

Uterine Artery Embolization Treatment of Uterine Fibroids: Effect on Ovarian Function in Younger Women

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PURPOSE: To evaluate how uterine artery embolization (UAE) treatment for uterine fibroids (UF) affects ovarian function in young Middle Eastern women.

MATERIALS AND METHODS: In this prospective study, 32 patients (mean age, 34 y; range, 26–45 y) underwent UAE treatment of symptomatic fibroids. Serum follicle-stimulating hormone (FSH) levels were measured before and after the embolization treatment. Preprocedural levels were determined on the second day of the menstrual cycle. Post-procedural levels were measured 3 months and 6 months after embolization. A detailed history of menstrual cycles was obtained before and after UAE.

RESULTS: Thirty premenopausal patients had normal menses before UAE. Mean FSH levels before and 3 months after UAE were 6.83 IU/L \pm 1.8 and 6.99 IU/L \pm 1.67, respectively ($P = .66$). Normal menstruation resumed 2–3 months after the procedure. In two perimenopausal women, who had irregular menses and decreased ovarian reserve, mean FSH levels increased transiently from 22 and 30 IU/L to 40 and 48 IU/L, respectively, 3 months after UAE; they developed transient amenorrhea.

CONCLUSION: In this study, UAE had no clinically relevant adverse effects on normally functioning ovaries and could be used safely in the treatment of symptomatic fibroids in premenopausal women. Larger studies are required for further support of this observation.

Index terms: Fibroid • Ovary, function • Uterine arteries, embolization • Uterus, neoplasms

J Vasc Interv Radiol 2002; 13:1017–1020

Abbreviations: FSH = follicle-stimulating hormone, UAE = uterine artery embolization, UF = uterine fibroids

UTERINE fibroids (UF) are the most common type of pelvic tumor and 20%–40% are present in women aged 35 years and older. The traditional treatment for symptomatic fibroids is hysterectomy (1–3). Myomectomy has

been used in women who wish to preserve future childbearing, but has been associated with greater risks (eg, greater loss of blood, longer procedure, longer hospital stay, and higher postoperative morbidity) than hysterectomy. Moreover, after myomectomy, recurrence of fibroids can occur in as many as 20%–25% of patients (1–3). During the last 5 years, uterine artery embolization (UAE) has emerged as a successful alternative to surgical treatment (4–6). However, controversy still surrounds this procedure because of a number of concerns, including the postprocedural risk of ovarian failure. The primary objective of this study was to address this concern, namely, ovarian dysfunction as a result of UAE, in response to several recent case reports that indicated tran-

sient or permanent ovarian failure after this procedure (6–10). Because a gradual rise in plasma gonadotropin levels is the earliest evidence of ovarian failure (11,12), follicle stimulating hormone (FSH) was used as the key indicator of declining ovarian function.

MATERIAL AND METHODS

Patients

Between October 1997 and March 2001, 32 women (mean age, 34 y; range, 26–45 y) underwent UAE treatment of symptomatic fibroids. Patients were included if they had symptomatic fibroids, were pre- or perimenopausal, and had no desire for future pregnancy.

Patients were referred after a gynec-

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None of the authors has identified a conflict of interest.

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gynecologist determined that symptoms were mainly related to UF and required invasive intervention. Informed consent was obtained from each patient. The study was approved by the Institutional Review Board for evaluating human research in Kuwait. Baseline workup included bimanual pelvic examination (performed by the same gynecologist), measurement of the levels of FSH, and a combination of endovaginal and transabdominal ultrasonography (US) performed by an experienced radiologist to determine the number and size of fibroids.

Options of intervention (UAE, myomectomy, hysterectomy), goals, and possible complications were explained in detail to the patients. Patients were informed that long-term effects of UAE on fertility have not been established because it is a relatively new procedure that not enough patients who desire future fertility have undergone. They were advised not to attempt to conceive after the procedure.

Study Endpoints

The primary endpoint of the study was to determine the effect of UAE on ovarian function. The secondary endpoint was to establish the efficacy of UAE for the treatment of UF.

