9 Cerebral Vascular Malformations in Pregnancy: Considerations for Diagnosis and Management

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Introduction

Vascular malformations of the nervous system comprise a diverse range of pathologies that have classically been divided into several categories: arteriovenous malformations (AVM), dural arteriovenous fistulas (DAVF), cavernous malformation (CM), developmental venous anomaly (DVA), and capillary telangiectasia [1]. Cerebral vascular malformations are complex problems and, although their occurArence in pregnancy is rare, they pose a unique challenge to clinicians seeking to balance optimal neurosurgical and obstetric care.

Stabilizing these lesions is important due to the risk of significant maternal and fetal morbidity and mortality, especially when associated with acute events such as rupture and hemorrhage. However, the natural history and indications for treatment of each type of lesion are unique and dependent on patient-specific factors. Therefore, decision making, and patient counseling require an intimate understanding of the literature and a collaborative approach between neurosurgical and obstetric providers. In this chapter, we will discuss in detail AVMs and CMs with particular attention to: (1) natural history, in particular the association of pregnancy and risk of rupture; (2) role of genetic and endocrinologic changes in malformation formation development; (3) management; (4) fetal risks and protective measures; and (5) mode and timing of delivery.

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Arteriovenous Malformation

Pathology and Pathogenesis of Arteriovenous Malformations

AVMs, more formally pial or parenchymal AVMs, are vascular anomalies characterized by abnormal, fistulous connections between arteries and veins bypassing the capillary network. These abnormal connections are typically tortuous in nature and form a localized cluster, termed the nidus, with a large, meningeal oriented base and a triangular, ventricular oriented apex. The lack

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of resistance, typically offered by capillary beds, results in high-flow arteriovenous shunting posing substantial risk for rupture and life-threatening hemorrhage (Fig. 9.1) [2]. The majority of AVMs are thought to be congenital lesions that arise spontaneously during development. This is supported by recent discovery of somatic mutations in genes of the Ras/MAPK pathway within AVM tissue [3, 4]. While causative germline mutations underlying these lesions have not been definitively identified, there is evidence associating polymorphisms in components of the tissue growth factor-beta (TGF-β) pathway with risk of AVM development [5, 6]. Moreover, polymorphisms in inflammation-related genes, including the interleukin-6 (IL-6) and tissue necrosis factor-alpha (TNF-α), correspond to the increased risk of AVM hemorrhage [7]. Familial cases of AVMs have also been described; however, it is unclear if these cases are coincidental, owing to the relative rarity of these lesions, or truly inherited [8, 9]. Finally, despite the widely held view that AVMs represent congenital lesions owing to dysfunctional processes during development, there is accumulating evidence implicating insults to the brain, such as stroke, injury, infection, and even surgery, as a cause of de novo AVMs [10, 11]. In a minority (2–5%) of AVM patients the lesion can be syndromic in origin. AVMs are most often associated with hereditary hemorrhagic telangiectasia (HHT), capillary malformation-arteriovenous malformation (CM-AVM) syndrome and, less commonly, Wyburn-Mason syndrome [2, 12, 13]. Screening guidelines for syndromic AVMs will be discussed in the "Counseling and Management of Arteriovenous Malformations" section.

Influence of Pregnancy and Sex Hormones on Arteriovenous Malformation Pathogenesis

The maternal cardiovascular and hemodynamic changes accompanying pregnancy include a 40–50% increase in plasma volume, a comparable increase in cardiac output, and a significant reduction in systemic vascular resistance and blood pressure. These changes are critical for placental-fetal development and begin early in gestation, reaching a nadir during the second

