Oral contraceptive and hormone replacement therapy in women with cerebral aneurysms

Michael Chen,[1] Bichun Ouyang,[1] Lindsay Goldstein-Smith,[1] Lisa Feldman[2]

[1]Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA
[2]Department of Neurological Surgery, Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence to
Dr M Chen, Rush University Medical Center, 1725 W Harrison St, Suite 1121, Chicago, IL 60612, USA; michael_chen@rush.edu

Received 24 September 2010
Revised 14 November 2010
Accepted 24 November 2010
Published Online First 17 December 2010

ABSTRACT

Background It is well known that cerebral aneurysms occur more frequently in women, with numerous studies suggesting a role for hormones in aneurysm pathogenesis. Estrogen promotes normal physiologic vascular endothelial function but also fluctuates during the menstrual cycle and drops significantly at menopause.

Methods A retrospective, case control study was conducted to determine if exogenous estrogen use, which stabilizes estradiol levels, had any association with the presence of cerebral aneurysms. 60 women with intradural cerebral aneurysms were interviewed about their basic medical and female reproductive health histories, including oral contraceptive pill and hormone replacement therapy use and duration of use. This information was compared with the same data collected from women in the general public, as represented by 4682 women contacted through random digit phone dialing in the National Institute of Child Health and Human Development sponsored Contraceptive and Reproductive Experiences Study, published in 2002.

Results Multivariate logistic regression showed a significant association between a lower rate of oral contraceptive (OR 2.1, CI 1.17 to 3.81; p=0.01) and hormone replacement therapy (OR 3.09, CI 1.54 to 6.22; p=0.002) use and the presence of a cerebral aneurysm.

Conclusion These data suggest that exposure to exogenous estrogen agents in women is associated with a lower frequency of cerebral aneurysms.

INTRODUCTION

Each year 30 000 people in the USA develop subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm. When compared with other vascular diseases of the brain, cerebral aneurysms are associated with a unique gender discrepancy.[1–3]

Multiple studies have reported this consistent gender inequality, including the International Study of Unruptured Intracranial Aneurysms study, which evaluated 4060 patients and found that 75% were women.[4] Similarly, of the 2143 patients in the International Subarachnoid Aneurysm Trial, 63% were women.[5] Another prospective study of aneurysmal SAH found that women have an age adjusted RR of 1.74 compared with men.[6]

Apart from female gender, other well described risk factors associated with cerebral aneurysm rupture include smoking, hypertension, alcohol abuse,[7 8] low socioeconomic status,[9] autosomal dominant polycystic kidney disease[7 10] and family history of SAH.[7 11] A gender related etiology is likely important because many of these risk factors, including hypertension, cigarette smoking and alcohol use, are generally more common in men.

The effects of estrogen on vascular structure and function have been described to occur via its pleiotropic effects on vascular endothelial cells, collagen and nitric oxide. Endothelial cell injury via wall shear stress is considered an initial step in aneurysm formation. The ability of endothelial cells to withstand the wall shear stress from pulsatile arterial blood flow depends on their ability to grow, proliferate and remodel efficiently. Estrogen has been found to contribute to this normal homeostatic process by stimulating endothelial proliferation and reducing vascular tone via its receptors on endothelial and vascular smooth muscle cells.[12] Endothelial remodeling is what leads to maintenance of a constant arterial lumen diameter, which promotes laminar, energy efficient blood flow, in spite of the energy inefficient configuration of the circle of Willis.

As such, changes in estrogen levels may have ramifications on vascular integrity. The estrogen loss that occurs at menopause is well known to be responsible for skin fragility because of its deleterious effects on collagen and elastin.[13] Through similar mechanisms, estrogen loss also leads to diminished elasticity in blood vessels.[14] This may compromise the ability of the vessel wall to effectively remodel to counteract the wall shear stress forces. There may be several clinical correlates to estrogen's effects on the cerebral vasculature. The increase in female prevalence of cerebral aneurysms does not occur until after the age of 40 years.[6 15] The peak age of incidence of aneurysmal rupture in women is between 50 and 59 years of age[15] while the median age of SAH is around 52 years.[5]

Our aim was to perform a clinical study to characterize the role estrogen plays, if any, in not only the rupture of, but also the pathogenesis of, cerebral aneurysms. Use of exogenous estrogen agents such as oral contraceptive pills (OCP) and hormone replacement therapy (HRT) normalizes the physiologic drops in estrogen seen during the menstrual cycle and particularly at menopause. The goal of this study was to compare the rate of exogenous estrogen use in a cohort of women with largely unruptured cerebral aneurysms, with large sample national averages.

