



CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Stroke in Pregnancy

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

Part Two: Acute Stroke Management during Pregnancy

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in collaboration with the Canadian Stroke Consortium*

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Canadian Stroke Best Practice Recommendations Acute Stroke Management during Pregnancy ~ Sixth Edition (July 2018)

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

Overview Stroke in Pregnancy Consensus Statements.

Introduction to stroke in pregnancy consensus statement series

Stroke, the sudden loss of neurological function due to neuronal injury of a vascular cause, is a leading cause of disability in adults. When stroke occurs during 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 et al, International Journal of Stroke, 2017], roughly 3 times higher than the risk in young adults [Singhal et al, Neurology, 2013]. Several aspects of pregnancy can increase the risk of stroke including: hypertensive disorders of pregnancy (gestational hypertension, preeclampsia with or without chronic hypertension, eclampsia, HELLP syndrome [hemolysis, elevated liver enzymes and low platelets syndrome]) and their complications: hematologic and prothrombotic changes, particularly in the third trimester and post-partum periods; hyperemesis resulting in hemoconcentration; and changes to cerebral vasculature (for example, reversible cerebral vasoconstriction syndrome (RCVS), as well as growth of existing arteriovenous malformations) [Leffert et al, Obstetrics and Gynecology, 2015]. Given this etiological variability, the practical limitations to clinical 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 either women with a past stroke wanting to get pregnant, or women who develop a stroke during or just 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 evidence on obstetrical and stroke management informed by 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. Most consensus statements are applicable to both ischemic and hemorrhagic stroke. In cases where the statements are applicable to one type or the other, these will be explicitly stated.

This set of consensus statements 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). A full list of existing best practice recommendations for stroke in women and obstetrical management 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 or in breast feeding (DART database: <https://toxnet.nlm.nih.gov/newtoxnet/dart.htm>, Lactmed: <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>, Motherisk website: www.motherisk.org/women/drugs.jsp; <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>).

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, consensus statements are based on the respective stroke and pregnancy literature. Unless otherwise explicitly stated, the statements reflect agreement within our interdisciplinary panel of experts where evidence is weak or not available.

Current state of research evidence: The majority of evidence and clinical trials in this area are derived from either general stroke studies or broad pregnancy cohorts. Pregnancy has been an exclusion criterion from virtually all acute stroke and prevention trials. As such, the existing data on stroke in pregnancy is largely found in 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., International Journal of Stroke, 2017]. There are case reports on administering intravenous alteplase for acute ischemic stroke during pregnancy but minimal evidence surrounding stroke 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 this consensus statement is health care professionals that manage stroke and/or pregnancy, including maternal-fetal medicine specialists, obstetricians, family physicians, obstetrical medicine specialists, obstetrical anesthetists, internists, neurologists and critical care specialists, emergency medicine, radiologists, nursing professionals from neurological, obstetrical and critical care backgrounds, and stroke rehabilitation specialists.

The following are important general considerations on the management of these complex and potentially high-risk scenarios that were shared among the contributors to this consensus statement. (ref: 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 consider 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 the 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, second, what needs to be modified due to pregnancy. Thus, these consensus statements will review common/important issues to consider that go beyond existing guidelines. It must be emphasized that 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 preferred** 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. Our consensus panel, with its broad composition of obstetric and medical caregivers, was intentionally recruited to reflect the interdisciplinary nature of care of women with stroke and pregnancy.
- 4) Decisions must be individualized and nuanced based on the specific situation.** There are multiple factors 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 in pregnancy; delivery and treatment; maternal age; other medical comorbidities;

access to subspecialty/interdisciplinary services; and the goals/preferences/philosophy of care of individual women.

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); see summary document by Swartz et al, International Journal of Stroke, 2017; and
- 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 includes 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 during 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/TIA WHO ARE PLANNING TO OR ARE ALREADY PREGNANT



FIGURE 2: WOMEN WHO EXPERIENCE A STROKE DURING PREGNANCY



Consensus Statement Methodology:

The *Stroke in Pregnancy consensus statements* were developed 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 an expert interprofessional writing group for the 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 in writing all actual and potential conflicts of interest. 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 debated the value of the evidence and through consensus develops a final set of proposed statements.

Recognizing that there is limited randomized controlled research evidence available for stroke in pregnancy to guide decision-making, this work was developed into consensus statements based on the existing literature and the collective expertise of the writing group and their colleagues on stroke management and obstetrical care. Therefore, evidence levels are not assigned to these statements. Using traditional guideline rating systems, most statements in this document would be considered as level 'C', reflecting the reliance on consensus and expert opinion. We acknowledge that 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 Management of Acute Stroke during Pregnancy during Pregnancy 2018 Module

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This consensus statement is published in the International Journal of Stroke and can be viewed through the following link:

<http://journals.sagepub.com/doi/full/10.1177/1747493018786617>

The companion consensus statement on the *Secondary Prevention of Stroke during Pregnancy* is also available in the International Journal of Stroke:

Swartz RH, Ladhani NNN, Foley N et al., Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy. Int J Stroke. 2017 Jan 1:1747493017743801. doi: 10.1177/1747493017743801. [Epub ahead of print]

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.

Introduction to Acute Stroke Management during Pregnancy Consensus Statement

This consensus statement is focused on the issues of acute stroke management for a woman who experiences an acute stroke during pregnancy or in the postpartum period (generally including the first 12 weeks post delivery). It starts with the onset of stroke symptoms, followed by assessment, diagnosis and clinical decision-making regarding emergent treatments for these women. Stroke is a time-sensitive emergency condition. Once the patient is medically stable, the acute goals shift to ongoing management of stroke sequelae and rehabilitation requirements that meet the goals of the patient (Swartz et al 2017).

Stroke in pregnancy may be due to ischemia, hemorrhage, or venous occlusion. In general, risk factors for any cause of stroke in pregnancy may be related to pre-existing maternal risk factors (e.g. systemic hypertension, pre-existing arterio-venous malformation); physiologic changes in pregnancy (e.g., increased blood volume, hypercoagulability of pregnancy); or disorders of pregnancy (e.g. eclampsia, HELLP syndrome) (Butalia 2018, Demel 2018). Stroke in pregnancy most often occurs close to the time of delivery (~ 40%) and in the early post-partum period (~50%), with a lower incidence (10%) earlier in pregnancy (Swartz et al 2017, Cordonnier 2017, Demel et al 2018).

When a stroke occurs in pregnancy, a standardized approach to coordinated emergent care is essential for investigation, diagnosis, and intervention planning with the goal of maximizing maternal and fetal wellbeing. In pregnancy, care requires careful consideration of the potential impacts of a stroke on the mother's health and survival, the fetus' health and survival, multiple competing etiologies, and the need for interdisciplinary perspectives, all while time is of the essence. Typical decision-making related to the non-pregnant patient must be nuanced by the timing of stroke within the pregnancy, stroke severity, expected maternal outcomes, and the known or theoretical impact of decisions and interventions on the fetus. Whenever possible, the same decisions for acute treatment and management outside of pregnancy should be considered for a woman who is pregnant. In these cases, maternal health is prioritized and delays or deferral of critical steps in diagnosis and life-saving care due to pregnancy should be minimized.

The current research evidence for the areas addressed in this consensus statement varies considerably. Due to ethical issues, low case incidence and other practical reasons, there is a lack of high quality randomized controlled research evidence to guide decision making for emergency stroke management in a pregnant women. Areas where evidence is stronger includes many of the acute treatments for stroke outside of pregnancy, treatment of eclampsia outside of stroke, use of antiplatelet and antithrombotics in pregnancy, observational data on the effects of alteplase on pregnancy, and management of hypertension in pregnancy.

With this in mind, this consensus statement summarizes key considerations and the best available evidence for assessment and management based on factors related to the stroke and to the pregnancy. Largely, this statement reflects expert interpretation of available information, professional and clinical experience, and is meant to provide guidance while acknowledging the gaps in research evidence. Clinically, decisions should be made on an individual case basis and informed by the factors noted above. These consensus statements do not take the place of integrated, interdisciplinary discussions related to specific cases, nor do they supersede clinician judgment and patient preferences. It should be acknowledged, however, that many decisions are time-sensitive and that rapid decision making is often necessary to prevent clinical morbidity and mortality.

