Vaginal mifepristone for the treatment of symptomatic uterine leiomyomata: an open-label study

Gil M. Yerushalmi, M.D., Ph.D.,a,c Yinon Gilboa, M.D.,a,c Ariella Jakobson-Setton, M.D.,a,c Yona Tadir, M.D.,b,c Chen Goldchmit, M.D.,b,c Danny Katz, Ph.D.,d and Daniel S. Seidman, M.D.a,c

Objective: To evaluate the efficacy and safety of 3 months of vaginal mifepristone treatment on leiomyoma volume and related symptoms.

Design: Prospective, open-label, two tertiary centers, phase II clinical trial.

Setting: Two tertiary medical centers in Israel.

Patient(s): Thirty-three enrolled women, ages 30–53 years, diagnosed with symptomatic uterine fibroids.

Intervention(s): Patients received 10 mg mifepristone vaginally daily for 3 months.

Main Outcome Measure(s): Reduction in uterine leiomyoma volume. Improvement in symptoms related to uterine fibroids.

Result(s): Mifepristone treatment significantly reduced leiomyoma volume from 135.3 ± 22.9 cc at enrollment to 101.2 ± 22.4 cc after 3 months of treatment. The UFS-QoL Score significantly decreased from 20.7 ± 0.7 at enrollment to 14.0 ± 0.8 after 3 months of treatment. The number of bleeding days significantly decreased by 3.5 days. Endometrial biopsies showed no evidence of endometrial hyperplasia or cellular atypia. There were no major side effects during the course of the study, and treatment was well tolerated.

Conclusion(s): Vaginal mifepristone may offer an effective treatment option for women with symptomatic uterine leiomyoma and can improve the patients’ quality of life.

Clinical Trial Registration Number: NCT00881140 (Fertil Steril® 2014;101:496–500. ©2014 by American Society for Reproductive Medicine.)

Key Words: Mifepristone, leiomyoma, fibroid, anti-progestins

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/yerushalmigm-mifepristone-leiomyoma-fibroid/

Teratine leiomyomas are the most common benign uterine tumors in women of reproductive age. In addition to anemia resulting from menorrhagia, fibroids can cause pelvic pain, pressure, dysmenorrhea, reduced quality of life, and infertility (1). Hysterectomy remains a major management option, although other treatment modalities include myomectomy, hysteroscopic removal, uterine artery embolization, and additional interventions performed under radiologic guidance (2). Medical options are currently of more limited and mostly short-term use. GnRH agonists can create an artificial menopausal state, resulting in reversible reduction of uterine and fibroid volume and aiding in the correction of anemia (3). Progestogen-releasing intrauterine systems appear to reduce menstrual blood loss in premenopausal women with uterine fibroids and has no effect on fibroid size. Oral progestogens do not reduce fibroid size or fibroid-related symptoms and may promote proliferation of fibroids (4).

The role of progesterone in promoting the growth of fibroids has stimulated interest in modulating the progesterone pathway. Oral mifepristone, an anti-progestin, was shown to reduce uterine leiomyoma size and improve related symptoms. A recent meta-analysis of three small randomized controlled studies of oral mifepristone showed a reduction in heavy menstrual bleeding and an
improvement in fibroid-specific quality of life. However, mifepristone was not found to reduce fibroid volume [5]. Oral ulipristal, a new antiprogestin, also was recently shown to reduce uterine leiomyoma size and improve related symptoms [6, 7].

Vaginal administration of mifepristone was studied in rats and humans by Heikinheimo et al. It was shown that the systemic bioavailability of vaginal delivery was much lower than that of oral delivery. In humans, the area under the receiver operating characteristic curve of oral versus vaginal delivery of mifepristone was 56:1, respectively, i.e., the human vaginal systemic bioavailability is <2% that of oral delivery. Uterine tissue concentration was not measured [8].

After vaginal administration of progesterone, uterine tissue concentration was found to exceed by more than tenfold the levels achieved by systemic administration, despite plasma levels in the latter case that were more than seven times higher [9, 10].

These results support the hypothesis that mifepristone administered vaginally may be distributed selectively to the uterus where tissue concentrations and effects could exceed expectations. Moreover, vaginal mifepristone may be of greater usefulness, because this route may offer rapid uptake, high local uterine levels, lower serum concentrations, absence of liver metabolism, and possibly fewer side effects.