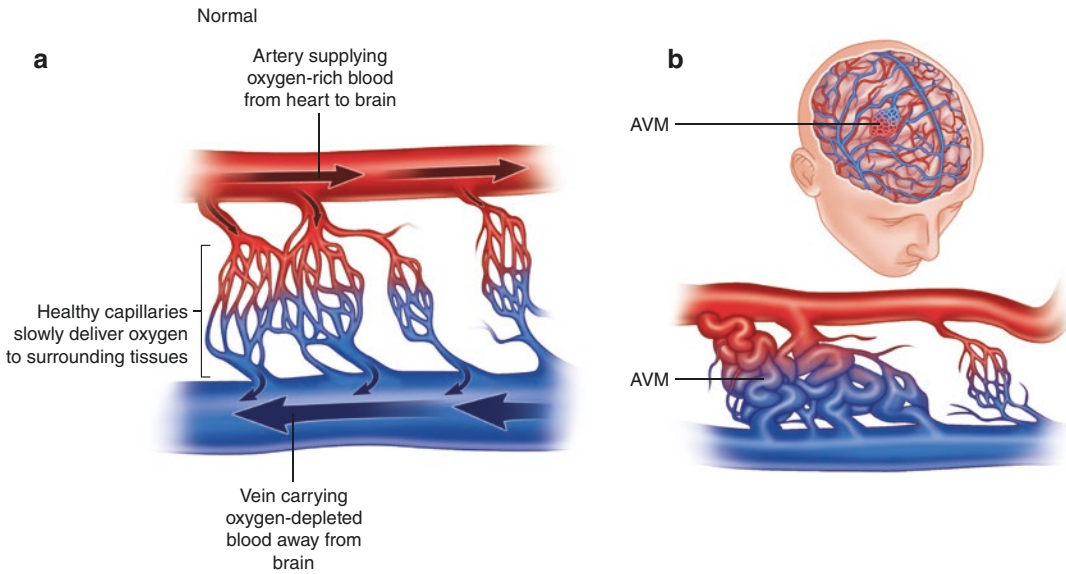

Fig. 9.1 (**a**) Normal vascular anatomy demonstrating capillary beds connecting high pressure arteries with low pressure veins. Hydrostatic pressure is gradually reduced across capillaries. (**b**) An AVM represents a tangle of blood vessels that results in direct, high-flow connections between arteries and veins without intervening capillary beds. As a result, veins are subjected to abnormally high pressure

trimester, before gradually returning to baseline [14]. Unlike other organs, such as the kidney, ovaries, and uterus in which perfusion is substantially increased, cerebral blood flow is maintained relatively constant during gestation due to the cranial cavity's relative intolerance to increased volume [15]. Mild estrogen-mediated increase in cerebral blood flow and transmission of hemodynamic force has been thought to underlie the reported risk of AVM hemorrhage during pregnancy. This is supported by the occurrence of rupture during the second and third trimesters, mirroring hemodynamic changes [16, 17]. Pregnancy is also associated with the release of a number of hormones and signaling factors including inflammatory mediators, chemokines, steroids, and growth factors which may influence AVM evolution. Moreover, animal studies have demonstrated heightened angiogenic activity in AVM tissues during late pregnancy, although there were no detectable differences in key angiogenic molecules or receptors [18]. The cerebrovascular and cardiovascular changes accompanying pregnancy are discussed in detail in Chap. 5.

Epidemiology, Presentation, and Natural Course of Arteriovenous Malformations

Scope of the Problem

Cerebral vascular malformations are relatively uncommon representing 5–9% of all intracranial space-occupying lesions; however, they are an important cause of neurologic morbidity and mortality in younger adults [19]. Developmental venous anomalies are considered the most common of these vascular malformations with a reported incidence of approximately 2% based on autopsy studies. However, these, along with capillary telangiectasias, exhibit a low tendency for neurological sequelae [20]. AVMs are relatively uncommon with prevalence between 10 and 20 per 100,000 [21–23]. While AVMs do not exhibit sex predilection, their tendency to present in young adulthood, most commonly in the third decade of life, makes them a significant concern in women of childbearing age [24].

Clinical Manifestations and Natural Course of Arteriovenous Malformations

AVMs can cause an array of neurological manifestations related to either mass effect or hemorrhage. AVMs are the most aggressive cerebrovascular lesions, with annual rupture rates reported between 2% and 4% [25]. Hemorrhage is, by far, the most common and devastating clinical manifestation of AVMs, accounting for 40–65%, followed by seizures in 18–35%, and chronic headache or focal neurological deficit in a small proportion [26–28]. Notably, hemorrhagic presentation has been shown to occur disproportionately in the youngest (<10 years) and oldest (>50) age groups, while presentation with seizures spikes between the ages of 20–29 [29]. Risk of hemorrhage increases substantially with previous hemorrhage and older age at diagnosis, in addition to morphologic features of the AVM including deep anatomic location, exclusive deep venous drainage, and associated aneurysms [25, 30].

