Management of Intrauterine Arteriovenous Malformation (AVM) in 14 Patients by Sonographically Guided Tisseel Application

Behandlung von intrauterinen Arteriovenous-Malformationen (AVM) durch sonografisch gezielte Tisseel-Applikation bei 14 Patientinnen

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Key words

- uterus
- AVM
- ultrasound
- treatment effects
- hemorrhage

Abstract

Purpose: AVMs are rare tumorous vascular lesions derived from placental tissue that may present with massive post-partum hemorrhage (PPH) causing potentially life-threatening anemic shock. Current treatment options include the embolization of uterine arteries and emergency postpartum hysterectomy. We present a new form of minimally invasive, highly specific sonographically guided treatment in the form of the application of a human fibrin sealant leading to the instant cease of blood loss.

Materials and Methods: A management protocol was established and a case series of 14 patients is presented. Diagnosis by endovaginal color Doppler sonography is followed by the sonographically guided application of biological glue (TISSEEL®), thus allowing for super-selective occlusion of the feeding vessels.

Results: The procedure was technically successful in all 14 patients, 3 of whom (21 %) had a repeated procedure after 4 – 7 days. The mean age (yrs.) of the patients was 31 (25 – 40), the gravity was median 2 (1 – 5) and the parity was median 1 (0 – 4), the lowest Hb value was on average 9.35 ± 2.25 (5.2 – 14.2) g/dl, the lowest Ht was on average 30.82 ± 6.02 (18 – 41 %). Spectral Doppler analysis revealed an average of 80.71 ± 11.2 (66 – 115) cm/sec for the maximal detectable PSV. In the period of 4 – 55 months after treatment, 7 patients (50 %) had 8 successful pregnancies and 2 miscarriages.

Conclusion: In PPH there is vital interest in timely diagnosis of the underlying cause, thus allowing fertility-sparing, minimally invasive and super-selective emergency treatment. In AVMs causing PPH, a positive impact on perinatal morbidity and mortality may be achieved by sonographically guided application of this biological glue.

Zusammenfassung

Zielsetzung: Arterio-venöse Malformationen (AVM) sind seltene Gefäßfehlbildungen ausgehend von Resten plazentaren Gewebes, die zu lebensbedrohlichen Blutungen in Form von massiven postpartalen Hämorrhagien (PPH), führen können. Embolisation der uterinen Gefäße oder aber einer notfallmäßigen Hysterektomie sind derzeit therapeutische Optionen. Wir präsentieren eine innovative, minimal-invasive Therapie mittels ultraschallgesteuerter, superselektiver Injektion eines Fibrinklebers, die zu einer unmittelbaren Blutstillung führt.

Material und Methoden: Ein Standart zum Management von intrauterinen AVM wurde erstellt und eine Fallserie von 14 Patienten wird präsentiert. Nach Diagnostik durch vaginale Farb-Doppler Sonographie erfolgt die Applikation eines biologischen zwei-Komponenten Gewebekleber unter Ultraschallkontrolle. Der Gewebekleber, gewonnen aus tiefgefrorenem, gepooltem, humanem Frischplasma, beinhaltet eine Mischung aus konzentriertem Fibrinogen, Fibronectin und Albumin. Die verwendete Thrombin-Lösung enthält Calciumchlorid. Durch diese beiden Komponenten wird eine superselektive Okklusion der zuführenden Gefäße zur AVM erreicht und das Restgewebe kann durch Abrasio und/oder Hysteroskopie entfernt werden.

Ergebnisse: Die Behandlung konnte in allen 14 Patienten erfolgreich durchgeführt werden, in 3 (21 %) Patienten musste der Eingriff innerhalb von 4 – 7 Tagen wiederholt werden. Das mittlere Alter der Patienten war 31 (25 – 40) Jahre, die Gravidität war median 2 (1 – 5) und die Parität median 1 (0 – 4). Der niedrigste Hb-Wert war im Mittel 9,35 ± 2,25, (5,2 – 14,2) g/dl, der niedrigste Hk-Wert war im Mittel 30,82 ± 6,02 (18 – 41)%. Spektral Doppler Analyse eine maximal nachweisbare PSV von 80,71 ± 11,2 (66 – 115) cm/sec. Im Abstand von 4 – 55 Monaten nach der Behandlung hatten 7 Patienten (50 %) eine erfolgreiche

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Schwangerschaft, wovon eine eine monochoriale Zwillingsschwangerschaft war. Zwei Patienten hatte eine frühe Fehlgeburt im ersten Trimenon.

Schlussfolgerung: Beim Auftreten einer PPH besteht die lebenswichtige Notwendigkeit einer zeitnahen Diagnostik, so dass noch rechtzeitig minimal invasive und superselektive Therapiemaßnahmen ergriffen werden können, um somit die perinatale Morbidität und Mortalität zu senken. Die Applikation eines biologischen zwei-Komponenten Gewebekleber unter Ultraschallkontrolle könnte die Rate an anämisierenden Metrorrhagien senken.

