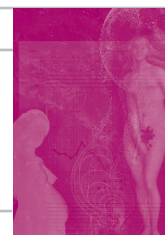


Ovarian function after uterine artery embolisation



A Prollius, MB ChB, MMed (O et G), FCOG (SA)

A Viljoen, MB ChB, MMed (O et G), FCOG (SA)

A du Plessis, MB ChB

H S Cronjé, MB ChB, MMed (O et G), FCOG (SA), MD

Department of Obstetrics and Gynaecology, University of the Free State, Bloemfontein

M Nel, MMedSc

Department of Biostatistics, University of the Free State

Objective. To evaluate ovarian function in 29 patients who underwent uterine artery embolisation (UAE).

Methods. Twenty-nine patients with myomas of the uterus underwent UAE using polyvinyl alcohol (PVA) particles with a diameter of 150 - 550 μm . Follicle-stimulating hormone (FSH) levels were measured before and after UAE.

Results. The median age of the patients was 39 years (range 19 - 51 years). Two patients (7%) were menopausal before UAE was attempted. In 3 patients (10.3%), normal pre-procedural FSH values rose to menopausal levels afterwards (95% confidence interval (CI) 3.6 - 26.4%). Only 1 of these patients was younger than 40 years of age (39 years). Of 15 patients less than 40 years of age, 6.7% (95% CI 1.2 - 29.8%) therefore developed a significant rise in FSH levels. One patient, aged 35 years, developed temporary amenorrhoea and endometrial atrophy, which returned to normal within a year.

Conclusions. UAE resulted in ovarian failure in 7% of patients younger than 40 years of age and 10% of patients overall.

Uterine artery embolisation (UAE) has been firmly established as a non-surgical modality for treatment of symptomatic myomas in women wishing to retain the uterus. Since the original paper by Ravina *et al.*¹ describing symptomatic relief and a dramatic decrease in uterine size after UAE, interventional radiologists together with gynaecologists have increasingly used this novel approach for treating myomas. Large cohort studies have since been published, all describing the excellent relief of symptoms related to myomas experienced after UAE.²⁻⁵ A remarkable feature of this modality is its reproducibility: there is a surprising similarity in the findings of different centres using UAE. A South African study on UAE has shown symptomatic improvement and complications comparable to the rest of the world.⁶

Exposure of the ovaries to radiation is a concern, especially if the patient desires future fertility. The calculated radiation dose to the ovaries is 20 rads during UAE. This dose is comparable to that for a barium enema or a hysterosalpingogram, but less than radiation treatment of Hodgkin's disease. Based on the well-established risks of pelvic radiation for Hodgkin's disease, it is concluded that the dose during UAE poses no risk for acute and long-term radiation injury, or to fertility.⁷ Measures to minimise the radiation to the ovaries include pulsed fluoroscopy (to decrease the radiation dose), avoidance of detailed fluorography and strict coning down to the catheter tip.

Premature menopause has been documented in 1 - 2% of patients after UAE and was believed to result from non-target embolisation of vessels to the ovaries from the uterine arteries.⁸ Doppler studies on ovarian vasculature showed evidence of significant vascular derangements in ovarian arterial circulation immediately after UAE, as evidenced by a complete loss of appreciable arterial flow or an increase in vascular impedance. These changes occur as a direct result of inadvertent embolisation of the ovary via uterine-ovarian arterial collaterals.⁸

Patients desiring future fertility must be counselled thoroughly on the risks of amenorrhoea versus the risks of any surgical alternative. The occurrence of amenorrhoea for variable lengths of time following the procedure is not uncommon. This was initially thought to be due to endometrial atrophy. The role of ovarian dysfunction, however, was only established in 2001 by Chrisman *et al.*,⁹ who demonstrated that 15% of 66 patients did not resume regular menses and all of them were older than 45 years of age. In a subgroup of patients who were ≥ 45 years of age, 9 of 23 (43%) became menopausal. In the following year, Spies *et al.*⁹ reported on follicle-stimulating hormone (FSH) levels, an indicator of menopause, before and up to 6 months after UAE.⁹ Although FSH levels did not change significantly, they increased significantly in 15% of cases in a subgroup of patients 45 years and older. Therefore, in older patients (≥ 45 years) UAE may introduce a menopause,

probably because the ovaries become less tolerant of embolisation.^{8,10} Of more importance, however, is iatrogenic menopause in patients under the age of 40 years, because they might desire to have more children. This study was designed to evaluate ovarian function in patients undergoing UAE with the emphasis on patients <40 years of age.

Methods

A prospective, descriptive study was performed. The Ethics Committee of the Faculty of Health Sciences, University of the Free State, approved the study and informed consent was obtained from all patients.

