Effects of Utero-ovarian Anastomoses on Basal Follicle-stimulating Hormone Level Change after Uterine Artery Embolization with Tris-acryl Gelatin Microspheres

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PURPOSE: To assess the prevalence of anastomoses between uterine and ovarian arteries on angiography and their impact on changes in basal follicle-stimulating hormone (FSH) level after uterine artery embolization (UAE).

MATERIALS AND METHODS: Consecutive premenopausal women who underwent UAE for symptomatic uterine leiomyomata according to a uniform embolization technique with tris-acryl gelatin microspheres at a single institution were included in the study. Basal FSH levels before UAE and 6 months after UAE were compared for patients with and without anastomoses between uterine and ovarian arteries on angiography.

RESULTS: Among 124 patients included in the study (mean age, 43.1 ± 5.7 years), patent anastomoses between the uterine and ovarian arteries were detected by angiography in 55 patients (44.4%). Overall, 11.3% of 124 patients showed an increase in basal serum FSH level of greater than 20 mIU/mL after UAE. In patients with utero-ovarian anastomoses, 18.2% showed an increase of greater than 20 mIU/mL after UAE, compared with 5.8% of patients without such anastomoses (P = .03). Mean basal FSH increase after UAE in patients with anastomoses was 8.4 ± 20.2 mIU/mL, compared with 2.7 ± 10.6 mIU/mL in patients without anastomoses (P = .047). Among patients with anastomoses, the 50- to 54-year age group had the highest percentage of patients with an FSH increase greater than 20 mIU/mL (50.0%) after UAE, followed by patients in the 45- to 49-year age group (15.4%).

CONCLUSIONS: Angiographically detected anastomoses between the uterine artery and the ovarian artery are not uncommon. UAE in patients with anastomoses is associated with a greater risk of significant increase of basal FSH level than in UAE in patients without anastomoses. The pathophysiologic processes resulting in change of FSH level may be a reflection of diminished ovarian function, but further study is warranted to delineate the precise mechanism.

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Abbreviations: FSH = follicle-stimulating hormone, PVA = polyvinyl alcohol, UAE = uterine artery embolization

STUDIES of preservation of ovarian function and fertility are increasingly

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important as uterine artery embolization (UAE) is gaining in popularity. The reported incidence of ovarian failure or clinical amenorrhea after UAE has been low, ranging from zero to 5% in large series (1–6). Spies et al (5) demonstrated that basal follicle-stimulating hormone (FSH) levels, as a reflection of ovarian function, showed an increase to more than 20 mIU/mL after UAE in 6.4% of 63 patients, all between 45 and 50 years of age, and only one of 63 patients showed an increase of more than 20 mIU/mL after UAE. Successful pregnancies after UAE have been reported (7,8); however, a higher ovarian failure rate of 14% has also been reported in one case series (9). Possible causes of amenorrhea or ovarian failure after UAE are thought to include exposure to radiation, inadequate blood flow to the ovaries, inadvertent ovarian embolization via utero-ovarian anastomoses, hormonal effects after an embolization procedure for uterine leiomyomata, and worsening ovarian reserve in women older than 45 years of age. Although the exact causes are not yet fully understood, one of the leading hypotheses is that embolization of ovarian parenchyma occurs during
UAE and leads to ovarian failure (5,9–14).

Natural anastomoses between the uterine and ovarian arteries are known to exist and have been defined in cadaver studies (15,16). Natural anastomoses in patients without gynecologic disease remain minute in caliber, making them very difficult to visualize on imaging studies or angiograms. An anastomosis becomes hypertrophied in the presence of uterine or ovarian lesions to supplement increased vascular demands (17,18). Karlsson et al (18) showed anastomoses in 46.9% of 32 patients studied by angiography when benign ovarian lesions were present. Razavi et al (19) also demonstrated anastomoses angiographically in 46.0% of 76 patients with uterine leiomyomata. However, the effect of a hypertrophied natural anastomosis combined with UAE on ovarian function has not been carefully studied.

The objective of this study was to assess utero-ovarian anastomoses by angiography in patients with uterine leiomyomata and their impact on ovarian function after treatment with UAE.