The aim of the present study was to evaluate the effect of 3 months of vaginal mifepristone treatment on leiomyoma volume, endometrium, and bleeding by performing a prospective open-label “proof of concept” study including side effect monitoring.

**MATERIAL AND METHODS**

A total of 33 women, ages 30–53 years, diagnosed with symptomatic uterine fibroids received 10 mg mifepristone vaginally daily for 3 months.

Primary outcome was defined as a reduction in uterine leiomyoma volume as assessed by ultrasonography at baseline, monthly during the course of therapy, and at the final follow-up 3 months after completing the study medications. Endometrial biopsies were obtained before, after 1 month of, and at the end of treatment. Relevant laboratory tests and bleeding patterns were recorded.

**Patients and Methods**

This prospective open-label study was conducted at two tertiary medical centers after obtaining approvals from the local hospitals’ Ethics Committees for human investigations (Institutional Review Board).

Healthy nonpregnant women referred for evaluation to the outpatient clinic due to leiomyoma-related symptoms were eligible for this study. All women gave their written informed consents before inclusion.

Exclusion criteria included pregnancy or active attempts to become pregnant, severe anemia (hemoglobin <9 g/dL), menopausal status, increase in uterine fibroid size during a short time, laboratory findings that would give suspicion of blood, liver, or renal dysfunction, abnormal Papanicolaou smear at screening, any contraindication for the use of mifepristone, current use of steroids, anticoagulants, herbs or botanicals with possible hormonal effects, oral contraception, or hormone replacement therapy during the study, and GnRH analogues or depomedroxyprogesterone within the past 3 months. The women were instructed to use barrier methods of contraception unless sterilized or having a vasectomized partner.

Pelvic vaginal ultrasound was conducted on average 21 days before the commencement of treatment and was repeated every 4th week during the treatment period and 3 months after the end of treatment. The uterus and leiomyoma volumes were determined by ultrasound examination. Assessments of hematologic, renal, and liver laboratory data were made every 4th week during the study duration.

Endometrial biopsies were obtained before and after 3 months of treatment.

The patients received 10 mg mifepristone vaginally every day. The duration of treatment was 3 months. The women returned all used and unused study pill packages at the end of each treatment visit.

**Ultrasonographic Examination**

The vaginal ultrasound was conducted with the use of a vaginal probe using Voluson 730 Expert (General Electric) equipment. All examinations were made or supervised by the same operators at each of the two centers. A defined protocol for the ultrasound investigation was used for each patient before the start of medication and carried out every 4th week during treatment and 3 months after the end of treatment. Uterine fibroids and the uterus were assessed by transabdominal or by transvaginal ultrasonography (depending on uterine fibroid size and location). The uterus was measured in three planes and the total volume calculated. The five largest uterine fibroids were identified, a volume calculated for each of the uterine fibroids, and the results averaged. Measured uterine volume was subtracted from baseline uterine volume, and volume changes were analyzed.

**Bleeding, Symptoms, and Quality of Life Assessment**

All of the women were asked to keep daily records of bleeding. Symptoms of uterine fibroids were assessed with the use of the “Uterine Fibroid Symptoms Quality of Life Questionnaire” (UFS-QoL) [11], which is a uterine fibroid–specific questionnaire comprising 37 questions specifically developed to evaluate the symptoms of uterine fibroids and their impact on health-related quality of life. The UFS-QoL has been used in a number of studies of uterine fibroid treatment [12], including studies of uterine artery embolization, radiofrequency thermal ablation, magnetic resonance–guided ultrasound surgery, and treatment with medication. It has demonstrated reliability and validity among women with uterine fibroids [11]. Effect size, a quantitative measure of change, was calculated by using the difference in mean UFS-QoL scores from baseline and dividing by the standard
deviation of baseline scores. Effect size was interpreted as small (0.20), moderate (0.50), or large (0.80) (12).

Any side effects were noted, as well as any medication used at the baseline or during the study.

Endometrial biopsies were obtained at baseline with the use of a biopsy catheter (Pipelle de Cornier; Prodimed) and after 3 months of treatment.

**Statistical Analysis and Sample Size Calculation**

A one-group chi-square test with a 0.050 two-sided significance level was considered to have 80% power to detect the difference between the null hypothesis proportion (PI), and the alternative proportion (PII) (effect = 25%; PI – PII), when the sample size is 30.

