



A Prospective Pilot Study of the Safety and Effectiveness of Uterine Artery Embolization for the Treatment of Endometriosis: The UAE-E Study

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Abstract

Purpose Uterine artery embolization (UAE) evidence is increasing in the setting of adenomyosis, which shares pathological similarities to endometriosis. Endometriosis is characterized by the presence of endometrium-like tissue outside of the uterus, and the retrograde menstruation hypothesis may account for disease development. In women where fertility is no longer desired, hysterectomy can be offered to improve pain-related symptoms. The authors hypothesize that this cohort of patients may similarly respond to UAE. The aim of this pilot study is to assess the safety and effectiveness of UAE in the management of endometriosis-related symptoms.

Methods Six-patient prospective single-arm pilot study in female, premenopausal patients over 40 years with symptoms of endometriosis. Institutional review board approval was obtained.

Inclusion criteria include completed family, premenopausal, pelvic endometriosis as confirmed by laparoscopy within the last 5 years, and symptoms of endometriosis impacting quality of life as evidenced by the British Society of Gynaecological Endoscopy pelvic pain and Short Form-36 questionnaires.

Results The primary endpoint will be safety, as assessed by the composite number of procedural and postprocedural complications during procedure, predischARGE, and at 6 weeks, 3 months, 6 months, and 12 months. Secondary endpoints will include technical success, clinical success, and durability.

Discussion This study will be a novel application of UAE in the setting of endometriosis and has the potential to improve patient quality of life. This pilot study will assess safety and allow the investigators to design a prospective randomized controlled study.

Keywords

- adenomyosis
- endometriosis
- pain
- chronic
- embolization

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Introduction

Uterine artery embolization (UAE) is a cost-effective treatment for symptomatic uterine leiomyomata,^{1,2} and there is increasing evidence of its efficacy in the setting of adenomyosis.³ Adenomyosis and endometriosis share many pathological similarities. Endometriosis is an estrogen-driven disease characterized by the presence of endometrium-like tissue outside of the uterus.⁴ It affects between 6 and 10% of premenopausal women and accounts for an estimated 34,200 hospital admissions annually in Australia.⁵ It may cause a range of potential symptoms including chronic pelvic pain, reduced fertility, dysmenorrhea, dyspareunia, and dyschezia, among many others. These symptoms cause significant impact on a patient's quality of life.⁶

While the exact mechanism of disease development is unknown, a postulated theory for the pathogenesis of endometriosis is the retrograde menstruation hypothesis. This proposes retrograde expulsion of endometrial cells from the uterine cavity into the pelvis via the fallopian tubes.⁶ Existing treatments for endometriosis depend on the severity of disease but are centered predominantly on medical management strategies.⁶ Surgery to ablate or excise ectopic endometrial tissue is effective, but disease and symptoms can recur.^{4,6}

In women where fertility is no longer desired, hysterectomy either with or without oophorectomy may be offered, theorized to reduce the supply of retrograde menstruation.^{4,7,8} In their recently published study, Sandström et al assessed the use of hysterectomy to treat pain symptoms in females with endometriosis in Sweden using a population-based registry. Over 5 years, 137 women were treated. The authors showed a significant reduction in pain particularly those with severe symptoms, including for those without concomitant oophorectomy, and they concluded that hysterectomy is valuable in women with endometriosis and severe pain.⁴ However, a review of complications after hysterectomy for benign disease by Varol et al showed an overall mortality rate of 1.5% in their cohort.⁹ Hysterectomy when combined with oophorectomy has also recently been shown to be associated with increased risk of stroke and cardiovascular disease.¹⁰ In addition, studies have also shown that hysterectomy in the setting of endometriosis is higher risk than in a non-endometriosis cohort.¹¹

Given the benefits associated with hysterectomy in patients with endometriosis, but the complications associated with hysterectomy in this cohort, an alternative treatment such as embolization may be desirable. The authors theorize that women with endometriosis may similarly respond to UAE by reducing the supply of retrograde menstruation after embolization.

