Risk for symptomatic hemorrhage of cerebral cavernous malformations during pregnancy

Clinical article

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Object. The threat of symptomatic hemorrhage from cerebral cavernous malformations (CCMs) during pregnancy remains poorly understood. The authors undertook this study to better define the risk of pregnancy-related hemorrhage in this population.

Methods. The records of female patients with sporadic (isolated lesions and negative family history) and familial forms of CCM, which were collected as part of the Barrow Neurological Institute CCM natural history study, were examined. Clinical data related to pregnancy, including type of delivery (vaginal or cesarean section) and any change in neurological status, were obtained from chart reviews and patient interviews.

Results. There were 168 pregnancies among 64 female patients with CCM (28 sporadic and 36 familial). Assuming an average of 46 weeks per pregnancy (40 weeks of gestation and 6 weeks of puerperium), patients were at risk for hemorrhage for a total of 148.6 years. Symptomatic hemorrhage (defined as new-onset or exacerbation of seizure activity or any change in neurological status) occurred during 5 pregnancies, with the most common symptom being seizures (4 cases). The overall risk for symptomatic hemorrhage was 3% per pregnancy; the risk was 1.8% per pregnancy in the sporadic group and 3.6% per pregnancy in the familial patients.

There were 19 deliveries by cesarean section: 5 for obstetrical reasons, 8 for fear of possible hemorrhage, and 6 for unknown reasons. Vaginal delivery was performed without complications for the remaining 149 pregnancies.

Conclusions. The authors’ experience suggests that the risk of symptomatic hemorrhage from a CCM during pregnancy is not increased and that a history of CCM is not a contraindication to pregnancy or vaginal delivery.

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Key Words • pregnancy • puerperium • hemorrhage risk • sporadic cerebral cavernous malformation • vascular disorders • familial cerebral cavernous malformation

Cerebral cavernous malformations are more common than generally realized. In large reviews of nonselected autopsy cases, Sarwar and McCormick\textsuperscript{20} reported an incidence of 0.4\% in 4069 cases, whereas Otten et al.\textsuperscript{13} reported an incidence of 0.53\% in a series of 24,535 cases. Remarkably similar results were noted in 2 large MRI reviews: Del Curling et al.\textsuperscript{3} cited an incidence of 0.39\% in a series of 8131 patients, whereas Robinson et al.\textsuperscript{18} found a 0.47\% incidence in a review of 14,035 sequential scans. These results were recently confirmed by Vernooij et al.\textsuperscript{21} in a study describing incidental findings on brain MRI in the general population. These authors reported the results of MRI studies in 2000 asymptomatic adult patients and found that 0.4\% of this population had incidental CCMs. The overall incidence of CCM in these 52,770 cases (MRI studies and autopsy studies) was 0.42\%; that is, approximately 1 case in every 250 individuals.

It is estimated that there will be 140 million births worldwide in 2011 (http://www.census.gov/population/international/data/idb/worldpopinfo.php). Assuming an incidence of 0.40\%, it can be expected that more than 580,000 of these pregnancies will occur in women with CCM. Despite the prevalence of CCM, there are few data
Pregnancy risk for cerebral cavernous malformations

on the risks of pregnancy in women with the disease and no clear guidelines regarding its management during pregnancy, delivery, and puerperium.

Multiple cases on the treatment of symptomatic CCMs during pregnancy have been documented. Although a number of reports have highlighted the ability of skilled neurosurgeons to care for symptomatic lesions at the time of pregnancy, they are frequently misinterpreted as suggesting that pregnancy is associated with an increased risk of symptomatic hemorrhage. Several authors have indicated that the size of CCMs can increase during pregnancy. But whether these isolated reports document a true tendency of growth during pregnancy is unclear. While a number of groups have speculated that these lesions may respond to hormones and that the flux of hormones during pregnancy may predispose CCMs to hemorrhage, data supporting the role of hormones in the biological behavior of CCM are sparse.

To determine whether pregnancy, delivery, and puerperium are associated with an increased risk of symptomatic hemorrhage and to quantify this risk, we reviewed the pregnancy history data collected from all women monitored as part of the Barrow Neurological Institute CCM natural history study.

Methods

The Barrow Neurological Institute Clinical Research Coordination Committee and the St. Joseph’s Hospital and Medical Center institutional review board approved this ongoing prospective observational study.

