Ovarian Function after Uterine Artery Embolization for Leiomyomata: Assessment with Use of Serum Follicle Stimulating Hormone Assay

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PURPOSE: To determine if uterine artery embolization (UAE) for leiomyomata causes a change in ovarian function as measured by serial basal follicle stimulating hormone (FSH) assay.

MATERIALS AND METHODS: Sixty-three patients undergoing UAE for symptomatic leiomyomata had blood samples obtained on day 3 of a menstrual cycle before UAE and on day 3 during menstrual cycles 3 and 6 months after treatment. Analysis of variance was used to detect differences in FSH levels among age groups at each interval. Repeated measures analysis of variance was used to determine if individual mean change occurred for the group as a whole and for each age group. Onset of new menopausal symptoms was compared between groups with use of the χ^2 test.

RESULTS: There was no significant change in basal FSH levels for the group as a whole ($P = .16$), but there was a statistically significant difference when age groups were compared ($P = .03$). Individual change of >2 SD from baseline mean FSH level occurred at 6 months in seven patients, all 45–50 years of age. Four of these patients (15% of patients over age 44) had FSH levels increase to more than 20 IU/L. χ^2 analysis did not reveal any difference among the groups studied in the onset of menopausal symptoms.

CONCLUSIONS: Most patients had no change in ovarian function as measured by basal FSH after UAE. For patients aged 45 or older, there is approximately a 15% chance of an increase in basal FSH into the perimenopausal range.

Index terms: Fibroids • Uterine arteries, embolization • Uterus, neoplasms

J Vasc Interv Radiol 2001; 12:437–442

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

IN recent years, uterine artery embolization (UAE) for leiomyomata has emerged as an alternative to myomectomy and hysterectomy, with a number of studies demonstrating that the procedure is safe and effective (1–6).

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However, there have been reports of amenorrhea occurring after the procedure (1,5,7). Most of these patients have been near the age of menopause, suggesting that minor changes in ovarian perfusion might cause dysfunction in ovaries with minimal residual function. Alternatively, it is possible that there might be a subclinical effect on ovarian function in patients of all ages that is only apparent in patients near menopause. One measure of ovarian function (or ovarian reserve) is follicle-stimulating hormone (FSH), with a higher serum level corresponding to a decrease in residual ovarian function. Basal FSH (a basal sample is obtained on day 3 of the menstrual cycle) level is commonly used as an indicator of fertility (8–10). In addition, serum FSH levels are known to increase progressively in women during their 40s (11).

We undertook this study to determine if uterine embolization for leiomyomata causes a change in ovarian function as measured by basal FSH levels before and after treatment.

MATERIALS AND METHODS

In October of 1998, we began to recruit patients for this study. The protocol was approved by the institutional review board as an amendment of our existing procedure protocol.

Table 1
FSH Results Pre- and Postembolization by Age Group

	FSH Level (IU/L)	*n*
Baseline FSH (overall)	8.1 ± 3.6	63
Age 30–39 y	7.3 ± 2.4	17
Age 40–44 y	8.1 ± 2.9	18
Age 45–50 y	8.5 ± 4.5	28
3-month FSH (overall)	9.5 ± 5.5	56
Age 30–39 y	6.5 ± 1.5	14
Age 40–44 y	9.1 ± 4.1	16
Age 45–50 y	11.2 ± 6.8	26
6-month FSH (overall)	9.2 ± 5.8	50
Age 30–39 y	7.0 ± 1.9	15
Age 40–44 y	8.3 ± 3.5	14
Age 45–50 y	11.5 ± 7.8	21

Note.—Values expressed as means ± SD where applicable.

Each patient provided their informed consent at the time of enrollment.

The population from which the study participants were chosen was the group of patients presenting for UAE at one institution. Only patients with symptomatic fibroids were treated. These symptoms include heavy menstrual bleeding, pelvic pain or pressure, dyspareunia, or urinary or rectal pressure. In each case, the size and location of the fibroids must have correlated with the symptoms and must have been the most likely cause of the symptoms. Postmenopausal patients were excluded, as were those taking exogenous hormones those with continuous or intermittent bleeding (such that a defined menstrual period could not be identified). From the qualified patients, those willing to be monitored for one menstrual period before the procedure and periods 3 and 6 months after the procedure were recruited for the study. Sixty-three patients were initially recruited to participate in the study and had their basal FSH level recorded. During follow-up, serum FSH samples were obtained in 56 patients (89%) at the 3-month interval and 49 (78%) at the 6-month interval. Questionnaire follow-up was obtained in 59 patients (94%) at 3 months and 48 patients (76%) at 6 months.

