A Preliminary Observational Study of Anovulatory Uterine Bleeding After Aneurysmal Subarachnoid Hemorrhage

CE 1.5 ANCC Contact Hour

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ABSTRACT

Introduction: It was observed that women with aneurysmal subarachnoid hemorrhage (aSAH) tended to have earlier menses than a typical 21- to 28-day cycle. The goal was to determine whether there is an association between aSAH and early onset of menses. **Methods:** All cases of aSAH in women aged 18 to 55 years who were admitted to our facility's neuroscience intensive care unit from June 1, 2011, to June 30, 2012, were reviewed. The electronic healthcare record for each of these patients was examined for documentation of menses onset, computed tomography of the head, brain aneurysm characteristics, modified Fisher score and Glasgow Coma Scale on admission, presence/absence of vasospasm, medical/surgical history, and use of medications that affect the menstrual cycle. The mean onset of menses in this study population was compared with the mean of 21 to 28 days with the 1-sample *t* test. **Results:** During the study period, 103 patients with subarachnoid hemorrhage were admitted. Sixty-one were women, and 15 were aged 18 to 55 years. Nine of the 15 (60%) had documentation of menses occurring during their initial week of hospitalization; 1 patient had documentation of menses on hospital day 12. There is a significant difference when the mean onset of menses in our patient population is compared with the approximate normal menstrual cycle of 21 to 28 days ($P < .01$). **Conclusion:** Early onset of menses or abnormal uterine bleeding after SAH may occur in women with aSAH and typically within the first 7 to 10 days after intracranial aneurysm rupture. The physiologic cause of early onset of menses after aSAH, whether primary or secondary, remains unknown.

Keywords: anovulatory uterine bleeding, intracranial hemorrhage, menstrual bleeding, stroke, subarachnoid hemorrhage, uterine bleeding, women

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening form of hemorrhagic stroke and is more common in women than men, typically occurring between 40 and 60 years old.[1] It was anecdotally observed that women with aSAH tend to experience their menses within the first week after their aSAH, but it was unclear as to whether this was related to stress hormone physiology or central hypothalamic-pituitary axis dysfunction. Such early menses after stress is now termed *anovulatory uterine bleeding* (AUB). The purpose of this study was to compare the onset of menses after aneurysm rupture in women with aSAH admitted to our neuroscience intensive care unit (ICU) with a normal menstrual cycle period of 21 to 28 days.

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Methods

After institutional review board approval, a retrospective medical record review was conducted of premenopausal women aged 18 to 55 years who were admitted to the neuroscience ICU from June 1, 2011, to June 30, 2012, with the diagnosis of aSAH. Their medical records were reviewed for specific documentation about the onset of menses during hospitalization. Each record was also examined for any contraceptive use such as oral, intrauterine devices, rings, implants, injections, and so forth or medication use that could affect menses, the patient's medical and surgical history (including gynecologic history such as hysterectomy), brain aneurysm location and size, Glasgow Coma Scale (GCS) score on admission, modified Fisher score for the severity of aSAH bleeding,[2] and development of cerebral vasospasm. All premenopausal patients with aSAH were evaluated, counting them as both case and controls for the purposes of this study because postmenopausal patients should not theoretically experience menses and therefore could not be used as controls.

To compare the statistical likelihood of early onset of menses in our study population, it was compared against the average menstrual cycle of approximately 21 and 28 days using the 1-sample *t* test, comparing the means for statistical significance. $P < .05$ was defined as significant. The means were also compared using a non-Gaussian distribution model (Wilcoxon rank sum test and the same *P* value for significance) because there was uncertainty whether aSAH-associated menses behave according to bell-shaped phenomenon. It should be noted the statistical comparison was considered purely exploratory because no published data could be found on early menses in aSAH in the literature or a database.