The approach to secondary prevention and recurrent risk management of a woman with a prior history of stroke who then becomes pregnant is addressed in the first part of this Stroke in Pregnancy Consensus Statement series, and can be found at <http://journals.sagepub.com/doi/full/10.1177/1747493017743801>.

Refer to summary of the evidence for details information.

Acute Stroke Management during Pregnancy

1.0 Initial Emergency Management

- i. Where possible, rapid access to a stroke center should be sought for all pregnant women with suspected acute stroke. Guidelines for acute stroke management outside the context of pregnancy can be found at www.strokebestpractices.ca, and these guidelines should be followed except when necessary to modify and/or individualize for maternal considerations and fetal safety.
 - a. Acute stroke management decisions should be based on stroke type, severity of symptoms, medical condition of the patient and, when available, consideration of the personal values and wishes of the patient and family members or next-of-kin.
 - b. Institutions with both obstetrical and stroke specialization should have protocols in place for rapid assessment and access to appropriate pregnancy and stroke-related diagnostic tests and interventions.
 - c. Management of acute stroke in pregnant women should reflect collaboration between stroke teams and obstetrics teams. Rapid involvement of both teams is important to ensure the best possible outcomes for the pregnant woman and the fetus.
 - d. Institutions that lack either obstetrical care or neurologic specialists should predefine pathways and protocols for emergent collaborative management in person or through telemedicine modalities, and consider transfer to a centre with appropriate neurological and obstetrical expertise if needed.
 - e. Education and coordination of care between the emergency department, obstetrics, stroke and radiology services should be in place to ensure a stroke during pregnancy is considered an emergency and to facilitate access to rapid intervention. The risks of delayed stroke care should be understood at all institutions caring for pregnant women. As well, arrangements should be in place to ensure an acknowledgement of the urgency in the management of severe preeclampsia with neurologic features.
 - f. Protocols and educational efforts should be in place to help practitioners collaborate and manage pregnant or peri-partum patients with either neurologic signs and symptoms and/or in the setting of possible severe preeclampsia.
- ii. Protocols for rapid brain and vascular imaging will help identify an acute stroke and inform stroke etiology which may guide management (e.g. stroke secondary to preeclampsia vs. due to an arterial occlusion vs. other causes).
 - a. Focal neurologic deficits are usually not part of preeclampsia and represent an emergency mandating interdisciplinary care. Since stroke can be secondary to preeclampsia, the presence of focal neurological deficits should alert obstetrical practitioners to the possibility of acute stroke.
 - b. Protocols should be in place to acutely manage severe hypertension (ie: sBP \geq 160 mmHg or dBP \geq 110 mmHg). In the setting of preeclampsia or severe hypertension with neurological symptoms, the goal is to achieve a urgent and sustained reduction of systolic and diastolic blood pressure to less than 160/110 mmHg to reduce the risk of maternal stroke. (Butalia et al, 2018).
 - c. The impact of blood pressure reduction on placental perfusion should be considered. Obstetrics/Maternal Fetal Medicine practitioners should be involved in ongoing assessments of the maternal-placental-fetal unit and decision-making related to blood pressure lowering and the approach to fetal monitoring and surveillance where appropriate. Care must be taken to not cause hypotension or hypoperfusion. (Butalia 2018; Nerenberg 2018)

- d. Protocols for magnesium sulphate administration in cases of severe preeclampsia, to reduce the risk of eclampsia, should be in place to help standardize and facilitate rapid care in these cases.
 - e. A stroke secondary to preeclampsia meets a classification of severe preeclampsia and has implications for the timing of delivery.
 - f. Other neurovascular syndromes such as reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES), may be associated with severe preeclampsia. *Refer to Society of Obstetrics and Gynecology of Canada guidelines 2014 for criteria of preeclampsia.*
- iii. New severe headaches in pregnancy may represent preeclampsia, a complication of delivery (e.g. post-LP headaches), or a more benign primary headache syndrome (e.g. migraine). However, vascular events have increased frequency in pregnancy and postpartum and the differential diagnosis of severe headaches in pregnancy should be broad, and include reversible cerebral vasoconstriction syndrome (RCVS), posterior reversible encephalopathy syndrome (PRES), cerebral venous sinus thrombosis (CVST), arterial dissection, pituitary apoplexy/Sheehan's syndrome, or subarachnoid hemorrhage (SAH).
- a. All pregnant patients with severe headaches should be screened for intensity at onset (i.e., thunderclap vs. gradual onset), and associated features (e.g. stiff neck, decreased level of consciousness, nausea/vomiting, visual loss or focal neurologic deficits) and if these are identified, the patient must be further investigated with maternal brain imaging, and potentially lumbar puncture if imaging is inconclusive. *Refer to Diagnostic Imaging Section below for more information.* (MacGregor, 2014)
- iv. In pregnant women who present to the hospital with acute stroke, gestational age should be established where possible. This will allow for the provision of appropriate risk/benefit information on available management strategies and information on the potential impacts to both mother and fetus.
- v. A urine or serum beta-hCG blood test is a recommended laboratory investigation for women of reproductive age with acute stroke or TIA who could be pregnant. *Refer to CSBPR PreHospital and Emergency Stroke Care section 4 for full list of suggested initial laboratory tests.*
- a. Efforts should be made to first rapidly establish likelihood of pregnancy by patient history, known last menstrual period, and use of contraception.
 - b. For acute stroke patients, drawing blood work and awaiting test results for pregnancy should not delay imaging or decisions regarding treatment with acute stroke treatments.

Refer to CSBPR Acute Stroke Management module, Section 4 for initial assessment and management of acute stroke in the emergency department.

2.0 Diagnostic Imaging

Refer to CSBPR Acute Stroke Management module, Section 4 for additional information on initial imaging of a suspected stroke patient.

- i. Counselling of pregnant patients on imaging-associated risk for both mother and fetus may be considered and coordinated between clinical and imaging teams. (ACOG).

Note: Many clinicians remain overly concerned about the fetal risk associated with neuroimaging and ionizing radiation (CT). The fetal dose of radiation, and corresponding risk, associated with neuroimaging is extremely small (<http://www.cmaj.ca/content/cmaj/179/12/1293.full.pdf>)

- ii. Where an acute stroke is suspected, given the severe maternal risk caused by potential delay in diagnosis when compared to the minimal risk to the fetus with computed tomography (CT) imaging, it is acceptable to conduct a CT scan of the head without first establishing pregnancy.

