



Case Report

Fertility outcomes following pelvic embolization in women with acquired uterine arteriovenous malformation

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ABSTRACT

Objective: Acquired uterine arteriovenous malformation (UAVM) is a rare, life-threatening disease. Angiography with uterine arterial embolization (UAE) is the diagnostic tool and a choice of fertility-sparing treatment. Here, we present a series of five successful pregnancies after embolization of UAVM. **Case reports:** Three reproductive aged women were treated for UAVM, resulting in five successful pregnancies. Their past history suggested that three cases had had previous uterine procedures, including second trimester abortion and elective dilatation and curettage. Intermittent heavy vaginal bleeding was the primary symptom of UAVM. One patient with anemia had two ineffective embolizations and achieved a singleton pregnancy after the third embolization. However, intrauterine fetal demise with severe fetal growth retardation was noted on the 28th gestation week. The other two women had temporary ovulation disorder after UAE. After Clomiphene Citrate (CC) treatment, successful pregnancies were achieved and carried to term uneventfully.

Conclusion: UAE is an acceptable method for preserving fertility and treatment in women with symptomatic UAVMs.

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Introduction

Uterine arteriovenous malformation (UAVM) is a rare condition that affects mostly 20–40 year-old women with life-threatening uterine bleeding [1]. Acquired UAVM may result from uterine trauma, previous abortion, or neoplastic disease [2]. Congenital forms are extremely rare. The main symptoms are mild intermittent vaginal bleeding to profuse menstrual flow. In 30% of cases, the bleeding is so heavy that blood transfusions are needed [3]. Recurrent pregnancy loss (RPL) has been reported in some UAVM cases [1,4]. Small cystic lesions detected in the myometrium or below the endometrium via gray scale trans-vaginal ultrasound (TVUS) would be a sign arousing suspicion. Abnormal hyper-vascular area with blood vessels in the myometrium via color Doppler ultrasound is the characteristic finding of arteriovenous malformation [3,5]. A low-impedance and high-flow feature

presented in ultrasound is also an important clue [3]. According to Timmerman et al. in 2006, the ultrasonographic features may aid in determining the management of UAVMs for which inappropriate uterine curettage could result in catastrophic bleeding [1,6].

Pelvic angiography is the gold standard diagnostic tool. The positive findings are two typical traits: engorgement of uterine vessels and rapid venous return. Previous case reports classified them into two categories: true AVMs and non-AVMs [6]. Non-AVMs lack typical angiographic traits and result from the sub-involution of the endometrial bed, and their incidence is much higher than true AVMs (83%: 17%; n = 15:3) [6]. Uterine arterial embolization (UAE) could be an effective and safe therapy for UAVM, although 17% of patients needed repeated embolization [1,7,8]. However, the preservation of fertility after embolization remains controversial [9–11]. In 2013, the American College of Obstetrics and Gynecology (ACOG) declared that UAE in treating uterine myoma or post-partum hemorrhage may affect further fertility [12]. Other case reports for true UAVMs after UAE are scattered and seldom mention their fertility outcomes. In a systemic review in 2011, 17 of 59 (29%) patients had been reported to have subsequent pregnancies after UAE for UAVM [1]. Therefore, it is important to share the experience

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of management of those cases that, in their reproductive age, attempt pregnancy. Here, we report our case series of women with UAVM after UAE and discuss fertility outcomes.

UAE methods

This case series was conducted retrospectively. All cases were enrolled based on angiographic diagnosis with the typical angiographic features: rapid venous filling of engorged uterine vessels.

All patients presented with heavy or intermittent vaginal bleeding between 2008 and 2016. In our series, UAVM was initially diagnosed with trans-vaginal Doppler ultrasound and confirmed by pelvic angiography. UAE was performed in a dedicated angiography suite by qualified interventional radiologists under sedation and local anesthetic. In all cases, one or the other side of the common femoral artery was punctured according the disease location. Under aseptic conditions, a 6 Fr. guiding catheter was introduced in one side of the internal iliac artery. Two microcatheters were placed in the branches of the bilateral internal iliac vessels, respectively, and were advanced to as near the vessel structure as possible. Once a stable position of the catheter was set up, embolizations were performed with glue polymerization (N-Butyl Cyanoacrylate/NBCA).

