Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Stroke & Pregnancy Consensus Statement

Secondary Stroke Prevention

Part Three: Underlying Causes

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Canadian Stroke Best Practice Recommendations
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Published Guidelines

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5.2.1 Dissection	
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	**Arterial Dissection Recommendations** 1. For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy for at least 3 to 6 months is reasonable (Class IIa; Level of Evidence B). 2. The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection (Class IIb; Level of Evidence B). 3. For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite medical therapy, endovascular therapy (stenting) may be considered (Class IIb; Level of Evidence C). 4. Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite medical therapy and also fail or are not candidates for endovascular therapy may be considered for surgical treatment (Class IIb; Level of Evidence C) No recs specific to stroke during pregnancy or the puerperium
5.2.2 Venous Sinus Thrombosis	
Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, Maino A, Martinelli I, Masuhr F, de Sousa DA. **European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis–Endorsed by the European Academy of Neurology.** ***Eur Stroke J* 2017; 2(3) 195–221**	PICO question 1: In pregnant and puerperal women with CVT, does the use of anticoagulant therapy improve the outcome without causing major risks to mother and foetus? Recommendation: We suggest therapy with subcutaneous LMWH in pregnant and puerperal patients with acute CVT. Quality of evidence: low Strength of recommendation: weak
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA	No recs that are specific to stroke during pregnancy or the puerperium Long-term anticoagulation might be reasonable for patients with spontaneous cerebral venous sinus thrombosis or a recurrent ischemic stroke of undefined origin and an inherited thrombophilia (Class IIb; Level of Evidence C).

Guideline	Recommendations
Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association. ***Stroke 2014*;45:2160-2236.**	
Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Piña IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. **Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2014;45:•••–•••.**	1. In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed (Class I; Level of Evidence C). 2. Screening for potential prothrombotic conditions that may predispose a person to CVT (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment (Class I; Level of Evidence C). 3. Testing for prothrombotic conditions, including protein C, protein S, or antithrombin deficiency; antiphospholipid syndrome; prothrombin G20210A mutation; and factor V Leiden can be beneficial for the management of patients with CVT. Testing for protein C, protein S, and antithrombin deficiency is generally indicated 2 to 4 weeks after completion of anticoagulation. There is a very limited value of testing in the acute setting or in patients taking warfarin (Class IIa; Level of Evidence B). 4. In patients with provoked CVT (associated with a transient risk factor), vitamin K antagonists may be continued for 3 to 6 months, with a target international normalized ratio of 2.0 to 3.0 (Class IIb; Level of Evidence C). 5. In patients with unprovoked CVT, vitamin K antagonists may be continued for 6 to 12 months, with a target international normalized ratio of 2.0 to 3.0 (Class IIb; Level of Evidence C). 6. For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia (ie, homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered, with a target international normalized ratio of 2.0 to 3.0 (Class IIb; Level of Evidence C). 7. For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target international normalized ratio of 2.0 to 3.0 should be continued for ≥6 weeks postpartum (for a total minimum duration of therapy of 6 months) (Class I; Level of Evidence C). 8. It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Further investigations regarding the underlying cause and a formal consultation with a hematologist or maternal fetal medicine specialist are reasonable (Class IIa; Level of Evidence B).

Guideline	Recommendations
	9. It is reasonable to treat acute CVT during pregnancy with full-dose LMWH rather than unfractionated heparin (Class IIa; Level of Evidence C). 10. For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is reasonable (Class IIa; Level of Evidence C).
Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY; on behalf of the American Heart Association Stroke Council and the Council on Epidemiology and Prevention. **Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/ American Stroke Association.** ***Stroke 2011*; 42(4):1158–1192.**	*"Because there are no secondary prevention trials of anticoagulation in adults with CVT, evaluation of prevention strategies can only be performed with observational studies that evaluate recurrence of CVT or VTE with or without ongoing anticoagulation."*
5.2.3 Cardioembolic Source	
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	General guidelines related to the detection and management of cardioembolic source, but none that are specific to pregnancy or the puerperium.

