Management of patients with unruptured cerebral arteriovenous malformations during pregnancy and childbirth

Francesca Gabriela Paslaru[1], Andrei Giovani[1], Elena Nestian[1], George Iancu[2,3], Dragos-Iosif Pirgaru[4], Alexandru Catalin Paslaru[5], Nicolae Gica[2,3], Anca Maria Panaitescu[2,3]

[1] Neurosurgical Department, "Bagdasar-Arseni" Clinical Emergency Hospital, Bucharest, Romania
[2] Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3] Department of Obstetrics and Gynecology, "Filantropia" Clinical Hospital, Bucharest, Romania
[4] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[5] Department of Physiology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Cerebral arteriovenous malformations (AVM) are fistulous connections between arterial and venous blood flow, consisting of an abnormal tangle of dysplastic arteries and veins, without capillary vessels or interposed functional brain parenchyma. Management of pregnant patients with unruptured AVMs remain a dilemma for both obstetricians and neurosurgeons, due to the scarcity of data about this condition. Decisions are made weighting the risk of bleeding during pregnancy and the neurological status of the patient against the risks associated with a neurosurgical intervention. Most studies suggest that the bleeding risk does increase slightly during pregnancy, but further large prospective studies are needed. This article selects and reviews literature data to convey recommended management strategies for unruptured cerebral vascular malformations during pregnancy, childbirth and puerperium.

Keywords: cerebral arteriovenous malformations, unruptured cerebral vascular malformations, pregnancy, childbirth

INTRODUCTION

Cerebral arteriovenous malformations (AVM) are fistulous connections between arterial and venous blood flow, consisting of an abnormal tangle of dysplastic arteries and veins, without capillary vessels or interposed functional brain parenchyma. This condition is relatively rare, although the true incidence and prevalence are still unknown. Detection rate was estimated to 1.11 per 100,000 person-years in one study [1]. In general population, for previously unruptured AVMs, bleeding rate is about 1% per year, the risk increasing fivefold after the first bleed [2]. Whether pregnancy modifies the tendency to rupture remains controversial, although some studies suggest that this is true. In one study, female patients of reproductive-age seemed to have a higher risk of AVM rupture (2.52%), highest being during pregnancy and puerperium (5.59%) [3]. Management of pregnant patients with unruptured AVMs remain a dilemma for both obstetricians and neurosurgeons, due to the scarcity of data about this condition. Decisions are made weighting the risk of bleeding during pregnancy and the neurological status of the patient against the risks associated with a neurosurgical intervention. This article selects and reviews literature data to convey recommended management strategies for unruptured cerebral vascular malformations during pregnancy, childbirth and puerperium.

METHODS

We performed a review in PubMed and Cochrane databases, as well as a hand-search of high-impact journals using the reference list of all identified articles, searching for randomized controlled trials and observational studies. The terms used for the search were "brain arteriovenous malformation", "cerebral arteriovenous malformation" or "intracranial arteriovenous malformation" combined with "pregnancy"," pregnant", "parturition", "puerperium" or "childbirth". To be eligible for inclusion, studies had to be case reports, case series, randomized controlled trials, written in english. Exclusion criteria were: unrelated, duplicated, unavailable full-text or abstract-only papers.

EPIDEMIOLOGY

Estimates of the prevalence of AVM in general population vary from 0.001% to 0.5% [4,5,6]. The true prevalence remains unknown, due to the relative rarity of the disease and the fact that many AVMs can remain clinically silent for decades. Al-Sahi et al. published a retrospective study based on the population of Scotland reporting an AVM prevalence rate of 15-18 per 100,000 adults [1]. Data from the New York Islands AVM Hemorrhage Study, a prospective, population-based survey of 10 million population, stated that the AVM average detection rate was 1.34 per 100,000 person-years [7]. J. Hillman published in 2001 a population-based analysis of AVM treatment during an 11-year period, harboring data from every patient diagnosed with a cerebral AVM in a population of 986,000 people. The incidence was 12.4 newly diagnosed AVMs per 1,000,000 population per year [8].

