Age-Dependent Radiographic Vasospasm and Delayed Cerebral Ischemia in Women After Aneurysmal Subarachnoid Hemorrhage

Pui Man Rosalind Lai, William B. Gormley, Nirav Patel, Kai U. Frerichs, M. Ali Aziz-Sultan, Rose Du

■ OBJECTIVE: **Recent literature suggests there are sex differences in delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (aSAH). Our study serves to compare sex differences in radiographic vasospasm, DCI, and clinical outcome after aSAH, and to determine whether there are age-dependent differences.**

■ METHODS: **A total of 328 patients with ruptured cerebral aneurysms were evaluated for radiographic vasospasm, clinical deterioration, cerebral infarction, and modified Rankin Scale–determined clinical outcome at 6 months to 1 year after rupture. Multivariate regression analyses were performed to evaluate the associations between these outcome measures and sex, adjusting for age, hypertension, aneurysm location, admission Hunt and Hess grade, and modified Fisher grade.**

■ RESULTS: **After multivariate adjustment, women had higher rates of radiographic vasospasm (β = 0.35; 95% confidence interval [CI], 0.068–0.63; P = 0.015), clinical deterioration (odds ratio [OR], 2.8; 95% CI, 1.3–6.0; P = 0.008) and cerebral infarction (OR, 2.4; 95% CI, 1.0–5.5; P = 0.039), but no difference was observed in follow-up modified Rankin Scale (mRS) outcome score at 6 months to 1 year (P = 0.96). Older women (age >55 years) have a higher rate of clinical deterioration than men in the same age group (OR, 3.5; 95% CI, 1.0–12; P = 0.043). In contrast, younger women (age ≤55 years) had increased radiographic vasospasm (β = 0.55; 95% CI, 0.17–0.93; P = 0.005) and worse mRS outcome score (β = 0.042; 95% CI, -0.021 to 1.1; P = 0.042) compared with men.**

■ CONCLUSIONS: **Female sex is associated with a higher risk of radiographic vasospasm, clinical deterioration, and cerebral infarction. Furthermore, this association appears to be age-dependent. This study further supports the unique role of sex, and highlights the need to better understand the possible role of female hormones in the development of complications of subarachnoid hemorrhage.**

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) causes major morbidity and mortality, resulting in a significant individual and societal burden.[1-3] Patients who survive the initial insult of aneurysm rupture are at risk for delayed cerebral ischemia (DCI), involving clinical deterioration and cerebral infarction and contributing to poor outcome.

The incidence of intracranial aneurysms is proportionally higher in women compared with men,[4,5] and accumulating evidence suggests sex-based differences in DCI after subarachnoid hemorrhage. The development of angiogenic vasospasm influenced by

Key words
- Cerebral infarction
- Delayed cerebral ischemia
- Delayed ischemic neurological deficit
- Sex
- Subarachnoid hemorrhage
- Vasospasm

Abbreviations and Acronyms
ACA: Anterior cerebral artery, anterior communicating artery, and pericallosal artery
aSAH: Aneurysmal subarachnoid hemorrhage
CI: Confidence interval
CT: Computed tomography
CTA: Computed tomography angiography
DCI: Delayed cerebral ischemia
DSA: Digital subtracted angiography
ICA: Internal carotid artery, ophthalmic artery, posterior communicating artery, and anterior choroidal artery
MCA: Middle cerebral artery
MRI: Magnetic resonance imaging
mRS: Modified Rankin Scale
OR: Odds ratio
SD: Standard deviation
TCD: Transcranial Doppler ultrasound
VBA: Vertebral artery, basilar artery, and posterior cerebral artery

Department of Neurosurgery, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

To whom correspondence should be addressed: Rose Du, M.D., Ph.D. [E-mail: rdu@bwh.harvard.edu]

Citation: World Neurosurg. (2019) 130:e230-e235. https://doi.org/10.1016/j.wneu.2019.06.040

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

female hormones is established in animal models, but clinical data remain conflicting.[6] Here we present a retrospective cohort study of 328 patients with aSAH performed to evaluate sex differences in the incidence of radiographic vasospasm, DCI, and clinical outcome.