Introduction

AVMs are defined as abnormal vessel connections that develop over time between high-pressure arteries and low-pressure veins that may – stimulated by trauma or hormonal change – change from an asymptomatic lesion with minimal shunting to one with active shunting leading to vascular engorgement and hypertension [1]. AVMs may be either congenital or acquired usually consisting of arteries and veins with abnormal structure and lacking any dampening effect of capillaries on the blood flow and have been reported in women aged 18 – 72 years. Few cases of intrauterine AVMs have been reported in the literature so far [2]. However, the lesion may be substantially underreported and published case reports may only represent the tip of the iceberg. Among asymptomatic women diagnosed by color Doppler (CD) sonography, AVMs resolve spontaneously in a high percentage of cases. Hence, conservative management is recommended [3]. For symptomatic women, menometrorrhagia being the most common symptom, AVM treatment options include pelvic surgical techniques for ligation of feeding arteries using various hysterscopic and laparoscopic approaches [4]. However, hysterectomy ultimately could not be avoided in numerous cases. More recently, AVMs have been treated successfully by transcatheter uterine artery embolization using different forms of particular substances such as gel foam, microfibrillar collagen, isobutyl cyanoacrylate and steel coil spring occluders [3 – 5]

We present a case series of 14 symptomatic patients with uterine AVMs managed by an innovative minimally invasive, highly specific sonographically guided treatment by applying a human fibrin sealant (TISSEEL®) to the feeding vessels, causing instant ceasing of hemorrhage.

Materials and Methods

After an initial case of successful emergency treatment by sonographically guided application of a biological glue at out-of-office hours in a patient presenting six weeks after delivery with heavy PPH causing hemorrhagic shock, a standardized protocol for the treatment of symptomatic AVMs was established in 2009 (Case 1). Approval of the protocol was given by the local ethics committee and a total of 13 additional patients having had a diagnosis of a symptomatic uterine AVM and ranging in age from 25 to 40 years were managed accordingly by one operator between 2009 and 2014 in two tertiary referral centers (Cases 2 – 14).

After approval by the research ethics board, we retrospectively reviewed the records of all symptomatic cases diagnosed with intrauterine AVM (n = 21). Only patients that underwent intrauterine interventions (n = 14) were included. The other 7 cases were managed conservatively. For each case we retrieved information on ultrasound findings, in particular color and pulse wave (PW) Doppler results at presentation, operative details, postoperative course and sonographic findings including CD and PW-Doppler and, whenever available, long-term outcome by a questionnaire. All patients received extensive multidisciplinary preoperative counselling and information about the experimental nature of the intervention. They were in particular counselled about the expected natural course of the lesion. We explained the option of expectant management and the risks and benefits of this experimental, yet minimally invasive procedure. According to the protocol, the procedure was carried out with the interventional radiologist on stand-by, thus giving the option of transcatheter uterine artery embolization as a second stage treatment.

The applied fibrin glue (TISSEEL®, Baxter Healthcare Corporation, Baxter International Inc.) is a biological substance derived from human donor plasma by means of cryoprecipitation, producing a highly concentrated solution of fibrinogen and other cryoglobulins. This fibrinogen contains the coagulation factor XIII and, in the presence of both thrombin and calcium, forms a filamentous precipitate of highly adhesive fibrin. TISSEEL® Fibrin Sealant is a two component fibrin sealant

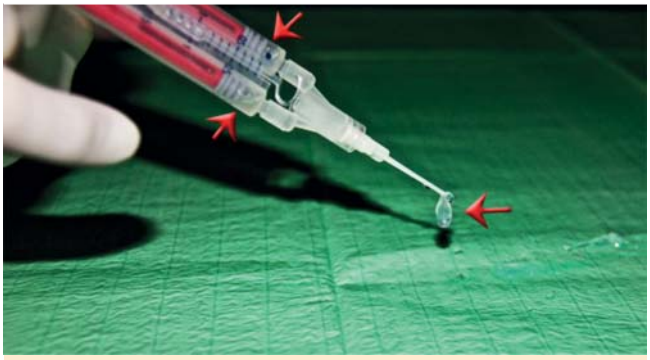

Fig. 1 Syringe showing the application of the two-component fibrin sealant containing human fibrinogen and aprotinin & human thrombin and calcium chloride kept separately in two columns (red arrows). When mixed together, the two components combine and mimic the final stages of the body's natural clotting cascade to form a rubber-like mass (red arrow) that achieves hemostasis by sealing or gluing vessels.

Abb. 1 Zweikomponenten-Fibrinkleber bestehend aus humanem Fibrinogen und Aprotinin sowie Thrombin und Calciumchlorid, welches in zwei Kammern getrennt vorgehalten wird (rote Pfeile). Beim Vermischen der beiden Komponenten in der Nadel wird der letzte Schritt der natürlichen Hämostase imitiert. Es entsteht eine gummiartige Masse (roter Pfeil), welche in der Lage ist die Gefäße zu verkleben.