Between 1986 and 2010, 94 female patients with CCM were prospectively monitored with serial interviews, comprehensive neurological examinations, and MRI studies of the brain at our institution, and the collected data were entered into a database. As part of the present study, an obstetrical history was obtained from all female patients, including information on the number of pregnancies, type of delivery (vaginal or cesarean section), and any changes in neurological function (including new-onset or exacerbation of seizures) occurring during pregnancy and the 6 weeks after delivery. The initial history included pregnancies prior to study enrollment. Follow-up data were collected by the study nurse coordinator during routine office visits, by questionnaire, or by telephone interviews. Records from this database were analyzed to determine the risk of symptomatic hemorrhage during pregnancy. There were 168 normal pregnancies among 64 pregnant patients with CCM: 36 familial cases, that is, multiple lesions with a clear family history; and 28 sporadic cases, that is, single, isolated lesions with no family history. Patients with a history positive for neurological change during pregnancy were seen in the office or contacted by phone to confirm the details of their obstetric histories.

In determining the number of CCMs on MRI, we counted only Type I, II, and III lesions and excluded Type IV lesions, which require a gradient echo sequence to visualize. In those cases in which more than 10 lesions occurred in patients with familial disease, we assumed a value of 10 lesions for all calculations.

Symptomatic hemorrhage was defined as the onset or exacerbation of seizures or any change in the neurological examination, including changes in motor or sensory function, visual field deficits, ataxia, dysmetria, nystagmus, or changes in the level of consciousness. For most patients the duration of pregnancy varied between 37 and 42 weeks. We assumed a gestation of 40 weeks for the patients in our study. Puerperium was defined as the 6 weeks immediately after delivery.

The risk of hemorrhage per pregnancy was calculated by dividing the number of symptomatic hemorrhages (as defined above) by the total number of pregnancies. The duration of the risk per pregnancy was calculated assuming an average of 40 weeks for pregnancy and 6 weeks for puerperium, and this value was used to calculate the risk of hemorrhage per patient per year (per patient-year) by dividing the number of symptomatic hemorrhages (as defined above) by the total number of pregnancy-years at risk. Separate calculations were performed for patients with sporadic and familial lesions, as well as for the study group as a whole.

Results

Table 1 summarizes the characteristics of the 64 patients and their 168 pregnancies. There were 5 symptomatic hemorrhages in 4 patients, with the most common symptom being new-onset or exacerbation of seizure activity (4 episodes), and 1 episode of temporary motor deficits. No patient required neurosurgical intervention for hemorrhage during pregnancy or puerperium. Ten patients underwent 19 deliveries by cesarean section (11.3% of total deliveries): 5 cases for obstetrical reasons, 8 for fear of possible hemorrhage, and 6 for unknown reasons. There were no episodes of hemorrhage in the 149 vaginal deliveries.

Assuming an average of 40 weeks of pregnancy and 6 weeks for puerperium, the patients were at risk for a total of 7728 weeks or 148.6 years. The overall risk of hemorrhage (5 cases) was calculated at 3% per pregnancy (3.4% per patient-year). The risk was lower in the sporadic group (1.8% per pregnancy, 2% per patient-year) than in the familial group (3.6% per pregnancy, 4% per patient-year). The clinical histories of the 4 patients with symptomatic pregnancies are summarized in Table 2.

Discussion

Although it is widely believed that pregnancy and puerperium are associated with an increased risk of aggressive behavior and hemorrhage in patients with CCM, quantitative data supporting this assumption are scarce. Evaluation of risk in this population requires a thorough knowledge of the natural history of these lesions.

A number of authors have documented the natural history of CCM. Reported hemorrhage rates vary widely across these studies depending on the author’s definition of hemorrhage and the population evaluated. Retrospective studies have assumed that all lesions had been present since birth and have relied on patients to recall episodes of hemorrhage. As a result, these stud-
ies probably underestimate the risk of hemorrhage. Using these assumptions, Del Curling and associates calculated an annual "clinically significant hemorrhage" risk of 0.25% per patient-year in a retrospective evaluation of 32 patients with CCM. Note, however, that only 6 of the 32 patients were asymptomatic despite their lesions, whereas 16 patients (50%) had a history of seizures and 10 (31%) had a history of focal neurological deficits referable to an appropriate lesion. If the authors had included these events (that is, seizures and focal deficits) in their definition, the risk of symptomatic hemorrhage would have been nearly 9 times higher (2.2% per patient-year). When patients are prospectively followed, the reported risk of hemorrhage is greater. Kondziolka and colleagues documented a retrospective hemorrhage risk of 1.3% per patient-year among 122 patients but a risk of 2.6% per patient-year during 34 months of prospective follow-up in the same group. Kim and associates calculated a rate of 2.3% per patient-year retrospectively but a rate of 3.8% per patient-year prospectively.

Porter and coauthors prospectively followed a group of 110 patients with CCMs for 46 months and reported an "event" rate of 4.2% per patient-year. As in the present study, this group defined an event as any neurological worsening of symptoms with or without radiologically proven hemorrhage.