METHODS

We obtained institutional review board approval for our study protocol. We conducted a structured, scripted telephone survey of all female patients, 18 years of age or older with at least one saccular cerebral aneurysm, >3 mm in maximal diameter, not associated with a brain arteriovenous malformation, seen on brain vascular imaging, who were under the care of a single physician (MC). We

recorded the circumstances in which patients did not participate (refusal, inability to locate patient, patient death or mental impairment due to stroke). For those patients who were mentally impaired or had passed away, we asked if an appropriate proxy was available. A structured questionnaire was used to obtain detailed information regarding past medical, social, family and gynecologic history, including their lifetime use and duration of use of OCP and HRT. Subjects were also questioned about their lifetime use of tobacco and whether a doctor ever diagnosed them with hypertension, diabetes or heart disease.

Our control group was obtained from the publicly available data set of 4682 women sampled from Atlanta, Detroit, Los Angeles, Philadelphia and Seattle as a part of the National Institute of Child Health and Human Development sponsored Contraceptive and Reproductive Experiences Study. This study investigated what role OCP and HRT played in the development of breast cancer. This control data set was obtained via unclustered, equal probability sampling of phone numbers. Trained interviewers, from 1994 to 1998, used questionnaires focused on reproductive, exercise and health histories, including use of OCP and HRT.[16] From these control data, we matched controls to our cases for both age (<45, 45–54 and >54 years) and educational level (≤12th grade, >12th grade). In each of the six subgroups, the case to control radio was fixed at 1:7.

Differences between study groups were examined with the χ^2 test for categorical variables and the Student's t tests for continuous variables. Logistic regression models were used to assess the association between the presence of a cerebral aneurysm and use of OCP and HRT as well as other factors, including body mass index, smoking, nulliparity and menopausal status, hysterectomy and number of pregnancies. Statistical significance was set at $p<0.05$. All statistical analyses were performed using SAS 9.1 (SAS Institute).

RESULTS

From 2008 to 2010, 134 patients with cerebral aneurysms were under the care of a single physician (MC); 68% (91) were women but only 66% (60) of those were available or had a reliable proxy to answer our survey questions. Age range was between 31 and 80 years, with 65% of cases involving an unruptured aneurysm. Table 1 shows the characteristics of the two study groups. Although we matched controls to our cases for age categories of (<45, 45–54 and >54 years), our cases were slightly older than controls on average. Also, our case group had a trend towards more frequent premature menopause. Other characteristics, including body mass index, age of menarche, smoking, nulliparity, number of pregnancies, menopausal status and rate of hysterectomy were comparable between the case and control groups.

Multivariate logistic regression was performed to calculate adjusted ORs for the presence of a cerebral aneurysm. Both OCP (OR 2.1, CI 1.2 to 3.8; p=0.01) and HRT (OR 3.1, CI 1.5 to 6.2) use were significant, indicating that women who used OCP and HRT were less likely to have cerebral aneurysms.

Comparison between ruptured and unruptured status within our case group, as shown in table 2, did not show any statistically significant differences in OCP and HRT usage. Although menopausal age was statistically different, this difference disappeared when controlling for rate of hysterectomy.

Table 1 Medical histories of women with aneurysms compared with women in the general public

Variable	Case (n=60)	Control (n=420)	p Value
Age (years)			
Mean (SD)	53.9 (12.53)	51.3 (7.85)	0.12
Body mass index (kg/m^2)			
Mean (SD)	27.8 (7.5)	27.3 (10.3)	0.73
Education (>12 grade)			
n (%)	27 (45.8)	193 (46)	0.99
Smoker			
n (%)	16 (26.7)	90 (21.4)	0.36
Menarche age (years)			
Mean (SD)	12.8 (1.7)	12.8 (1.8)	0.81
Nulliparous (yes)			
n (%)	9 (15)	56 (13.4)	0.73
No of pregnancies (≥3)			
n (%)	30 (50)	185 (44.2)	0.39
Age first live birth (years)			
Mean (SD)	21.7 (5.6)	21.8 (6.4)	0.97
Age first live birth ≥30			
n (%)	5 (10)	41 (11.3)	0.79
Menopause age (years)			
Mean (SD)	43.4 (8.5)	44.3 (8.5)	0.53
Premature menopause (menopause age <45)			
n (%)	20 (50)	106 (34)	0.18
Post-menopause			
n (%)	40 (66.7)	228 (61.2)	0.45
Hormone replacement therapy			
n (%)	14 (23.7)	188 (44.8)	0.002
Oral contraceptive pill			
n (%)	36 (60)	326 (77.6)	0.003

DISCUSSION

Consistent with our hypothesis was the finding that women with cerebral aneurysms used OCP and HRT significantly less frequently than women in the general population. Furthermore, there was a trend towards a younger mean age of menopause and a more frequent premature menopause (defined as age <45 years) in our case group. These results support the hypothesis that physiologic drops in estrogen and/or low endogenous levels of estrogen that occur during the menstrual cycle and particularly at menopause may not only play an important role in cerebral aneurysm formation but may serve as a potential therapeutic target.