Contrasting the predominance of ischemic stroke in the general population, hemorrhagic stroke—such as that resulting from rupture of vascular lesions—is the most common type during pregnancy [31]. In fact, the most common cause of intracerebral hemorrhage in the expectant patient is rupture of an AVM [32]. There is a body of evidence demonstrating an association between pregnancy and/or vaginal delivery and risk of aggressive behavior (i.e., growth, rupture/hemorrhage) of AVMs [27, 33–36]. One recently published report utilizing State Inpatient Databases and employing a cohort-crossover design demonstrated a greater than threefold increase in the rate of intracranial hemorrhage during pregnancy among patients with AVMs [37]. This is considered a consequence of the hemodynamic stress that evolves through pregnancy and peaks during the second stage of labor. However, there is substantial opposing evidence, including a systematic review which was not sufficient to support increased risk of AVM hemor-

rhage in pregnancy [17, 38]. Therefore, there is a need for enhanced, more rigorous future research, specifically through execution of a multicenter, prospective, case crossover study.

Diagnostic Considerations for Arteriovenous Malformations in the Pregnant Patient

Initial diagnosis of AVMs is typically via non-invasive imaging during workup for the presenting cause (i.e., intracranial hemorrhage, seizures, etc.). Advancements in and availability of imaging have also increased the rate of incidental diagnosis of these pathologies [28, 39]. The presence of multiple AVMs should raise suspicion of a syndromic cause [40]. Multiple AVMs occurring in association with recurrent epistaxis, and pulmonary/hepatic AVMs are indicative of HHT [2]. While most pregnancies occur normally in patients with HHT, the potential complications including heart failure, intracranial hemorrhage, pulmonary hemorrhage, and stroke (related to paradoxical emboli) make such pregnancies "high risk" [41].

Neuroradiological Features of Arteriovenous Malformations

In the pregnant patient, acquisition of the necessary data for clinical decision making must be balanced with the concern of ionizing radiation exposure to the fetus. Computed tomography (CT) relies on ionizing radiation thereby posing potential fetal risk; however, in head and neck CT the fetus is out of the range of the scan and therefore exposed to limited radiation. In the pregnant patient, CT still remains the standard for the evaluation of suspected intracranial hemorrhage with precautions taken to reduce fetal exposure (i.e., lead shielding of abdomen and pelvis) [33, 42]. Hemorrhage from an AVM typically appears as hyperdensity in an intraparenchymal or lobar distribution, however, this is not sufficient for diagnosis. Therefore, MRI is often necessary to delineate the anatomical features, particularly the "tangle of signal voids" on T2-weighted imaging [43].

Vascular imaging, including both CT and MR angiography (CTA/MRA) is critical for the diagnosis and evaluation of AVMs [44]. Definitive diagnosis and treatment planning of a cerebral AVM is often reliant on conventional digital subtraction angiography (DSA), a catheter-based modality that utilizes ionizing radiation and iodinated contrast. DSA provides the highest spatial and temporal resolution necessary to delineate features of the AVM that are critical to management decision making. In addition to the radiation exposure, risks associated with DSA include thromboembolic complications (i.e., stroke) [45]. Despite such risks, DSA remains indicated in pregnant patients with appropriate shielding and limitation of beam time. The estimated fetal radiation exposure during DSA is between 0.17 and 2.8 mGy, sufficiently lower than the accepted limit of 50 mGy. To reduce the overall radiation exposure time while acquiring the most relevant information, it is prudent for members of the cerebrovascular team contemplating treatment to perform the DSA [38, 45]. Considerations for neuroimaging in the pregnant patient are discussed in detail in Chap. 3.

Counseling and Management of Arteriovenous Malformations

Diagnosis of an AVM is frightening for anyone, but particularly for the pregnant patient or the young adult patient, hoping to become pregnant. Such a diagnosis often leaves the expectant patient questioning how to manage both her pregnancy and the lesion in sync. Decision making regarding management in these settings is highly complex and dependent on anatomic and morphologic features of the lesion itself in addition to the patient's individual clinical factors. The occurrence of rupture and hemorrhage is a key pivotal point in decision making, with a tendency toward conservative management in unruptured or clinically silent AVMs and toward invasive management in those that have ruptured or are otherwise symptomatic. The approach to man-

agement is especially complex in the pregnant patient due to the need to balance both maternal and fetal harm. Unfortunately, there is only scarce literature and no guidelines or consensus statements to inform this unique situation.