- a. For severe disabling stroke, standard of care for the diagnosis of acute stroke includes immediate imaging of both the brain and cerebrovascular system, **within minutes** of hospital arrival.
 - *Note: in patients displaying mild or transient stroke symptoms who are not being considered for emergent stroke intervention, brain imaging and vessel imaging should still be undertaken in accordance with timelines as defined in CSBPR Acute Stroke Management Section 2 Table 2A.*
 - b. In most centres, this is achieved with immediate CT with CT Angiography (CTA) of the Head and Neck. In some cases, CT Perfusion (CTP) or MRI may also be used to identify potential candidates for intravenous thrombolysis with alteplase and/or acute endovascular thrombectomy. Both CT angiography and CT Perfusion use intravenous contrast and have higher doses of radiation than a CT Head.
 - c. In the time-sensitive emergency of severe disabling stroke, the health of the mother is paramount and CT with contrast is often the most accessible option to determine if patients are eligible for acute endovascular thrombectomy.
 - Where immediately available as part of a local acute stroke protocol, magnetic resonance imaging (MRI) of the brain with time-of-flight (non-contrast) imaging of the blood vessels may be used in place of CT/CTA to visualize the brain and vasculature (*Refer to iii below*).
 - In select cases (e.g. presence of a hyperdense middle cerebral artery on NCCT), CT angiography may be deferred in a pregnant women in favor of moving directly to digital subtraction angiography for potential treatment of a proximal occlusion appropriate to explain the symptoms.
 - d. Based on currently available evidence, the ionizing radiation associated with non-contrast CT Head in pregnant patients does not expose the fetus to the high levels of radiation associated with increased risks of abortion, malformation or other adverse pregnancy outcomes. (Tremblay Radiographics. 2012 May-Jun;32(3):897-911; ACOG committee opinion number 723. October 2017. Guidelines for Diagnostic Imaging during Pregnancy and Lactation. Obstetrics and Gynecology. 130:4).
 - A typical CT of the mother's head carries a fetal radiation dose exposure of 0.001 mGy. The typical occupational limit for fetal radiation is 5 mGy. Therefore, the fetal exposure from a maternal CT head is 5000 times less than the allowable occupational exposure and carries negligible risks for fetal malformation, abortion or other pregnancy complications when compared to the general risks of pregnancy (Health Protection Agency, Royal College of Radiologists 2009 at <https://www.aafp.org/afp/2010/0901/p488.html>; McCollough CH et al., RadioGraphics 2007;27(4):909-917; RSNA Guideline (Tirada et al, RadioGraphics Oct 2015)
 - A typical CT head exposes the fetus to a negligible amount of radiation. Owing to the distance of the mothers head away from the uterus there is a low amount of scatter and minimal fetal exposure.
 - If CT scanning is used, efforts to minimize radiation exposure such as shielding of the abdomen/pelvis, and minimizing extra scans are encouraged.
 - e. There is a lack of available evidence on any known harm identified in human or animal studies of exposure to CT contrast dye.
 - For breastfeeding, less than 1% of CT contrast dye is excreted in breast milk; of that, less than 1% is absorbed in infant GI tract. Continuation of breastfeeding after exposure to CT contrast dye is reasonable.
- iii. MRI, without gadolinium, does not expose the mother or fetus to ionizing radiation. When appropriate and available, and where the results can assist in clinical decision-making, MRI is

therefore a reasonable option in pregnancy. *However, in many centers MRI is not readily and rapidly available; in the setting of disabling acute stroke, the most available imaging modality should be utilized to avoid delaying treatment.*

- a. Time of flight imaging modalities (non-contrast MR angiography or venography) can often provide sufficient vascular information for emergency stroke decision-making in pregnancy and is preferred over contrast scanning.
 - b. Magnetic resonance imaging at 1.5 or 3.0 tesla (T) without gadolinium does not increase the risk of adverse fetal outcomes, whether exposure occurs in the first trimester (Ray, 2016) or later (ACOG 2017). MRI of the fetus has been shown to be safe in the second and third trimesters. [JOGC, The use of MRI in the obstetric patient 2014]
 - c. Gadolinium exposure in the first trimester may be associated with an increased risk of adverse outcomes (Ray 2016). Even outside of pregnancy, gadolinium is rarely needed in the setting of acute stroke diagnosis. Therefore, gadolinium is not recommended for stroke assessment in women with known pregnancy.
- iv. Institutional protocols on imaging in pregnancy and established methods for counselling pregnant women, or their next-of-kin, on risk/benefits and decision-making may be helpful to assist practitioners, especially in the time-sensitive setting of hyperacute stroke.
- a. When possible, pregnant women should be wedged during supine imaging to allow for left uterine displacement, as of 24 weeks or when symptoms (e.g., lightheadedness) necessitate.

3.0 Acute Ischemic Stroke Treatment: Intravenous Thrombolysis and Endovascular Treatment

Refer to CSBPR 2018 Acute Stroke Management module, Section 5 for administration of hyperacute stroke treatments for ischemic stroke. All consensus statements in this section are aligned to these recommendations.

3.1 Intravenous Alteplase

- i. Acute stroke treatment decisions should be based on severity of symptoms, medical condition of the patient and, when available, consideration of the personal values and wishes of the patient and her family or next-of-kin.
- ii. Treatment options for a pregnant woman with an acute stroke should promptly be considered in consultation with an interdisciplinary team with expertise in neurology, obstetrics and gynecology, maternal-fetal medicine, and interventional radiology where possible and available.
- iii. Acute intravenous thrombolysis with alteplase (tPA) has been shown to reduce morbidity in the non-pregnant population. There are a limited number of case reports published using alteplase during pregnancy. (Tate and Bushnell 2011, Ritchie, 2015, BMJ Case reports).
- iv. It is reasonable to consider giving IV alteplase to a pregnant patient with disabling ischemic stroke who meets existing criteria for thrombolysis. The risk-benefit considerations can be complex in the setting of pregnancy; thus, the decision should be undertaken in consultation with a physician with experience in acute stroke treatment either in person or through telestroke modalities. (Turrentine MA *et al* 1995; Murugappan A, *et al* 2006). *Refer to CSBPR Acute Stroke Management module, Section 5 for administration of hyperacute stroke treatments for ischemic stroke.*
 - a. While there are risks of hemorrhage (intracranial and otherwise) from intravenous alteplase, the decision to administer acute thrombolysis should be based on the maternal risks associated with the acute stroke.
 - b. Placental abruption can occur with or without alteplase, and it is not known whether alteplase increases the risk of abruption. Close monitoring and prompt recognition is

important.

- c. Alteplase is a large molecule (59,000 daltons) and does not cross the placenta (Gardman 2013). Therefore, alteplase is not expected or known to pose direct intracranial or systemic bleeding risks to the fetus.
- d. The safety and efficacy of intravenous alteplase in the early postpartum period (<14 days after delivery), especially related to risk of maternal postpartum hemorrhage, have not been well established.
 - Case reports suggest that bleeding risk may be increased after alteplase administration, and may be further increased if given following Cesarean delivery. Maternal risk of postpartum hemorrhage should be balanced with the risk of a thromboembolic event. (Akazawa M and Nishida M. 2017)
 - The literature to guide assessment of risks from epidural or spinal anaesthesia after alteplase administration is limited, but risks of bleeding complications may be increased.

Note: Intravenous alteplase is listed with the FDA as pregnancy category 'C' according to the package label, indicating "possible risk" only. There are limited case reports (approximately 30 at time of publication) of IV alteplase in pregnancy for stroke and other conditions, but only one case of fetal demise due to abruption. Other, more common causes of fetal demise in these case reports are related to spontaneous or planned abortion which may also be related to the underlying illness.

3.2 Endovascular Thrombectomy

- i. Pregnancy should not be considered a contraindication to angiography and endovascular thrombectomy for proximal large vessel occlusions causing acute disabling stroke. These cases should be treated according to existing guidelines (*refer to 2018 CSBPR Acute Stroke Management module, Section 5 on Endovascular Thrombectomy*).
 - a. Efforts to avoid or reduce the risk of fetal injury such as abdominal shielding and judicious use of x-ray exposures are reasonable.
 - b. It is not reasonable to delay or defer necessary maternal care for severe disabling stroke secondary to the pregnancy. The acknowledgement of possible fetal risks is appropriate: risks may include radiation and contrast exposure, infections, and arterial puncture complications that could result in both maternal and fetal compromise. However, given the very high morbidity and mortality associated with acute ischemic stroke due to large vessel occlusions, these risks are generally outweighed by the benefits of treatment.
- ii. For patients with large vessel occlusions eligible for and with rapid access to endovascular thrombectomy, proceeding directly to EVT without administering intravenous alteplase could be considered.