PATHOPHYSIOLOGY

A cerebral arteriovenous malformation is an abnormal tangle of dysplastic arteries and veins, without capillary vessels or interposed functional neural tissue. The absence of a capillary bed leads to arteriovenous shunting through one or multiple fistulas [9]. Some authors state that an underlying developmental derangement could be attributed to at least some AVMs, rendering them congenital lesions, as suggested by their diagnosis usually in younger patients, even in utero [10] and their unique angioarchitecture and pathological features [9]. Possible causes could be miscommunications during embryogenesis, when arteries and veins are directly connected, without intervening capillaries. If this miscue persists after birth, an AVM arises, instead of developing into normal vasculature [11]. The absence of functional brain tissue inside the nidus seem to lead to a response of neural networks, such as translocation of language area, distinct from the reorganization of the cerebral cortex secondary to acute lesions [12]. Researchers have developed animal models that allowed them to observe changes in vessels that are characteristic for cerebral AVMs, such as lack of tight and adherent junctions, splitting of elastic lamina and changes in the vessel wall thickness [13]. Regarding the genetic basis of AVM formation information is still being elucidated, though multiple candidate genes have already been identified. Cerebral AVMs can be either sporadic, or resulting from associated syndromes, such as Osler-Rendu-Weber (hereditary hemorrhagic teleangiectasia), a disease linked to insufficiency of transforming growth factor β (TGF-β) pathway signaling genes SMAD4 and ENG, or Cobb's syndrome, linked to spinal AVMs, patients exhibiting an abnormal expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase 9 (MMP-9) and platelet endothelial cell adhesion molecule 1 (PECAM-1) [14].

DIAGNOSIS

Cerebral AVMs are typically found in the cerebral hemispheres, commonly affecting distal arterial branches in the border-zone region of the anterior, middle and posterior cerebral arteries [15], but may be located in any region, including spinal cord, brainstem and cerebellum. Size may also vary, from angiographically occult AVMs to giant ones. Due to the heterogeneity in size and location, AVMs may cause a broad range of neurological symptoms. The most common presentation in unruptured AVMs are seizures, either focal or generalized, occurring in 20-30% of the patients [16]. Still, many lesions can be incidental findings [17]. Other possible presentations of AVMs include headache, pulsatile tinnitus, ischemic steal or mass effect [16].

Several imaging methods are being used for the diagnosis of cerebral AVMs. These modes include digital subtraction angiography (DSA), magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) [18].