METHODS

We reviewed the records of 328 consecutive patients seen at our hospital's neurosurgical service between 2000 and 2017 with computed tomography (CT) scan evidence of nontraumatic subarachnoid hemorrhage and angiographic diagnosis of at least 1 cerebral aneurysm. The study was approved by the hospital's Institutional Review Board, which waived the requirement for informed consent.

Data Extraction

For each patient, we extracted basic demographic information from clinical notes and radiographic data, including age, sex, hypertension, date of service, Hunt and Hess grade at initial presentation, modified Fisher grade of first radiographic scan, and location of the ruptured aneurysm. Modified Fisher grade was calculated based on the criteria of Frontera et al.,[7] with all patients with a grade of 0 with documented xanthochromia on lumbar puncture. Location of the aneurysms was stratified using the Koivisto categories,[8] a charting system for categorizing aneurysms commonly used in studies since 2000: ACA (anterior cerebral artery, anterior communicating artery, and pericallosal artery), MCA (middle cerebral artery), ICA (internal carotid artery, ophthalmic artery, posterior communicating artery, and anterior choroidal artery), and VBA (vertebral artery, basilar artery, and posterior cerebral artery). For cases with multiple aneurysms, only the site of rupture was considered.

Outcome Measures

The outcome measures recorded included radiographic vasospasm, DCI (i.e., clinical deterioration and cerebral infarction), and modified Rankin Scale (mRS) outcome score. Radiographic vasospasm was defined as arterial narrowing on digital subtraction angiography (DSA) or CT angiography (CTA). Arteriosclerosis and vessel hypoplasia were excluded. Radiographic vasospasm was classified as none, mild (<30%) moderate (30%–50%), or severe (>50%) in comparison to vessel size on angiography at admission. All patients underwent at least 1 routine DSA or CTA within 14 days posticta for radiographic assessment of vasospasm, typically on posticta day 6 or 7. In addition, all patients underwent daily transcranial Doppler ultrasound (TCD) for at least 10 days or until TCD readings normalized. Patients with radiographic vasospasm on CTA/DSA, increase in TCD values indicative of vasospasm, or clinical symptoms concerning for DCI underwent additional imaging with CTA or DSA and treatment with hypertensive therapy. Patients who remained symptomatic despite hypertensive therapy were treated with intra-arterial verapamil or papaverine (before 2005) with or without balloon angioplasty. Nimodipine was given to all patients until discharge or posticta day 21, whichever occurred first.

DCI was measured after review of daily clinical notes using the criteria of Vergouwen et al.[9] and subcategorized into clinical deterioration and cerebral infarction. Clinical deterioration is defined as an occurrence of focal neurologic impairment, including hemiparesis, aphasia, apraxia, hemianopia, or neglect, or a decrease of at least 2 points on the Glasgow Coma Scale for at least 1 hour not explained by surgical complication, aneurysm rerupture, hydrocephalus, seizure, infection, metabolic disturbances, or causes attributed to CT or magnetic resonance imaging (MRI) findings. Cerebral infarction was defined as the presence of a low-density area on CT scan or a hyperintense area on diffusion-weighted MRI sequence in a vascular territory within 6 weeks after aSAH or the latest CT scan or MRI performed before death within 6 weeks. Infarct within 48 hours after aneurysm occlusion or a known complication from surgical clipping or endovascular treatment was excluded.

The mRS score at a 6-month to 1-year follow-up was assessed based on neurosurgical clinical notes at the time of follow-up. The mRS score, ranging from 0 to 6, was determined based on the physician's description of the patient's level of daily activity, including the ability to work and ambulate and assisted living requirements. Patients who died during hospitalization were assigned a score of 6 for the follow-up assessment.