MATERIALS AND METHODS

Patient Group

A study was conducted among all patients treated with UAE for symptomatic uterine leiomyomata between 2001 and 2004 at our institution. Consecutive patients treated with UAE by a single operator (H.S.K.) according to a uniform embolization technique with tris-acryl gelatin microspheres (Embosphere; Biosphere Medical, Rockland, MA) as the embolization agent were included in the study. The study inclusion criteria were set to reduce potential bias from different embolization techniques by several operators and different embolic materials. For inclusion in this study, participants had to be premenopausal women 30–54 years of age, with symptomatic uterine leiomyomata, regular menses, and available serum FSH test results 3 days before UAE and 6 months after UAE. Only women with basal FSH levels no greater than 25 mIU/mL measured within 3 months before UAE were included. Women with amenorrhea for more than 3 months in the 6 months before UAE, those receiving birth control pills or gonadotropin-releasing hormone agonists (ie, leuprolide acetate), and those undergoing hormone replacement therapy were excluded from this study. Patients who received UAE before hysterectomy or myomectomy or who underwent repeat UAE or ovarian artery embolization were also excluded. The institutional review board granted authorization to collect data prospectively on patients treated with UAE and approved the study. All patients had a thorough clinical evaluation by gynecologists and interventional radiologists before UAE, including basal serum FSH levels. Basal FSH measurements were obtained on day 3 of the menstrual cycle. Benefits and possible risks were discussed with patients before informed consent was obtained. Presence of utero-ovarian anastomosis on angiography and basal FSH levels before UAE and 6 months after UAE were recorded prospectively and analyzed.

Embolization Technique

Before UAE, patients received 12.5 mg of dolasetron mesylate (Anzemet; Aventis, Bridgewater, NJ) for possible nausea and 1 g of cefazolin (Baxter, Deerfield, IL) as a prophylactic antibiotic. Intraoperatively, patients received intravenous midazolam (B lidford Labs, Bedford, OH) and fentanyl (Baxter) for moderate sedation and 60 mg of intravenous ketorolac (Abbott Laboratories, North Chicago, IL) to counteract inflammation and cramping.

UAE was performed via single right common femoral artery access. After initial aortography with use of a 5-F OmniFlush catheter (Angiodynamics, Queensbury, NY), the left internal iliac artery was selected with a 5-F Glide Bentson-Hanafee-Wilson JB-1 or hockey stick–shaped catheter (Terumo, Somerset, NJ).

In an attempt to embolize the distal peritrofymoma plexus and to avoid embolization of vaginal, cervical, and vesical branches, the ascending portion of the uterine artery was subselected with a 3-F Renegade Hi-Flo Microcatheter (Boston Scientific, Natick, MA). Whereas the ascending portion of the uterine artery was subselected with a 3-F microcatheter, the 5-F catheter was kept in the internal iliac artery, leaving cannulation of the uterine artery with only a 3-F microcatheter. This preserved the natural uterine blood flow, which could carry particles to the peritrofymoma plexus distally. It also minimized the risk of uterine artery spasm.

We performed uterine arteriography with dynamic contrast material administration by a power injector at 3 mL/sec for 3–5 seconds for a total of 9–15 mL of contrast material administered at 800 psi (2) and a rate increase of 0.3 seconds via a 3-F Renegade Hi-Flo Microcatheter (Boston Scientific). We injected 9–15 mL of iodinated contrast agent (Omnipaque 350; Nycomed, Princeton, NJ) depending on the size of uterine arteries to fill and cause reflux in any significant collateral vessels, including anastomoses between uterine and ovarian arteries (Figs 1–3). Power injection caused sustained injection of contrast agent, which also helped fill collateral vessels. These techniques allowed contrast visualization of significant utero-ovarian arterial anastomoses. A power injector was used for uterine arteriography, rather than hand injection, to maintain a uniform protocol, thereby eliminating operator-dependent variability.

