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Hysteroscopic Management of Uterine Arteriovenous Malformation

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ABSTRACT

Background and Objectives: Uterine arteriovenous malformation (AVM) is characterized by shunts between the myometrial arteries and veins. Treatment is based on the severity of uterine bleeding and ranges from conservative medical approaches to embolization of affected arteries. The aim of study was to evaluate the feasibility and safety of hysteroscopy for management of uterine AVM.

Methods: This was a retrospective study of a cohort of 11 cases occurring between March 2012 and December 2015 in our Regional Center of Excellence in Hysteroscopy, University of Florence. The diagnosis of AVM was made by transvaginal ultrasonography with high-definition flow in patients with mild to moderate symptoms. In all cases, we used the hysteroscopic platform Gynecare VersaPoint II (Ethicon, Somerville, New Jersey, USA), equipped with a 4-mm electrosurgical loop and associated with the SPIES (Storz Professional Image Enhancement System) system (Karl Storz, Tuttlingen, Germany).

Results: All patients were successfully treated with operative hysteroscopy with no reported complications. No patient had residual disease detected by ultrasonography performed after a month. At this writing, of the 11 patients treated with operative hysteroscopy, 4 had achieved a pregnancy that carried to term, 1 was pregnant at 20 wk, and 1 had a miscarriage in the first trimester.

Conclusions: Hysteroscopy is a feasible and safe alternative treatment modality for AVM. Patients treated with surgical hysteroscopy have high fertility outcomes, a 100% success rate after the first treatment, no complications related to the surgical procedure, and a short hospital stay.

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INTRODUCTION

Uterine arteriovenous malformation (AVM) is a vascular hamartoma of the myometrium characterized by the presence of shunts between the myometrial arteries and veins. Most AVMs are acquired after damage to uterine tissue. A miscarriage or a voluntary pregnancy termination, dilation and curettage (D&C), cesarean section, vaginal delivery, carcinoma of the cervix or endometrium, uterine infection, trophoblastic disease, endometriosis, or exposure to diethylstilbestrol are among the reported causes of AVM.[1–3]

Histologically, AVM is characterized by a very thick venous structure, in which the arteries have an interrupted or absent elastic membrane and a completely absent muscular tunica media.[4,5] Diagnosis is usually performed by transvaginal ultrasonography with color high-definition (HD) Doppler flow, showing a characteristic vascular mosaic pattern with high flow rates and low resistance.[6,7] Hysteroscopy can be used as a confirmatory imaging modality.[8,9] Angiography is rarely performed for diagnosis and is currently reserved for patients requiring surgical treatment or therapeutic embolization.[6]

The most frequent presenting symptom of AVM is profuse menorrhagia or metrorrhagia that does not respond to medical treatment, eventually leading to anemia; other symptoms are lower abdominal pain and dyspareunia.[6] In a systematic review, bleeding was reported in 84% of patients with AVM,[10] and in 30% of cases of bleeding, a blood transfusion was necessary.[11]

There is no clear consensus on the best treatment for AVM. The current medical and surgical options are based on clinicians' experience and published case reports. The treatment depends on the extent of bleeding; in mild to moderate cases, when the patient is hemodynamically stable, the bleeding episode has resolved, or the bleeding is persistent but mild or is an incidental diagnosis,[12] the first clinical approach would be conservative for a maxi-

mum period of 3–6 months. Conservative management consists of medical therapy with methylergonovine maleate, danazol, and Gn-RH agonists and it is associated with a high rate of failure, with persistent bleeding.[13] When conservative management fails, the indicated treatment is the embolization of the uterine artery or iliac/uterine artery ligation, to effectively treat the lesion and at the same time preserve fertility.[14,15] Embolization is effective in 57% of cases and a second embolization may be necessary in up to 32% of patients for persistent bleeding.[16,17] Major risks for the patient after embolization of the uterine artery are postembolization syndrome (massive necrosis and infarction of the uterus, uterine artery rupture, and pelvic pain), transient or permanent amenorrhea, and radiation exposure.[18]

