RESEARCH ARTICLE

Female Hormone Therapy and Risk of Intracranial Hemorrhage From Cerebral Cavernous Malformations

A Multicenter Observational Cohort Study

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Abstract

Background and Objectives

Female hormone therapy (oral contraception in female patients of reproductive age and menopausal hormone therapy in postmenopausal patients) is not withheld from patients with cerebral cavernous malformations (CCMs), although the effects of these drugs on the risk of intracranial hemorrhage are unknown. We investigated the association between female hormone therapy and intracranial hemorrhage in female patients with CCM in 2 large prospective, multicenter, observational cohort studies.

Methods

We included consecutive patients with a CCM. We compared the association between use of female hormone therapy and the occurrence of intracranial hemorrhage due to the CCM during up to 5 years of prospective follow-up in multivariable Cox proportional hazards regression. We performed an additional systematic review through Ovid MEDLINE and Embase from inception to November 2, 2021, to identify comparative studies and assess their intracranial hemorrhage incidence rate ratio according to female hormone therapy use.

Results

Of 722 female patients, aged 10 years or older at time of CCM diagnosis, 137 used female hormone therapy at any point during follow-up. Female hormone therapy use (adjusted for age, mode of presentation, and CCM location) was associated with an increased risk of subsequent intracranial hemorrhage (46/137 [33.6%] vs 91/585 [15.6%] and adjusted hazard ratio 1.56, 95% CI 1.09–2.24; $p = 0.015$). Use of oral contraceptives in female patients aged 10–44 years adjusted for the same factors was associated with a higher risk of subsequent intracranial hemorrhage (adjusted hazard ratio 2.00, 95% CI 1.26–3.17; $p = 0.003$). Our systematic literature search showed no studies reporting on the effect of female hormone therapy on the risk of intracranial hemorrhage during follow-up.

Discussion

Female hormone therapy use is associated with a higher risk of intracranial hemorrhage from CCMs. These findings raise questions about the safety of female hormone therapy in clinical practice in patients with CCM. Further studies evaluating clinical factors raising risk of thrombosis may be useful to determine which patients may be most susceptible to intracranial hemorrhage.

Classification of Evidence

This study provides Class III evidence that female hormone therapy use is associated with a higher risk of intracranial hemorrhage in patients with CCM.

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Glossary

CCM = cerebral cavernous malformation; **IQR** = interquartile range.

Cerebral cavernous malformations (CCMs) can lead to seizures and stroke due to intracranial hemorrhage or nonhemorrhagic focal neurologic deficit.[1] Stroke due to intracranial hemorrhage in patients with a CCM might be triggered by thrombus formation in the dilated sinusoidal vessels of CCM through which the blood flows very slowly.[2,3] The 5-year estimated risk of intracranial hemorrhage varies from around 4%–31% during untreated follow-up. Patients with a brainstem location and a previous intracranial hemorrhage carry the highest risk.[4]

Female hormone therapy includes oral contraception use in female patients of reproductive age and menopausal hormone therapy in postmenopausal patients. Female hormone therapy has been shown to increase the risk of stroke and venous thrombosis.[5-7] However, few data are available on the effect of female hormone therapy on the risk of intracranial hemorrhage in patients with CCM, leaving guidelines unable to make recommendations.[8]

The existing literature assessing the latter regards a case report associating hormone therapy with and increased risk of intracranial hemorrhage,[9] as well as a single observational study that found estrogen therapy in female patients diagnosed with a CCM to increase the likelihood of presenting with intracranial hemorrhage.[10] Prospective, large cohort data are still lacking.

Therefore, the objective of our study was to investigate the association between female hormone therapy and intracranial hemorrhage in female patients with CCM in 2 large prospective, multicenter, observational cohort studies with long-term follow-up. We also performed a systematic review on the association between female hormone therapy and intracranial hemorrhage from CCM.

Methods

Study Design and Participants

We used data from female patients (defined by their biological sex) aged 10 years or older diagnosed with a CCM who were consecutively admitted to the University Hospital Essen, Germany, and the Mayo Clinic, Rochester, United States. Patients are included in a 17 years' time frame between January 1, 2003, and November 1, 2020, in Germany. Since 2008, patients are prospectively followed up in a specialized outpatient department in Germany. In the United States, patients are included in a 6 years' time frame between January 1, 2015, and October 1, 2021.

