REVIEW

Stroke in Pregnancy and Post-partum – Latest Developments in Conduct and Management

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Abstract

Stroke in pregnancy and post-partum is a rare occurrence, yet with increasing incidence in the last decades. With a crude incidence rate of up to 30 per 100,000 pregnancies, high morbidity and mortality, research is needed to standardize prevention, diagnosis, treatment, and management of these cases.

We present stroke particularities during pregnancy and puerperium and the current information from published articles regarding the latest developments in medical conduct.

The mechanisms of stroke in pregnancy differ from those in the general population and are mostly in relation to the physiological changes during pregnancy. Stroke during pregnancy and post-partum is a rare but debilitating occurrence; with limited evidence and no clear guidelines, the treatment should be always individualized, and the risk-benefit ratio should always be considered.

Keywords: stroke, pregnancy, vascular disease, puerperium

Rezumat

Accidentul vascular cerebral în sarcină și post-partum este un eveniment rar, dar cu o incidență în creștere în ultimele decenii. Având o incidența de până la 30 la 100.000 de sarcini, cu morbiditate și mortalitate ridicate, accidentul vascular in sarcină este o patologie ce impune cunoașterea celor mai noi studii privind prevenirea, diagnosticarea, tratamentul și gestionarea acestor cazuri.

Prezentăm particularitățile accidentului vascular cerebral în timpul sarcinii și lăuziei și informațiile actuale cu privire la cele mai recente evoluții în conduita medicală.

Mecanismele accidentului vascular cerebral în sarcină diferă de cele din populația generală și sunt în mare parte în relație cu modificările fiziologice din timpul sarcinii. Accidentul vascular cerebral în timpul sarcinii și postpartum este un eveniment rar, dar cu impact major; cu dovezi limitate și fără protocoale clare, tratamentul trebuie întotdeauna individualizat, iar raportul risc-beneficiu ar trebui să fie întotdeauna luat în considerare.

Keywords: accident vascular cerebral, sarcină, patologie vasculară, lăuzie

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INTRODUCTION

Although considered a rare complication, stroke incidence in pregnancy and puerperium is rising, and strategies for management and treatment are challenging. Approximation of stroke incidence in pregnancy varies widely, mostly because of a lack of trials, studies developed with small cohorts, and debatable conduct in those existing. In Canada incidence rose from 10.8 per 100,000 deliveries in 2003/2004 to 16.6 per 100,000 in 2015/2016[1], in U.K. the risk was estimated at only 1.5 cases per 100,000 deliveries from 2007 to 2010[2], in Taiwan the risk was approximated at 21.3 per 100,000 from 1992 to 2004[3], and in the U.S. the stroke rate was estimated at 22 per 100,000 deliveries in 2005/2006, rising in comparison to 15 per 100,000 deliveries in 1994/1995[4]. A Japanese analysis on the incidence of strokes associated with pregnancy estimated the incidence at 10.2 per 100,000 deliveries[5].

American Heart Association (AHA) / American Stroke Association (ASA) appreciates the risk of stroke at 34 per 100,000 deliveries[6]. In a review that pooled data from 85,055,405 pregnancies, the crude rate of pregnancy-related stroke was 30.0 per 100,000 pregnancies[7]. The incidence of ischemic stroke in the general young non-pregnant population is approximately 10 per 100,000[8].

The mechanisms of stroke in pregnancy differ from those in the general population and are mostly in relation to the physiological changes during pregnancy. Because of higher metabolic demand, the circulatory system adapts by increasing plasma volume, with insufficient red blood cell increase that leads to subsequent anemia (due to hemodilution). Adaptations reflect in up to a 50% increase in cardiac output, stroke volume, and heart rate.

A constant in pregnancy is the rise of hormonal levels. Due to the increased production of clotting factors promoted by estrogen, the venous dilation promoted by progesterone, and the compression effect of the gravid uterus on the inferior vena cava, stroke is more common in the third trimester of pregnancy. As for puerperium strokes, the decrease in progesterone and the consecutive venous constriction could predispose to ischemia. A 9-fold increased risk of stroke during the peripartum period and a 3-fold increased risk during early postpartum have been reported[9].

Vascular changes have also been considered as promoters of cerebrovascular disorders during pregnancy, but the relationship is uncertain. One study found that pregnancy might be associated with adjustments of arterial composition, contractility, and endothelial reactivity - increase of contractile force, decrease of peripheral vascular stiffness and alteration in cerebral vessel response to certain relaxant substances[10]. Thus, pregnancy exposes vulnerable vessels to greater hemodynamic stress.

Skilton et al. conducted a study on 1005 women and concluded that pregnancy may also lead to rapid progression of atherosclerosis by elevation in lipids, insulin resistance, oxidative stress, inflammation and hemodilution[11].