- The sealer protein solution contains human fibrinogen and a synthetic fibrinolysis inhibitor, aprotinin, which helps prevent premature degradation of the fibrin clot.
- The thrombin solution contains human thrombin and calcium chloride.

When mixed together, the 2 components combine and mimic the final stages of the body's natural clotting cascade to form a rubber-like mass that adheres to the wound surface and achieves hemostasis by sealing or gluing tissues (**Fig. 1**). The injection setup was adapted from the setup used for oocyte retrieval in ART including a TVS needle guide and a 22-cm 20-gauge needle (Cook Medical Inc.). The TISSEEL Kit (Freeze-Dried) is stored at 2 – 25 °C, the TISSEEL Pre-filled Syringe (Frozen) at ≤ -20 °C.

Intervention Protocol

Transvaginal sonography (TVS) with grayscale, color, and spectral Doppler imaging was performed on a Phillips IU 22 (Philips Healthcare, P.O. Box 10.000,5680 DA Best, The Netherlands) or Voluson E8 (Voluson™ GE Healthcare Technology) in all patients by the same operator (PS). A 6 – 9 MHz probe was used with an image of 140°. The filter was set to 50 Hz and the Doppler sample volume was 2 mm. The echogenicity of the endometrium and the overall appearance of the myometrium were described paying special attention to the presence of retained products of conception and focusing on subtle myometrial heterogeneity and small anechoic spaces in the myometrium. CD sonography scanning of the entire uterus was focused on the tangle of vessels with multidirectional turbulent high-velocity blood flow producing a "color mosaic" pattern. Spectral Doppler analysis depicted arterio-venous shunting with low-resistance/high-velocity flow pattern (**Fig. 2, 3**). The flow parameters included pulsatility index (PI), resistance index (RI), peak systolic (PSV) and time-averaged maximum velocity (TAMXV). Multiple areas of blood flow were sampled and the set of results with the highest PSV and the corresponding values for TAMXV, PI and RI were recorded [5]. A blood sample was taken from all patients and full blood count and ß-human chorionic gonadotropin (ß-HCG) testing were performed to exclude the possibility of GTD in each case. After managing the anemia, an outpati-

