Effecacy of Uterine Artery Embolization in the Management of Symptomatic Uterine Myomata

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Abstract

Objective: The aim of the our study is to evaluate the results of the uterine artery embolization (UAE) as a modality for the treatment of uterine fibroids as regard to improvement of symptoms and reduction of fibroid size, and pregnancy after uterine artery embolization.

Design: Prospective clinical study.

Setting: Zagazig University Hospital, Obstetrics and Gynecology Department, Radiology Department. From period between January 2009 to July 2013.

Population: A total of 40 patients having symptomatic uterine fibroids (abnormal uterine bleeding, pelvic pain or bulk related symptoms) 20 of them were virgins and 20 were nullipara. Their ages ranged from 20-40 years.

Methods: All patient subjected to history taking, general examination, routine laboratory evaluation, ultrasound evaluation.

For all cases ultrasonography (abdominal and/or vaginal) was performed to measure the size of fibroid (s) before UAE. Then UAE using gel foam was performed occluding the feeding vessels for myomata. Evaluation of cases for reduction of tumour size and improvements of symptoms was performed one month, 3 months and 6 months after the procedure, long term follow-up of pregnancy occurrence.

Main outcome measures: Duration of technique, reduction of tumour size, significant improvement of symptoms, complications, pregnancy occurrence.

Results: The procedure was successful in 36 out of 40 cases (90%). Difficult or failed technique was encountered in four cases only. There was a significant reduction of tumour size and a non significant improvement of symptoms after one month. There were a significant and a highly significant improvement of symptoms after 3 and 6 months respectively and a highly significant reduction of tumour size at both 3 and 6 months. Subcutaneous hematoma, a small leak of contrast medium, fever with or without offensive vaginal discharge and pelvic pain were the complications noticed during or after UAE. Pregnancy occurred in 22/40 (55%) patients (some virgin patient married and got pregnancy) during long term flow-up. The fate of pregnancy was 2 abortions, 3 preterm labour, 1 IUFD, 16 term pregnancies.

Conclusions: UAE is an endovascular method for treatment of uterine fibroids that is clinically effective in most patients reducing the tumour size. It is invasive but relatively safe technique. Pregy can occur with long term follow-up.

Key Words: Uterine artery embolization — Uterine myomata.

Introduction

UTERINE fibroids are the most common pelvic tumors, the prevalence in autopsies is 35-40% in women above 35 years, but only a minority of these requires treatment. Hysterectomy, or occasionally myomectomy has previously been the treatment of choice, and symptomatic fibroids account for 1/3 of all hysterectomies in the USA and Western Europe. In 1998, 180,000 hysterectomies for fibroids were performed in the USA and 22,000 in England III.

Leiomyomas are clinically important because they are a major cause of abnormal uterine bleeding and are the most commonly cited reason for hysterectomy [2]. Traditional treatment for leiomyomas has been surgical removal through either hysterectomy or myomectomy. Also, surgical techniques such as hysteroscopic or laparoscopic removal of leiomyomas, or uterine arterial embolization are now being tested as effective but less invasive methods of treatment. Non-surgical treatment of leiomyomas has been primarily through the use of Gonadotropin-releasing hormone agonists that suppress circulating levels of estradiol and progesterone [3].
In women with symptomatic uterine fibroids, uterine artery embolization has been reported to be a safe, effective, and minimally invasive alternative to traditional therapies such as hysterectomy, myomectomy and hormone therapy. In larger series of patients, a number of authors have reported that embolization contributed to the improvement of clinical symptoms associated with uterine fibroids and resulted in tumor and uterine volume reduction with few complications during the follow-up period [4].

The uterine and fibroid volumes registered a statistical volume decrease at 30 and 90 days in comparison with the volumes before embolization. Absence of uterine anastomoses led to proper fibroid decrease. Longer evaluation time is needed for an accurate evaluation of volume reduction degree [5]. Will uterine artery embolization for myomas replace surgery? Should this procedure be offered as an alternative to all patients considering surgery for fibroids? [6].

Patients and Methods

The aim of the this study is to evaluate uterine artery embolization (UAE) as a new modality for the treatment of uterine fibroids. It is designed to evaluate the result of UAE as treatment of uterine fibroid regarding the improvement of symptoms, reduction of fibroid size, and pregnancy after UAE.

