a significantly reduced risk of high blood pressure (RR= 0.53, 95% CI 0.38-0.74, $p<0.0001$).

Statin Use

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 due to their potential teratogenicity. Several reports comparing the pregnancy outcomes of

women accidentally exposed to statins during pregnancy with those of women not exposed, have been published. The results are ambiguous, with some studies suggesting a significant increased risk of congenital abnormalities associated with statin use, particularly during the first trimester. In the largest cohort study (Bateman et al. 2015), statin use was associated with a significantly increased risk in the incidence of birth defects in unadjusted analysis (6.34% vs. 3.55%, 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 & Koren (2014) included the results from 6 controlled studies in a meta-analysis, and reported that the use of statins during pregnancy was not associated with an increased risk of birth defects (RR=1.15, 95% CI 0.75-1.76, p=0.52), although there was a significant increase in risk of miscarriage (RR=1.35, 95% CI 1.04-1.75). In a case-control study, Winterfeld et al. (2013) reported 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 frequency of pre-term delivery, miscarriage or fetal death was significantly higher in the statin-exposed group. Most recently, Karalis et al. (2016) 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.

Diabetes

Women with gestational diabetes are at increased risk of antenatal stroke (Scott et al. 2012, James et al. 2005), and may be at risk for future stroke up to 7 years after delivery (Goueslard et al. 2016). In studies that have examined the relationship between gestational diabetes and future risk of cardiovascular disease, including stroke, the strength of the relationship is attenuated after adjusting for age and subsequent diabetes or menopausal status (Archambault et al. 2014, Savitz et al. 2014, Shah et al. 2008). 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 (Ma et al. 2014). 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 (Thompson et al. 2013).

Management considerations for specific Stroke etiologies in Pregnancy

There is limited evidence concerning 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, treatment with either oral anticoagulants or antiplatelets (aspirin) appears to be common practice.

Outside of pregnancy, cervical artery dissections are usually treated with either a vitamin K antagonist or antiplatelet (aspirin) 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 may be used (Shanmugalingam et al. 2016, Baffour et al. 2012, Waidelich et al. 2008) without adverse effects on the mother or baby. The use of anticoagulants or antiplatelet drugs among a series of 62 women who presented with CVST during pregnancy was reported by Ciron et al. (2013). The preventative strategies used during subsequent pregnancies included no treatment (n=3), anticoagulation therapy during entire pregnancy, with and without aspirin; anticoagulation therapy during 3rd trimester of pregnancy, with and without aspirin; and anticoagulation therapy during entire pregnancy and puerperium. Demir et al. (2013) reporting on 19 cases of pregnancy-associated CVST, noted that all women were

treated with LWMH (enoxaparin) at a dose of 95 IU/kg twice daily for the duration of their pregnancy. Both aspirin and warfarin were used for secondary prevention in a study including 68 women who sustained CVST during pregnancy (Lamy et al. 2000).

[Prevention of Stroke During Pregnancy Evidence Tables and Reference List](#)

[Vascular Risk Reduction](#)

[Underlying Causes](#)

Appendix 1: Stroke and Pregnancy Consensus Statement

Stroke Prevention during Pregnancy Participants

NAME	PROFESSIONAL ROLE	LOCATION	COI CR COMPLETED Y/N
Rick Swartz Co-Chair	Medical Director North East GTA Regional Stroke Program; Director, University of Toronto Stroke Program Assistant Professor, Department of Medicine (Neurology), University of Toronto Rick.swartz@sunnybrook.ca	Ontario	No conflicts to declare
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Michael Hill	Stroke Neurologist, Director, Stroke Unit, Calgary Stroke Program, Alberta Health Services, Professor, Cumming School of Medicine, University of Calgary hillmd@ucalgary.ca	Alberta	<p>Potential Conflict: Unlikely for pregnancy consensus statement, Medtronic. Nature of relationship: Grant to the University of Calgary for the HERMES collaboration</p> <p>Potential Conflict: Unlikely for pregnancy consensus statement. Stryker Nature of relationship: Grant to the University of Calgary for the UNMASK EVT project.</p> <p>Potential Conflict: Unlikely for pregnancy consensus statement. Beohringer Ingelheim</p> <p>Nature of relationship: Grant to the University of Calgary for the QuICR program.</p> <p>Potential Conflict: Unlikely for pregnancy consensus statement. Bayer Nature of relationship: Grant to the University of Calgary for the QuICR program. Potential Conflict. Unlikely for pregnancy consensus statement</p>

Andra H. James	Professor of Obstetrics & Gynecology - Division of Maternal-Fetal Medicine Duke University andra.james@duke.edu	Durham, NC USA	No conflicts
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Sylvain Lanthier	Stroke Neurologist, Hôpital du Sacré-Coeur de Montréal; Associate Professor, Faculty of Medicine, Université de Montréal sylanthier@gmail.com	Quebec	<p>Conflict: Bayer Nature of relationship: Lecturer and Advisory Board member Bayer is commercializing a NOAC (rivaroxaban) and an antiplatelet agent (AAS), which can be used in stroke patients</p> <p>Conflict: Boehringer-Ingelheim Nature of relationship: Lecturer and Advisory Board member. Boehringer-Ingelheim is commercializing a NOAC (dabigatran) and an antiplatelet agent (Aggrenox), which can be used in stroke patients</p> <p>Conflict: Bristol-Myers-Squibb - Pfizer Alliance Nature of relationship: Lecturer and Advisory Board member. Bristol-Myers Squibb - Pfizer is commercializing a NOAC (apixaban) and Bristol-Myers-</p>

			<p>Quibbs is commercializing an antiplatelet drug (clopidogrel), which can be used in stroke patients</p> <p>Conflict : Servier Nature of Relationship: Servier is commercializing a NOAC (Edoxaban) and antihypertensive agents (perindopril and indapamide), which can be used in stroke patients.</p>
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