The Impact of Pregnancy on Hemorrhagic Stroke in Young Women

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Keywords

Hemorrhagic stroke · Stroke etiology · Stroke in pregnancy

Abstract

Background: Pregnancy is a sex-specific risk factor for causing hemorrhagic stroke (HS) in young adults. Unique physiological characteristics during pregnancy may alter the relative risk for HS in pregnant/postpartum (PP) women compared to HS in other young women. We compared patient characteristics and HS subtypes between young non-pregnant and PP women. **Methods:** We reviewed the medical records of all women 18–45 years old admitted to our center with HS from October 15, 2008 through March 31, 2015, and compared patient characteristics and stroke mechanisms using logistic regression. **Results:** Of the 130 young women with HS during the study period, 111 were non-PP women, and 19 PP women. PP women had lower proportions of vascular risk factors such as hypertension, prior stroke, and smoking, and a higher proportion of migraine (36.8 vs. 14.4%, $p = 0.01$). After adjusting for hypertension, smoking, migraine, prior stroke and prior myocardial infarction, PP women had lower odds of having an underlying vascular lesion (OR 0.14, 95% CI 0.04–0.44, $p =$

0.0009) and a higher proportion of the reversible cerebral vasoconstriction syndrome (RCVS) as cause of their HS. **Conclusions:** Women with pregnancy-associated HS had fewer cerebrovascular risk factors, lower odds of having underlying vascular lesions, and higher proportion of migraine and RCVS compared with similar-aged non-pregnant women. Pregnancy-associated HS appears to represent a unique pathophysiological process, requiring targeted study.

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Introduction

Hemorrhagic stroke (HS) accounts for one-third to one-half of strokes in young adults between 20 and 44 years of age [1, 2]. Among sex-specific risk factors for HS in the young, pregnancy plays a prominent role [3, 4]. Prior research has suggested that pregnancy-associated HS may differ significantly in pathophysiology when compared with HS in other young adults [4], but epidemiological studies of this disorder [5] lack many clinical details that may help to better elucidate the underlying pathophysiology.

Aims

We compared causes of HS and comorbidities in pregnant/postpartum (PP) young women with HS in other young women admitted to our center, hypothesizing that the subtypes of HS would differ between groups, and thus suggest differences in underlying pathophysiology.

Methods

Permission to review the electronic medical records for all patients ranging in age from 18–45 years old with HS from January 1, 2008 through March 15, 2015 was granted by the Institutional Review Board of Columbia University Medical Center, and the requirement for informed consent was waived. All women aged 18–45 at the time of the index event admitted or diagnosed during admission with HS, specifically intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), were included in the cohort. Women with traumatic ICH, traumatic SAH, or hemorrhagic conversion of an ischemic stroke were excluded from the analysis. Those with ICH and SAH due to venous infarction with hemorrhage from cerebral venous sinus or cortical vein thrombosis were also excluded; while pregnancy is a known risk factor for venous sinus or cortical vein thrombosis, and can cause hemorrhage, we chose to exclude these cases as the underlying pathophysiology is thrombotic, not hemorrhagic. Of 6,842 total stroke patients included in the database during the study period, 130 met criteria for inclusion into the study.

Participants were considered to have pregnancy-associated HS if the index event occurred during pregnancy or up to 12 weeks postpartum [6]. We reviewed participants' electronic medical records for comorbidities and stroke mechanisms. We categorized HS into 6 mechanisms: primary ICH (defined as ICH with no underlying vascular lesion and without presence of the reversible cerebral vasoconstriction syndrome [RCVS]); ICH with underlying vascular malformation (arteriovenous malformation or cavernous malformation); ICH due to RCVS, aneurysmal SAH, non-aneurysmal SAH due to RCVS, or other SAH (such as perimesencephalic SAH). RCVS was defined as single or recurrent thunderclap headache with concomitant ICH or cortical SAH and absence of an underlying vascular lesion, in accordance with criteria shown to have >96% specificity for this disorder [7]. Patients were considered to have an underlying vascular lesion if the presence of the lesion was confirmed on cerebral vessel imaging (computed tomographic angiography [CTA], digital subtraction angiography [DSA], or magnetic resonance angiography [MRA]).

