

TREATMENT OF REFRACTORY MENORRHAGIA BY UTERINE ARTERY EMBOLIZATION IN WOMEN DESIRING FUTURE FERTILITY

By

Ashraf M. Enite*, Samy Amin M Gebreel**,
Eman A. El Moneim Alkholy**, and *** Aya Fouda

Departments of *Radiology, and **Obstetrics & Gynecology, Faculty of Medicine Al-Azhar University,
and ***Obstetrics & Gynecology, Health Insurance Hospitals

ABSTRACT

Background: Menorrhagia is prolonged excessive menstruation that might be interfere with the woman's physical, emotional, social and material quality of life. It may be idiopathic or due to fibroids, adenomyosis, pelvic congestion and arterio-venous malformations or coagulation disorders.

Objective: Evaluation of the effectiveness of uterine artery embolization in the management of refractory menorrhagia conserving the patient's fertility when other treatment options are not applicable.

Patient and methods: This study was conducted between February 2011 and September 2015 on a total 7 female patients. The mean age was 35.4 ± 3.7 years and age range of between 28–42 years. This retrospective study was treating the patients with severe refractory menorrhagia not responding to medical treatment and have local uterine pathology {multiple fibroids, adenomyosis or arteriovenous malformation (AVM)} and requiring fertility preserving treatment option. They referred from the Gynecological clinic, Al-Azhar University Hospitals, Health insurance hospitals and Cairo health care centre, and selected to undergo uterine artery embolization (UAE).

Results: Seven patients underwent UAE. Two (29%) patients experienced clinical failure; the first patient underwent hysterectomy due to development of infection and offensive vaginal discharge, and the second patient experienced no improvement treated by AVM re-embolization. After 6 months of follow-up, the overall clinical success rate was based on the cessation of bleeding which was 5 (72%) patients. Temporary amenorrhea was experienced for 6.5 ± 2.6 months in 6 (86%) patients. The mean uterine fibroid diameter was 7.4 ± 3.2 cm (range 1.8- 11.5) before UAE and decreased to 4.3 ± 2.4 cm (range 1.2–7.5) 6 months after UAE.

Conclusion: UAE is a percutaneous procedure that involves no general anesthesia, no surgical incision, and no blood loss or risk of blood transfusion. It can be used in refractory amenorrhea treatment and alternative to a hysterectomy, to conserve the uterine fertility. Recovery and time to return to work and daily living activities is relatively short.

Key words: Arteriovenous malformations (AVM), Digital subtraction angiography (DSA), Doppler ultrasonography (US), uterine artery embolization (UAE).

INTRODUCTION

Menorrhagia is defined as prolonged (>7days) and/or excessive menstruation (West, 2010). The British National Institute of Health and Clinical Excellence (NICE) introduced the term heavy menstrual bleeding (HMB) to describe excessive menstrual blood loss that

interfere with the woman's physical, emotional, social and material quality of life (NICE, 2007). The prevalence of menorrhagia accounts for 12% of gynecological referrals in UK (West, 2010). Menorrhagia may be idiopathic or due to fibroids, adenomyosis, pelvic congestion and AVM or coagulation disorders.

Leiomyomas are the most common benign pelvic tumor and affect 20-50% of women (Kalina et al., 2016). They account for 30% of hysterectomies in USA (Deshmukh et al., 2012). Adenomyosis is characterized by the presence of heterotopic endometrial glands within the myometrium with myometrial hyperplasia. Adenomyosis frequency is 8.8-31% (Kim et al., 2007). Gestational trophoblastic tumors are highly vascular and associated with the formation of AVM which persist in 10-15% of patients (Lim et al., 2002).

Medical treatment with tranexamic acid with or without mefenamic acid is the first line treatment. They are given only during menstruation days (Lethaby et al., 2004 and Hardman et al., 2009). Iyer et al. (2000) reported that refractory cases should be investigated and any pathology such as fibroids should be treated, e.g. by myomectomy. Hormonal treatment in the form of oral contraceptive pills or long acting progestogens (Depo-Provera) have proved effective in many cases. Other treatment options include gonadotropin releasing hormone analogues (GnRH analogues), intrauterine progesterone releasing device Mirena, endometrial ablation and hysterectomy. The above mentioned treatment modalities may lead to temporary inhibition of pregnancy (e.g. oral contraceptive, Mirena and Depo-provera) or permanent fertility loss (e.g. hysterectomy and endometrial ablation).