This study was done at Zagazig University Hospital, Obstetrics and Gynecology Department. From period between January 2009 to July 2013. All patients designed to have UAE. All patients were in patient care prepared for operative intervention. Information about the study was available to patient during consenting. The authors (W.S, M.S. and H.S.) had discussed the procedures with patients and they accepted and consented.

Funding:
All patient included in study at fund of Zagazig University Hospitals.

Study population:
In this study 40 patients allocated from Obstetrics and Gynecology Department underwent uterine artery embolization for their fibroid uteri.

Patients selection:
The study group were selected from 200 patients assessed ultrasonographically for abnormal uterine bleeding, pelvic pain, bulk related symptoms. Some patients were referred from Gynecological Specialist or other centers.

Inclusion criteria:
The patients had to present the flowing:
• Symptomatic fibroid uterus in the form of uterine bleeding (menorrhagia, metrorrhagia), pelvic pain, bulk related symptoms (pressure symptoms e.g. frequency of urination).
• Age ranged from (20-40) years.
• Virgin, or nullipara.
• Cooperative.
• The lesion present is fibroid not other lesion.
• Single or multiple fibroid uterus.
• Uterine size not more than 28 weeks.

Exclusion criteria:
Patients presenting with any of the flowing were not included in this study:
• Pregnancy.
• Active pelvic infection.
• Active vasculitis.
• History of pelvic irradiation.
• Evidence for pelvic malignancy (endometrial hyperplasia with atypia or neoplasia).
• Life threatening contrast allergy.
• Uncontrollable coagulopathies.
• Uterine size more than 28 weeks pregnancy.
• Severe renal insufficiency (in patients not undergoing dialysis).
• Patients who have undergone irradiation of the pelvis or who have vascular diseases may be at risk for necrosis caused by the decreased ability to form collateral circulation after UAE.
• Chronic salpingitis or endometritis may increase the chance of infection and therefore a relative contraindication.
• Contrast material allergies or renal failure are also relative contraindications to the use of embolization as a treatment option.

Pre-embolization preparation:
• Full history taking:
  Present history, past history, obstetric history and full menstrual history including:  
  1- First day of last menstrual period.  
  2- Duration of blood loss.  
  3- Amount and character of blood loss.  
  4- Dysmenorrhea.  
  5- Menorrhagia, or metrorrhagia.
Symptoms related to leiomyomas were classified in three categories; abnormal bleeding, and bulk-related symptoms.

General examinations including vital signs and evidence of systemic disorders.

- Abdominal examination.
- Bimanual examination to exclude clinically detectable organic lesions and evaluate uterine size.
- Abdominal and/or transvaginal ultrasonography to determine the size, site, and number of uterine fibroid(s) and measure the dimensions of the largest fibroid.
- Laboratory investigations; including hemoglobin percent, hepatitis markers.
- Correction of anemia.
- Patient counseling.

All patients were informed that uterine artery embolization is a new technique for management of myoma as an alternative method to surgical approach. The procedure was explained to them regarding the benefits and possible risks. Information given to patients emphasized the following:

a- Uterine artery embolization may need another setting.

b- The procedure is an alternative to myomectomy or hysterectomy with more rapid recovery, earlier return to daily activities and without anesthesia just analgesia for pain.

- Lastly informed written consent was obtained from every patient.

Angiography and embolization:

After percutaneous insertion of a 5-French sheath introducer (Super sheath) via the unilateral or bilateral common femoral artery, a pelvic arteriogram should acquire using a 5-French catheter placed above the aortic bifurcation next, a 5-French loop catheter, is inserted into the left uterine artery and a micro catheter is advanced coaxially into the arch segment. The diameters of the inner lumen of the micro catheters are 0.022-0.027 inches.

Gelatin sponge particles mixed with saline, contrast medium, are infused very slowly under fluoros-copy, using 60ml syringes. The solution is made of 40mL of saline solution, 20mL of contrast medium. And gelatin sponge particles made from 2-4 gelatin sponge sheets. The procedure is continued until the proximal ascending uterine artery is completely occluded under fluoroscopy. Uterine arteriography is performed immediately after embolization to ensure that the ascending uterine artery is occluded and that the arch segment and the main descending uterine arteries are patent at the end of the procedure. Then the contra lateral uterine artery is embolized using the same procedure. Low-frequency pulsed fluoroscopy is used during the procedure to reduce radiation exposure to the patients as much as possible.

