Uterine artery embolization for postpartum and postabortion hemorrhage : A retrospective analysis of complications, subsequent fertility, and pregnancy outcomes

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ORIGINAL ARTICLE

Uterine artery embolization for postpartum and postabortion hemorrhage: a retrospective analysis of complications, subsequent fertility and pregnancy outcomes

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Abstract

Purpose To evaluate the impact of UAE for postpartum and postabortion hemorrhage on future infertility, especially in patients undergoing infertility treatment, along with angiographic endpoints.

Materials and methods Sixty-two sessions performed emergent or prophylactic UAE for postpartum or postabortion hemorrhage between 2008 and 2017 were selected. Subsequent pregnancy outcomes and complications were investigated as primary outcomes. The cases were divided into two groups based on the presence of massive hemorrhage. The relationships between angiographic endpoints and complications were also evaluated as secondary outcomes.

Results The mean patient age was 34.1 ± 6.5 years. Fourteen of the 23 patients (60.9%) with desired fertility achieved pregnancy and 10 patients achieved live births (43.5%). In the patients during infertility treatment, three of the four patients had complications of severe adhesion after caesarean section or placenta accreta. In the group of patients with massive hemorrhage, the occurrence of uterine infection was significantly high ($p = 0.014$), but the angiographic endpoints were not significant, regardless of the occurrence of uterine infection.

Conclusion It was unnecessary to modify embolic endpoint according to seriousness of the hemorrhage. The pregnancy and live birth rates were acceptable, although patients undergoing infertility treatment had a higher rate of delivery complications.

Keywords Uterine artery embolization · Complication · Postpartum hemorrhage · Pregnancy

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Introduction

Uterine artery embolization (UAE) has been widely accepted as a safe and effective method for hemostasis that also preserves fertility. However, complications after UAE, such as uterine infection and ovarian dysfunction, are known to influence future fertility and childbearing potential. In particular, these complications are crucial for patients with reproductive demands and those undergoing infertility treatment.

Generally, complication rates after UAE are 5.3% for uterine infections, 0–10.3% for ovarian dysfunction, 0–60% for abortion, and 7–33% for abnormal placentation [1–5]. However, these data are insufficient because these studies focused on symptomatic leiomyoma after UAE and because a limited number of patients were included in studies on UAE for postpartum hemorrhage.

Therefore, more information about complications and future fertility is necessary, to determine the optimal therapy in critical situations.

Moreover, with the technical innovation and widespread use of infertility treatments, retained placenta of conceptions by dilatation and curettage (D&C) performed for implantation failure after in vitro fertilization has increased, resulting in an increase of UAE cases.

Additionally, it is sometimes performed to prevent the risk of massive hemorrhage due to retained products of conception prior to D&C or hysteroscopic resection. In such cases, UAE is prophylactically performed under hemodynamically stable conditions, which allows time to modify the degree of embolization that in turn reduces the possibility of uterine damage.

Uterine infection is related to endometrial ischemia and utero-ovarian anastomosis (UOA), the vascular connection from the uterine artery (UA) to the ovarian artery via a tubal branch, was associated with ovarian dysfunction after UAE for symptomatic leiomyomas [6]. Angiographically, endpoint of UAE was generally supposed to stasis of ascending segment of UA. However, we experience the cases where blood flow of intrauterine branches remains despite the clinical hemostasis has already been achieved.

No studies have evaluated whether the angiographic endpoints of an embolic depth of UA influence complications after UAE for patients with postpartum or postabortion hemorrhage. Reduction of complications by modifying the degree of embolization for securing hemostasis can be clinically useful. With these backgrounds, we investigated factors that influence complications after UAE in patients with reproductive demands, based on patient backgrounds and angiographic endpoints. Furthermore, we studied future pregnancy outcomes, especially in patients undergoing infertility treatment.