Uterine artery embolization (UAE) is first described by Brown and his Colleagues in 1979 (Ganguli et al., 2011). It is a minimally invasive therapeutic method (Kalina et al., 2016), when initial medical treatment fails to stop bleeding (Ganguli et al., 2011). It is an alternative treatment option to hysterectomy (Kalina et al., 2016), especially in a thrombocytopenic situation (Hardman et al., 2009).

PATIENTS AND METHODS

This study was conducted between February 2011 and September 2015 on a total 7 female patients. The mean age was 35.4 ± 3.7 years, and age range was between 28-42 years. This retrospective study was treating the patients with severe refractory menorrhagia not responding to medical treatment and have local uterine pathology (multiple fibroids, adenomyosis or AVM) and requiring fertility preservation. All patients gave their informed written consent.

Exclusion criteria: Chronic uterine or adnexal infection suspected from tenderness at local vaginal examination, expectation of pregnancy, coagulopathy and severe renal insufficiency.

Pre-embolization Assessment: All patients had been seen in Al-Azhar University and Health insurance hospitals at obstetrics and gynecology out patient's clinics and Cairo health care centre for chronic menorrhagia. All patients had pelvic US and/or MRI scans obtained as part of the routine workup to assess the volume of the uterus and largest leiomyoma. The AVM was assessed and uterine artery pulsatility index measured with Doppler ultrasonography (US).

UAE Technique: The UAE was protocol performed via bilateral or unilateral right common femoral artery. All procedures were performed with fluoroscopy (Philips Allura Clarity and Toshiba Infinix-iv Cath-labs). Under road-mapping, Terumo (Terumo Radifocus, Tokyo, Japan) guide wire and a 5-French Cobra C2 catheter (Boston scientific corporation, USA) were used to selectively catheterize the horizontal portion of the uterine artery. The microcatheter used was Progreat (Terumo, Tokyo, Japan), HI-FLO type. A 2 mL of 0.2% Lignocaine injected directly into the uterine artery before embolization. The mixture of PVA

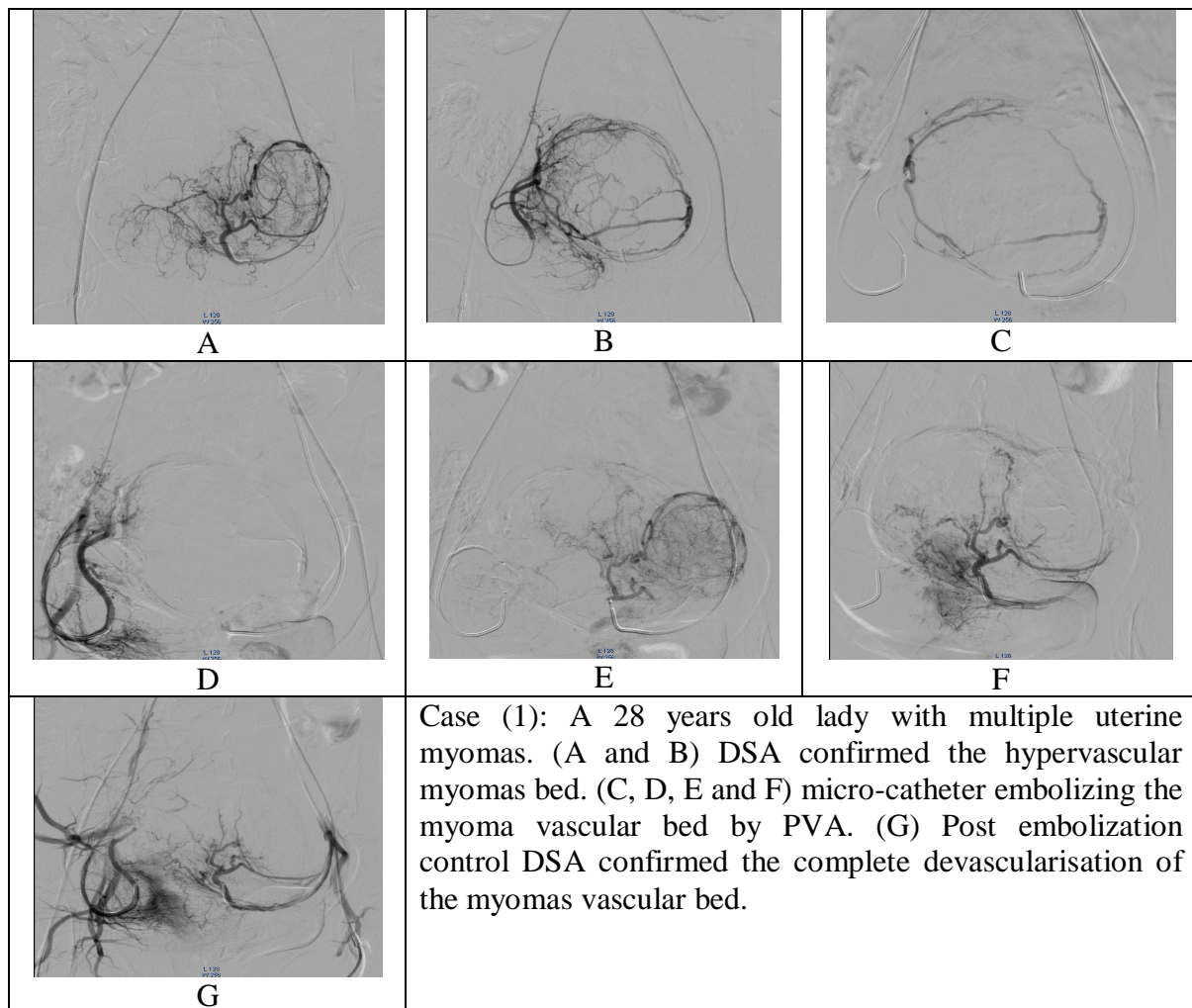
particles (Boston scientific corporation, USA) ranged in size from 300-700 μ m embolized via the micro-catheter. The AVM was embolized by mixture of lipiodol and amcryl.