The following statistical tests were used to analyze the data in this study. Paired *t* test or rank-sign test (as appropriate) was used for testing the statistical significance of the changes in volume of uterine fibroids and uterus and of all measured laboratory tests: hemoglobin, liver, and renal functions from baseline to all post-baseline measurements. Rank test or sign-rank test (as appropriate) was used for testing the statistical significance of the differences in symptoms and menstrual bleeding, as assessed by questionnaire, between baseline and all post-baseline time points. All tests applied are two-tailed, and a *P* value of ≤ 5% was considered to be statistically significant. The data were analyzed with the use of SAS software version 9.1 (SAS Institute).

**RESULTS**

**Demographic Data**

Women were enrolled from April 2009 to May 2012. A total of 33 women were eligible for the study. During the study, three women withdrew (one chose to undergo a scheduled hysterectomy after 1 month of treatment, one because of exacerbation of a preexisting cardiac condition, and one because of inadequate compliance) and one other did not arrive for the final visit. The study is therefore based on the 29 women for whom complete data was available. The mean age (+SE) was 44.3 ± 0.7 years. The mean endometrial thickness was 7.9 ± 0.9 mm. The mean body mass index was 26.7 ± 1.2 kg/m². Twenty-one women were nonsmokers, three were past smokers, and six were current smokers. All patients participating in the study were Caucasian.

**Effect on Leiomyoma and Uterine Volume**

The average volume (+SE) of the dominant leiomyoma changed from baseline to the end of treatment from 135.3 ± 22.9 cc (range 8.2–487.2) to 101.2 ± 22.4 cc (4.6–527.6). Three months after treatment was completed, the average volume of the dominant leiomyoma was 107.7 ± 21.0 cc (5.6–378.3). The percentage volume change of the dominant myoma was significantly reduced after 2 (−23.6%; *P* < .001) and 3 (−26.4%; *P* < .001) months of treatment (Fig. 1A) as well as 3 months after treatment ended (−18.5%; *P* < .002).

The mean total uterine volume was not significantly reduced in this study by mifepristone treatment. At baseline the mean total uterine volume (+SE) was 490.5 ± 62.1 cc (range 182.1–1,449), at the end of treatment it was 432.3 ± 64.5 cc (112–1,742), and 3 months after treatment was completed it was 573.8 ± 84.5 cc (173.1–1,756).

**Effects on Uterine Bleeding and Patient-Reported Symptoms**

We observed significant changes in bleeding pattern and amount among women treated with vaginal mifepristone. Baseline bleeding days were 7.8 ± 0.9, and basal vaginal bleeding intensity was 4.1 ± 0.2 (on a scale of 1 [light] to 5 [heavy]).

Thirteen patients (44.8%) had amenorrhea. There were significantly fewer bleeding days after 2 (−3.3 ± 1.3 d; *P* < .02) and 3 (−3.5 ± 1.1 d; *P* < .005) months of treatment (Fig. 1B). There was a trend of reduction in bleeding days even 3 months after medication was stopped (−1.5 ± 0.7 d; *P* = .054). There was a significant reduction in bleeding intensity evaluated by the patient (Fig. 1C) as early as after 1 month of treatment (−1.0 ± 0.3; *P* < .001). This effect continued even after the medication was stopped (−0.8 ± 0.3; *P* < .001).

The symptoms of uterine fibroids were assessed with the use of the UFS-QoL. We observed a significant reduction in UFS-QoL score throughout the treatment period and 3 months after the end of treatment (*P* < .001: from a mean (+SE) UFS-QoL score of 20.7 ± 0.7 at enrollment to 17.9 ± 0.9 [effect size −0.76], 14.1 ± 0.8 [−1.50], and 14.0 ± 0.8 [−1.40] after 1, 2, and 3 months of treatment, respectively, and then increasing to 16.9 ± 0.8 [−0.95] 3 months after treatment (Fig. 1D). The calculated effect size was large (>0.8) for all time points except for the first visit after 1 month of treatment.

**Effects on Hemoglobin, Liver Functions, Lipid Profile, and the Endometrium**

We observed no significant differences in blood hemoglobin values as measured at baseline (12.2 ± 0.2 g/dL) and at the end of treatment (12.2 ± 0.3 g/dL). No significant changes were observed throughout the study period in the serum creatinine, liver transferase enzyme profile (aspartate transaminase, alanine transaminase), or lipid profile (high-density lipoprotein, low-density lipoprotein, triglyceride) of the patients.