The pregnancy rate after treatment for AVM with uterine artery embolization (UAE) varies in published reports; however, in the largest systematic review, it ranged between 17.4% in observational studies and 27% in case reports.[10] Pregnancies after UAE may be affected by complications such as spontaneous abortion, placenta previa or accreta,[19,20] postpartum hemorrhage, and a higher cesarean section rate than in the general population.[20] In case of life-threatening bleeding or if the embolization fails several times, a debulking treatment with hysterectomy is necessary.[21] Uterine embolization via laparotomy and AVM excision is an alternative treatment rarely used.[20,22] Laparoscopic uterine artery ligation and AVM excision has been reported as an alternative minimally invasive procedure compared with laparotomy, but it carries the well-known risks of a major surgery under general anesthesia, and the published case reports are too few to provide a real estimate of its true potential.[14,18] The lack of a consensus on current treatment of AVM is based on the unsatisfactory rate of success of current conservative management in moderate cases of AVM and the fertility and obstetric complications after embolization treatment. Indeed, AVMs occur at a median age of 30 years, when the patient's fertile life expectancy is still high.[10] Therefore new experimental treatment modalities are advocated for this condition.

In this study, we propose a novel hysteroscopic minimally invasive treatment of AVMs, to increase the subsequent pregnancy rate and minimize complications. Data on our first series of patients are presented in this retrospective case series study, with a focus on a description of the hysteroscopic technique and the postsurgical fertility rate of our study population.

MATERIALS AND METHODS

This is a retrospective study of all the consecutive cases of uterine AVM treated at our institution (Center of Excellence in Hysteroscopy, Palagi Hospital, Florence, Italy) between March 2012 and December 2015. The study was approved by the hospital ethics committee. The patients were referred to our tertiary hysteroscopy center from minor city hospitals and outpatient clinics for evaluation of menorrhagia or metrorrhagia. At the enrollment time point, menorrhagia was assessed with pictorial blood loss assessment charts (PBACs).[23] Inclusion criteria were having a diagnosis of AVM by transvaginal ultrasonography with HD flow, a PBAC score of at least 100, metrorrhagia, and mild-to-moderate symptoms. We included only patients who were hemodynamically stable, with a resolved intermenstrual bleeding episode, or with persistent mild or moderate bleeding. Gestational trophoblastic disease was excluded with a β-human chorionic gonadotropin serum level $<$30 mUI/mL (the lower value in the range of our laboratory equipment) and absence of residual gestational tissue ascertained by ultrasonography. HD flow is a bidirectional power Doppler technique that delivers HD axial resolution and increased sensitivity for imaging small vessels. In addition, it reduces the spatial overlap of tissue signals by the application of small sample volumes and provides optimal clutter elimination with adaptive wall filtering.[24] The ultrasonography examinations were performed with vaginal (5–7.5 MHz) and transabdominal (3.5–5 MHz) probes, yielding gray-scale, color, and spectral Doppler images. Two expert sonographers performed all the imaging. The initial examination consisted of meticulous attention to the size of the uterus and the appearance of the myometrium, after which the uterine cavity was surveyed. AVM is characterized ultrasonographically as a mass of multiple cystic or tubular hypoechoic areas in the context of the myometrial and endometrial junctions. The sonographic features used to detect an AVM through the use of gray scale were heterogeneous myometrial anechoic areas in the myometrium and image retention of the placenta. The addition of color Doppler ultrasonography was used to visualize vascularization of the uterus and can demonstrate the vascular nature of AVMs (**Figure 1**), showing a characteristic mosaic pattern and vessels with high-flow velocities and low resistance index. Color gain adjustment was calibrated on the correspondent myometrium such that no signal was visible outside of the uterus.[6,10,15,25] Peak systolic velocity (PSV) is a good prognostic factor in AVMs: a PSV $<$ 0.39 meters\second has a good possibility of spontaneous res-