The gelatin sponge particles used in uterine artery embolization are made by the operators from gelatin sponge sheets. The sheets were cut into thin slices using a scalpel and compressed until paper like, then cut into very small fragments using small scissors. The size of most gelatin sponge particles when compressed is approximately 500-1000µm, which is measured with a ruler.

The duration of technique range from 1-3 hours.
Efficacy of Uterine Artery Embolization in the Management

Sedation and analgesia:

Cramping that occurred after the procedure is treated with medication, e.g., an intramuscular injection of pethedine 50mg and 75mg of diclofenac sodium are administered. Antibiotics (cefaizolin sodium) are dripped IV in the dose of 2g in two divided portions for 2 days. And thereafter ofloxacin is administered Orally in a daily dose of 200mg in divided portions for the next 2 days.

After embolization:

- Good compression at the site of puncture to avoid subcutaneous hematoma formation.
- Embolization of the lower limb catheterized for 6-8 hours.
- Good fluid intake (iv and/or oral=3000cc/1St day).
- Strong antibiotics (3rd generation cephalosporin).
- Strong analgesia (pethedine 50-100mg in the 1st day) and declofenac sodium 75mg/12 hours for the 1st and 2nd days.
- Hospital stay for 12-24 hours.
- Hospital discharge on antibiotics (e.g., ofloxacin, or 1st generation cephalosporin and metronidazole and gentamycin for 2-7 days.
Flow-up:

a- Short term follow-up:

A clinical examination was performed for each patient every 2 hours during hospitalization. All symptoms were recorded; fever, pain, headache, and bleeding. Systematic follow-up after discharge from the hospital included clinical and sonographic examinations at 1, 3 and 6 months. Sonographic examinations were always performed with a 3.5 MHz abdominal probe and with a 4-8 MHz transvaginal probe. Evolution of clinical symptoms was classified as increased, unchanged, improved, or absent (i.e., symptom-free). Evolution of sonographic finding was analyzed by measuring the size of the uterus and the diameters of leiomyoma.

b- Long term follow-up:

Long term follow-up starting after 6 months for follow-up the pregnancy occurrence and pregnancy fate.

The results were recorded, tabulated, and subjected for analysis and discussion.

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Results

The study population comprised 40 adult women (age range, 20-40 years; mean age, 30 years). 20 patients (50%) were virgins, 20 patients (50%) were nullipara. All patients preferred embolization to surgery because a strong desire to keep the uterus or to avoid surgical procedure (Figs. 1, 2).

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Fig. (9): Abdominal ultra-sonographic picture of virgin case post-embolization after 1 month showing cervical fibroid size (83.5mm x 69.8mm). The fundal fibroid is absent. (before UAE Fig. 1).

Fig. (10): Abdominal ultra-sonographic picture of virgin case post-embolization after 3 months showing cervical fibroid size (59.4mm x 51.6mm). The fundal fibroid is absent. (before UAE Fig. 1).

Fig. (11): Abdominal ultra-sonographic picture of virgin case post-embolization after 6 months showing cervical fibroid size (39.5mm x 35.5mm). (before UAE Fig. 1).

Fig. (12): Trans vaginal ultrasonic picture after 3 months of embolization showing fibroid size.

Fig. (13): Number of patient included virgin 20 and nullipara 20 patients.
Efficacy of Uterine Artery Embolization in the Management of Uterine Fibroids

Symptoms related to leiomyomas were classified in three categories: abnormal bleeding (menorrhagia, metrorrhagia), bulk-related symptoms (frequency of urination, sensation of pressure or mass), and pelvic pain. The distribution of symptoms was as follows: abnormal bleeding (n=16), bulk-related symptoms (n=6), pelvic pain (n=2), abnormal bleeding and bulk-related symptoms (n=8), abnormal bleeding with pelvic pain (n=4), bulk-related symptoms with pelvic pain (n=2), and abnormal bleeding with bulk-related symptoms and pelvic pain (n=2). Moreover, abnormal bleeding was responsible for anemia in 9 patients (range of hemoglobin level, 4-10mg/d1) (Fig. 3).