Changes in all three of the Virchow`s triad elements during pregnancy and puerperium can be identified:
- Hypercoagulability - increased levels of clotting factors, such as von Willebrand factor, factor VII and factor I (fibrinogen); protein C resistance and reduced levels of protein S, increased levels of plasminogen activator inhibitors (PAI 1 and PAI 2), and hyperprolactinaemia, that promotes platelet aggregation;
- Venous stasis - compression of pelvic vessels by the gravid uterus, prolonged bed rest;
- Endothelial injury - trauma during delivery[12].

Major risk factors for cerebrovascular disorders in pregnancy include age greater than 35, African-American race, hypertension (pre-existing, gestational, preeclampsia and eclampsia), HELLP syndrome, diabetes, valvular heart disease, hypercoagulable disorders, sickle cell disease, lupus, migraine, and abuse of tobacco and other substances[13].

STROKE CLASSIFICATION

Both ischemic and hemorrhagic stroke can occur during pregnancy and postpartum. Ischemic strokes occur due to preeclampsia and eclampsia, thromboembolism, cardiac embolism, amniotic fluid embolism, peripartum cardiomyopathy, and postpartum cerebral angiopathy. Cerebral venous thrombosis can lead to both ischemic and hemorrhagic stroke. Hemorrhagic strokes are usually related to cerebral arteriovenous malformations, cerebral cavernous malformations, and subarachnoid hemorrhage (2.4-5.8 per 100,000 deliveries) due to aneurysm rupture or hypertensive disorders[14].

The most reported stroke type related to pregnancy is the ischemic stroke. In a review analyzing a large

number of cases, the crude rate of non-hemorrhagic stroke was 19.9 per 100,000 pregnancies, while the crude rate of hemorrhagic stroke was 12.2 per 100,000 pregnancies[7.]

Although the physiological changes in pregnancy explain venous thrombosis as a cause of stroke, studies show an incidence of arterial infarction similar to that of venous infarction or even higher.

Witlin et al. analysed stroke cases reported in a single center for 20 years. Out of 13 cerebral infarction cases, 7 were reported as venous, while 6 were arterial. The number of cases with intracerebral hemorrhage was 5, compared to the 13 cases of cerebral infarction[15].

Jaicobin et al. also report a higher incidence of ischemic strokes compared to hemorrhagic strokes (21 vs. 13). When analyzing the pathology of the ischemic events, arterial infarction was more common than venous infarction (13 vs. 8), usually occurring during the third trimester or puerperium. Venous infarction was more common in the postpartum period[16].

However, there are studies that report a similar or higher incidence of hemorrhagic stroke compared to ischemic stroke.

A former study performed by Sharshar et al. found that the incidence of non-hemorrhagic strokes in the maternities of Ile de France was 4.3 per 100,000 deliveries, while the incidence of intraparenchymal hemorrhage was 4.6 per 100,000 deliveries[17].

A study conducted in Canada on 3.9 million deliveries identified 524 cases of stroke, out of which 58.6% were hemorrhagic. 51.5% of them occurred postpartum[1].

A retrospective analysis conducted in 736 stroke teaching hospitals in Japan analyzed data from 2,1 million patients, with 151 pregnancy-related strokes that occurred between 2012 and 2013. The hemorrhagic type was responsible for 73.5% of the cases, the ischemic type for 24.5%, while in 2% of the cases there was a mixed etiology. Out of the hemorrhagic stroke group, 53.1% of the cases had preexisting cerebrovascular diseases. The timing of onset of the hemorrhagic stroke was during pregnancy, at delivery or during puerperium, each accounting for 50.5%, 14.4%, and 35.1% of the cases, respectively. The ischemic events were mostly due to arterial infarction during pregnancy and postpartum, while venous infarction was more frequent during postpartum period. The higher incidence of the hemorrhagic strokes in pregnancy reported by this study compared to existing literature could be explained by racial differences, knowing that hemorrhagic strokes in Chinese and Japanese population are twice more common than in white people[5].

PREVENTION

Data from studies and trials regarding prevention of stroke during pregnancy is not abundant in literature. Theories suggesting anticoagulation and antiplatelet therapy as lines of prevention are still debated and few major developments have been made recently.

For the preventable risk factors such as hypertension, the AHA/ASA[6] advises on the use of hypotensive medication that is safe in pregnancy, such as methyldopa, calcium-channel blocking drugs - nifedipine, beta blocker drugs, out of which pindolol and metoprolol appear safe for use, and magnesium sulfate for seizure prophylaxis. For women with chronic primary or secondary hypertension or previous pregnancy-related hypertension, low-dose aspirin is recommended from the 12th week of gestation until delivery (Class I; Level of Evidence A). Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated.