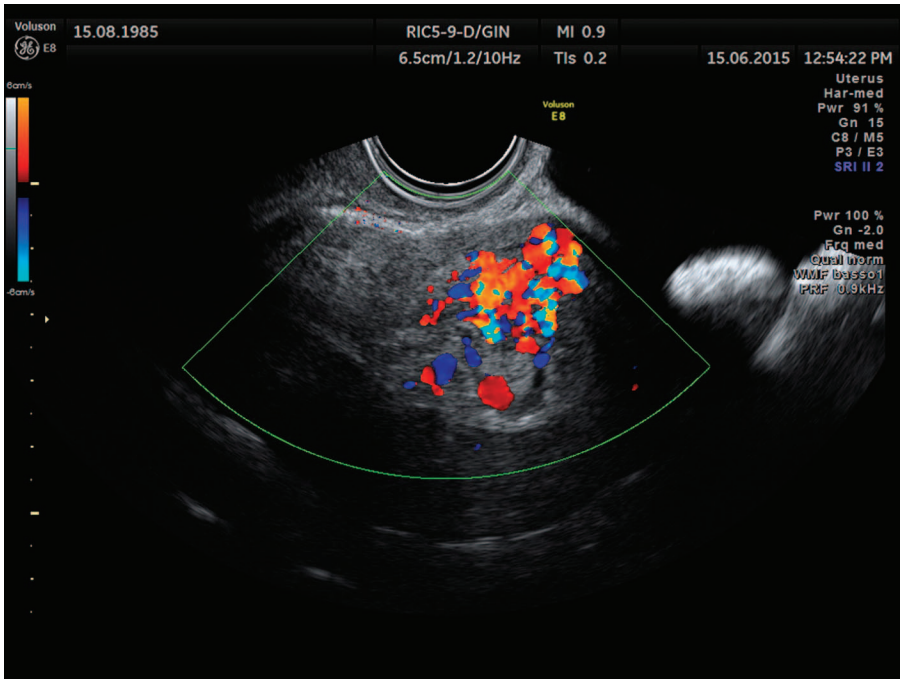

Figure 1. Visualization with transvaginal ultrasound with color Doppler AVM.

olution, whereas a PSV > 0.83 meters\second usually requires medical or surgical treatment.[6,26]

Angiography was not required, because we did not perform selective embolization of uterine arteries in any of the patients. All patients underwent surgical hysteroscopy, to maintain future fertility. The procedure requires general anesthesia. After dilatation of the cervical canal with a Hegar dilator up to size 10, we introduced the hysteroscope (Gynecare VersaPoint II; Ethicon, Somerville, New Jersey, USA) equipped with a 4-mm electrosurgical loop and associated with the SPIES (Storz Professional Image Enhancement System) system (Karl Storz, Tuttlingen, Germany). The distention medium was saline solution for use with bipolar currents. We used a peristaltic pump with outflow and inflow pressure of 140 mm Hg and flow of 400 mL. During the procedure, 2 g of intraoperative cephalosporins, 20 UI of Syntocinon in 500 mL of saline solution, and 2 vials of methylergonovine maleate were administered. The diagnosis of AVM was subsequently confirmed in all cases by histologic analysis of the gross specimen. Histologically, there is a proliferative vascular nidus characterized by arteriovenous shunt that is predominantly composed of dilated vascular structures, thin-walled and sometimes thickened. Hamartomatous vascular walls are lined internally by endothelial cells that form vascular intima, and immunohistochemical investigations are positive for CD31 and CD34. The intima contains connective tissue that is free of elastic lamina, which can be highlighted in the arterioles by Weigert hematoxylin.[27] To distinguish the histomorphologic characteristic of venules from arterioles, the tunica media in the thickened wall of vascular structures must consist of only fibrous connective tissue or fibromuscular tissue, including connective tissue and 2–3 layers of smooth muscle fibers. Therefore, the diagnosis of uterine AVM is based on quantitative and qualitative evaluation of components of tunica media smooth muscles.[28]

For this evaluation, immunohistochemical markers for muscle tissue, including smooth muscle actin, muscle-specific actin, and desmin, were used. Presenting symptoms, length of hospital stay, recurrence of symptoms, and elapsed time to the occurrence of the obstetric event were recorded for each patient. Patients' data are expressed as median (range). All the patients had a follow-up sonogram at 1 month after hysteroscopy, to evaluate the healing process and the resolution of the uterine lesion. We considered 1 month to be a reasonable amount of time for the tissue repair process to be completed.

Table 1.
Demographic and Obstetric Patients' Data

Patient	Age (years)	BMI (kg/m^2)	Gravidity	Parity	Previous Spontaneous Abortions	Previous Voluntary Abortion	Previous Viable Pregnancy
1	18	22.8	1	0	1	0	0
2	28	25.9	2	0	1	1	0
3	37	21.3	2	1	1	0	1
4	23	24.2	2	1	1	0	1
5	44	28.6	2	1	1	0	1
6	26	23.7	2	1	1	0	1
7	30	26.5	1	0	1	0	0
8	34	25.1	2	1	1	0	1
9	21	20.8	1	0	1	0	0
10	32	22.7	2	1	1	0	1
11	31	23.9	1	1	0	0	1
Median (range)	30 (18–44)	23.9 (20.8–28.6)					