Statistical Analysis

All statistical analyses were performed using Stata 12.0 (StataCorp LP, College Station, Texas, USA). Outcome measures included radiographic vasospasm, clinical deterioration, cerebral infarction, and mRS score at follow-up. Baseline characteristics were compared between men and women using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Logistic regression was used to evaluate binary outcomes, and linear regression was used to evaluate radiographic vasospasm and mRS outcome score. In the multivariate model, covariates used were age, hypertension, aneurysm location, admission Hunt and Hess grade, and modified Fisher grade. Subgroup analyses were performed with patients stratified by age $\leq$55 and >55 years. Statistical significance was specified by a P value of <0.05.

RESULTS

Our patient cohort comprised 328 patients with radiographically confirmed ruptured cerebral aneurysm from 2000 to 2017. Patient baseline characteristics are presented in **Table 1**. The mean (±SD) age was 57.3 ± 14 years, with women presenting at a later age (58 ± 14 vs. 54 ± 15 years in men; $P = 0.037$). There was a significant female predilection (n = 253; 77%). Admission Hunt and Hess grade, modified Fisher grade, and history of hypertension were not significantly different between men and women. Men had a higher percentage of ACA aneurysms ($P = 0.001$).

In the univariate regression model, women had higher rates of radiographic vasospasm ($\beta = 0.31$; 95% CI, 0.03–0.58; $P = 0.032$) and clinical deterioration (OR, 2.49; 95% CI, 1.23–5.05; $P = 0.011$). No sex-based difference was observed in cerebral infarction (OR, 1.80; 95% CI, 0.86–3.74; $P = 0.12$) or in follow-up mRS score ($\beta = 0.42$; 95% CI, -0.10, to 0.94; $P = 0.12$).

In the multivariate analyses (**Table 2**), radiographic vasospasm, clinical deterioration, and cerebral infarction were higher in

Table 1. Demographic and Clinical Parameters of Patients With Ruptured Cerebral Aneurysms

Characteristic	Male (N = 75)	Female (N = 253)	Total (N = 328)	*P* Value
Age (years), mean ± SD	54 ± 15	58 ± 14	57 ± 14	0.037
Hypertension	42 (59)	130 (53)	172 (54)	0.35
Hunt and Hess grade				0.067
1	23 (31)	36 (14)	59 (18)	
2	18 (24)	70 (28)	88 (27)	
3	14 (19)	74 (29)	88 (27)	
4	13 (17)	49 (19)	62 (19)	
5	7 (9)	22 (9)	29 (9)	
Modified Fisher grade				0.18
0	2 (2.7)	8 (3.2)	10 (3)	
1	6 (8.1)	8 (3.2)	14 (4.3)	
2	7 (9.5)	21 (8.4)	28 (8.6)	
3	33 (45)	99 (39)	132 (41)	
4	26 (35)	115 (46)	141 (44)	
Aneurysm location				
ACA	39 (52)	80 (31)	119 (36)	0.001
MCA	10 (13)	40 (16)	50 (15)	0.60
ICA	19 (25)	89 (35)	108 (33)	0.11
VBA	7 (9)	44 (17)	51 (16)	0.096
Radiographic vasospasm				0.032
None	17 (23)	28 (12)	45 (14)	
Mild	16 (22)	60 (25)	76 (24)	
Moderate	20 (27)	65 (27)	85 (27)	
Severe	20 (27)	90 (37)	110 (35)	
Clinical deterioration (%)	11 (16)	72 (33)	83 (41)	0.011
Cerebral infarction	10 (14)	53 (22)	63 (25)	0.12
mRS score at 6 months to 1 year				0.12
0	21 (31)	50 (22)	71 (24)	
1	29 (43)	88 (39)	117 (40)	
2	4 (6.0)	29 (13)	33 (11)	
3	4 (6.0)	17 (7.5)	21 (7.1)	
4	2 (3.0)	10 (4.4)	5 (4.1)	
5	0 (0)	5 (2.2)	5 (1.7)	
6	7 (10)	28 (12)	35 (12)	