Guideline	Recommendations
January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. **2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.** ***J Am Coll Cardiol 2014*;64:2246–80.**	General guidelines related to the detection and management of atrial fibrillation, but none that are specific to pregnancy or the puerperium.
Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. **2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** ***J Am Coll Cardiol* 2014;63:2438–88.** **(selected)**	**CLASS I** 1. Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis. (Level of Evidence: B) 2. Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimesters. (Level of Evidence: B) 3. Discontinuation of warfarin with initiation of intravenous UFH (with an activated partial thromboplastin time [aPTT] >2 times control) is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis. (Level of Evidence: C) 4. Low-dose aspirin (75 mg to 100 mg) once per day is recommended for pregnant patients in the second and third trimesters with either a mechanical prosthesis or bioprosthesis. (Level of Evidence: C) **CLASS IIa** 1. Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg per day or less after full discussion with the patient about risks and benefits. (Level of Evidence: B) 2. Dose-adjusted LMWH at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg per day to achieve a therapeutic INR. (Level of Evidence: B) 3. Dose-adjusted continuous intravenous UFH (with an aPTT at least 2 times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is greater than 5 mg per day to achieve a therapeutic INR. (Level of Evidence: B)

Guideline	Recommendations
Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, American College of Chest Physicians. **VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.** ***Chest* 2012; 141(2 Suppl):e691S–e736S**	General guidelines-no recs that are stroke specific
5.2.4 Cryptogenic Stroke	
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	No recs that are specific to stroke during pregnancy or the puerperium

Cervical Artery Dissection

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Shanmugalingam et al. 2016 **Australia** **Case series**	4 cases of vertebral artery dissection (VAD), all associated with hypertensive disorders of pregnancy. Two occurred antenatally and 2 postpartum	NA	NA	Case 1: 32-year-old primigravid, presented at 38+2 weeks in early labor with 4-day history of neck pain. She underwent cesarean section. There was ongoing neck pain. VAD was confirmed and she was started on aspirin 100 mg daily. A repeat brain and neck CTA at 3 months postpartum showed resolution of the dissection and aspirin was ceased. Case 2: 33-year old primigravid with VAD at 36 weeks gestation admitted for management of pre-eclampsia. On day 4 of admission, she developed right-sided neck pain and VAD was confirmed. She underwent an emergency caesarean section and was initiated on heparin post-operatively, and then transitioned to aspirin, which was ceased at 3 months postpartum. Case 3: 30-year-old G2P2, presented 6 days postpartum with a 2-day history of headache, chest tightness, shortness of breath and bilateral pedal oedema. 2 days into admission, she complained of right-sided neck pain. VAD was confirmed. She was initiated on LMWH. At 6-weeks, MRA demonstrated resolution of the thrombus and MWH was replaced by aspirin for an additional 6 weeks to complete a total of 3 months of therapy. Case 4: A 30-year-old G2P2 presented at 6 days postpartum with left sided neck pain appearing within 24 h of discharge. A CTA demonstrated a left VAD, and she was initiated on aspirin 100 mg daily. There was resolution of the thrombus at 3 months after which aspirin was ceased.
Baffour et al. 2012 **USA**	34-year old woman with bilateral cervical internal carotid artery dissection and cerebral infarctions, who presented to the ER day 14 postpartum	NA	NA	There was no history of HTN. Blood pressures were 140 –186 mm Hg systolic and 56 –70 mm Hg diastolic during the

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Case Report				peripartum period. The patient was anticoagulated with i.v. unfractionated heparin and warfarin. At the 6-month follow-up, the patient's neurologic deficits had resolved and she was switched from warfarin to aspirin. "*The appropriate treatment for extracranial cervical artery dissection has not been established by prospective randomized trials. Current American Stroke Association guidelines for nonpregnant patients state that it is reasonable to treat patients with ischemic stroke or transient ischemic attack and extracranial cervical arterial dissection with antithrombotics for at least 3 to 6 months. The relative efficacy of anticoagulation compared with antiplatelet therapy to prevent neurologic morbidity has not been established. There are no evidence based-data to guide management of labor and delivery in pregnant patients with cervical artery dissection, and treatment must be individualized*."
Waidelich et al. 2008 **USA** **Case report**	36-year old woman with no history of vascular disease developed a pounding headache on day 4 postpartum, which did not resolve with rest and medication. On day 8, an MRI was performed and a with left internal carotid artery dissection detected. Neurological exam was normal. On day 10, there was an episode of right-hand numbness and right-sided visual blurring, which resolved spontaneously after 5 min. She was discharged home on day 11.	NA	NA	LMWH and warfarin were initiated day 9. The patient continued anticoagulation with warfarin for 8 months until the dissection resolved, at which time long-term aspirin therapy was prescribed instead.
Abisaab et al. 2004	35-year old woman presented to the ER 9 days following the birth of her third child, by cesarean section, with	NA	NA	Anticoagulation with intravenous heparin and oral warfarin were initiated.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **Case report**	bilateral headache that had persisted for 3 days. Her pregnancy was uncomplicated. Recorded BPs during labour were 50-60/100-1110 mm Hg with no protein in the urine. The patient was treated with sumatriptan and released. She returned the next day when symptoms persisted. An MRI was initially misread as negative. A bilateral carotid artery dissection was eventually identified.			The patient was discharged home with no stroke-related deficits and received Coumadin for 6 months. MRI without contrast obtained 7 months after initial ED presentation showed interval improvement in bilateral carotid artery dissection, with recanalization of the vessels. Warfarin was discontinued and low-dose (81 mg) aspirin was started.