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

We identified 11 patients with AVM: in 10 cases, the AVM was consequent to uterine curettage for abortion, and in the remaining case, to a vaginal delivery. Median patient age was 30 (18–44) years and BMI was 23.9 (20.8–28.6) kg/m^2 (**Table 1**). The average size of the

Table 2.
AVMs Characteristics, Procedure Time, Follow-Up Data

Patient	Size of the Lesion (mm)	Position of the Lesion in the Uterus	PSV (m/sec)	Duration of the Procedure (minutes)	Follow-up (months)	Pregnancy Outcome	Time from Procedure to Pregnancy (months)
1	40	Anterior	1.05	40	24		
2	20	Right Side	0.95	45	6	Miscarriage	4
3	20	Anterior	0.89	30	24	Term vaginal delivery	8
4	20	Anterior	0.91	30	22		
5	15	Right Side	0.50	40	20		
6	30	Posterior	0.99	15	26	Term vaginal delivery	12
7	15	Right Side	0.90	20	28		
8	35	Right Side	1.15	45	30	Term vaginal delivery	7
9	20	Posterior	0.97	20	29	Term vaginal delivery	9
10	45	Anterior	1.11	35	4		
11	35	Left Side	1.20	30	14	Currently at 20 weeks, uneventful	8
Median (range)	20 (15–45)		0.97 (0.5–1.2)	30 (15–45)	24 (4–30)		8 (4–12)

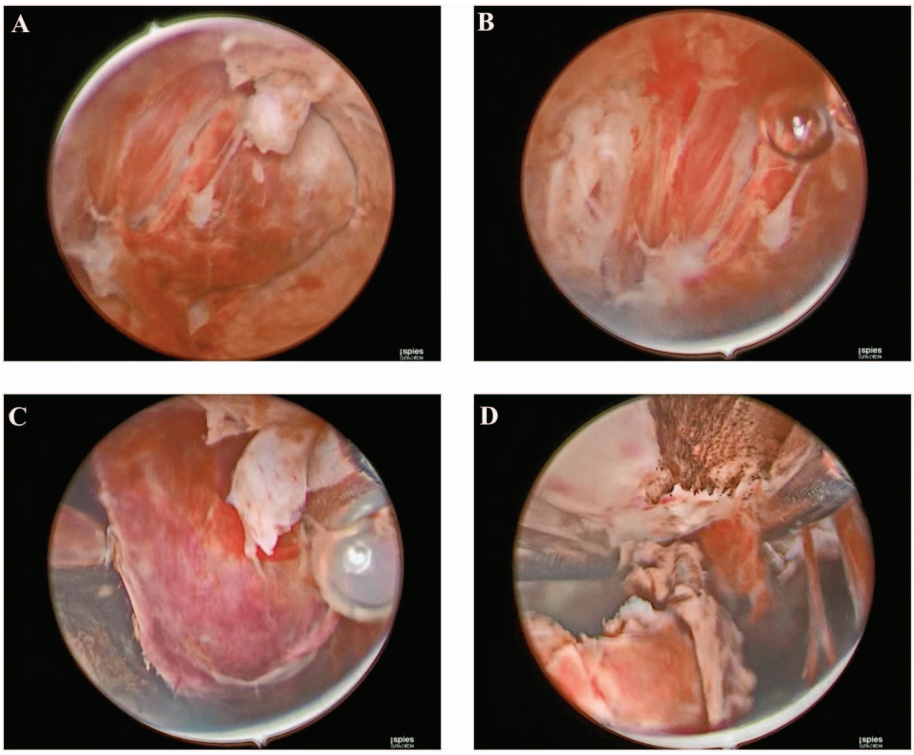

Figure 2. A, **B**, Visualization of AVM in the uterine cavity. **C**, **D**, Hysteroscopic resection of the lesion.