The aim of this pilot study is to assess the safety and effectiveness of UAE in the management of endometriosis-related symptoms, and the hypothesis is that UAE will be safe and effective. This study will provide preliminary data and will be used to determine if a larger feasibility and randomized controlled study will be undertaken.

Study Design

Reporting Standard

The reporting of this study protocol is according to the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.¹²

Research Design

This is a prospective single-arm pilot study in female, premenopausal patients over 40 years with symptoms of endometriosis.

Ethics Committee Approval

The study has been approved by the Alfred Hospital Human Research and Ethics Committee, number 226/22 and was prospectively registered on the World Health Organization-approved clinical trials registry (Australian New Zealand Clinical Trials Registry, number ACTRN12622001301752), approval date 07/10/2022.

Participant Recruitment and Consent

Potential patients will be recruited in a community outpatient setting, by a consultant gynecologist with specialist interest in management of endometriosis-related chronic pelvic symptoms. Patients will consult with the study interventional radiologists in a tertiary academic hospital, will be provided with patient information and consent form, and informed consent obtained before the procedure.

Baseline Assessment

After consultation with both gynecologist and interventional radiologist and providing consent, patients will receive baseline blood testing (full blood examination, creatinine, and coagulation profile), and will complete the British Society of Gynaecological Endoscopy (BSGE) pelvic pain questionnaire and 36-Item Short Form Health Survey (SF-36) Quality of Life questionnaire. The timeline of events is shown in ►Table 1.

Inclusion Criteria

- Completed family—no desire for future pregnancy.
- Premenopausal, defined as the presence of menstrual bleeding in the previous 3 months and no change in typical menstrual regularity in the past year.
- Pelvic endometriosis as confirmed by laparoscopy within the last 5 years.
- Symptoms of endometriosis impacting quality of life as evidenced by the BSGE pelvic pain questionnaire and including at least one of the following:
 - Period-related pain (dysmenorrhea) affecting daily activities and quality of life.
 - Deep pain during or after sexual intercourse (dyspareunia).
 - Period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements (dyschezia).
 - Period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine.

Table 1 Timeline of patient assessment, procedure, and follow-up

	Preprocedure –30 to 7 d	Procedure	Discharge	Postprocedure			
				6 wk	3 mo	6 mo	12 mo
Interventional radiologist consultation	X			X		X	X
Gynecologist consultation	X				X		X
Laparoscopic confirmation of endometriosis ^a	X						
Pelvic pain questionnaires ^b	X			X		X	X
Preprocedure blood testing	X						
Procedure		X					
Assessment for adverse events		X	X	X	X	X	X

^aLaparoscopy within 5 years confirming endometriosis.

^bBritish Society of Gynaecological Endoscopy pelvic pain questionnaire and SF-36 Quality of Life questionnaire.

- Signed study participant information and consent form.
- Eastern Cooperative Oncology Group 0 to 1.

Exclusion Criteria

- Desire for future pregnancies or fertility treatment.
- Perimenopausal, defined as changes in typical menstrual regularity in the past year or amenorrhea for the previous 3 months.
- Postmenopausal, defined as > 12 months of amenorrhea.
- Previous hysterectomy, bilateral oophorectomy, or UAE.
- Other comorbidities that are likely to be causing chronic abdominal or pelvic pain.
- Iodine contrast allergy.
- Active pelvic infection or inflammatory disease.
- Severe renal insufficiency.
- Gynecological malignancy.

Procedure

Procedures will be performed by study investigators who are subspecialty trained interventional radiologists and holders of the European Board of Interventional Radiology with a combined 24 years' experience.