Materials and methods

Patient profiles

This retrospective study was approved by the institutional review board of both institutions. Informed consents for UAE were obtained from all patients. The approval number was 1310. Subjects included in this study were 75 women from 79 consecutive sessions from two tertiary referral centers from the Okinawa prefecture, Japan. These women underwent UAE for postpartum or postabortion hemorrhage between 2008 and 2017. Cases of hemorrhage due to malignancy was excluded and the cases without detailed angiogram images or clinical information were also excluded. Finally, 59 patients who underwent 62 sessions of UAE in total were eligible, which including primary postpartum hemorrhage in 19 sessions, secondary postpartum hemorrhage in 5 sessions, postabortion hemorrhage in 27 sessions, cervical pregnancy in 11 sessions.

Data on patient characteristics such as age, pregnancy histories, past illness including uterine surgery such as caesarean section (C/S), D&C and hysteroscopic resection, history of infertility treatment and desire of childbearing, background diseases that resulted in receiving UAE, history of massive hemorrhage, and preoperative hemoglobin level were extracted from the medical records of the two medical centers. We defined massive hemorrhage as a state with a shock index of more than 1.0, or with extravasation demonstrated by contrast-enhanced computed tomography or demonstrated angiographically during UAE. Embolic materials, degree of embolization of the uterine artery, and visualization of UOA on the uterine angiography before embolization were evaluated as angiographic items. Combination treatment, including the cases performed D&C or transcervical resection after UAE, was also recorded.

As primary outcomes, subsequent pregnancy and pregnancy complications such as placenta accreta were considered primary outcomes. With regards to cases of pregnancy and miscarriage, cumulative number of cases was also described.

As secondary outcomes, acute complications of uterine infections and ovarian dysfunction were evaluated. We defined uterine infection as a condition with prolonged fever accompanied by lower abdominal pain, chills, and shivering cured by administration of intravenous antibiotics. Cases that could be retrospectively regarded as post-embolization syndrome, non-infection conditions presenting as transient fever and lower abdominal pain, were carefully excluded. Ovarian dysfunction was based on serum follicular stimulating hormone (FSH) elevation of more than 40 mIU/ml according to the definition given in a previous randomized-controlled trial about ovarian reserve after UAE for patients

with leiomyomas [7, 8]. In addition, resumption of regular menses was regarded as normal ovarian function.

The degree of embolization of the UA was classified by a score from 0 to 2 depending on the stasis of the intrauterine branch of the UA (Fig. 1a–d). Score 0 was defined as the state in which even a small amount of flow from the intrauterine branch of the bilateral UA remained. Score 1 was defined as stasis of flow from the intrauterine branch on unilateral side. Score 2 was defined as stasis on both sides of the intrauterine branches, and flow maintained from a horizontal or ascending segment of the UAs. In addition, visualization of the UOA before embolization was also evaluated (Fig. 2a, b).

IVR procedure

In almost cases, a 5-F sheath (Medikit, Tokyo, Japan) was generally inserted from the unilateral femoral artery through which a 5-F pig tail catheter (Fansac IV, Terumo-Clinical Supply, Gifu, Japan) was advanced to abdominal aorta prior to select UA. Pelvic aortography was performed to ensure arterial anatomy, especially the involvement of non-UA was