In case of a hemorrhagic event, cerebral angiography should be performed given that the pregnant patient is provided adequate shielding in order to reduce radiation exposure and the consequent risk of potential fetal development abnormalities. If the necessary measures are implemented (abdominal lead shielding, modern imaging equipments, limited fluoroscopy proximal to the uterus), pregnancy does not contraindicate the digital subtraction angiopraghy. Nonetheless, it must be noted that iodinate contrast agents can cross the placental barrier and may cause transient neonatal hypothyroidism [19].
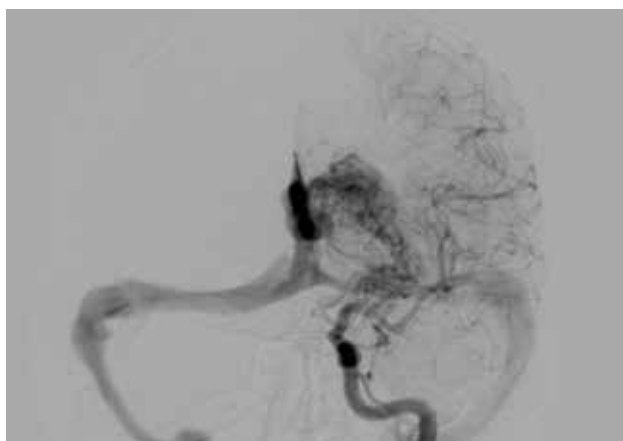
Magnetic resonance imaging (MRI) has the ability to allow a detailed view of cross-sectional anatomy without using ionizing radioations [20]. To our
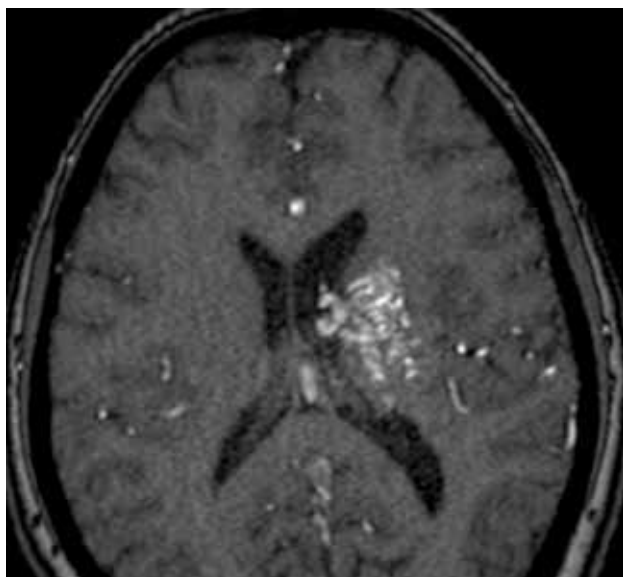
FIGURE 1. TOF MRI scan showing a left thalamic AVM in a 29-year old pregnant patient suffering from recurrent headaches
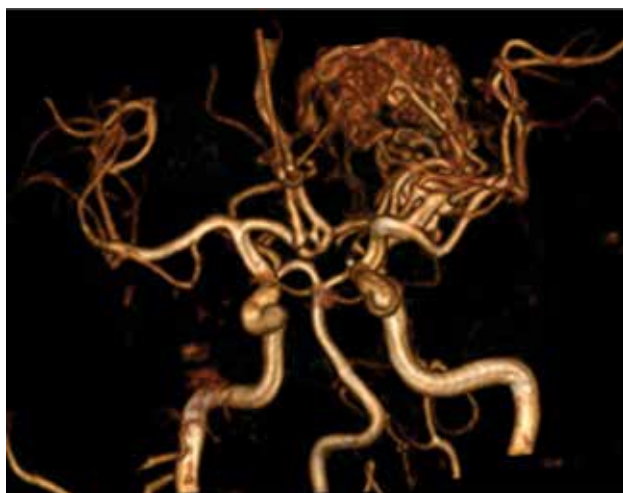
FIGURE 2. 3D TOF MRI reconstruction of the left thalamic AVM in the same patient

FIGURE 3. Digital-substraction angiography showing a left thalamic AVM connecting the left middle cerebral artery with the left straight sinus in the same patient

knowledge, there are no studies that have shown any harms attributable to MRI during any trimester of pregnancy, but large prospective and longitudinal studies are still lacking. According to the American College of Obstetrics and Gynecology (ACOG) guidelines, radiation exposure from computed tomography scan (CT) is at a dose lower than the exposure dose associated with fetal harm. If these techniques are necessary, they should not be withheld from a pregnant patient [21].

GRADING SYSTEMS

Most commonly used in day-to-day clinical practice for estimating the risk of morbidity and mortality following neurosurgical treatment of cerebral AVMs is the grading system proposed by Spetzler and Martin, in 1986 [22]. The lesion is graded based on the size, venous drainage and eloquence of the brain region (Table 1). A numerical value is assigned for each category and the grade is derived by summing the points, the lowest being grade I and highest being grade V.

