



Stroke recurrence in pregnancy: Experience at a regional referral center

Adeeb Khalifeh^{a,b}, Andrea Berghella^c, Sindy Moreno^d, Kathryn Corelli^b, Emily Leubner^b, Gabriele Saccone^{e,*}, Badih Daou^f, Pascal Jabbour^g



^a Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Einstein Medical Center, Philadelphia, PA, United States

^b Department of Obstetrics and Gynecology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, United States

^c Brown University, Providence, RI, United States

^d Department of Obstetrics and Gynecology, Flushing Hospital Medical Center, Flushing, NY, United States

^e Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

^f Department of Neurosurgery, University of Michigan, Ann Arbor, MI, United States

^g Department of Neurological Surgery, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, United States

ARTICLE INFO

Article history:

Received 17 December 2018

Received in revised form 28 February 2019

Accepted 4 March 2019

Keywords:

Stroke

Pregnancy

NICU

Neonatal outcome

Cesarean delivery

ABSTRACT

Background: Although stroke is more common with advancing age, especially in the elderly, women of reproductive age may still suffer from stroke, and from its deleterious consequences. Women of reproductive age who suffer a stroke may do so either due to a specific predisposition, or due to pregnancy-related hypertensive emergencies.

Objective: To assess the risk of stroke recurrence in pregnancy and the postpartum period in women who have suffered a stroke before pregnancy.

Study design: This was a retrospective cohort study conducted at Thomas Jefferson University Hospital from January 2005 to December 2015. This is a tertiary referral center for high-risk obstetrics and one of the largest stroke referral centers for neurosurgery. All consecutive pregnant women that had a viable pregnancy (≥ 24 weeks of gestation) and a history of stroke prior to pregnancy were identified. The primary outcome of this study was stroke recurrence in pregnancy or the postpartum period defined as 6 weeks after delivery.

Results: Forty-eight pregnancies with a history of stroke before pregnancy were identified in 24 women. Thirty-one pregnancies (64.6%) had a history of an ischemic stroke, 11 (22.9%) had a history of transient ischemic attack, and 6 (12.5%) had a history of a hemorrhagic stroke. There was no stroke recurrence during pregnancy or the postpartum period for the three groups of stroke. In the ischemic stroke group, 8 (25.8%) had recurrence in the non-pregnant state compared to none in the TIA and the hemorrhagic stroke group.

Conclusion: There was no stroke recurrence during pregnancy or the postpartum period for the three groups of stroke.

© 2019 Elsevier B.V. All rights reserved.

Introduction

Although stroke is more common with advancing age, especially in the elderly, women of reproductive age may still suffer from stroke, and from its deleterious consequences [1]. Women of reproductive age who suffer a stroke may do so either due to a specific predisposition, such as a brain aneurysm or a specific clotting disorder, or due to pregnancy-related hypertensive emergencies [2].

Hypertensive disorders in pregnancy remain a major cause of maternal morbidity mortality in the United States [3]. Stroke in pregnancy and the peripartum period is a known complication of hypertensive emergencies, and continues to be a serious clinical challenge despite national safety bundles to minimize the deleterious effects of such acute emergencies [4].

Fortunately, many women of reproductive age who suffered a stroke, have a good prognosis [5]. They often present either for prenatal or preconception counseling to assess the maternal risks to help in their decision-making whether to start, continue or terminate a pregnancy. While counseling women who have suffered a stroke may be guided by the patient's predisposing risk factors, it remains challenging to counsel patients about the possibility of stroke recurrence in pregnancy.

* Corresponding author.

E-mail address: gabriele.saccone.1990@gmail.com (G. Saccone).

Thus, the aim of this study was to assess the risk of stroke recurrence in pregnancy and the postpartum period in women who have suffered a stroke before pregnancy.

Materials and methods

This was a retrospective cohort study conducted at Thomas Jefferson University Hospital from January 2005 to December 2015. This is a tertiary referral center for high-risk obstetrics and one of the largest stroke referral centers for neurosurgery. This study was approved by the Institutional Review Board of Thomas Jefferson University.