During one menstrual period before the procedure (usually the period immediately preceding the procedure), a blood sample for serum FSH was obtained on day 3 of the period, which established the basal FSH level. If day 3 occurred on a Sunday, a day 4 sample was obtained. To ensure high participation and accurate sampling, a phlebotomist obtained the samples in either the patient's home or office. In a few cases, the patient chose to come to our office to have the sample obtained. Regardless of the location of the sampling, the timing was the same. The samples were obtained in the same manner during menstrual periods occurring in months 3 and 6 after embolization.

All but two samples for the group were collected and assayed by a single laboratory with use of a standard chemoluminescence methodology. Two patients were unable to use the primary laboratory as they did not live in our region. Each of these patients had their samples obtained from a hospital in their cities, with pre- and postprocedural samples obtained and analyzed in the same manner. For any individual patient, each sample was analyzed by the same laboratory.

Embolization was performed in all patients in the same manner by the same physician team. Bilateral uterine embolization was completed with catheters placed in the transverse portion of the uterine artery within the cardinal ligament. Polyvinyl alcohol particles (500–710 μm; Contour; Boston Scientific/Medi-tech, Natick MA) were used in all cases. The embolic material was flow-directed, with care taken to avoid reflux into the tubo-ovarian vascular arcade. The endpoint of embolization was occlusion of the apparent fibroid feeding vessels with stasis or near stasis of flow in the uterine arteries. Gelatin sponge pledgets or coils were not used in any case. Postprocedural care and follow-up protocol have been described previously (5).

The data were collected and analyzed initially with use of descriptive statistics to obtain the mean values, SDs, and ranges. To determine if age was factor in FSH levels before or after therapy, patients were placed in one of three age groups: 30–39 y, 40–44 y, and 45–50. This grouping was used based on a previous population study of FSH levels (11). We grouped all women under age 40 together because the reference population study had a lower age limit of 35 y. Analysis of variance was used to determine if there was a difference between groups' FSH levels at baseline and at each follow-up interval. Fisher's protected least significant difference test was used for post-hoc analysis.

The individual patient change was evaluated with use of a two-way repeated measures analysis of variance for the group as a whole and for each age group. In addition, those patients who had an increase of greater than 2 SD in FSH value were individually evaluated. A change from less than 20 IU/L to more than 20 IU/L was considered a clinically significant marker of transition to the perimenopausal state. The use of 20 IU/L as the level marking a potentially important transition was arbitrary but is based in part on local laboratory and clinical practice.

As part of the follow-up symptom analysis, patients were asked if they had developed any of seven new common menopausal symptoms. These symptoms were chosen because they are commonly associated with perimenopause and are among those used in other studies (12). They included hot flashes, mood swings, vaginal dryness, bleeding after sexual intercourse, irregular menstrual bleeding, weight gain around the hips and waist, and bleeding more often than every 3 weeks. Patients were divided into those with new symptoms and those without. A χ^2 test of independence was performed, comparing the group as a whole with those with a change in basal FSH level of greater than 2 SD of the baseline mean, and comparing patients aged 45 years or older with those 44 years or younger.

All statistical analyses were performed with use of Statview version 5.0 (SAS, Cary, NC). Statistical signif-

Table 2
Analysis of Variance by Age Group

	Sum of Squares	F Value	*P* Value
Baseline (overall)	14.7	.569	.57
Fisher's PLSD test	Mean difference		
Age 30–39 y, age 40–44 y	−.85		.49
Age 30–39 y, age 45–50 y	−1.17		.29
Age 40–44 y, age 45–50 y	−.32		.77
3-month (overall)	100.5	3.6	.03
Fisher's PLSD test	Mean difference		
Age 30–39 y, age 40–44 y	−2.59		.19
Age 30–39 y, age 45–50 y	−4.78		.01
Age 40–44 y, age 45–50 y	−2.18		.20
6-month (overall)	96	3.2	.05
Fisher's PLSD test	Mean difference		
Age 30–39 y, age 40–44 y	−1.3		.52
Age 30–39 y, age 45–50 y	−4.5		.02
Age 40–44 y, age 45–50 y	−3.1		.11
Repeated Measures Analysis of Variance			
Overall change in FSH	56.8	1.9	.16
Analysis comparing age groups	322.7	3.8	.03

icance was assumed at a *P* level of 0.05 or less.

RESULTS

The mean age was 42.9 y, with a SD of 4.5. The median age was 44 years and age ranges from 33 to 50 years.

Table 1 presents the data on the FSH assays including mean values, SDs, and patient counts. The mean baseline FSH value was 8.1 IU/L with an increase to 9.5 IU/L at 3 months after treatment. Six months after embolization, the mean value was 9.2 IU/L.