Counseling: Patients with Arteriovenous Malformation Planning to Become Pregnant and Hereditary Concerns

Historically, the purported association between pregnancy and aggressive behavior of cerebral vascular malformations, particularly AVMs, has led women with such lesions to be sterilized, counseled against pregnancy, or to even have their pregnancies terminated. In those women in whom gestation did proceed, cesarean delivery was recommended due to concern for rupture [27, 46]. However, as described above, there is a lack of consensus on whether or not pregnancy truly confers increased risk for rupture. For a woman of childbearing age with a diagnosed AVM, a critical question may be: Should I undergo treatment before becoming pregnant? The patient should be counseled appropriately on the evidence regarding the association between pregnancy and risk of hemorrhage, which at this point is conflicting and insufficient. Therefore, the decision to treat an unruptured AVM prior to pregnancy should be consistent with the characteristics of the lesion and clinical history (i.e., previous hemorrhage) [25, 30, 47]. In a woman with a high-risk lesion or one producing severe symptoms, in whom management of the malformation is indicated, it is certainly safer for treatment to occur prior to pregnancy. It is important to note that, while radiosurgery remains an attractive approach for management of AVMs, particularly in difficult to access regions of the brain, a major limitation is its failure to achieve immediate obliteration and reduction of hemorrhage risk [39, 48]. In a study of women who became pregnant during the latency period, 2 of 18 (11.1%) experienced AVM hemorrhage compared to 2.5% of nonpregnant women [49]. Based on this evidence, albeit with limited sample size, we recommend women who are treated with radiosurgery to await attempts at pregnancy until confirmed obliteration of the lesion.

Syndromic malformations represent another topic of concern in patients who are pregnant or considering becoming pregnant. In women who appear to suffer from AVMs associated with a syndromic cause, screening is warranted. HHT is one of the most common syndromes associated with cerebral AVMs and is characterized by the presence of cutaneous telangiectasias in addition to pulmonary, hepatic, and cerebral AVMs. HHT is transmitted in an autosomal dominant pattern, therefore the risk to one's offspring is 50% [50]. Screening for cerebral and pulmonary AVMs is recommended in all offspring of parent's with HHT, unless the disease is excluded by genetic testing. It has also been recommended that those screened for cerebral AVMs during infancy undergo a follow-up screen after puberty due to the potential for AVMs to grow and remodel throughout childhood [51]. Women with HHT are also recommended to be screened and treated for pulmonary AVMs prior to pregnancy; asymptomatic pulmonary AVMs identified during pregnancy should not be treated until after delivery. Finally, screening of the spine with MRI in women with HHT may be necessary to rule out spinal AVMs and thus permit regional anesthesia [41].

Management of Unruptured Arteriovenous Malformations in Pregnancy

Management of unruptured AVMs is a highly contested topic, especially in the aftermath of the heavily critiqued "A Randomized Trial of Unruptured Brain Arteriovenous Malformations" (ARUBA) study published in 2014 which was terminated early due to superiority of medical management over interventional therapy [52]. The complex decision making in management of unruptured AVMs is further complicated in the setting of pregnancy, with additional concerns regarding modality for treatment and timing in relation to delivery. The currently available

