Cavernous Malformations in Pregnancy

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Abstract

Cavernous malformation is a relatively rare disease, but is important in the etiology of cerebral hemorrhage in pregnant and puerperal women. The risk of bleeding is particularly high in patients with a previous history of bleeding, patients with a family history of cavernous malformations, and patients with the causative cerebral cavernous malformation gene. Cavernous malformations are more likely to bleed or to increase in size during pregnancy, under the influence of female hormones and vascular growth factors such as vascular endothelial growth factor. We report our strategy for the treatment of cavernous malformations in pregnant women, with reference to the relevant literature. Asymptomatic patients and those with mild symptoms are usually followed up conservatively by magnetic resonance imaging, without active treatment, but surgical treatment is indicated in patients with severe or progressive symptoms; surgery should also be considered in patients with mild symptoms having risk factors for bleeding. If surgical treatment is selected, the operation plan needs to be devised in collaboration with the specialties of anesthesiology and obstetrics and gynecology, rather than by the brain surgeon alone, in view of the possibility of occurrence of complications specific to pregnant women, such as complications related to weight gain and difficulty in securing the airway, which develop during the perioperative period.

Key words: cavernous malformation, pregnancy, treatment

Introduction

Cavernous malformations (CMs) are among the important causes of cerebral hemorrhage in pregnant women. This vascular malformation is detected predominantly in patients aged 30–39 years, at a reported incidence of 0.47%.²⁹,³⁶ The major symptoms are bleeding-related neurological symptoms and seizures.²¹ The annual incidence of bleeding at all lesion sites is 0.6% to 0.7%, and the re-bleeding rate following the first bleeding episode is relatively high (4.5%/year), particularly in young women.²²,²⁹ Cases of familial CM are also encountered, with a higher reported incidence of bleeding (1.1%/year) in this subset of patients.⁴¹ Cerebral CM (CCM) genes CCM1, CCM2, and CCM3 have been identified as the causative genes. The incidence of bleeding is particularly high in patients with CCM3 on chromosome 3.⁵,¹⁴,²⁴ CMs are often accompanied by venous anomalies, more frequently in women and in cases of CM in the posterior cranial fossa; in such cases also, the annual incidence of bleeding has been reported to be relatively high.¹¹ Bleeding is well-known to be more likely to occur from CMs of the brainstem. The reported annual incidence of bleeding from brainstem CMs is 2.5% to 5.0%, and is even higher in cases with malformations over 1 cm in diameter, patients aged under 35 years, and patients with associated venous anomalies.²₂,²³,²⁷ Seizures associated with CMs are more likely to be intractable than those attributable to other organic diseases.³¹ Magnetic resonance (MR) imaging is the most useful imaging modality for the diagnosis of CMs. This imaging tool allows not only localization of the lesion, but also evaluation of the presence or absence of venous anomalies and the timing of bleeding in cases with hemorrhage.²¹,⁴¹
Surgical resection of CM is indicated in patients with hemorrhage, and may be expected to yield good seizure control in patients with poor seizure control. If the lesion is located in areas of the brain that are difficult to approach, such as brainstem lesions, stereotactic radiosurgery such as gamma-knife therapy is indicated. However, the indications for such therapy need to be judged carefully, in view of potential complications, such as radiation-induced necrosis, which are seen at a high incidence of approximately 27%.12,16,19)

We report the characteristics and measures for CMs in pregnant women on the basis of previous reports and discuss the treatment strategy for this condition.

**Features of CMs in Pregnancy**

Pregnant women often exhibit changes in the morphological and clinical features of CMs under the influence of various factors. For example, CMs are more likely to grow in size and the incidence of bleeding from CMs is also higher during pregnancy.17,28,32,40,42) However, the accurate rupture rate is unknown. These changes have been reported to be associated with female hormones, including estrogen and progesterone.6,42) Not only CMs, but also other vascular malformations, such as arteriovenous malformations and moyamoya disease, are known to undergo morphological changes under the influence of female hormones.7,8,30) In addition, the blood levels of vascular growth factors, such as vascular endothelial growth factor and basic fibroblast growth factor, increase during pregnancy to stimulate placenta formation.40) These vascular growth factors can induce angiogenesis and growth in the size of CMs, and also increase the likelihood of bleeding from these lesions.18,31) Some reports suggest no increase of hemorrhage risk during pregnancy, but do not specify the definite reason.26,39) Many authors recognize the relationship between the some changes of CMs during pregnancy and female hormones, and we also follow the opinion.

Pregnant women show similar changes in aneurysmal-subarachnoid hemorrhage (SAH). Some previous reports have suggested increased risk of aneurysmal SAH during pregnancy and delivery,7,25,33,37) whereas some studies concluded that pregnancy and delivery do not increase the risk of aneurysm rupture.15,20,38) Neither of these studies was based on a large sample, so that the result and conclusion are controversial.

Clearly, both bleeding and growth in the size of CMs are more likely to occur during pregnancy. In one reported case series of 62 operated women with brainstem CMs, surgery was carried out during pregnancy in 7 cases (11%).27)

**Problems of Pregnancy Associated With the Presence of CMs**

Of all patients with CMs, only 9% are diagnosed below 18 years of age.21) Thus, since pre-pregnancy diagnosis of CMs is difficult, measures to prevent the complications of CMs during pregnancy and child delivery are also difficult to take. Furthermore, detailed intracranial examinations using modalities such as MR imaging in all pregnant women would be unrealistic.