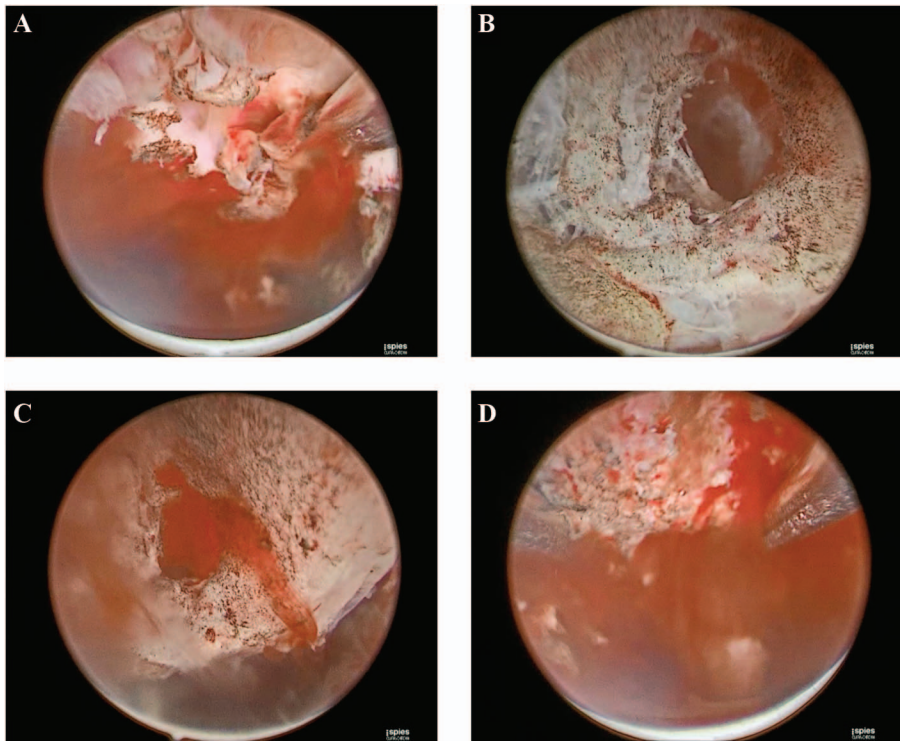

Figure 3. A, **B**, **D**, Visualization during hysteroscopic resection of large size vessels, with massive bleeding. **C,** Visualization of the blood vessel during high–flow hysteroscopy.

AVM was 20 mm, and the presenting symptom of all the patients was mild to moderate menorrhagia or intermenstrual bleeding. The position of the AVM in the uterus was anterior, posterior, right side, or left side. The sonographic Doppler analysis showed a PSV >0.89; only 1 patient had a PSV of <0.83, but it was still higher than 0.39 (**Table 2**), therefore surgical management was indicated in all the cases.

All patients were successfully treated with hysteroscopy; median duration of hysteroscopy surgery was 30 min (15–45), with no reported complications. No patient had residual disease at ultrasonography performed after a month. Of the 11 patients treated with operative hysteroscopy, at this writing, 4 had achieved a pregnancy that carried to term, 1 was pregnant at 20 wk, and 1 had a miscarriage in the first trimester (**Table 2**). The first pregnancy was obtained at the fourth postsurgical month; overall, the median time between the procedure and the pregnancy was 8 (4–12) months. The median follow up was 24 (4–30) months, as shown in **Table 2**.

DISCUSSION

In this study, we demonstrated that hysteroscopy is a feasible and safe alternative treatment modality for AVM. Currently, UAE is the most frequently used treatment modality (59%) in cases involving AVM, followed by hysterectomy (29%), but it carries a risk of failure and complications after the operation.[10] Indeed, the largest published series of 100 uterine AVMs treated via embolization reported recurrence in 17% of cases and the need for hysterectomy in 6 patients with uncontrolled bleeding.

In our study, all cases were treated successfully as outpatients in a single session of surgical hysteroscopy (**Figures 2–5**), with no recurrence during the follow-up period. Our patients had no complications during the surgery and throughout the follow-up. In contrast, after UAE, the literature reports a higher rate of complication.[29–30] Despite the rarity of serious complications of UAE, some can be dramatic, as compared with the minimal complications that can occur during surgical hysteroscopy.

The median hysteroscopic procedure time was 30 minutes, significantly lower than the reported 60 minutes