Analysis of variance comparing the values of FSH by age group is detailed in **Table 2** and presented graphically in **Figure 1**. At baseline, there was no significant difference in FSH levels among the groups ($P = .57$). At 3 months after treatment, the ANOVA did reveal a statistically significant difference among the groups ($P = .03$), with the Fisher's post hoc test revealing a significant difference between the 30–39-year and 45–50-year groups ($P = .01$) with use of pair-wise comparison. At 6 months postembolization, the differences among the groups were only marginally significant ($P = .05$) although the post hoc analysis again revealed a difference between the 30–39-year group and the 45–50-year group ($P = .02$).

In assessing individual change in FSH level, the repeated measures analysis of variance revealed no difference among the patients as a whole ($P = .16$). When comparing individual change by age group, a difference was detected ($P = .03$), indicating that change in individuals did vary significantly at different ages. However, when the analysis was repeated for the group with greatest mean change (3.1 IU/L mean change for patients aged 45–50 y), the average change for these individuals was not statistically significant ($P = .13$), perhaps reflecting the relatively small size of this group ($N = 20$).

To explore individual change more closely, we defined a potentially clinically significant change as greater than 2 SD (7.2 IU/L) increase from baseline in FSH level. Seven patients had increases greater than 7.2 IU/L from baseline at 3 months after treatment. Of these, one patient was younger than age 45 (41 y) and the others were 45 years of age or older. The results from this group are given in **Table 3**. Four of these patients, all 45 years of age or older, had an increase to >20 IU/L 3 months after therapy. One additional patient (age 48) had a rise in FSH level to >20 IU/L only at the 6-month interval. Among the patients whose FSH levels increased significantly, only one had a value at 6 months that exceeded the value obtained at 3 months and the value decreased at 6 months in four of six patients in whom data were available. Two patients in this group, including the 41-year-old, had FSH values return to near baseline at 6 months.

The onset of new menopausal symptoms are illustrated in **Figures 2 and 3**. There were no patients who became amenorrheic after therapy. The χ^2 analysis did not detect any significant difference in new symptoms between patients younger than 45 years of age and those 45 years of age or older. Similarly, there was no difference in symptoms based on FSH change at 6 months after the procedure, although a very low incidence of significant FSH change does limit the analysis.

DISCUSSION

A number of studies reporting the results of UAE for leiomyomata have shown that symptoms are controlled in 81%–94% of patients with few complications (1,2,4–6). With the growing acceptance of this therapy, it is important to study the potential effect of this treatment on reproductive function and in particular ovarian function.

The question of a potential effect on ovarian function was first raised by Bradley and Reidy (7) when one of their patients became amenorrheic after embolization. A random serum FSH level in that patient was 59.8 IU/L (well within the menopausal range), suggesting ovarian dysfunction as a likely cause of the amenorrhea. Since that time, there have been other scattered reports of amenorrhea postembolization (1,5,13). A recent study of 60 patients by Chrisman (14) detected a much higher rate of amenorrhea (15% of patients, with 43% of them over age 45) has raised additional questions about the potential effect of embolization on ovarian function (14). In most series, the incidence appears to be lower than 5% (1–6).

To assess the possible effect of UAE on ovarian function, we chose to use FSH levels obtained on day 3 of the menstrual cycle. FSH is a glycoprotein secreted by the anterior pituitary that initiates the development of follicles in the ovary. In the late luteal phase (before menses), serum FSH levels begin to rise, and this rise continues into the early follicular phase of the subsequent menstrual cycle (15). The levels obtained in the early part of the follic-

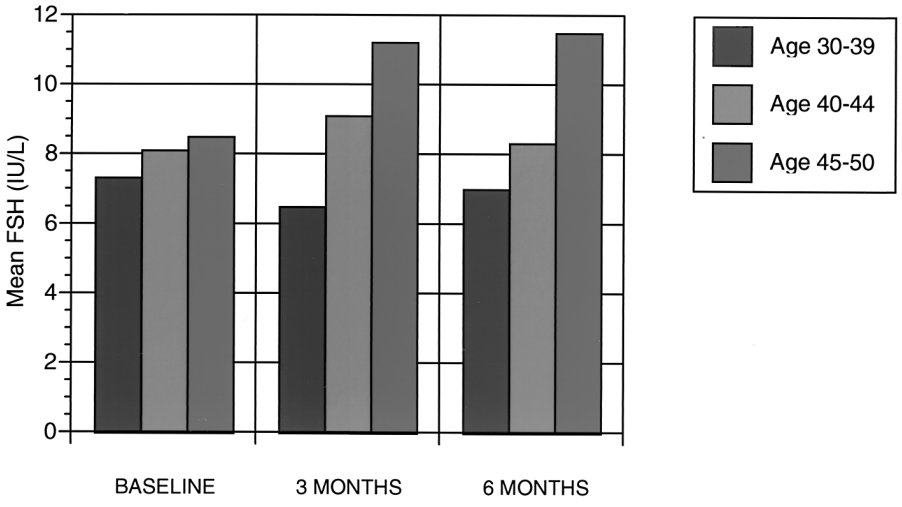

Figure 1. Results of FSH analysis by age group.

