Role of pregnancy and female sex steroids on aneurysm formation, growth, and rupture: a systematic review of the literature

Milli Desai, MHS,¹ Arvin R. Wali, MD, MAS,² Harjus S. Birk, MD,² David R. Santiago-Dieppa, MD,² and Alexander A. Khalessi, MD, MS²

¹School of Medicine and ²Department of Neurological Surgery, University of California, San Diego, California

OBJECTIVE Women have been shown to have a higher risk of cerebral aneurysm formation, growth, and rupture than men. The authors present a review of the recently published neurosurgical literature that studies the role of pregnancy and female sex steroids, to provide a conceptual framework with which to understand the various risk factors associated with cerebral aneurysms in women at different stages in their lives.

METHODS The PubMed database was searched for “(“intracranial” OR “cerebral”) AND “aneurysm” AND (“pregnancy” OR “estrogen” OR “progesterone”)” between January 1980 and February 2019. A total of 392 articles were initially identified, and after applying inclusion and exclusion criteria, 20 papers were selected for review and analysis. These papers were then divided into two categories: 1) epidemiological studies about the formation, growth, rupture, and management of cerebral aneurysms in pregnancy; and 2) investigations on female sex steroids and cerebral aneurysms (animal studies and epidemiological studies).

RESULTS The 20 articles presented in this study include 7 epidemiological articles on pregnancy and cerebral aneurysms, 3 articles reporting case series of cerebral aneurysms treated by endovascular therapies in pregnancy, 3 epidemiological articles reporting the relationship between female sex steroids and cerebral aneurysms through retrospective case-control studies, and 7 experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms. The studies in this review report similar risk of aneurysm rupture in pregnant women compared to the general population. Most ruptured aneurysms in pregnancy occur during the 3rd trimester, and most pregnant women who present with cerebral aneurysm have caesarean section deliveries. Endovascular treatment of cerebral aneurysms in pregnancy is shown to provide a new and safe form of therapy for these cases. Epidemiological studies of postmenopausal women show that estrogen hormone therapy and later age at menopause are associated with a lower risk of cerebral aneurysm than in matched controls. Experimental studies in animal models corroborate this epidemiological finding; estrogen deficiency causes endothelial dysfunction and inflammation, which may predispose to the formation and rupture of cerebral aneurysms, while exogenous estrogen treatment in this population may lower this risk.

CONCLUSIONS The aim of this work is to equip the neurosurgical and obstetrical/gynecological readership with the tools to better understand, critique, and apply findings from research on sex differences in cerebral aneurysms.

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KEYWORDS cerebral aneurysm; pregnancy; female sex steroids; estrogen

PHYSIOLOGICAL changes that occur during a woman's lifetime may predispose her to different levels of risk for cerebral aneurysm formation, growth, and rupture. Female sex has been studied as a significant independent risk factor for intracranial aneurysm formation and

growth,¹⁰ and the International Study of Unruptured Intracranial Aneurysms evaluated 4060 patients and found that 75% were women.³² Two instances during which women are believed to have a unique risk for the development or rupture of cerebral aneurysms due to hormonal and hemo-

ABBREVIATIONS aSAH = aneurysmal SAH; AVM = arteriovenous malformation; CCA = common carotid artery; CI = confidence interval; C-section = caesarean section; GDC = Guglielmi detachable coil; HBMEC = human brain microvascular endothelial cell; HRT = hormone replacement therapy; OR = odds ratio; SAH = subarachnoid hemorrhage.

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dynamic changes are during pregnancy and menopause. For example, cardiac output increases by 30%–50% during pregnancy and peaks by the 3rd trimester,¹⁶ and estrogen, which is increased in pregnancy, appears to enhance cerebral blood flow.¹⁹ In contrast to pregnancy during which female sex steroids are increased, hormones such as estrogen are decreased in peri- and postmenopause. Studies suggest that this estrogen deficiency leads to endothelial dysfunction and inflammation and explains the increased risk for aneurysmal rupture in women through menopause, but the exact mechanisms remain unspecified.²⁵

Cerebral aneurysms in pregnancy represent a rare but important cause of subarachnoid hemorrhage (SAH), as management and treatment are complicated by considerations of both the mother and the fetus. The incidence of unruptured aneurysms in pregnancy is not well established in the literature, and the rate of ruptured aneurysms ranges from 3 to 11 per 100,000 pregnancies.¹² Fifty percent of all aneurysm ruptures in women younger than 40 years are reported to be pregnancy related.² Aneurysm rupture has been shown to have greater mortality risk in pregnant patients than in nonpregnant patients.¹⁸ There are limited studies on the relationship of pregnancy and cerebral aneurysms: the incidence is rare, and additionally it is not feasible to study cohorts of pregnant women through randomized controlled trials. The risk of aneurysm rupture during pregnancy and subsequent options for treatment and delivery are controversial. Previous studies have reported an increased risk of aneurysm rupture and subsequent SAH during pregnancy and delivery, with as many as 77% of 154 cases of verified intracranial hemorrhage during pregnancy caused by aneurysm rupture.⁵ However, the aforementioned study did not include a control group and is therefore limited in interpretation, and more recent studies indicate the risk of aneurysm rupture during pregnancy is similar to that of the general population.¹¹ Treatment modalities for aneurysms have changed since early case reports in 1965 showed the options for a ruptured aneurysm in pregnancy were intracranial surgery versus bed rest with imminent death.²² Current treatment modalities include endovascular treatment with a focus on minimizing morbidity from intracranial surgery, as well as minimizing fetal exposure to angiography.¹⁷ We rely on epidemiological data and reviews of cases to identify which trimester of pregnancy patients present with aneurysm rupture, how aneurysms grow during pregnancy, treatment options, and whether vaginal versus caesarean section (C-section) deliveries are indicated to minimize the risk of aneurysmal SAH (aSAH) during pregnancy.