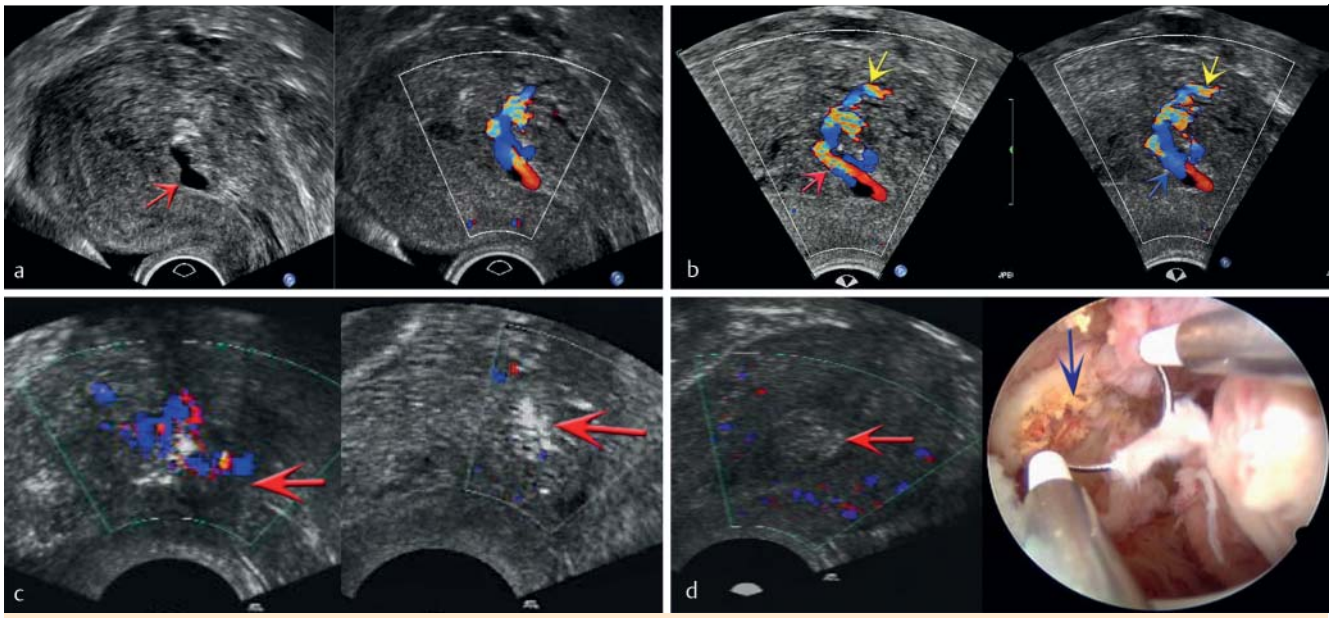

Fig. 2 (Case 1) A 24-year-old patient, who had delivered her first baby by vaginal delivery a month ago, presented with massive menorrhagia, tachycardia (125 bpm), Hct 18 % and Hb 5.2 g/dL and paleness. **a** Longitudinal section of the uterus depicting suspected retained products of conception with B-mode sonography showing a punched 15 × 8 mm anechoic space (red arrow) on the myometrial/endometrial border and in CDS a tangle of vessels with multidirectional turbulent high-velocity blood flow/low-resistance flow pattern. **b** Cross-section highlighting arterio (red arrow) and venous (blue arrow) elements of the lesion in the form of pulsations and the feeding vessel (yellow arrows) derived from a spiral artery. **c** Sonographically guided application of 2 ml of TISSEEL® Duo S Immuno to the feeding vessels by a 20 g needle (red arrow) producing a "flash-like" artifact in CDS. The turbulent flow immediately decreased after application producing a "snowstorm"-like pattern (red arrow). **d** Longitudinal section of the uterus 7 days after application revealing signs of retained products of conception (red arrow) without increased flow pattern on CDS. Removal of the retained products (blue arrow) on the posterior wall of the uterus is shown by hysteroscopy using a cutting loop.

Abb. 2 (Fall 1) Eine 24-jährige Patientin, die ihr erstes Kind vor einem Monat durch vaginale Entbindung zur Welt brachte, präsentierte sich mit Menorrhagie, Tachykardie (125/min), Hkt 18 % und Hb 5,2g/dl, sowie deutlicher Hautblässe. **a** Längsschnitt der Gebärmutter in der B-Bild-Sonographie, bei Verdacht auf Plazentarest , zeigt einen 15 x 8 mm messenden, echoarmen Bereich (roter Pfeil) an der Grenze zwischen Myometrium und Endometrium. In der Farbdopplersonographie zeigt sich aufgrund der vorherrschenden turbulenten Strömung ein Mosaikmuster (hohe PSV bei gleichzeitig niedrigem RI). **b** Farbdopplersonographie mit hervorgehobenen arteriellen (roter Pfeil) und venösen (blauer Pfeil) Elementen einer tumorösen Gefäßanomalie, inklusive Darstellung – ausgehend von einer Spiralarterie – des zuführenden Gefäßes (gelbe Pfeile). **c** Sonografisch gesteuerte Applikation von 2 ml TISSEEL® Duo S Immuno zu den zuführenden Gefäßen mit einer 20 G-Nadel (roter Pfeil), Entstehung eines „Blitzlicht" Artefaktes (Aufleuchten) in der Farbdopplersonografie. Unmittelbar nach Applikation kommt es zu einem rapiden Abfall der turbulenten Durchblutung, erkennbar am neu entstandenen „Schneesturm"-ähnlichen Muster (roter Pfeil). **d** Die Ultraschalldarstellung der Gebärmutter 7 Tage postoperativ zeigt Schwangerschaftsresiduen (roter Pfeil), allerdings ohne relevante Durchblutung. Die hysteroskopische Entfernung des verbliebenen Materials (blauer Pfeil) an der hinteren Wand des Uterus wird durch eine Elektroschlinge (cutting loop) vorgenommen.