The maximum diameter of the largest fibroid, the number of fibroids per patient, the location of the dominant fibroid, and the uterine volume were obtained on baseline ultrasonography then defining the largest fibroid as the dominant fibroid. 30 patients (75%) had multiple fibroid uterus, 6 patients (15%) had cervical fibroid and 4 patients (10%) had posterior wall fibroid. The diameters of fibroid range from 3x5x6cm to 7x9x13cm. All patients were informed of the potential benefits and risks of uterine artery embolization for uterine fibroids and obtaining oral and written informed consent from patients. Informing all patients that although the data have not always been sufficient, several publications have reported pregnancy after uterine artery embolization for uterine fibroids (Table 1).

Table 1: Of data of studied fibroids.

<table>
<thead>
<tr>
<th>Diameter (cm)</th>
<th>Type</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3x5x6 to 7x9x13</td>
<td>Multiple fibroid</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Cervical fibroid</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Posterior wall</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40</td>
<td>100</td>
</tr>
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Both uterine arteries were canulated without problem in 36 patients (90%). Difficulties of catheterization and failed technique in 4 patients (10%), two patients were uncooperative and moved her lower limb during procedure, in the other two patient uterine arteries couldn't be visualized on fluoroscopy (Fig. 4).

There was mild subcutaneous hematoma in 8 patients (20%) that was resolved in 5-12 days. A small leak of contrast medium occurred in two patient (5%) during catheterization of the left uterine artery. This complication, which was caused by vascular perforation, was immediately and successfully treated by embolization of uterine artery with a gelatin sponge particles.

Flow up: During hospitalization 30 (75%) patients had no post-procedural complications. Two patient (5%) was feverish (38°C) for 16hr after embolization. Fever resolved spontaneously without specific treatment. Four patients (10%) developed severe pelvic pain in the 1st 12hrs. Pain was controlled by increasing dose of pethedine by 50mg.
After discharge from hospital: Two weeks after embolization, two patient (5%) suffer from pelvic pain associated with offensive vaginal discharge that was controlled by metronidazole 500mg three times daily, 3rd generation cephalosporin and gentamycin (Fig. 5).

After one month of embolization: Of 36 patients symptoms remained unchanged in 10 patients (27.77%), were improved in 20 (55.55%), and had resolved in 6 patients (16.66%). Sonographic examinations revealed a significant reduction in leiomyoma size by 15% (Fig. 6).

At 3 months: Of 36 patients; abnormal bleeding had increased in two patient (5.55%) after period of stability. A second embolization procedure was necessary for two patient (5.55%) with posterior wall fibroid, but 2 patient prefer surgical treatment (myomectomy) to avoid pain which suffered from in previous embolization. Symptoms remained unchanged in 6 patients (16.66%), were improved in 16 patients (44.44%), and had resolved in 12 patients (33.33%). Sonographic examinations showed a significant reduction in leiomyoma (s) size by 25% (Fig. 7).

At 6 months: Of 34 patients symptoms remained unchanged in two (5.88%), and were improved in four (11.76%). The other 28 patients were symptom-free. Sonographic examinations showed a mean reduction in leiomyoma size of 43% (Fig. 8).

After 3 years after UAE Pregnancy occurred in 22/40 (55%) patients during long term flow-up. The fate of pregnancy was 2 (9%) abortions, 3 (13.6%) preterm labour, 1 IUFD (4.5%), 16 (72.72%) term pregnancies, 14 of term pregnancy delivered by caeserian section and 2 delivered vaginally. The 2 of preterm labor delivered vaginally with one baby saved in incubator and live and another died after 3 days and one delivered by caesarian section which died at incubator after 8 days.
Effecacy of Uterine Artery Embolization in the Management of Term Preterm Abortin IUFD

Fig. (22): Fate of pregnancy after UAE.

Discussion

The procedure was successful in 36 out of 40 cases (90%). Difficult or failed technique was encountered in four cases only. There was a significant reduction of tumour size and a non significant improvement of symptoms after one month. There were a significant and a highly significant improvement of symptoms after 3 and 6 months respectively and a highly significant reduction of tumour size at both 3 and 6 months. Subcutaneous hematoma, a small leak of contrast medium, fever with or without offensive vaginal discharge and pelvic pain were the complications noticed during or after UAE. Pregnancy occurred in 22/40 (55%) patients during long term flow-up.