4.0 Management of Acute Hemorrhagic Stroke during Pregnancy (subarachnoid hemorrhage, intracerebral hemorrhage)

- i. Following imaging confirmation of a hemorrhagic stroke, vessel imaging (time-of-flight MR Angiography, CT Angiography, catheter angiography) is preferred to guide further management decisions except in presence of devastating hemorrhage with very poor prognosis. *The overall goal is to minimize the risk of rebleeding.*
- ii. Pregnancy should not be regarded as a contraindication for angiography and endovascular treatment of a vascular cause for hemorrhage.
 - a. Endovascular procedures are reasonable to consider where appropriate and expertise is

- available without delay.
- b. Efforts to avoid or reduce the risk of fetal injury are reasonable, such as abdominal shielding and judicious exposures.
 - c. It is not reasonable to delay or defer necessary maternal care secondary to the pregnancy. The acknowledgement of possible fetal risks is appropriate: risks may include radiation and contrast exposure, infections, and arterial puncture complications that could result in both maternal and fetal complications.
- iii. **For intracerebral hemorrhage**, priority should focus on managing blood pressure, and on identifying and correcting coagulopathies. Efforts to reduce blood pressure to an initial target of below 160/110 mmHg, followed by titration of medications to consistently lower than 140/90 mmHg. *Refer to SOGC Hypertensive Disorders of Pregnancy guidelines for additional management information. Refer to Hypertension Canada Guidelines for Management of Hypertension in Pregnancy 2018 for medication selection and dosing.*
- a. In pregnancy, first-line medications for blood pressure control are labetalol, methyldopa and long acting nifedipine. Selection of specific antihypertensive medication should consider side-effect profiles for the woman, fetus or neonate. *Refer to Hypertension Canada Guidelines for Management of Hypertension in Pregnancy 2018 for medication selection and dosing.*
 - b. 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.
- iv. For cases of **unruptured cerebral aneurysm**, an MRI without contrast (with time-of-flight MR angiography) is reasonable to define the lesion.
- a. If the patient's neurological and overall clinical status is stable, consider deferring treatment until the postpartum period.
- v. **Ruptured aneurysm** should be treated urgently based on accepted standards of care.
- a. The choice to coil or clip the rupture aneurysm should be based on the best available option for the patient, regardless of her pregnancy status.
 - b. Efforts to reduce hypertension to a target of less than 140/90 mmHg, if clinically indicated, are reasonable.
 - c. The treatment of ruptured aneurysms requires an urgent interdisciplinary approach including neurosurgeon and/or endovascular interventionalist, neurologist and physicians with expertise in maternal-fetal medicine whenever possible.
 - d. Maternal safety and outcomes should be considered throughout all discussions of management and may require treatment decisions that potentially compromise the pregnancy or the fetus.
 - e. If the timing corresponds with a viable gestational age, where neonatal outcomes are considered favourable, an interdisciplinary team including, for example, neurosurgery and/or neurointerventionalists, maternal-fetal medicine, obstetrics, neonatology, neurology, anaesthesia, and obstetrical medicine where available may consider the benefits of a concurrent Cesarean delivery.
 - f. If the timing corresponds to a pre-viable gestational age, treatment should proceed as it would outside of the context of pregnancy in order to maximize maternal safety and

outcomes.

- vi. **Arterio-venous malformation (AVM)** should be treated based on accepted standards of care.
 - a. Management of **unruptured AVM** (without bleeding) requires an individualized approach. Considerations for medical management (i.e., blood pressure control to primary prevention targets, and treatment of emerging neurological symptoms), with or without surgical intervention, should be guided based on patient factors and the features of the AVM.
 - b. The choice of treatment for **ruptured AVM** should be based on the best available treatment option(s) for the patient, regardless of her pregnancy status.
 - c. Low grade symptomatic AVM amenable to surgical resection should be resected (with or without pre-operative embolization) in the same time-frame as it would be for non-pregnant women, with every possible effort to reduce fetal risk of injury during endovascular or surgical treatment.
 - d. The treatment timing of high grade AVM, requiring multimodality approach (endovascular/surgery or endovascular/radiosurgery) should be made with an interdisciplinary team, including neurosurgery, neurology and expertise in maternal-fetal medicine.
 - e. Maternal safety and outcomes should be considered throughout all discussions of management and may require treatment decisions that potentially compromise the pregnancy or the fetus.
 - 1. If the timing corresponds with viable gestational age, where neonatal outcomes are considered favourable, an interdisciplinary team including, for example, neurosurgery and/or neurointerventionalists, maternal-fetal medicine, obstetrics, neonatology, neurology, anaesthesia, and obstetrical medicine, where available, may consider the benefits of a concurrent Cesarean delivery.
 - 2. If the timing corresponds to a pre-viable gestational age, treatment should proceed as it would outside of the context of pregnancy in order to maximize maternal safety and outcomes.
 - 3. The acknowledgement of possible fetal risks is appropriate: risks include radiation and contrast exposure, as well as blood loss that could result in both maternal and fetal compromise.

5.0 Anesthetic Management in the setting of Acute Stroke during Pregnancy

- i. The anesthetic care can be tailored to the needs of the pregnant woman and her fetus for the specific clinical scenario, which may include, but is not limited to, concurrent Cesarean delivery and resection of a vascular lesion, or the peripartum management of a woman with an intrapartum stroke.
- ii. Optimal care can be facilitated by:
 - a. Close communication between the anaesthesia, neurology, maternal-fetal medicine, and obstetrics teams including discussion of optimal blood pressure parameters and intracranial pressure related to stroke management.
 - b. Consideration of potential anaesthesia-related benefits (e.g., neuraxial anaesthesia for labor to allow for an assisted delivery, thereby reducing Valsalva efforts, and decreasing circulating catecholamines).
 - c. Identification of stroke or treatment-related contraindications to neuraxial anaesthesia (e.g. the presence of mass effect and/or increased intracranial pressure or active

anticoagulation) Leffert, L. Butwick et al, 2017

- d. Interdisciplinary team goals for maternal blood pressure and intracranial pressure that can be incorporated into overall anesthetic plans.
- e. In the setting of stroke, alternatives to general anaesthesia should be considered to avoid sedation if possible.
- f. Where general anesthetic cannot be avoided, hemodynamic changes inherent to intubation and extubation should be taken into consideration.

6.0 Early Post-Stroke Management in a Pregnant Woman

- i. The risk of stroke is highest in the postpartum period (usually considered the first 12 weeks following delivery). Women at risk should be alerted to signs of stroke occurrence or recurrence, and the need to immediately contact emergency health services or notify healthcare professionals if already in hospital.
 - a. Women who are post-partum and with previous history of stroke require education and monitoring, especially in the first 6 weeks after delivery when recurrent stroke risk rates have been reported to be highest.
- ii. Etiology of stroke should be established to guide early recurrent/secondary stroke prevention management decisions.
- iii. Rehabilitation should start early during acute care following current standards of rehabilitation for stroke patients (Hebert et al 2016). Rehabilitation goals and plans may need to be modified based on patient factors and in consultation with obstetrics, neurology and physical medicine and rehabilitation.
- iv. Secondary prevention decisions including antithrombotic use, blood pressure management and other risk reduction can be complex in pregnancy. *Refer to to Secondary Prevention of Stroke during Pregnancy module for detailed information on stroke prevention management and pharmacotherapy.* [Swartz et al, International Journal of Stroke, 2017]

7.0 Post-Stroke Antenatal Obstetric Considerations for Women with a Stroke in Pregnancy

- i. Where possible, obstetric care should be managed with access to, or in collaboration with, stroke care. Risk of recurrence and practicality of care should be considered when decisions regarding place of care are made.
- ii. Antenatal fetal surveillance regimens should follow local protocols established for all pregnant women. Increased fetal surveillance in pregnancy may be required in women with a history of stroke given the likelihood of underlying vascular disease and other comorbidities that may increase the risk of growth restriction or compromised fetal wellbeing.
 - a. Placental studies in the second trimester and serial growth ultrasound studies in the third trimester should be considered.
- iii. Timing of delivery decisions should take into consideration the general condition of the mother, gestational age, fetal status, and neonatal viability.
- iv. Antenatal anesthesia consultation, and the creation of an anesthetic plan of care, is warranted to avoid any uncertainty regarding neuraxial anesthesia in labour.
- v. Wherever possible, decisions should be made with an interdisciplinary team (e.g. maternal-fetal medicine, obstetrics, neonatology, and neurology) and should consider the preferences of the patient and family.
- vi. Postpartum depression and depression after a stroke both have high incidence. Consider

screening pregnant patients who experience a stroke for signs and symptoms of depression, especially those patients with previous history of mood disorders.

- a. As with all pregnancies, screening for depression in the postpartum period should be considered for all patients who have experienced a stroke in pregnancy.
- b. Pathways for referral to appropriate care providers for management of depression may be established.

Refer to to Secondary Prevention of Stroke during Pregnancy module for detailed information on stroke prevention management and pharmacotherapy.