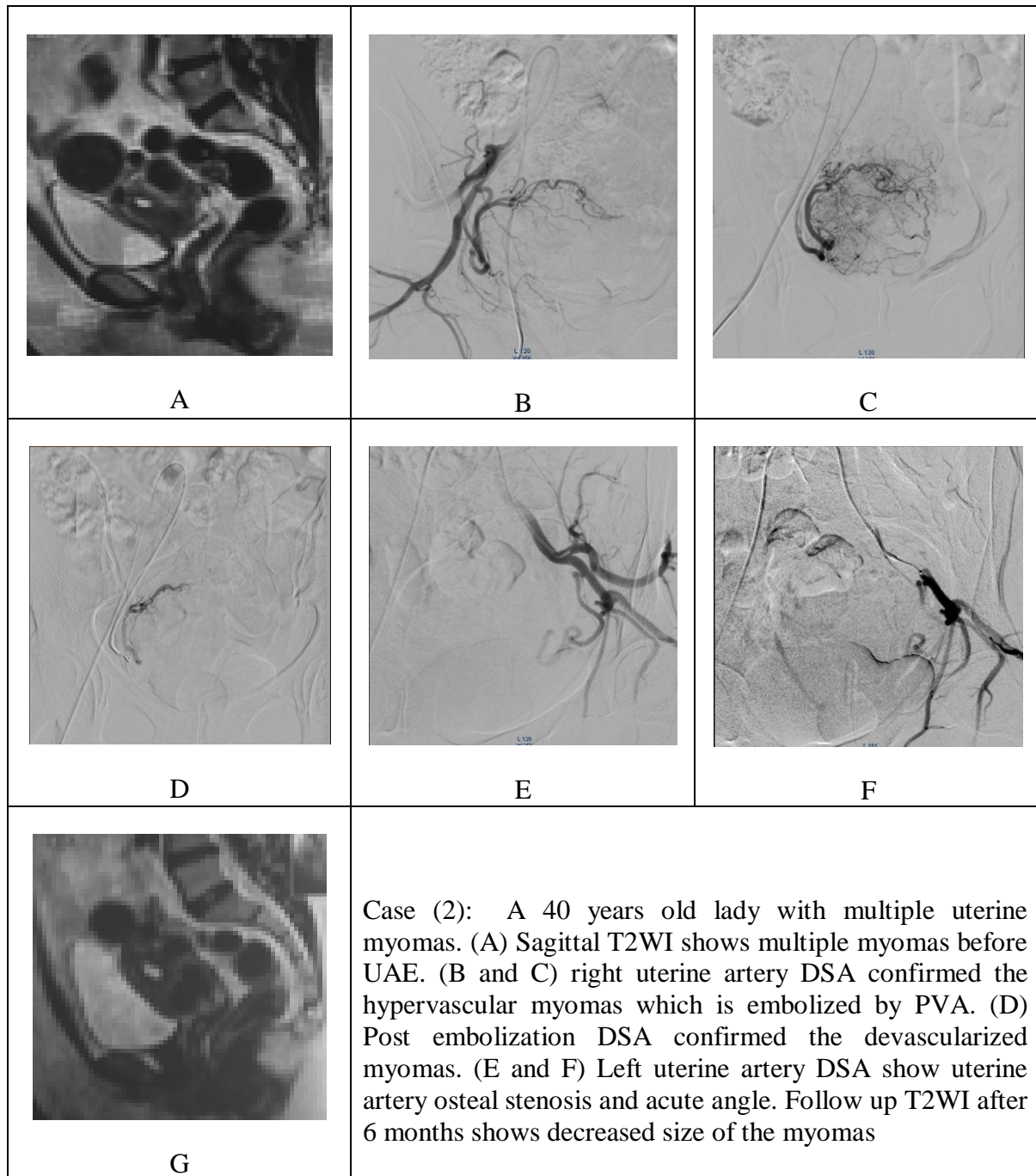
Post-embolization Assessment: Post-embolization US and/or MRI was performed to assess characteristics of the leiomyomas including numbers, location and size.