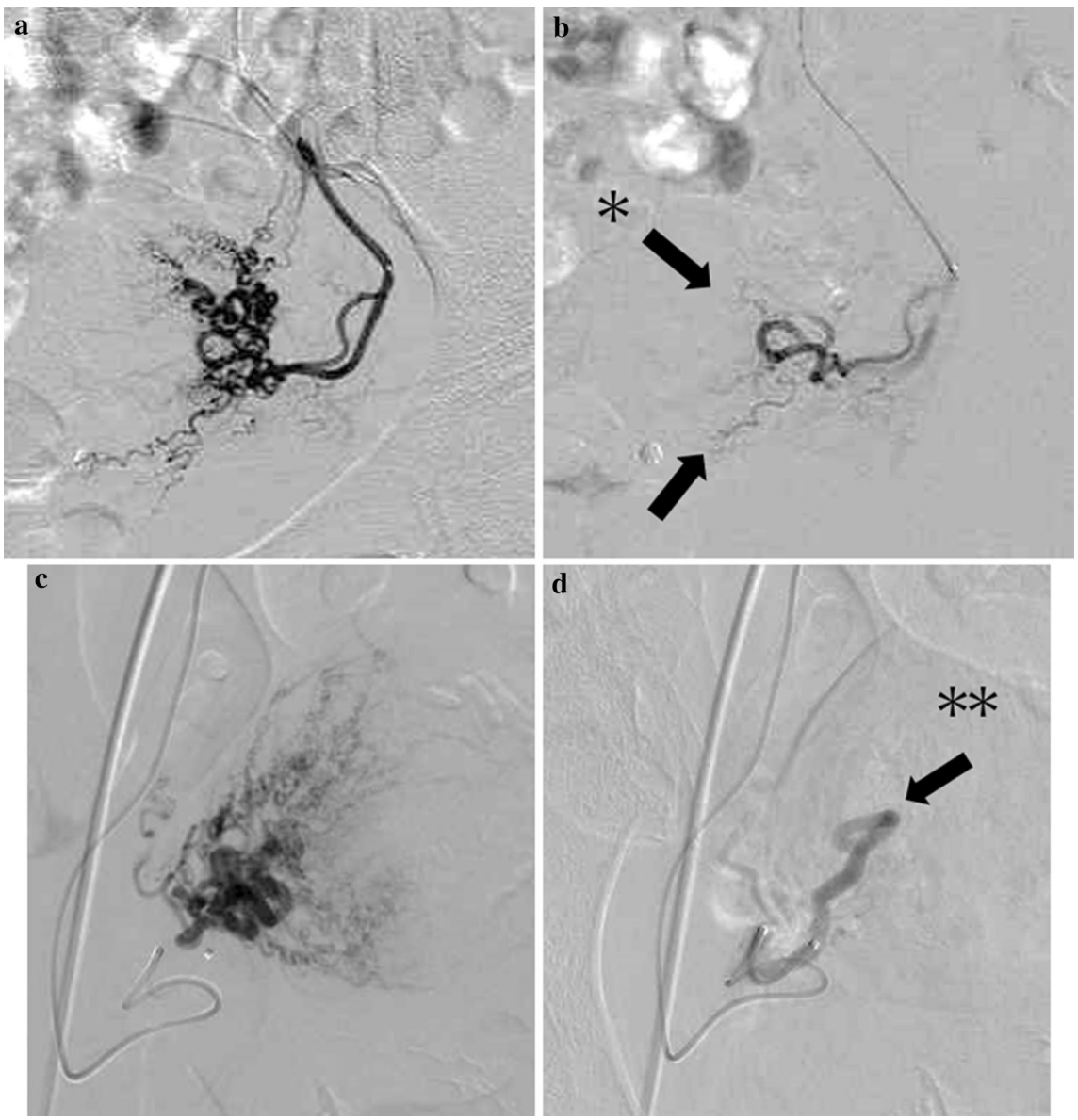

Fig. 1 An angiographic endpoint of the uterine artery (UA). **a** and **c** show pre-embolization digital subtraction angiography (DSA) of the UA. **b** and **d** show post-embolization DSA of the UA, maintained the flow of intrauterine branches (asterisk) and ascending segment of UA (double asterisk), respectively. Score 0—post-embolization DSA of both UAs show the same endpoint as **b**. Score 1—post-embolization DSA of either UA shows the same endpoint as **c**, but not both. Score 2—post-embolization DSA of both UA show the same endpoint as **c**