Procedure

The right common femoral artery was accessed with use of the Seldinger technique. Pelvic arteriography was performed on a digital angiographic unit (Advantax LCA; GE Medical Systems, Milwaukee, WI). Selective catheterization of the contralateral uterine artery was performed with use of a 4-F, C-1 glide catheter (Terumo, Somerset, NJ). In nine patients, a turbo Tracker-18 microcatheter (Boston Scientific/Medi-tech, Galway, Ireland) was employed in a coaxial fashion to secure a more distal position in the left uterine artery to start embolization.

A Waltman loop was formed with a 4-F, C-1 catheter and used to selectively catheterize the ipsilateral uterine artery. In 29 patients, a kink was encountered and the catheter was changed to a 5-F, C-1 glide catheter (Cordis Europa, Roden, The Netherlands). A Waltman loop was formed and used to catheterize the anterior

division of the ipsilateral internal iliac artery. A Tracker-18 microcatheter-seeker combination was used for subselective catheterization and embolization of the ipsilateral uterine artery.

Polyvinyl alcohol particles (500–700 μm ; Cook, Bloomington, IN) were used for embolization in all patients. An average of 600 mg (400–800 mg) was used for bilateral embolization. The embolization endpoint was the cessation of antegrade blood flow in the uterine artery.

Immediately before starting the procedure, patients were administered 1 g of intravenous Rocephin (Roche, Basel, Switzerland) and a Foley catheter was inserted and not removed until 6 hours after the procedure. Conscious sedation was achieved with intravenous midazolam (2–5 mg; Roche) and fentanyl (50–125 μg ; Janssen Pharmaceutica, Beerse, Belgium). The procedure was completed in an average of 90 minutes (range, 45–120 min) and an average of 120 mL (60–150 mL) of Omnipaque (240 mgI/mL; Nycomed, Cork, Ireland), diluted in saline solution, was used. All procedures were performed by the same interventional radiologist (A.A.).

The procedures were uneventful except for one, in which the patient developed a groin hematoma. She did not require blood transfusion and the hematoma resolved spontaneously.

Follow-up

Patients underwent gynecologic and a combination of transabdominal and endovaginal US on follow-up examinations performed 1 and 6 weeks, and 3 and 6 months after embolization. US was performed by an experienced body-imaging-trained radiologist, who was blinded to the study. Number, size, and volume of fibroids were recorded and compared with preprocedural measurements. Levels of FSH were obtained on the second day of menstrual cycles 3 and 6 months after embolization. Patients were monitored for development of symptoms of vasomotor instability ("hot flashes"), and resumption of menstruation.

Statistical Analysis

The formula for a prolate ellipsoid (volume = $0.5233 \times D1 \times D2 \times D3$),

where D1, D2, and D3 are the three maximum longitudinal, anteroposterior, and transverse diameters, was used to calculate the UF volumes (13). The data were analyzed with use of the SPSS software package (SPSS, Chicago, IL). Continuous variables were expressed as means \pm SD. The paired Student *t* test was used to compare changes in serum FSH levels at 3- and 6-month follow-up. The Wilcoxon signed-rank test was used to compare percent reduction in fibroid volumes. *P* values < .05 were considered significant.

RESULTS

Thirty-two patients (mean age, 34 y; range, 26–45 y) were included in this study. Symptoms were excessive menstrual bleeding ($n = 8$), pelvic pain or pressure ($n = 10$), or both ($n = 14$). Nine patients were anemic because of menorrhagia. Two patients had irregular menstrual periods with vague symptoms of insomnia and decreased energy. Four patients had undergone previous myomectomies with recurrence of fibroids. Seven patients had undergone previous cesarean sections and one had left ovarian resection because of torsion of an ovarian cyst.

Patients underwent technically successful embolization of both uterine arteries. All patients had at least 30% reduction in fibroid size. The most significant difference was a decrease in fibroid volume from a median of 283.5 cm^3 (range, 140–500 cm^3) to 151 cm^3 (range, 0–300 cm^3 ; $P < .001$) at 6-month follow-up US.