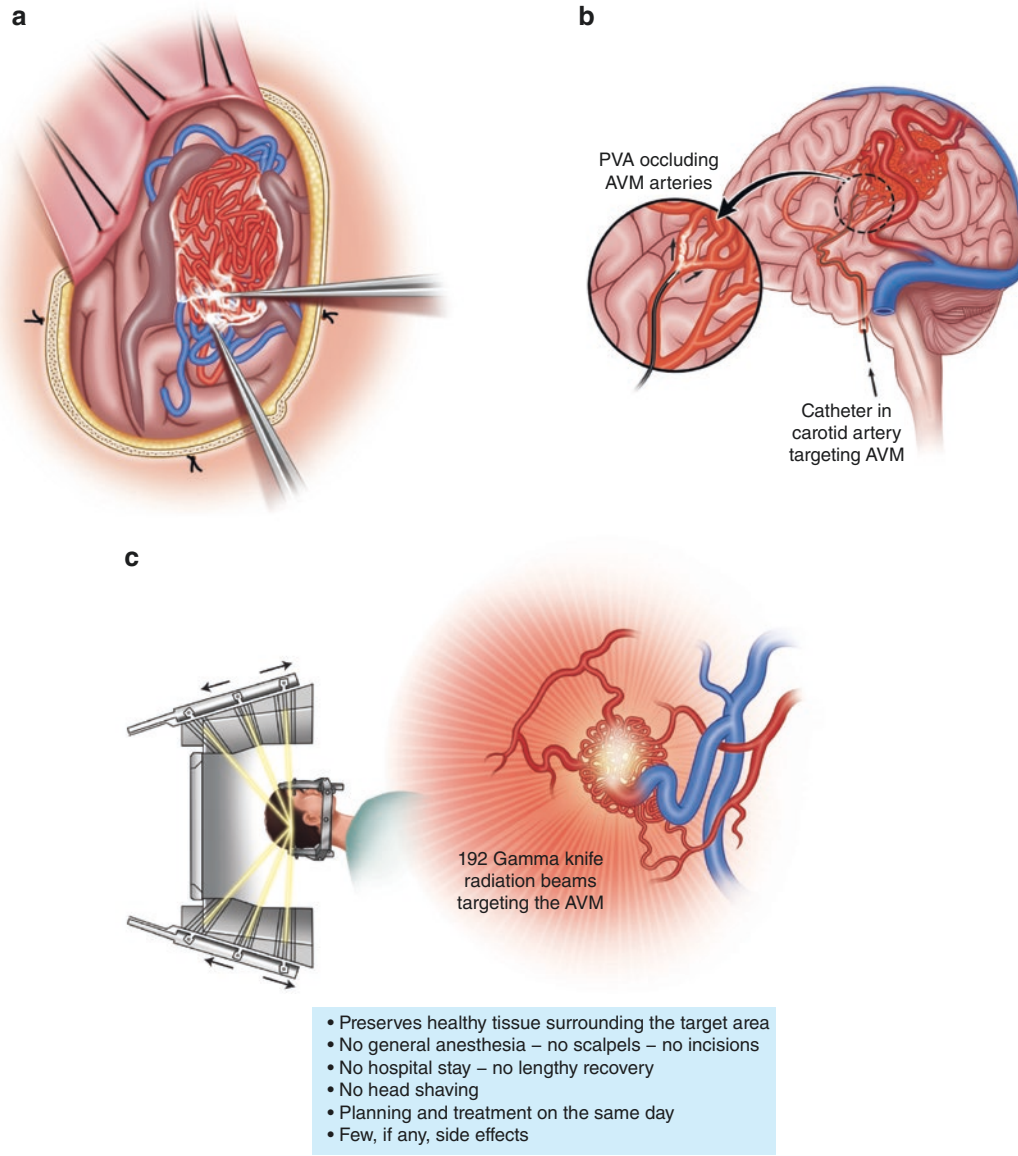

Fig. 9.2 Treatment options available for treatment of AVMs includes: (**a**) microsurgical resection, (**b**) endovascular embolization, and (**c**) radiosurgical obliteration

modalities for AVM treatment include microsurgery, neoadjuvant endovascular embolization, and radiosurgical obliteration, each with their own risk/benefit profile (Fig. 9.2). Generally, unruptured AVMs presenting in pregnancy should be approached conservatively due to their relatively low risk profile, even despite some reports of elevated rupture risk in pregnancy [38, 53]. Further supporting this, in a report of 12 patients presenting with unruptured AVM during pregnancy, all managed conservatively, one (8.3%) developed bleeding during gestation. All patients were followed to full term, with ten undergoing cesarean section and two delivering vaginally [54]. As such, intervention during pregnancy should be based on neurosurgical indications while accounting for obstetrical concerns. However, due to the paucity of data on this topic,

we are unable to make specific recommendations on selection of patients for management of unruptured AVMs in pregnancy. An interdisciplinary team including a representative or representatives specialized in microsurgery, radiosurgery, and interventional procedures, as well as obstetrics/gynecology and neurocritical care should be involved in the decision making process. Guiding factors in this process should include: (1) risk of catastrophic hemorrhage, (2) maternal-fetal risk of individual therapies, and (3) stage of pregnancy. Increased risk of hemorrhage is conferred by deep venous drainage, associated nidal aneurysms, and previous rupture and these patients may warrant intervention of their unruptured AVM [25, 30]. In considering microsurgical resection, the grade of the AVM can help to predict risk of complications; for example, Spetzler-Martin grade I or II lesions have relatively low surgical risk and high probability of complete resection and obliteration [55]. Similar grading models can be applied for prediction of complications and outcomes in radiosurgery or endovascular embolization [56]. There is precedent for delay of surgery for small, low risk, ruptured AVMs until fetal maturity and delivery has occurred; this may even be extended to 2 months following delivery to permit restoration of normal cardiovascular and hemostatic factors [57, 58]. This same logic may be considered in dealing with unruptured AVMs identified during pregnancy. As with all decisions made in the clinical setting, we must strive to achieve equipoise between the true risks of the lesion and the risks associated with therapy; in the setting of unruptured AVMs in pregnancy, the risks of therapy compared to those of the lesion typically favor conservative management. In those in whom intrapartum intervention occurs, vaginal delivery in accordance with obstetric indications appears safe in patients with completely resected or obliterated AVMs [59].