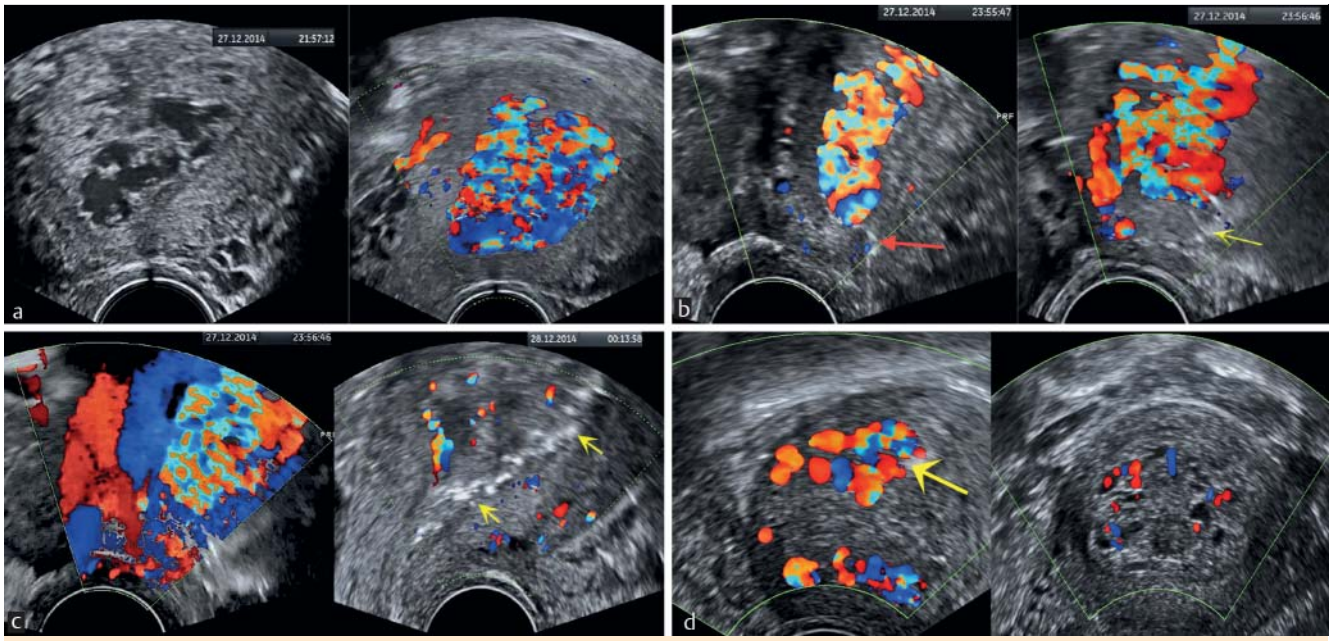

Fig. 3 (Case 14) A 27-year-old patient presented 7 weeks after termination of pregnancy performed by uneventful prostaglandin induction with abundant metrorrhagia, headaches and anemia (Hb 6.5 g/dl). **a** Longitudinal section of the uterus depicting an intrauterine mass with a maximum size of 5.37 × 2.67 cm bulking the anterior-left part of the myometrium with numerous tortured and high-flow feeding vessels with characteristics of a vascular malformation producing a PSV of more than 115 cm/sec within the lesion. **b** Transvaginal sonographically guided application of a total of 6 ml of TISSEEL® Duo S Immuno glue to the feeding vessels in 3 steps by a 20 g needle (red arrow) in sedo-analgesia. After the first step of the application in CDS, part of the turbulent flow had immediately decreased after the application (mind the time insertion) giving way to a "snowstorm"-like pattern (yellow arrow). **c** 6 ml of glue were applied to the myometrium in a fan-shaped manner in 3 steps juxtaposed around the vessels producing a flash-like pattern in CDS. CD flow immediately decreased after application displaying a "snowstorm"-like pattern (yellow arrows) on the myometrial/endometrial border. **d** Doppler ultrasonography three days after the first application suggested reopening of one feeding vessel to the AVM (yellow arrow) that had decreased in size to 2.99 × 1.79 cm. After application of another 2 ml of TISSEEL® Duo S Immuno glue to the feeding vessel in a repeated procedure, CDS showed a hyperechoic mass with no relevant vascularization within the uterus measuring 3x1x1 cm that could be removed easily by D&C.

Abb. 3 (Fall 14) Eine 27-jährige Patientin präsentierte sich 7 Wochen nach medizinisch induzierter Beendigung ihrer Schwangerschaft (mittels Prostaglandin) mit massiven Zwischenblutungen, Kopfschmerzen und einer Anämie (Hb 6,5 g/dl). **a** Sonografie des Uterus. Es zeigt sich eine intrauterine Masse im anterioren, linken Bereich des Myometriums mit einer maximalen Größe von 5,37 x 2,67 cm. Erkennbar sind die zahlreichen, gewundenen Gefäßstrukturen in denen – AVM typisch – hohe Strömungen (PSV) von bis zu über 115 cm/sek herrschen. **b** transvaginale, sonographiegestützte Appklikation von insgesamt 6 ml TISSEEL® Duo S Immuno zu den die AVM speisenden Gefäßen. In Sedo-Analgesie wird mit einer 20 G-Nadel (roter Pfeil) in 3 Schritten die Malformation verödet. Unmittelbar nach dem ersten Schritt der Anwendung kann im Farbdoppler ein deutlicher Rückgang der turbulenten Strömung dargestellt werden. Man beachte das kurze Zeitintervall zwischen erster Applikation und nachfolgender Kontrolle des nun „Schneesturm"-ähnlichen Musters der Läsion (gelber Pfeil). **c** 6ml TISSEEL wurden fächerförmig innerhalb des Myometrium in 3 Schritten nahe den dargestellten Gefäßen appliziert, wodurch es im Farbdoppler zur charakteristischen „Blitzlicht"-Symptomatik kommt. Die hohen Strömungsgeschwindigkeiten fielen rasch ab und es präsentierte sich ein Schneesturm-ähnliches Bild an der myo-/endometrialen Grenze (gelbe Pfeile). **d** Die Doppler-Sonografie drei Tage nach der ersten Anwendung ließ eine Wiedereröffnung einer der zuführenden Gefäße zur AVM vermuten (gelber Pfeil), welche bereits auf 2,99 x 1,79 cm zusammengeschrumpft war. Nach der Applikation einer weiteren Dosis von 2 ml TISSEEL® Duo S Immuno um das entsprechende Gefäß zeigte sich im Farbdoppler eine echoreiche Masse ohne relevante Strömungsanomalien von 3 x 1 x 1 cm, welche mittels anschließender D&C problemlos entfernt werden konnte.

