Effects of the Selective Progesterone Receptor Modulator Asoprisnil on Uterine Artery Blood Flow, Ovarian Activity, and Clinical Symptoms in Patients with Uterine Leiomyomata Scheduled for Hysterectomy

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Introduction: Asoprisnil, a novel orally active selective progesterone receptor modulator, is being studied for the management of symptomatic uterine leiomyomata. The exact mechanism of action is not yet discerned. The primary objectives of this double-blind, randomized, placebo-controlled study included evaluation of the effect of asoprisnil on uterine artery blood flow. Furthermore, we assessed effects of asoprisnil on leiomyoma symptoms.

Patients and Methods: Thirty-three premenopausal patients scheduled for hysterectomy due to symptomatic uterine leiomyomata were recruited in four centers and treated with 10 or 25 mg asoprisnil or placebo for 12 wk before surgery. At baseline and before hysterectomy, all patients underwent sonographic assessment to measure impedance to uterine artery blood flow, determined by resistance index and pulsatility index, as well as volumes of largest leiomyoma and uterus. In addition, patients recorded intensity and frequency of menstrual bleeding on a menstrual pictogram. Each asoprisnil treatment was compared with placebo.

Results: The increased pulsatility index in both asoprisnil groups and the statistically significantly increased resistance index within the 25-mg asoprisnil group suggest a moderately decreased uterine artery blood flow. Analysis of menstrual pictogram scores showed a statistically significant larger decrease in frequency and intensity of bleeding for both asoprisnil groups compared with placebo. Bleeding was suppressed by asoprisnil 25mg in 91% of patients. Asoprisnil treatment was well tolerated when administered daily for a 12-wk period, and no serious adverse events occurred.

Conclusion: Asoprisnil moderately reduced uterine artery blood flow. This effect may contribute in part to the clinical effects of asoprisnil. **(*J Clin Endocrinol Metab* 93: 4664–4671, 2008)**

Uterine leiomyomata are benign smooth muscle tumors originating from the myometrium. They are present in up to 70% of women even though asymptomatic in over half of the cases with 20–25% of women of reproductive age clinically affected (1, 2). The commonest symptoms are heavy menstrual bleeding (HMB) and pressure symptoms. With currently limited options for medical therapy, uterine leiomyomata are the second most frequent indication for hysterectomy in the United Kingdom

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Abbreviations: ANCOVA, Analysis of covariance; AE, adverse event; E_1G, estrone glucuronide; ELA, evidence of luteal activity; HMB, heavy menstrual bleeding; MP, menstrual pictogram; NELA, no evidence of luteal activity; NSAID, nonsteroidal antiinflammatory drug; PdG, pregnanediol glucuronide; PI, pulsatility index; RI, resistance index; UFS-QOL, Uterine fibroid symptom and health-related quality-of-life.

(3, 4). In the United States, 600,000 hysterectomies are performed annually with HMB as the most common indication (5).

There is growing evidence that progesterone and the progesterone receptor play a key role in fibroid growth and development. Contrary to previous understanding that leiomyoma growth is mainly estrogen related, recent data from clinical and *in vitro* studies indicate that progesterone plays a pivotal role (6, 7). Some clinical studies have shown that synthetic progestins reverse the effect of GnRH agonists on leiomyoma volume, which indirectly indicates the effects of GnRH agonists on leiomyomata may be due partly to cessation of progesterone secretion (8). Furthermore, a reduction in mean leiomyoma volume was demonstrated in small, uncontrolled, clinical studies with the progesterone receptor antagonist mifepristone (9). Mifepristone has been shown to reduce uterine artery blood flow in patients with uterine leiomyomata (10). Collectively, these data suggest that progesterone may have a stimulatory effect on leiomyoma growth.

Asoprisnil (J867) is a novel, orally active and selective progesterone receptor modulator (SPRM), which exhibits partial and mixed agonist and antagonist effects on various progesterone target tissues in animals and humans (11–13). Asoprisnil exhibits endometrial antiproliferative effects in nonhuman primates in the presence of follicular-phase estradiol levels (11, 14).

