Cavernous malformation

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Kalani and Zabramski provide the best estimates of the risk for symptomatic hemorrhage of a cerebral cavernous malformation (CCM) during pregnancy. They identified 168 pregnancies among 64 women in a prospectively collected database. The end point was symptomatic hemorrhage defined as new or worsening seizures or a change in neurological condition. There were 5 events (4 seizures and 1 neurological change), amounting to a 3% risk of hemorrhage per pregnancy. When considering the sporadic and familial types separately, the risk was 1.8% per pregnancy in sporadic CCMs and 3.6% per pregnancy in familial CCMs, suggesting a different risk in these situations, although the numbers are small. Notably, 149 pregnancies (89%) were delivered vaginally with no reported problems. No woman died, and it is not clear if there was any substantial permanent morbidity from the symptoms they experienced during pregnancy. Outcomes in the children are not mentioned. It is also interesting to note that among the 4 patients with symptoms, there were 11 pregnancies, 5 of which were associated with symptoms. Thus, even within this subgroup, the chances of symptoms were less than 50%.

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Why would the risk of hemorrhage be higher during pregnancy? Perhaps because of hemodynamic changes during pregnancy. Blood volume increases in pregnancy, peaks at 32 weeks, and remains elevated until delivery. Hematocrit falls slightly and systemic vascular resistance decreases, resulting in a decreased systolic blood pressure until midpregnancy. Blood pressure and vascular resistance tend to normalize around term. Cardiac output also increases 30%–50% over prepregnancy values, peaking at about 20–24 weeks. There are marked changes during labor, including greater increases in cardiac output and blood pressure and increases in intracranial pressure during contractions. Most serum coagulation and thrombolytic factors increase, although there is no overall major change in routine clotting assays. Tidal volume and minute ventilation increase with unchanged vital capacity and compliance but decreased PCO₂ and functional residual capacity. Many hormones change, including estrogen, progesterone, human chorionic gonadotropin, and relaxin, some of which are known to exert effects on connective tissue and the vasculature.

What effects these changes might have on CCMs seem to be speculative at this point. Unlike in aneurysms and arteriovenous malformations (AVMs), the hemodynamic changes might be expected to be less important given that studies measuring the pressure in CCMs during surgery found relatively small changes in pressure when the blood pressure was changed. Thus, the basis for an effect of pregnancy and delivery on CCMs, if any exists, remains theoretical at this point.

What are some of the limitations of their report? The numbers of events and patients are quite small, so the confidence interval for the 3% risk of hemorrhage during pregnancy is wide (my calculation, probably incorrect, put the 95% CIs from about 0% to 7%). The definition of hemorrhage included seizures without any imaging evidence of hemorrhage, so the estimates may represent a worst-case scenario. We do not know whether anticonvulsants were stopped, for example, during pregnancy, so that some of the events were just seizures and not hemorrhages. Seizures due to toxemia could occur and are more common than CCM-related seizures overall. In any case, including seizures leads to an estimate that should be on the high side.

The hemorrhage rate during pregnancy was compared with those in noncontemporaneous studies of other patients in the literature rather than with the rate in a simultaneously collected cohort. Yearly rates of hemorrhage in these studies ranged from 1.3% to 4.2% per year, depending on the definition of hemorrhage and assumptions about when the CCM arose during a patient’s life. The risk was slightly higher in familial type cases, regardless of pregnancy. We also do not know how these patients got to the Barrow Neurological Institute. It is unlikely that the authors’ sample is population based, so while these data are the best we have now, they do have some limitations from a strict epidemiological point of view.

One thing that was interesting was another report from the Barrow Neurological Institute that mentions in its Discussion that 7 of 62 patients with brainstem cavernous malformations had hemorrhages during pregnancy. I was not able to determine if these 7 patients were included in the current series.

Overall, the authors’ findings seem consistent with my clinical impressions and the literature. There are more reports of aneurysm and AVM rupture during preg-
nancy. Roughly calculating, one can estimate the prevalence of CCM, brain AVM, and cerebral aneurysm as 0.4%, 0.018%, and 2.3%, respectively (the last rate will be lower in young women of childbearing age). If the risk of hemorrhage were the same during pregnancy, then we would expect the most common source of hemorrhage in pregnancy to be aneurysm, followed by CCM and then AVM. The lower number of reports on CCMs “fits” with a lower risk.

Intracranial hemorrhage in pregnancy is uncommon. In 9 papers including pregnant women between the years 1945 and 2001, there were 63 intracranial hemorrhages in 1,240,058 pregnancies, for a bleeding frequency of 1 case in 19,683 pregnancies (range from 1 case in 3900 pregnancies to 1 case in 34,358 pregnancies). In a study that excluded subarachnoid hemorrhage, there were 16 intracerebral hemorrhages in 348,295 deliveries between 1989 and 1991, for a risk of 4.6 cases per 100,000 deliveries or 6 cases per 100,000 patient-years. Etiologies were eclampsia (7), AVM (2), CCM (2), aneurysm (2), and undetermined (3). Four patients died, although none because of a documented CCM. Other authors have found similar rates of intracranial hemorrhage with fewer deaths.10 Looked at another way, maternal death is rare during pregnancy and the puerperium, and intracranial hemorrhage due to a vascular malformation or aneurysm is an uncommon cause of it. Berg et al. found a pregnancy-related mortality rate of 9 cases/100,000 live births for the years 1987–1990. The most common causes of death were obstetrical hemorrhage, embolism, and pregnancy-induced hypertension. Less than 10% of pregnancy-related deaths were attributable to intracranial hemorrhage.