Women are at highest risk for aneurysm rupture in the perimenopausal and postmenopausal state.⁴ The relationship between postmenopausal estrogen deficiency and aSAH has been studied and described more extensively through experimental studies using animal models.²⁵ Understanding the current literature about experimental models to explain the pathophysiology of cerebral aneurysms in estrogen-deficient states and epidemiological data to understand population health components will shed light on the overall role of female sex steroids and hormones on the development of cerebral aneurysms. These findings can be applied to multiple scenarios of aneurysm formation,

growth, and rupture. Furthermore, these findings point to the development of hormone therapy and targeted therapy to prevent the formation of aneurysms, halt growth, and prevent aneurysm rupture. Understanding the role of female sex steroids such as estrogen will also contribute to an understanding of the underlying sex disparities that exist in presentation of cerebral aneurysms. Here, we review the literature on the role of pregnancy and sex steroids on cerebral aneurysms and summarize salient findings from epidemiological and experimental studies.

Methods

A systematic review to analyze the role of pregnancy and sex steroids in cerebral aneurysms was performed through the PubMed registry with articles dating from January 1, 1980, to February 1, 2019. Search terms were “(“intracranial” OR “cerebral”) AND “aneurysm” AND (“pregnancy” OR “estrogen” OR “progesterone”).” This search yielded a total of 392 results from the PubMed database. Articles were included within this review if they presented primary human or animal data or investigated the epidemiology of pregnancy, sex steroids (i.e., estrogen and/or progesterone), and cerebral aneurysms. Case-series analyses were included. Articles were excluded if aneurysms were not differentiated from other intracranial vascular abnormalities (i.e., arteriovenous malformations [AVMs]). Single case reports were excluded from our review because multiple articles have already synthesized the published single case reports as case series.

The extracted articles were then divided into two categories: 1) epidemiological studies about the formation, growth, rupture, and management of cerebral aneurysms in pregnancy; and 2) investigations on female sex steroids and cerebral aneurysms (animal studies and epidemiological studies). Epidemiological studies were reviewed for study design, sample size of population studied, age and gestational age if applicable, and outcomes of cerebral aneurysm formation, growth, rupture, treatment, and management. Animal studies were evaluated for study design (in vivo vs in vitro), subject type, injury model, number of animals included in experimental and control groups, and outcomes of cerebral aneurysm formation, growth, rupture, treatment, and management.

Results

Three hundred ninety-two articles were initially identified from the PubMed database. After applying inclusion and exclusion criteria, 20 papers were selected for review and analysis. Using the search criteria, no prospective or randomized controlled trials in pregnancy were identified. The 20 articles presented here include 7 epidemiological articles on pregnancy and cerebral aneurysms, 3 articles reporting case series of cerebral aneurysms treated by endovascular therapies in pregnancy, 3 epidemiological articles reporting the relationship between female sex steroids and cerebral aneurysms through retrospective case-control studies, and 7 experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms. Figure 1 is a flow-chart describing the paper selection process.

FIG. 1. Flow diagram demonstrating the search algorithm to identify literature from the PubMed database. A total of 392 articles were initially identified using our search criteria, of which 20 met the inclusion and exclusion criteria and were included within this review.

Epidemiological Studies of Cerebral Aneurysms in Pregnancy

Seven epidemiological articles reporting cerebral aneurysms in pregnancy were included. A full description of results from these investigations can be found in Table 1. Within the 7 articles, we include 1 case crossover study, 1 retrospective cohort study, 2 retrospective reviews, 1 retrospective review and literature review of cases, 1 case-series report, and 1 literature review of cases. Among 89 cases from single case reports that have been summarized in 2 studies, 72 (approximately 80%) represented cases of ruptured aneurysms in the 3rd trimester of pregnancy.^{1,23} This finding is consistent with previous studies and case-series reports that have found that aneurysms are most likely to rupture in the 3rd trimester of pregnancy and up to 6 weeks postpartum.^{12,24} Studies that summarized case reports also indicated aneurysm occlusion through surgical clipping in 53.8% of cases and with an endovascular procedure in 36.5% of cases,²³ and coil embolization being associated with a lower complication rate than clipping in patients with ruptured aneurysms (9.5% vs 23.1%).¹ One study in our analysis reported that 19.8% (22 of 111 cases) of hemorrhagic stroke in pregnancy was due to aneurysm rupture.³³ In 2 longitudinal studies in our analysis with a combined sample size of 1130 patients, the relative risk of rupture during pregnancy and deliveries was comparable to the annual rupture risk in the general population (1.4%, 95% confidence interval [CI] 1.35%–1.57%) during pregnancy and 0.05% (95% CI 0.0468%–0.0634%) during delivery; and in the second study, 0.4% (95% CI 0.2%–0.9%) during pregnancy, delivery, or the puerperium.^{11,30} In

a study of 5 aneurysms in pregnancy with monitoring of aneurysm growth, the aneurysms in 4 pregnancies did not change in size, remaining 2–5 mm, while in 1 pregnancy, the aneurysm increased from 6 to 7 mm during the 3rd trimester, but returned to its original size in the postpartum period.²⁸ Of the 5 studies we include that compared C-section and vaginal delivery rates in pregnant women with cerebral aneurysms, all reported increased rates of C-sections as the method of delivery, regardless of aneurysm rupture or nonrupture.^{1,11,23,24,28} A C-section followed by aneurysm treatment was reported in 1 study as the accepted delivery method for ruptured aneurysms,²⁴ whereas in 2 other studies the widespread use of C-sections in unruptured aneurysms was reported to be unnecessary.^{11,30}