Results

During the study period, 103 SAH cases were identified from a prospective cerebrovascular registry at our center. However, 42 were excluded because the patients were men or the origin of the SAH bleeding was nonaneurysmal (eg, pretruncal or traumatic). The remaining 61 cases were women with aSAH, and 15 met the age criterion of 18 to 55 years. Five of the 15 cases did not have documented onset of menses during their neuroscience ICU stay (all 5 were 44 years or older, 1 was older than 50 years). Four of these patients were possibly postmenopausal, but there was no documentation of postmenopausal state. Table 1 outlines patient age, aneurysm location and size, history of migraine, GCS score, modified Fisher grade, and number of days after admission when menstruation started for the remaining 10 cases. Nine patients (90%) had documented menses starting during their initial week of hospitalization after aSAH admission. Only 1 patient had menses documented after the initial week, on hospital day 12. It is also important to note that 1 patient represented a second aSAH within the study time frame, is included in the case series twice (cases 6 and 7), and had AUB documented twice. None of the patients were taking oral contraceptives or had any other contraception method (eg, intrauterine device, rings, etc).

> The majority of women aged 18–55 with aSAH had onset of menses during the first week of hospitalization.

Table 2 outlines other stress-induced conditions observed in these aSAH patients, including Cushing ulcer, Terson syndrome (intraocular bleeding), and the neurocardiologic profile including their electrocardiogram, transthoracic echocardiogram, and cardiac enzymes (B-type natriuretic peptide and troponin T). One patient (case 1) had an abnormal electrocardiogram without reduction in the left ventricular ejection fraction. Two patients (cases 3 and 9) had Takotsubo cardiomyopathy on transthoracic echocardiogram with wall motion abnormalities.

This patient population had a median age of 43.5 years, and according to a study analyzing the natural history of the menstrual cycle based on various ages, they would be expected to have a mean menstrual cycle of 25.4 days.[3] Furthermore, the mean onset of menses in this study population (3.8 days) was compared with the normal expected mean onset of menses for both 21 and 28 days, assuming a Gaussian distribution. This is based on the assumption that these patients had a normal frequency of menstruation when their aSAH occurred. The comparison of means by 1-sample *t* test (2-tailed *P* values) yielded a *P* value less than .01 when comparing 3.8 with 21 days, which suggests that the early onset of menses after aSAH was unlikely due to chance. When the mean onset of menses of 3.8 days was compared with a mean of 28 days, it showed a similar *P* value less than .01. However, the 1-sample *t* test model does assume a Gaussian, or bell-shaped, normal distribution. When assuming a non-Gaussian distribution, we used the Wilcoxon rank-sum test yielding statistical significance versus 28 days ($P < .01$). This would suggest that this

TABLE 1. Patient Characteristics With AUBSAH

Case	Age, y	Modified Fisher Scale	Location of Aneurysm	Securement	Size of Aneurysm, mm	History of Migraine	GCS Score	Onset of Menses (No. Days After Hospital Admission)
1	42	3	ACOM	Clipping	8	Yes	14	4
2	50	4	ACOM	Clipping	2.5	No	15	4
3	48	4	Left PICA	Coiling	7	Yes	15	4
4	45	4	Left PCOM	Clipping	4	No	10	0
5	35	4	Left PCOM	Coiling	6	No	14	0
6[a]	40	4	Right PCOM	Coiling	5.5	No	15	3
7[a]	40	3	Right PCOM	Coiling	5.5	No	15	4
8	39	4	ACOM	Coiling	6	No	14	12
9	51	4	Right PICA	Coiling	6	No	13	4
10	49	4	Right MCA	Clipping	8	No	14	3
Mean	43.9	3.8			5.85		14	3.8
Median	43.5	4			6		14	4
Standard deviation (confidence intervals)								3.29 (1.4–6.1)
1-sample *t* test comparison of means (3.8 vs 21 d), 2-tailed *P* value, assuming Gaussian distribution								$P < .01$
Wilcoxon signed rank-sum test (3.8 vs 21 and 28 d of mean onset of menses), non-Gaussian distribution								$P < .01$

Abbreviations: ACOM, anterior communicating artery aneurysm; GCS, Glasgow Coma Scale; MCA, middle cerebral artery; PCOM, posterior communicating artery aneurysm; PICA, posterior inferior cerebellar artery.
[a]Cases 6 and 7 refer to the same patient with 2 separate aneurysmal subarachnoid hemorrhages 27 days apart.

study population had an earlier onset of menses compared with a normal 21- to 28-day menstrual cycle.