More people have departed from this world during the act of conception than ever will from a CCM—and certainly from rupture of a CCM during pregnancy.10 Until further data become available, the authors’ conclusions seem reasonable; women with CCMs should not worry unduly about pregnancy, nor should their obstetricians alter the course of delivery because of the presence of an asymptomatic CCM.

(Disclosure)

Dr. Macdonald receives grant support from the Physicians Services Incorporated Foundation, Brain Aneurysm Foundation, Canadian Institutes for Health Research, and the Heart and Stroke Foundation of Canada; and is a consultant for Actelion Pharmaceuticals and the Chief Scientific Officer of Edge Therapeutics, Inc.

References


Response

JOSEPH ZABRAMSKI, M.D., AND M. YASHAR S. KALANI, M.D., PH.D.

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We are grateful for Dr. Macdonald’s detailed and
Editorial

insightful editorial. We agree with his comments about the limitations of our study. More data are needed, and a larger multinstitutional study would be useful. Identifying patients for enrollment, particularly those with asymptomatic lesions, would provide useful information but would require large-scale screening with MRI. Assuming a 0.4% prevalence of CCM, the screening of 20,000 asymptomatic women of childbearing age would be required to identify just 80 potential candidates for enrollment.

As pointed out by Dr. Macdonald, our definition of symptomatic hemorrhage may represent a worst-case scenario. By not requiring imaging confirmation of hemorrhage, we may well have overestimated the risk of symptomatic hemorrhage during pregnancy. However, for a study with such broad implications, overestimating the risks is preferable to underestimating them. Imaging documentation of hemorrhage can be problematic with these lesions. By definition, all CCMs demonstrate MRI evidence of hemorrhage, and frequent changes in imaging characteristics are well documented.1–3

To be certain that seizures are the result of hemorrhage during pregnancy, it would be necessary to obtain an MRI shortly after pregnancy was confirmed and then again soon after the onset of seizures. Although MRI has not been directly linked to teratogenic effects, current guidelines from the FDA require labeling MRI devices to indicate that the safety of MRI with respect to the fetus “has not been established.”

A small number of studies have raised the possibility of teratogenic effects of MRI exposure during early pregnancy. A reduction in crown-rump length was seen in fetal mice exposed to MRI midgestation.2 Exposure to the electromagnetic fields simulating a clinical study caused eye malformations in a genetically predisposed mouse strain.3 When chick embryos were exposed to a strong static magnetic field and rapid electromagnetic gradient fluctuations during the first 42 hours of incubation, there were an excess number of dead or abnormal chick embryos when examined on the 6th day of incubation.6 Possible mechanisms for apparent deleterious effects include the heating effect of MR gradient changes and direct nontermal interaction of the electromagnetic field with biological structures. Although most studies evaluating the safety of MRI during pregnancy show no ill effects, a cautionary approach should be taken regarding fetal exposure to MRI, particularly for elective studies during the first trimester.

As Dr. Macdonald noted, the risk of symptomatic hemorrhage during pregnancy was higher in the group of patients with the familial form of this disease. However, it is important to recognize that those with the familial disease harbored multiple CCMs (mean 4.8 lesions). If we calculate the risk per lesion per year of pregnancy (475.7 lesion-years), the risk of hemorrhage is actually somewhat lower: 0.8% per lesion-year in the familial groups versus 2% per lesion-year in the sporadic group. It is reassuring that these calculations result in similar risks per lesion-year for both groups.

Finally, with regard to the risk of hemorrhage in patients with brainstem CCMs, in a previous report of our experience managing 100 patients with brainstem CCMs, 7 of 62 female patients presented with a history of hemorrhage during pregnancy.4 Patients with brainstem CCMs, particularly those with a history of symptoms, may have an increased risk of symptomatic hemorrhage. However, only 1 of these patients was referred for resection of the CCM during pregnancy. In the majority of cases, hemorrhage was inferred by history. These 7 patients were collected over a 13-year interval from a wide national and international referral base. Only 1 of the patients from this earlier report was included in the present study, because inclusion was limited to patients enrolled in the prospective Barrow Neurological Institute CCM Natural History Study.

Although we recognize its limitations, our study is a first attempt to address the challenging question of how to advise women with CCM as regards their risks during pregnancy. Overall, our data suggest that women harboring CCMs do not have an increased risk of hemorrhage during pregnancy and that vaginal delivery seems safe. Patients with brainstem lesions may have an increased risk of hemorrhage, particularly if there is a history of symptomatic hemorrhage, but additional data are needed to address this question as well as to confirm our findings.

References


Please include this information when citing this paper: published online October 5, 2012; DOI: 10.3171/2012.4.JNS12592.