ent setting was chosen to perform the procedure preferably under sedo-analgesia or spinal anesthesia. A 22-cm 20-gauge needle (Cook Medical Inc.) was connected to the TISSEEL® device (**Fig. 1**) and the needle was directed under ultrasound guidance towards the AVM lesion. The needle tip was guided to the feeding arterial vessels and 2 – 5 ml of glue were applied in a fan-shaped manner in 1 – 3 steps juxtaposed around the vessels producing a flash-like pattern on CD sonography. The effect of the treatment was confirmed in all cases on grayscale, color and spectral Doppler imaging depicting a "snowstorm"-like picture and replacing the abundant CD flow pattern that was seen before. In the first 6 cases removal of the retained products of conception was performed 7 – 10 days later, preferably by a cutting loop on hysteroscopy. In cases 7 – 14, the cavity was evacuated within a few minutes after the intervention preferably by D&C under ultrasound guidance. Follow-up was done by TVS including CDS 4 – 8 weeks after the procedure. Follow-up information was obtained by a questionnaire sent 4 – 68 months after the treatment.

Results

The procedure was technically successful in all 14 patients that had therapeutic sonographically guided application of biological glue (TISSEEL®). The procedure had to be repeated in 3 women after 4 – 7 days. The mean age (yrs.) of the patients was 31 (25 – 40), the median gravity was 2 (1 – 5) and the median parity was 1 (0 – 4). There were varying degrees of anemia before and during the

Table 1 History and lab findings of the 14 patients undergoing sonographically guided (TISSEEL®) application.

case	age	G/P	related pregnancy and time interval to diagnosis of AVM	mode of last delivery	Hb g/dl	Ht %
case 1	25	G1 / P1	normal vaginal delivery (4 wks ago)	vaginal	5.2	18
case 2	40	G3 / P2	induced abortion (trisomy 18) at 17 weeks of gestation (6 wks ago)	vaginal	8.9	28
case 3	39	G1 / P1	vaginal delivery, PPH 1500 ml (6 wks ago)	vaginal	7.6	n.d.
case 4	25	G2 / P1	vaginal delivery, PPH 900 ml, repeated D&C for RPOC after delivery (1 wk ago)	vaginal	7.4	23
case 5	31	G1 / P1	normal vaginal delivery (4 wks ago)	vaginal	6.9	20
case 6	30	G2 / P2	vaginal delivery, VE, D&C for RPOC after delivery (1 wk ago)	vaginal	8.4	31
case 7	28	G5 / P4	IUD after PROM and placental abruption at 17 weeks of gestation, amnion infection (3 wks ago)	vaginal	10.4	33
case 8	34	G3 / P2	early miscarriage at 8 weeks of gestation (8 wks ago)	vaginal	13.7	41
case 9	35	G2 / P1	early miscarriage at 10 weeks of gestation, molar pregnancy (3 wks ago)	sectio caesarea	14.2	40
case 10	36	G3 / P0	early recurrent miscarriage at 10 weeks of gestation, molar pregnancy (4 wks ago)	nullipara	12.2	37
case 11	34	G5 / P3	early recurrent miscarriage at 10 weeks of gestation (5 wks ago)	sectio caesarea	7.0	23
case 12	25	G2 / P0	early miscarriage at 11 weeks of gestation (7 wks ago)	nullipara	13.1	39
case 13	31	G1 / P0	top at 8 weeks of gestation (16 wks ago)	nullipara	9.4	29
case 14	27	G1 / P0	induced abortion for teratogenic medication (4 wks ago)	nullipara	6.5	23

D&C: dilatation & curettage, PPH: post-partum hemorrhage, RPOC: retained products of conception, VE: vacuum extraction, IUD: intrauterine death, PROM: premature rupture of membranes, TOP: termination of pregnancy, Ht: hematocrit, Hb: hemoglobin g/dl, n.d.: not documented.

Table 2 Clinical and sonographic findings of the 14 patients undergoing sonographically guided (TISSEEL®) application.

