Featured Abstract from the 2000 SCVIR Annual Meeting

The Impact of Uterine Fibroid Embolization on Resumption of Menses and Ovarian Function[1]

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Abbreviations: FSH = follicle stimulating hormone, PVA = polyvinyl alcohol, UFE = uterine fibroid embolization

PURPOSE: To evaluate the effect of uterine fibroid embolization (UFE) on menstruation and ovarian function.

METHODS: The authors performed an observational study of UFE for the treatment of symptomatic fibroids. All patients had regular predictable menses before intervention and none had clinical or laboratory findings of menopause. UFE was performed with use of standard methods with 355–700-μm-diameter polyvinyl alcohol (PVA) foam particles. The incidence of ovarian failure was calculated for women younger than 45 years and for those 45 years or older, based on retrospective stratification by age. The authors assessed statistical differences in ovarian failure between the two age groups with use of the χ^2 test.

RESULTS: Sixty-six premenopausal women (age range, 30–55 years) underwent bilateral UFE and were followed for an average of 21 weeks (range, 12–77 weeks). In 56 of 66 (85%) patients, regular menses resumed after an average of 3.5 (range, 1–8) weeks. In 10 of 66 (15%) patients, regular menses did not resume. Clinical and biochemical findings consistent with ovarian failure and presumed menopause were seen in nine of 10 patients without resumption of menses (14% of total patients). Ovarian failure occurred in nine of 21 (43%) women older than 45 years and in none of the 45 women younger than 45 years ($P < .05$). There were no differences in presenting symptoms, amount of PVA used, or fibroid size between patients who did and did not resume menses.

CONCLUSION: The majority of patients undergoing UFE will have resumption of menses, but the incidence of postprocedure ovarian failure is considerably higher than reported to date. Loss of menses induced by UFE is significantly more likely to occur in women older than 45 years.

UTERINE fibroid embolization (UFE) for the treatment of symptomatic leiomyomata is gaining acceptance as an effective alternative to traditional surgical methods. The minimally invasive nature of UFE, along with shorter recovery times, high clinical success rates, and the psychologic component of an organ-preserving treatment all appear to play a critical role in a patient's decision-making process.

A number of published reports have demonstrated the effectiveness of UFE in relieving symptomatic fibroids (1–9). However, to our knowledge, no study has directly addressed the effect of UFE on resumption of menses and ovarian function. The purpose of this investigation is to review our experience with UFE to identify its effect on menstruation and ovarian function.

MATERIALS AND METHODS

• Patient Selection

Sixty-six women with symptomatic fibroids were treated with UFE

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from April 1998 to September 1999 at two institutions. One institution was a major tertiary care university medical center and the other was a community hospital with an active interventional radiology section. Indications for UFE included menorrhagia unresponsive to hormonal therapy and/or progressive bulk/pelvic pain symptoms. All patients were believed to be premenopausal and had been evaluated by an attending gynecologist to confirm the diagnosis of uterine fibroids and to exclude endometrial cancer. In addition, clinical consultation with an attending interventional radiologist and nurse practitioner occurred before UFE. All patients completed a questionnaire concerning their symptoms and menstrual history and had baseline ultrasonography (US) performed. Patients with preprocedural clinical or biochemical findings suggestive of peri-menopause were treated with UFE but were excluded from this study. These included patients with irregular menses, clinical symptoms such as hot flashes or night sweats, and known elevated (>20 IU/L) follicle stimulating hormone (FSH) levels.

• Procedure

Our patient preparation and embolization protocol is similar to what has been previously discussed in the literature (2–4). All but one patient had bilateral UFE performed in a standard fashion with use of single femoral access and 355–700-μm polyvinyl alcohol (PVA) to an angiographic endpoint of near or complete stasis of flow in the uterine artery. Depending on vessel size, either a microcatheter or 4-F catheter was used for embolization from the mid-horizontal portion of the main uterine artery. In addition, early in our experience, 14 patients received either surgical gelatin (Gelfoam; Upjohn, Kalamazoo, MI) pledgets or coils. A single patient underwent embolization with only surgical gelatin pledgets.