Statistical Analysis

Groups were compared using chi-squared tests for categorical variables, Fisher's exact test where appropriate, and Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables. Crude and adjusted logistic regression analyses were used to assess odds of having a vascular lesion between non-PP women and PP women. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

There were 130 young women admitted with HS during the study period: 111 (85.4%) non-PP women and 19 (14.6%) PP women. All 19 of the PP women had dedicated cerebrovascular imaging (either CTA, MRA, DSA or a combination of these). Of the 111 non-PP women, 106 (95.5%) had dedicated cerebrovascular imaging; of the 5 women who did not, 3 had magnetic resonance imaging (MRI) of the brain with and without intravenous gadolinium contrast, 1 had MRI of the brain without contrast, and 1 had only CT of the brain without contrast due to a massive pontine hemorrhage resulting in rapid clinical deterioration. Baseline characteristics and imaging modalities used for the 2 groups are shown in Table 1. There were striking differences in stroke subtypes between groups as presented in Figure 1. Compared with non-PP women, PP women had fewer vascular risk factors, higher proportions of migraine, lower proportions of aneurysmal SAH, and higher proportions of RCVS as a cause for HS (13 of 19 PP women [68.4%] vs. 2 of 130 non-PP women [1.5%], $p < 0.0001$). PP women had lower odds of having an underlying vascular lesion (OR 0.14, 95% CI 0.04–0.44, $p = 0.0009$) when compared with non-PP women, after adjusting for hypertension, smoking, migraine, prior stroke, or prior myocardial infarction. Case characteristics in the PP group are detailed in Table 2. The timing of stroke with regard to subtype was also striking. Among PP women, HS clustered in the second trimester, all of which were due to a vascular lesion, and in the second week postpartum, none of which were due to a vascular lesion (Fig. 2). Of the 12 postpartum HS, 10 (83.3%) were due to RCVS. Among the 19 PP women, 6 (31.6%) had preeclampsia during pregnancy.

Discussion

The distribution of etiologies and comorbidities for HS in young women differs by pregnancy/postpartum status. In our cohort of 130 women aged 18–45, PP women had lower odds of having underlying vascular lesions, lower proportion of vascular risk factors, and a higher proportion of migraine compared with non-PP women. RCVS, a rare cause of HS in non-PP women, accounted for two-thirds of pregnancy-associated HS and almost all of the strokes in the postpartum period.

Our study adds to a growing body of evidence suggesting that the pregnancy-associated stroke, and in particu-

Table 1. Baseline characteristics for women aged 18–45 with hemorrhagic stroke

Characteristics/risk factors	Non-pregnant/postpartum women (<i>n</i> = 111)	Pregnant/postpartum women (<i>n</i> = 19)	<i>p</i> value
Age, median	39 (19–45)	34 (19–41)	0.08
Race/ethnicity, <i>n</i> (%)			0.21
White	25 (28.4)	6 (33.3)	
Non-hispanic black	20 (22.7)	2 (11.1)	
Hispanic	22 (25)	8 (44.4)	
Other	21 (23.9)	2 (11.1)	
Hypertension, <i>n</i> (%)	36 (32.5)	1 (5.3)	0.01
Diabetes, <i>n</i> (%)	8 (7.2)	0	0.22
Hyperlipidemia, <i>n</i> (%)	6 (5.4)	0	0.30
Obesity, <i>n</i> (%)	27 (27)	5 (27.8)	0.94
Prior stroke/MI, <i>n</i> (%)	16 (14.4)	0	0.10
Active smoking, <i>n</i> (%)	27 (24.3)	0	0.02
Migraine, <i>n</i> (%)	16 (14.4)	7 (36.8)	0.01
Sickle cell disease, <i>n</i> (%)	2 (1.8)	1 (5.3)	0.35
Cocaine use, <i>n</i> (%)	13 (11.7)	0	0.11
Alcohol use, <i>n</i> (%)	10 (9.0)	1 (5.3)	0.58
Cerebral vascular imaging modalities used, <i>n</i> (%)			
Digital subtraction angiography	81 (75)	13 (68.4)	0.17
CT angiography	90 (83.3)	12 (63.2)	0.03
MR angiography	41 (38.0)	13 (68.4)	0.01
Multiple imaging modalities	82 (73.9)	14 (73.7)	0.97

MI, myocardial infarction; CT, computed tomography; MR, magnetic resonance.

lar the postpartum stroke, represents a unique pathophysiological entity.