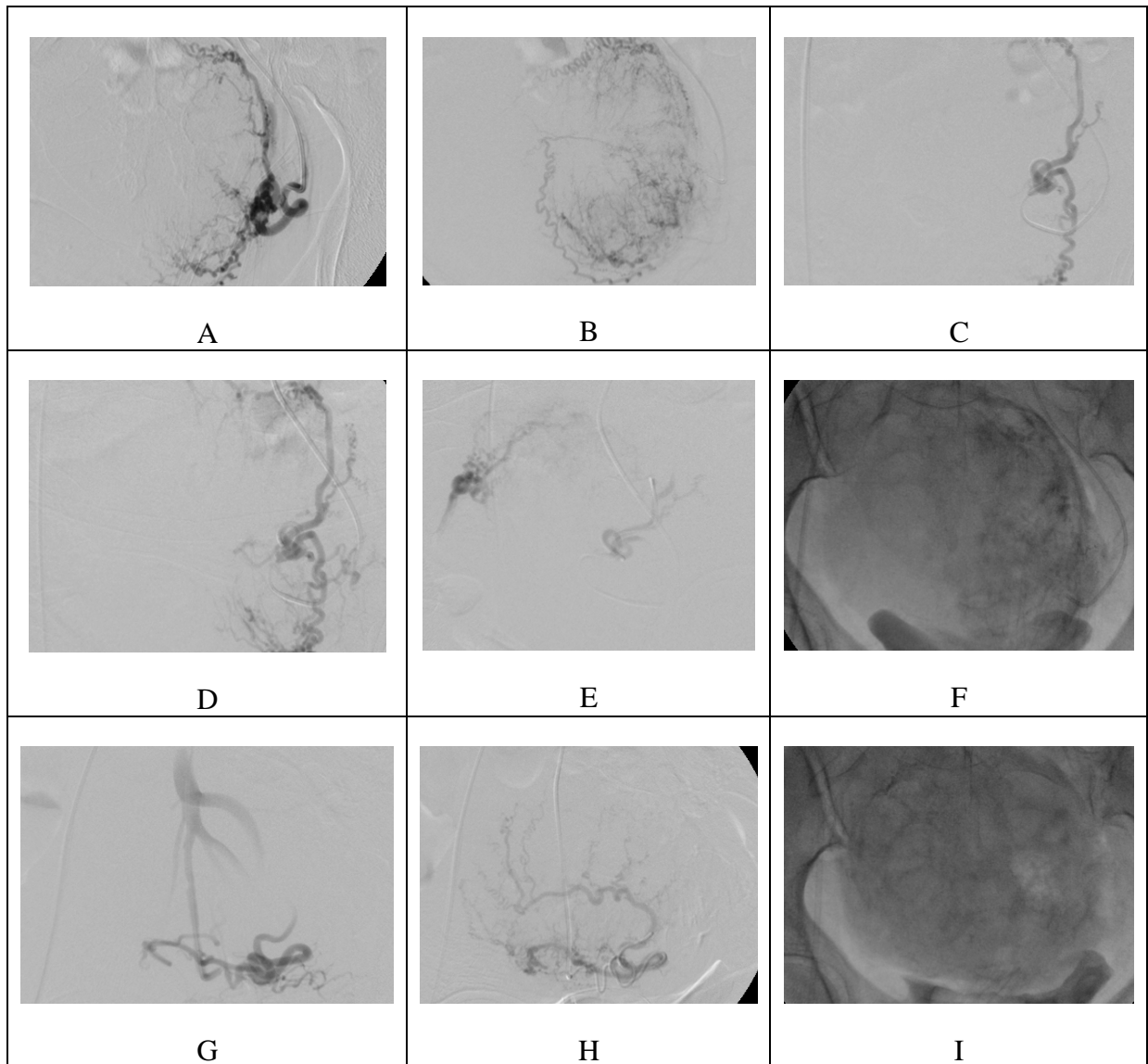
Out comes: Data on the control of hemorrhage (based on the need for repeat UAE or surgical intervention) and conception were obtained during follow up. Side effects such as pain, infection, or systemic symptoms resulting from the

procedure (and time to second embolization, if applicable) were also documented. A successful embolization was defined as a complete cessation of uterine hemorrhage.