Given that the most likely presentation of an *unruptured* AVM is seizures, it is of importance to briefly discuss the approach to management of seizures in pregnancy. Adequate control of seizures is critical for preservation of maternal and fetal health: seizures induce lactic acidosis, increases in uterine pressure and blood flow, and are associated with maternal and fetal hypoxia [60]. It is established that many antiepileptic drugs increase risks of congenital anomalies, such as congenital heart disease, cleft palate, neural tube defects, and finger hypoplasia. Traditional antiepileptics, such as valproate and phenobarbital, exhibit the highest risk of major malformations while newer agents, such as lamotrigine and levetiracetam, are associated with lower risk profiles [61]. Major considerations for administration of antiepileptics in the pregnant patient include supplementation of folic acid and use of monotherapy when possible for seizure control [54]. Considerations for the selection of antiepileptic agents during pregnancy are discussed in detail in Chap. 28.

Management of Ruptured Arteriovenous Malformations in Pregnancy

Ruptured AVMs resulting in intracranial hemorrhage result in substantial maternal and fetal morbidity and mortality. Emergent restoration of normal blood pressure (<140 mmHg) in hypertensive (150–220 mmHg) patients is recommended in the setting of acute intracranial hemorrhage [62]; however, it is important to balance this with maintenance of uteroplacental blood flow and utilization of safe pharmacologic agents such as labetalol, hydralazine, or nifedipine [63]. Diagnosis of the pregnant patient with intracranial hemorrhage from any cause, including AVM, should warrant consult with specialists from obstetrics/gynecology.

After initial management related to the intracranial hemorrhage, options for definitive management of the ruptured AVM include the same modalities as unruptured AVMs: microsurgical resection, endovascular embolization, radiosurgical obliteration, or a combination of the three. As in the case of unruptured AVMs, decision making in ruptured AVMs should be based on neurosurgical indications with special consideration to obstetrical concerns. After initial stabilization, the primary principle guiding management in the

setting of a ruptured AVM is reducing the risk of rebleeding. It is well established that prior hemorrhage is a significant risk factor for future hemorrhage, particularly in the first year following rupture where rebleed rates spike to double that of other time points [64]. Owing to the relatively low risk of immediate rebleeding (<1% per month) from ruptured AVMs, contrasting the risk in ruptured aneurysms, delayed intervention of at least 4 weeks has been proposed to permit rehabilitation following initial hemorrhage in the general population [65]. However, it is important to note that there is evidence of increased risk of rebleeding in pregnant patients, with reported rates near 25%, compared to an annual risk of rebleeding of 7.45% in a general cohort [33, 34, 46, 57, 66]. In the pregnant patient, delayed management may be reasonable, particularly for patients in the late third trimester in whom delivery may be able to proceed prior to intervention. Delay is also supported in pregnant patients with small amounts of hemorrhage that are otherwise not at high risk for re-rupture until several weeks postpartum when maternal hemodynamics have been restored [57]. In such cases in which fetal maturity permits pre-intervention delivery, it is prudent to deliver via cesarean section [67]. If the fetus is not viable, the re-rupture risk is high, and the lesion is amenable to intervention, treatment during pregnancy is warranted [59]. Intervention during pregnancy has been reported successfully utilizing surgical [67], endovascular [68], and radiosurgical [69] means.