TABLE 1. Spetzler-Martin grading system for cerebral arteriovenous malformations [22]

Size	< 3 cm	1 point
	3-6 cm	2 points
	> 6 cm	3 points
Eloquence	non-eloquent	0 points
	eloquent	1 point
Venous drainage pattern	superficial	0 points
	deep	1 point

Many different grading systems have been published in the literature, most of them being complex and difficult to use at the bedside. Lawton et al. published in 2010 a supplementary and complementary grading scale for deciding which AVM patients should undergo surgical treatment, taking into account the following parameters: age (less than 20-years old = 1 point, 20-40-years old = 2 points, over 40-years old = 3 points, unruptured presentation (1 point), diffuse nidus (1 point) [23]. Spetzler and Ponce suggested, in 2011, a consolidation of the Spetzler-Martin scale in 3 new classes combining grades I and II into class A, grade III being classified as class B and grades IV and V being combined into class C), based on similar surgical results, providing simplified management recommendations and superior statistical value for comparative studies [24]. To the best of our knowledge, no grading scale has been yet designed specifically for the pregnant and postpartum population.

RUPTURE RISK IN PREGNANCY

The highly controversial prospective multicenter randomized controlled trial ARUBA (A Rand-

omized Trial of Unruptured Brain Arteriovenous Malformations) was the first study to compare medical management to combination of medical management and prophylactic surgical, endovascular or radiation therapy (alone or combined). The trial was halted at 33.3 months follow-up, after an interim analysis proved that medical management alone was superior to combination of interventional therapy and medical management in terms of preventing symptomatic strokes or death [25]. The design of the study was heavily criticized, especially in regard to the 5-year follow up period, which many authors stated that would detect all the procedure-related complications, but not the long-term benefits of prophylactic interventional treatment [26]. In 2020, Mohr et al. published the final follow-up of the ARUBA trial, further confirming that medical management alone was superior to combined management for preventing death or symptomatic stroke [27]. However, there is still a scarcity of data regarding the pregnant and postpartum population. Empirical data suggest that pregnancy alters the natural rupture tendency of AVMs. More so, even women of reproductive age who are not pregnant seem to have a higher risk of bleeding than general population [3]. It is still unclear if interventional therapy could bring more advantages in this particular group of patients, but every treatment strategy must be weighted-against potential risks, to both mother and the fetus.

NEUROSURGICAL TREATMENT AND ANESTHETIC CONSIDERATIONS

Neurosurgical treatment of unruptured AVMs in pregnant women can be performed either during pregnancy or postpartum, multiple factors needing to be considered. The already mentioned grading systems are useful tools to aid in the decision-making process. The risk of bleeding during surgery must be carefully evaluated. General consensus is that the smaller the gestational age, the higher is the risk of fetal adverse effects in case of blood loss. Even though bleeding may occur anytime during pregnancy, AVM ruptures are most common between the 15th and 20th weeks of pregnancy [28]. During vaginal delivery, the risk of rupture increases, due to the high cardiac output and CSF pressure. For this reason, caesarean section is recommended if postpartum surgery is chosen. The age of the fetus is another important aspect to be considered. For example, the risk of hemorrhage is higher in patients with less developed fetuses [19]. Moreover, the Spetzler-Martin classification is also a key element when making this decision.

Regarding the anesthetic considerations, the key points are to maintain stable systemic, as well as cerebral and placental hemodynamics. Sustaining oxygenation and avoiding an increase in intracranial pressure are also crucial elements [28]. General anesthesia can be satisfactorily used in case of emergencies. Maternal monitoring should consist of standard monitoring for anesthesia, mean arterial pressure (MAP), invasive arterial blood pressure, heart rate, blood oxygen level (SpO2). The intra-cranial pressure as well as utero-placental perfusion are maintained at appropriate levels by stabilizing the MAP within certain limits. Special consideration regarding the side effects of the anesthetic towards the fetus must be given. For this reason, remifentanil should be avoided [28].

ENDOVASCULAR TREATMENT AND RADIOSURGERY

Endovascular treatment for cerebral AVMs in pregnancy should be decided according to their symptomatic manifestations and angiographic characteristics, guided by the primum non nocere principle: radiation exposure to the pregnant patient must be limited only to those cases in which it is necessary, due to the effects on fetus development [19].