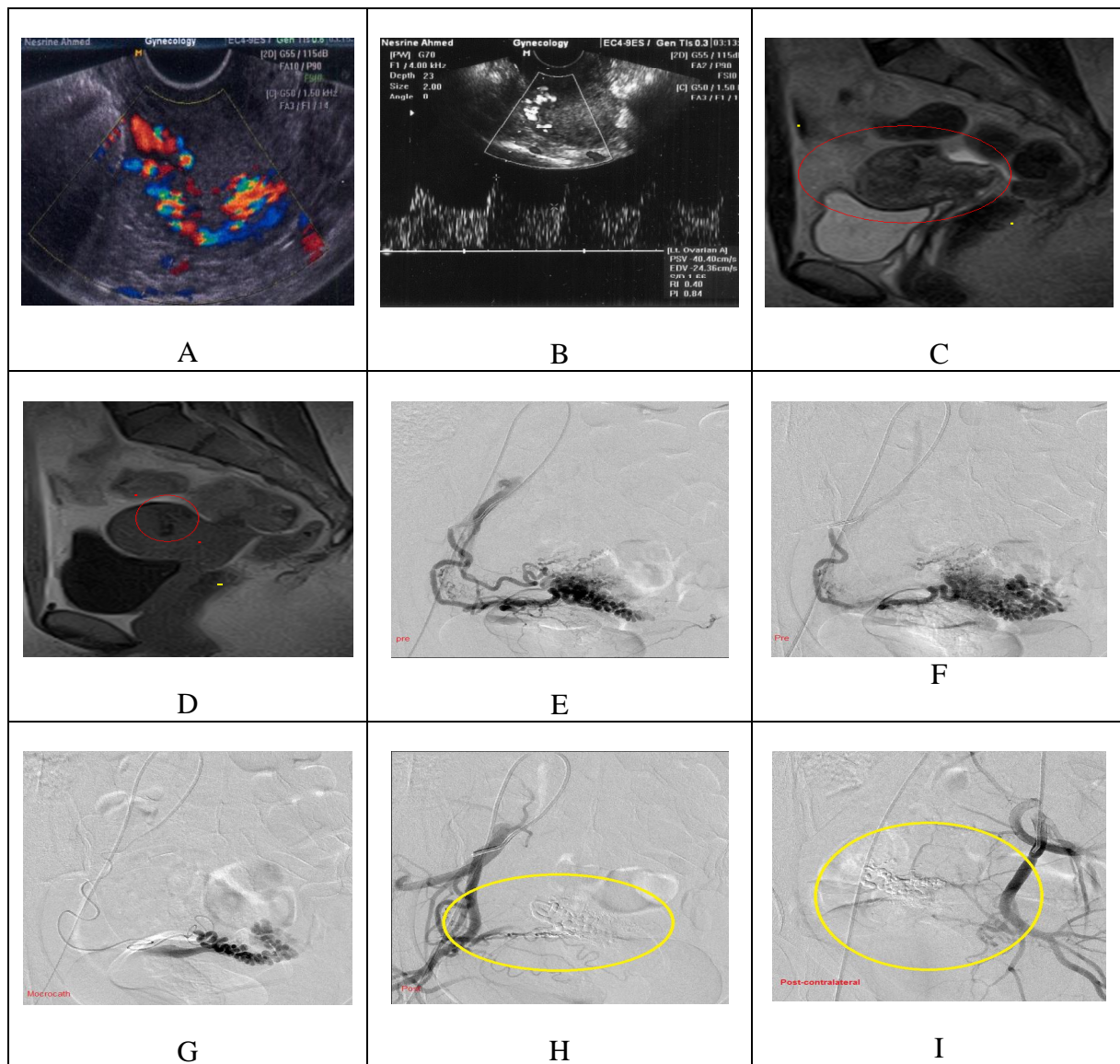
Statistical Analysis: Data analysis was performed using Microsoft office 2013 and SPSS (statistical package for social science) Vr 16. Parametric data were expressed as mean \pm SD and non-parametric data were expressed as number and percentage. Paired t-test was used for comparing parametric data, and Chi square test was used to compare non-parametric data. $P \leq 0.05$ was considered significant.