Endovascular Treatment of Cerebral Aneurysms in Pregnancy

Three articles reporting case series of cerebral aneurysms treated by endovascular therapies in pregnancy were identified. A full description of results from these investigations can be found in Table 2. Summaries of case reports that we have included report that in 89 cases of cerebral aneurysms in pregnancy, occlusion of the aneurysm was achieved through surgical clip placement in 53.8% of cases.²³ Surgical clipping of aneurysms is still used and reported in the literature, but the most recent neurosurgical literature has discussed endovascular coil embolization of aneurysms as a treatment option. In the combined 8 cases of aneurysms treated endovascularly in pregnancy that we include in this review, all were treated successfully with Guglielmi detachable coils (GDCs) and without the need

TABLE 1. Seven epidemiological studies on pregnancy and cerebral aneurysms

Authors & Year	Study Type	Title	Yrs	Sample Size	Maternal Age & Gestational Age	Relative Risk	Vaginal Birth vs C-Section	Conclusions
Tiel Groene- stege et al., 2009	Case cross- over study	The risk of aneurys- mal subarachnoid hemorrhage during pregnancy, delivery, and the puerperium in the Utrecht population	1987–2006	244	18–42 yrs	Relative risk of aSAH during preg, deliv, or puerpe- rium was 0.4% (95% CI 0.2–0.9%); based on no. of women aged 18–42 yrs w/ in catchment area & no. of pregs w/in study period, expected no. of pts w/ aSAH during preg, deliv, or puer- perium was 12, resulting in standardized incidence ratio of 0.6% (95% CI 0.2–1.1%)	NA	aSAH risk is not incr during preg, labor, or puerpe- rium; no need to advise against preg in women w/ an incr risk of SAH & no evidence to advise against vaginal deliv in such women
Kim et al., 2013	Retro cohort study	Cerebral aneurysms in pregnancy and delivery: pregnancy and delivery do not increase the risk of aneurysm rupture	1988–2009	714 RAs in preg, 172 RAs in deliv	NA	Rupture risks during preg & delivs were 1.4% (95% CI 1.35–1.57%) & 0.05% (95% CI 0.0468–0.0634%), respectively	Of 218 delivs performed w/ UA, 153 were C-section delivs (70.18%, 95% CI 64.06–76.30%), suggest- ing the rate of C-section delivs in pts w/ UAs is significantly higher than in general population (p <0.001)	An incr association btwn preg or deliv & risk of rupture of cerebral aneu- rysms was not identified; the significantly higher rate of C-section delivs performed in pts w/ UAs may not be necessary
Tanaka et al., 2017	Retro review	Impact of pregnancy on the size of small cerebral aneurysm	2005–2013	5	34–39 yrs	No aneurysmal ruptures during preg; in 4 preg, cerebral aneurysms did not change in size during preg, remaining 2–5 mm; in 1 preg, aneurysm incr from 6 to 7 mm during 3rd trimester, but returned to original size in postpartum period	1 vaginal deliv, 4 C-section delivs	If cerebral aneurysm is small (≤ 5 mm), it is likely to remain unchanged de- spite the incr in circulat- ing blood vol during preg; cerebral aneurysms >5 mm but w/o blebs, irregular shape, high-risk location, or incr aspect ratio are also at low risk of rupture & are not likely to change during preg

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TABLE 1. Seven epidemiological studies on pregnancy and cerebral aneurysms

Authors & Year	Study Type	Title	Yrs	Sample Size	Maternal Age & Gestational Age	Relative Risk	Vaginal Birth vs C-Section	Conclusions
Yoshida et al., 2017	Retro review	Strokes associated with pregnancy and puerperium: a nationwide study by the Japan Stroke Society	2012–2013	151 preg-associated strokes	NA	Causes & frequencies of 111 hemorrhagic strokes were aneurysm, 22 (19.8%); AVM, 19 (17.1%); PIH, 13 (11.7%); HELLP syndrome, 9 (8.1%); cavernous angioma, 8 (7.2%); RCVS, 5 (4.5%); moyamoya disease, 2 (1.8%); other CVDs, 8 (7.2%); other obstetric complications, 7 (6.3%); & undetermined, 18 (16.2%)	NA	May be differences in proportion of hemorrhagic stroke among pregnant Japanese women vs women in Western countries
Robba et al., 2016	Retro review & lit review of cases	Aneurysmal subarachnoid hemorrhage in pregnancy—case series, review, and pooled data analysis	1995–2005	52 (7 from retro analysis of internal data & 45 from lit data extraction)	31.5 ± 5.8 yrs (range 20–42; median 31); 73.1% (n = 38) in 3rd trimester, 19.2% (n = 10) in 2nd semester, & 7.7% (n = 4) in 1st trimester; mean gest was 29.0 ± 8.10 wks (range 9–39 wks, median 32 wks)	Mean H&H score (8 cases) NA) 2.7 ± 0.9 (range 2–5; median 2); Fisher score was described for 67.3% (n = 35) pts; of these, 65.7% (n = 23) had Fisher score IV & 34.3% (n = 12) had Fisher score btwn I & III; distribution of aneurysms was in 76.9% of pts in anterior circulation (n = 15 ICA, n = 9 MCA, n = 6 AComA, n = 2 ACA, n = 7 PComA) & 23.0% in pst circulation (n = 8 VA, BA, or PICA, & n = 4 PCA); aneurysm occlusion was achieved by surgical clipping in 53.8% of cases (n = 28) & w/ endo procedure in 36.5% (n = 19)	Data on mode of deliv were available for 49/52 women; 3 (6.4%) did not deliver at all (1 abortion & 2 deaths in utero); of remaining 46 pts, 72.3% (n = 34) had C-section, of which more than 70% were emergency procedures; remaining 25.5% (n = 12) had vaginal deliv	RAs in pregnant pts w/ aSAH may be safely secured in timely manner; diagnostic & Tx strategy for each of these pts should consider peculiar maternal & obstetric factors & requires multidisciplinary assessment involving obstetricians, neurosurgeons, & intensivists