All patients after UAE were followed until cessation of vaginal bleeding and their deliveries. Data were collected through electronic or paper chart records with informed consent from all patients.

Case reports

Case 1

A 22-year-old female, gravida 3, abortion 3, had received second trimester termination at 15 weeks of gestation due to preterm premature rupture of the membrane (PPROM) at a local clinic. Before that episode, she had undergone two elective abortions at 8

weeks' gestation. Menorrhagia occurred 2 months after the last abortion. TVUS revealed a 2.6 cm heterogeneous uterine lesion at the anterior fundus with strong turbulent flow. The serum beta-hCG level showed below 5 mIU/ml. With the suspicion of uterine AVM, selective pelvic angiography was performed to confirm the diagnosis. Then embolization was performed by supra-selection of bilateral uterine arteries with glue (25% n-Butyl Cyanoacrylate/NBCA). Three months after the procedure, TVUS revealed complete resolution of the AVM. However, anovulation bleeding was noticed for 3 months. Clomiphene Citrate 100 mg per day from day 3 to day 7 was given for 5 cycles. Serial monitoring of the follicle size and subcutaneous injection of human chorionic gonadotropin (Ovidrel 6500IU) was performed. Eleven months after UAE and 5 cycles of CC, she achieved pregnancy and had an uneventful term vaginal delivery. Three years later, she had another pregnancy without medical assistance. However, the second birth was accompanied by precipitate labor, post-partum hemorrhage and a small gestational age (Tables 1 and 2).

Case 2

A 38-year-old female had had three elective abortions over the previous 10 years. She had suffered from hypo-menorrhea after the most recent abortion. In recent months, she had experienced severe abdominal pain accompanied by heavy vaginal bleeding after strenuous activity. According to her statement, the condition became worse gradually. TVUS revealed a 3.6 cm heterogeneous cystic myometrial mass with strong turbulent flow at the posterior fundus. Waveform study also showed a decreased resistant index (RI). A posterior UAVM was diagnosed by angiography and selective UAE was performed through supra-selection of both uterine arteries. Post-embolization suprapubic pain was controlled by morphine. Complete stasis of AVM was noted by TVUS one month after embolization. However, dysfunctional uterine bleeding (DUB) was noted for 2 months after UAE. She attended our hospital for a failed trial of pregnancy

Table 1

Clinical characteristics of three women with true UAVM, treatment and outcome.

Case	Abortions/uterine surgery history	Age (year-old)	Initial symptoms	UAE	Fertility outcome
1.	SA1AA2 (SA at 15 weeks of pregnancy)	22	Menorrhagia 2 months after abortion, 2.6 cm AVM at anterior fundus, nidus at midline.	Supraselection of bilateral uterine arteries with NBCA 25%, complete resolution.	Pregnancy achieved by clomiphene citrate (CC), 11 months after embolization. The 2nd pregnancy achieved without medical assistance.
2.	AA3	38	Severe abdominal pain and menorrhagia, 3.6 cm AVM at posterior fundus, nidus at midline.	Supraselection of bilateral uterine arteries with NBCA 30%, complete resolution, post-TAE ischemic pain.	Pregnancy achieved 2 years after embolization. The 2nd pregnancy achieved without medical assistance. All were term with vaginal delivery.
3.	AA1	34	Massive vaginal bleeding attacked 3 years after D&C, 3.8 cm AVM at posterior fundus, nidus deviation to right side.	Bilateral internal iliac arteries with NBCA and lipidol, TAE completed after 3 trials	Pregnancy achieved 1 year after last embolization. A 28 weeks of pregnancy complicated with IUFD, IUGR and pre-eclampsia. (Birth weight 600 g).