Discussion

We theorize that an early onset of menses may occur after aSAH in women. Furthermore, this issue is an important sex-specific observation that may be previously unrecognized in the ICU. Although there is uncertainty as to the pathophysiologic origins of AUB after aSAH (AUBSAH), it is speculated that aSAH causes substantial stress hormone response in women.

In 1932, Dr Harvey Cushing first described the association of peptic ulcers occurring postoperatively in his neurosurgical patients.[2] This discovery suggested a brain-body relationship that could influence different organs in the body under stress. It is plausible that brain aneurysm rupture may induce physical and psychological stress that causes some form of neurohormonal dysregulation and AUB. However, given our limited size and study design, we cannot entirely exclude other association biases inherent to this preliminary study causing AUB. Other associations of stress and its effects have been described such as Takostsubo cardiomyopathy, which has been identified in women after aSAH[4–7] and was also noted in some of our patients (Figure 1). After our finding, we hypothesize that AUBSAH could be present in other brain injury models such as traumatic brain injury or traumatic SAH.

In this study, it was found that most women with aSAH aged 18 to 55 years had onset of menses documented during the first week of hospitalization after aSAH, which seems unlikely due to chance. Although frequency of menstruation varies for each individual, it is improbable that the onset of menses seen in this patient population falls within the normal mean menstrual cycle published in the literature (27.7 ± 2.4 days or 21-28 days).[8,9] According to Sherman and Korenman,[3] and this population's mean age of 43.5 years, a mean menstrual cycle of 25.4 days would be expected, assuming that women with aSAH have normal menstrual cycles. However, the more extreme range of normal menses of 21 to 28 days was used against this population, and it still showed notable differences in early onset of menses. Therefore, this observation may represent a previously unrecognized phenomenon in women with aSAH in the ICU setting. Undoubtedly, this phenomenon may have been overlooked because of higher-priority critical care issues in this patient population. Nonetheless, this phenomenon is an important sex-specific issue that should be recognized going forward.

TABLE 2. Stress-Related Phenomenon in the Patients Studied

Case	ECG Abnormalities	Admission BNP (Normal, 0–75 pg/mL)	Admission Troponin T (Normal, 0.00–0.10 ng/mL)	TTE Findings	Cushing Ulcer, Peptic Ulcer, or GI Bleeding During Hospitalization	Terson (Intraocular Bleeding) Syndrome
1	Normal sinus rhythm Possible septal infarct (poor R wave progressive anteriorly) Nonspecific ST abnormality Prolonged QT QTc: 489 ms	NA	0.04	Hyperdynamic left ventricular systolic function Calculated LVEF, 70% Abnormal left ventricular geometry consistent with concentric left ventricular hypertrophy Diastolic dysfunction grade I (abnormal relaxation)	Negative[a]	Negative
2	No ST-T wave acute changes Normal sinus rhythm Prolonged QT QTc: 493 ms	95 (mildly elevated)	<0.01 (normal)	Normal LVEF, 53%, and otherwise normal ventricular function	Negative[a]	Negative
3	Normal sinus rhythm. No acute ST-T wave changes. QTc: 497 ms Prolonged QT	7 (normal)	0.10 at admission (borderline elevated) and then, 8 h later, 0.03 (normal)	Takotsubo cardiomyopathy (LVEF 30%) with regional wall abnormalities (Figure 1), acute mild pulmonary hypertension, and pulmonary edema Doppler-derived pulmonary artery mean pressure, 27 mm Hg Findings consistent with mild pulmonary hypertension (26-40 mm Hg) Estimated right ventricular systolic pressure, 37 mm Hg Mildly dilated inferior vena cava with no inspiratory collapse Findings resolved in 9 d on repeat TTE; LVEF 63%, with no pulmonary hypertension	Negative[a]	Negative
4	Normal ECG QTc: 457 ms Normal sinus rhythm	67 (normal)	<0.01	Abnormal left ventricular geometry consistent with concentric remodeling Hyperdynamic left ventricular systolic function Calculated LVEF, 70% Estimated right ventricular systolic pressure; 34 mm Hg, consistent with mild pulmonary hypertension (26-40 mm Hg)	Negative[a]	Negative

(continues)