Moriarity and colleagues prospectively followed 68 patients with CCM for a mean of 5.2 years to determine the rate of hemorrhage and seizures. Hemorrhage was defined as a change in neurological status with MRI evidence of extralesional hemorrhage. Eleven symptomatic extralesional hemorrhages occurred for an overall symptomatic hemorrhage rate of 3.1% per patient-year. The authors specifically noted that none of the hemorrhages occurred during pregnancy.

In the present study, we identified 5 symptomatic hemorrhages during 168 pregnancies. The overall risk of a symptomatic hemorrhage event associated with pregnancy for all patients in the study was calculated at 3% per pregnancy, or 3.4% per patient-year. This percentage is well within the range reported for the natural history of this disease in the studies reviewed above.

Not unexpectedly, the risk of hemorrhage was somewhat higher for patients with multiple familial lesions (4% per patient-year) than in those with sporadic disease (single lesions, 2% per patient-year). Labauge et al. evaluated a group of 40 familial CCM patients harboring 232 lesions (mean lesions per patient 5.9) by using serial

### TABLE 1: Summary of data in 64 female patients with CCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sporadic CCM</th>
<th>Familial CCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>no. of pregnancies</td>
<td>56</td>
<td>112</td>
</tr>
<tr>
<td>vaginal deliveries</td>
<td>47</td>
<td>102</td>
</tr>
<tr>
<td>cesarean section deliveries</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>CCM lesions†</td>
<td>28</td>
<td>173</td>
</tr>
<tr>
<td>average no. of lesions</td>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>pregnancies w/ symptomatic hemorrhage‡</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>symptom of hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>seizure</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>motor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>risk of hemorrhage per pregnancy (%)‡</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td>yrs of pregnancy follow-up‡</td>
<td>49.5</td>
<td>99.1</td>
</tr>
<tr>
<td>risk of hemorrhage per patient-yr of pregnancy (%)§</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Assuming a maximum of 10 lesions per patient.
† Hemorrhage defined as new-onset or exacerbation of seizure activity or any change in neurological status.
‡ Pregnancy defined as a mean of 40 weeks gestation and 6 weeks postpartum. Overall mean risk per pregnancy 3%.
§ Mean risk of hemorrhage per patient-year of pregnancy 3.4%.

### TABLE 2: Summary of symptomatic hemorrhage cases*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of CCM</th>
<th>Age at Symptom Onset (yrs)</th>
<th>Pregnancy Age (yrs)</th>
<th>Symptomatic Pregnancy</th>
<th>Type of Delivery</th>
<th>Type of Symptoms</th>
<th>CCM Surgery/Age at Surgery (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S</td>
<td>25</td>
<td>27</td>
<td>yes</td>
<td>V</td>
<td>motor</td>
<td>yes/40</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>9</td>
<td>19</td>
<td>yes</td>
<td>V</td>
<td>seizures</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>8</td>
<td>16</td>
<td>yes</td>
<td>V</td>
<td>seizures</td>
<td>yes/8</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>12</td>
<td>28</td>
<td>yes</td>
<td>Ccm</td>
<td>seizures</td>
<td>no</td>
</tr>
</tbody>
</table>

* Ccm = cesarean section related to concerns over cavernous malformation; Co = cesarean section for obstetrical reasons; F = familial; S = sporadic; V = vaginal.
MRI studies and reported a symptomatic hemorrhage rate (symptoms associated with MRI evidence of hemorrhage) of 5.5% per patient-year during 127 patient-years of follow-up. Zabramski and colleagues conducted prospective follow-ups with clinical examinations and serial MRI studies at 6-month intervals in a group of 21 familial CCM patients with 128 lesions (mean lesions per patient 6.5). Symptomatic hemorrhage occurred in 3 patients during a mean of 2.2 years of follow-up, for a symptomatic hemorrhage rate of 6.5% per patient-year.

No patient in the present study required neurosurgical intervention during pregnancy or puerperium. Two patients underwent resection of CCMs thought to be symptomatic during pregnancy: 1 patient at 7 weeks after delivery and 1 patient at 10 years after her last pregnancy. The first patient had a strong family history of CCMs and at 8 years of age had undergone resection of a right temporal lobe CCM for seizure control. At 19 years of age she presented with recurrent seizures after the uncomplicated pregnancy and delivery of her second child. Two days after the birth, she had focal seizure episodes involving the right face and arm and lasting approximately 1 minute. Additional episodes occurred over the following weeks and became more frequent. An MRI study performed 7 weeks postpartum (Fig. 1) demonstrated a left insular CCM with a large subacute component of hemorrhage (Type I lesion), and resection was recommended. Following complete surgical removal of this lesion, seizures were well controlled. Seizures recurred early in the 6th month of her third pregnancy; however, follow-up MRI was negative for acute hemorrhage, and she required no further surgical intervention. Her fourth pregnancy was asymptomatic.