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved by the local university institutional review board (review board identification 14-5751-BO, 15-6636-BO and 19-8662-BO). Written informed consent was obtained from all patients. With institutional review board approval, in January 2015, Mayo Rochester established a prospective CCM registry. Adult patients with a CCM and research authorization were included.

Data Collection

The mode of presentation was categorized by the symptoms and signs that led to the initial CCM diagnosis according to the following classification and in line with reporting standards: symptomatic hemorrhage, CCM-related epilepsy, nonhemorrhagic focal neurologic deficit, nonhemorrhagic cavernous-related epilepsy, or asymptomatic.[1] Two experienced specialists in CCM MRI in Germany (staff neuroradiologist, neurosurgeon P.D.) and 2 in the United States (staff neuroradiologist, neurologist K.D.F.) verified CCM diagnoses according to the accepted criteria and collected data on CCM location and imaging evidence of intracranial hemorrhage. We collected baseline demographics and medical history from patient medical records. Additional vascular risk factors were defined as medically treated known previous disease and assessed by a questionnaire: factor V Leiden, arterial hypertension, hyperlipidemia, diabetes mellitus, and nicotine abuses (current smoking). Obesity at the time of diagnosis was defined as a body mass index of 30 or greater and calculated as weight in kilograms divided by height in meters squared. We identified treatment and outcomes using prospective surveillance of patient medical record. We collected data on female hormone therapy from the patient medical record and standardized questionnaires. Specifically, we assessed those female patients taking female hormone therapy after the diagnosis of CCM was established but before censor of complete surgical excision, death, or first prospective CCM hemorrhage. Female hormone therapy includes all types of oral contraceptive pills (estrogen and/or progesterone) in female patients of reproductive age and all types of oral, transdermal, and local menopausal hormone therapy in postmenopausal patients at any time after CCM diagnosis before the first outcome event or the end of follow-up if the outcome event did not occur. Patients with intrauterine devices (n = 25) were included into our analysis but not regarded as receiving female hormone therapy. The analyzed outcome was new intracranial hemorrhage attributed to the CCM, defined according to the specific published criteria.[1] Two investigators assessed outcome events using available clinical and radiologic information, masked to female hormone therapy use. We excluded patients with unclear hormone therapy status (n = 3) and patients with radiation-induced CCMs (n = 16).

Search Strategy and Selection Criteria of the Systematic Review

We performed a search of Ovid MEDLINE and Embase from inception until August 1, 2021, to identify studies describing the association between female hormone therapy in patients with CCM and intracranial hemorrhage (eAppendix 1, links.lww.com/WNL/C628). In addition, we searched the Cochrane Library,

Table 1 Baseline Characteristics of Patients in the Observational Multicenter Cohort Study, Stratified by Use of Female Hormone Therapy

	No female hormone therapy use after presentation (n = 585)	Female hormone therapy use after presentation (n = 137)	*p* value
Demographics			
Median age (IQR), y	44.0 (32.8–54.0)	33.5 (23.7–49.1)	
Comorbidities			
Hypertension	108 (19.1%)	23 (17.3%)	0.634
Diabetes mellitus	17 (3.0%)	4 (3.1%)	0.967
Hyperlipidemia	57 (10.5%)	11 (8.5%)	0.512
Factor V Leiden	7 (1.4%)	0 (0.0%)	0.219
Obesity	80 (17.0%)	25 (20.2%)	0.415
Nicotine abuse	81 (15.6%)	17 (12.7%)	0.399
Anticoagulation and/or antiplatelet therapy	47 (10.0%)	14 (14.3%)	0.207
Mode of CCM presentation			
Intracranial hemorrhage	220 (37.6%)	54 (39.4%)	0.694
CCM imaging characteristics			
Multiple CCM	83 (17.1%)	22 (21.4%)	0.307
Developmental venous anomaly	220 (41.4%)	56 (43.4%)	0.683
Brainstem CCM	149 (25.5%)	34 (24.8%)	0.874

Abbreviations: CCM = cerebral cavernous malformation; IQR = interquartile range.

ClinicalTrials.gov, ISRCTN Registry, and a manual search of the bibliographies of relevant publications describing the association between female hormone therapy in patients with CCM and intracranial hemorrhage. We considered publications for inclusion if they reported original data on intracranial hemorrhage during follow-up according to female hormone therapy without language restriction and excluded case reports. Two authors (S.M.Z. and K.D.F.) did the literature search. Any disagreements were resolved by a third reviewer (P.D.). The outcome was the occurrence of intracranial hemorrhage after CCM diagnosis during all available follow-up.