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TABLE 1. Seven epidemiological studies on pregnancy and cerebral aneurysms

Authors & Year	Study Type	Title	Yrs	Sample Size	Maternal Age & Gestational Age	Relative Risk	Vaginal Birth vs C-Section	Conclusions
Roman et al., 2004	Case series	Subarachnoid hemorrhage due to cerebral aneurysmal rupture during pregnancy	1992–2000	8	31.5 ± 4.8 yrs; 6 pts were in 3rd gestational trimester, 1 in 2nd trimester, & 1 in 1st trimester	Aneurysm was responsible for SAH in 6 cases & for cranial nerve palsy by aneurysmal compression in 2 cases; surgical clipping was performed in 4 cases; 2 pts admitted w/ grade III & IV status, respectively, were treated 3 days after C-section when status had improved; 1 pt had surgical clipping at 12 wks' gest; 1 pt had aneurysmal surgery before deliv, at 34 wks' gest, but a few hrs later C-section was performed; IVE was performed on 2 pts	Emergency C-section was performed on 5 pts w/ 3rd trimester gest & it preceded aneurysm Tx in 4 cases; vaginal deliv was performed on 1 pt who had complete aneurysmal clipping during 1st trimester & in 1 pt w/ 2nd trimester undetected SAH; there was no deliv for pt 7 due to death of fetus, followed a few hrs later by death of pt	If gestational age allows it, immediate deliv should be performed whenever possible; otherwise, fetal monitoring should be performed systematically; C-section followed by aneurysmal Tx appears to be a widely accepted strategy; outcome of pts w/ good clinical status is as favorable as that of nonpregnant series
Barbarite et al., 2016	Lit review of cases	The management of intracranial aneurysms during pregnancy: a systematic review	1991–2015	44	NA	Rupture was confirmed on imaging in 36 aneurysms (72%), & most aneurysms ruptured during 3rd trimester (77.8%); coil embolization was associated w/ lower complication rate than clipping in pts w/ RAs (9.5% vs 23.1%); for pts w/ UAs, surgical management was associated w/ 31.9% fewer complications vs no Tx	Most pts underwent C-section deliv (84%), & a combined neurosurgical obstetrical procedure was used for 8 pts w/ RAs near term	Tx of intracranial aneurysms during preg is safe & effective; furthermore, endo coiling was suggested as 1st-line Tx over surgical clipping

ACA = anterior cerebral artery; AComA = anterior communicating artery; BA = basilar artery; CVD = cardiovascular disease; deliv = delivery; endo = endovascular; gest = gestation; HELLP = hemolysis, elevated liver enzymes, low platelet count; H&H = Hunt and Hess; ICA = internal carotid artery; incr = increase(d); IVE = intravascular embolization; lit = literature; MCA = middle cerebral artery; NA = not available; PCA = posterior cerebral artery; PComA = posterior communicating artery; PICA = posterior inferior cerebellar artery; PIH = pregnancy-induced hypertension; preg = pregnancy; pst = posterior; pt = patient; RA = ruptured aneurysm; RCVS = reversible cerebral vasoconstriction syndrome; retro = retrospective; Tx = treatment; UA = unruptured aneurysm; VA = vertebral artery.

TABLE 2. Three case series on cerebral aneurysm rupture and treatment/management in pregnancy

Authors & Year	Type of Study	Title	No. of Cases	Maternal Age & Gestational Age	Clinical Presentation & Tx	Vaginal Deliv vs C-Section	Conclusions
Kizilkilic et al., 2003	Case series	Endovascular treatment of ruptured intracranial aneurysms during pregnancy: report of three cases	3	25, 26, & 39 yrs at 10, 18, & 28 wks' gest	Aneurysms treated in preg w/ GDCs: 1) H&H grade 2 PComA, 10 × 7 mm; 2) H&H grade 2 lt ICA, 20 × 12 mm; 3) H&H grade 1 AComA, 2 × 3 mm	1 pt's aneurysm arose during fetal period (8th wk of preg); elective abortion was performed due to probable injury to fetus from radiation exposure	Pregnant women can be successfully treated for ruptured intracranial aneurysms w/ endo approach
Plotin et al., 2001	Case series	Endovascular treatment of acutely ruptured intracranial aneurysms in pregnancy	2	28 yrs at 32 wks' gest, 31 yrs at 22 wks' gest	Aneurysms treated in preg w/ GDCs: 1) 4-mm aneurysm at bifurcation of rt ICA; embolization procedure performed w/ superselective catheterization of aneurysm under fluoroscopic control; 2) 8-mm aneurysm of rt supraclinoid carotid artery; w/ pt under general anesthesia & w/ shielding of fetus, superselective catheterization of aneurysm allowed aneurysm occlusion w/ platinum GDCs	1) C-section before endo Tx of aneurysm; 2) vaginal deliv after endo Tx of aneurysm	Successful maternal & fetal outcomes were achieved in both cases w/o craniotomy & aneurysmal surgical exposure
Meyers et al., 2000	Case series	Endovascular treatment of cerebral artery aneurysms during pregnancy: report of three cases	3	34 yrs at 33 wks' gest; 36 yrs, mid-3rd trimester; 36 yrs, late 3rd trimester (in labor)	1) pterional craniotomy revealed fusiform aneurysm, which could not be directly clipped during 11th wk, then coiling in 33rd wk fusiform aneurysm of proximal rt PCA; 2) 7-mm basilar terminus aneurysm & 1.4-mm lt superior cerebellar aneurysm, 4 GDC-10 coils deployed, resulting in complete occlusion of basilar terminus aneurysm; 3) 7-mm aneurysm in rt PComA, 4 GDC-10 coils, producing complete occlusion after C-section deliv	1) vaginal deliv; 2) unknown; 3) C-section of twins before endo Tx of aneurysm	Limited alterations in maternal-fetal physiology, low relative risk of significant radiation exposure to fetus when appropriate techniques are observed, & successful outcomes suggest endo approach to aneurysms during preg is warranted & may be less invasive to both mother & fetus than conventional neurosurgery