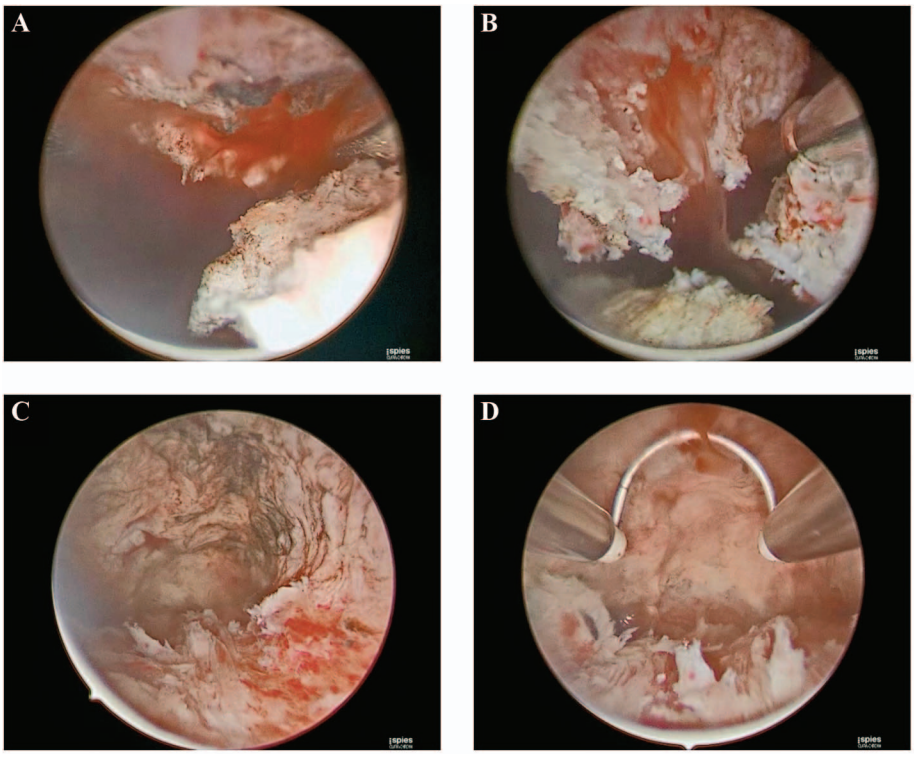

Figure 4. A, **B,** During hysteroscopic resection, partial reduction of bleeding. **C, D,** Phases vessels coagulation myometrial at increased bleeding.

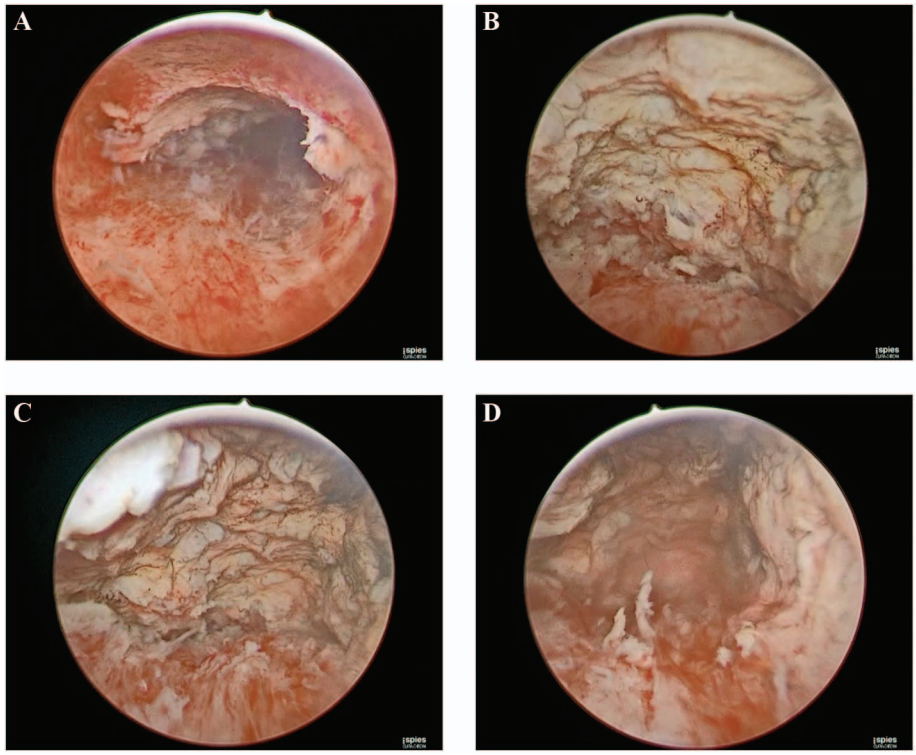

Figure 5. A–D, Ultimate vision of the uterine cavity after complete resection of the AVM. **A,** View of the uterine cavity near isthmus. **B, C,** Appreciate the void in myometrial wall in the area that was previously occupied by AVM. **D,** Restoring the integrity of the uterine cavity.

necessary for UAE. We were able to achieve such a short procedure time because of the excellent view inside the uterine cavity obtained throughout the hysteroscope, as opposed to only an indirect intrauterine view during UAE.