In 1982 when the second patient was 25 years of age, multiple sclerosis was diagnosed after the sudden onset of nausea, nystagmus, and right-sided weakness that gradu-

![Fig. 1. Case 3. Axial T1-weighted (A) and T2-weighted (B) MR images obtained 2 months after the uncomplicated pregnancy and delivery of this 16-year-old’s first child. The patient had a strong family history of CCM and at 8 years of age had undergone resection of a right temporal lobe cavernous malformation to control seizures. Note the focal postsurgical atrophy involving the right temporal lobe on the T1-weighted images (straight arrows, A), as well as the paramagnetic artifact caused by residual hemosiderin on the T2-weighted images (curved arrow, B). There is no evidence of acute or subacute hemorrhage. Axial T1-weighted (C) and T2-weighted (D) MR images obtained when the patient was 19 years old at 7 weeks after the birth of her second child when she presented with complaints of focal seizures involving the right face and arm. The first episode occurred 2 days after an uncomplicated delivery and lasted approximately 1 minute. Additional episodes occurred over the ensuing weeks and gradually became more frequent and longer in duration. Images demonstrating a Type I cavernous malformation in the left insula with a large focus of subacute hemorrhage (straight arrows, C). Note the edema surrounding the area of hemorrhage on the T2-weighted images (curved arrows, D). Follow-up axial T1-weighted (E) and T2-weighted (F) MR images obtained 8 months after the delivery of her third child when she was 23 years old. Late in her second trimester she had a single episode of complex partial seizure activity. She had been off seizure medications. Her neurologist restarted her medication, and she had no further symptoms during the remainder of the pregnancy. There is no evidence of new CCMs and no acute or subacute hemorrhage in the existing lesions. Postsurgical atrophy is again noted in the right temporal lobe on imaging (straight arrows, E). Paramagnetic artifact is seen on the T2-weighted images at the sites of previous resection in the right temporal lobe and left insula (curved arrows, F).](image-url)
ally resolved. Two years later, during the delivery of her first child, she demonstrated right leg weakness and foot drop that rapidly improved but left her with some subtle weakness. A second pregnancy at 30 years of age was unremarkable. In 1996 when she was 40 years old, she presented with a 1-year history of progressive right-sided weakness. Magnetic resonance imaging demonstrated a single Type II CCM involving the medulla at the cervical medullary junction. Her family history was negative. She underwent resection of the lesion and fared well for 14 years before presenting with a recurrent lesion at the same site.

Previous publications have established seizures as the most common manifestation of supratentorial CCM, accounting for 40%–80% of presenting symptoms. In our study, seizures accounted for 4 (80%) of the 5 hemorrhagic events reported during pregnancy, for a seizure risk of 2.7% per patient-year. This rate correlates well with that noted by Moriarity et al., who documented 17 episodes of seizures during 352.9 patient-years of follow-up, for a 4.8% risk of seizures per patient-year.

Finally, some authors have suggested that vaginal delivery in patients with a CCM may increase the risk of hemorrhage. Only 19 of 168 deliveries in this series occurred by cesarean section. There were no documented episodes of hemorrhage in the 149 pregnancies with vaginal delivery.

Limitations of this study include the fact that symptomatic hemorrhage was defined solely on the grounds of clinical criteria and did not require confirmation by diagnostic imaging. This may have led to an overestimation of the risk of hemorrhage. On the other hand, we depended on a retrospective recall of events during pregnancy to determine the risk of hemorrhage; this could result in an underestimation of the risk of bleeding, although pregnancy and childbirth are major life events that probably enhance the memory of unexpected neurological events. Despite these limitations, this study represents the first attempt to quantify the risk of hemorrhage during pregnancy for a well-defined group of 64 patients with CCMs.

Conclusions

The results of this study suggest that there is no increased risk of hemorrhage associated with pregnancy and delivery in patients with the sporadic and familial forms of CCM. When hemorrhage does occur, intervention should be based on type of hemorrhage and severity of symptoms. The small number of reports describing the resection of CCMs during pregnancy would suggest that the need for emergency neurosurgical intervention is rare. Although some physicians advocate cesarean section as the delivery method of choice in patients with known CCMs, there are no quantitative data to support this recommendation, and the method of delivery should be based on obstetrical considerations.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Zabramski. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: Kalani. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Zabramski. Statistical analysis: both authors. Study supervision: Zabramski.

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