Case (3): A 39 years old lady with adenomyosis. (A, B, C, D, G and H) DSA shows tortuous and dilated uterine arteries. (E, F and I) post-embolization control images confirmed occlusion of hypervascular adenomyosis with PVA particles casting the vascular bed.



Case (4): A 30 years old lady with post gestational trophoblastic uterine AVM. (A and B) Duplex US shows serpentine, mosaic vascular flow by the overlapping vessels. Spectral analysis revealed low resistance flow, high PSV. (C and D) MRI shows bulky uterus with multiple serpeginous flow related signal void s and prominent para-metrial vessels. (E, F and G) DSA shows complex vascular connections supplied by hypertrophied uterine arteries. (H and I) Embolization was performed by mixture of lipiodol and amcryl.

RESULTS

A total of 11 patients were eligible for the study. One patient refused to participate in the study, and another three were excluded because they had associated adnexal complex mass lesion, chronic

salpingitis or hepatic cirrhosis induced coagulopathy. The remaining 7 patients offered the option of undergoing UAE rather than hysterectomy. Two (29%) patients experienced clinical failure, the first patient underwent hysterectomy due to development of infection and offensive

vaginal discharge and the second patient experienced no improvement treated by AVM re-embolization. After 6 months of follow-up, the overall clinical success rate, based on the cessation of bleeding, was 5 (72%) patients. Temporary

amenorrhea for 6.5 ± 2.6 months occurred in 6 (86%) patients. Right unilateral embolization only was performed in one (14%) patient due to left uterine artery marked osteal stenosis.

Table (1): Patient's criteria

Parameters	Criteria
Age	
Mean \pm SD	35.4 \pm 3.7
Range	28-42
Primary infertility before UAE	4(57%)
Hormonal treatment	2(29%)
Adenomyosis	1(14%)
AVM	1(14%)
Fibroid	5(72%)
No. fibroids	33
Type <i>mural</i>	17(52%)
<i>Sub-mucosal</i>	11(33%)
<i>Sub-serous</i>	5(15%)
Diameter (cm)	
<i>Pre UAE</i>	7.4 \pm 3.2
<i>Post UAE</i>	4.3 \pm 2.4
Clinical failure	2(29%)
Treated by:	
<i>Hysterectomy</i>	1(14%)
<i>Re-embolization</i>	1(14%)
Complications	
<i>Contrast reaction</i>	1 (14%)
<i>Groin hematoma</i>	2(29%)
<i>Severe pelvic pain</i>	1 (14%)
<i>Post-embolization syndrome</i>	2(29%)
<i>Vaginal discharge</i>	1(14%)
<i>Urinary tract infection</i>	3(43%)
<i>Temporary amenorrhea</i>	4(57%)
<i>Blood Transfusion</i>	1(14%)
UAE Agent	
<i>Fibroid by PVA</i>	5(72%)
<i>Adenomyosis by PVA</i>	1(14%)
<i>AVM by Lipiodol & amcryl mixture</i>	1(14%)
Satisfaction	
<i>Yes</i>	4(57%)
<i>No</i>	3(43%)
P value	>0.05

The mean dominant fibroid volume decreased after 6 months of follow-up. The mean uterine fibroid diameter was 7.4 ± 3.2 cm (range 1.8-11.5) before UAE and decreased to 4.3 ± 2.4 cm (range 1.2-7.5) after UAE ($P < 0.05$).

The patients' complications included two (29%) patients with post-embolization syndrome, and one (14%) with severe pelvic pain ($P < 0.05$). The patient (14%) who underwent hysterectomy was readmitted because of anemia and to undergo blood transfusion.

The patients who underwent UAE resumed their routine activities after a mean of $6.5 \text{ days} \pm 3.21$, as compared with the patient who underwent hysterectomy who resumed her routine activities after at least 4 weeks.

After 6 months of follow-up, the patients who underwent UAE were asked whether they would undergo the same treatment again; 4 (57%) answered yes and 3 (43%) answered no ($P > 0.05$) (Table 1).

In all cases laboratory investigations were required especially negative pregnancy test, creatinine (≤ 1.2 mg/dL), platelet count ($\geq 150 \times 10^9/L$) and haemoglobin (≥ 9 g/dL) levels. The procedure and potential complications were explained during the consultation.