Classification of Evidence

The object of this study was to determine the association between female hormone therapy use and the risk of symptomatic intracranial hemorrhage from CCM. This study provides Class III evidence that female hormone therapy use is associated with a higher risk of intracranial hemorrhage in patients with CCM.

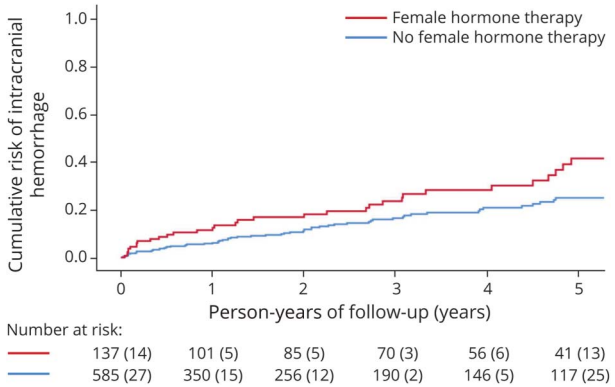
Data Availability

Study data are available on reasonable request.

Statistical Analysis

We compared baseline characteristics and outcomes between patients with ever and never female hormone therapy (pregesteron or progesterone/estrogen). In addition, we subdivided the group into patients aged 10–44 years (patients under oral contraceptive pills) and 45 years or older at initial diagnosis (patients under menopausal hormone therapy). Continuous variables obeying a normal distribution are reported as mean ± SD or as median with interquartile range, and categorical variables are reported as number and percentages. For statistical comparisons between the 2 groups, we used the χ^2 test or, in case of low frequencies, the Fisher exact test. For continuous variables, we used the unpaired *t*-test or Mann-Whitney *U* test, as indicated. We quantified the completeness of the follow-up data.[11] We used Kaplan Meier survival analysis up to 5 years of follow-up, followed by multivariable Cox Regression analysis if proportional hazard assumptions were satisfied[12] with prespecified adjustment for mode of CCM presentation (dichotomized as intracranial hemorrhage at diagnosis vs no intracranial hemorrhage at diagnosis), location of CCM (dichotomized as brainstem [midbrain, pons, or medulla] vs other locations).[4] We also adjusted for age because of the baseline imbalance between patients with or without female hormone therapy. We censored follow-up at CCM treatment with complete neurosurgical excision or death not due to an intracranial hemorrhage. We performed predefined subgroup analysis in which we studied the influence of cigarette smoking. All data were analyzed using IBM SPSS Statistics version 25.0.

Figure 1 Kaplan-Meier Plot of the Risk of First Intracranial Hemorrhage Due to CCM According to Female Hormone Therapy Use During 5 Years of Follow-up



CCM = cerebral cavernous malformation.

Role of the Funding Source

The sponsors of this study did not take any part in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit this report for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Results

There were 722 female patients diagnosed with a CCM (n = 313 US cohort, n = 409 Germany cohort). Of these 722 patients, 137 used female hormone therapy at any point during follow-up (92 [67.2%] were younger than 45 years; 82 of 92 [89.1%] under oral contraceptive pill) and 585 did not use female hormone therapy. Of the patients under female hormone therapy, 22 patients used transdermal hormones. Patients who used female hormone therapy were younger (median age 44.0 years vs 33.5 years, Table 1). There were no other significant differences in baseline characteristics between both groups. Of patients aged 10–44 years at the time of diagnosis, 82 of 393 (20.9%) used oral contraceptive pills. There were no significant differences in baseline characteristics between both groups (eTable 1, links.lww.com/WNL/C629).

We followed up the 722 female patients with CCM for the outcome of intracranial hemorrhage related to CCM up to November 2, 2021, until the first outcome of intracranial hemorrhage or censoring (total of 2,400 person-years of follow-up; mean follow-up 3.33 years, SD 4.66). Patients using female hormone therapy developed a higher prospective hemorrhage (46/137 [33.6%] during 619 person-years of follow-up until first outcome or censoring, incidence rate of 7.44 events per 100 person-years) than patients not using female hormone therapy (91/585 [15.6%] during 1781 person-years of follow-up, incidence rate of 5.11 events per 100 person-years; Figure 1). After confirming the proportional hazards assumption and adjusting for age, mode of presentation, and CCM location, use of female hormone therapy was associated with an increased risk of the outcome of intracranial hemorrhage (adjusted hazard ratio 1.56, 95% CI 1.09–2.24; $p = 0.015$; Table 2). Use of oral contraceptives in female patients aged 10–44 years at diagnosis was associated with a higher risk of the outcome of intracranial hemorrhage (adjusted hazard ratio 2.00, 95% CI 1.26–3.17; $p = 0.003$). Initially, menopausal hormone therapy was associated with a nonsignificant increased risk of the outcome