ACA, anterior cerebral artery, anterior communicating artery, and pericallosal artery; MCA, middle cerebral artery; ICA, internal carotid artery, ophthalmic artery, posterior communicating artery, and anterior choroidal artery; VBA, vertebral artery, basilar artery, and posterior cerebral artery; mRS, modified Rankin Scale.

women ($\beta = 0.35$; 95% CI, 0.068–0.63; $P = 0.015$; OR, 2.8; 95% CI, 1.3–6.0; $P = 0.008$; and OR, 2.4; 95% CI, 1.0–5.5; $P = 0.039$, respectively). However, mRS outcome score at 6 months to 1 year was not significantly different between men and women ($P = 0.96$). In the multivariate analyses, vertebrobasilar and ICA aneurysms were associated with less cerebral infarction, but there were no differences in radiographic vasospasm, clinical deterioration, or mRS outcome score. Hunt and Hess grade was associated with cerebral infarction and a poorer mRS outcome score.

Table 2. Multivariate Analyses for Radiographic Vasospasm, Clinical Deterioration, Cerebral Infarction, and mRS Outcome Score at 6-Month to 1-Year Follow-Up

Parameter	Coefficient (β)*/OR†	95% CI	*P* Value
Radiographic vasospasm*			
Female sex	0.35	0.068–0.63	0.015
Age	−0.022	−0.031 to −0.013	1.0×10^{-6}
Hypertension	0.17	−0.061 to 0.41	0.15
Aneurysm location			
ACA (reference)	—	—	—
MCA	−0.21	−0.55 to 0.14	0.24
ICA	0.013	−0.26 to 0.29	0.92
VBA	−0.33	−0.70 to −0.024	0.067
Hunt and Hess grade	0.098	−0.007 to 0.20	0.067
Modified Fisher grade	0.091	−0.041 to 0.22	0.18
Clinical deterioration†			
Female sex	2.80	1.3–6.0	0.008
Age	1.00	0.99–1.0	0.58
Hypertension	1.11	0.64–1.9	0.71
Aneurysm location			
ACA (reference)	—	—	—
MCA	0.59	0.26–1.3	0.21
ICA	0.67	0.35–1.3	0.23
VBA	0.47	0.20–1.1	0.089
Hunt and Hess grade	1.19	0.92–1.5	0.18
Modified Fisher grade	0.98	0.72–1.3	0.92
Cerebral infarction†			
Female sex	2.4	1.0–5.5	0.039
Age	0.99	0.97–1.0	0.60
Hypertension	1.2	0.66–2.3	0.51
Aneurysm location			
ACA (reference)	—	—	—
MCA	0.49	0.20–1.2	0.12
ICA	0.38	0.18–0.78	0.009
VBA	0.16	0.049–0.50	0.002
Hunt and Hess grade	1.90	1.4–2.5	1.0×10^{-5}
Modified Fisher grade	0.94	0.64–1.4	0.78
mRS outcome score at 6-month to 1-year follow-up*			
Female	0.025	−0.11 to 0.12	0.96
Age	0.0070	0.034–0.011	1.0×10^{-6}
Hypertension	−0.046	−0.15 to 0.053	0.36
Aneurysm location			
ACA (reference)	—	—	—
MCA	−0.10	−0.25 to 0.044	0.17
ICA	−0.11	−0.23 to 0.0032	0.057
VBA	−0.10	−0.25 to 0.053	0.20
Hunt and Hess grade	0.11	0.68–0.16	1.0×10^{-8}
Modified Fisher grade	0.031	−0.025 to 0.087	0.27

OR, odds ratio; CI, confidence interval; ACA, anterior cerebral artery, anterior communicating artery, and pericallosal artery; MCA, middle cerebral artery; ICA, internal carotid artery, ophthalmic artery, posterior communicating artery, and anterior choroidal artery; VBA, vertebral artery, basilar artery, and posterior cerebral artery; mRS, modified Rankin Scale.