AA (artificial abortion), DUB (dysfunctional uterine bleeding), SA (spontaneous abortion), UAE (uterine arterial embolization).

Table 2

Pregnancy outcome after embolization of uterine arteriovenous malformation in the study.

Case	Maternal Age at pregnancy (years)	Gestational Age (weeks)	Gender	Weight	Apgar score	Complications
1.	24	39	F	3020 g	9' → 9'	N/A
	25	39	F	2370 g	9' → 9'	SGA, Post-partum hemorrhage
2.	40	37	F	2892 g	9' → 9'	N/A
	42	37	M	2850 g	9' → 9'	N/A
3.	36	28	F	600 g	0' → 0'	IUGR and IUFD

SGA (small for gestational age).

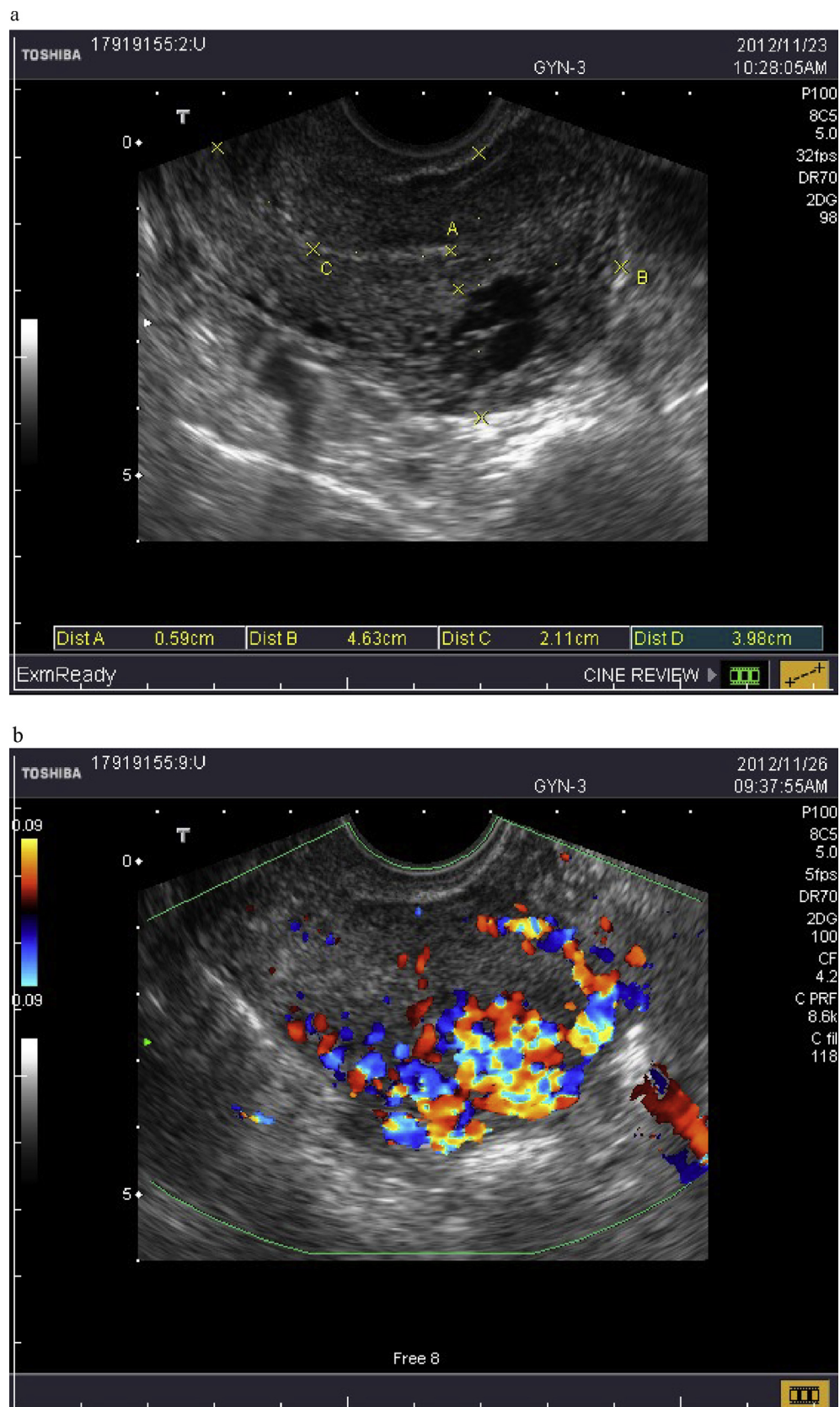


Fig. 1. A bulging cystic mass with strong flow covered half the myometrium of uterus in case 3; a fireball in uterine wall (a: gray scale; b: Doppler color).



Fig. 2. Uterine arterial embolization through internal iliac arteries in case 3 (a: before embolization; b: after embolization).

for 6 months. A workup for her subfertility showed hyperprolactinemia and left tubal obstruction. Bromocriptine and Clomiphene Citrate were administered for 2 months and 5 cycles respectively. Twenty-two months after UAE, She became

pregnant by nature intercourse and had two term vaginal deliveries (Tables 1 and 2).

Case 3

A 34-year-old female, gravida 1, abortion 1, received uterine curettage because of an incomplete abortion 2 years previously. After the abortion, she experienced progressive menorrhagia which had become worse in the previous 3 months. The bleeding was so heavy that her hemoglobin was down to 7.1 g/dl. UAVM was diagnosed via TVUS, which revealed a 3.8 cm bulging hypoechoic lesion (Fig. 1a) with strong turbulent flow around the myometrium of the uterus. “A fire ball sign in uterine wall” presented by color Doppler ultrasound (Fig. 1b). Thereafter, emergency pelvic angiography and embolization were conducted through the bilateral internal iliac arteries with NBCA and lipidol (Fig. 2). The procedure did not block the AVM completely due to the sharp angle of the feeding artery. Despite much