All our patients were discharged the same day of the procedure. UAE requires hospital admission. Some researchers have reported that their patients with UAE remained in the hospital for a minimum of 24 hours. All patients in O'Brien et al[15] were discharged from the hospital within 48 h after the procedure, and in two studies,[15,30] the mean hospital stay was 2 and 4 days, respectively, after embolization.

In addition, after the surgery, there was no need for pain control medication, whereas after UAE, pain usually must be controlled with oral nonsteroidal anti-inflammatory and analgesic drugs.[26]

Six of 11 patients (55%) obtained a pregnancy after the hysteroscopic procedure. The earliest pregnancy was obtained 4 months after surgery and the median delay between the procedure and pregnancy was 8 months. Of the remaining 5 patients who did not have a pregnancy after the procedure, 1 was 44 years old, so the chance of spontaneous pregnancy was very low, regardless; 1 had given birth a few months before and did not desire another pregnancy. Peitsidis et al,[10] in their review, identified 24 articles reporting pregnancies in 27% of patients after AVM treatment with UAE, with median elapsed time from the procedure to pregnancy of 15 months. In our study sample, at this writing, 4 of the 11 patients had achieved uneventful term pregnancies, 1 was pregnant 20 wk, and 1 had had a miscarriage in the first trimester of pregnancy.

Reported obstetric complications after UAE are spontaneous abortion, placenta previa or accreta,[19,20] postpartum hemorrhage, and a higher cesarean section rate than in the general population.[20] Although there is no consensus on an appropriate mode of delivery, in our experience, all patients gave birth by vaginal delivery.

The follow-up was ~24 months, during which the patients did not present clinical symptoms of persistent AVM. A limitation of our study is that we did not

exclude other causes of infertility in the patients and their partners. The inclusion criterion for our study was having a symptomatic AVM with menorrhagia or metrorrhagia. More studies in infertility centers are needed to further assess the relationship between AVM and infertility.

In conclusion, the patients treated with surgical hysteroscopy had high fertility outcomes, a 100% success rate after the first treatment, no complications related to the surgical procedure, and no hospital admission. The surgical procedure time is short and the patient is not exposed to ionizing radiation. However, hysteroscopic treatment should be reserved only for hemodynamically stable patients with no profuse bleeding. In addition, it should always be performed in referral centers, with sonographers, endoscopists, and expert pathologists. Larger clinical trials are needed to further support our conclusion and to test this approach to treatment in a broader reference population.

References:

1. Diwan RV, Brennan JN, Selim MA, et al. Sonographic diagnosis of arteriovenous malformation of the uterus and pelvis. *J Clin Ultrasound*. 1983;11:295–298.

2. Fleming H, Ostor A, Pickel H, Fortune D. Arteriovenous malformations of the uterus. *Obstet Gynaecol*. 1989;73:209–213.

3. Huang MW, Muradali D, Thurston WA, Burns PN, Wilson SR. Uterine arteriovenous malformations: gray-scale and Doppler US features with MR imaging correlation. *Radiology*. 1998;206:115–123.

4. Vijayakumar A, Srinivas A, Chandrashekar BM, Vijayakumar A. Uterine vascular lesions. *Rev Obstet Gynecol*. 2013;6:69–79.

5. Stillo F, Baraldini V, Dalmonte P, for the Italian Society for the study of Vascular Anomalies (SISAV). Vascular Anomalies Guidelines by the Italian Society for the Study of Vascular Anomalies (SISAV). *Int Angiol.* 2015;34(suppl 1):1–45.

6. Timmerman D, Wauters J, Van Calenbergh S, et al. Color Doppler imaging is a valuable tool for the diagnosis and management of uterine vascular malformations. *Ultrasound Obstet Gynecol*. 2003;21:570–577.

7. Lee TY, Kim SH, Lee HJ, et al. Ultrasonographic indications for conservative treatment in pregnancy-related uterine arteriovenous malformations. *Acta Radiol*. 2014;55:1145–1152.

8. Scioscia M, Zantedeschi B, Trivella G, Fratelli N, Cosma S, Minelli L. A suggestive diagnosis of uterine arteriovenous fistula based on ultrasonography and hysteroscopy. *Eur J Obstet Gynecol Reprod Biol* 2012;160:116–117.

9. Calzolari S, Cozzolino M, Castellacci E. Uterine arteriovenous malformation: hysteroscopic identification is possible. *J Minim Invasive Gynecol*. 2016;23:293–294.