*Coefficient (β): radiographic vasospasm, mRS outcome score at 6-month to 1-year follow-up.

†OR: clinical deterioration, cerebral infarction.

Subgroup analyses were performed in patients age ≤55 years and >55 years (Table 3). In the younger subgroup, women had a higher rate of radiographic vasospasm in univariate (β = 0.56; 95% CI, 0.19–0.93; P = 0.003) and multivariate (β = 0.55; 95% CI, 0.17–0.93; P = 0.005) analyses, but this effect was not observed in the older subgroup. Similarly, women in the younger subgroup had worse mRS outcome scores on univariate (β = 0.64; 95% CI, 0.039–1.2; P = 0.037) and multivariate (β = 0.58; 95% CI, -0.0021 to 1.1; P = 0.042) analyses compared with the older subgroup (P = 0.25). Women in the older subgroup had a higher rate of clinical deterioration in both univariate (OR, 2.9; 95% CI, 1.0–8.0; P = 0.046) and multivariate (OR, 3.5; 95% CI, 1.0–12; P = 0.044) analyses compared with the younger subgroup.

DISCUSSION

DCI after aSAH remains a major cause of morbidity and mortality. Women have a higher incidence of cerebral aneurysm, but sex-specific effects of DCI are less clear. The aim of this study was to investigate the role of sex on the risk of developing aSAH complications and on outcomes. We found higher rates of radiographic vasospasm, clinical deterioration, and cerebral infarction in women compared to men. Interestingly, despite the higher rates of radiographic vasospasm and DCI observed in women, we did not find an association with mRS outcome score at 6 months to 1 year. To determine whether this effect is age-dependent, we performed subgroup analyses of women age ≤55 years and those age >55 years. We found worse radiographic vasospasm and worse mRS outcome scores in the younger group, but this effect was not observed in the older group. In contrast, clinical deterioration was greater in older women compared with men, and there was a trend toward increased cerebral infarction in older women compared with men.

Table 3. Subgroup Analyses of Female Patients Age ≤55 Years and >55 Years

	Age ≤55 Years			Age >55 Years		
Outcome Measures	**β*/OR†**	**95% CI**	***P* Value**	**β*/OR†**	**95% CI**	***P* Value**
Radiographic vasospasm*						
Univariate	0.56	0.19—0.93	**0.003**	0.15	−0.24 to 0.55	0.44
Multivariate	0.55	0.17—0.93	**0.005**	0.05	−0.38 to 0.48	0.82
Clinical deterioration†						
Univariate	2.0	0.73—5.3	0.18	2.9	1.0—8.0	**0.046**
Multivariate	2.1	0.71—6.2	0.18	3.5	1.0—12	**0.043**
Cerebral infarction†						
Univariate	1.7	0.59—4.9	0.33	1.8	0.65—5.04	0.26
Multivariate	1.9	0.56—6.6	0.30	2.9	0.86—10	0.086
mRS outcome score at 6-month to 1-year follow-up*						
Univariate	0.64	0.039—1.2	**0.037**	−0.058	−0.86 to 0.75	0.89
Multivariate	0.58	−0.021 to 1.1	**0.042**	−0.48	−1.3 to 0.33	0.25

This multivariate analysis includes female sex, hypertension, location of aneurysm, Hunt and Hess grade, and modified Fisher grade as covariates. Significant *P* values are in bold type.
OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale.
*Coefficient (β): radiographic vasospasm, mRS outcome score at 6-month to 1-year follow-up.
†OR: clinical deterioration, cerebral infarction.