Cerebral Venous Sinus Thrombosis

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ciron et al. 2013 **France** **Retrospective study**	62 women, aged 15-40 years, admitted to one of 4 hospitals from 1995-2012 with a diagnosis of cerebral venous thrombosis (CVT)	Telephone interviews with patients were conducted in 2012 to determine obstetrical outcomes, the course of pregnancies, complications, the use of anticoagulants or antiplatelet drugs and birth parameters. Medical records could also be accessed for pregnancy outcomes if patients agreed.	CVT recurrence	Mean age at the time of stroke was 27 years. 61 women had a good outcome at the end of the acute phase (mRS 0 or 1). One patients died in the acute phase and one died during follow-up. The follow-up group was composed of 60 patients. Mean duration of follow-up was 89.5 months (median 76 months). There were 45 pregnancies among 25 women resulting in 24 completed pregnancies, 20 terminated pregnancies (5 voluntary abortions, 14 spontaneous miscarriages, 1 medical abortion) and one pregnancy in progress during the study. One patient suffered a recurrence of CVT during the first trimester. Preventative strategies used during subsequent pregnancies included: No treatment (n=3) Anticoagulation therapy during entire pregnancy,

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				with aspirin until week 34 (n=1) and without aspirin (n=3) Anticoagulation therapy during 3rd trimester of pregnancy, with aspirin until week 34 (n=7) and without aspirin (n=8) Anticoagulation therapy during entire pregnancy and puerperium (n=2)
Demir et al. 2013 **Case series** **Turkey**	19 pregnant women with CVST, confirmed by MRI, followed in a single neurology unit from 2002-2009. Mean age was 27.5 years.	Data were obtained through chart review	Clinical management, maternal and infant outcomes	Symptom onset occurred during the third trimester in most cases (n=13). Severe headache, vomiting, papilledema and seizures were the most common presenting symptoms. All patients were treated with LWMH (enoxaparin) at a dose of 95 IU/kg twice daily. All but one infants were delivered by caesarean section, with 5 women undergoing the procedure under general anesthetic. There were no fetal deaths during pregnancy and no deaths within 3 months of delivery. There were no reported neonatal hemorrhages or congenital abnormalities.
Mehraein et al. 2003 **Germany** **Retrospective study**	39 consecutive women treated for cerebral venous and sinus thrombosis (CVST) from 1976-1996, who of childbearing age when the stroke occurred. 4 women presented with pregnancy-related CVST. Mean age was 25.6 years.	Data were obtained by phone interviews using a standardised questionnaire.	Recurrence of CVST, incidence of other venous thrombotic events, incidence of other pregnancy related complications, and the use and duration of anticoagulation with heparin.	Mean duration of follow-up was 10 years. There were no recurrences of CVST. There were 22 subsequent pregnancies among 14 women. Low dose heparin was given subcutaneously during five pregnancies: in two cases during the entire pregnancy and puerperium, in one case from the 16th week of gestation and in two cases from the 36th gestation week until two to eight weeks after delivery. No anticoagulation was given during the remaining 14 pregnancies and puerperium periods.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lamy et al. 2000 **France** **Retrospective study**	441 women aged 15-40 years with a previous admission to one of 9 hospitals for ischemic stroke (n=373) or cerebral venous thrombosis (CVT, n=68). Mean age at the time of stroke was 31.4 years.	Patients were asked to participate in a semi-structured telephone interview and queried with respect to recurrent vascular events and current antithrombotic treatment, reproductive history (number of live births, induced or spontaneous abortions, mode of delivery, fetal outcome, and contraceptive use), modification of the family, and limitations in professional functioning.	Stroke recurrence	Mean duration of follow-up was 5 years. Among the 68 initial CVT, 9 occurred during the puerperium, two of which were associated with hematologic disease. Antithrombotic treatment was advocated for 54 patients. Regimens included antiplatelets (n = 8) and warfarin (n=46). Information was missing for 14 patients. At the time of the interview, 23 (34%) women were taking antiplatelet drugs (n = 16), warfarin (n = 6), or both (n = 1). There were 26 subsequent pregnancies among women who had experienced an initial CVT. Antithrombotic treatments during the first trimester included: No treatment n=18, antiplatelet n=4, heparin n=1, both n=0, unknown n=3 Antithrombotic treatments during the second trimester included: No treatment n=14, antiplatelet n=6, heparin n=3, both n=0, unknown n=3 Antithrombotic treatments during the third trimester included: No treatment n=14, antiplatelet n=5, heparin n=3, both n=1, unknown n=3 Antithrombotic treatments during the puerperium included: No treatment n=7, antiplatelet n=0, heparin n=13, both n=3, unknown n=3
Nagaraja et al. 1999 **India**	150 women with puerperal CVT occurring within one month of delivery or abortion.	The outcomes of 73 women who received 2,500 U of heparin, 3x/day initiated within 24 hours of hospitalization and	Maternal deaths	There were 8 deaths in the heparin group and 19 deaths in the control group