Table 2 Cox Proportional Hazards Regression Model of Associations With Intracranial Hemorrhage Due to CCM During Follow-up

Variable	Outcome events/sample size, n (%)	Logrank *p* value	Unadjusted hazard ratio (95% CI), *p* value	Adjusted hazard ratio[a] (95% CI), *p* value
CCM location	—	$p < 0.0001$	2.58 (1.85–3.61), $p < 0.001$	1.42 (0.99–2.02), $p = 0.057$
Brainstem	68/183 (37.2%)	—	—	—
Nonbrainstem	69/539 (12.8%)	—	—	—
Mode of CCM presentation	—	$p < 0.0001$	5.67 (3.89–8.28), $p < 0.0001$	5.06 (3.38–7.59), $p < 0.0001$
Intracranial hemorrhage	100/274 (36.5%)	—	—	—
Other	37/448 (8.3%)	—	—	—
Age at presentation (per y increase)	NA	NA	0.995 (0.98–1.01), $p = 0.396$	1.00 (0.99–1.01), $p = 0.645$
Female hormone therapy after presentation	—	$p = 0.021$	1.52 (1.06–2.16), $p = 0.022$	1.56 (1.09–2.24), $p = 0.015$
Yes	46/137 (33.6%)	—	—	—
No	91/585 (15.6%)	—	—	—

Abbreviation: CCM = cerebral cavernous malformation.

of intracranial hemorrhage (adjusted hazard ratio 1.44, 0.68–3.05; p = 0.336). After excluding the 22 transdermal users, female hormone therapy (adjusted hazard ratio 1.73, 95% CI 1.20–2.50; p = 0.004), oral contraceptives use in female patients aged 10–44 years (adjusted hazard ratio 2.03, 95% CI 1.27–3.23; p = 0.003), as well as menopausal hormone therapy use in female patients aged 45 years or older (adjusted hazard ratio 2.39, 95% CI 1.11–5.14; p = 0.026) remained and became associated with an increased risk of subsequent intracranial hemorrhage. Our study found a statistically significant higher risk of intracranial hemorrhage for female patients using oral contraception vs patients under menopausal hormone therapy (adjusted hazard ratio of 1.575, 95% CI 1.102–2.253; p = 0.013). In addition, owing to the described differences between both cohorts, as well as recent findings indicating a possible influence of antithrombotic therapy and risk of intracranial hemorrhage from CCM after an initial bleeding,[2] we adjusted both abovementioned variables to our multivariable analysis. Use of female hormone therapy remained associated with an increased risk of the outcome of intracranial hemorrhage (adjusted hazard ratio 1.57, 95% CI 1.03–2.40; p = 0.036).

Post hoc sensitivity analyses revealed a strong association between female hormone therapy and the outcome of intracranial hemorrhage when the cohort was restricted to smokers (adjusted hazard ratio 2.71, 1.01–7.28; p = 0.047), in particular for female patients on oral contraceptives, aged 10–44 years (unadjusted hazard ratio 4.92, 1.30–18.65; p = 0.019).

Of the 6 records identified in the systematic review, none of the studies met our criteria for inclusion. According to female hormone therapy, none of the 6 studies on patients with CCM had original data on intracranial hemorrhage during follow-up.

Discussion

Our study indicates that female hormone therapy is associated with an increased risk of intracranial hemorrhage in female patients after CCM diagnosis during 5 years of follow-up in a multicenter, observational cohort study, especially in young female patients on oral contraceptive pill.