TABLE 2. Stress-Related Phenomenon in the Patients Studied, Continued

Case	ECG Abnormalities	Admission BNP (Normal, 0–75 pg/mL)	Admission Troponin T (Normal, 0.00–0.10 ng/mL)	TTE Findings	Cushing Ulcer, Peptic Ulcer, or GI Bleeding During Hospitalization	Terson (Intraocular Bleeding) Syndrome
5	Sinus rhythm with first-degree atrioventricular block Otherwise normal ECG QTc: 441 ms	22	<0.01	Hyperdynamic left ventricular systolic function Calculated LVEF, 71% Abnormal left ventricular geometry consistent with concentric left ventricular hypertrophy Normal left ventricular diastolic function	Negative[a]	Negative
6[b]	Normal sinus rhythm Possible left atrial enlargement Right bundle branch block QTc: 507 ms	84 (elevated)	<0.01	Abnormal left ventricular geometry consistent with concentric left ventricular hypertrophy Normal global and regional left ventricular systolic function Calculated LVEF, 64% Normal left ventricular diastolic function	Negative	Negative
7[b]	Normal sinus rhythm Right bundle branch block QTc: 479 ms	NA	<0.01	NA	Negative[a]	NA
8	Sinus bradycardia (heart rate, 56) Otherwise normal ECG QTc: 447 ms	215 (elevated)	<0.01	Abnormal left ventricular geometry consistent with concentric remodeling Normal global and regional left ventricular systolic function LVEF, 71% Indeterminate diastolic function	Negative[a]	Positive in the left eye (6 small, <2 mm) neurofiber layer and blot hemorrhages by ophthalmologist
9	Normal sinus rhythm Delayed precordial R wave progression Prolonged QT QTc: 501 ms	101 (elevated)	0.47 (peak at admission) decreasing to 0.37 on the following day	Abnormal systolic function with regional wall motion abnormalities present Calculated LVEF, 51%	Negative	Negative

(continues)

TABLE 2. Stress-Related Phenomenon in the Patients Studied, Continued

Case	ECG Abnormalities	Admission BNP (Normal, 0–75 pg/mL)	Admission Troponin T (Normal, 0.00–0.10 ng/mL)	TTE Findings	Cushing Ulcer, Peptic Ulcer, or GI Bleeding During Hospitalization	Terson (Intraocular Bleeding) Syndrome
10	Left anterior fascicular block Poor R wave progression; possible previous anterior infarct QTc: 436 ms	NA	<0.01	Abnormal left ventricular geometry consistent with concentric left ventricular hypertrophy Normal global and regional left ventricular systolic function Calculated LVEF, 53% Diastolic dysfunction grade IA (elevated filling pressure)	Negative	Positive in left eye: <20 scattered inner retina (<2 mm) hemorrhages

Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiogram; GI, gastrointestinal; INT, interval; LVEF, left ventricular ejection fraction; NA, not assessed; QTc, corrected QT interval; TTE, transthoracic echocardiogram.

[a]There was no documentation of any evidence of GI bleeding, ulcer, peptic ulcer, melena, or hematochezia during hospitalization; however, all patients were put on proton-pump inhibitors (pantoprazole or equivalent) at hospital admission.

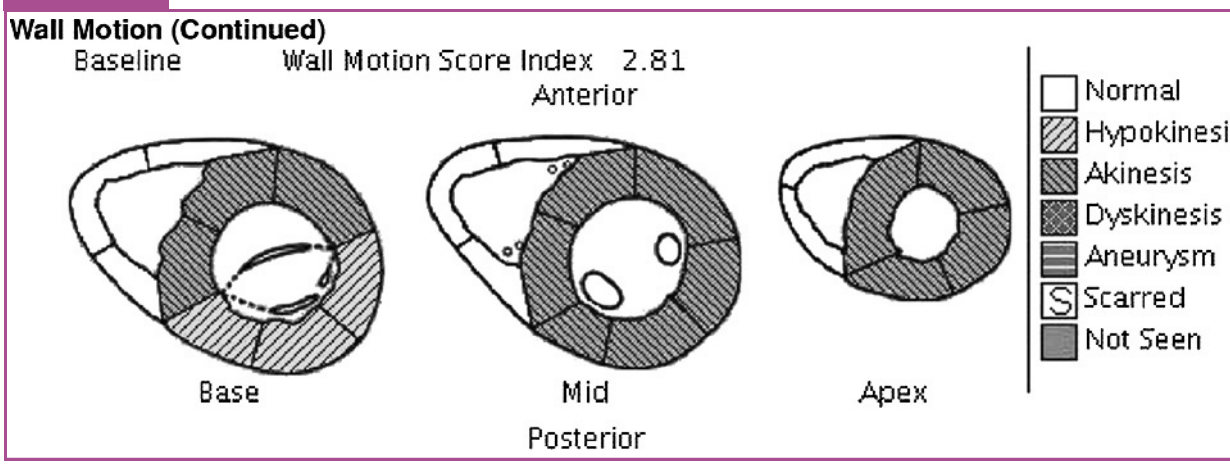
[b]Cases 6 and 7 refer to the same patient with 2 separate SAHs 27 days apart.