case	symptoms	pre-treatment	PSV cm/sec	ß-hCG	treatment	recurrence with treatment and 2nd procedure	fertility after treatment
1	menorrhagia+lower abdominal pain	tranexamic acid	neg.	98	TISSEEL® injection+HSC	no/7 weeks	yes
2	menorrhagia	none	neg.	72	TISSUCOL® injection+D&C	no/n.d.	yes
3	menorrhagia+anemia	none	neg.	64	TISSUCOL® injection+HSC	no/6 weeks	yes
4	menorrhagia+anemia+hypotension	D&C	neg.	72	TISSUCOL® injection+HSC	no/6 weeks	no
5	menorrhagia	MTX+D&C	neg.	84	TISSEEL® injection+D&C	yes/3 month.	yes
6	menorrhagia	D&C	neg.	68	TISSEEL® injection+HSC	no/1 week	yes
7	menorrhagia+anemia+cephalalgia	none	neg.	95	TISSEEL® injection+D&C3	yes/2 month	no
8	menorrhagia+lower abdominal pain	none	neg.	84	TISSEEL® injection+D&C	no/3 month	no
9	hypomenorrhagia	D&C	2380	70	TISSEEL®/injection+D&C	no/n.d.	yes
10	hypermenorrhagia	D&C	neg.	66	TISSEEL® injection+D&C	no/1 week	no
11	hypermenorrhagia+lower abdominal pain	D&C	neg.	85	TISSEEL® injection+D&C	no/1 week	no
12	lower abdominal pain	none	neg.	69	TISSEEL® injection+D&C	no/n.d.	yes
13	menorrhagia	none	neg.	88	TISSEEL® injection+D&C	no/2 weeks	no
14	menorrhagia+anemia+cephalalgia	cytotec	neg.	>115	TISSEEL® injection+D&C	yes/1 month	no

D&C: dilatation & curettage, HSC: hysteroscopy, RI: resistance index, PSV: peak systolic velocity cm/sec., n.d.: not documented.

procedure. The lowest Hb value was on average 9.35 ± 2.25, (5.2 – 14.2) g/dl, and the lowest Ht was on average 30.82 ± 6.02 (18 – 41 %). Spectral Doppler analysis revealed an average of 80.71 ± 11.2 (66 – 115) cm/sec for the maximal detectable PSV. **Table 1** lists selected patient characteristics, while **Table 2** summarizes the clinical and sonographic results of the 14 patients treated according to the protocol. In the period of 4 – 55 months after treatment, 7 patients (50 %) had 8 successful pregnancies, one of which was a monochorionic twin pregnancy, and 2 miscarriages.

Discussion

AVMs can occur in any organ in the body, including the pelvic vasculature and rarely in the uterus. The first case of AVM was reported in 1926 [6]. AVM is a potentially life-threatening vascular anomaly arising from normal and abnormal pregnancies that may be more common than previously thought. The incidence of UVM developing after abortion or delivery was prospectively evaluated using transvaginal color Doppler ultrasonography. Of 959 patients, 6 (0.63 %) were identified with UVMs, including 1 (0.10 %) with a uterine AVM [7]. Scarce data suggest a relatively higher incidence in patients after abortion [1]. It appears that only 2 % of uterine AVMs are symptomatic and cause chronic or heavy bleeding [8]. The pathogenesis of uterine AVMs may be either congenital or acquired, the former are less frequent and associated with a defect in the embryonic development of vascular structures resulting in multiple abnormal communications between arteries and veins and tend to have multiple feeding arteries, a central nidus and numerous large draining veins. More commonly AVMs are acquired, representing multiple small arteriovenous fistulas between intramural arterial branches and the myometrial venous plexus and appear as a vascular tangle. In the majority of cases, the etiology of acquired AVMs remains ob-

scure, though it is attributed to curettage, abortion, endometrial and cervical cancer or gestational trophoblastic disease [2]. Both the nidus in congenital AVMs and the fistulas of acquired AVMs represent a hybrid of arteries and veins with extremely delicate wall structures. They are thought to be tumorous vascular lesions and may be the underlying cause of abnormal vaginal bleeding, thereby causing severe and potentially life-threatening hemorrhage requiring immediate and effective treatment.

A wide spectrum in etiologies, symptoms, natural courses and prognoses create a considerable challenge with regard to both diagnosis and treatment. At present, numerous noninvasive diagnostic methods have been proposed to diagnose uterine AVM, such as contrast-enhanced computed tomography (CT), MRI and color Doppler ultrasound [9 – 14], the latter being the standard screening investigation by changing the preoperative management and giving patients the choice for low-risk procedures [15]. In B-mode sonography an AVM is depicted as multiple tortuous heterogeneous or anechoic spaces in the myometrium without mass effect. CD sonography reveals intense color fill-in with juxtaposed reds and blues in a turbulent flow pattern representing high peak velocity and low resistance allowing for accurate and immediate detection [8]. Typical findings in spectral color Doppler ultrasonography are low-resistance flow and mixing of arterial and venous waveforms and intensive rapid blood flow disorder. High-velocity arterial and pulsatile venous flow in the myometrium is also seen, the systolic and diastolic velocities being 4 to 6 times higher than observed in normal myometrial vessels [16]. Doppler examination should be done prior to D&C, which should be avoided in these women because it is likely to worsen the bleeding. MRI, particularly angiography, provides the location and accurate data about the size of the lesion, the feeding arteries and relationship with the pelvic vasculature [17]. Arteriography shows dilated vascular spaces supplied by enlarged uterine arteries, with high flow vascular dynamics [18]. Digital subtraction angiography is an invasive method of confirming the diagnosis of AVM and treating it by embolization. In addition, measurement of β-HCG is important for differentiating vascular malformation from trophoblastic disease or neoplasia. These methods for the diagnosis of AVM may provide some guidance for choosing the appropriate treatment for AVM [19].