A few case reports suggested that the radiation dose of stereotactic radiosurgery and endovascular treatment for cerebral AVM during pregnancy was below the safety threshold (250 mGy at 16-25 weeks and 500 mGy after 25 weeks) [29,30].

DELIVERY MODES

Some studies have indicated that labor and delivery is not associated with an increased incidence of AVM rupture [31-33]. Several, though not all, authors suggested that it would be acceptable to permit vaginal delivery in this patient population [31,34]. However, it has been stated that cesarean section can control the maternal blood pressure, thus avoiding sudden intense hemodynamic changes of intracranial vascular pressure, leading to an increase in the stress on the vessel wall [19].

CONCLUSIONS

Decisions on unruptured cerebral AVM during pregnancy treatment are made weighting the risk of bleeding and the neurological status of the patient against the risks associated with a neurosurgical intervention. Most studies suggest that the bleeding risk does increase slightly during pregnancy, but further large prospective studies are needed.

REFERENCES

1. Zhu D, Zhao P, Lv N, Li Q, Fang Y, Li Z, Zhang H, Duan G, Hong B, Xu Y, Liu J, Huang Q. Rupture Risk of Cerebral Arteriovenous Malformations During Pregnancy and Puerperium: A Single-Center Experience and Pooled Data Analysis. *World Neurosurg.* 2018 Mar;111:e308-e315.
2. Lawton MT, Rutledge WC, Kim H, Stapf C, Whitehead KJ, Li DY, Krings T, terBrugge K, Kondziolka D, Morgan MK, Moon K, Spetzler RF. Brain arteriovenous malformations. *Nat Rev Dis Primers.* 2015 May 28;1:15008.
3. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP; Scottish Intracranial Vascular Malformation Study Collaborators. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke.* 2003 May;34(5):1163-9.
4. English LA, Mulvey DC. Ruptured arteriovenous malformation and subarachnoid hemorrhage during emergent cesarean delivery: a case report. *AANA J.* 2004 Dec;72(6):423-6.
5. Fleetwood IG, Steinberg GK. Arteriovenous malformations. *Lancet.* 2002 Mar 9;359(9309):863-73.
6. Friedlander RM. Clinical practice. Arteriovenous malformations of the brain. *N Engl J Med.* 2007 Jun 28;356(26):2704-12.
7. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. *Lancet Neurol.* 2005 May;4(5):299-308.
8. Cerbo RM, Cabano R, Radicioni M, Stronati M. Cerebral arteriovenous shunts regression in two preterm newborns with heart failure in utero. *Am J Perinatol.* 2009 Oct;26(9):637-9.
9. Lazar RM, Marshall RS, Pile-Spellman J, Hacein-Bey L, Young WL, Mohr JP, Stein BM. Anterior translocation of language in patients with left cerebral arteriovenous malformation. *Neurology.* 1997 Sep;49(3):802-8.
10. Stapf C, Mohr JP, Sciacca RR, Hartmann A, Aagaard BD, Pile-Spellman J, Mast H. Incident hemorrhage risk of brain arteriovenous malformations located in the arterial borderzones. *Stroke.* 2000 Oct;31(10):2365-8.
11. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg.* 1986 Oct;65(4):476-83.
12. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al.; international ARUBA investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet.* 2014 Feb 15;383(9917):614-21.
13. Elhammady MS, Heros RC. Editorial: The ARUBA study: where do we go from here? *J Neurosurg.* 2017 Feb;126(2):481-485.
14. Mohr JP, Overbey JR, Hartmann A, Kummer RV, Al-Shahi Salman R, Kim H, et al.; ARUBA co-investigators. Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. *Lancet Neurol.* 2020 Jul;19(7):573-581.
15. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. *Neurosurgery.* 2010 Apr;66(4):702-13.
16. Stapf C, Mast H, Sciacca RR, Berenstein A, Nelson PK, Gobin YP, Pile-Spellman J, Mohr JP; New York Islands AVM Study Collaborators. The New York Islands AVM Study: design, study progress, and initial results. *Stroke.* 2003 May;34(5):e29-33.