Almost one-third of the PP women in our cohort had preeclampsia, which is strongly associated with HS [8]. Preeclampsia, an endotheliopathy characterized by hypertension during pregnancy and multi-organ dysfunction, shares common features with RCVS and the posterior reversible encephalopathy syndrome [9, 10]. The prominent role that RCVS appears to play in the pathogenesis of postpartum stroke suggests that RCVS may represent a spectrum of pregnancy-associated angiopathy or vasculitis [11]. Postpartum angiopathy has been recognized, since Call and Fleming described it in 1988 [12], and like other forms of RCVS, can range in severity from mild to fulminant [13–15].

“Pregnancy-related angiopathy” may be a more apt term for this phenomenon, which may have features not present in other forms of RCVS. For example, animal studies have shown that exposing healthy rat brains to proinflammatory cytokines present in sera from normal pregnant rats led to activation of microglia and neuronal hyperexcitability. These effects were primarily mediated by tumor necrosis factor- α and were absent when the blood-brain barrier (BBB) was intact, thereby suggesting

that impairment in BBB function may partially underlie the increased vulnerability for PRES and pregnancy-related stroke [16]. In support of this hypothesis, follow-up in vitro studies demonstrated that serum from healthy pregnant women increased BBB permeability of rat cerebral arterioles by sixfold compared to controls; moreover, serum from preeclamptic women had an even larger effect size (18-fold) than serum from healthy pregnant women in increasing BBB permeability [17]. Placental ischemia, a key disturbance in preeclampsia, has been shown to impair cerebral blood flow autoregulation and enhance BBB permeability in rats, an effect that is mediated primarily by tumor necrosis factor- α [18, 19]. Additional studies demonstrated that reduced uterine perfusion pressure in pregnant rats led to increased vascular permeability and PRES-like changes [20]. Preeclampsia may represent the extreme on a continuum of pregnancy-induced cerebrovascular changes induced by either proinflammatory or hypertension-related factors that impair endothelial function. Animal models may be critical to enhance our understanding of the mechanisms that lead to pregnancy-associated stroke.

Headache is often a feature of preeclampsia, and by diagnostic criteria established in 2013, is sufficient to

Table 2. Characteristics, stroke mechanisms, and outcomes of PP women with hemorrhagic stroke ($n = 19$)

Age	Parity	Medical comorbidities	Pregnancy complications	Stroke type	Stroke mechanism	Stroke timing	Discharge mRS
19	G2P1	None	Intrauterine fetal demise after stroke	ICH	AVM	19 weeks	5
19	G1P0	Migraine, pneumonia	Preeclampsia	SAH	RCVS	33 weeks	0
21	G2P2	Sickle cell disease	Chorioamnionitis, preeclampsia	ICH/SAH	RCVS	PP day 11	4
29	G2P2	Obesity	None	ICH	AVM	27 weeks	0
30	G1P1	None	None	SAH	Aneurysm	17 weeks	2
30	G5P5	Migraine	None	ICH	RCVS	PP day 6	1
32	G1P1	Obesity, chronic hypertension	Preeclampsia	ICH	Hypertensive	PP day 1	4
32	G4P4	Migraine	Preeclampsia	SAH	RCVS	PP day 9	0
33	G2P1	Migraine, obesity	None	SAH	RCVS	PP day 8	0
34	G1P1	UTI	Gestational diabetes	ICH	AVM	22 weeks	4
35	G2P2	UTI, asthma	None	ICH	AVM	24 weeks	4
35	G1P1	None	Elective termination	ICH	AVM	15 weeks	5
37	G1P1	Polycystic ovarian syndrome	Cholestasis of pregnancy	SAH	RCVS	PP day 1	0
37	G4P4	None	Preeclampsia	SAH	RCVS	PP day 8	0
37	G12P13	Migraine	Multiple gestation	SAH	RCVS	PP day 12	1
38	G1P2	Obesity, pseudotumor cerebri	Multiple gestation	SAH	RCVS	PP day 11	1
38	G3P3	Migraine	None	ICH/SAH	RCVS	PP day 10	4
40	G1P1	Migraine, obesity, Hashimoto thyroiditis	None	SAH	RCVS	PP day 7	0
41	G1P1	None	Preeclampsia	ICH	Hypertensive	PP day 21	3