8.0 Intrapartum Considerations

8.1 Mode of Delivery

- i. A history of stroke is not an absolute contraindication to vaginal birth. An understanding of the etiology of the previous stroke and the risks posed by Valsalva efforts is necessary.
 - a. Shared decision making with the obstetrics team, neurology team, and consideration of patient preference is required when deciding preferred mode of delivery.
 - b. Cesarean delivery may be necessary for standard obstetric indications (e.g., maternal history, fetal presentation, fetal status).
- ii. In situations where some amount of increased intracranial pressure can be tolerated (i.e., low risks of Valsalva), vaginal births without assisted delivery may be considered.
- iii. Women in whom increased intracranial pressure should be avoided may be candidates for a vaginal birth with an assisted second stage of labour.
 - a. Expert opinion suggests that an assisted second stage of labour, with vacuum or forceps, may reduce Valsalva efforts in women where increased effort or intracranial pressure may be contraindicated.
 - b. Neuraxial anaesthesia can facilitate a forceps or vacuum-assisted 2nd stage vaginal delivery to avoid Valsalva in the absence of contraindications such as increased intracranial pressure/mass effect. Typically, a concentrated dose of local anesthetic is administered through the epidural catheter at the end of the first stage of labor to diminish the sensation of needing to push and any pain associated with the subsequent forceps or vacuum procedure.
- iv. In women at very high risk for intracranial bleeding (acute ischemic stroke with hemorrhagic transformation, an unsecured aneurysm, arterio-venous malformation, or a CVST with elevated intracranial pressure), Cesarean delivery may be considered, acknowledging that there are inherent maternal risks with Cesarean delivery as well.
- v. Decisions regarding mode of delivery should also take into consideration patient preferences and should be made on an individualized basis.

8.2 Intrapartum Fetal Surveillance

- i. Intrapartum fetal surveillance should follow local protocols and guidelines and be based on gestational age and the preferences for fetal intervention by the patient.
- ii. A history of stroke, and any corresponding vascular abnormalities, places the woman in a risk category that would render continuous fetal monitoring appropriate.
- iii. In cases where delivery is anticipated in preterm or extremely preterm gestations, potentially due to stroke-related complications, maternal-fetal medicine and neonatal counselling is necessary to

guide plans for intervention and to implement a plan for fetal monitoring and neonatal management, where appropriate.

9.0 Post-Partum Management

Refer to the Secondary Prevention of Stroke Best Practice Recommendations and the Secondary Prevention of Stroke during Pregnancy consensus statement for detailed information on recurrent stroke risk reduction and post stroke and post-partum management of stroke risk factors (www.strokebestpractices.ca).

- i. Post-partum pain management should be administered according to local protocols; where possible, avoidance of sedatives is preferred after stroke. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) are avoided in the setting of severe preeclampsia and HELLP syndrome. (SOGC 2014)
- ii. For women who sustain a stroke in pregnancy, long term postpartum follow up arrangements with primary care practitioners should be made including management for secondary prevention of stroke recurrence. [Swartz et al, International Journal of Stroke, 2017].
- iii. Pre-pregnancy counseling should be offered to all women prior to a future pregnancy.

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 clinical 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), along with 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 shortly 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.
- Protocols to ensure rapid transfer of patients to a centre with acute stroke and obstetrical services available

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 and morbidity (venous thromboembolism, disability, postpartum hypertension) 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.

5. Number of women who experience an acute stroke during pregnancy or within 6 weeks post-partum.
 - a. Percentage of strokes occurring per stage of pregnancy
 - b. Gestational age at time of stroke
 - c. Stroke severity
6. Number and percentage of women who experience an acute ischemic stroke during pregnancy who are administered intravenous alteplase.
7. Number and percentage of women who experience an acute ischemic stroke during pregnancy who undergo acute endovascular thrombectomy.
8. Number and percentage of women who experience an acute hemorrhagic stroke during pregnancy who undergo aneurysm clipping or coiling.
9. Adjusted mortality percentage and rates for women who experience an acute stroke during pregnancy or within 6 weeks post-partum (stratified by type of stroke, stage of pregnancy, and include all-cause, within 7 days and 30 days of stroke onset).
10. Fetal mortality and rates of fetal complications (analyzed separately) in cases where maternal stroke occurs during pregnancy.
11. Development of data collection surveillance 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.
12. 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.

Implementation Resources and Knowledge Transfer Tools

For Professionals

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

Initial Emergency Management

While stroke during pregnancy presents several additional challenges, initial emergency investigations and treatment of stroke during pregnancy, or within the 6 weeks thereafter, are similar to treatment in the non-pregnancy state. Rapid presentation to a stroke centre for timely assessment and management and avoidance of any delays in diagnosis and treatments represent the best opportunity for a good outcome for both mother and baby. Hypertension and headaches, which are both common during pregnancy, may also indicate more serious conditions. In particular, rapid identification and treatment of hypertension in a woman presenting with neurological symptoms with a history of preeclampsia is of critical importance, given its strong association with stroke. Crovetto et al. (2013) reported that 33% of women who suffered a stroke had concomitant pre-eclampsia-eclampsia. Hypertensive treatment should be initiated to achieve and maintain a systolic blood pressure of <160 mm Hg (Magee et al. 2014). It should be noted that women with severe preeclampsia and eclampsia do not always present with elevations in diastolic blood pressure (Martin et al. 2005). While common during pregnancy, and often benign, headaches may also occur as the result of more serious neurological conditions. Their history and characteristics should be queried. Thunderclap headache may be a symptom of subarachnoid hemorrhage, while a headache with atypical aura, may result from a stroke or TIA. Headache will accompany ischemic stroke in 17% to 34% of cases and are usually nonspecific in quality, and of moderate intensity. (MacGregor et al. 2014).

Diagnostic Imaging

Many pregnant women and their care providers are concerned about the fetal risk associated with neuroimaging and ionizing radiation. These fears need to be balanced with the potential negative consequences to the mother caused by possible delays in diagnosis of stroke. Therefore, neuroimaging with computed tomography (CT) scan without first confirming a pregnancy is deemed an acceptable practice. In fact, the fetal radiation dose associated with head or neck CT is considered very low (0.001 to 0.01 mGy) (AROC 2017). Most estimates suggest that fetal radiation doses of <50 mGY have negligible risk of fetal malformation, abortions or other pregnancy complications when compared to the general risk of pregnancy (McCullough et al. 2007; Tirada et al. 2015). Magnetic resonance imaging (MRI) is also considered safe at 3.0 tesla or less, (Patenaude et al. 2014) and is not associated with any long-term negative risks. Specifically, no significant increases in neonatal deaths (RR: 1.68; 95% CI: 0.97 to 2.90); congenital abnormalities (HR: 1.16; 95% CI: 0.96 to 1.40); and hearing (HR: 1.50; 95% CI: 0.94 to 2.40) or vision loss (HR: 1.04; 95% CI: 0.75 to 9.6) were documented in a review of over one million births after 20 weeks of gestations in Ontario (Canada) (Ray et al. 2016). However, the use of gadolinium contrast should be avoided unless no alternative exists, or the potential benefits outweigh the risks (ACOG Committee Opinion No. 723, 2017, Patenaude et al. 2014, Thomsen et al. 2013, Brass et al. 2007). Ray et al. (2016) found that compared to no MRI exposure, exposure to gadolinium MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions (adjusted HR, 1.36; 95% CI, 1.09 to 1.69). The risk of stillbirth/neonatal death was significantly higher in the gadolinium MRI group (17.6 vs. 6.9/1,000 person-years, adjusted RR=3.70,

95% CI 1.55-8.85).

When diagnostic imaging is required during the post-partum period, less than 1% of contrast dye is excreted into breastmilk, and the dose of iodinated contrast agent in the breastmilk absorbed by infants is 0.5% of the maternal dose (Trembley et al. 2012; ACOG 2017). Thus, the continuation of breastfeeding after exposure to CT contrast does not pose any risk to the infant. However, discarding breastmilk for 24 hours after injection may be recommended to mothers who express concern (Trembley et al. 2012).