All consecutive pregnant women that had a viable pregnancy (≥ 24 weeks of gestation) and a history of stroke prior to pregnancy were identified. Only women with confirmed documentation of stroke by established criteria were included. This was done first by identifying patients who had a history of a stroke and presented to the Obstetrics and Gynecology Department for prenatal care or preconception counseling. Second, the database of the neurosurgery department was accessed to identify all women of reproductive age (18–45) who were admitted and treated for a stroke. These patients' medical records were reviewed; patients were also subsequently reached and interviewed over the phone for their detailed obstetrical and medical history.

Information on maternal characteristics such as maternal age, gravidity and parity, BMI, pregnancy-associated hypertensive disorders and gestational age for delivery was recorded. A detailed history about each patient's stroke was collected. The type of stroke was classified according to the American Stroke Association: ischemic, hemorrhagic or transient ischemic attack (TIA) [6]. Any predisposing factor for a stroke was recorded. If there were any neurological deficits after the stroke, a detailed neurological history was taken.

The primary outcome of this study was stroke recurrence in pregnancy or the postpartum period defined as 6 weeks after delivery. Secondary outcomes included pregnancy outcomes.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Data are shown as means \pm standard deviation (SD), or as medians (range), or as numbers (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square with continuity correction. Comparisons between groups were

performed with the use of the *t*-test to test group means with SD by assuming equal within-group variances, and with the use of the Mann-Whitney U test to calculate group medians with range. A *p*-value < 0.05 was considered to indicate statistical significance.

Results

Forty-eight pregnancies with a history of stroke before pregnancy were identified in 24 women. The primary outcome of stroke recurrence of these patients was available for all patients. Obstetrical outcome including mode of delivery was available for 42 pregnancies.

Thirty-one pregnancies (64.6%) had a history of an ischemic stroke, 11 (22.9%) had a history of transient ischemic attack, and 6 (12.5%) had a history of a hemorrhagic stroke.

Baseline characteristics of the three groups of stroke are shown in Table 1.

African American race was significantly more common (70.8%) compared to white (20.8%) or Hispanic race (4.1%) ($p < 0.05$). Five patients (16.1%) with a history of ischemic stroke had prophylactic anticoagulation with low molecular weight heparin at prophylactic dose; almost half of the women were on low-dose aspirin 81 mg

Eleven women had chronic hypertension and five had hypertensive disorders of pregnancy (either preeclampsia or gestational hypertension). Nine patients were smokers.

There was no stroke recurrence during pregnancy or the postpartum period for the three groups of stroke. In the ischemic stroke group, 8 (25.8%) had recurrence in the non-pregnant state compared to none in the TIA and the hemorrhagic stroke group (Table 2).

There was no difference in the incidence of hypertensive disorders in pregnancy or gestational age at delivery among the three groups of stroke. The incidence of cesarean delivery was significantly higher in the hemorrhagic stroke group compared to the ischemic or TIA group ($p < 0.05$) (Table 3).

Discussion

While the risk of stroke is low among women of reproductive age [6], this cohort of women does present with pregnancies that are clinically challenging in their management given the concern for stroke recurrence during pregnancy. In our study we found a 0%

Table 1
Demographic characteristics.

	Ischemic Stroke n = 31	TIA n = 11	Hemorrhagic Stroke n = 6	p value
Race				
Black	17 (54.8)	11 (100)	6 (100)	0.14
White	10 (32.3)	–	–	–
Hispanic	2 (6.5)	–	–	–
Other	2 (6.5)	–	–	–
Maternal age (years)	31.3 \pm 5.4	26.7 \pm 5.4	30.5 \pm 6.6	0.47
History of substance abuse	4 (12.9)	0 (0)	0 (0)	0.95
History of Tobacco abuse	9 (29)	0 (0)	0 (0)	0.74

Data are presented as number (percentage) or as mean \pm standard deviation.

Table 2
Prior stroke details and related Pregnancy Management.

	Ischemic Stroke N = 31	TIA N = 11	Hemorrhagic Stroke N = 6	p value
Stroke recurrence in non-pregnant state	8 (25.8)	0 (0)	0 (0)	–
Maternal age of first stroke	23.9 \pm 7.6	22.5 \pm 3.0	26 \pm 8.3	0.41
Interval stroke to pregnancy (years)	6.7 \pm 4.7	4.3 \pm 4.1	4.5 \pm 3.1	0.75
Anticoagulation in pregnancy	5 (16.1)	3 (27.3)	0 (0)	0.12
Aspirin in pregnancy	13 (41.9)	0 (0)	2 (3.3)	<0.01

Data are presented as number (percentage) or as mean \pm standard deviation. Boldface data, statistically significant.

