Oral contraceptive and hormone replacement therapy in women with cerebral aneurysms

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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 disparity.1–3

Multiple studies have reported this consistent gender inequality, including the International Study of Unruptured Intracranial Aneurysm study, which evaluated 4060 patients and found that 75% were women.4 Similarly, of the 2143 patients in the International Subarachnoid Aneurysm Trial, 65% 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 disease7,10 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 age16 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, >3mm 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
referred 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.

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 ratio was fixed at 1:7.

Differences between study groups were examined with the χ² 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 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 ratio was fixed at 1:7.

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.

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. 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). Additional case control studies and a meta-analysis of three longitudinal and four population based case control studies showed no effect of OCP use on SAH risk. In contrast, a more recent case control study found that OCPs may be protective.
from SAH with an OR of 0.64 but this was not statistically significant. 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 SAH. These effects appear to be additive, and women with parity (adjusted OR 4.23) were associated with an increased risk of 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 16,680 healthy post-menopausal women, 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 portions 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 hormone replacement therapy 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 was 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 has been demonstrated in the past, suggesting this type of reporting may be reliable.
A better understanding of the exact role estrogen has on vascular endothelial physiology may serve as a potential therapeutic target.

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.

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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. BD designed and executed the statistical analysis of all data reported. LS-S participated in the design of the study questionnaire and collected the majority of the data included.

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