Review paper

Archives of Psychiatry Research 2023;59:95-100
DOI:10.20471/may.2023.59.01.12

Stroke in Pregnancy and Puerperium – Current Knowledge, Questions and Controversies

Aleksandra Pavlović[1]

[1]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

Abstract - Stroke associated with pregnancy and the postpartum period (SiPP) is not common but its consequences can be devastating both for the mother and the child. Pregnancy confers a substantially increased risk of stroke, especially during the third trimester and until 6 weeks postpartum. SiPP is heterogeneous both in aetiology and presentation as it includes both ischemic and haemorrhagic events as well as cerebral venous thrombosis. Specific risk factors for SiPP have been identified and well described, such as hypertensive disorders of pregnancy and a prothrombotic state. However, it is still a controversial issue if pregnancy should be considered a risk factor for stroke, although pregnancy and postpartum period clearly increase the stroke risk compared to non-pregnant time. Recent European Stroke Organization [ESO] guidelines addressed the management of acute SiPP while other issues, particularly primary and secondary prevention are still under investigated. There is also a lack of research and knowledge regarding long-term mother and foetus/child outcomes post-SiPP. This paper addresses current knowledge on SiPP management and prognosis and discusses new challenging clinical scenarios including the relationship between COVID-19 infection and SiPP.

Key words: intracranial thrombosis; diagnostic techniques, cardiovascular; postpartum period; pregnancy

e-mail: apr.kbcsm@gmail.com • www.http://apr.kbcsm.hr

Introduction

The risk of stroke among pregnant and postpartum women is 3 to 6 times increased in comparison with non-pregnant women of similar age [1]. The estimated incidence of stroke during reproductive age is 10 – 20 per 100,000 person-years, compared to the reported incidence of 30 strokes per 100,000 deliveries among all pregnancies, with data varying between 4 and 40 per 100,000 deliveries [2-4]. The incidence of stroke in pregnancy and puerperium (SiPP) depends on gestational age, with the greatest risk observed during the third trimester, delivery, and the early postpartum period [5]. Recent reports showed an increase in the SiPP incidence, mainly due to a rise in hypertensive disorders of pregnancy (HDP) and cardiac disease in pregnant women [5,6]. There are, however, conflicting results as well [7].

SiPP is heterogeneous both in aetiology and presentation as it includes ischemic and haemorrhagic stroke as well as cerebral venous thrombosis (CVT) [5]. In addition, cerebrovascular disorders such as posterior reversible encephalopathy syndrome (PRES) or reversible cerebral vasoconstriction syndrome (RCVS) typically occur in the peripartum or puerperium [6,8]. Although pregnancy and postpartum period increase the stroke risk compared to non-pregnant time, it is still controversial if pregnan-

Correspondene to:
Assist. Prof. Aleksandra Pavlović, MD, PhD, University of Belgrade, Faculty of Special Education and Rehabilitation, Visokog Stevana 2, Belgrade, Serbia, Phone: +381 11 218 30 36, Mob: +381 64 164 83 47, Fax: +381 11 218 30 81
E-mail: aleksandra3003@yahoo.com

cy should be declared a risk factor for stroke [9]. Specific risk factors for SiPP have been identified and well described, such as HDP which includes gestational hypertension, pre-eclampsia and eclampsia, and a prothrombotic state, which increases the risk of arterial and venous thrombosis [4,7,9]. Furthermore, data are indicating that a history of migraine (adjusted OR 8.5) and gestational diabetes (adjusted OR 26.8) also increase the risk of SiPP [7,10]. Another review showed that hypertensive disorders, obesity, and heart disease pre-pregnancy complicated 32 % of antenatal admissions and 53 % of post-partum admissions [11]. Moreover, other neurological conditions may complicate pregnancy but also mimic stroke [12].

Revealing stroke mechanisms in SiPP is important as they indicate prognosis, risk of recurrence, and treatment options. Clearly, SiPP requires a multidisciplinary approach, in terms of acute management, aetiology investigation, rehabilitation, and outcome assessment [13-15]. Stroke in pregnant and postpartum women effects profoundly their lives as well as the lives of their families [13]. Training of neurologists, anaesthesiologists, obstetricians, general practitioners, allied health professionals, and all health personnel dealing with pregnancy and postpartum period about this topic is imperative to prevent SiPP, reduce acute injury to the brain and prevent significant disability and death.