Table 3

Stroke before pregnancy and subsequent pregnancy outcomes.

	Ischemic Stroke n = 31	TIA n = 11	Hemorrhagic Stroke n = 6	p value
Stroke recurrence in pregnancy	0 (0)	0 (0)	0 (0)	–
Miscarriage	6 (19.4)	0 (0)	2 (33.3)	<0.01
Ectopic	1 (3.2)	1 (9.1)	0 (0)	0.21
Hypertensive disorder in pregnancy	3 (9.7)	2 (18.2)	0 (0)	0.09
Gestational age at delivery (weeks)	37.9 ± 1.9	38.5 ± 1.3	38.3 ± 1.5	0.45
Vaginal delivery	15 (62.5)	4 (40)	0 (0)	0.08
Cesarean delivery	6 (25.0)	5 (50)	4 (100)	<0.01

Data are presented as number (percentage) or as mean ± standard deviation. Boldface data, statistically significant.

Table 4

Prior studies of women with prior stroke and subsequent pregnancy.

	N	Type of prior stroke	Number of subsequent pregnancies	N/N (%) recurrence of stroke in pregnancy or 6 weeks post-partum
Lamy et al. [7]	441	373 ischemic stroke; 68 cerebral venous thrombosis	187	2/187 (1%)
van Alebeek et al. [8]	213	132 ischemic stroke; 81 transient ischemic attack	569	0/569 (0%)
Soriano et al. [9]	12*	7 ischemic stroke; 3 transient ischemic attack; 3 amaurosis fugax	15	4/15 (27%)
Fischer-Betz et al. [11]	20*	12 ischemic stroke; 8 transient ischemic attack	23	3/23 (13%)
Coppage et al AJOG 2004 [10]	23	6 ischemic stroke; 1 cerebral venous thrombosis; 16 type not identified	35	0/35 (0%)
Cruz-Herranz et al. [12]	102	64 ischemic stroke; 24 transient ischemic attack; 12 cerebral venous thrombosis; 1 intracranial hemorrhage	32	0/32 (0%)

* All patients with thrombophilia predisposing them to thromboembolic events.

recurrence rate of stroke during pregnancy. This is consistent with other studies, such as a French study that reviewed 187 pregnancies with a history of ischemic stroke and found a recurrence rate of 1% [7].

A more recent larger study, this one from the Netherlands, that reviewed 213 pregnant women with a history of stroke also found a recurrence rate of 0% during pregnancy [8]. Our results, however, were not consistent with a smaller study of 12 patients with thrombophilia, which found a 27% rate of stroke recurrence [9].

Unlike our study, which looked at all subtypes of strokes including history of hemorrhagic stroke, other studies either

included only women with a history of ischemic stroke or TIA [7–10] or did not at all define the subtypes of strokes [11].

Another interesting finding in our study was that even in patients that had stroke recurrence in the non-pregnant state, stroke did not occur in pregnancy. This was consistent with the recent Dutch study [8].

All women with a history of an ischemic stroke or a TIA had a cesarean delivery for obstetrical indications. However, those with a history of a hemorrhagic stroke had planned caesarean deliveries despite the lack of consensus on mode of delivery even in the absence of cerebrovascular malformations, such as brain aneurysms.

Table 5

Characteristics of women with stroke recurrence in pregnancy.