Selective UAE was performed on 29 patients at the interventional radiology unit at Universitas Hospital, a teaching hospital of the University of the Free State, irrespective of age. Indications for the procedure included symptomatic myomas of the uterus, a desire to retain the uterus and/or a fear of surgery. Patient recruitment and assessment were performed by the Department of Obstetrics and Gynaecology. Patients were screened before the procedure with assessment of FSH levels, kidney function, blood count and clotting time. A Pap smear was routinely performed on all patients. Patients with abnormal uterine bleeding were investigated with ultrasound and endometrial sampling to exclude malignancy.

Uterine artery embolisation was performed by two interventional radiologists in the Department of Radiology with unilateral femoral artery access and sequential catheterisation of each uterine artery. Selective arteriography demonstrated arterial blushing of the blood supply to a specific myoma before embolisation. Embolisation was performed using polyvinyl alcohol (PVA) particles with a particle size ranging from 150 to 550 µm in diameter. PVA particle injection was terminated as soon as the vasculature of the myoma was occluded and decreased flow within the uterine artery demonstrated. On completion an arteriogram was performed, revealing complete occlusion of the branches supplying the myomas, with at least partial preservation of flow to normal myometrial branches. A Siemens Multistar Angiography unit (Siemens, Erlangen, Germany) was utilised for the procedure, which was done under local anaesthesia in all cases. The right femoral artery was routinely used with the introduction of a 4-French sheath. A 4-French renal double curve catheter with a 0.35 Terumo guidewire was used to select the left uterine artery before embolisation.

Standard care was employed after the procedure. Patients were evaluated before the procedure and afterwards at 6 weeks, 6 months and 1 year. Symptoms were assessed using a three-point Likert symptoms scale (better, same, worse). Specific note was taken of the presence of amenorrhoea. A blood sample was taken at the 3-month visit and the FSH level was determined. If the level was raised to post-menopausal levels (>20 IU/l in our

laboratory), the FSH level of that specific patient was performed on serum obtained before UAE and stored at -4°C for possible analysis at a later stage.

Descriptive statistics, namely medians and percentiles for continuous variables, and frequency and percentages for categorical variables, were determined. The prevalence of increased FSH values was described by means of 95% confidence intervals (CI) for prevalence. The data analysis was done using SAS.¹²

Results

The median age of all the patients was 39 years (range 19 - 51 years). Post-UAE FSH values rose to menopausal levels in 5/29 patients (17.2%). Two of these had raised values pre-UAE (7%), so in 3/29 the value increased from below to over the threshold value after UAE (10.3%, 95% CI 3.6 - 26.4%). The number of patients younger than 40 years experiencing a rise in FSH was 1/15 (6.7%, 95% CI 1.2 - 29.8%). The patients who experienced a significant rise in FSH were 39, 46 and 51 years of age, respectively.

Three patients (10.3%) had amenorrhoea at the 6-month follow-up. One of these had been post-menopausal before the procedure (performed mainly for pressure effects), a second patient was in the group >45 years that experienced ovarian failure after the procedure, and the third had normal ovarian function as measured by FSH. The latter patient was investigated further with endometrial biopsy, which revealed endometrial atrophy. She started to menstruate spontaneously again and at the 1-year follow-up visit her menstrual cycle was normal. Therefore, in our series 1/29 (3.4% with a 95% CI 0.8 - 14.1%) had transient endometrial atrophy at 6 months after the procedure. This patient was 35 years of age.

Discussion

A significant number of patients presented with an increase in FSH values after UAE, suggesting ovarian failure. The overall percentage was consistent with the figures quoted in previous studies, although the percentage of patients with premature ovarian failure (<40 years) was higher than previously reported.⁸ The fact that this represents only 1 patient does, however, make interpretation difficult and reflects this study's limitation with regard to size.

The most important risk factor for developing premature menopause is age. Possible contributing factors may be multiple myomas typical of an African population, since it could be reasoned that more PVA particles might be needed to embolise these uteri. However, that has not been proven conclusively with the numerous studies concerning particle size and UAE techniques.^{8,11,12} The ideal particle size has not been established, but current opinion is that the particles should not be <350 µm in diameter as smaller particles have a higher risk of

causing endometrial atrophy by penetrating deeply into small-calibre vessels. Conversely, particles should also not be >550 µm as they can accidentally obliterate non-target vessels.

Testing the ovarian reserve may predict the patient who is at risk of developing premature menopause. An elevated FSH level on the 3rd day of the menstrual cycle will identify ovarian failure. If this is raised beyond the threshold value for the specific laboratory, patients should be advised that ovarian reserve is already seriously impaired and raised levels (especially >20 IU/l) are associated with poor performance during *in vitro* fertilisation.^{13,14} If the day 3 FSH is normal and the patient is >40 years of age, further assessment of the ovarian reserve can be undertaken.