17. Can A, Gross BA, Du R. The natural history of cerebral arteriovenous malformations. *Handb Clin Neurol.* 2017;143:15-24.
18. Agarwal N, Guerra JC, Gala NB, Agarwal P, Zouzias A, Gandhi CD, Prestigiacomo CJ. Current treatment options for cerebral arteriovenous malformations in pregnancy: a review of the literature. *World Neurosurg.* 2014 Jan;81(1):83-90.
19. Lawton MT, Rutledge WC, Kim H, Stapf C, Whitehead KJ, Li DY, Krings T, terBrugge K, Kondziolka D, Morgan MK, Moon K, Spetzler RF. Brain arteriovenous malformations. *Nat Rev Dis Primers.* 2015 May 28;1:15008.
20. Rangel-Castilla L, Russin JJ, Martinez-Del-Campo E, Soriano-Baron H, Spetzler RF, Nakaji P. Molecular and cellular biology of cerebral arteriovenous malformations: a review of current concepts and future trends in treatment. *Neurosurg Focus.* 2014 Sep;37(3):E1.
21. Tu J, Karunanayaka A, Windsor A, Stoodley MA. Comparison of an animal model of arteriovenous malformation with human arteriovenous malformation. *J Clin Neurosci.* 2010 Jan;17(1):96-102.
22. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations. Clinical article. *J Neurosurg.* 2011 Mar;114(3):842-9.
23. Forster DM, Kunkler IH, Hartland P. Risk of cerebral bleeding from arteriovenous malformations in pregnancy: the Sheffield experience. *Stereotact Funct Neurosurg.* 1993;61 Suppl 1:20-2.
24. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. *Neurosurgery.* 1990 Dec;27(6):867-71.
25. Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. Stroke in Pregnancy Study Group. *Stroke.* 1995 Jun;26(6):930-6.
26. Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. *Neurosurgery.* 1990 Dec;27(6):855-66.
27. Hillman J. Population-based analysis of arteriovenous malformation treatment. *J Neurosurg.* 2001 Oct;95(4):633-7.
28. Lv X, Liu P, Li Y. The clinical characteristics and treatment of cerebral AVM in pregnancy. *Neuroradiol J.* 2015 Jun;28(3):234-7.
29. Nagayama K, Kurita H, Tonari A, Takayama M, Shiokawa Y. Radiosurgery for cerebral arteriovenous malformation during pregnancy: A case report focusing on fetal exposure to radiation. *Asian J Neurosurg.* 2010 Jul;5(2):73-7.
30. Yu C, Jozsef G, Apuzzo ML, MacPherson DM, Petrovich Z. Fetal radiation doses for model C gamma knife radiosurgery. *Neurosurgery.* 2003 Mar;52(3):687-93.
31. Devroe S, Van de Velde M, Rex S. General anesthesia for caesarean section. *Curr Opin Anaesthesiol.* 2015 Jun;28(3):240-6.
32. Lum M, Tsiouris AJ. MRI safety considerations during pregnancy. *Clin Imaging.* 2020 Jun;62:69-75.
33. Cheng YC, Chen HC, Wu CH, Wu YY, Sun MH, Chen WH, Chai JW, Chi-Chang Chen C. Magnetic Resonance Angiography in the Diagnosis of Cerebral Arteriovenous Malformation and Dural Arteriovenous Fistulas: Comparison of Time-Resolved Magnetic Resonance Angiography and Three Dimensional Time-of-Flight Magnetic Resonance Angiography. *Iran J Radiol.* 2016 Mar 28;13(2):e19814.
34. Committee Opinion No. 723: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. *Obstet Gynecol.* 2017 Oct;130(4):e210-e216.