Uterine leiomyomata were embolized with 500- to 700-μm tris-acryl gelatin microspheres (Embosphere; Biosphere Medical). When an anastomosis was detected between the uterine and ovarian arteries during selective angiography, careful slow embolization was initially performed with 500- to 700-μm microspheres. As peritrofymoma contrast staining increased and main uterine artery resistive pressure increased, we switched to larger-sized (700- to 900-μm or 900- to 1,200-μm) microspheres for embolization. Slow and careful embolization with larger microspheres was attempted to avoid nontarget embolization of the ovarian parenchyma. We tried to avoid any reflux via an anastomosis during embolization. However, although reflux to the anastomoses was unavoidable at times to achieve the embolization endpoints, embolization was aborted when reflux reached the ovarian parenchyma. The endpoints of embolization were occlusion of the peritrofymoma plexus of
known leiomyomata, stasis of flow in the distal part of the uterine artery, and reduced flow in the proximal part of the main uterine artery. Attention was given to the maintenance of patency of the main uterine artery.

With use of a 5-F Glide Bentson-Hanafee-Wilson JB-1 or hockey stick–shaped catheter (Terumo), a Waltman loop was created and the right internal iliac artery was selected. The ascending portion of the right uterine artery was subselected with a 3-F Renegade Hi-Flo Microcatheter (Boston Scientific). Uterine arteriography and embolization were performed by the same technique as in the left uterine artery.

After UAE, patients were admitted to the interventional radiology service for overnight observation at the hospital. Patients were monitored clinically and underwent basal FSH level measurements at follow-up visits.

Study Endpoints

The study endpoints were (i) no significant change in basal FSH levels 6 months after UAE or (ii) basal FSH level increase less than 20 mIU/mL after UAE. An increase in FSH level greater than 20 mIU/mL was considered as a significant marker of transition to the menopausal state. This value was arbitrary but was selected to aid comparison with the findings of the first reported study of ovarian function after UAE (5) and was considered a satisfactory indicator for the perimenopausal state by laboratories used for our FSH determinations.

Clinical records, angiographic images, and FSH levels before and after UAE were studied.

Minor complications were defined as temporary and self-limiting symptoms without any clinical sequelae, and major complications were defined as those requiring further intervention and/or hospitalization or those producing permanent sequelae (20).

Statistical Analysis

Statistical analysis was performed with SPSS software (version 11.0; SPSS, Chicago, IL). Continuous variables are reported as means ± SD. Comparisons were performed with the Student t test. P values less than .05 (two-tailed) were considered to indicate statistically significant differences.

RESULTS

In all, 124 patients who met the inclusion criteria were included in the study. Anastomoses between uterine and ovarian arteries were demonstrated by angiography in 55 patients (44.4%). Of these 55 patients (mean
age, 43.6 ± 6.2 y) with anastomoses, 18 (32.7%) had bilateral anastomoses, 22 (40.0%) had anastomoses on the left, and 15 (27.3%) had anastomoses on the right.

There were no significant differences in age or ethnicity between the two groups (Table 1). There were no significant differences in mean basal serum FSH levels between the two groups: the mean basal FSH level in patients with anastomoses was 7.4 mIU/mL and that in patients without anastomoses was 7.3 mIU/mL (Table 1).

Table 2 shows mean embolic particle volumes and changes in serum FSH levels 7 months after UAE. Mean embolic volume used for patients without anastomoses was 11.3 mIU/mL, whereas that of patients without anastomoses was 10.0 mIU/mL (P = .059). Mean increase in basal FSH level after UAE was 8.4 mIU/mL in patients with anastomoses and 2.7 mIU/mL in patients without anastomoses (P = .047).

In the evaluation of individual basal FSH levels, it was noted that there was a significant difference between groups in the number of patients who showed an increase in basal FSH level of more than 20 mIU/mL after UAE (Table 2). Ten patients with anastomoses (18.2%) showed an increase in basal FSH level greater than 20 mIU/mL, compared with four patients without anastomoses (5.8%; P = .030).

By age group, a trend toward an increase in basal FSH level after UAE with increasing age was observed. In patients with anastomoses, 50% of patients in the 50- to 54-year age group showed a basal FSH level increase of greater than 20 mIU/mL, followed by 15.4% in the 45- to 49-year age group. In patients without anastomosis, all four patients with an increase in basal FSH level greater than 20 mIU/mL were 40–49 years of age (Table 3).