The effects of 3 months treatment with asoprisnil in women with uterine leiomyomata have been reported. Asoprisnil suppressed uterine bleeding in 28, 64, and 83% of subjects at 5, 10, and 25 mg, respectively, and reduced leiomyoma and uterine volumes (15).

The current study was designed to evaluate the mechanism of action of asoprisnil in patients with symptomatic leiomyomata scheduled for hysterectomy. The primary objectives were to assess the effects of asoprisnil on uterine artery blood flow through measurements of impedance (resistance and pulsatility indices). The effects on endometrial, myometrial, and leiomyomata morphology, have been reported elsewhere (16). Furthermore, we investigated effects of asoprisnil on leiomyoma symptoms, including semiquantitative assessment of uterine bleeding using a menstrual pictogram (MP), and ovarian activity.

Subjects and Methods

Women studied

Premenopausal women were recruited from four centers (Edinburgh, Southampton, Glasgow, and Liverpool). All subjects were in good health and scheduled for hysterectomy due to symptomatic uterine leiomyomata, mostly due to HMB. Each patient had at least one leiomyoma (diameter ≥ 2 cm) or multiple small leiomyomata (uterine volume ≥ 200 cm^3) confirmed by ultrasonography. In all cases, the clinical decision for hysterectomy was taken before recruitment. Inclusion and exclusion criteria were applied as previously described (16). Patients were required to have a washout period of 2–12 months for hormonal medications before screening. Non-steroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid were permitted during screening and treatment periods. All patients provided informed consent. The study protocol was approved by the Multicenter Research Ethics Committee.

Study design

This was a phase II, multicenter, randomized, double-blind, placebo-controlled study of asoprisnil administered to patients with symptomatic uterine leiomyomata for 12 wk. Dose selection was based on previous phase I and II studies. A treatment regime with doses of 10 and 25 mg asoprisnil for a duration of 12 wk had been shown to effectively suppress uterine bleeding and reduce leiomyoma and uterine volumes while being safe and well tolerated (15).

Screening procedures and enrollment were carried out as previously described (16). Subjects in three parallel dose groups in a 1:1:1 ratio received once-daily oral doses of asoprisnil of 10 or 25 mg asoprisnil or placebo. They and all study personnel were blinded to treatment groups. Treatment was initiated no later than the fifth day of the patient's menstrual cycle and continued for 12 wk until hysterectomy. Hysterectomy was performed within 24 h of the final dose. Throughout the study, each patient was closely monitored for occurrence of adverse events (AEs) and standard laboratory safety parameters.

Sonographic assessment

Color Doppler imaging by transvaginal ultrasound was employed to determine blood flow of the uterine arteries before the first study drug dose and after 12 wk. Blood flow was estimated using two impedance indices: resistance index (RI) and pulsatility index (PI) defined as follows: RI = systolic − end diastolic peak velocity/systolic peak velocity; PI = systolic − end diastolic peak velocity/time-averaged maximum velocity (17). For each impedance index, two measurements were taken from left and right arteries, respectively; each side's index was calculated using the mean of the two, and further analyses used the mean of both sides (18). Study sites used the same color Doppler imaging methods. Scans were performed by the same ultrasonographer at each site. The largest leiomyoma and uterus were measured and the volumes estimated using the volume of an ellipsoid. The position of the fibroids within the uterus was not specifically recorded further to previous evidence that symptoms of HMB do not appear to correlate with fibroid location (19).

MP

At screening, patients were issued a MP in a daily diary to be kept throughout the study. Patients recorded daily any uterine bleeding. Whenever uterine bleeding exceeded spotting, the amount of blood loss was quantified and documented in the MP. Patients were supplied with standardized sanitary products. The MP scores, representing blood loss in milliliters, were calculated as described previously (20) and then summed for each patient for the last full menstrual cycle before randomization menses normalized to 28 d and for each 28-d treatment period, producing a total score for each subject for baseline, wk 1–4, wk 5–8, and wk 9–12. The number of days with bleeding was calculated from the diaries for the pretreatment cycle and the three 28-d treatment periods. To evaluate improvement in uterine bleeding, change of MP scores and of days with bleeding from baseline to each month and final month was calculated and summarized. The percentage of subjects with suppression of uterine bleeding during the treatment period was calculated for each treatment group.