mRS, modified Rankin scale score; G, gravida; P, para; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; AVM, arteriovenous malformation; RCVS, reversible cerebral vasoconstriction syndrome; UTI, urinary tract infection; PP, pregnant/post partum.

Fig. 1. Hemorrhagic stroke subtypes in women aged 18–45. Cumulative bar graph of hemorrhagic stroke subtypes in non-pregnant women ($n = 111$) and pregnant/postpartum women ($n = 19$). Some patients had more than one subtype. * Primary ICH was defined as ICH with no underlying vascular lesion. ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; RCVS, reversible cerebral vasoconstriction syndrome.

qualify preeclampsia as “with severe features” even in the absence of proteinuria [21, 22]. Migraine has been associated both with hypertensive disorders of pregnancy [23] and hemorrhagic complications of RCVS [24]. The incidence of RCVS in the general population is unknown, but the condition is likely underdiagnosed where some patients with self-reported “migraines” may actually have RCVS [25–27]. In our cohort, the history of migraines appeared more frequently with HS in PP women,

but not in other young women. Thus, it is possible that migraine may represent either a risk factor or a marker for increased risk of pregnancy-associated HS in some women. The relationship between migraine, RCVS, preeclampsia, and pregnancy-related stroke is complex and not well characterized, and should be explored in future studies.

The second-trimester cluster of hemorrhages due to vascular lesions is also intriguing. Whether pregnancy in-

Fig. 2. Timing of pregnancy-associated hemorrhagic strokes in women 18–45 years old at a tertiary care center, 2008–2015. Light gray circles indicate SAH. Dark gray circles indicate ICH. Red perimeter indicates concomitant RCVS. Doughnut indicates pregnancy complicated by PEC. No strokes occurred in the first trimester or after postpartum day 21. All the strokes in the second trimester were due to the rupture of vascular lesions (1 aneurysm, 5 arteriovenous malformations). PEC, pre-eclampsia; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; RCVS, reversible cerebral vasoconstriction syndrome.

creases the risk of bleeding from unruptured vascular lesions is debated, with some data indicating increased risk [28, 29], and other data not supporting this [30–32]. However, previous series have also shown a tendency for ruptures, when they do happen, to occur in the second or the early third trimester [28, 31]. This could be related to the dramatic increase in plasma volume seen in the second trimester, reaching its peak at 32 weeks gestation, along with hormonally mediated alterations in vessel-wall elasticity and compliance that also peak during the second trimester [33]. This also warrants further investigation, as it may have implications for management of unruptured lesions.

Our exploratory study has limitations. It is a small sample confined to a single tertiary care center, which may limit the generalizability of our results. While all the PP women had vessel imaging, lack of vessel imaging in a few non-PP women may have led to under-diagnosis of vascular lesions in that group. However, since under-diagnosis would tend to bias towards a smaller difference between groups, this is unlikely to have changed our results.

Conclusions

In our sample of young women with HS, women who had pregnancy-related HS had fewer cerebrovascular risk factors and more migraine, were less likely to have underlying vascular lesions, and had higher proportions of

RCVS as the cause of their stroke than similarly aged non-PP women. Pregnancy-associated HS may be caused by a unique pregnancy-related angiopathy, producing a specific pathophysiology, and requiring a targeted study.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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