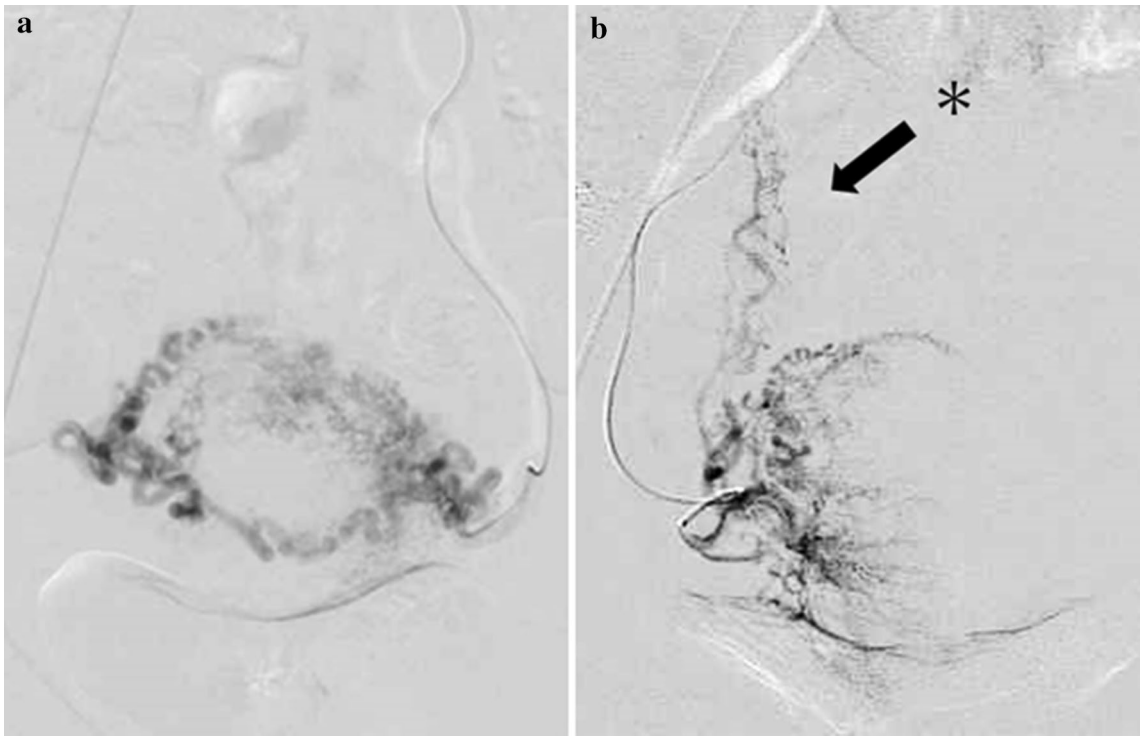

Fig. 2 Visualization of utero-ovarian anastomosis (UOA). **a** and **b** show the DSA just before embolization of the UA, indicating the case without visualization of UOA (asterisk) and with visualization of UOA, respectively

carefully evaluated. After selective catheterization of each UA using a 5Fr cobra shaped catheter with a guide wire (0.035, angle type; Radifocus, Terumo, Tokyo, Japan) and a standard coaxial 2.8F-microcatheter system (Renegade™, Boston Scientific Corp.), embolization was performed with gelatin sponge by pumping method. After bilateral UA embolization, obstetrician examined and confirmed hemostasis clinically. If active bleeding persists, the other feeding artery was detected and embolized.

Statistical analysis

We divided the 62 cases into two groups based on the presence of massive hemorrhage and 23 patients who had a desire for childbearing were also divided according to whether they were undergoing infertility treatment or not.

R software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Continuous variables are expressed as the mean ± SD, and categorical values are expressed as numbers and frequencies. Comparison of qualitative variables in the two groups was performed using Fisher's exact test or the Chi-square test for independence. Comparisons of quantitative variables in the two groups were performed using student's *t* test. The UA scores were compared between the two groups using the Mann–Whitney *U* test. The comparison of UA scores with the occurrence of uterine infection was also analyzed using the Mann–Whitney *U* test. A p value of < 0.05 (two-tailed) was considered statistically significant.