Postprocedural care was standard; most patients stayed in the hospital overnight with continuous parenteral administration of antiinflammatory drugs, narcotics, and antiemetics.

• Follow-up

Patients were followed-up at 2 weeks, 3 months, 6 months, and 1 year (when applicable). In addition, follow-up US was performed at 3 months in all patients. A standard set of questions was used to evaluate the clinical effectiveness of the procedure. In addition, patients were asked whether menses resumed and, if so, when it resumed; whether resumption of menses was regular or irregular; and, if menses did not resume, whether hot flashes or night sweats occurred. Other potential menopause symptoms such as irritability, mood swings, or vaginal dryness were not specifically addressed.

All patients who had not begun menstruating after 8 weeks or who had clinical symptoms of menopause had serum FSH levels measured. For the purposes of our study, patients were defined as having ovarian failure if they were amenorrheic, had elevated FSH levels (>20 IU/L), and had clinical symptoms suggestive of menopause.

The relationship between preprocedural symptoms, amount of PVA used, fibroid size, and resumption of menses was also assessed. Preprocedural symptoms were defined as either menorrhagia or bulk-related (pressure, constipation, or urinary symptoms). When both existed, the patient was categorized according to the clinical complaint that was most problematic for the patient. For purposes of fibroid size, we measured the dominant (largest) fibroid size with use of US for consistency.

• Statistics

The incidence of ovarian failure was calculated for women younger than 45 years and for those 45 years or older. We assessed statistical differences in ovarian failure in the two age groups with use of the χ^2 test. Statistical significance was assessed at the $P < .05$ level.

RESULTS

Sixty-six premenopausal women (age range, 30–55 years) underwent bilateral UFE and were followed for an average of 21 weeks (range, 12–77 weeks). All patients included in the study had technically successful bilateral embolizations and all were available for follow-up. Patients who underwent UFE either refused any surgical intervention, were considered poor myomectomy candidates by their gynecologist, or did not desire future fertility. For example, a 30-year-old patient in our study, as a result of the extent of her fibroids, was thought to have her options limited to UFE or a hysterectomy.

Fifty-six of our 66 patients (85%) reported resumption of normal, predictable menses on an average of 3.5 weeks (range, 1–8 weeks) after their procedure. In 10 of 66 patients (15%), menstruation did not resume after treatment, with an average follow-up of 49 weeks (range, 24–76 weeks). Nine of 10 patients who did not menstruate (14% of total patient population) had clinical and biochemical findings consistent with ovarian failure, and a single patient remained amenorrheic with normal FSH levels **(Table 1)**. This patient was scheduled for a 3-month follow-up with her gynecologist. Nine patients who were categorized as having ovarian failure received 355–500-μm PVA only, whereas the 10th patient, who has remained amenorrheic, received surgical gelatin pledget embolization only. All 14 patients who received PVA with coils or pledgets resumed menses. Ovarian failure occurred in nine of 21 (43%) women over age 45 and in none of the women under age 45, a statistically significant difference ($P < .05$). There were no significant differences in presenting symptoms, amount of PVA used, and dominant fibroid size between patients who did and did not resume menses **(Table 2)**.

Table 1
Ten Patients Who Developed Amenorrhea

Patient No.	Age (y)	Hot Flashes/Night Sweats	FSH (IU/L)	Follow-up (wks)
1	50	Yes	29.4	76
2	54	Yes	80	72
3	45	Yes	83.2	52
4	48	Yes	62.9	52
5	51	Yes	68.4	44
6	55	Yes	81.4	48
7	47	Yes	35	36
8	48	Yes	100	54
9	47	Yes	100.3	24
10	37	No	10	30

Table 2
Comparison between Patients Who Did and Did Not Resume Menses

Group	PVA (average)	Dominant Symptom	Dominant Fibroid Diameter (average mm)
Menses	4.6 vials	54% bleeding 46% bulk	58
No menses	4.4 vials	50% bleeding 50% bulk	48

DISCUSSION

The primary purpose of this study was to document the effect of UFE on menses and to measure the incidence of ovarian failure. In a multiinstitutional retrospective and prospective review of 66 patients, we determined that UFE is associated with ovarian failure in 14% of all patients. However, when stratifying our data by age, 43% of women 45 years of age or older developed ovarian failure, whereas no women younger than 45 years of age developed ovarian failure. Determination of the incidence of ovarian failure after UFE has particular health relevance as more women are treated with this promising technique.