for open craniotomy.^{13,17,21} Endovascular treatment occurred before vaginal deliveries, as well as after C-section deliveries.^{13,17,21} Time of endovascular treatment ranged from 1st, 2nd, and 3rd trimester of gestation; the only adverse pregnancy outcome reported was an elective abortion after successful endovascular treatment of an aneurysm during the 8th week of gestation due to concern for fetal injury from radiation exposure.¹³

Epidemiological Studies of Female Sex Steroids and Cerebral Aneurysms

Three epidemiological articles reporting the relationship between female sex steroids and cerebral aneurysms through retrospective case-control studies were included. A full description of results from these investigations can be found in Table 3. In 76 postmenopausal women with cerebral aneurysms compared to matched controls, both later menopause age (odds ratio [OR] 0.79, 95% CI 0.63–0.996, $p = 0.046$) and ever use of hormone replacement therapy (HRT; OR 0.23, 95% CI 0.13–0.42, $p < 0.0001$) were significantly associated with a lower risk of aneurysm in women in the case group.⁶ Conversely, and showing the same results, in 60 postmenopausal women with intracranial aneurysms compared to matched controls, there was a significant association between a lower rate of oral contraceptive (OR 2.1, 95% CI 1.17–3.81, $p = 0.01$) and HRT (OR 3.09, 95% CI 1.54–6.22, $p = 0.002$) use and the presence of a cerebral aneurysm.³ In a study of 233 women in which 43 had hysterectomies, the women with a history of hysterectomy had fewer large aneurysms (8% vs 24%, $p = 0.03$), and fewer presented with a ruptured aneurysm (28%) than the nonhysterectomy group (51%, $p = 0.004$).²⁰

Experimental (animal and cell model) Studies Investigating Female Sex Steroids and Cerebral Aneurysms

Seven experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms were included. A full description of results from these experimental investigations can be found in Table 4. All 7 studies used *in vivo* experiments, with 1 study using both *in vivo* and *in vitro* (human brain microvascular endothelial cell [HBMEC]) experiments. Four studies used rat models, 2 studies used mice models, and 1 study used a rabbit model, for a total of 264 animals in the experimental groups, and a total of 98 animals in the control groups. Mechanisms to create cerebral aneurysms in animal models were ligation of a common carotid artery (CCA) and bilateral posterior renal arteries,^{7–9,27} hypertensive diet, and angiotensin II,⁷ and injection of elastase into the CSF with deoxycorticosterone acetate salt hypertension.²⁶ Estrogen deficiency was induced through bilateral oophorectomy^{7–9,15,26,27} and estrogen E2 receptor blockade.⁷ Ovariectomized female mice had a significantly higher incidence of aneurysms than male mice with sham ovariectomy,²⁶ and 3 times higher incidence of cerebral aneurysm formation than females without bilateral oophorectomy.⁸ Estrogen deficiency has been shown to cause endothelial dysfunction, which may lead to changes in vascular wall integrity and contribute to aneurysm formation. Aneurysm changes in animal models with oopho-

rectomy and HRT were limited to stage I or II, whereas most changes in animal models with oophorectomy but no HRT were identified as saccular dilation (stage III).⁹ Estrogen deficiency induced endothelial dysfunction and reactive oxygen species generation in animal models and HBMECs, which triggered endothelial damage that led to cerebral aneurysms.²⁷ Estrogen deficiency may lead to inflammatory changes that contribute to aneurysm rupture. Estrogen-deficient mice had more aneurysm ruptures than control mice, and were found to upregulate IL-17A, which downregulates E-cadherin, encouraging macrophage infiltration in the aneurysm vessel wall.⁷ Hypertension is an additional risk factor for aneurysm development in animal models with estrogen deficiency.^{9,31} Animal models with estrogen deficiency and induced hypertension had significantly higher vascular damage scores in multiple regions of the circle of Willis, signifying that hypertension and estrogen deficiency make the circle of Willis more vulnerable to flow-induced aneurysmal remodeling and tortuosity.³¹ While estrogen deficiency itself has been reported by the previously mentioned studies to increase risk for cerebral aneurysm complications, exogenous estrogen treatment in an estrogen-deficient state has been shown to be protective from cerebral aneurysm complications in the following 3 studies. Treatment with estradiol,⁷ a selective estrogen receptor modulator such as bazedoxifene,¹⁵ and estrogen²⁶ was shown to decrease the amount of aneurysm ruptures in animal models of estrogen deficiency.

Discussion

Sex differences in the care of patients with cerebral aneurysms provide a unique opportunity for collaboration among multiple physician specialties: neurosurgeons, obstetricians/gynecologists, perinatologists, anesthesiologists, radiologists, intensivists, and primary care providers. This systematic review describes the spectrum of risk for women in pregnancy and in estrogen-deficient states (i.e., menopause, surgical oophorectomy, etc.) and provides readers with the information that female sex steroids may impact women and their cerebrovascular anatomy differently at different stages of their life.