improvement in her symptoms, the residual UAVM was easily detected by TVUS one month later. Her symptoms recurred 3 months after the first embolization. Therefore, we arranged another embolization and achieved complete stasis after two trials. Two months after her last embolization, her symptoms were relieved and the residual lesion was minimal. One year later, she achieved pregnancy without medical assistance. However, fetal growth fell behind from 16 weeks of gestation. Then, fetal condition worsened and severe oligohydramnios was detected. The pregnancy ended with intrauterine fetal demise, pre-eclampsia and the preterm birth of a female fetus of 600 g at 28 weeks' gestation. One year after delivery, a UAVM 5 cm in diameter was seen again by TVUS.

All three patients were summarized in Table 3.

Discussion

Acquisition of UAVMs

All cases in this report had therapeutic or spontaneous abortions preceding the diagnosis of UAVMs. Previous studies suggested that the pathogenesis of acquired UAVM could be a local immune response and angiogenesis induced by endometrial agitation, or other mechanisms like subinvolution of the placental bed or abnormal vessel communication by chorionic villi implantation [1,2,13].

To our knowledge, an unsuccessful pregnancy, complicated abortion course such as the retained products of conception, or unsatisfactory uterine procedures may contribute to the formation of a UAVM. Interestingly, recurrent pregnancy loss (RPL) has also been reported in association with UAVMs [1,4].

Acquired UAVMs were classified into high flow (true AVMs) and low flow lesions (non-AVMs) based on angiographic diagnosis in 2000 from Timmerman et al. [3]. Non-AVMs present as hyperemic myometrium and are often misdiagnosed as true AVMs. Expectant management for non-AVMs could be possible [5]. Therefore, we excluded two cases with abnormal uterine bleeding following medical abortion with Mifepristone and Misoprostol, as were

Table 3
Summary data of all three patients.