Discussion

Consequences for mother and child

SiPP accounts for up to 15 % of maternal deaths [16]. In addition, pregnancy-associated stroke is the most common cause of serious long-term disability after pregnancy [17]. One-third of pregnant or postpartum patients with ischemic strokes and half of those with hemorrhagic strokes will have residual deficits [18]. In particular, 50 % of pregnancy-associated hemorrhagic strokes are fatal [18]. Fatality in hemorrhagic SiPP is reported to be 13.9 %, compared with 3.4 % in ischemic SiPP [13]. Poststroke recovery may be additionally complicated in this setting, with poststroke depression which may be exacerbated by the pregnant or postpartum state [19].

Despite clear evidence of the improved functional outcome of acute ischemic stroke with current reperfusion therapy with the use of strict inclusion and exclusion criteria, pregnant or postpartum women are less likely to receive intravenous thrombolysis (IVT) monotherapy, mainly because of concerns for the infant and the risk of recent surgery. The recent ESO guidelines on Stroke in Women stated that the available data do not allow a specific recommendation on IVT or mechanical thrombectomy (MT) in pregnant women with acute ischemic stroke, but an Expert consensus statement was given with a recommendation by a majority of members that pregnant women with acute disabling ischemic stroke, who otherwise meet eligibility criteria, can be treated with IVT or MT after assessing the benefit/risk profile [4]. All guideline working group members suggest that pregnant women with acute ischemic stroke and large vessel occlusion, who otherwise meet eligibility criteria, can be treated with MT after an appropriate assessment of the benefit/risk profile, and a majority of members suggest that in pregnant women with acute ischemic stroke related to large vessel occlusion if MT is available, MT alone should be preferred over IVT or bridging therapy (IVT + MT) [4]. According to the current evidence, the outcomes in pregnant/postpartum women receiving reperfusion therapy were overall comparable to those observed in non-pregnant/non-postpartum women [4]. Regarding the postpartum period, defined as $\geq$ 10 days $<$ 3 months after birth, available data do not allow a specific recommendation on IVT or MT in postpartum women with acute ischemic stroke [4]. All members of the guidelines working group suggest that postpartum women with disabling ischemic stroke, occurring at least 10 days after delivery, who otherwise meet eligibility criteria, can be treated with IVT with alteplase after proper evaluation, as well that it is reasonably plausible that postpartum women with acute ischemic stroke meeting eligibility criteria, might benefit from MT after adequate assessment [4].

A prolonged length of hospital stay of longer than 4 days is still more common in the pregnant or postpartum group compared to controls (72 % vs. 41.7 %) [4]. There is no systematic study reviewing SiPP outcome, which can be explained by the rarity of the event and heterogeneity of vascular events mechanisms. Therefore, a prospective registry of SiPP designed by the ESO research group WISE dedicated to research of stroke impact in women, has been created and the study rationale and design published recently [20]. Data on both short- and long-term outcomes of the mother and child, including specific safety outcomes, will be collected with the maximal time follow-up of a mother of 24 months and of a child of 12 months [20].

Pregnancy in women with a history of stroke

Data on subsequent pregnancies and the health of women with a history of pregnancy-associated stroke are limited [5]. An early small observational study analyzing the risk for recurrent stroke in 23 pregnant women with a history of the previous stroke showed a small risk of recurrence [21]. Various stroke risk factors and mechanisms in mothers were involved in reported cases ranging from thrombophilia sickle cell disease and hypertension as the most frequent but also including maternal cardiac malformations, cerebral arteriovenous malformations, endocarditis, and cryptogenic cases [21]. No recurrent thrombotic episodes during pregnancy or after delivery were documented, and three of 34 pregnancies (9 %) resulted in infants of small-for-gestational age (SGA) [21]. In a more recent publication from Finland by Aarnio and associates, a total of 45 mothers had 68 pregnancies after stroke [22]. The authors reported a higher incidence of pregnancy- and delivery-related complications in mothers with ischemic stroke compared to stroke-free mothers [22]. In another recent review on SiPP outcome, in a subsequent pregnancy, the incidence of pregnancy complications was comparable to that of the general population, and the risk of stroke recurrence during pregnancy was 2 % [5].