Results

Table 1 shows patient characteristics and primary outcomes. The mean age was 34.1 ± 6.5 years. Most of cases (49 cases, 79.0%) had histories of previous uterine surgery such as C/S and D&C. The causes of bleeding included primary postpartum hemorrhage in 19 cases (25.8%), secondary postpartum hemorrhage in 5 cases (8.1%), postabortion hemorrhage in 27 cases (43.5%), cervical pregnancy in 11 cases (17.7%). Ten of the 23 patients (43.5%) with a desire of childbearing underwent infertility treatment. There were 27 cases (43.5%) of massive hemorrhage. Gelatin sponge by pumping method was mainly used as the embolic material. In one case with massive hemorrhage, 20% NBCA was used for right UA to prevent early re-canalization, following by gelatin sponge injection. In one case of retained products of placenta (RPOC) combined with arteriovenous malformation, an absolute ethanol was used to eradicate nidus and venous sac. Bilateral UA was embolized by 0.5 ml absolute ethanol for each injection in total 9 ml, followed by pushable metallic coil embolization. In two cases of vaginal

Table 1 Patient characteristics and outcomes

Items (cases)	Cases (%)
Cases, patients	62 cases, 59 patients
Mean age (range)	34.1 ± 6.5 (17–49)
Parity: nullipara, multipara	22 (35.5%), 40 (64.5%)
Previous uterine surgery	49 (79.0%)
Desire to future fertility	23 (37.1%)
Patients with infertility treatment	10 (43.5%)
Preoperative Hb level (g/dl)	10.2 ± 2.6 (2.5–14)
Massive hemorrhage	27 (43.5%)
Embolic material	GS 61, coil 3, NBCA 1, ethanol 1
UA score (score 0:1:2)	Score 0:43, score 1:13, score 2:6
Visualization of UOA	15 (24.2%)
Combination treatment	30 (51.6%)
Technical success	59 (95.2%)
Uterine infection	10 (16.2%)
Ovarian dysfunction	2 (4.9%)
Cumulative pregnancy	20
Cumulative miscarriage	8
Live birth (infants)	12
Delivery complication	4

UA uterine artery, *UOA* utero-ovarian anastomosis, *Hb* hemoglobin, *GS* gelatin sponge, *NBCA* *n*-butyl cyanoacrylate

lacerations, middle colic artery or internal pudendal artery was also embolized in each case, respectively.

The clinical success rate of UAE combined with hysteroscopic resection or D&C was 95.2% (59/62 cases). Three patients of them received two UAEs; two patients for relapsed hemorrhage by cervical pregnancy and RPOC, the other one for a placental accreta after eight years from previous UAE.

Regarding the UA score, 43 cases had score 0, 13 cases had score 1, and 6 cases had score 2. UOA was visualized in 15 cases (24.2%). UA score was 0 in all two cases of relapsed hemorrhage.

After UAE, 10 cases of uterine infections (16.2%) and 2 cases of ovarian dysfunctions (4.9%) occurred. Two of the patients with uterine infection resulted in subsequent hysterectomy and one patient resulted in Asherman's syndrome. In 10 case with uterine infection, gelatin sponge was used in all cases and metallic coil in 1 case. The UA scores were as follows: score 0 for 5 cases, score 1 for 4 cases, score 2 for 1 case. There was no difference of UA score whether an occurrence of uterine infection or not ($p = 0.297$). Pregnancy outcomes included 20 cumulative pregnancies in 14 patients, 12 live births in 10 patients, and 8 cumulative miscarriages. Pregnancy rate and live birth rate were 60.9% (14 of 23 patients) and 43.5% (10 of 23 patients) respectively. The delivery route of the 12 live births was normal spontaneous vaginal delivery in 7 patients and elective C/S in 5 patients. Regarding complications at birth, four patients had placenta accreta, one of whom had severe peritoneal adhesion during elective C/S and another had atonic bleeding.