Irregular menstrual cycles are common, of varying origins, and caused by a variety of factors.[3,8] After menarche, the intermenstrual intervals are long, and before menopause, the cycle duration shortens.[3] As women pass their reproductive years, there is ovarian follicular depletion accompanied by a change in intermenstrual bleeding. This transition to menopause is called perimenopause and occurs on average at 47.5 years old.[10] Menopause is clinically recognized after 12 consecutive months of amenorrhea. There is a wide variability in onset of presentation, but in healthy women, menopause typically occurs around 51 years old.[11] The postmenopausal state starts 1 to 5 years after the final menstrual period and is further characterized by a permanent decrease in ovarian hormone function leading to accelerated bone loss[12] and other sequelae. With a mean age of 43.5 years, a normal menstrual cycle should have taken place in most of our study population up until their aSAH. However, other factors may affect the frequency of menstruation including smoking, medications such as contraceptives, genetics, diet, and exercise.[13] Anovulatory uterine bleeding (previously called dysfunctional uterine bleeding) is defined as excessive, prolonged, or unpredictable bleeding from the endometrium that is unrelated to structural or systemic disease, such as the premature onset of what was documented as menses in this study.[14,15]

A previous study suggested a lack of estrogen in Takotsubo cardiomyopathy.[16] Estrogen has a cardioprotective factor against the toxic effects of catecholamines,[17,18] which supports the idea that changes in hormone levels can lead to secreted substances that exert themselves at distant sites, perhaps causing otherwise unexplained brain-body syndromes.[7] However, this phenomenon cannot be entirely implicated to the central nervous system stress response because one description was found in the literature describing AUB after acute musculoskeletal trauma.[19] Therefore, similar to Takotsubo cardiomyopathy, it is typically the magnitude of the stress itself (eg, GCS) that correlates with the cardiac condition or postmenopausal status. Other pathophysiologic causes of this phenomenon described in the literature include transient central hypogonadotrophic hypogonadism, which can cause hormonal disruption and lead to AUB,[19,20] or breakthrough menstrual bleeding in premenopausal women.

A final etiology to AUBSAH may be related to matrix metalloproteinases (MMPs), which are upregulated in most brain injury models. Matrix metalloproteinases are capable of degrading the constituents of the basal lamina and extracellular matrix. A number of MMPs are involved in both normal and abnormal endometrial bleeding.[21] Matrix metalloproteinases have been implicated in a variety of intracerebral and extracerebral functions in patients after aSAH.[22] Plasma levels of

FIGURE 1 **Wall Motion Abnormalities Compatible With Takotsubo Cardiomyopathy From Case 3 in the Study. Graphic Illustrates Akinesis From the Base to the Apex of the Left Ventricle. Follow-Up Echocardiogram Performed 9 Days Later Showed Normal Ventricular Function.**



MMP-9 have been shown to be appreciably elevated during the first 14 days after presenting with aSAH.[23] Therefore, a possible mechanism of AUBSAH may be due to the increased inflammatory cytokines after aSAH, which subsequently upregulate MMPs that can facilitate sloughing of the endometrial lining. Measuring theses inflammatory markers could be considered for future studies.