Case #	Cerebrovascular event	Underlying thrombophilia	Situation in which stroke occurred	Prophylactic treatment	Other complications of pregnancy
1 (Lamy et al.)	Arterial ischemic stroke	Thrombocytopenia	Third-trimester, associated with preeclampsia	LMWH for duration of pregnancy	
2 (Lamy et al.)	Arterial ischemic stroke	Primary APS	After spontaneous abortion	None	
3 (Soriano et al.)	TIA	Protein S, C deficiency	32 weeks of pregnancy	LMWH and ASA 100 mg/day through at least 6 weeks postpartum	None
4 (Soriano et al.)	TIA – Temporary paresthesia of the left arm	APS		LMWH and ASA 100 mg/day through at least 6 weeks postpartum	Preeclampsia with severe features
5 (Soriano et al.)	TIA – Recurrent amaurosis fugax	APS		LMWH and ASA 100 mg/day through at least 6 weeks postpartum	None
6 (Soriano et al.)	TIA – Recurrent amaurosis fugax	APS		LMWH and ASA 100 mg/daily through at least 6 weeks postpartum	None
7 (Fischer-Betz et al.)	TIA – Slurred speech and numbness of left hand	Primary APS	34 weeks of pregnancy	LMWH and ASA, after event ASA dose increased to 300mg	None
8 (Fischer-Betz et al.)	TIA – Monocular vision loss	Primary APS	4 weeks postpartum after caesarean section at 35 weeks due to preeclampsia and IUGR	LMWH and ASA throughout pregnancy, patient discontinued ASA after delivery	Preeclampsia and IUGR
9 (Fischer-Betz et al.)	Arterial ischemic stroke – Paresthesia of the right hand	Secondary APS	1 week postpartum after caesarean section at 36 weeks due to HELPP syndrome	LMWH and 100 mg/day ASA, switched to warfarin 3 weeks postpartum	HELLP syndrome

APS- Antiphospholipid antibody syndrome.

After reviewing the literature, there were 909 pregnancies that had a history of stroke before pregnancy. About 1% (9 patients) had stroke recurrence in pregnancy (Table 4). After reviewing all patients' characteristics, the most common predisposing risk factor for stroke recurrence was antiphospholipid antibody syndrome (APS), occurring in 7 patients (Table 5). This is an important finding as this would help guide the clinician's counseling regarding the risks for stroke recurrence.

Our study's main strength is that it included patients with a history of all subtypes of strokes, including hemorrhagic stroke. The number of patients in this subcategory, however, remains small, making it difficult to generalize pregnancy management. Also, our study collected all the data in literature regarding stroke recurrence in pregnancy and identified the individual characteristics of patients who had a stroke.

Nevertheless, our study adds further evidence to the literature that pregnancy after a stroke without deleterious neurological consequences has a very low risk of stroke recurrence with proper management including anticoagulation. This finding will help with patient counseling in the preconception and the prenatal period.

Disclosure statement

The authors report no conflicts of interest

Financial support

No specific funding was received for this study

References

- [1] Thrift AG, Thayabaranathan T, Howard G, Howard VJ, et al. Global stroke statistics. *Int J Stroke* 2017;12(January 1):13–32.
- [2] Cleary KL, Siddiq Z, Ananth CV, et al. Use of antihypertensive medications during delivery hospitalizations complicated by preeclampsia. *Obstet Gynecol* 2018;131(March 3):441–50.
- [3] American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine, Kilpatrick SK, Ecker JL. Severe maternal morbidity: screening and review. *Am J Obstet Gynecol* 2016;215(September 3):B17–22.
- [4] Bernstein PS, Martin Jr. JN, Barton JR, Shields LE, et al. National partnership for maternal safety: consensus bundle on severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol* 2017;130(August 2):347–57.
- [5] Leys D, Bandu L, Hénon H, Lucas, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002;59(July 1):26–33.
- [6] Sacco RL, Kasner SE, Broderick JP, Caplan LR. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(July 7):2064–89.
- [7] 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. *Neurology* 2000;55:269–74.
- [8] Alebeek ME, Vrijer MD, Arntz RM, et al. Increased risk of pregnancy complications after stroke. *Stroke* 2018;49:877–83.
- [9] Soriano D, Carp H, Seidman DS, et al. Management and outcome of pregnancy in women with thrombophilic disorders and past cerebrovascular events. *Acta Obstet Gynecol Scand* 2002;81:204–7.
- [10] Fischer-Betz R, Specker C, Brinks R, Schneider M. Pregnancy outcome in patients with antiphospholipid syndrome after cerebral ischaemic events: an observational study. *Lupus* 2012;21:1183–9.
- [11] 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: 1331e4.
- [12] Cruz-Herranz A, Illán-Gala I, Martínez-Sánchez P, Fuentes B, Díez-Tejedor E. Recurrence of stroke amongst women of reproductive age: impact of and on subsequent pregnancies. *Eur J Neurol* 2015;22: 681–e42.