The efficacy of UFE for reducing menorrhagia and controlling bulk-related symptoms has been well-documented by other authors (1–9). Our clinical results are comparable to those of these other large series (3,4,7) **(Table 3)**. However, these other studies have not focused on the impact of UFE on the development of ovarian failure.

Table 3
Effect of Uterine Artery Embolization on Menorrhagia and Bulk-related Symptoms

Symptom	No. of Patients (n = 35)
Menorrhagia	
Improved	32 (91)
No change	3 (9)
Worse	0 (0)
Bulk Symptoms	(n = 31)
Improved	27 (87)
No change	2 (10)
Worse	1 (3)

Note.—Numbers in parentheses are percentages.

In one series of 12 patients with obstetric hemorrhage who underwent Gelfoam embolization, 11 (92%) resumed normal menses and all three patients who desired pregnancy achieved full-term healthy newborns (10). The authors concluded: ". . . women who undergo this procedure can expect to have a return of normal menses with no adverse effect on fertility" (10). However, this case series evaluated a smaller group of much younger patients (average age, 30.5 years) than did ours. Additionally, women with obstetric hemorrhage may represent an entirely different patient population than women with symptomatic fibroids. Other authors performing UAE for obstetric hemorrhage in a variety of clinical situations also have concluded that it is a safe and effective procedure (11–13).

The reported rate of permanent post-UFE amenorrhea has previously been considered by other authors to be low. For example, in Ravina's original article on fibroid embolization (1), 10 of 11 responders had resumption of normal menstrual cycles. Of the 57 premenopausal patients treated by Goodwin et al (3), a single patient had "permanent amenorrhea with a documented FSH increase to menopausal levels." Although not directly assessed, Kirsch et al (4) reported no complications of permanent amenorrhea in 53 patients and concluded that ". . . UFE has the advantage of allowing preservation of uterine function (ie, normal menses and pregnancy)." An early report by Katz et al (14), in a much smaller group of 10 patients, raised the issue of amenorrhea. The age of these patients was not stated.

Our ovarian failure incidence of 14% is higher than that reported by most other authors. For example, disparity in ovarian failure rates might result from differences in technique and/or patient selection criteria. We do not believe that these factors are operative here. Our embolization technique is virtually identical to that used by numerous other investigators (1–4). Regarding patient selection, we did specifically eliminate those women for whom future fertility was an issue or concern, but these same criteria are also in widespread use;