Each modality bears its own important risks. Microsurgical resection is substantially riskier in higher grade lesions [70]. In addition to the risk of neurological deficit associated with surgery, there is additional concern for fetal harm in the pregnant patient, particularly fetal hypoperfusion and hypoxia. Maintenance of adequate maternal hydration and hemodynamic status is critical for maintaining uterine and fetal perfusion but can be compromised in the setting of surgery via blood loss, diuresis, and even patient positioning. Diuretic agents, such as mannitol, are typically employed during microsurgical resection to minimize cerebral swelling but may cross the placenta and result fetal hypovolemia and dehydration [54]. In a small cohort of patients undergoing craniotomy for various indications, mannitol was used without complication for brain relaxation suggesting that judicious use is safe and effective in the setting of pregnancy [71]. Moreover, maternal hypotension during surgery can result in fetal hypoperfusion and hypoxia [72]. Endovascular embolization, particularly as monotherapy, does not provide total obliteration of the AVM but does allow for elimination of high-risk features such as perinidal or intranidal aneurysms which increase the re-rupture risk [73]. In addition, exposure to ionizing radiation in pregnant patients is of particular concern due to the potential fetal harm that may result. Fortunately, most reports suggest that fetal exposure during cerebral diagnostic angiography and neuroembolization is far below the safety threshold [59]. To minimize the risk of fetal harm from ionizing radiation it is critical to maintain appropriate abdominal shielding; efforts should also be made to reduce fluoroscopy time (i.e., via selective angiography of targeted vessels) and beam angling [53, 58]. Although iodinated contrast is not contraindicated in pregnancy, utilization of half strength contrast may also enhance procedural safety during embolization [53]. A major limitation of radiosurgery is the inability to achieve immediate obliteration of the AVM that would allow a patient to be freed from the risk of devastating intracranial hemorrhage. In fact, the latency of radiosurgery is typically considered to be 2 years from treatment completion; this would not warrant any protection to the pregnant patient if performed during gestation but would expose the fetus to potentially hazardous ionizing radiation [39]. We conclude, in concordance with previous groups, that radiosurgery is not an appropriate intervention to be undertaken in the pregnant patient [58].

Cavernous Malformations

Pathology and Pathogenesis of Cavernous Malformations

CMs, also known as cavernomas or cavernous angiomas, are malformations consisting of a cluster of thin-walled, dilated capillaries recognizable by their characteristic "mulberry" appearance. Histologically, the vessels, referred to as caverns, are constituted by a simple endothelial lining surrounded by a thin, fibrous adventitial layer [74]. CMs arise in two distinct forms: (1) sporadic, which are classically solitary lesions associated with a developmental venous anomaly, and (2) familial, which often presents with multiple lesions and a strong family history of neurological disease [75]. Mutations in three protein-encoding genes (*CCM1*, *CCM2*, and *CCM3*) have been identified as causative of CM and are transmitted in an autosomal dominant pattern. These proteins contribute to a larger signaling pathway that regulates angiogenesis, vessel formation, and cellular proliferation [76].

Influence of Pregnancy and Sex Hormones on Cavernous Malformation Pathogenesis

While the hemodynamic changes of pregnancy may influence pathogenesis and hemorrhage of CMs, they are low-flow lesions and generally considered to be less subject to these stresses. Consistent with this, a recently published prospective analysis of 367 deliveries demonstrated no instances of hemorrhage during this period in which acute hemodynamic stresses are expected to occur [77]. Like AVMs, CMs are influenced by circulating factors associated with pregnancy including growth factors and inflammatory mediators. Elevated levels of vascular endothelial growth factor and basic fibroblast growth factor during pregnancy are thought to underlie growth and potentiate rupture of CMs [47].

Epidemiology, Presentation, and Natural Course of Cavernous Malformations

Scope of the Problem

CMs are the second most common vascular anomaly and have a reported prevalence ranging between 0.3% and 0.5% in both autopsy and imaging studies [78–80]. Assuming a prevalence of 0.4% and an estimated 114 million births worldwide, it is expected that over half a million pregnancies will occur in women with CM [81]. Similar to AVMs, CMs tend to present during young adulthood making them a concern in women of childbearing age [82].

Clinical Manifestations and Natural Course of Cavernous Malformations

CMs rupture at an annual rate of 0.3–2.3%, making them slightly less aggressive than AVMs [30, 83]. Moreover, hemorrhagic CMs are typically less destructive due to the low flow nature of these lesions. Therefore, small hemorrhages in noneloquent tissue may be clinically silent. Any deficits related to hemorrhage are often transient and resolve within a period of days to weeks as blood is absorbed [30, 84]. Of note, there is some evidence supporting female sex as a risk factor for CM hemorrhage, although this is not conclusive [83]. The most common presentation of CM involving the cerebral hemispheres is seizures, owing to the inherent epileptogenicity of iron found at the border of the lesions [82]. Similar to AVMs, there is previous evidence suggesting that pregnancy and/or vaginal delivery confers increased risk of aggressive behavior (i.e., growth, rupture/hemorrhage) of CMs [85]. This was postulated to result from cardiovascular and hemodynamic factors as well as pregnancy-associated hormones including progesterone and growth factors [47]. However, this is refuted by more recent evidence from several large prospective and retrospective cohorts [77, 81, 86].