In a prospective study of stroke in the young named FUTURE study [Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation], women with young stroke showed higher rates of pregnancy loss throughout their lives [23]. In this study, the occurrence of pregnancy, miscarriages, and pregnancy complications in 223 women aged 18 to 50 years with a first-ever ischemic stroke/transient ischemic attack was assessed [23]. In nulliparous women after stroke ($n = 22$), in comparison with the Dutch population, there was a high prevalence of HDP (33.3 versus 12.2 %; $P < 0.05$) and early preterm delivery < 32 weeks (9.0 versus 1.4 %; $P < 0.05$) [23]. Interestingly, in primi/multiparous women after stroke, although 29 events occurred during follow-up, none happened during subsequent pregnancies, indicating less serious pregnancy complications [23].

In the largest reported study on this topic, women with a stroke history were more likely to have an early-term delivery (37-38 weeks; relative risk (RR 1.49) and a pre-labor caesarean (RR 2.83) [24]. No differences in stillbirths and neonatal deaths between women with and without a history of prior stroke were noted, and a slightly higher proportion of women with a history of stroke had a small-for-gestational age infant, but this difference was not statistically significant [24]. However, in a Finish study, the incidence rate ratio (IRR) for perinatal death of the child was 3.43 (95 % CI 0.57 - 20.53) in mothers without stroke and 8.88 (95 % CI 0.81 - 97.95) after stroke [22].

COVID-19

There are still gaps in knowledge about SiPP, such as stroke mechanisms, best preventive and therapeutic options, as well as long-term prognosis for both mother and child, with the additional challenge of rare but alarming cases of COVID-19 co-existence or potential causative effect. Published cases of COVID-19 infection in pregnancy are quite infrequent but add new knowledge regarding mechanisms of vascular injury in pregnancy [25-27]. COVID-19 is an independent risk factor for both

ischemic stroke and cerebral venous thrombosis, with cerebrovascular event incidence ranging up to 4.9 % [25,26]. Potential mechanisms comprise the affinity of the SARS-CoV-2 virus for angiotensin-converting enzyme (ACE) 2 receptors expressed in the endothelium and arterial smooth muscle cells in the brain, activation of a vascular and systemic inflammatory response, altered vasomotor reactivity, disruption of the renin-angiotensin–aldosterone system as well as evidence of prothrombotic state and coagulopathy [28]. SARS-CoV-2 may directly invade the central nervous system, via blood but also via neuronal retrograde pathways, and systemic endothelial dysfunction in COVID-19 has been well-demonstrated [28].

In a recent scoping review by Magelhaes and Sampaio-Rocha-Filho cases of COVID-19 neurological complications in pregnant women published by November 2021 have been described and discussed [29]. Only 18 case reports were detected, half of them requiring admission to the ICU, and two with a cerebrovascular event [29]. One patient experienced an extensive cerebral infarct with a haemorrhagic transformation and a possible arterial obstruction, while the other had an infarct due to cerebral venous thrombosis associated with positive antinuclear antibodies and prothrombin heterozygous mutation [30]. The experience is increasing with another recent case report of a 22-year-old woman in early pregnancy (10 gestational weeks) presenting with headache and focal neurological deficit, but with a good functional outcome [31]. There is also only one case report at the moment (September 2022) of a spontaneous intracerebral haemorrhage (ICH) associated with pregnancy and COVID-19 so this complication appears to be quite rare [32]. An increased risk of ICH in pregnant women has been shown in HDP, coagulopathy, and a history of tobacco use [33]. The authors reported a case of a 27-year-old woman with COVID-19 infection who presented with a sudden neurological deterioration and basal ganglia hematoma a week after caesarean section [32]. The patient did not have any risk factors for ICH and did not receive anti-thrombosis prophylaxis for COVID-19 disease, implying possible causality between postpartum status, SARS-CoV-2 infection, and ICH [32].