10. Peitsidis P, Manolakos E, Tsekoura, Kreienberg R, Schwentner L. Uterine arteriovenous malformations induced after diagnostic curettage: a systematic review. *Arch Gynecol Obstet* 2011; 284:1137–1151.

11. Manolitsas T, Hurley V, Gilford E. Uterine arteriovenous malformation a rare cause of uterine haemorrhage. *Aust N Z J Obstet Gynaecol*. 1994;34:197–199.

12. Dar P, Karmin I, Einstein MH. Arteriovenous malformations of the uterus: long-term follow-up. *Gynecol Obstet Invest*. 2008; 66:157–161.

13. Nonaka T, Yahata T, Kashima K, Tanaka K. Resolution of uterine arteriovenous malformation and successful pregnancy after treatment with a gonadotropin-releasing hormone agonist. *Obstet Gynecol*. 2011;117:452–455.

14. Patton EW, Moy I, Milad MP, Vogezang R. Fertility-preserving management of a uterine arteriovenous malformation: a case report of uterine artery embolization (UAE) followed by laparoscopic resection. *J Minim Invasive Gynecol*. 2015;22:137–141.

15. O'Brien P, Neyastani A, Buckley AR. Uterine arteriovenous malformations: from diagnosis to treatment. *J Ultrasound Med*. 2006;25:1387–1392.

16. Yang JJ, Xiang Y, Wan XR. Diagnosis and management of uterine arteriovenous fistulas with massive vaginal bleeding. *Int J Gynaecol Obstet*. 2005;89:114–119.

17. Sanguin S, Lanta-Delmas S, Le Branche A. Uterine arteriovenous malformations: diagnosis and treatment in 2011. *Gynecol Obstet Fertil*. 2011;39:722–727.

18. Wu YC, Liu WM, Yuan CC, Ng HT. Successful treatment of symptomatic arteriovenous malformation of the uterus using laparoscopic bipolar coagulation of uterine vessels. *Fertil Steril*. 2001;76:1270–1271.

19. Soeda S, Kyozuka H, Suzuki S, Yasuda S, Nomura Y, Fujimori K. Uterine artery embolization for uterine arteriovenous malformation is associated with placental abnormalities in the subsequent pregnancy: two cases report. *Fukushima J Med Sci*. 2014;60:86–90.

20. Delotte J, Chevallier P, Benoit B. Pregnancy after embolization therapy for uterine arteriovenous malformation. *Fertil Steril*. 2006;85:228.e1–228.e7.

21. Grivell RM, Reid KM, Mellor A. Uterine arteriovenous malformations: a review of the current literature. *Obstet Gynecol Surv* 2005;60:761–767.

22. Milingos D, Doumplis D, Sieunarine K, Savage P, Lawson AD, Smith JR. Uterine arteriovenous malformation: fertility-spar-

ing surgery using unilateral ligation of uterine artery and ovarian ligament. *Int J Gynecol Cancer*. 2007;17:735–737.

23. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990;97:734–739.

24. Hata T. Modern 3D/4D sonographic studies on fetal heart. *Ultrasound Rev Obstet Gynecol* 2006;6:115–122.

25. Timmerman D, Van den Bosch T, Peeraer K, et al. Vascular malformations in the uterus: ultrasonographic diagnosis and conservative management. *Eur J Obstet Gynecol Reprod Biol* 2000;92:171–178.

26. Vaknin Z, Sadeh-Mefpechkin D, Halperin R, Altshuler A, Amir P, Maymon R. Pregnancy-related uterine arteriovenous malformations: experience from a single medical center. *Ultraschall Med*. 2011;32(suppl 2):E92–E99.

27. Young B, Woodford P, O'Dowd G. Wheater's Functional Histology: A Text and Colour Atlas. 6th ed. London: Churchill Livingstone; 2013.

28. Rosai J. Rosai and Ackerman's Surgical Pathology. 10th ed. St. Louis: C. V. Mosby, 2011.

29. Ghai S, Rajan DK, Asch MR. Efficacy of embolization in traumatic uterine vascular malformations. *J Vasc Interv Radiol*. 2003;14:1401–1408.

30. Maleux G, Timmerman D, Heye S, Wilms G. Acquired uterine vascular malformations: radiological and clinical outcome after transcatheter embolotherapy. *Eur Radiol*. 2006;16:299–306.