Studies included in this review suggest that the rate of aneurysm rupture in pregnancy is not increased compared to the general population. Neurosurgeons can be prepared to manage pregnant women with aneurysms similarly to the general population. As our review indicated, it may not be necessary to advise pregnant women with cerebral aneurysms against vaginal deliveries, and obstetricians can use these data to collaborate with neurosurgeon colleagues and provide risk stratification to their patients accordingly.^{11,30} An older study from 1990 reports a fetal case fatality rate of approximately 17% as a result of ruptured intracranial aneurysms in pregnancy.⁵ A more recent retrospective review of case reports describes a fetal case fatality rate of approximately 6.5%.²³ In reviewing published papers, studies have not commented extensively on adverse pregnancy outcomes through the natural history of a patient with a ruptured aneurysm or through treatment, perhaps because study design is limited to retrospective and case-series formats. We hypothesize that fetal case fatality rates have de-

TABLE 3. Three epidemiological studies on female sex steroids and cerebral aneurysms in women

Authors & Year	Type of Study	Title	Yrs	Sample Size	Age	Relative Risk	Conclusions
Nisson et al., 2018	Retro case-control	Cerebral aneurysms differ in patients with hysterectomies	2010–2013	233: history positive for hysterectomy was present in 18.5% (43/233) of study population, none had oophorectomies recorded; only female pts & pts equal or older in age to youngest pt in hysterectomy group were included in control group	NA	Pts in hysterectomy group more often presented in good neurological condition before surgery (88% vs 74%, $p = 0.04$) & had fewer large aneurysms (8% vs 24%, $p = 0.03$); fewer presented w/ RA (28%) than nonhysterectomy group (51%, $p = 0.004$); 7.7% (3/39) of hysterectomy pts had large aneurysms vs 23.7% (40/169) in nonhysterectomy group	Female pts w/ surgical history of hysterectomy have lower rates of large aneurysms, present in better neurological condition, & are less likely to present w/ RA than females w/o hysterectomy
Ding et al., 2013	Retro case-control	Younger age of menopause in women with cerebral aneurysms	2007–2011	76 postmenopausal women w/ cerebral aneurysms (under care of single physician); case group data were matched w/ those of control group for age (in categories of <45, 45–54, & >54 yrs) & education level (≤ 12 th grade, >12th grade)	Age at menopause was subdivided into premature menopause (<40 yrs), early menopause (41–44 yrs), normal menopause (45–55 yrs), & late menopause (>56 yrs)	Both later menopause age (OR 0.79, 95% CI 0.63–0.996, $p = 0.046$) & ever use of HRT (OR 0.23, 95% CI 0.13–0.42, $p < 0.0001$) were significantly associated w/ lower risk of aneurysm in women in the case group; for each categorical incr in menopause age, risk of cerebral aneurysm decr by 21%	Trend showing that earlier age at menopause is associated w/ presence of cerebral aneurysm; this suggests that loss of estrogen earlier in a woman's life may contribute to pathogenesis of cerebral aneurysm; these data may identify a risk factor for cerebral aneurysm pathogenesis & also a potential target for future therapies
Chen et al., 2011	Retro case-control	Oral contraceptive and hormone replacement therapy in women with cerebral aneurysms	2008–2010	60 women w/ intradural cerebral aneurysms	NA	Multivariate logistic regression showed significant association btwn lower rate of oral contraceptive use (OR 2.1, 95% CI 1.17–3.81, $p = 0.01$) & HRT (OR 3.09, 95% CI 1.54–6.22, $p = 0.002$) & presence of cerebral aneurysm	These data suggest that exposure to exogenous estrogen agents in women is associated w/ lower frequency of cerebral aneurysms

decr = decrease(d).