Intravenous Thrombolysis and Endovascular Treatment

The use of alteplase is considered a relative exclusion criterion during pregnancy, largely because of the absence of clinical trial data to support its safety for mother and fetus. However, accumulating evidence from case series and case reports suggest there may be an indication for its use during pregnancy in women who would otherwise be eligible for treatment if they were not pregnant. Reports on the pregnancy outcomes of women who received t-PA during the first trimester (Elford et al 2002, Li et al. 2012, Tversky et al. 2016), the second trimester (Wiese et al. 2006, Tassi et al. 2013, Landis et al. 2017), the third trimester of pregnancy (Johnson et al. 2005, Mantoan Ritter et al. 2014, Ritchie et al. 2015) and in the early post-partum period (DeKoninck et al. 2008, Ronning et al. 2010) have been published. Both the intravenous (Wiese et al. 2006, Ritchie et al. 2015, Tversky et al. 2016, Landis et al. 2017) and intra-arterial (Ronning et al. 2010) routes have been used. The initial stroke severity of women who were treated with t-PA in these reports ranged from minor (NIHSS 3, Landis et al. 2017) to moderately-severe (NIHSS 22, Ritchie et al. 2015). Generally, the mother experienced marked improvement or complete recovery following treatment and delivered a healthy baby. The incidence of symptomatic intracerebral hemorrhage (sICH) was low, and comparable to non-pregnant patients. The use of thrombolysis in pregnancy has also been reported in other thromboembolic conditions, such as pulmonary embolism, thrombosis of cardiac valve prosthesis, myocardial infarction, and venous embolism. Overall, the reported complication rates were similar to those of nonpregnant patients; in addition to low rates of maternal mortality, fetal loss, and preterm delivery (Gartman 2013, Leonhardt et al. 2006).

Treatment with thrombolytic agents in the early post-partum period (≤ 48 hours) is more controversial, given the increased risk of bleeding. Akazawa & Nishida (2017) documented 13 cases where thrombolytics were given to women during this period. The most common indication for treatment was pulmonary embolus, with a single case of ischemic stroke. Blood transfusions were required in all but one case. Subsequent laparotomy to control bleeding was required in five cases, all following cesarean delivery.

To date, there are 4 reported cases of women treated with mechanical thrombectomy during pregnancy, all of which occurred during the third trimester (Bhogal et al. 2017, Aaron et al. 2016). Second-generation devices were used in all cases. The baseline NIHSS scores were ≥ 15 in 3 cases and could not be assessed in the fourth. The maternal outcomes were good in 3 cases (mRS scores 0-1), with greater residual disability in the fourth case (mRS 2). The pregnancy was ongoing in one published report (Bhogal et al. 2017), while 3 women delivered healthy babies. There were no cases of symptomatic intracerebral hemorrhages (ICH).

Acute Hemorrhagic Stroke Treatment

Pregnancy and the postpartum period are associated with an increased risk of cerebral hemorrhage. Although estimates vary, and reports are limited, the incidence of intracerebral hemorrhage (ICH) per 100,000 pregnancies have been reported to range between 4.6 (Simolke et al. 1991) and 25.4 (Liang et al. 2006). Relative to women who are not pregnant, the risk of ICH appears to be highest after delivery (RR=28.3, 95% CI 13.0–61.4), compared with the risk during pregnancy (RR=2.5, 95% CI 1.0–6.4) (Kittner et al. 1996). The most common risk factors for ICH during pregnancy include increased age, cardiac disease, hypertension, eclampsia/pre-eclampsia and smoking (Bateman et al. 2006). The most common

etiologies for ICH include vascular anomalies and AVMs (Liang et al. 2006). While in-hospital mortality for pregnancy-associated ICH has been reported to be as high as 20.3% (Bateman et al. 2006), a more recent report suggests that pregnant women had significantly lower risk in-hospital mortality compared with non-pregnant women (10.1% vs. 19.6%, $p=0.002$, $OR=0.57$, 95% CI 0.34-0.94) (Leffert et al. 2015). There are several factors that may increase the risk of arteriovenous malformations (AVM) or aneurysmal rupture during pregnancy, including increased blood volume and cardiac output, and structural changes in the vascular wall. However, whether pregnancy truly increases the risk of rupture is a topic of ongoing debate. Liu et al. (2014) reported the odds for rupture of AVM during pregnancy and puerperium were significantly lower compared with the control period ($OR=0.71$, 95% CI 0.61–0.82). The study included 979 women referred to a single teaching hospital between 1960 and 2010 with an AVM confirmed by angiography or histology. A total of 393 patients had an AVM rupture during 16,367 patient-years of follow-up. Similarly, Bateman et al. (2006) reported no significant increased risk of intracranial hemorrhage from cerebrovascular malformations during pregnancy (0.50 vs. 0.33 per 100,000 person-years for pregnant versus nonpregnant patients, respectively). In contrast, Porras et al. (2017) reported a significant increase in the risk of AVM hemorrhage during pregnancy or the puerperium among 191 women with AVM who became pregnant before obliteration. The annual rate of hemorrhage was 5.7% in pregnant women compared with 1.3% in non-pregnant women ($RR=4.43$, 95% CI 1.98–8.65, $p<0.001$).

Anesthetic Management for Acute Stroke Treatment during Pregnancy

Women who are pregnant and experience a stroke may require anesthesia associated with procedures related to delivery, the need for emergency neurosurgery, or both. Whether cesarean section or neurosurgical intervention should be prioritized or performed simultaneously is an important issue, as is the decision to use general or spinal and epidural anesthesia when a cesarean section is indicated. In addition to significant maternal physiological changes, the potential for fetal harm should be considered during anesthetic management. The goals of anesthesia should include both fetal and maternal well-being. Where a Caesarean delivery is necessary, the type of anesthesia used should be made in consideration of the mother's overall risk to risk. Yoshitani et al. (2013) suggested hyperventilation to reduce intracranial pressure (ICP) should be kept in the range of 25-30 mm Hg since the normal range of $PaCO_2$ during pregnancy decreased to 30-32 mm Hg due to increased ventilation and progesterone. Moreover, excessive deep anesthesia should be avoided to prevent hemodynamic instability. Fluid management; however, has yielded conflicting recommendations, with some studies suggesting that when mannitol is used to control ICP, there is an associated risk of fetal dehydration; while, individual case reports have shown that 0.2 to 0.5 mg/kg of mannitol has no significant effect on fetal fluid balance (Yoshitani et al. 2013). Special considerations are required for women with preeclampsia. A review of over 300,000 women who underwent a Caesarean delivery found that general anesthesia for Caesarean delivery was associated with increased risk of stroke when compared to neuraxial anesthesia in preeclamptic women (aHR: 2.38; 95% CI: 1.33 to 4.28) (Huang et al. 2010). Regardless of the preeclamptic status of the mother, maintenance of adequate oxygenation and hemodynamic stability are important for both maternal and fetal safety (Yoshitani et al. 2013; Ohno et al. 2013).

Post-Stroke Antenatal Obstetric Considerations for Women with a Stroke in Pregnancy

For a woman who experiences a stroke during pregnancy, the risk of a recurrent event is increased. A prospective cohort study following women after an incident ischemic stroke or TIA in the Netherlands noted the risk of a recurrent vascular event was 35.2% (95% CI: 21.3 to 49.9%) among primi/multiparous women, and 19.6% among nulliparous women during average follow-up of 9.5 years (van Alebeek et al. 2018). Therefore, once the etiology of the stroke is determined, secondary prevention strategies such as antithrombotics and/or antihypertensives should be initiated, as appropriate.

The same approaches to rehabilitation in the non-pregnant condition can be applied to a woman who is pregnant, with modifications as needed. The elements associated with improved functional outcome following a moderately-disabling stroke include adequate intensity of therapy, task-oriented training, and

excellent team coordination. Early, intensive rehabilitation has been shown to improve functional recovery. It is important that the rehabilitation therapies be tailored to the tasks that need to be retrained and developed, as well as to the activities of the patient's choice and to their social roles. The need for a highly-coordinated, specialized team, who meet regularly to discuss the rehabilitation goals and progress, is also vital.