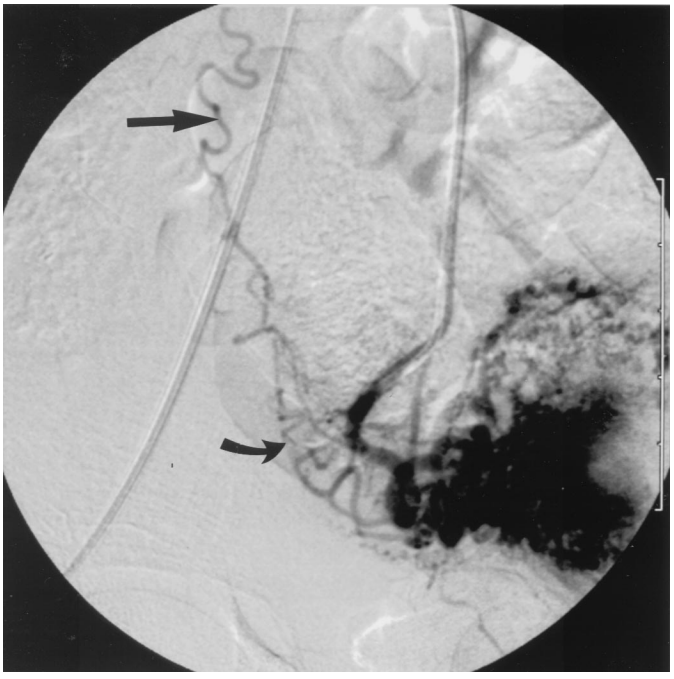

Figure 1. Demonstration of uterine-ovarian anastomoses. Oblique selective right uterine arteriogram shows filling of ovarian arterial plexus (curved arrow) and retrograde opacification of right ovarian artery (arrow) via anastomotic vessels arising off proximal uterine branches.

our mean age (44 years) and presenting symptoms were also very similar to those in other large series (3,4). Additionally, the definition of menopause and ovarian failure varies may account for differences in reported rates.

Although the etiology of ovarian failure in our patients remains uncertain, we postulate a number of possible etiologies, including vascular causes and changes in the local (uterine/ovarian) hormonal milieu.

An understanding of the vascular supply of the uterus and adnexa may provide a partial answer to this question. Sampson, in his original 1912 article on the blood supply of uterine fibroids, stated: "each uterine artery and its. . . free anastomoses with the ovarian artery of the side is well known" (17). These anastomoses can occasionally be angiographically depicted if carefully evaluated with oblique imaging and other views **(Fig 1)**. After observing a number of these ovarian vessels, we postulate that they are potentially embolized to some degree during UFE. The degree to which a woman's ovaries are inadvertently embolized and the effect that this process has on ovarian function is unknown at this time. This issue deserves more research.

Because our data indicate that ovarian failure is much more pronounced in older patients, we hypothesize that the older ovary may have diminished blood supply and, therefore, a small amount of PVA may result in a level of ischemia that might be tolerated without symptoms in younger women. The presumed susceptibility of the older ovary to nontarget embolization could be related to one of three mechanisms:

1. The older ovary may have less total functional ovarian reserve, and therefore may be intolerant of any embolic insult; support for this notion can be found in the work of Beavis et al (15), who stated that in those patients who had undergone partial ovarian resection, "[i]t is apparent that one residual ovary assumes sole function less effectively in older than in younger women."
2. Vascular flow in the older ovary may well be diminished such that a greater percentage of embolic material reaches the ovary and does more damage.
3. Statistical coincidence. Our average patient who became menopausal after UFE was 49 years old, an age at which an estimated 35% of all women are menopausal (15). Given the rapidly increasing rate at which older women undergo menopause (from 4% incidence at 45 years to 35% at 49 years), it is conceivable that at least some of our patients might have lost ovarian function in the 3-month period of observation even if embolization had not been performed.

Regarding the issue of so-called local and/or hormonal changes, the gynecologic literature has evaluated (albeit incompletely) the effect of myomectomy and hysterectomy on ovarian function. The limited available data show a similar rate of surgically induced ovarian failure as compared to UFE. For example, in one study of premenopausal patients undergoing abdominal hysterectomy (with ovarian conservation), the authors reported an approximate 15% ovarian failure rate (15). This paper and others (16) discuss

the role that a viable uterus plays in normal ovarian function. For example, in some animal species, the actual presence of a uterus is essential for normal ovarian function (15,16). In light of the gynecologic data noted previously and the complexity of the local hormonal environment, it seems reasonable to assume that a similar effect of UFE on ovarian function is possible.

We recognize that there are certain significant limitations in our study. First, not all patients received the same embolization material. Although this reflects our early experience and unlikely has affected clinical outcome, standardization would have been preferable. Our current practice of obtaining pre- and postprocedural hormonal levels on all patients was not started until late in our study. These data may allow preprocedural identification of patients at risk for ovarian failure. Similarly, we limited our clinical questions to hot flashes and night sweats. Other symptoms associated with perimenopause, such as vaginal dryness, insomnia, mood swings, and others, were not specifically addressed. Therefore, a portion of our patients that were perimenopausal may not have been identified before UFE. Additionally, we acknowledge that a portion of our patients do not meet the strict definition of menopause—usually a retrospective diagnosis—because not all patients were without menses for 12 months. As has been shown in other studies, patients have resumed menses 4–5 months after UFE (7). Nonetheless, because the current shortest follow-up in any of our amenorrheic patients is 24 weeks, we believed that all of these patients had experienced ovarian failure and included them in our results.