Of the 124 patients, 114 (91.9%) stayed in the hospital overnight for observation. Ten patients (8.1%) stayed in the hospital 2 days or more. Mean hospital stay was 1.1 days. There were no immediate major perioperative complications. Three patients (2.4%), two with anastomoses and one without, experienced postembolization syndrome, which required readmission to the hospital. These three patients were treated conservatively with intravenous hydration, pain medication, and empiric antibiotic treatment without clinical sequelae. No evidence of infection or pyometrium was noted. No emergent surgical procedures were performed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Demographics</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>With Anastomosis (n = 55)</td>
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<tr>
<td>Mean age ± SD (y)</td>
<td>43.6 ± 6.2</td>
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<tr>
<td>Age &lt; 45 y</td>
<td>30 (54.5)</td>
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<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>25 (45.5)</td>
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<tr>
<td>White</td>
<td>29 (52.7)</td>
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<tr>
<td>Other</td>
<td>1 (1.8)</td>
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<tr>
<td>Mean Basal FSH level before UAE (mIU/mL)</td>
<td>7.4 ± 9.3</td>
</tr>
<tr>
<td>Basal FSH level &lt;10 mIU/mL before UAE</td>
<td>43 (78.2)</td>
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Note.—Values in parentheses are percentages.
DISCUSSION

We were able to demonstrate utero-ovarian anastomoses by selective uterine angiography in 44.4% of 124 patients with uterine leiomyomata who were undergoing UAE. We believe the detection of utero-ovarian anastomoses on angiography is possible in patients with symptomatic leiomyomata because existing anatomic anastomoses undergo hypertrophy over time as a result of increased demand for blood flow to supply leiomyomata.

Increasing serum FSH levels have been considered the earliest hormonal sign of menopause, reflecting a worsening of ovarian reserve (21–23). We detected an increase in FSH levels of more than 20 mIU/mL after UAE in 18.2% of patients with anastomoses, whereas only 5.8% of patients without anastomoses showed such an increase after UAE. Because baseline demographics and basal FSH levels were not significantly different between the two groups, and the same UAE techniques and embolic materials (in similar volumes) were used for all patients, we believe the significant differences in basal FSH increase after UAE between the two groups were caused at least in part by the presence of anastomoses between uterine and ovarian arteries. Anastomoses visualized on angiography can provide a channel for embolization particles to flow and potentially embolize ovarian arterial branches or parenchyma during UAE (11). It is possible that these emboli occlude all or part of the hilar blood vessels in the ovary, causing transient ischemic effects. These ischemic events may not be histologically apparent but could cause physiologic disturbances such as decreasing estrogen production in ovarian follicles, leading to an increase in FSH production by the pituitary gland.

However, causes of ovarian failure may be multifactorial, given that 5.8% of the patients without an anastomosis on angiography did have an increase in FSH of more than 20 mIU/mL. Because there was a trend toward a greater increase in FSH with increasing age in both groups, age-related changes in blood flow or overall function may be additional factors in FSH changes after UAE. Such a trend is in accordance with the findings of previously published studies (5,24). In our age-assembled cohorts, 19.6% of women 45 years of age or older showed an increase in FSH level of more than 20 mIU/mL after UAE, whereas such a significant increase occurred in only 4.4% of women younger than 45 years of age. When patient groups with advancing age and anastomoses were combined, 50.0% of the women in the 50- to 54-year age range showed an increase in FSH that exceeded 20 mIU/mL, followed by 15.4% among 45- to 49-year-old women with anastomoses. Only 2.6% of the women younger than 45 years of age without anastomoses showed an increase in FSH level that exceeded 20 mIU/mL. Previous studies, all of which used polyvinyl alcohol (PVA) as the embolic material, reported lower rates of FSH increase after UAE (5,24–26). Spies et al (5) and Ahmad et al (24) reported FSH level increases greater than 20 mIU/mL in 6.34% of 63 patients and 3.1% of 32 patients, respectively, in women in a perimenopausal age group. Healey et al (25) and Tropeano et al (26) reported no significant FSH increase after UAE in all cohorts and young patients, respectively. These studies lack information on patent utero-ovarian anastomosis, and direct comparison with the current study is difficult.