Diagnostic Considerations for Cavernous Malformations in the Pregnant Patient

The initial step in identification of a CM is via non-invasive imaging during the evaluation of headache, neurological deficit, or, most often, new-onset seizures. There is also an increased propensity for incidental detection with advancements and widespread availability of neuroimaging [39].

Neuroradiological Features of Cavernous Malformations

Unless the lesion is large or recently bled, CMs are typically difficult to identify on head CT. This makes MRI the gold-standard for diagnosis of CMs due to the ability to delineate key anatomic and pathologic features. Classically, CMs exhibit a reticular core with a "berry" or "popcorn" appearance that is often surrounded by a low-intensity halo [84]. In contrast to AVMs whose angioarchitecture is highlighted on angiography, the most notable radiological feature of CMs is that they are angiographically occult: that is, they do not appear on these dedicated vascular imaging studies [87].

Counseling and Management of Cavernous Malformations

Counseling: Patients with Cavernous Malformation Planning to Become Pregnant and Hereditary Concerns

Based on the most recently available and reliable data, there is no reason that the presence of a cavernous malformation should preclude a woman from considering pregnancy [77, 81, 86]. Therefore, treatment should be guided by neurosurgical considerations including anatomic location, presence of symptoms (i.e., seizures), and prior hemorrhage. When treatment is indicated, it may be prudent to intervene prior to conception to mitigate surgical or radiation risks posed to the fetus. In the setting of familial CM, which displays autosomal dominant inheritance, screening is recommended via molecular genetic testing in those in whom the familial genetic variant is isolated or otherwise via MRI of the brain and spinal cord [88].

Management of Cavernous Malformations in Pregnancy

The severity of CMs varies significantly: small hemorrhage may be clinically silent or produce transient neurological symptoms, while hemorrhage of brainstem CMs can be acutely debilitating and life-threatening. The clinical data regarding management of CMs in pregnancy is particularly limited. A treatment strategy has been proposed by Yamada et al. in which asymptomatic and mildly symptomatic lesions are managed conservatively, while those with severe or progressive symptoms are surgically resected. Certain risk factors, such as previous hemorrhage or family history may warrant intervention in a lesion that would otherwise be approached conservatively [47]. A review of 16 cases of CM identified during pregnancy determined that neurosurgical intervention is seldom necessary [89]. When surgical management is necessary, it is recommended to occur after delivery so long as there is no substantial threat to maternal or fetal wellbeing [47]. However, in cases where maternal-fetal life is compromised, such as catastrophic hemorrhage, treatment preceding delivery can be accomplished without obstetric complication [89, 90]. Historic concerns regarding CM hemorrhage in association with maternal hemodynamic changes during labor have led to a tendency for patients with asymptomatic and symptomatic lesions to undergo cesarean delivery. However, a more recent study found that vaginal delivery occurred without hemorrhagic complication in 149 of 168 pregnancies in 64 female patients with CMs [81]. Therefore, choice of delivery method should be dictated by obstetrical considerations, rather than concern for hemorrhage.

Conclusion

Management of cerebral vascular malformations is especially complicated in the context of pregnancy and requires multidisciplinary collaboration between the patient, family, obstetricians, and neurologists/neurosurgeons. While there is some evidence supporting pregnancy as a risk factor for aggressive behavior of vascular malformations (i.e., rupture, hemorrhage, progression), we do not find the evidence sufficient to definitively confirm such a relationship. For women with vascular lesions seeking counseling on becoming pregnant, we conclude that those at high risk should be treated prior to attempts at pregnancy. Women diagnosed with an unruptured or asymptomatic/mildly symptomatic lesions during pregnancy should be managed based on neurosurgical indications in consult with a team of interdisciplinary and multimodal experts; intervention is typically not warranted. Women diagnosed with a hemorrhagic lesions during pregnancy should be managed in an effort to reduce maternal and fetal morbidity and mortality; interventions taken should be in such a way as to reduce risk of fetal harm. Vaginal delivery generally appears safe in unruptured or resected/obliterated AVMs and CMs, while cesarean delivery is likely the safest approach to delivery in women with ruptured AVMs.

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