In pregnant women who frequently experience migraine, migraine treatment might be reasonable, although evidence is lacking that it reduces the risk of first stroke. (Class IIb; Level of Evidence C). For migraine with aura associated with smoking, smoking cessation is recommended (Class IIb; Level of Evidence B).

Pregnant women with gestational diabetes have a higher risk of antenatal stroke, so patients are advised to follow a low glycemic index diet and maintain glycemic targets established by diabetes guidelines[18].

DIAGNOSIS

In the presence of clinical suspicion, the diagnosis should be confirmed in a timely manner using neuroimaging. Magnetic resonance imagining (MRI), computed tomography (CT) and even MR and CT angiography should be undertaken if necessary. MRI is not associated with increased fetal risks[19] and concerns over ionizing radiation exposure (via CT) have been settled by experts.

The usual radiological examinations expose the fetus to doses safely below the threshold calculated for developmental abnormalities to occur. Regarding the effects

of exposure on the long run, low-dose irradiation has been linked to a higher risk of cancers, especially childhood leukemia. It is estimated that there is a 6% increase in risk of childhood cancers per 100 rad, but this level of exposure is hardly achievable[20]. The American College of Radiology (ACR) advises that irradiation with doses below 50 mGy (5 rad) during pregnancy has no deterministic effects, regardless of the gestational age. For CT investigations with the highest direct exposure, usually involving the lumbar spine or pelvis, the maximum dose reaches 20mGy (2 rad). When investigations are aimed at the head or the neck, the conceptus is exposed to scattered radiation, lowering the dose[21]. For comparison, environmental exposure of the fetus during pregnancy is 0.23 rad[20].

Iodinated contrast agents are considered category B medication according to the FDA. There is no available data indicating potential harm to the fetus via IV or intra-arterial maternal injection, therefore ACR does not recommend withholding the use of iodine mediums if needed for diagnosis. Furthermore, they do not recommend routine screening for pregnancy prior to contrast media use[22]. The European Society of Urogenital Radiology recommends that if iodine-based contrast agents are used during pregnancy, thyroid function should be checked in the neonate during the first week[23].

Gadolinium-based contrast agents have not been incriminated for fetus adverse effects if the correct dosage was used. It is probably safe during pregnancy, as excessive quantities are not expected to cross the placenta or to be toxic to the fetus if they do[24]. It is estimated that in the fetus, 0.01% of the dose is found after 4 hours, and only traces after 24 hours. In mice, the gadolinium-based agent that passed through the placenta was redistributed to the mother, so that after 48 hours there was undetectable fetal concentration[25]. However, no well-controlled studies have been performed in order to assess the safety of its usage during pregnancy. ACR advises gadolinium-based agents should only be used if the need is considered critical and the potential benefits justify the potential unknown risk to the fetus[22]. The European Society of Urogenital Radiology advises that if gadolinium-based contrast media must be used, then the smallest possible dose of one of the most stable gadolinium contrast agents is to be employed. No neonatal tests are necessary afterwards[23].

TREATMENT

When dealing with cerebrovascular events, antithrombotic therapy has a well-established place in the treatment plan. Unfractioned heparin (UFH) and low molecular weight heparin (LMWH) are safe during pregnancy, do not transfer transplacentally, do not cause fetal hemorrhage, and are safe during breastfeeding as well. However, due to its long half-life, if UFH is used close to labor, it increases the risk of bleeding; LMWH is not associated with severe peripartum bleeding. Warfarin is safe during the first 6 weeks of pregnancy and while breastfeeding; otherwise, it crosses the placenta and may cause bleeding in the fetus and teratogenic effects[26].

More research should be done for specific treatments and their efficacy and safety.

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is widely used in non-pregnant patients with acute ischemic stroke. In pregnancy, only a limited number of cases were reported. Major concerns regard teratogenicity, placental abruption, premature labor, and fetal death. Due to its large molecular size, rt-PA does not cross the placenta, and no teratogenic risk has been reported in animal[27]. The route of administration is usually intravenously, although intra-arterial administration has been taken into account, considering the incidence of arterial infarction in stroke etiology. Reported cases of neurologic thrombosis during pregnancy treated with thrombolytic therapy, mostly rt-PA, show no maternal deaths linked to the thrombolytic agent, no major bleeding events, and one preterm delivery, out of 18 cases analyzed[28]. A systematic review on thrombolytic therapy during pregnancy for serious thrombotic events treated with rt-PA or streptokinase reported 4 maternal deaths, 12 major bleeding cases, 13 mild or moderate bleeding cases, 14 preterm deliveries, and 2 fetal deaths out of 141 cases analyzed[29].