Previous studies of sex-related differences in DCI have shown mixed results. Earlier studies found no association between female sex and symptomatic vasospasm or DCI,[10-12] whereas later studies found an increased association with female sex.[13-15] Germans et al.[15] presented the largest study to date using pooled data from 10 studies with 6713 patients (including data from BRANT, CONSCIOUS-1, D-SAT, EPO-STATIN, HHU, IHAST, IMASH, ISAT, and SHOP), and reported a greater risk of DCI in women, but no difference in the risk of cerebral infarction or outcomes.[15] A more recent study by Darkwah Oppong et al.[16] of 994 patients identified female sex as an independent predictor of symptomatic vasospasm and reported that women appeared to be at greatest risk for DCI and unfavorable outcome at age 55—74, but this effect was not observed in men. Our study is consistent with the more recently reported findings of a higher rate of DCI in women. Similar to Germans et al.,[15] we found no sex-based difference in overall outcome; in contrast, however, we found a higher rate of cerebral infarction in women.

Our data support previously postulated sex-related differences in DCI and outcomes that may be age-dependent. After stratification by age ≤55 years and age >55 years, we found that women age >55 years had a higher risk for clinical deterioration compared with men of the same age group, consistent with Darkwah Oppong et al.[16] Interestingly, we found a higher rate of radiographic vasospasm and poor outcomes in women compared with men in the younger age group. This suggests a dissociation between radiographic vasospasm and clinical deterioration in DCI, which has been attributed to impaired autoregulation, inflammation, microthrombosis, and cortical spreading depolarization.[17-19] We used age 55 years as the threshold to be consistent with cutoffs used in previous studies and to account for hormonal changes at menopause in women. Perimenopause begins at approximately age 45 years, and the median age at menopause in industrialized countries ranges between 50 and 52 years.[20,21] The differences observed between the sexes in the different age groups may be associated with changes in sex hormone profiles in women as they reach menopause. It has been postulated that postmenopausal women have a higher rate of aSAH due to the loss of estrogen,[22,23] which plays a role in vascular physiology through its effects on the vasculature and inflammatory process.[24] The endogenous estrogens, estradiol and estrone, bind to estrogen receptors to mediate long-term alteration of downstream gene expression. In animal studies, estrogens have been shown to decrease attenuation of cerebral vasospasm by inducing nitric oxide expression.[25] However, in this study, younger females had a higher rate of radiographic vasospasm despite having the highest estrogen levels, possibly suggesting that the hormonal influence is more complex in humans, and that estrogens alone do not explain the differences observed.

The main limitations of this study are its retrospective nature, which precluded us from accounting for hormonal status or the use of hormonal therapy. Furthermore, we could not account for patients who died before reaching the hospital. However, the study's single-institution nature provides consistency in the diagnosis and treatment of the patients included. Finally, clinical deterioration is difficult to identify, and misinterpretation of changes in neurologic status due to another cause is possible.

CONCLUSIONS

In this study, we examined the association of female sex with post-aSAH complications and found that women had higher rates of radiographic vasospasm and DCI, including cerebral infarction and clinical deterioration. After stratification by age, we also found a higher rate of clinical deterioration in women compared with men in the older age group, but a higher rate of radiographic vasospasm and worse outcomes in women in the younger age group. This study highlights the unique role of sex and our need to better understand the mechanism behind these differences.