On the basis of our observations, a hypothesis of ovarian parenchymal embolization in patients with low ovarian reserve can be made in perimenopausal women with patent utero-ovarian anastomosis. Histologic studies that used tris-acryl gelatin microspheres have documented that the embolization particles can be found in the ovaries (11,27,28). Two of the studies reported the size of microspheres used: 500–700 μm (27) and 500–700 μm and 700–900 μm (11), respectively. One may speculate that, because older women have decreasing numbers of ovarian follicles, their ovarian tissue may be more sensitive to slight ischemic changes with damage to the few existing follicles, without the creation of apparent ovarian parenchymal infarcts. Such changes could give rise to increased FSH levels than in younger women, who have a larger number of viable follicles and therefore greater ovarian reserve. To reduce the risk of such unintended embolization of the ovarian parenchyma, Pelage et al (29) advocated the use of 700–900-μm microspheres in the presence of anastomoses. In our study, we also used 700–900 μm and 900–1,200 μm microspheres in patients with utero-ovarian anastomoses. Histopathologic studies with
careful evaluation of adnexa are warranted. However, other causes may also contribute, such as radiation, hormonal changes, endometrial atrophy, or unknown factors.

Potential occlusion of anastomoses that are the sole vascular supply for ovarian parenchyma in the absence of perfusion from the ovarian artery remains a topic to be investigated. Ryu et al (13) demonstrated that the initial transient loss in arterial supply to the ovary on sonography after UAE was compensated for later, as documented on follow-up sonography. Therefore, ischemic infarction of the ovary may not occur in the short term. However, such decreases in perfusion in volume or pressure may contribute at least partially to ovarian failure in the months after UAE.

One unanswered question concerns the effects of the type of embolic particle used, given that the significant FSH change may be particle related. To our knowledge, no published pathologic study has shown PVA particles in ovarian parenchyma after UAE. Recent histopathologic studies of surgical samples after UAE with PVA showed no PVA particles in ovarian parenchyma, although PVA particles in the mesosalpinx were noted in one case in each of two studies (30,31). Because PVA particles proximally aggregate and cause embolization more proximally than microspheres (32), it can be theorized that PVA particles are associated with lower risk of ovarian embolization compared with microspheres. Whether such proximal embolization with PVA particles translates to a lower risk of a significant FSH increase after UAE needs further study.

A limitation of the present study was the potential inability to detect anastomoses in some patients with significant hypervascular leiomyomata. Despite high-volume dynamic contrast agent administration with a power injector, significant flow to leiomyomata in some patients may have prevented filling of contrast agent and visualization of some potentially significant anastomoses. In addition, operator bias cannot be entirely excluded despite standardization of embolization technique. Because the uterine angiogram is obtained before UAE, knowing whether utero-ovarian anastomoses were present might have affected the treatment to some extent. However, the use of a significantly greater embolic particle volume in this study in patients without utero-ovarian anastomoses than in patients with anastomoses further distinguishes the role of anastomoses as potential channels for particulate passage.

The last limitation of the study concerns the assessment of basal serum FSH levels as the study endpoint for ovarian failure. We recognize that other hormonal markers, such as serum inhibin A, B or dimeric glycoprotein anti-Müllerian hormone, may be more sensitive reflectors of the status of ovarian function (33–36). However, basal FSH testing is relatively inexpensive and can be performed easily, whereas inhibin A, B and anti-Müllerian hormone determinations are relatively expensive assays that are not available at our institution, making them less feasible and practical. Other sensitive histochemical techniques might demonstrate ischemic changes, but these studies usually require an invasive procedure to obtain ovarian biopsy specimens. Future studies that include measurement of inhibin A, B and anti-Müllerian hormone levels before and after UAE would be helpful.

Although the causes of ovarian failure after UAE treatment may be multifactorial and still require further investigations, our results indicate that utero-ovarian anastomoses appear to be an important contributor to increases in basal FSH levels after UAE with tris-acryl microspheres. Our findings also pose a challenge in the treatment of symptomatic uterine leiomyomata in premenopausal patients with utero-ovarian anastomoses. Less than adequate embolization to avoid premature worsening of ovarian function might lead to incomplete infarction of intended uterine leiomyomata, potentially resulting in symptom recurrence (37). Further studies that involve different types of particles, different embolization endpoints, and/or microcoil embolization of utero-ovarian anastomoses are needed.

In conclusion, we have demonstrated that the presence of patent anastomoses during UAE is associated with significant increases of basal FSH levels. A secondary risk factor for the increase in basal FSH level is advancing age at the time of UAE.

References