Case	Severity of UAVM	Repeated UAE	DUB after UAE	Recurrence of UAVM	Pregnancy after UAE	Complication
1.	Mild/moderate	–	+	–	CC	N/A
2.	Mild/moderate	–	+	–	NI	N/A
3.	Severe	+	–	+	NI	Third trimester pregnancy loss and secondary infertility

CC (Clomiphene Citrate), NI (natural intercourse).

diagnosed as sub-involution of placental beds (non-AVMs) and could be managed conservatively.

Reviewing our cases, the lesion size and disease severity can be observed (Table 1). “A fire ball sign in uterine wall” with color Doppler ultrasound is the typical sign of arteriovenous malformation (Fig. 1.). Milder cases (cases 1 and 2) had only intermittent vaginal bleeding, however, which would affect sexual life and chance of getting pregnancy. After selective embolization, temporary dysfunctional uterine bleeding (DUB) was noticed in cases 1 and 2. Chronic anovulation (WHO type II) seemed to be the cause for their subfertility. However, after achieving pregnancy, their outcomes were fairly good and uneventful. A review of the literature in 2016 discussed the risk of non-target embolization impacting on ovarian circulation, but at present, evidence suggests that UAE does not affect ovarian function, especially in young women [14]. It may be doubtful whether all cases should receive selective UAE because alternative expectant management for mild UAVM induced by medical abortion has been reported [5]. On the contrary, a case report in 2003 demonstrated a successful twin pregnancy after correction of UAVM in a case with habitual abortion; therefore, it may be appropriate to propose embolization as an initial treatment [4]. Due to the small case numbers, the link between UAVM and RPL is poorly understood, however; we still lack evidence for the claim that the use of UAE for mild cases would be over-treatment.

In a retrospective study, the severity of UAVMs cannot be evaluated only by imaging modalities. Severe cases are those with anemia, recurrence, previous D and C and severe imaging findings [15]. Compatible with case 3 in our study, the patient in this study presented severe clinical phenomena after receiving emergency embolization. The strong turbulent flow of the uterine lesion occupied half the myometrium and the failed attempts of two UAEs were documented.

Fertility outcome

A review of the literature revealed inconsistency in fertility outcome after UAE for post-partum hemorrhage and symptomatic uterine fibroids. Increased risk of spontaneous abortion and post-embolization uterine necrosis had been reported [9,10,11]. A 17% of repeated embolization rate and a 29% subsequent pregnancy rate had also been reported [1]. In 2013, ACOG and the Society of Interventional Radiology recommended that uterine arterial embolization should be used with caution among those who desire future childbearing, as that the impact on infertility is still unclear [12]. Our third case received repeated embolizations and her pregnancy ended with IUGR and fetal death. The abrupt cessation of fetal growth at early 3rd trimester arouses the suspicion of acute placental insufficiency. However, even though the placental pathology provided evidence of ischemia or thrombus formation, we still cannot conclude that UAE is the causative factor because subsequent pregnancy of case 3 has not occurred and it was not an early abortion but a 3rd trimester pregnancy loss.

Multiple UAEs do not necessarily contribute to adverse pregnancy outcomes. In a retrospective study in 2003 with 15 patients, a case—after receiving six embolizations—finally delivered a full term pregnancy [8]. For cases having received ineffective UAEs, revascularization of the AVM through another collateral circulation might be possible and cause the residual lesion to reoccur. Other

studies suggested hysterectomy after failed embolization because underlying neoplastic diseases need to be considered [6].

Regrettably, we did not record the uterine artery flow during pregnancy and there was no subsequent pregnancy for case 3. Age-related infertility also played a part. Observing these patients, mild to severe UAVMs could have different impacts on future fertility. Mild cases may have good response; however, severe cases may not.

Conclusion

In our study, patients with UAVMs would present with abnormal uterine bleeding and characteristic finding of “a fireball in uterine wall” by color Doppler ultrasound. Restoring fertility after the correction of UAVM may be possible. However, for severe case with multiple embolizations, a poor pregnancy outcome and secondary infertility, further investigation toward subsequent pregnancy, and the injury of the uterine vessel, myometrium or endometrium, is warranted.

Conflicts of interest

All authors declare no conflicts of interest.

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