Concerning COVID-19 vaccination in pregnancy and stroke risk, it is important to note that pregnancy is an independent risk factor for severe COVID-19. The current recommendations from the World Health Organization and Centers for Disease Control and Prevention state that pregnant, postpartum, and lactating women should receive COVID-19 vaccination as it reduces SARS-CoV-2 infection morbidity and mortality [34]. On the other side, there are increasing reports of various types of stroke including ischemic stroke, and haemorrhagic stroke, as well as cerebral venous sinus thrombosis (CVST) after COVID-19 vaccination [35]. As pregnancy was an exclusion criterion in initial clinical trials of covid-19 vaccines, observational data so far confirm that the benefits of vaccination outweigh the potential risks in this population. Currently, no pregnancy-specific safety concerns with COVID-19 vaccination have been confirmed, although additional data is needed for non-mRNA vaccines, vaccination early in pregnancy, the optimal timing of vaccination in pregnancy for neonatal/infant benefit, and longer-term outcomes in infants [34].

Stroke in Pregnancy and Postpartum is a rare but challenging situation for patients, their families, and health professionals. There are still many gaps in the knowledge of multifaceted stroke mechanisms in SiPP, long-term outcomes both for mother and infant, and optimal secondary prevention options.

Acknowledgements

None.

Conflict of interest

None to declare.

Funding Sources

None.