During the transition to menopause, different changes in lipid metabolism and cholesterol also occur and can lead to increased atherosclerosis and blood vessel intracranial changes. Matthews and colleagues[24] reported a substantial increase in low-density lipoprotein cholesterol (LDL-C) and a modest increase in high-density lipoprotein cholesterol in women close to the final menstrual period. Patients with at least 7.32-mg/dL annual increase in LDL-C had a 50% greater chance of carotid plaque index greater than 2 in the postmenopausal years compared with those who had a lower LDL-C increase.[24] The increased risk of developing atherosclerosis puts women at risk to experience cerebrovascular accidents, which is a historical term for stroke, includes SAH, and is confounded by advancing age and many other factors.

Limitations

There are several limitations of this study. First, the lack of baseline frequency of menstruation in this population is a limitation of the study because menstrual cycles do vary by individual and throughout the reproductive years and cause different physiologic changes.[3,8,24] Another limitation of this study is the retrospective chart data abstraction of the menstrual cycle characteristics, although those with menses were identified prospectively by neuroscience ICU nurses and documented in the record. Another limitation was the relative lack of extensive clinical documentation of contraceptive methods, menses, and menstrual status in the medical record, including the volume of menses made (eg, milliliters or weight) and the character of the bleeding thickness and color. Nonetheless, ICU nursing was able to capture the needed information about onset, which was insightful into this potentially sex-specific issue that otherwise seemed underappreciated. It was also discovered that menopause is difficult to define because at least a year of amenorrhea has to pass and likely this event occurs more on a continuum rather than an exact date.

The relatively small sample size must be acknowledged; however, more than 100 SAH patients were screened during the period to make this observation in 61 patients with nursing documentation of their menses timing. Of this larger cohort, only 15 patients met our final age criteria of 18 to 55 years and were presumably premenopausal or perimenopausal. This age range was chosen to capture the most patients who might still be premenopausal, but that is highly variable and specific to each woman. Another item that could not be captured was the sympathetic outflow after aSAH in these patients, which can increase in response to pain or emotional stress and could be a pathophysiologic trigger of this phenomenon similar to neurohormone-induced stress-related diseases such as Takotsubo cardiomyopathy.[5–7] A final limitation of this study was that a gynecologic history taken from the patients themselves was not always feasible or reliable due to depressed or altered levels of consciousness after aSAH. Two of our 10 cases (20%) presented with a GCS score of 13, making it difficult to obtain a detailed menstrual history. However, menses can be easily identified by physical examination of the vaginal area.

Strengths

The study describes a potentially important sex-specific issue occurring in women with aSAH. Second, this study may have implications in evaluating total blood loss in the ICU with so-called *ICU vampirism* anemia or phlebotomy-related blood loss from repeated laboratory draws, as well as providing better documentation of blood loss in menstruating women in the ICU. This study also provides benefit for designing future observational studies on this issue in terms of improved collection of gynecologic history and examination in the ICU and obtaining additional historic details of the patient's normal menstrual cycle characteristics, date of last menstrual period, methods of contraception, and other potential biomarkers such as MMP and estrogen and other hormone levels after aSAH.[25] However, because we acknowledge that this work is only a retrospective study, it does not definitively prove cause and effect. In other words, it has yet to be proven that cases of aSAH in women actually have the opposite phenomenon that central nervous system hypothalamic-pituitary-ovarian axis neurohormonal disturbance occurs and leads to aneurysmal rupture and subsequent SAH bleeding and menses. Only larger prospective observational studies with biomarker analysis might help establish causal relationships.

Future studies should also consider blood sampling of hypothalamic-pituitary hormones in premenopausal women with unruptured brain aneurysms and those with aSAH for comparison. However, it was not possible to blood endocrine test every woman every day with an unruptured aneurysm as a baseline hormone change before aneurysm rupture because this would likely be too costly given relatively low rupture rates of most aneurysms. Future studies could use methods similar to the ones used in this study, albeit with better gynecologic history with measurements of drops in estrogen or progesterone levels.

Conclusion

This small, retrospective study suggests that aSAH may disrupt the normal menstrual cycle of premenopausal women, leading to earlier breakthrough menstrual bleeding or AUB. To our knowledge, this is the first description of this potentially sex-specific and stress-related phenomenon in women with aSAH. A future prospective study is suggested to evaluate the neuroendocrinologic profile in similar patients to better understand the effects of aSAH on hypothalamic-pituitary-ovarian-uterine pathophysiology.

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