Uterine fibroid symptom and health-related quality-of-life (UFS-QOL) questionnaire

Before commencing the study drug and before hysterectomy, patients completed the Uterine Fibroid Symptom and Health-Related Quality-of-Life questionnaire (UFS-QOL) (21) with its subscales of concern, effect on activities, energy/mood, control, self-consciousness, sexual function, and symptom severity.

Ovarian activity

Urine aliquots (first voided urine of the day) were collected twice weekly during screening and throughout the treatment period and frozen at −20 C for subsequent analysis. Ovarian activity was determined by assessing urinary pregnanediol glucuronide (PdG) and estrone glucuro-

nide (E_1G) levels, which were measured using ELISA. Hormone concentrations were corrected for creatinine excretion and expressed as ratios of the creatinine concentration to urine volume (22).

Evidence of luteal activity (ELA) *vs.* no evidence of luteal activity (NELA) was determined from urinary PdG levels using two algorithms (23); in the first algorithm, a PdG level was considered ELA if it was at least three times the minimum 3-concentration moving average of the past 4 wk; the second algorithm had an additional criterion that, to be considered ELA, a PdG level had to be at least 0.5 mmol/mol creatinine. For each 4-wk period and each treatment group, the percentage of patients with NELA and 95% exact confidence intervals were calculated.

Ovarian follicular activity during treatment was determined by comparing E_1G concentrations during the 12-wk treatment period to pretreatment follicular phase concentrations (baseline). Based on the method described by Brown *et al.* (24), ovarian activity was labeled as continued ($E_1G \geq 50\%$ above baseline on at least two occasions, separated by ≥13 d, with no E_1G concentrations ≥50% above baseline), partially suppressed (E_1G concentration ≥50% above baseline on at least one occasion while not meeting the definition of continued follicular activity), or totally suppressed ($E_1G < 50\%$ above the baseline throughout treatment period). Number and percentage of patients belonging to each category were calculated for each treatment group.

Data analysis and statistical methods

Comparison of each asoprisnil treatment with placebo was performed using pairwise comparisons within the framework of analysis of covariance (ANCOVA) models for assessments of change in RI, PI, and MP scores, number of days with bleeding, and UFS-QOL scores. The ANCOVA models for RI and PI included factors of treatment and investigator as fixed effects and baseline value as a covariate, whereas the models for MP scores, number of days with bleeding, and UFS-QOL scores included treatment as a factor and baseline value as a covariate. In addition, a paired *t* test was performed for RI and PI on the change from baseline to final visit for each treatment group. Percent change in volume of the largest leiomyoma and the uterus was compared between each asoprisnil group and placebo using Wilcoxon's rank sum test. Percentage of patients with suppression of uterine bleeding was compared by Fisher's exact test. For efficacy endpoints, Hochberg's multiple comparison method was applied to control for pairwise comparisons at a significance level of 0.05. No statistical inference was performed on safety variables.

The planned sample size for this study was 15 patients per treatment arm. This sample size would provide greater than 95% power to detect a 0.08 difference in RI between the asoprisnil and the placebo group using a two-tailed two-sample *t* test with a common SD of 0.05 (with a 0.05 significance level).

The study was closed with a total of 33 patients. With 11 patients per group and assumptions as above, the power to detect a 0.08 difference in RI was 94%.