Endometrial biopsies were collected at baseline and 3 months after treatment. None of the biopsies showed any evidence of hyperplasia or malignancy. Mean endometrial thickness did not change significantly during the course of the study.

There were no major side effects during the course of the study. Hot flushes at some point during treatment were reported by 3/29 (10.3%); nausea was reported at some point by 2/29 (6.9%); and a feeling of weakness was experienced by 2/29 (6.9%). Abdominal pain was reported at some point by 7/29 (24.1%), and vaginal discharge was reported at some point by 6/29 (20.7%). One patient experienced dryness of the cornea as well as thickened endometrium (31 mm) which later resulted in heavy bleeding. The endometrial biopsy in that patient was normal.
DISCUSSION

The results of this study demonstrate that 3 months of treatment with 10 mg vaginal mifepristone led to a significant reduction in leiomyoma size, less uterovaginal bleeding, and reduced symptoms, as expressed by lower UFS-QoL scores. The effect was noted even 3 months after cessation of medical treatment. We observed no significant adverse reactions, and there was no evidence of endometrial abnormality throughout the course of the treatment.

Several studies evaluating the safety and efficacy oral mifepristone and other selective progesterone-receptor modulators have suggested that these agents may be useful in treating fibroids (5–7). The present study is the first that evaluated the safety and efficacy of vaginal administration of mifepristone for the treatment of uterine leiomyomas.

Earlier trials have used oral mifepristone in doses ranging from 2.5 mg (13, 14) to 50 mg (15) daily. Clinical efficacy was noted mostly in doses >5 mg/d (13). We used 10 mg vaginal mifepristone, which proved to be clinically effective.

The reduction in uterine leiomyoma volumes that we observed are similar to the results of studies using similar doses of mifepristone orally (5, 14, 16–19). Unlike other studies, the total uterine volume measured (leiomyoma excluded) did not decrease significantly. This observation may be attributed to the position of the uterus in the bony pelvis and its highly irregular shape in the markedly myomatous uterus. However, a significant clinical improvement was demonstrated, which, in our opinion, shows that actual changes in leiomyoma or uterine volumes do not reflect actual clinical gains.

This seems to be similar to other noninvasive treatment modalities, such as magnetic resonance–guided high-intensity focused ultrasound, which also report modest decreases in leiomyoma size together with significant improvement in leiomyoma–related symptoms (20, 21). Regarding the most frequent adverse effects of mifepristone, our data concur with the results of other studies using lower (13, 19) or similar doses of oral mifepristone (17, 22). There is still a need to determine the lowest effective dose of vaginal mifepristone and the optimal treatment protocol.

We noted that the beneficial effect of vaginal mifepristone lasted after treatment had ended. We speculate that this finding may relate to apoptosis of leiomyoma cells (23). We suggest that following the initial treatment period it may be possible to achieve long-term safe and effective relief of fibroid symptoms and fibroid volume reduction with the use of vaginal mifepristone intermittently every several months. The safety of this approach can be assumed based
on the observation that cases of endometrial hyperplasia were noted mostly in women receiving mifepristone for treatment of fibroids for $\geq 6$–12 months [24].

We did not observe a significant elevation in hemoglobin levels among our patients despite a significant decrease in excessive vaginal bleeding, unlike some of the previous studies [22, 25]. This may be due to the fact that on enrollment most patients had normal hemoglobin levels.

A limitation of the present study is that the duration of treatment was restricted to 3 months. The fibroids of some of the women in our study did seem to enlarge within 3 months after the end of treatment. This suggests that a more prolonged treatment or a maintenance dose of mifepristone may be of benefit for such women. Further studies are required to establish the efficacy and safety of more prolonged treatment. The use of lower or weekly doses of vaginal mifepristone should also be considered.

The vaginal preparation of mifepristone was well received by the women enrolled in our study. None of them discontinued the study because of vaginal irritation or other complaints related to the vaginal preparation.

In conclusion, treatment with vaginal mifepristone at a daily dose of 10 mg for 3 months was safe and effective in controlling bleeding, decreasing fibroid volume, and reducing discomfort in women with symptomatic leiomyoma. Once an optimal treatment protocol is defined, this new approach might become the treatment of choice for patients who want to reduce further growth of uterine fibroids or perimenopausal women with symptomatic fibroids who wish to avoid surgery.

Acknowledgment: The authors thank Ms. Shlomit Cohen for her outstanding work to coordinate this study.

REFERENCES