Our results also raise a number of important questions. Perhaps the pivotal question is whether UFE should be recommended for women who desire future fertility and/or maintenance of ovarian function. This key issue will likely be answered as more experience is gained with UFE. Until this time, very few studies (including this one) have adequately evaluated the short- or long-term effect of UFE on ovarian function in younger women. Until this research is performed, this and other questions will remain unanswered.

We conclude that UFE for the treatment of symptomatic fibroids is safe and effective. However, the incidence of ovarian failure, especially in patients older than 45 years, is higher than previously reported, and before UFE is offered widely in all patient populations, further studies need to be performed.

References

1. Ravinia JH, Herbreateau D, Ciraru-Vigneron N. Arterial embolization to treat uterine myomota. Lancet 1995; 346:671–672.
2. Goodwin SC, Vendantham S, McLucas B, et al. Preliminary experience with uterine artery embolization. JVIR 1997; 8:517–526.
3. Goodwin SC, McLucas B, Lee M, et al. Uterine artery embolization for the treatment of uterine leiomyoma: midterm results. JVIR 1999; 10:1159–1165.
4. Worthington-Kirsch RL, Popky GL, Hutchins FL. Uterine arterial embolization for the management of leiomyomas: quality-of-life assessment and clinical response. Radiology 1998; 208:625–629.
5. Hutchins FL, Worthington-Kirsch RL, Berkowitz RP. Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri. J Am Assoc Gynecol Laporascop 1999; 6:279–284.
6. McLucas B, Goodwin SC, Vendantham S. Embolic therapy for myomata. Minim Invas Ther Allied Technol 1996; 5:336–338.
7. Spies JB, Scialli AR, Jha RC, et al. Initial results from uterine fibroid embolization for symptomatic leiomyomata. JVIR 1999; 10:1149–1157.
8. Goodwin SC. New horizons in gynecologic embolotherapy: uterine artery embolization for the treatment of uterine fibroids. JVIR 1998; 9(part 2):53–59.
9. Spies JB, Barth KH, Scialli AR, et al. Uterine artery embolization for uterine fibroids: initial experience and short-term outcome. Presented at The Radiological Society of North America Scientific Assembly and Annual Meeting; 1999: Chicago, IL.
10. Stancato-Pasik A, Mitty HA, Richard III HM, et al. Obstetric embolotherapy: effect on menses and pregnancy. Radiology 1997; 204:791–793.
11. Vendantham S, Goodwin SC, McLucas B, et al. Uterine artery embolization: an underused method of controlling pelvic hemorrhage. Am J Obstet Gynecol 1997; 176:938–948.
12. Poppe W, Van Assche FA, Wilms G, et al. Pregnancy after transcatheter embolization of a uterine arteriovenous malformation. Am J Obstet Gynecol 1987; 156:1179–1180.
13. Greenwood LH, Glickman MG, Schwartz PE, et al. Obstetric and nonmalignant gynecologic bleeding: treatment with angiographic embolization. Radiology 1987; 164:155–159.
14. Katz RN, Mitty HA, Stancata-Pasik A, et al. Comparison of uterine artery embolization for fibroids using gelatin sponge pledgets and polyvinyl alcohol [abstract]. JVIR 1998; 9(suppl 1):184.
15. Beavis ELG, Brown JB, Smith MA. Ovarian function after hysterectomy with conservation of the ovaries in pre-menopausal women. J Obstet Gynaec Brit Cwlth 1969; 76:969–978.
16. Beling CG, Marcus SL, Markham SM. Functional activity of the corpus luteum following hysterectomy. J Clin Endocrinol 1970; 30:30–39.
17. Sampson JA. The blood supply of uterine myomata. Surg Gynecol Obstet 1912; 14:215–234.