Thirty patients had normal baseline ovarian function, including normal menstrual cycles and mean FSH levels (\pm SD) of 6.8 IU/L \pm 1.8. At 3- and 6-month follow-up, FSH levels in these patients were 6.99 IU/L \pm 1.67 ($P = .66$) and 6.7 IU/L \pm 1.18 ($P = .62$), respectively. Normal menstrual cycles resumed 2–3 months after the procedure. Two perimenopausal women, who had irregular menses before UAE, had high baseline FSH levels (30 IU/L and 22 IU/L, respectively). At 3-month follow-up, FSH levels had increased to 48 IU/L and 40 IU/L, respectively, and patients reported amenorrhea and hot flashes. At 6-month follow-up, FSH had returned to baseline levels (26 IU/L and 27 IU/L, re-

spectively). This indicated transient ovarian dysfunction. In these two patients, normal menstrual cycles resumed 8 and 10 months after the procedure, respectively.

DISCUSSION

UAE is not a new procedure. It has been used for treatment of obstetric emergencies for more than 20 years. UAE has been considered to be a safe, well-tolerated, and effective procedure. During this time, it was not reported to adversely affect menses or subsequent pregnancies (14–20). However, with the most recent use of UAE in treating fibroids, cases of transient and permanent amenorrhea have been reported (6–10). There is concern that UAE might adversely affect ovarian function, an issue that we address in this study.

The purpose of this study was to evaluate ovarian function before and after UAE treatment of UF. We had no specific age criterion for choosing patients, but patients were asked not to attempt to conceive after the procedure. Middle-Eastern women usually complete child-bearing at a young age. Therefore, the usual unintentional bias against choosing younger patients with fibroids did not exist in this study and most of our patients were between 30 and 35 years of age. All except two, who were perimenopausal, were considered premenopausal.

Perimenopause is an ill-defined interval that begins with sporadic abnormalities or failure of ovulation (manifesting as intermittent FSH elevation) and progresses to end stage persistent anovulation—at a highly variable rate (11). Menstrual irregularities are not uncommon during this period (11,12). Although absolute FSH values could be misleading in distinguishing premenopausal women, it appears that a cutoff point of 24 IU/L is reasonable from a clinical standpoint (11,12,21). Persistent anovulation and cessation of menstruation for at least 1 year defines menopause and is associated with substantially increased FSH levels, usually greater than 40 IU/L (11,12).

In this study, we found that only the two perimenopausal women, who had proven decreased ovarian reserve before the procedure (higher FSH and irregular menses), were adversely af-

ected. They experienced transient ovarian dysfunction manifested by transient amenorrhea and a transient mild elevation of FSH level. However, premenopausal patients, who had normal menstrual and hormonal patterns, experienced no change after the procedure.

To explain the postprocedural transient ovarian dysfunction in some perimenopausal women, we had the following hypotheses: (i) patients who had higher baseline FSH levels are likely to have worse baseline ovarian function and, therefore, a higher sensitivity to vascular insults; (ii) patients with failing ovaries could have compensatory enlargement of the ovarian branch of uterine artery, which predisposes them to a higher number of embolization particles deposited at these ovarian branches and a higher risk of postprocedural ischemia (this is only theoretical because we have no angiographic proof); (iii) the perimenopausal phase is an ill-defined period clinically and hormonally, with erratic secretion of estradiol and intermittent worsening of ovarian function and FSH elevation. Could the minimal change of hormonal levels in some of the perimenopausal women be just a natural phenomenon, regardless of UAE?

We believe that our study, in agreement with two other reports (22,23), confirms that younger patients (younger than 40 years) are more likely to have normal ovarian function that would not be compromised by UAE. Although Chrisman et al (22) attempted to exclude perimenopausal women (with use of menstrual history and FSH criteria), age remained an important factor in determining the end result after UAE, with women older than 45 years at higher risk of ovarian failure after UAE. Therefore, age, menstrual history, and FSH levels should be considered in predicting ovarian dysfunction after UAE.

We conclude that UAE appears to be a safe procedure and women with normal ovarian function are not likely to develop postprocedural ovarian failure. However, because the number of our patients, especially those who were perimenopausal, was small, we believe that larger multicenter studies are required to confirm our observations.

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