Symptoms related to leiomyomas were classified in three categories; abnormal bleeding (menorrhagia, metrorrhagia), bulk-related symptoms (frequency of urination, sensation of pressure or mass), and pelvic pain. The distribution of symptoms was as follows; abnormal bleeding (n=16), bulk-related symptoms (n=6), pelvic pain (n=2), abnormal bleeding and bulk-related symptoms (n=8), abnormal bleeding with pelvic pain (n=4), bulk-related symptoms with pelvic pain (n=2), and abnormal bleeding with bulk-related symptoms and pelvic pain (n=2). Moreover, abnormal bleeding was responsible for anemia in 9 patients (range of hemoglobin level, 4-10mg/d1).

There was no significant difference between virgins and nullipara as regard results, no significant difference between two age groups (20-30 and 30-40 years) and no significant change in the symptoms after first month but there was significant change in the symptoms after third and sixth month. The reduction of fibroid size was highly significant after 3 and 6 months but only significant after 1 month of UAE.

After one month of embolization; of 36 patients symptoms remained unchanged in 10 patients (27.77%), were improved in 20 (55.55%), and had resolved in 6 patients (16.66%). Sonographic examinations revealed a mean reduction in leiomyoma size of 15%. At 3 months; of 36 patients; abnormal bleeding had increased in two patient (5.55%) after a period of stability. A second embolization procedure was necessary for two patient (5.55%) with posterior wall fibroid, but patient preferred surgical treatment (myomectomy) to avoid pain suffered from in previous embolization. Symptoms remained unchanged in 6 patients (16.66%), were improved in 16 patients (44.44%), and had resolved in 12 patients (33.33%). Sonographic examinations showed a mean reduction in leiomyoma (s) size of 25%. At 6 months: Of 34 patients symptoms remained unchanged in two (5.88%), and were improved in four (11.76%). The other 28 patients were symptom-free. Sonographic examinations showed a mean reduction in leiomyoma size of 43%. After 3 years starting to detect pregnancies tell 22/40 (55%) of studied patients. The fate of pregnancy was 2 abortions, 3 preterm labour, 1 IUFD, 16 term pregnancies.

Strengths and limitations of the study:

The major strength of this trial was the Prospective clinical design, which has, to be one of the best of our knowledge. Long term follow-up which detect cases of pregnancy after uterine artery embolization.

The maximum diameter of the largest fibroid, the number of fibroids per patient, the location of the dominant fibroid, and the uterine volume were obtained on baseline ultrasonography (abdominal and endovaginal) in this concept we in the same direction with Goodwin et al., Bradley et al., [8] and Katsumori et al., [9]. But other authors prefer MRI e.g. Okizuka et al.,[10].

Regarding the material used for UAE, polyvinyl alcohol (PVA) was used by Spies et al., Bradley et al., [8] and Goodwin et al., [12].

In this study, we followed Katsumori et al., [9] protocol using gelatin sponge (gel foam) avoiding complications of PVA particles and high cost. The technique was similar to others used by many [7,9,10].

The mean time was taken for UAE in this study was 1-3hrs and this coincided with Goodwin et al., [12] who mentioned that the procedure generally requires approximately 1 hour to perform, and radiation exposure is comparable to that received...
during one or two barium enemas. Additional time may be required to embolize the uterine arteries because of anatomic variations. Up to 3-4 hours may be required to complete the procedure.

Two weeks after embolization, two patient (5%) suffered from pelvic pain associated with offensive vaginal discharge that was controlled by metronidazole 500mg three times daily, 3rd generation cephalosporin and gentamycin and this may be encountered with any organ embolization. Target organ embolization complications include uterine infection [7] and this also occur with Mehta et al., [13].

This study gave results nearly similar to that of Goodwill et al., [12]; Spies et al., [111]; Klein & Schwartz [14]; Katsumori et al., [9]; Horhoianu IA. [6]; Kojima T. [15]; Toor SS. [16]; Tomislav S. [17] and Koh J. [18].