Women who experience a stroke during pregnancy may experience a higher incidence of miscarriage and fetal death. A prospective cohort study following women after an incident ischemic stroke or TIA in the Netherlands noted that compared to women in the general population, miscarriage and fetal death occurred at a significantly higher rate at 35.2% vs. 13.5%, and 6.2% vs. 0.9%, respectively (van Alebeek et al. 2018). Therefore, pregnant women with a history of stroke, or with neurological symptoms consistent with stroke should be managed, and plan to deliver at a facility equipped to treat patients with stroke; where full-time neurosurgeons and/or diagnostic imaging tools suitable for the diagnosis of stroke are readily accessible (Yoshimatsu et al. 2014).

Intrapartum Consideration

While a women's risk for stroke increases during pregnancy, her odds of a cerebrovascular event following a Caesarean delivery are significantly higher compared to a vaginal delivery. In a review of 1.4 million deliveries across 900 hospitals in the USA, Laska et al. (2000) estimated there were 13.1 cases of peripartum stroke per 100,000 deliveries and 116 cases of peripartum intracranial venous thrombosis (IVT) per 100,000 deliveries. Caesarean delivery was noted to be a significant predictor of stroke (aOR: 3.56; 95% CI: 2.62 to 4.83) in both the peripartum and postpartum period compared to vaginal births. Vaginal delivery may be considered providing in an otherwise uncomplicated case of stroke during pregnancy, provided there is no diagnosis of aneurysm, or there has been no neurosurgical intervention within the week before delivery. However, Caesarean delivery should be considered before neurological intervention, and should be performed before craniotomy after 28 to 32 weeks of gestation as interventions during neurosurgery (e.g. management of hypotension, use of osmotic diuretics, and mechanical hyperventilation) are risks for the fetus (Yoshitani et al. 2013). Regardless of mode of delivery, choice of anesthesia should be made in consultation with other health providers, considering the wishes of the mother. In addition, fetal monitoring should continue according to local guidelines, and to the reassurance of the pregnant patients.

Post-Partum Management

The postpartum period is associated with an increased risk of both ischemic stroke and cerebral hemorrhage (Tate & Bushnell 2011). While the median time of stroke onset post partum has been reported to be 8 days (range 3 to 35 days) (Wiltin et al. 2000), the risk appears greatest up to 6 weeks after delivery. Kamel et al. (2014) reported the odds of stroke was highest during the first 6 weeks postpartum compared with the period 6 weeks plus one year postpartum (OR=8.5, 95% CI 4.9-14.8). The risk of stroke is especially increased in the 12-month post-partum period for women with a history of eclampsia-eclampsia (hemorrhagic stroke OR=19.9, 95% CI: 7.75 to 51.11; ischemic stroke OR=4.35, 95% CI 0.58–32.92) (Tang et al. 2009). Although rare, post-partum stroke carries a mortality rate of 2%-10% (Yoshida et al. 2017, Miller et al. 2016, Leffert et al. 2015). Women with pregnancy-related strokes are less likely to have vascular risk factors such as hyperlipidemia or history of thromboembolism, and more likely to have cerebral venous thromboses (Miller et al. 2016). Nevertheless, secondary stroke prevention strategies should be included during the postpartum period, as appropriate, to reduce the risk of thrombotic complications. Moreover, both clinicians and women should be aware that the risk of blood clots extend beyond the traditional post-partum period of 6 weeks. For high-risk women, extending the recommendation duration of prophylactic anticoagulant therapy may be worth examining. Finally, all women should be educated of the warning signs of potential post-partum stroke, such as difficulty breathing, sudden and severe headaches, or sudden change in consciousness, speech, balance strength or sensation to one side of the body.

Acute Stroke Management during Pregnancy Evidence Tables and Reference List

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Appendix 1: Stroke and Pregnancy Consensus Statement
Acute Stroke Management during Pregnancy Participants

WRITING GROUP

NAME	PROFESSIONAL ROLE	LOCATION	COI CR COMPLETED
Noor Niyar N. Ladhani Co-Chair	MD, MPH, FRCSC Associate Scientist, Evaluative Clinical Sciences, Women & Babies Research Program, Sunnybrook Research Institute,; Maternal-Fetal Medicine Specialist, Sunnybrook Health Sciences Centre Assistant Professor, Department of Obstetrics and Gynecology, University of Toronto	Ontario	No conflicts to declare
Rick Swartz Co-Chair	MD, PhD Medical Director North East GTA Regional Stroke Program; Director, University of Toronto Stroke Program Assistant Professor, Department of Medicine (Neurology) Sunnybrook Health Sciences Centre	Ontario	No conflicts to declare
Patrice Lindsay Senior and Corresponding Author	RN, PhD Director, Stroke; Heart and Stroke Foundation	Ontario	No conflicts
Norine Foley	Adjunct Professor, Western University, London, Ontario and Partner, workHORSE Consulting Group, London, Ontario	Ontario	No conflicts to declare
Kara Nerenberg	MD, MSc, FRCPC Assistant Professor, University of Calgary Departments of Medicine, Obstetrics & Gynecology and Community Health Sciences	Alberta	No conflicts to declare
Eric E. Smith	MD, MPH, FRCPC, FAHA Associate Professor, Dept of Clinical Neurosciences, Radiology and Community Health Sciences Member, Hotchkiss Brain Institute, Katthy Taylor Chair in Vascular Dementia, University of Calgary	Alberta	No conflicts to declare
Gordon Gubitza	Stroke Neurologist, Director, Neurovascular Clinic, Queen Elizabeth II Health Sciences Centre, Assistant Professor of Medicine (Neurology), Dalhousie University	Nova Scotia	Bayer – advisory board, anticoagulants for stroke prevention; Boehringer Ingelheim – advisory

			board, anticoagulants for stroke prevention
Dariusz Dowlatshahi	MD, PhD Associate Professor, University of Ottawa, Scientist, Ottawa Hospital Research Institute, Stroke Neurologist, The Ottawa Hospital	Ontario	Potential Conflict: Bayer Nature of relationship: Honoraria Potential Conflict: BMS/Pfizer Nature of relationship: Honoraria
Jayson Potts	Clinical Assistant Professor, Department of Medicine, University of British Columbia; Obstetrics Internal Medicine - BC Women's Hospital	British Columbia	No conflicts to declare
Joel G. Ray	MD, MSc, FRCPC Professor of Medicine and Obstetrics and Gynaecology; St. Michael's Hospital; University of Toronto	Ontario	No conflicts to declare
Barrett, Jon (Yosef)	MBBch, MD, FRCOG, FRCSC Fred Waks Research Chair, Professor, University of Toronto; Research Program Director, Women and Babies Program; Division Chief of Maternal Fetal Medicine, Sunnybrook Health Sciences Centre; Co-Director, Clinical Trials Services (CTS)/The Centre for Mother, Infant and Child Research (CMICR)	Ontario	No conflicts to declare
Cheryl Bushnell	MD, MHS Professor of <u>Neurology</u> ; Director, Wake Forest Baptist Stroke Center; Wake Forest Baptist Health	Winston Salem, NC USA	No conflicts to declare
Simerpreet Bal	MD, DM, FRCPC Clinical Assistant Professor, Department of Clinical Neurosciences, University of Calgary	Alberta	No conflicts to declare
Wee-Shian Chan	MD, MSc, FRCPC FACP Head, Department of Medicine; Lead, Obstetric Medicine, Internal Medicine Group; and Clinician, Obstetric General Internal Medicine for BC Women's Hospital	British Columbia	No conflicts to declare
Radha Chari	MD, FRCS-C Professor and Chair, Department of Obstetrics and Gynecology, University of Alberta Zone Clinical Department Head, Women's Health, Alberta Health Services	Alberta	No conflicts to declare
Meryem El	Research Assistant in Vascular Neurology - Centre hospitalier de l'Université de Montréal	Quebec	No conflicts to declare