References

1. Elgendy IY, Bukhari S, Barakat AF, Pepine CJ, Lindley KJ, Miller EC, et al. Maternal stroke: a call for action. Circulation. 2021;143:727-38.
2. Tibæk M, Dehlendorff C, Jørgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: a registry-based study. J Am Heart Assoc. 2016;5:e003158.
3. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, et al. The incidence of pregnancy-related stroke: a systematic review and metaanalysis. Int J Stroke. 2017;12:687-97.
4. Kremer C, Gdovinova Z, Bejot Y, Heldner MR, Zuurbier S, Walter S, et al. European Stroke Organisation guidelines on stroke in women: management of menopause, pregnancy and postpartum. Eur Stroke J. 2022;7:I-XIX.
5. Karjalainen L, Tikkanen M, Rantanen K, Laivuori H, Gissler M, Ijäs P. Pregnancy-associated stroke − a systematic review of subsequent pregnancies and maternal health. BMC Pregnancy Childbirth. 2019;19:187.
6. Leffert LR, Clancy CR, Bateman BT, Bryant AS, Kuklina EV. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. Obstet Gynecol. 2015;125:124-31.
7. Elgendy IY, Gad MM, Mahmoud AN, Keeley EC, Pepine CJ. Acute Stroke During Pregnancy and Puerperium. J Am Coll Cardiol. 2020;75:180-90.
8. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:1545-88.
9. Cordonnier C, Sprigg N, Sandset EC, Pavlovic A, Sunnerhagen KS, Caso V, et al. Stroke in women - from evidence to inequalities. Nat Rev Neurol. 2017;13:521-32.
10. Scott CA, Bewley S, Rudd A, Spark P, Kurinczuk JJ, Brocklehurst P, et al. Incidence, risk factors, management, and outcomes of stroke in pregnancy. Obstet Gynecol. 2012;120:318-24.
11. Moatti Z, Gupta M, Yadava R, Thamban S. A review of stroke and pregnancy: incidence, management and prevention. Eur J Obstet Gynecol Reprod Biol. 2014;181:20-7.
12. Zafarmand S, Javanmardi H, Ameri M, Maneshi M, Mansouri-Mehrabadi S, Zolghadrasli Y, et al. Evaluation of the Neurological Complaints during Pregnancy and Postpartum. Galen Med J. 2019;8:e1616.
13. Khalid AS, Hadbavna A, Williams D, Byrne B. A review of stroke in pregnancy: incidence, investigations and management. Obstet Gynaecol. 2020;22:21-33.
14. Miller EC, Leffert L. Stroke in Pregnancy: a focused update. Anesth Analg. 2020;130:1085-96.
15. Camargo EC, Singhal AB. Stroke in Pregnancy: A Multidisciplinary Approach. Obstet Gynecol Clin North Am. 2021;48:75-96.
16. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Heal. 2014;2:e323-33.
17. Liu S, Chan WS, Ray JG, Kramer MS, Josep KS, Canadian Perinatal Surveillance System [Public Health Agency of Canada]. Stroke and cerebrovascular disease in pregnancy incidence, temporal trends, and risk factors. Stroke. 2019;50:13-20.
18. Miller EC. Maternal stroke associated with pregnancy. Continuum [Minneap Minn]. 2022;28:93-121.
19. Caropreso L, de Azevedo Cardoso T, Eltayebani M, Frey BN. Preeclampsia as a risk factor for postpartum depression and psychosis: a systematic review and meta-analysis. Arch Womens Ment Health. 2020;23:493-505.
20. Lorenzano S, Kremer C, Pavlovic A, Jovanovic DR, Sandset EC, Christensen H, et al. SiPP [Stroke in Pregnancy and Postpartum]: a prospective, observational, international, multicentre study on pathophysiological mechanisms, clinical profile, management and outcome of cerebrovascular diseases in pregnant and postpartum women. Eur Stroke J. 2020;5:193-203.
21. Coppage KH, Hinton AC, Moldenhauer J, Kovilam O, Barton JR, Sibai BM. Maternal and perinatal outcome in women with a history of stroke. Am J Obstet Gynecol. 2004;190:1331-4.
22. Aarnio K, Gissler M, Grittner U, Siegerink B, Kaste M, Tatlisumak T, et al. Outcome of pregnancies and deliveries before and after ischaemic stroke. Eur Stroke J. 2017;2:346-55.
23. van Alebeek ME, de Vrijer M, Arntz RM, Maaijwee NAMM, Synhaeve NE, Schoonderwaldt H, et al. Increased risk of pregnancy complications after stroke: the FUTURE Study [Follow-up of transient ischemic attack and stroke patients and unelucidated risk factor evaluation]. Stroke. 2018;49:877-83.
24. Austin K, Seeho S, Ibiebele I, Ford J, Morris J, Torvaldsen S. Pregnancy outcomes for women with a history of stroke: a population-based record linkage study. Aust N Z J Obstet Gynaecol. 2021;61:239-43.
25. Belani P, Schefflein J, Kihira S, Rigney B, Delman BN, Mahmoudi K, et al. COVID-19 Is an independent risk factor for acute ischemic stroke. AJNR Am J Neuroradiol. 2020;41:1361-4.
26. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, et al. Mechanisms of Stroke in COVID-19. Cerebrovasc Dis. 2020;49:451-8.
27. Gama MDP, Angelo Júnior JRLA, de Cunha-Correia C. Stroke in COVID-19 and pregnancy: a case report. Rev Soc Bras Med Trop. 20210;54:e03012021.
28. Tang X, Zheng F. A review of ischemic stroke in COVID-19: currently known pathophysiological mechanisms. Neurol Sci. 2022;43:67-79.
29. Magalhães JE, Sampaio-Rocha-Filho PA. Pregnancy and neurologic complications of COVID-19: a scoping review. Acta Neurol Scand. 2022;146:6-23.
30. Gunduz ZB. Venous sinus thrombosis during COVID-19 infection in pregnancy: a case report. Sao Paulo Med J. 2021;139:190-5.
31. Mahmoud A, Ekin U, Kania B, Shrouf A, Maroules M. Cerebral venous sinus thrombosis in pregnancy presenting with hemiplegia: a case report. Radiol Case Rep. 2022;17:3713-7.
32. Dini P, Aminimoghaddam S, Mirzaasgari Z, Rahimian N, Khotbehsara ST, Abolmaali M. Spontaneous Intracerebral Hemorrhage [ICH] associated with pregnancy and SARS-CoV-2 infection: a case report. BMC Pregnancy Childbirth. 2022;22:14.
33. Meeks JR, Bambhroliya AB, Alex KM, Sheth SA, Savitz SI, Miller EC, et al. Association of primary intracerebral hemorrhage with pregnancy and the postpartum period. JAMA Netw Open. 2020;3:e202769.
34. Badell ML, Dude CM, Rasmussen SA, Jamieson DJ. Covid-19 vaccination in pregnancy. BMJ. 2022;378:e069741.
35. Kakovan M, Ghorbani Shirkouhi S, Zarei M, Andalib S. Stroke associated with COVID-19 vaccines. J Stroke Cerebrovasc Dis. 2022;31:106440.