Navot's clomiphene challenge test¹⁵ is more sensitive to ovarian reserve than a day 3 FSH level, and is performed as follows: clomiphene is administered at a dose of 100 mg per day on days 5 through 9. An FSH level is repeated on day 10 and this is compared to the day 3 level. When ovarian reserve is low, the pituitary responds paradoxically with an exaggerated FSH response, probably due to diminished inhibin levels from the ovary. A response of more than two standard deviations above the control (day 3) or a value of 26 IU/l or more, is considered to indicate poor ovarian reserve. An abnormal response predicts a poor prognosis for fertility either spontaneously or with *in vitro* fertilisation.

There is evidence suggesting that hysterectomy and possibly myomectomy also carry a significant risk of premature ovarian failure.^{16,17} No comparison has been drawn between the outcome of ovarian function comparing UAE with myomectomy, although such studies are in progress. The practical value of this is that women who wish to retain ovarian function cannot be guaranteed it, whether UAE or myomectomy is applied.

One of the handicaps of UAE studies is the lack of a control group. A true control group would, however, be extremely difficult to motivate, as the patients in the placebo arm would have to be catheterised and not embolised.

In conclusion, UAE resulted in decreased ovarian function in 7% of women <40 years of age and 10% overall. Women with impaired ovarian reserve <40 years of age and women >45 years of age are at particular risk of becoming menopausal. Patients should be counselled adequately on this issue before a decision regarding UAE is taken. Unfortunately, preliminary data showed that myomectomy may also limit postoperative ovarian function.

Daleen Struwig, Medical Writer, is acknowledged for assisting in the preparation and submission of the article.

Funding: Departmental funds and routine services in hospital; **conflict of interest:** none identified.

1. Ravina JH, Merland JJ, Herbreteau D, Houdart E, Bouret JM, Madelenat P. Preoperative embolization of uterine fibroma. Preliminary results (10 cases). *Presse Med* 1994; 23: 1540.
2. Ravina JH, Herbreteau D, Ciraru-Vigneron N, et al. Arterial embolisation to treat uterine myomata. *Lancet* 1995; 346: 671-672.
3. Pelage JP, Le Dref O, Soyer P, et al. Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up. *Radiology* 2000; 215: 428-431.
4. Spies JB, Scialli AR, Jha RC, Lage JM, Nicolic B. Initial results from uterine fibroid embolization for symptomatic leiomyomata. *J Vasc Interv Radiol* 1999; 10: 1149-1157.
5. Goodwin SC, Walker WJ. Uterine artery embolization for the treatment of uterine fibroids. *Curr Opin Obstet Gynecol* 1998; 10: 315-320.
6. Prollius AP, De Vries C, Loggenberg E, et al. Uterine artery embolization for symptomatic fibroids. *Int J Gynaecol Obstet* 2004; 84: 236-240.
7. Nikolic B, Spies JB, Lundsten MJ. Patient radiation dose associated with uterine artery embolization (UAE) for leiomyomas. *Radiology* 1998; 209: 183.
8. Spies JB, Roth AR, Gonsalves SM, Murphy-Skrzyniarz KM. Ovarian function after uterine artery embolization for leiomyomata: assessment with use of serum follicle stimulating hormone assay. *J Vasc Interv Radiol* 2001; 12: 437-442.
9. Chrisman HB, Saker MB, Ryu RK, et al. The impact of uterine fibroid embolization on resumption of menses and ovarian function. *J Vasc Interv Radiol* 2000; 11: 699-703.
10. Itkin M, Shlansky-Goldberg R. Uterine fibroid embolization for the treatment of symptomatic leiomyomata. *Appl Radiol* 2002; 31: 9-17.
11. Tropeano G, Litwicka K, Di Stasi C, Romano D, Mancuso S. Permanent amenorrhea associated with endometrial atrophy after uterine artery embolization for symptomatic uterine fibroids. *Fertil Steril* 2003; 79: 132-135.
12. Goodwin SC. Uterine artery embolization for the treatment of uterine fibroids. *Fertil Steril* 2003; 79: 136-137.
13. Toner JP, Philput CB, Jones GS, Muasher SJ. Basal follicle-stimulating hormone level is a better predictor of *in vitro* fertilization performance than age. *Fertil Steril* 1991; 55: 784-791.
14. Speroff L, Glass RH, Kase NG. *Clinical Gynaecological Endocrinology and Infertility*. 6th ed. Baltimore: Lippincott Williams & Wilkins, 1999: 428-432.
15. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. *Lancet* 1987; 2: 645-647.
16. Cooper GS, Thorp JM Jr. FSH levels in relation to hysterectomy and to unilateral oophorectomy. *Obstet Gynecol* 1999; 94: 969-972.
17. Kovacs P, Stangel JJ, Santoro NF, Lieman H. Successful pregnancy after transient ovarian failure following treatment of symptomatic leiomyomata. *Fertil Steril* 2002; 77: 1292-1295.