Table 3
Analysis of Individual Significant Change in FSH Level

		FSH Level (IU/L)			
Pt. No.	Age (y)	Baseline	3-month	6-month	Greatest Interval Change (IU/L)*
1	41	6.0	17.1	8.5	11.1
2	47	9.1	26.5	20.2	17.4
3	50	11.7	25.8	–	14.1
4	48	3.5	5.4	49.7	44.3
5	49	1.7	14.2	3.1	12.5
6	48	16.3	24.9	22.6	8.6
7	46	7.1	20.9	13.3	13.8
8	46	2.4	13.3	13.3	10.9

Note.—Significant change defined as greater than 2 SD from the baseline mean (SD $3.6 \times 2 = 7.2$ IU/L).
* Largest difference in FSH level between a contiguous follow-up interval.

ular phase are usually stable and repeatable in a woman in her 30s and early 40s. The cycle-to-cycle variation was determined to be 4.2 U/mL in a group of 81 patients reported by Scott (16). The variability is least pronounced in patients with basal FSH concentrations less than 15 U/mL, and, in Scott's study, it was only 2.6 U/mL. Early in the reproductive years (a patient's 20s and 30s), the ovarian follicles are receptive and relatively little FSH is required to stimulate a follicle. The measured serum levels are corresponding low, usually lower than 7 IU/L.

As a woman ages, the ovarian follicles become progressively more resistant to stimulation by FSH and there is a corresponding rise in the serum FSH level in the years before menopause. A large population-based study assessed gonadotropin levels in women between the ages of 35 and 60 (11). The geometric mean FSH concentration value was 5.74 IU/L for women aged 35–39 years, 7.13 IU/L for women aged 40–44 years, 14.34 IU/L for women aged 45–49 years, and 37.18 IU/L for women aged 50–54 years. The rise reflects the progressive resistance to stimulation of the follicles by FSH.

Serum FSH level has been used as a marker for potential success of in vitro fertilization. When obtained on day 3 of the menstrual cycle (basal level), serum FSH is a statistically significant predictor of a higher rate of success with in vitro fertilization (8–10). Although basal FSH levels can be used to estimate success for in vitro fertilization, it does not necessarily correspond to ovarian function. It is more a measure of ovarian reserve or responsiveness. There are no measures of ovarian function available that can predict the age of menopause. Because a sudden rise in basal FSH level would be unexpected (at least in women with a level lower than 15 IU/L), we chose to use serial basal FSH as a proxy for ovarian function.

For the three age groups, we saw little variation of the baseline FSH, with an overall mean of 8.1 IU/L. Although the overall repeated measures analysis did not show any change after embolization, when patients were divided by age group, a significant change was detected, with greater change in the older age groups. The individual analysis supported this finding, with changes >2 SD seen nearly exclusively in patients aged 45 years and older. Only one patient younger than age 45 had a transient significant change in FSH, which returned to within 1 SD of the mean by 6 months after the procedure. Our findings suggest that, for the large majority of women and, in particular, those younger than 45 years of age, there is no effect on ovarian function as measured by basal FSH as a result of UAE.

The mechanism for the apparent change in ovarian function that occasionally occurs after UAE is not known. We suggest three possibilities: First, because UAE requires fluoroscopic and angiographic imaging, the radiation exposure may affect the function of the ovaries. We have studied the estimated ovarian dose during UAE. With our current technique, the mean estimated ovarian dose is 9.38 cGy (17). Based on data for patients treated with pelvic radiation (18,19), it appears that the likely threshold for ovarian dysfunction is 200 cGy. Although radiation might cause temporary dysfunction in a woman with very limited residual ovarian reserve, it seems unlikely that this is the primary cause of ovarian failure. A second possibility is that embolic material can pass through the tubo-ovarian arcade to the ovary and cause a direct ovarian injury. A third possibility is that some women's ovaries may depend on flow from the uterine artery.