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Case-control study		continued for 30 days post partum day or until symptomatic relief were compared with those of 77 women who did not receive heparin (control group).		

Cardioembolic Source

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Goland & Ikayam 2012 **USA** **Narrative review**	Management of various cardiac conditions with anticoagulation during pregnancy was reviewed, including prosthetic heart valves, mitral stenosis, and atrial fibrillation, peripartum cardiomyopathy and pre-existent dilated cardiomyopathy	NA	NA	*"The incidence of AF during pregnancy is low and is usually secondary to congenital or rheumatic valvular disease, hypertrophic cardiomyopathy, thyroid disease, or a pre-excitation syndrome."* ***"In pregnant women who develop AF, the role of anticoagulation to prevent systemic arterial embolism has not been systematically studied in pregnant patients with nonvalvular AF."*** *"Anticoagulation therapy is not required in pregnant women with a short lone episode of AF. If spontaneous conversion to normal sinus rhythm does not occur, cardioversion should be considered within 48 hours of the onset of AF to avoid the need for anticoagulation."* *"Patients with chronic AF, who are considered to be at increased risk for embolic stroke, should be anticoagulated during pregnancy."*
DiCarlo-Meacham & Dahlke 2011 **USA** **Case report**	Woman presenting at 22 weeks gestation with a 1-hour history of left-sided chest pain, palpitations, and the sensation that she could not catch her breath. There were no prior similar episodes and no personal or family history of heart disease. Blood pressure	NA	NA	Electrocardiograph confirmed AF with a rapid ventricular response. She received an initial bolus of 5 mg intravenous metoprolol over 2 minutes, with 3 repeated doses every 5 minutes to achieve a target heart rate of <100 bpm.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
	was normal, and the heart rate ranged from 160 to 180 bpm during her initial evaluation.			Tachycardia (160-180 bpm) resumed with new-onset hypotension that required synchronized cardioversion. She was sedated and had 1 electric shock administered in biphasic mode at 100 J and immediately converted to a normal sinus rhythm (88 bpm). She remained in sinus rhythm for the next 24 hours and was discharged on metoprolol (25 mg orally b.i.d). She had no symptoms or relapse of AF and delivered vaginally at 27 weeks gestation.

Reference List

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Baffour FI, Kirchoff-Torres KF, Einstein FH, Karakash S, Miller TS. Bilateral internal carotid artery dissection in the postpartum period. *Obstet Gynecol* 2012;119(2 Pt 2):489-492.

Ciron J, Godeneche G, Vandamme X et al. Obstetrical outcome of young women with a past history of cerebral venous thrombosis. *Cerebrovasc Dis* 2013;36(1):55-61.

Demir CF, Inci MF, O¨ zkan F, et al. Clinical and radiological management and outcome of pregnancies complicated by cerebral venous thrombosis: a review of 19 cases. *J Stroke Cerebrovasc Dis* 2013; 22: 1252–1257.

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Lamy C, Hamon JB, Coste J, Mas JL. Ischemic stroke in young women: risk of recurrence during subsequent pregnancies. French Study Group on Stroke in Pregnancy. *Neurol* 2000;55(2):269-274.

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Mehraein S, Ortwein H, Busch M, Weih M, Einhaupl K, Masuhr F. Risk of recurrence of cerebral venous and sinus thrombosis during subsequent pregnancy and puerperium. *J Neurol Neurosurg Psychiatry* 2003;74(6):814-816.

Shanmugalingam R, Reza Pour N, Chuah SC, Vo TM, Beran R, Hennessy A, et al. Vertebral artery dissection in hypertensive disorders of pregnancy: a case series and literature review. *BMC Pregnancy and Childbirth* 2016;16(1):164.

Waidelich JM, Bullough AS, Mhyre JM. Internal carotid artery dissection: an unusual cause of postpartum headache. *Int J Obstet Anesth* 2008;17(1):61-65.