MR imaging is the most widely used imaging modality for the diagnosis of CMs. Gadolinium-enhanced MR imaging is more useful, and is indispensable for the diagnosis of associated venous anomalies and assessment of their features.21,41) However, use of gadolinium as a contrast agent is usually contraindicated in pregnancy because of its potential adverse influence on the fetus. Rebleeding, requiring reoperation has developed after child delivery in pregnant women with CMs in whom surgery was performed after non-contrast-enhanced MR imaging, without adequate preoperative evaluation of the malformation.4) Some investigators have proposed that the use of gadolinium for contrast enhancement during pregnancy is safe and that use during pregnancy is acceptable if there is clear benefit to the mother.11) If or when surgery is planned, adequate evaluation of the lesion with the use of gadolinium as a contrast agent is desirable.

Surgery under general anesthesia in pregnant women involves several problems. Changes in the maternal body seen during pregnancy include weight gain, increase in the circulating blood volume, presence of pregnancy-induced hypertension, etc. One of the most difficult problems encountered during pregnancy is the difficulty in securing the airway before induction of anesthesia. This is the most common cause of fatal adverse events associated with general anesthesia in pregnant women.13) The posture at the time of surgery is also important. After 24 weeks of pregnancy, compression of the inferior vena cava becomes significant. For this reason, the left lateral decubitus position is preferable to the supine position during surgery.9) In addition, hypotensive anesthesia and hypothermic operation, often adopted for neurosurgery, should be avoided in pregnancy, because they can reduce placental blood flow. Therefore, collaboration between the neurosurgeon, obstetrician/gynecologist, and anesthesiologist for adequate preoperative assessment and planning is of the utmost importance.
**Treatment Strategy for CMs in Pregnancy**

The general strategies for the treatment of CMs are as follows: Asymptomatic cases are followed up conservatively, without active treatment. Cases with bleeding or rebleeding and those with intractable seizures should be evaluated for surgical treatment.22,34,35,43) No strategy endorsed by sufficient evidence is available for the treatment of CMs during pregnancy. The treatment strategy for individual cases during pregnancy seems to vary depending on the experience at each facility, the treating neurosurgeon, and other factors. However, the number of pregnant women with CMs encountered at a single facility is not likely to be so large. Therefore, we may say that the therapeutic strategy is often decided on the basis of previous experience in a small number of cases. It is plausible to imagine that conservative therapy is selected as far as possible in view of the above-mentioned surgical risks specific to pregnant women, and that surgical treatment is selected only in cases where surgery is unavoidable. However, the presence of factors specific to pregnant women, such as the high risk of bleeding, the problem of anesthesia or the position during surgery, would seem to make the therapeutic decision process more complex.

The treatment strategy for CMs has been reported by Burkhardt et al.4) Based on this report, we have been using the algorithm shown in Fig. 1 in deciding the therapeutic strategy for individual cases at our institution. There can be no question about asymptomatic cases being followed up conservatively without active treatment. Follow up without active treatment may also be selected for symptomatic cases if the symptoms are mild, for example, slight numbness of the extremities. Surgical treatment is selected for patients with symptoms affecting the activities of daily living or with progressive symptoms. Surgical treatment also deserves consideration in patients without significant symptoms, if they have a history of bleeding, familial-type CM, or associated venous anomalies. In cases of familial CMs, it would be advisable to perform gene analysis and to consider active treatment if the CCM gene is detected. For pregnant women at a gestational stage safe for delivery, early induction of labor may be considered, possibly at 32 weeks of pregnancy when the weight of the fetus would be 2000 g. To avoid excessive blood pressure elevation, cesarean delivery or painless delivery should be selected, as a rule. According to the nationwide inpatient sample database in U.S. for years 1988 to 2009, the rate of cesarean delivery was 25.5%. In contrast, among patients with a diagnosis of unruptured aneurysm, the rate of cesarean delivery was 70.2%. Even the increase of rupture rate during labor is controversial, as many obstetricians choose the cesarean delivery to avoid the hemodynamic changes during vaginal delivery.20) In cases requiring surgery after child delivery, surgery should be undertaken as soon as possible, as the risk
Representative Case

A 39-year-old woman with a husband and one child consulted a neighborhood clinic with the chief complaints of intense headache and dizziness. MR imaging revealed abnormalities and she was referred to our department. At the first examination at our department, she was found to be pregnant (week 4 of pregnancy). MR imaging revealed a mass approximately 4 cm in maximum diameter in the left frontal lobe, visualized as an area of a mixture of high and low intensity on both T1- and T2-weighted images, showing partial contrast enhancement (Fig. 2A–C). Susceptibility-weighted imaging revealed markedly low intensity of the lesion, leading to the diagnosis of hemorrhagic lesion (Fig. 2D). Angiography detected no apparent vascular anomalies. The woman was informed of her condition and the available methods of treatment, including conservative treatment. She desired to discontinue the pregnancy and undergo surgery. Therefore, scheduled craniotomy for hematoma evacuation was performed after artificial termination of pregnancy (Fig. 2E, F). The histological diagnosis was CM, surrounded by old as well as fresh hematoma (Fig. 3). Postoperatively, no new neurological deficits occurred, and the patient was discharged from the hospital in good general condition, without requiring assistance for the activities of daily living.

Conclusion

A review of the literature on CMs in pregnant women and our treatment strategy for this condition are presented. Because the number of pregnant women with CMs encountered at any single facility is not likely to be large, it may be difficult to establish a unified treatment strategy for CMs in pregnant women on the basis of past experience. We have presented our therapeutic strategy as one of the examples for the establishing appropriate treatment strategies from now on. The important factor is to devise a therapeutic strategy tailored to the features of individual cases through collaboration between the specialties of neurosurgery, obstetrics/gynecology, and anesthesiology.

Conflicts of Interest Disclosure

The author reports no conflict of interest or finan-
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