The occurrence of uterine infection was significantly higher in the group with massive hemorrhage than that in the group without ($p = 0.014$) (Table 2). Comparing the angiographic endpoints between the two groups, neither the difference in the UA score ($p = 0.109$), nor the difference in the visualization of the UOA ($p = 0.111$) was significant.

In the patients undergoing infertility treatment or not, patients undergoing infertility treatment were older (mean age 36.3 vs. 30.1 $p = 0.012$). Four of the nine nulliparous patients undergoing infertility treatment achieved live births. However, three of these four patients had delivery complications such as abnormal placentation and severe abdominal adhesion. There were 5 cases of miscarriages in 9 pregnant patients undergoing infertility treatment, and 3 cases in 11 pregnant patients not undergoing infertility treatment. The difference of history of previous uterine surgery was not significant ($p = 0.161$). Median time to conception was 184 days (range 101–948 days) and 330 days (range 95–925 days) for the patients undergoing infertility treatment or not, respectively (Table 3).

Discussion

The 95.2% clinical success rate of UAE (59 of 62 cases) combined with hysteroscopic resection or D&C achieved in the current study was within the allowable range [9–11]. Three patients of them received two UAEs, two patients for relapsed hemorrhage by cervical pregnancy and RPOC, the other one for a placental accreta after eight years from previous UAE. Regarding the primary outcome, the rate of uterine infection was 16.2% (10 of 62 cases), including two cases of subsequent hysterectomy, which was higher than that in the study of Inoue et al. of 5.3% [1]. Although the rate of uterine infection was high, the diagnosis of uterine infection was dependent on the clinical situation and it was difficult to distinguish between post-embolization syndrome and uterine infection.

Ovarian dysfunctions occurred in two cases (4.9%), which was less than the 10.3% reported by Santihes et al. [5] and almost equivalent to the 5.6% reported by Gaia et al. [3]. The reason could be that some cases of permanent amenorrhea may not be included due to an insufficient postoperative follow-up, leading to underestimation of ovarian dysfunction.

Regarding secondary outcomes, the pregnancy and live birth rates were 60.9% (14 of 23 patients) and 43.5% (10 of 23 patients), respectively. According to a systematic review about fertility rate after UAE, the pregnancy rates were 62–100% in patients who underwent UAE for postpartum hemorrhage, which were similar to those reported

Table 2 Comparisons between the two groups with or without massive hemorrhage

Items (cases)	Massive hemorrhage	No massive hemorrhage	*p* value
N cases/patients	27/26	35/33	0.240
Mean age (range)	35.2 ± 4.8 (26–45)	33.3 ± 7.5 (17–49)	0.167
Nullipara	7	15	< 0.01*
Previous uterine surgery	17	32	< 0.01*
Preoperative Hb (g/dl)	8.1 ± 2.2	11.8 ± 1.3	< 0.01*
Embolic material	GS (27), coil (3), NBCA (1)	GS (33), coil (1), ethanol (1)	
Technical success (%)	26 (96.3%)	33 (94.3%)	0.598
UA score (score 0:1:2)	17:9:2	26:4:4	0.109
Visualization of UOA	4	11	0.111
Combination treatment	10	20	0.116
Uterine infection	8	2	0.014*
Ovarian dysfunction	0	2	0.192
Desire to future fertility (patients)	4	19	< 0.01
Cumulative Pregnancy	2	18	
Cumulative Miscarriage	1	7	
Live birth (infants)	1	11	
Delivery complication	1	3	

*$p < 0.05$

Hb haemoglobin, *GS* gelatin sponge, *NBCA* *n*-butyl cyanoacrylate, *UA* uterine artery, *UOA* utero-ovarian anastomosis