Endovascular treatment of acute large vessel occlusion stroke has become a standard treatment for the general population. However, its safety in pregnancy has not been evaluated on large cohorts. Recent papers presenting cases of mechanical thrombectomy for stroke during pregnancy prove that these procedures should be considered, since they are both safe and effective. Seven cases have been presented with good outcome after stent retriever thrombectomy, direct aspiration first pass technique (ADAPT) and direct

aspiration followed by two attempts with stent retriever thrombectomy that finally required a rescue balloon mounted coronary stent[30]. Other authors present good outcomes of mechanical thrombectomy in pregnancy, but also following both systemic thrombolysis and endovascular therapy for the same patient[31,32].

There is no consensus regarding intracerebral hemorrhage management during pregnancy. Mannitol, used to prevent cerebral edema, may decrease uterine perfusion and increase uterine vascular resistance, leading to fetal hypoxia, acidosis, and low Apgar score[33]. Antiepileptics and nimodipine carry the risk of teratogenicity. The priority in these cases should be lowering the blood pressure to below 160/110 mmHg initially, then below 140/90 mmHg, and identifying and correcting coagulopathies. For ruptured aneurysms, urgently clipping or coiling the aneurysm should be done; a concurrent Cesarean delivery could be taken into account in the presence of a viable gestational age[34].

PROGNOSIS

The prognosis for stroke related to pregnancy depends on the type of stroke and individual factors. Usually, mortality is linked to hemorrhagic strokes or secondary hemorrhage after ischemic stroke.

Ischemic strokes have a better prognosis, with low fatality and usually a smaller rate of severe disability compared with the hemorrhagic cases[17]. In recent studies it was demonstrated that the single cause of maternal death from stroke was intracranial hemorrhage; the calculated case-fatality risk of stroke during pregnancy was 20%, the case-fatality risk of hemorrhagic stroke 50%, and the mortality rate 0.3 per 100,000 deliveries[2]. James et al. found a death rate of 1.4 per 100,000 deliveries[35].

A less frequent but serious occurrence is the subarachnoid hemorrhage. With an incidence of 5.8 per 100,000 deliveries, it is responsible for 4.1% of all pregnancy-related in-hospital deaths[36].

SECONDARY PREVENTION

Stroke is a debilitating disorder with great impact on patients and their families. Women with a personal history of stroke deserve special consideration when planning for or dealing with pregnancy. All efforts should be made to discover the cause and to address it, but this is not always possible. General strategies promote lifestyle changes, encourage a healthy diet, exercise, weight balance, and advise against tobacco and alcohol use.

The Canadian stroke best practice consensus statement advises that in cases where the underlying cause has been identified and resolved, with the patient achieving a risk of stroke similar to the general population, no antithrombotic prophylaxis is necessary[19]. When analyzing cases of pregnancy in women with a personal history of stroke, Kajalainen et al. found the risk of stroke recurrence during pregnancy to be 2%[37].

For patients with indication of antiplatelet therapy it is recommended to transition to low dose acetylsalicylic acid (75mg) preconceptionally, or as soon as the pregnancy is confirmed[19]. Feared side effects of acetylsalicylic acid such as premature closure of the ductus arteriosis, fetal renal impairment and gastroschisis were not endorsed by trials (EAGeR, ASPRE)[38]. Acetylsalicylic acid therapy could be considered during breastfeeding due to low excretion in breast milk, but more insight into Reye's syndrome in infants should be acquired[39].

There are no human-based studies on the safety of clopidogrel as an antithrombotic agent. The FDA includes clopidogrel in B class recommendation (animal studies with no fetal risk but without controlled human studies).

When anticoagulation is needed low molecular weight heparin is preferred to warfarin, which is potentially teratogenic, and to direct oral anticoagulants, which have not been studied sufficiently in pregnancy. Six weeks postpartum the patient can switch back from LMWH to warfarin since it is safe even when breastfeeding[18].

Women with a history of stroke should closely monitor blood pressure. The medication used is detailed in the Prevention section above. Prior treatment with statins should be interrupted preconceptionally and restarted after breastfeeding cessation[18].

Gestational diabetes increases the risk of antenatal stroke and up to 7 years postpartum[40]. For patients with stroke history, gestational diabetes should be considered and tested for earlier in pregnancy, at 20 weeks gestational age[18].

Since there is no standardized practice yet, studies have been made regarding specialists' conduct. In the U.S., practitioners dealing with pregnant patients with a personal history of stroke agreed that prophylaxis is advisable during the first trimester. However, there was no consensus regarding the drugs to be used. Regardless

of the previous stroke being pregnancy-related or not, over 80% of the practitioners would use antithrombotic drugs (such as 75 mg acetylsalicylic acid and, in a smaller percentage, clopidogrel) and a smaller but considerable percentage would use low molecular weight heparin or unfractioned heparin[41].

Conclusion

Recent research shows that antithrombotic medication, anticoagulant therapy and both systemic thrombolysis and mechanical thrombectomy are safe and effective. Further research on larger cohorts is duly required to regulate and develop guidelines for clinical use.

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