Pre and post UAE hormonal profile was performed to assess the patient's fertility confirmed that there was no significant changes before and after UAE (Table 2).

Table (2): Patient's hormonal profile before and after UAE.

Parameter	Number	Mean	Std. Deviation	Std. Error Mean
FSH (mIU/ml)				
Before	7	5.4571	1.38427	0.52320
After	7	6.7571	3.85524	1.45714
LH (IU/L)				
Before	7	4.9714	1.66304	0.62857
After	7	5.5143	2.68355	1.01429
TSH (uIU/ml)				
Before	7	2.0571	0.59682	0.22558
After	7	2.3286	0.77183	0.29172
Prolactin (ng/mL)				
Before	7	17.6714	4.87056	1.84090
After	7	19.3571	6.22973	2.35462
E2 (pg/ml)				
Before	7	59.5857	8.46393	3.19906
After	7	55.8286	11.06100	4.180
AMH (ng/ml)				
Before	7	1.0429	0.33594	0.12697
After	7	1.714	0.53140	0.20085

DISCUSSION

Uterine leiomyoma is a very common gynecological condition. The risk for a woman over the age of 45 years of having leiomyomas is > 60% (**Wong et al., 2014**). It accounts 30% of hysterectomies in USA (**Deshmukh et al., 2012**). Adenomyosis is characterized by heterotopic endometrial glands within the myometrium. Adenomyosis frequency reported up to 31% (**Kim et al., 2007**). Gestational trophoblastic tumors are associated with the formation of uterine AVM. These AVM persist in 10-15% of patients (**Lim et al., 2002**). Our study included 7 patients for UAE. 5 (72%) patients had multiple leiomyoma, 1(14%) patient had adenomyosis and 1 (14%) patient had post gestational trophoblastic tumors with AVM.

Our study showed that the main patient's complain was refractory menorrhagia. This was in agreement with **Parker (2007)** who stated that the patients commonly present with menorrhagia, pain, and urinary symptoms due to uterine enlargement (**Kim et al., 2007**). Multiple treatments exist for menorrhagia with the hormone therapy is the first option (**Hardman et al., 2009**). The conservative management include myomectomy, UAE, and MRI guided high-intensity focused ultrasound, radiofrequency ablation and laparoscopic occlusion of uterine vessels (**Wong et al., 2014**). Hysterectomy is considered a definitive management (**Kim et al., 2007**). Our study aimed to treat the patients with UAE as they insist on preserving fertility. Hormonal treatment was excluded as it is a contraceptive method.

The UAE eliminates the need of a hysterectomy, avoiding anesthesia, surgical trauma and post-surgical complications (**Dobrokhotova et al., 2015**). Our results were in agreement with **Gupta et al. (2012)** who was comparing UAE versus surgery. UAE offers an advantages of a shorter hospital stay and a quicker return to routine activities. There was no difference in major complication and ovarian failure rates.

The effectiveness of UAE had high technical success rate (100%) and dramatic reduction in menorrhagia in the study. Further benefits of UAE included the avoidance of surgical risks and fertility preservation. For comparison, in hysterectomies, the median length of hospital stay was 5 days, and the morbidity and mortality rates were 34.9% and 1.6%, respectively (**Shellhaas et al., 2009**).

The reasons for low utilization of UAE cited in the study included limited number of modern angiography units and the coast of UAE procedure. These utilization findings were consistent with the study of **Ganguli et al., (2011)**. Some centres have begun to develop multidisciplinary algorithms and rapid-response teams to optimize outcomes. At our hospitals, we encouraged gynecologists to give opportunity to the UAE. We did not know the number of women who underwent initial hysterectomy without referral to UAE during this time period.

In our study, we used the embolic agent according to the menorrhagia etiology. We used PVA in treatment of myomas or adenomyosis. We used a mixture of lipiodol and amcryl in treatment of AVM. For all cases, we did

not use metallic embolization microcoils due to proximal permanent and coasty occlusion.

In our study, the pre and post UAE hormonal profile was performed to assess the patient's fertility confirmed that there was no significant changes before and after UAE. **Tropeano et al. (2010)** established no effect to UAE on the level of follicle-stimulating hormone (FSH), estradiol, the number of ovarian follicles and ovarian volume within 1 year of observation. **Delotte et al. (2009)** concluded that UAE offers a safe and conservative alternative to surgery in women who desire to preserve fertility. **Dobrokhotova et al. (2015)** reported data on 56 pregnancies that ended in the birth of 33 (58%) cases. **Hardman et al. (2009)** reported that there is a possible reduced fertility. However, UAE maintains a greater chance of fertility than surgical resection. The pregnancies after UAE have a higher risk of preterm labour (16%), spontaneous abortion (24%), and mal-presentation (11%). Other risks associated with UAE are similar to those of all angiography procedures including reaction to the contrast dye as well as of hematoma and/or infection at the femoral catheterization site.