Table 3 Comparisons between the two groups with or without infertility treatment

Item (patients)	Infertility treatment	No infertility treatment	*p* value
N	10	13	
Mean age	36.3 ± 6.5 (27–49)	30.1 ± 5.6 (21–40)	0.012*
Nullipara	9	5	0.017*
Previous uterine surgery	10	10	0.161
Massive hemorrhage	1	2	0.602
Embolic material	GS 10	GS 12, coil 2, ethanol 1	
UA score (score 0:1:2)	7:3:0	11:2:0	0.205
Visualization of UOA	4	1	0.089
Combination treatment	1	10	0.002*
Uterine infection	0	3	0.161
Ovarian dysfunction	2	0	0.178
Cumulative pregnancy (cases/patients)	9/6	11/8	0.693
Cumulative miscarriage (cases/%)	5 (55.6%)	3 (27.3%)	0.205
Live birth (infants/patients)	4/4	8/6	0.552
Delivery complication (patients)	3	1	0.119
Time to conception (days)	Median 184 (101–948)	Median 330 (95–927)	

GS gelatin sponge, *UA* uterine artery, *UOA* utero-ovarian anastomosis

*$p < 0.05$

in other studies [3, 12–14]. These studies also demonstrated the relatively higher live birth rate than the current study, although, we included ten patients undergoing infertility treatment, who underwent multiple abortions in the course of their infertility treatment. In fact, there is little information not only about future pregnancy but also about delivery complications in patients undergoing infertility treatment. We demonstrated a 20% ovarian dysfunction rate, a 60% pregnancy rate and a 40% live birth rate in patients undergoing infertility treatment, a 55.6% miscarriage rate, and a 75% delivery complication rate, which could be significant information for patients undergoing infertility treatment. Inoue et al. reported the rates of miscarriage and delivery complications including

placenta accreta and postpartum hemorrhage to be 21.4% and 40.0%, respectively [1]. These were lower than in the current study. The current study includes low number of patients, however, patients undergoing infertility treatment could be at a higher risk of delivery complications. Moreover, it was indicated that UAE itself could be the factor of a delivery complication because of no significant deference in history of previous surgery, massive hemorrhage and angiographic endpoint in the patients undergoing infertility treatment or not. Therefore, the results of the pregnancy rate of 60.9% and live birth rate of 43.5%, including patients undergoing infertility treatment, were acceptable, considering 62–100% of pregnancy rate and 20% of miscarriage rate by the past researches.

There was a significant difference in the occurrence of uterine infection after UAE for massive hemorrhage ($p = 0.014$). Multiple factors were considered as the cause of the results. Requiring more embolic materials such as a gelatin sponge to achieve equivalent angiographic endpoints and changes in the endometrial environment under massive hemorrhage due to a "vasospasm", often experienced during an emergent UAE for hemodynamically unstable patients, resulted in endometrial ischemia. The increased use of a gelatin sponge, conventionally used for UAE in postpartum or postabortion hemorrhage, may cause inflammatory reactions, which in turn cause inflammation around the occluded arteries [15], and could be responsible for uterine infection and synechia resulting in future miscarriages or abnormal placentation. In general, gelatin sponge was mainly used, however, other embolic materials should be selected depending on hemodynamical condition or target artery. Regarding angiographic endpoints, we could not demonstrate a reduction in complications by adjusting angiographic endpoints. However, it suggests the validity to firmly embolize intrauterine branches of UAs, even in the patients undergoing infertility treatment, considering that there was no significant difference in increase of UA score and occurrence of uterine infection and all UA scores in UAE failure cases were score 0.

The limitations of the current study are that this study is retrospective and included a small number of cases because of missing detailed angiographic data. Moreover, the differences in the patients' background diseases and those between the operators of the UAE were not considered, and follow-up of only postoperative complications and pregnancy outcomes could be insufficient.

In conclusion, it was unnecessary to modify angiographic endpoint for each patient according to the seriousness of the hemorrhage and suggesting the validity to firmly embolize an intrauterine branch of UA, even in the patients undergoing infertility treatment. The pregnancy rate and live birth rate were acceptable. However, there could be a higher rate of miscarriages and delivery complications in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval This study was approved by the institutional review board. Informed consents for uterine artery embolization were obtained from all patients. The Approval No. was 1310.

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