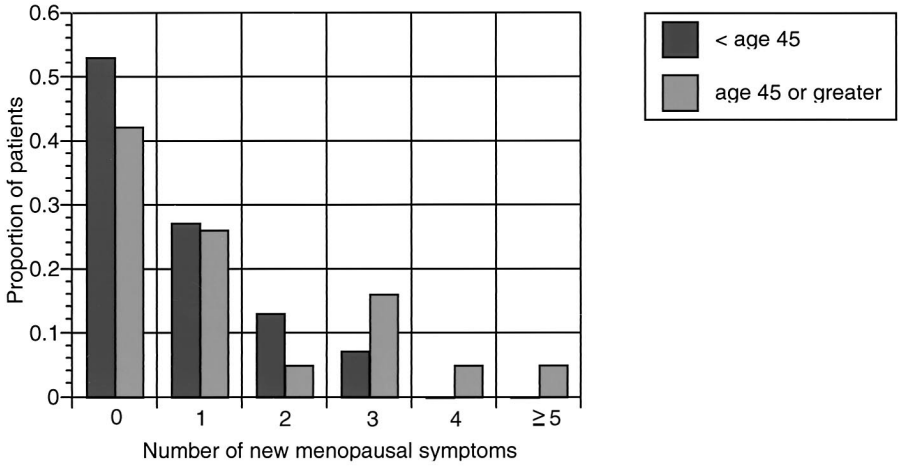

Figure 2. Proportion of patients with new menopausal symptoms by age group.

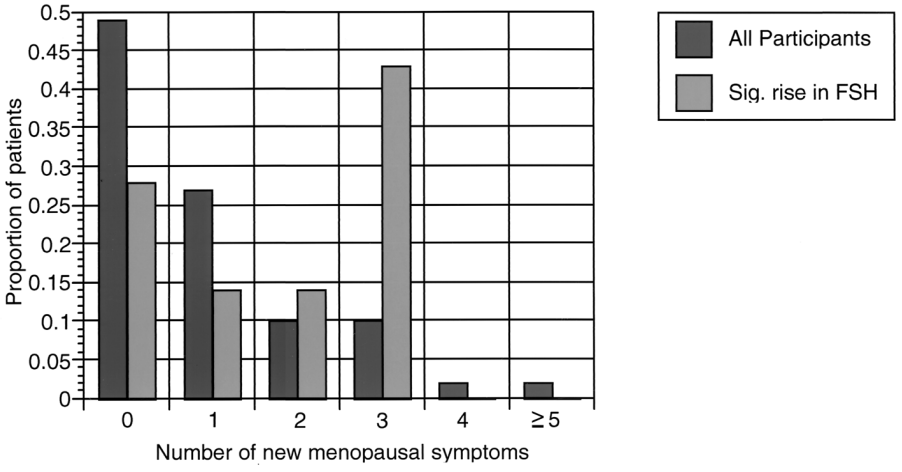

Figure 3. Comparison of patients with significant increase in FSH compared to all participants.

Therefore, the diminution in flow in the uterine arteries that results from embolization might decrease the perfusion of the ovaries. Further study is needed to determine the cause of ovarian dysfunction that can occur after embolization.

There are some weaknesses in our approach to this study. First, gonadotropins are usually secreted in a pulsatile manner, leading to some variability from minute to minute (20). However, evidence suggests that the secretion of FSH is more stable than that of luteinizing hormone and that the fluctuation is much greater after menopause. Regardless, the short-term variability could be a source of error in our analysis. We relied on the data published by Scott (16) to overcome this potential pitfall. Scott (16) found that the individual cycle-to-cycle variability for patients with basal FSH levels lower than 15 was 2.6 U/mL, whereas it was 7.3 U/mL for those with levels higher than 15. Because our group averaged 8.1 IU/L with an SD of 3.6 at baseline, allowing for a change of 2 SD from the baseline mean as a indicator of potentially significant change should exclude the change that is a result of inter-cycle variability. Although the postprocedural SD of the older group did increase to 6.8 at 3 months, it was still within our threshold of 2 SD of the baseline mean.

There was little relation between menopausal symptoms and change in FSH level. This is not surprising, because many patients experience menopausal symptoms for years before there is a measurable change in FSH, and gynecologic interventions may cause temporary vasomotor symptoms. Most patients did not experience any new menopausal symptoms and the frequency was not different for those with large changes in FSH levels. We had no patients in the study group become amenorrheic as a result of therapy.

We conclude that there is little evidence for changes in ovarian function as measured by basal FSH levels in women younger than age 45. For those 45 year of age or older, there is an approximately 15% chance of a change in basal FSH to greater than 20 IU/L after UAE. Further study is needed to determine the mechanism of this change.

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