The majority of our cases consisted of women with unruptured aneurysms (65%). Evaluation of a hormonal etiology behind unruptured cerebral aneurysms in women is unprecedented, most likely because non-invasive brain vascular imaging has only recently been a widely used diagnostic study.

Jamous *et al* used animal experiments to demonstrate the protective role HRT plays in rats subjected to experimental aneurysm induction and oophorectomy.[17] After a 10 week treatment with 17β-estradiol, the cerebral arteries were evaluated under electron microscopy for aneurysmal changes. Only one of the 15 rats (7%) given 17β-estradiol, as opposed to eight of 15 (53%) rats not given exogenous estrogen, developed saccular aneurysmal changes, indicating a protective role for estrogen in aneurysm development.

Prior clinical data on the relationship between OCP use and SAH have been inconsistent. For example, a meta-analysis of 11 studies revealed a significant relationship between OCP use and SAH with an RR of 1.42 (95% CI 1.12 to 1.80; p=0.004).[18] Additional case control studies[19 20] and a meta-analysis of three longitudinal and four population based case control studies[7] showed no effect of OCP use on SAH risk. In contrast, a more recent case control study found that OCPs may be protective

Table 2 Univariate analysis comparing patients with ruptured and unruptured cerebral aneurysms

Variable	Unruptured (n=39)	Ruptured (n=21)	p Value
Age			
Mean (SD)	53.4 (12.7)	54.9 (12.4)	0.66
Median	52	54	
Body mass index (kg/m^2)			
Mean (SD)	28.5 (7.6)	26.5 (7.2)	
Median	28.4	26.7	0.34
Education (>12 grade)			
n (%)	20 (52.6)	7 (33.3)	0.15
Smoker			
n (%)	10 (25.6)	6 (30)	0.72
Menarche age (years)			
Mean (SD)	12.6 (1.8)	13.1 (1.5)	
Median	12.5	13	0.28
Nulliparous (yes)			
n (%)	5 (13.9)	2 (9.5)	1.0
No of pregnancies			
Mean (SD)	3.3 (2.5)	3.2 (1.5)	
Median	3	3	0.82
Age first live birth (years)			
Mean (SD)	21.7 (7.6)	19.6 (5.6)	
Median	20.5	20	0.62
Menopause age (years)			
Mean (SD)	41 (9)	47.1 (6.3)	0.02
Median	42	48.5	
Premature menopause (menopause age <45)			
n (%)	14 (58.3)	6 (37.5)	0.2
Post-menopause			
n (%)	24 (61.5)	16 (76.2)	0.25
Hysterectomy			
n (%)	16 (43.2)	5 (25)	0.17
Hormone replacement therapy			
n (%)	11 (28.2)	3 (15)	0.34
Hormone replacement therapy duration among users (years)			
Mean (SD)	14.3 (13.6)	5.5 (6.4)	
Median	6.5	5.5	0.67
Oral contraceptive pill			
n (%)	25 (64.1)	11 (52.4)	0.38
Oral contraceptive pill duration among users (years)			
Mean (SD)	5.8 (6.8)	5 (4.8)	
Median	4.5	3	0.89

from SAH with an OR of 0.64 but this was not statistically significant.[3] Other studies show more support for a protective role of OCP use and SAH. For instance, a population based case control study showed that having a history of OCP use in the past is protective from both hemorrhagic and ischemic stroke later in life.[20] Similarly, a case control study of 124 women with SAH, aged 30–79 years, found that several factors, including earlier age of menarche (adjusted OR 3.24) and nulliparity (adjusted OR 4.23) were associated with an increased risk of SAH. These effects appear to be additive, and women with both early menarche and null gravidity have correspondingly increased risk (adjusted OR 6.37).[21]

Previously published data on OCP use and SAH have been conflicting, likely because of significant variability of both formulations and dosages over time. Since the introduction of OCPs in 1960, initial dosages administered were in the range of 50 μg of ethinyl estradiol. Modern OCPs use fractional doses of estrogen, and most include varying doses of progestins. Furthermore, because these are observational studies, there is no consistency or regulation on the types or dosages of exogenous hormones used, duration of their use, compliance of use or which decade(s) of women's lives the pills were taken. The historical changes in formulations and dosages could very well account for the varying results reported in the literature.