REFERENCES

1. Rivero-Arias O, Gray A, Wolstenholme J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost Eff Resour Alloc*. 2010;8:6.
2. King JT Jr. Epidemiology of aneurysmal subarachnoid hemorrhage. *Neuroimaging Clin N Am*. 1997;7:659-668.
3. Zacharia BE, Hickman ZL, Grobelny BT, et al. Epidemiology of aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am*. 2010;21:221-233.
4. Longstreth WT Jr, Koepsell TD, Yerby MS, van Belle G. Risk factors for subarachnoid hemorrhage. *Stroke*. 1985;16:377-385.
5. Kongable GL, Lanzino G, Germanson TP, et al. Gender-related differences in aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1996;84:43-48.
6. Lin CL, Shih HC, Dumont AS, et al. The effect of 17beta-estradiol in attenuating experimental subarachnoid hemorrhage-induced cerebral vasospasm. *J Neurosurg*. 2006;104:298-304.
7. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified Fisher scale. *Neurosurgery*. 2006;59:21-27 [discussion: 21-27].
8. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. *Stroke*. 2000;31:2369-2377.
9. Vergouwen MD, Vermeulen M, van Gijn J, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391-2395.
10. Kale SP, Edgell RC, Alshekhlee A, et al. Age-associated vasospasm in aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis*. 2013;22:22-27.
11. Smith ML, Abrahams JM, Chandela S, Smith MJ, Hurst RW, Le Roux PD. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: the Fisher grade revisited. *Surg Neurol*. 2005;63:229-234 [discussion: 234-235].
12. Charpentier C, Audibert G, Guillemin F, et al. Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. *Stroke*. 1999;30:1402-1408.
13. Kozak N, Bereczki D, Szabo S. Predictors of symptomatic vasospasm after subarachnoid hemorrhage: a single center study of 457 consecutive cases. *Turk Neurosurg*. 2016;26:545-549.
14. Duan W, Pan Y, Wang C, et al. Risk factors and clinical impact of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: analysis from the China National Stroke Registry. *Neuroepidemiology*. 2018;50:128-136.
15. Germans MR, Jaja BNR, de Oliviera Manoel AL, Cohen AH, Macdonald RL. Sex differences in delayed cerebral ischemia after subarachnoid hemorrhage. *J Neurosurg*. 2018;129:458-464.
16. Darkwah Oppong M, Iannaccone A, Gembruch O, et al. Vasospasm-related complications after subarachnoid hemorrhage: the role of patients' age and sex. *Acta Neurochir (Wien)*. 2018;160:1393-1400.
17. Vergouwen MD, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. *J Cereb Blood Flow Metab*. 2008;28:1761-1770.
18. Carr KR, Zuckerman SL, Mocco J. Inflammation, cerebral vasospasm, and evolving theories of delayed cerebral ischemia. *Neurol Res Int*. 2013;2013:506584.
19. Woitzik J, Dreier JP, Hecht N, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2012;32:203-212.
20. Trévoux R, De Brux J, Castanier M, Nahoul K, Soule JP, Scholler R. Endometrium and plasma hormone profile in the peri-menopause and post-menopause. *Maturitas*. 1986;8:309-326.
21. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 2008;61:4-16.
22. Tabuchi S. Relationship between postmenopausal estrogen deficiency and aneurysmal subarachnoid hemorrhage. *Behav Neurol*. 2015;2015:720141.
23. Tu J, Jufri NF. Estrogen signaling through estrogen receptor beta and G-protein-coupled estrogen receptor 1 in human cerebral vascular endothelial cells: implications for cerebral aneurysms. *Biomed Res Int*. 2013;2013:524324.
24. Harrod CG, Batjer HH, Bendok BR. Deficiencies in estrogen-mediated regulation of cerebrovascular homeostasis may contribute to an increased risk of cerebral aneurysm pathogenesis and rupture in menopausal and postmenopausal women. *Med Hypotheses*. 2006;66:736-756.
25. Lin CL, Dumont AS, Wu SC, et al. 17beta-estradiol inhibits endothelin-1 production and attenuates cerebral vasospasm after experimental subarachnoid hemorrhage. *Exp Biol Med (Maywood)*. 2006;231:1054-1057.

Conflict of interest statement: M. Aziz-Sultan serves as a proctor for Covidien and Codman; W. Gormley serves as a proctor for Codman.

Received 10 April 2019; accepted 3 June 2019

Citation: World Neurosurg. (2019) 130:e230-e235.
https://doi.org/10.1016/j.wneu.2019.06.040

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***