TABLE 4. Seven experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Group	Control Group	Findings	Conclusions
Hoh et al., 2018	Estrogen deficiency promotes cerebral aneurysm rupture by upregulation of Th17 cells and interleukin-17A which downregulates E-cadherin	In vivo	Mice	Cerebral aneurysm (lt CCA & rt renal artery were ligated, hypertensive diet, angiotensin II); estrogen deficiency (OVE or by estrogen E2 receptor blockade)	18	19	Estrogen deficiency upregulates Th17 cells & IL-17A & promotes aneurysm rupture; estrogen-deficient mice had more ruptures than controls (47% vs 7%, $p = 0.04$); estradiol supplementation or IL-17A inhibition decr the no. of ruptures in estrogen-deficient mice (estradiol 6% vs 37%, $p = 0.04$; IL-17A inhibition 18% vs 47%, $p = 0.018$)	Estrogen deficiency promotes cerebral aneurysm rupture by upregulating IL-17A, which downregulates E-cadherin, encouraging macrophage infiltration in aneurysm vessel wall
Maekawa et al., 2017	Bazedoxifene, a selective estrogen receptor modulator, reduces cerebral aneurysm rupture in ovariectomized rats	In vivo	Rat	Cerebral aneurysm & estrogen deficiency (OVE, hemodynamic changes, & HTN)	n = 84; 28 vehicle, 28 0.3 mg/kg/day BZA, 28 1.0 mg/kg/day BZA	28	During 12-wk observation, incidence of aneurysm rupture was 52% in ovariectomized rats; w/ no effect on blood pressure, Tx w/ 0.3 or 1.0 mg/kg/day BZA lowered this rate to 11% & 17%, almost the same as in HTN rats (17%)	BZA decr the incidence of aneurysm rupture in ovariectomized rats
Tutino et al., 2015	Hypertension and estrogen deficiency augment aneurysmal remodeling in the rabbit circle of Willis in response to carotid ligation	In vivo	Rabbit	Intracranial aneurysm & estrogen deficiency (HTN & estrogen deficiency, then bilateral CCA ligation)	8	3, ligation only	Compared to ligation-only rabbits, ligation + HTN & estrogen deficiency group had significantly higher vascular damage score in 3 regions: BA (16.8 ± 2.9 vs 7.8 ± 1.8 , $p = 0.025$), SCA origin (10.6 ± 1.6 vs 5.6 ± 1.2 , $p = 0.025$), & PComA origin (11.1 ± 1.5 vs 6.6 ± 1.2 , $p = 0.031$)	HTN & estrogen deficiency make circle of Willis more vulnerable to flow-induced aneurysmal remodeling & tortuosity; we propose they do so by lowering tolerance of vascular tissue to hemodynamic forces caused by CCA ligation, thus lowering the threshold necessary to incite vascular damage
Tada et al., 2014	Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice	In vivo	Mice	Intracranial aneurysms (single injection of elastase into CSF w/ deoxycorticosterone acetate salt HTN)	3 female mice w/ bilat OVE (surgical menopause), 4 ovariectomized female mice w/ estrogen Tx (surgical menopause + estrogen replacement)	1 male mouse w/ sham OVE (laparotomy), 2 female mice w/ sham OVE	Ovariectomized female mice had significantly higher incidence of aneurysms than male mice w/ sham OVE (59% vs 15%, $p < 0.01$); there was also a trend for estrogen Tx to reduce incidence of aneurysms in ovariectomized female mice (38% vs 59%, $p = 0.06$)	Results are consistent w/ epidemiological studies that showed female preponderance of aneurysms after perimenopausal age

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TABLE 4. Seven experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Group	Control Group	Findings	Conclusions
Jamous et al., 2005 ⁹	Role of estrogen deficiency in the formation and progression of cerebral aneurysms. Part I: experimental study of the effect of oophorectomy in rats	In vivo	Rat	Cerebral aneurysm (ligation of rt CCA & bilat pst renal arteries, OVX)	30 rats in groups II & III underwent ligation of rt CCA & bilat pst renal arteries; 1 mo after ligation procedure, group II rats underwent OVX	15; group I consisted of intact females	Incidence of cerebral aneurysm formation in group II (60%) was 3× higher than that in group III (20%), & mean aneurysm size in group II (mean $76 \pm 27 \mu\text{m}$) was larger than that in group III ($28 \pm 4.6 \mu\text{m}$; $p < 0.05$); no aneurysm developed in controls (group I), & no significant difference in plasma gelatinase activity among the 3 groups	OVX incr the susceptibility of rats to aneurysm formation, indicating that hormones play a role in pathogenesis of cerebral aneurysms
Jamous et al., 2005 ¹⁰	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	In vivo	Rat	Cerebral aneurysm (ligation of rt CCA & bilat pst renal arteries, OVX)	Animals in groups A (n = 15) & B (n = 15) were subjected to cerebral aneurysm induction procedure (renal HTN & rt CCA ligation) followed 1 mo later by OVX; after an additional wk, rats in group A received 17 beta estradiol continuous-release pellets	15 group C	Aneurysmal changes (stages I, II, & III) occurred in 1/3 of rats that had undergone oophorectomy & were receiving HRT (group A), compared w/ 87% of rats that had oophorectomy but did not receive HRT (group B); though most of aneurysmal changes identified in group A rats were limited to stage I or II, most changes in group B rats were identified as saccular dilation (stage III)	Findings showed significant protective role of estrogen against formation & progression of cerebral aneurysms; it appears to be related to beneficial effects of estrogen on function & growth of endothelial cells, which play a major role in preserving integrity of vascular wall

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TABLE 4. Seven experimental studies using animal and/or cell models to understand the relationship between female sex steroids and cerebral aneurysms

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Group	Control Group	Findings	Conclusions
Tamura et al., 2009	Endothelial damage due to impaired nitric oxide bioavailability triggers cerebral aneurysm formation in female rats	In vivo & in vitro	Rat, HBMECs	Cerebral aneurysm (ligation of rt CCA & bilat pst renal arteries, OVX)	Hypertensive rats (n = 20), OVX (n = 18), oophorectomized hypertensive (n = 18), oophorectomized hypertensive w/ HRT (n = 15), oophorectomized hypertensive rats w/ ARB (n = 16)	15 sham	Incidence of aneurysmal changes (higher than stage I) was higher in OVX & oophorectomized hypertensive than in hypertensive rats (p <0.05 vs HTN), suggesting that OVX markedly exacerbated endothelial damage; 1/2 of oophorectomized hypertensive rats developed saccular aneurysms (stage III); this was true for 10% of hypertensive rats & 17% of OVX rats (p <0.05); significantly fewer oophorectomized hypertensive rats receiving HRT than untreated oophorectomized hypertensive rats exhibited cerebral aneurysmal changes (p <0.05); there was no statistical difference btwn untreated & ARB-treated oophorectomized hypertensive rats; incidence of saccular aneurysms was significantly lower in oophorectomized hypertensive rats receiving HRT or ARB than in oophorectomized hypertensive rats receiving no Tx (p <0.05)	Results suggest that estrogen deficiency induces endothelial dysfunction & reactive O ₂ species generation, triggering endothelial damage that leads to cerebral aneurysms, & that HTN is additional risk factor; therapy targeted at endothelium & management of HTN may help prevent cerebral aneurysms

ARB = angiotensin II receptor blocker; BZA = bazedoxifene; HTN = hypertension; OVE = ovariectomy; OVX = bilateral oophorectomy; SCA = superior cerebellar artery.