This study gave better results than that of Brunereau et al., [19]; Spies et al., [111]; Messina et al., [19] and Pinto et al., [20]. Because in this study, the number of patients were more and using gel foam alone as embolic agent which decrease incidence of complication and hence avoid hysterectomy thus increasing number of patients in follow-up period.

Regarding pregnancy in this study occurred during long term follow-up of patient with some similarity to that of McLucas B. [21] and Redecha M. Jr., et al., [22].

Some limitations to this study may apply. In terms of long term follow-up of patients, the acceptance to some patients were difficult, using only gel foam as it is cheap and available and not using another form of embolization, technical difficulties, and complications.

This study gave results less than that of Goodwin et al., [7]; Siskin et al., [141]; Andersen et al., [23]; Bai et al., [24]; Du et al., [25]; Tranquart et al., [26]; Wang et al., [27] and Zupi et al., [28]. Because in this study, the number of patients were less, using only gel foam as embolic agent, and the follow-up period was shorter.

In this study there were technical difficulties in 4 cases and this is similar to that mentioned by Bum et al., [29] Technical difficulties in cannulating the arteries may occur as a result of anatomical variation or arterial spasm.

Regarding the complications that occur in this study, there were mild subcutaneous hematoma in 8 patients (20%) that resolved in 5-12 days as in series of Vedanmam et al., [30]. A small leak of contrast medium occurred in two patient (5%) during catheterization of the left uterine artery. This complication, which was caused by vascular perforation, was immediately and successfully treated by embolization of uterine artery with gelatin sponge particles. This complication was also reported by Katsumori et al., [9] Two patient (5%) was feverish (>38°C) for 16 hours after embolization. Fever resolved spontaneously without specific treatment.

Four patients (10%) developed severe pelvic pain in the 1st 12 hours. Pain was controlled by increasing dose of pethedine by 50mg. The pain was a common complication as Spies et al., [111] mentioned.

Redeca M. Jr., et al., [22] reported that; A total of 98 patients underwent uterine artery embolization for symptomatic myomas; 21 expressed their wish to become pregnant, out of which 6 had successful spontaneous conception (23.08%) and 1 patient was pregnant twice, and altogether there were seven pregnancies. During gestation and delivery, there was no serious complication. There was one missed abortion and one placental retention. Myomas did not show growth pattern during pregnancy. Data from further prospective, randomized trials comparing fertility and pregnancies after UAE with other treatment modalities are needed. UAE, with the new techniques of superselective microcatheterization, could be, in the future, a possible approach even in women with future maternity plans [22].

**Interpretation:**

Before applying the results to other populations and settings, several factors have to be considered, the larger number is needed for more evaluation, long term follow-up for years detects cases with pregnancy outcome.

All over the uterine artery embolization is an effective modality for management of uterine fibroids, with good fertility and pregnancy outcome on short and long term follow-up.

McLucas B. 1211 reported that; Forty-four women under the age of 40 embolized between 1996 and 2010 stated a desire for fertility. Twenty-two of these women have reported 28 pregnancies. Of these pregnancies, 20 live births, three miscarriages, and three instances of premature labor were reported. Seventeen of these pregnancies were delivered by caesarean section and six pregnancies were
vaginal deliveries. And one woman is currently pregnant. No perfusion problems, either during pregnancy or labor, were reported. The course of pregnancy and delivery was largely normal after embolization with three cases of premature labor and three miscarriages reported. Forty-eight percent of women who were under 40 and desired pregnancies were able to have successful term pregnancies.

Conclusion:

U.A.E. is safe and effective modality in management of well-selected cases uterine fibroid. U.A.E. is more acceptable to patients as it is associated with rapid recovery and short hospital stay (as out-patient procedure). U.A.E. by gelatin sponge particles alone is more safe and give nearly the same results of U.A.E. by poly vinyl alcohol without serious complications. Careful patient selection is essential point to avoid complications and gain good results. Pregnancy can occur after UAE with good fetal outcome on long term follow-up.

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Disclosure of interests:

None.

Contribution to authorship:

W.S., M.S. and H.S. contributed to the protocol, co-ordinated the study, interviewed the parents, analysed the data and drafted the article. M.T. and his team did radiologic uterine artery embolization. W.S., M.S. and H.S. contributed also to the revision and final approval of the article.

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