Although the relationship between OCP use and SAH has been inconsistent in the literature, HRT appears to have a more consistently favorable effect on SAH risk. Given the significantly greater drop in in vivo estrogen after menopause compared with the milder, albeit more frequent, drops in estrogen found during the normal menstrual cycle, it follows that the impact of exogenous hormones in the post-menopausal period may play a larger role in affecting cerebral aneurysm pathogenesis. Longstreth *et al*, via a 1:2 age matched case control study, evaluated 103 women with only ruptured cerebral aneurysms and found a higher frequency of post-menopausal women and those who never took HRT among SAH cases.[22] Mhurchu *et al* also performed a prospective, population based, case control study looking at 286 patients and found that any use of HRT was associated with a significant 36% reduction in the odds of SAH.[2] The association between ever use of HRT and SAH was further validated by demonstrating no significant differences in relation to age, cholesterol level, BMI, smoking habits, history of hypertension or level of education between those who had ever used HRT and those who never used HRT.[2]

Study limitations

The primary limitations of this report are those associated with our control group data. Finding ideal controls for unruptured as opposed to ruptured cerebral aneurysms is inherently more difficult and time consuming. Ideal controls would be women matched for age, race and socioeconomic background with documented normal brain vascular imaging. However, unlike prior studies evaluating SAH, greater logistical challenges existed in identifying women with normal brain vascular imaging compared with asking the question if they had ever experienced a SAH. Obtaining a sufficient control size within a reasonable amount of time proved difficult because brain vascular imaging, unlike brain parenchymal imaging, is not often performed as a screening or initial study.

The significant disparity in HRT use between our cases and controls is confounded by practice pattern changes in prescribing HRT during the past two decades. Until 2002, when the Women's Health Initiative investigators published their data from interviews of 16 608 healthy post-menopausal women,[23] oral HRT had been routinely given for the short term treatment of hot flashes and other menopausal symptoms. At a mean of 5.2 years of follow-up, the trial was halted because of a statistically significant increased risk for breast cancer, in addition to a small but increased risk of heart disease, stroke, blood clots and abnormal mammograms. Since this publication, HRT prescriptions have dropped significantly. Therefore, because the data for the control group were conducted between the years 1994–1998, and the data from our cases were collected from 2008 to 2010, a portion of our cases not only underwent menopause after 2002 but also were susceptible to this confounder. Control data obtained during the same time points of 2008–2010 would represent a more accurate control.

Another limitation of this study is that all hormonal data were based on self- or proxy report. This information was not confirmed on medical record review which may have resulted in misclassification of exposures. Nevertheless, a high agreement between self-report and medical records regarding the use of HRT[24] has been demonstrated in the past, suggesting this type of reporting may be reliable.

Key messages

- Several hormonal mechanisms have been studied in animals and in humans to explain the gender disparity found in cerebral aneurysm rupture.
- We tested the hypothesis that the estrogen fluctuations found during the menstrual cycle and particularly at menopause contribute to cerebral aneurysm formation.
- Compared with large sample, age matched controls, our cohort of women with largely unruptured cerebral aneurysms used estrogen modifying agents—namely, oral contraceptives and hormone replacement therapy—significantly less often.
- A better understanding of the exact role estrogen has on vascular endothelial physiology may serve as a potential therapeutic target.

An additional confounding factor is the relationship between OCP use and smoking. Because smoking while taking exogenous hormones is associated with a higher risk of blood clots and adverse cardiovascular events, women are strongly discouraged from smoking while taking OCPs. Therefore, women taking exogenous hormones may be less likely to smoke than women not taking hormones, potentially sparing them the aneurysm risks associated with smoking. However, rate of smoking between the two groups was accounted for in our multivariate analysis.

CONCLUSION

Current medical management options with patients with unruptured cerebral aneurysms are limited, consisting largely of smoking cessation and blood pressure control. Furthermore, excessive attention is directed towards further refining the anatomic exclusion of the visible cerebral aneurysm, an intervention that fails to address the underlying vascular predisposition. Perhaps our focus should be less on episodic, essentially temporizing, procedures, including more clip and coil iterations, stents, balloons and other devices. Such an approach leads to prognostic uncertainty and a future filled with anxiety provoking surveillance imaging for the patient.

The results of this study may not only provide additional insight into cerebral aneurysm pathophysiology but more importantly may lead to more pathology based therapies to patients either harboring an unruptured cerebral aneurysm or at risk of developing one.