Procedures will be performed under intravenous conscious sedation using titrated boluses of midazolam and fentanyl. Patients will receive premedication according to an existing internal treatment protocol including administration of the following preprocedure medications: ondansetron 8 mg intravenously, droperidol 0.625 mg intravenously, metronidazole 500 mg intravenously, cephazolin 1 g intravenously, paracetamol 1 g intravenously, parecoxib 40 mg intravenously, and morphine 5 mg intravenously. All procedures will be performed via transfemoral route using 5-French sheath access. Diagnostic angiography will be performed from the iliac artery on each side to assess preintervention uterine vascularity, and uterine arteries will be selected with a microcatheter in all patients to reduce nontarget embolization and vasospasm (2.7 Fr 135 cm Progreat, Terumo, Japan). Embolization will be performed using aspherical polyvinyl alcohol (PVA) particles of size 355 to 500 μ m (Contour PVA, Boston Scientific, United States).¹³ The

embolization endpoint will be reduced forward flow. An arterial closure device will be used on all patients. Patients will be admitted to the hospital for overnight monitoring and management of any potential post-embolization syndrome.

Statistics

Six patients will be recruited for this pilot study. Data will be collected including demographics, procedure-related data, adverse events, and BSGE/SF-36 questionnaire data (baseline, 6 weeks, 6 months, 12 months). More details are available in ►Table 1.

Outcome Measures

Primary Endpoint

- Safety, as assessed by the composite number of procedural and postprocedural complications during procedure, pre-discharge, and at 6 weeks, 3 months, 6 months, and 12 months.

Secondary Endpoints

- Technical success of UAE as defined by a significant reduction in forward flow of both uterine arteries on angiography at the discretion of the proceduralist.
- Clinical success at 6 and 12 months as defined by an improvement in the BSGE pelvic pain questionnaire and SF-36 Quality of Life questionnaire.
- Durability of symptom relief at 12 months.

Adverse Events

These will be collected according to the 2017 Cardiovascular and Interventional Radiological Society of Europe classification system.¹⁴ Potential complications from this procedure may include:

- Access site complications including bleeding, hematoma, pseudoaneurysm, occlusion, embolus, or superficial skin infection.
- Severe post-embolization syndrome.
- Uterine necrosis.

- Uterine or pelvic infection.
- Nontarget embolization.
- Procedure-related hysterectomy.
- Allergy to contrast agent.

Discussion

Although UAE is an established procedure in the setting of leiomyomata and gaining further interest in the setting of adenomyosis,^{1,2} this study will be a novel application of this procedure. The basis of the causative effect with UAE builds upon existing evidence for pain improvement in women treated with hysterectomy,^{4,7,8} and the retrograde menstruation hypothesis.⁶

As such, the authors hypothesize that UAE will reduce retrograde menstruation by reduction of menstruation supply and thus has the potential to improve symptoms of endometriosis. There is a risk of confounding from any concomitant adenomyosis in this cohort given the available evidence to support symptom improvement for embolization in patients with adenomyosis alone, and the overlap of disease in this group.³ While patients with adenomyosis would not be excluded, the presence will be recorded to allow for appropriate post hoc assessment.

However, despite the hypothesized mechanism presented, there may also be no benefit to this patient group. As such, the primary endpoint in this pilot study is safety. Given the challenges associated with providing appropriate statistical measurement of pain-related symptom improvement, a large and direct comparative study with a control group is needed to assess short- and long-term efficacy and will form the basis of a future direction after this pilot study is performed.

Ethical Approval

Ethical approval is not required for publication of this study protocol, however, approval was obtained for the described study by The Alfred Human Research and Ethics Committee.

Informed Consent

Informed consent is not required for publication of this study protocol, however, informed written consent will be obtained for individual participants in the study.

Consent for Publication

Consent is not required for publication of this study protocol, however, written consent will be obtained for individual participants in the study including consent for publication.

Clinical Registration

WHO approved clinical trials registry: Australian New Zealand Clinical Trials Register, approval number ACTRN12622001301752, approval date 07/10/2022.

Funding

None.

Conflict of Interest

None declared.

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