FIG. 2. Diagrammatic algorithm of how to clinically approach a patient who presents with an incidental aneurysm diagnosed during pregnancy. *Can use MRI to evaluate aneurysm growth during pregnancy. Further research is necessary to elucidate size cutoffs that are clinically meaningful in this population. **Coiling thought to be a safe treatment and may be preferred to clipping in pregnancy. Consider abdominal lead shielding and radiation exposure. ***There is no evidence to suggest that maternal or fetal outcome is improved by C-section delivery in comparison with closely supervised vaginal delivery.

creased due to advancements in obstetric care, but further research is needed to evaluate this topic.

Based on the data that we present, we have created a diagrammatic algorithm of how to approach a patient who presents with an incidental aneurysm diagnosed during pregnancy (Fig. 2). We conclude that if unruptured intracranial aneurysms in pregnancy are stable and asymptomatic, they may be observed. Symptomatic and/or enlarging unruptured aneurysms may be treated on an individual basis. Ruptured intracranial aneurysms in pregnancy are treated as they would be in nonpregnant patients. Neurosurgical considerations generally take precedence over obstetric considerations for ruptured, symptomatic, and/or growing intracranial aneurysms. Surgical clipping has historically been accepted as the treatment for ruptured intracranial aneurysms during pregnancy, but endovascular coiling is now believed to be a safe treatment and may be preferred to clipping. Because there are no prospective or randomized controlled trials investigating this subject, we rely on retrospective and case report data to inform our clinical decision-making. We have included 2 studies that address this topic. In a retrospective cohort analysis, endovascular coiling had lower mortality rates in pregnant women with ruptured aneurysms compared to clipping.¹¹ In a previous literature review, endovascular coiling was found to have lower complication rates than surgical clipping in pregnant women with ruptured aneurysms.¹ In both studies, surgical management of ruptured intracranial aneurysms during pregnancy was found to be superior to no treatment. Considerations for endovascular coiling of intracranial aneurysms during pregnancy include concern for harmful effects of radiation to the fetus and potential

harmful effects of anticoagulation. Given that the probability of radiation damage increases with increasing absorbed dose, the radiation dose and stage of fetal development at the time of exposure should be evaluated for endovascular coiling procedures during pregnancy. An International Commission on Radiation Protection report recommended that with optimized abdominal lead shielding, coiling-related fetal radiation can be neglected.²⁹ In the studies we include that used coiling for ruptured aneurysms, radiation exposure was limited through abdominal lead shielding, limited fluoroscopy in proximity to the uterus, and precautions to limit radiation exposure to the patient as well as adequate fetal monitoring.^{11,14,17} Regarding anticoagulation during the endovascular procedure, heparin is not teratogenic and has previously been used for coiling of ruptured intracranial aneurysms during pregnancy, but would need to be discontinued before a C-section.¹⁴ Further research is needed to evaluate additional endovascular treatment options such as stent-assisted coiling during pregnancy, and whether aspirin and/or clopidogrel are safe to use in this setting.

This review elucidates the potential with which neurosurgeons and gynecologists can determine how estrogen deficiency contributes to endothelial dysfunction and inflammation, which may lead to cerebral aneurysm formation, growth, and rupture as reported by multiple studies in this review. Estrogen HRT is commonly used among postmenopausal women, and this review presents animal data that suggest improvement in aneurysmal outcomes with HRT.^{3,6} Hormonal therapies and the effect of targeted drugs on cerebral aneurysms should be further studied in human clinical trials.

Our review suggests that estrogen deficiency in animal models contributes to aneurysm formation and rupture.^{7,8,26,27,31} Pregnancy is a high-estrogen state, which might suggest less aneurysm formation and rupture during this time through the findings of estrogen as a protective cerebrovascular factor in animal studies. However, our review of epidemiological data in pregnant women with cerebral aneurysms shows a similar rate of rupture as the general population. In addition to hormonal and hemodynamic factors, there may be additional factors inherent to pregnancy that raise the risk of aneurysm rupture compared to that of the general population, despite a high estrogen state during pregnancy. We hope this review article encourages additional longitudinal research in prospective cohorts to further characterize the underlying causes of pregnancy and sex steroid effects on cerebral aneurysms.

Conclusions

The mechanisms of cerebral aneurysm formation, growth, and rupture during pregnancy and in estrogen-deficient states are complex. This review article summarizes the current literature of hormonal- and pregnancy-related risks for cerebral aneurysms, and can help guide clinical decision-making for both neurosurgeons and obstetricians and multiple members of the healthcare team about treatment and management options for pregnant women with cerebral aneurysms. This article helps readers understand the current research on estrogen deficiency contributing to vascular abnormalities, and the future research of targeted drugs and therapies to prevent aneurysmal growth and rupture. Given the sex differences in cerebral aneurysms, this review article allows readers to understand risk prediction for individual patients and populations of women with cerebral aneurysms at various stages of their life, from pregnancy to menopause.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Khalessi, Desai, Wali, Santiago-Dieppa. Acquisition of data: Desai, Wali. Analysis and interpretation of data: Desai, Wali, Santiago-Dieppa. Drafting the article: all authors. Critically revising the article: Khalessi, Desai, Wali, Santiago-Dieppa. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Khalessi. Statistical analysis: Desai, Wali. Administrative/technical/material support: Khalessi, Desai, Wali. Study supervision: Khalessi, Desai, Wali.

Correspondence

Alexander A. Khalessi: University of California, San Diego, CA. akhalessi@ucsd.edu.