Management depends on hemodynamic stability and the amount of bleeding as well as on the patient's age and her desire to preserve fertility. In recent years an increasing number of women have been treated conservatively with success and hysterectomy has been considered to be the exception. In stable women, expectant management, medical therapies like estrogens, progestins, methylergonovine, danazol, and 15-methyl-prostaglandin F2alpha [20, 21], surgical removal of an AVM, laparoscopic bipolar coagulation of the uterine blood vessels and long-term medical therapy with combined oral contraceptive pills are reported [5, 22 – 24]. Timmerman et al. [5] showed that, 9 of 265 patients with abnormal premenopausal bleeding had uterine AVMs diagnosed on ultrasonography. Of these, 6 had spontaneous resolution, 2 patients with hydatidiform mole needed chemotherapy and the AVMs resolved after chemotherapy, and only 1 required embolization. Some of the women become asymptomatic with time, suggesting that traumatic AVMs may regress spontaneously. Additionally an approach under hysterscopic guidance with a neodymium, yttrium-aluminum-garnet laser fiber held several millimeters above the AVM, was presented. There are, however, reports of hysteroscopy being abandoned because of heavy blood loss during the procedure and therefore its value is limited.

Nevertheless, uterine AVMs may result in sudden and massive vaginal bleeding that may be life-threatening. It may occur as late postpartum hemorrhage or post-abortion hemorrhage, and the bleeding results from spontaneous vessel rupture or vessel rupture triggered by a D&C. Severe or persistent perinatal vaginal blood loss requires effective management to avoid complications, such as acute abdominal pain, tachycardia, hypotension, anemia, angina, coma, shock or even death. To avoid any of the above symptoms, it is crucial to make a prompt diagnosis by excluding or confirming the presence of AVMs and proceed to a suitable treatment. Therefore, it is important to consider the possibility of uterine vascular malformations (UVMs) in any patient with episodes of unexplained uterine bleeding giving rise to follow-up analysis using color Doppler ultrasonography. Such an approach will facilitate accurate diagnosis and lead to appropriate clinical management to prevent unnecessary and dangerous repeated D&Cs, which might enhance profuse uterine bleeding in the short term and cause intrauterine scarring, which entails an increased incidence of Asherman`s Syndrome in the long term [25]. The diagnosis and treatment of uterine vascular abnormalities including AVMs has been shown to be an essential part of the work-up in post-partum menorrhagia [26].

Currently, uterine artery embolization has revolutionized the management of uterine AVMs. Acute management includes measures to stabilize the patient, uterine tamponade with Foley's catheter or rolled gauze packing to prepare for uterine artery embolization, which has been used successfully for treating AVMs in emergency settings and when other treatment modalities have failed. Although it may not always succeed and subsequent treatment may be required [27], selective uterine artery embolization is currently considered the treatment of choice in women of all age groups [28, 29]. Yang et al. [30] reported the long-term success rate of embolization for uterine AVMs as 79 % and Kwon et al. [31] as 90 %. Ghai et al. reported the overall efficacy as 93 % in a retrospective review of 15 patients over 10 years. Embolization failure has been successfully managed with unilateral uterine artery and ovarian ligament ligation in a 32-year-old woman with post-molar uterine AVM after 2 attempts at embolization had failed [32] as a second stage treatment. There are no reports of infertility or fetal growth restriction following bilateral uterine artery embolization. However, long-term data are scarce and availability, in particular in smaller units and at “out of office” hours, is limited. Therefore, we present our experience with a different approach involving the sonographically guided application of biological glue to achieve instant caseation of the hemorrhage. TISSEEL® is a fibrin sealant indicated for use as an adjunct to hemostasis in adult and pediatric patients undergoing surgery when control of bleeding by conventional surgical techniques is ineffective or impractical. It mimics the final coagulation cascade step as it has all relevant components to form a clot and is effective in heparinized patients and in patients medicated with anti-platelet drugs. We used this filamentous precipitate of highly adhesive fibrin derived from human plasma and containing a concentrated composition of fibrinogen, thrombin and calcium, thus allowing for well-tolerated superselective occlusion of the feeding vessels in the AVMs of our 14 patients. With regard to the striking effect of shrinking AVMs, potential fetal and placental applications, such as treatment of sacrococcygeal teratomas and sequestration of the lungs or injection into cervical and scar pregnancies, are under consideration. Hypersensitivity or allergic/anaphylactic reactions can occur, especially if TISSEEL® is applied repeatedly over time or in the same location, or if systemic aprotinin has been administered previously. However,

we did not see this reaction in any of the 14 patients treated from 2008 – 2014.

In summary in our 14 patients sonographically guided glue application appeared to be feasible and cost-effective by preventing excessive blood loss, thus potentially being a fertility-sparing, minimally invasive and super-selective emergency treatment of AVMs causing PPH.

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