The association between female hormone therapy and a higher risk of intracranial hemorrhage from CCM is consistent with the hypothesis that the occurrence of intracranial hemorrhage may be triggered by thrombus formation in the dilated caverns of CCM in which blood flow is slow or in an associated developmental venous anomaly (DVA).[3,13] A comparable pathophysiologic mechanism underlies hemorrhagic infarcts in patients diagnosed with cerebral venous thrombosis. There is also an increased risk of cerebral venous thrombosis in female patients who use oral contraceptives.[14]

Our findings are in line with previous studies that found that oral contraceptive use and menopausal hormone therapy in female patients increase the risk of arterial and venous thrombosis. The association with arterial and venous thrombosis has been described as stronger for oral contraceptive use than menopausal hormone therapy in previous studies.[15] A Cochrane meta-analysis found that the risk of arterial ischemic stroke is 1.6-fold increased in female patients using combined oral contraceptives than with nonoral contraceptives users.[16] The risk of venous thrombosis is more than 3 times increased in female patients using combined oral contraceptives compared with nonoral contraceptive use.[17] In our study, we found a 2 times increased risk of intracranial hemorrhage due to oral contraceptive use. Menopausal hormone therapy was associated with a significantly increased risk of arterial stroke in a review of the literature of randomized controlled trials including 37,272 female participants, with a relative risk of 1.17.[18] Menopausal hormone therapy was also associated with increased risks of venous thrombosis, with a relative risk of 1.60 in randomized controlled trials including 42,292 female participants.[18] In our study, we initially found a nonsignificant increased risk of intracranial hemorrhage due to menopausal hormone therapy of 1.44. The hazard ratio of 1.60 (from the abovementioned study) and 1.44 from our cohort are similar in strength. However, after excluding the transdermal users from the female hormone therapy group, we found a significant higher risk of the outcome of intracranial hemorrhage of 2.39 in patients under menopausal oral hormone therapy, which correlates with the abovementioned study.

Of interest, female patients aged 10–44 years at initial CCM diagnosis who were current smokers and used oral contraceptives had a five-fold higher risk of intracranial hemorrhage than female patients aged 10–44 years who were current smokers and did not use oral contraceptives in our study. Previous studies also found that cigarette smoking increase the risk of arterial and venous thrombosis, in particular when they use oral contraceptives.[19,20] Pomp et al.[20] found that smoking seems to be a risk factor for venous thrombosis with the greatest relative effect among young female patients using oral contraceptives. Our study has strengths, including a multicenter, prospective design with long-term follow-up. Our study also has some limitations. For instance, reasons leading to female hormone therapy, as well as timing of menopause, were not assessed in our analysis. Moreover, the designs of the studies were nonrandomized designs. However, we had prespecified statistical adjustment for 2 potential confounders and adjusted for the imbalance in age, after which the associations we found remained statistically significant. We were able to adjust for these imbalances and explore risk in relation to sporadic CCM and the presence of DVAs. We did not assess the dose of female hormone therapy nor the duration of use and compliance. Considering the rather wide date of inclusion going up to 2003 in some cases, this could have led to discrepancies between patients under same medication regimen. An additional potential limitation to our study is the lack of segregating types of menopausal

hormone therapy in postmenopausal patients (oral, transdermal, and local). We did not include the use of intrauterine devices into the cohort of patients under female hormone therapy, as well as assessed the precise hormone used in the medication. Moreover, potential biases such as female hormone therapy before diagnosis, coagulation disorders, dysfunctional uterine bleeding, or levels of hemostatic factors were not analyzed in our cohorts, which could have influenced the risk of hemorrhage found in our analysis. Our study, found a statistically significant high risk of intracranial hemorrhage in patients under oral contraception, as well as a significant increased risk of intracranial hemorrhage due to intake of menopausal hormone therapy after exclusion of transdermal users. Moreover, this risk was significantly stronger in patients using oral contraception after comparing both groups.

Our findings have implications for clinical practice. The international guideline on CCM does not give a recommendation regarding female hormone therapy in female patients.[8] The associations we have found raise concern for the use of female hormone therapy, in particular oral contraceptives in female patients aged 10–44 years in clinical practice. The possible increased risk of intracranial hemorrhage associated with oral contraceptive use might make physicians reluctant to prescribe oral contraceptives to female patients diagnosed with CCM. Physicians should inform female patients diagnosed with CCM about the potential increased risk of intracranial hemorrhage due to oral contraceptive use, and alternative methods of contraception that are not associated with thrombosis might be offered. The possibility that female hormone therapy increases the risk of intracranial hemorrhage from CCM, perhaps due to thrombus formation that may trigger these events, raises a hypothesis that call for additional prospective studies, as well as other prospective cohort studies. In summary, we did find evidence of a harmful association between the use of female hormone therapy and intracranial hemorrhage from CCM in a multicenter observational cohort study, especially in young female patients on oral contraceptives.

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