Acknowledgments The authors thank Barbara Soltes, MD, for her assistance with the background for the project.

Competing interests None.

Ethics approval This study was conducted with the approval of the Rush University Medical Center Institutional Review Board, ORA No 09101201-GR01.

Contributors LF conceived the study, participated in the design of the study, helped to design the study questionnaire used, helped to collect the data and helped to draft the manuscript. MC oversaw the design of the study, organized the appropriate use of control data, oversaw the statistical analysis of the data and helped to draft the manuscript. BO designed and executed the statistical analysis of all data reported. LG-S participated in the design of the study questionnaire and collected the majority of the data included.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Longstreth WT Jr,** Koepsell TD, Yerby MS, *et al*. Risk factors for subarachnoid hemorrhage. *Stroke* 1985;**16**:377—85.
2. **Mhurchu CN,** Anderson C, Jamrozik K, *et al*. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: an international population-based, case-control study. *Stroke* 2001;**32**:606—12.
3. **Broderick JP,** Viscoli CM, Brott T, *et al*. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. *Stroke* 2003;**34**:1375—81.
4. **Wiebers DO,** Whisnant JP, Huston J III, *et al*. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;**362**:103—10.
5. **Molyneux A,** Kerr R, Stratton I, *et al*. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;**360**:1267—74.
6. **Eden SV,** Meurer WJ, Sanchez BN, *et al*. Gender and ethnic differences in subarachnoid hemorrhage. *Neurology* 2008;**71**:731—5.
7. **Teunissen LL,** Rinkel GJ, Algra A, *et al*. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke* 1996;**27**:544—9.
8. **Ruigrok YM,** Buskens E, Rinkel GJ. Attributable risk of common and rare determinants of subarachnoid hemorrhage. *Stroke* 2001;**32**:1173—5.
9. **Petitti DB,** Sidney S, Bernstein A, *et al*. Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996;**335**:8—15.
10. **Schievink WI,** Torres VE, Piepgras DG, *et al*. Saccular intracranial aneurysms in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1992;**3**:88—95.
11. **Bromberg JE,** Rinkel GJ, Algra A, *et al*. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. *BMJ* 1995;**311**:288—9.
12. **Stirone C,** Duckles SP, Krause DN. Multiple forms of estrogen receptor-alpha in cerebral blood vessels: regulation by estrogen. *Am J Physiol Endocrinol Metab* 2003;**284**:E184—92.
13. **Brincat M,** Moniz CF, Studd JW, *et al*. Sex hormones and skin collagen content in postmenopausal women. *BMJ (Clin Res Ed)* 1983;**287**:1337—8.
14. **Gangar KF,** Vyas S, Whitehead M, *et al*. Pulsatility index in internal carotid artery in relation to transdermal oestradiol and time since menopause. *Lancet* 1991;**338**:839—42.
15. **Stober T,** Sen S, Anstatt T, *et al*. Direct evidence of hypertension and the possible role of post-menopause oestrogen deficiency in the pathogenesis of berry aneurysms. *J Neurol* 1985;**232**:67—72.
16. **Marchbanks PA,** McDonald JA, Wilson HG, *et al*. The NICHD Women's Contraceptive and Reproductive Experiences Study: methods and operational results. *Ann Epidemiol* 2002;**12**:213—21.
17. **Jamous MA,** Nagahiro S, Kitazato KT, *et al*. Role of estrogen deficiency in the formation and progression of cerebral aneurysms. Part II: experimental study of the effects of hormone replacement therapy in rats. *J Neurosurg* 2005;**103**:1052—7.
18. **Johnston SC,** Colford JM Jr, Gress DR. Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis. *Neurology* 1998;**51**:411—18.
19. **Bonita R.** Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke* 1986;**17**:831—5.
20. **Schwartz SM,** Siscovick DS, Longstreth WT, *et al*. Use of low-dose oral contraceptives and stroke in young women. *Ann Intern Med* 1997;**127**:596—603.
21. **Okamoto K,** Horisawa R, Kawamura T, *et al*. Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: a case-control study in Nagoya, Japan. *Stroke* 2001;**32**:2841—4.
22. **Longstreth WT,** Nelson LM, Koepsell TD, *et al*. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. *Ann Intern Med* 1994;**121**:168—73.
23. **Rossouw JE,** Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321—33.
24. **Jain MG,** Rohan TE, Howe GR. Agreement of self-reported use of menopausal hormone replacement therapy with physician reports. *Epidemiology* 1999;**10**:260—3.