Approximately, 80% of patients experience post-embolization syndrome. It is characterized by pain, fever, and nausea. It subsides within 5 days. The time course allows differentiation from post-procedural infection. Follow up confirm cessation of bleeding, typically at 1-2 weeks (**Hardman et al., 2009**).

Hardman et al. (2009) reported that the rate of complications includes non-target embolization, infection, and

premature ovarian failure to be up to 9%. Non-target embolization to the extremities, gut, or other locations occurs in less than 1% of procedures. Deaths have been reported after UAE due to sepsis and a pulmonary embolism.

Carrillo (2008) stated that the UAE radiation dose is unlikely to result in radiation injury to a patient or infertility. However, it remains important to minimize radiation dose to the ovaries by coning down on the catheter tip and using pulsed fluoroscopy. This is not consistent with our study as there were 2(29%) of the patents developed post embolization syndrome and 1 (14%) patient developed endometritis and vaginal discharge. No UAE procedure mortality.

CONCLUSION

UAE can be used in refractory amenorrhea treatment and alternative to a hysterectomy, to conserve the uterine fertility. Recovery and time to return to work and daily living activities was relatively short.

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أشرف محمد عنايت * سامى أمين محمد جبريل ** إيمان عبد المنعم الخولى ** آية فودة***

قسمى الأشعة* وأمراض النساء والتوليد** بكلية الطب جامعة الأزهر

وأقسام أمراض النساء والتوليد*** بمستشفيات الهيئة العامة للتأمين الصحى.

خلفية البحث: يعتبر الحيض المفرط مؤثراً سلبياً على المرأة عاطفياً و إجتماعياً و مادياً. وهناك عدة أسباب قد تؤدي إلى الحيض المفرط منها الأورام الليفية، والرحم الغدى، وإحتقان الحوض، والتشوهات الشريانية الوريدية و اضطرابات تخثر الدم.

الهدف: تقييم فعالية إنصمام الشريان الرحمى في علاج الحيض المفرط مع المحافظة على خصوبة المريضا.

المرضى والطرق: أجريت هذه الدراسة فى الفترة بين فبراير 2011 وسبتمبر 2015 على 7 سيدات، بمتوسط عمرى 35.4 + 3.7 سنوات، والفئة العمرية بين 28-42 عاما. وهذه دراسة إستيعادية لعلاج المريضا اللاتى عانين من الحيض المفرط مع عدم إستجابتهن للعلاج الطبى، ولديهن أمراضاً موضعية بالرحم (مثل الأورام الليفية المتعددة، و الرحم الغدى، و التشوهات الشريانية الوريدية) ، تتطلبن خيارات العلاج التحفظى للخصوبة بإنصمام الشريان الرحمى.

النتائج: خضعت 7 مريضات لإنصمام الشريان الرحمى: شهدت سيدتين (29%) عدم نجاح للعلاج بإنصمام الشريان الرحمى، أول مريضة خضعت لإستئصال الرحم بسبب عدوى و إتهابات وإفرازات مهبلية، والمريضة الثانية شهدت عدم تحسن و تم علاج التشوهات الشريانية الوريدية بإعادة إنصمام الشريان الرحمى و بعد 6 أشهر من المتابعة، كانت نسبة النجاح الشامل فى الحيض المفرط فى 5 (72%) مريضات. و إنقطع الطمث مؤقتاً من 6.5 + 2.6 أشهر فى 6 (86%) مريضات. وكان متوسط قطر الورم الليفي بالرحم 7.4 + 3.2 سم (المدى 1.8 - 11.5) قبل إنصمام الشريان الرحمى وإنخفض متوسط قطر الورم الليفي إلى 4.3 + 2.4 سم (المدى 1.2-7.5) بعد 6 أشهر من إنصمام الشريان الرحمى.

الخلاصة: إنصمام الشريان الرحمى هو إجراء عن طريق الجلد و لا ينطوي على التخدير العام، أي شق جراحي، وعدم فقدان الدم أو مخاطر نقل الدم. ويمكن إستخدامه في علاج الحيض المفرط وكبديل لإستئصال الرحم، من أجل الحفاظ على خصوبة الرحم. كما أن فترة النقاهة و العودة إلى العمل وأنشطة الحياة اليومية يحدث سريعا نسبيا.