Amrani	(CHUM)		
Shital Gandhi	MD, FRCPC, MPH Associate Professor, University of Toronto Department of Medicine, Division of General Internal Medicine; Fellowship Director, Obstetric Medicine	Ontario	No conflicts to declare
Michael Hill	MD, MSc, FRCPC Stroke Neurologist, Director, Stroke Unit, Calgary Stroke Program, Alberta Health Services, Professor, Cumming School of Medicine, University of Calgary	Alberta	<p>Potential Conflict: Unlikely for pregnancy consensus statement, Medtronic.</p> <p>Nature of relationship: Grant to the University of Calgary for the HERMES collaboration</p> <p>Potential Conflict: Unlikely for pregnancy consensus statement. Stryker</p> <p>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</p> <p>Nature of relationship: Grant to the University of Calgary for the QuICR program. Potential Conflict. Unlikely for pregnancy consensus statement</p>
Andra H. James	MD, MPH Professor of Obstetrics & Gynecology - Division of Maternal-Fetal Medicine; Consulting Professor of Medicine – Division of Hematology, Duke University	Durham, NC USA	No conflicts

Thomas Jeerakathil	BSc, MD, MSc, FRCPC Professor, Neurology/Medicine; University of Alberta	Alberta	No conflicts
Albert Jin	PhD, MD, FRCPC Associate Professor, Division of Neurology, Department of Medicine, Queen's University, Medical Director, Stroke Network of Southeastern Ontario	Ontario	No conflicts
Adam Kirton	MD, MSc, PRCPC Professor, Pediatrics and Clinical Neurosciences, Faculty of Medicine, University of Calgary, Alberta Children's Hospital Research Institute (ACHRI), Director, Calgary Pediatric Stroke Program	Alberta	No conflicts
Sylvain Lanthier	MD, OD, CSPQ Stroke Neurologist, Hôpital du Sacré-Coeur de Montréal; Associate Professor, CME Director, Department of Neurosciences, Université de Montréal	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-Quibbs is commercializing an antiplatelet drug (clopidogrel), which can</p>

			be used in stroke patients Conflict : Servier Nature of Relationship: Servier is commercializing a NOAC (Edoxaban) and antihypertensive agents (perindopril and indapamide), which can be used in stroke patients.
Andrea Lausman	Assistant Professor, Maternal-Fetal Medicine, Obstetrics and Gynaecology University of Toronto and Maternal-Fetal Medicine Specialist, and Head of Labour and Delivery, St. Michael's Hospital	Ontario	Potential Conflict: Ferring Pharmaceuticals Nature of relationship: Speaker
Lisa Rae Leffert	Chief of Obstetric Anesthesia, Vice-Chair Faculty Development; Massachusetts General Hospital	Boston, MA USA	No conflicts to declare
Jennifer Mandzia	MD, PhD, FRCPC Stroke Neurologist, CNS Department Co-Medical Director, Southwestern Ontario Stroke Network; Assistant Professor, Western University	Ontario	No conflicts to declare
Bijoy Menon	MD, DM, MSc Assistant Professor, Department of Clinical Neurosciences, Radiology and Community Health Sciences, Cumming School of Medicine, University of Calgary; Stroke Neurologist, Calgary Stroke Program	Alberta	Potential Conflict: QuikFlo Health Inc. Nature of relationship: Stock Ownership
Aleksandra Pikula	MD Assistant Professor, Department of Medicine (Neurology), University of Toronto; Clinic Lead, Stroke in Young Adults/Women; Co-Director, Combined CNS Vasculitis Program MSH/TWH; Director, Stroke Neurology Research Program, UHN/Toronto Western Hospital	Ontario	No conflicts to declare
Alexandre Poppe	MD, CM, FRCPC Clinical Associate Professor, Department of Neurosciences, Université de Montréal ; Stroke Neurologist/Stroke Fellowship Program Director, CHUM	Quebec	No conflicts to declare
Gustavo Saposnik	Director, Stroke Research Unit, Mobility Program, St. Michael's Hospital, Scientist in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Associate Professor, Medicine, St. Michael's	Ontario	Conflict: HSF Career Award Conflict Limited: AHA

	Hospital, University of Toronto		Associate Editor
Mike Sharma	Associate Professor , Division of Neurology, Department of Medicine, McMaster University	Ontario	<p>Potential Conflict: Bristol Myers Squibb Nature of relationship: Speaker</p> <p>Potential Conflict: Bayer Nature of relationship: Speaker</p> <p>Potential Conflict: Boehringer Ingelheim Nature of relationship: Speaker</p> <p>Potential Conflict: AZ Therapies Nature of relationship: Consulting Fees</p> <p>Potential Conflict: Daiichi Sankyo Nature of relationship: Consultant</p>
Bhogal, K. Sanjit	PhD Associate Member, workHORSE Consulting Group, London, Ontario	Ontario	<p>Potential Conflict: WorkHORSE Consulting Group Nature of relationship: I am paid to prepare the evidence tables</p>
Elisabeth Smitko	Senior Specialist, Knowledge translation and Best Practices, Heart and Stroke Foundation	Ontario	No conflicts

Appendix 2: Stroke in Pregnancy Consensus Statement

External Reviewers

NAME	PROFESSIONAL ROLE	LOCATION	COI
Blacquiere, Dylan	MD, MSc, FRCPC Stroke Neurologist, Horizon Health Network; Assistant Professor of Medicine, Dalhousie University (New Brunswick); Assistant Professor of Medicine, Memorial University of Newfoundland; Saint John Regional Hospital	New Brunswick	Bayer – funded research; Pfizer – speaker, Advisory Board; Servier – funded research; Boehringer-Ingelheim – funded research
Buck, Brian	Stroke Neurologist Associate Professor, Division of Neurology, Department of Medicine, University of Alberta	Alberta	Bayer – Advisory Board; Medtronic – funded research
Gallagher, Patricia	RN MN Unit Manager 4BS and NICU, Horizon Health NB	NB	No conflicts
Gioia, Laura	MD FRCPC MSc Assistant Professor of Neurology, University of Montreal, Stroke Neurologist, CHUM-Centre, Hospitalier de l'Université de Montreal	Quebec	Bayer Inc. – speaker, Honoraria Advisory Board; BMS Pfizer - Honoraria Advisory Board
Helm-Neima, Trish	BScPT Provincial Stroke Coordinator, Health PEI	PEI	No conflicts
Kapral, Moira	Professor, Department of Medicine, Staff Physician, University Health Network/Mount Sinai Hospital	Ontario	No conflicts to declare
Lavoie, Pascale	MScM MD, FRCPS Neurosurgeon, Assistant Professor, Department of Surgery, Laval University	Quebec	No conflicts to declare
Mackey, Ariane	MD, FRCP(C) neurologue Professeur agrégé de médecine, Université Laval, Québec, Directrice du Centre de Recherche en Neurovasculaire CHU de Québec/ Hôpital de l'Enfant-Jésus	Quebec	No conflicts to declare
Miller, Eliza	MD Assistant Professor of Neurology, Division of Stroke and Cerebrovascular Disease; Columbia University Vagelos College of Physicians and Surgeons	New York	No conflicts

NAME	PROFESSIONAL ROLE	LOCATION	COI
Pandian, Jeyaraj	MD, DM, FRACP, FRCP, FESO Professor and Head, Department of Neurology; Christian Medical College	India	No conflicts
Sacco, Simona	MD Associate Professor of Neurology; Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila	Italy	No conflicts
Sauvé, Nadine	MD, FRCPC Internist, Specialized in Obstetric Medicine, Centre intégré universitaire de santé et des services sociaux de l'Estrie-CHUS; Professor of Medicine, University of Sherbrooke	Quebec	No conflicts
Towfighi, Amytis	Director, Neurological Services, Innovation, and Quality, Los Angeles County Department of Health Services; Associate Professor of Neurology (Clinical Scholar), Keck School of Medicine, University of Southern California; Chair, Department of Neurology and Director, Chronic Care Management; Rancho Los Amigos National Rehabilitation Center	California	No conflicts
Vaida, Sonia	Professor of Anesthesiology, Obstetrics and Gynecology; Vice Chair, Research Director, Obstetric Anesthesia, Department of Anesthesiology, Penn State College of Medicine	Pennsylvania	No conflicts
Vasantha, M.V. Padma	MD, DM, FAMS, FNASc, FIAN Professor, Head Unit II Neurology; All Indian Institute of Medical Sciences	India	No conflicts