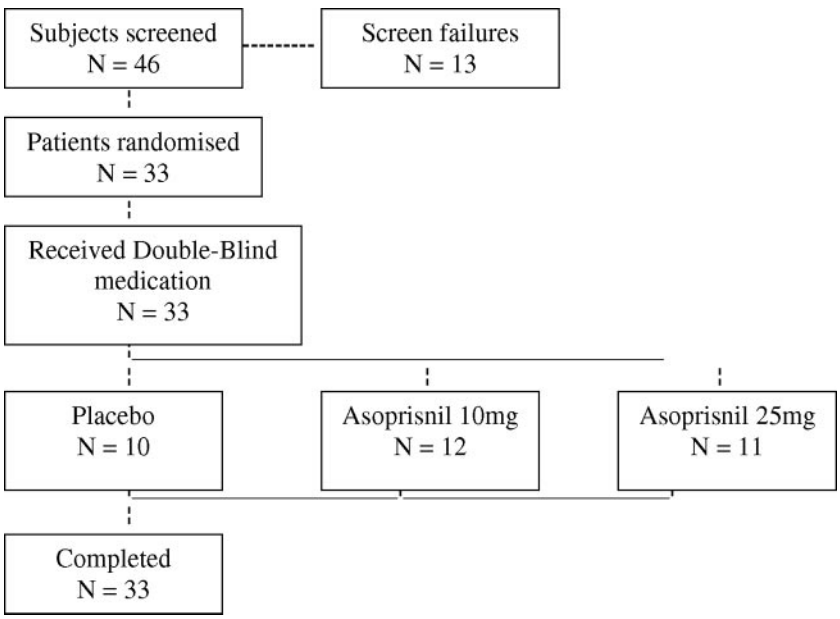

FIG. 1. Patient enrollment: numbers of patients at different stages of the clinical study.

Results

Patient demographics

Thirty-three patients were enrolled. Thirteen screen failures occurred. Ten, 12, and 11 patients received placebo and 10 and 25 mg asoprisnil, respectively. All 33 patients completed the study including 12 wk treatment, the scheduled hysterectomy, and follow-up after 6 wk (Fig. 1).

Treatment and placebo groups were well matched regarding race, age, height, and weight (Table 1). Drug compliance was satisfactory in all groups. No patients developed withdrawal criteria during the study or received the wrong treatment or an incorrect dose. Three patients (one on placebo and two on 25 mg asoprisnil) took tranexamic acid to control menstrual bleeding, but the median use per month was nil in each group. Median intake of NSAIDs was higher in the 10-mg asoprisnil group (1.2 d/month) than in the placebo or 25-mg asoprisnil groups (median of nil per month). During treatment, NSAIDs were primarily taken for headache, joint, or muscular pain and for dysmenorrhea. The differences between groups were not expected to influence study results.

Effects on uterine artery blood flow

Neither asoprisnil group had a change from baseline to final visit in RI that was statistically significantly different from placebo. There was, however, a statistically significant increase in RI from baseline to final visit within the 25-mg asoprisnil group, indicating decreased uterine artery blood flow (Table 2).

The PI increased statistically significantly from baseline to final visit in both asoprisnil groups compared with placebo, indicating decreased uterine artery blood flow. From baseline to final visit, the PI increased in the 25-mg asoprisnil group although unchanged after asoprisnil 10 mg with a statistically significant decrease within the placebo group (Table 2).

Effects on volume of largest leiomyoma and uterus

From baseline to final visit, the median percent change in largest leiomyoma volume showed a decrease after 25 mg asoprisnil (−25.8%) and a small increase in the placebo group (4.9%), with a very minor decrease after asoprisnil 10 mg (−0.4%). The differences between each asoprisnil group and placebo in percent change of largest leiomyoma volume or uterine volume were not statistically significant.

TABLE 1. Demographic data at baseline

Variable	Treatment group			
	Placebo (n = 10)	Asoprisnil 10 mg (n = 12)	Asoprisnil 25 mg (n = 11)	All subjects (n = 33)
Race, n (%)				
Black	1 (10)	2 (16.7)	1 (9.1)	4 (12.1)
Caucasian	9 (90)	10 (83.3)	10 (90.9)	29 (87.9)
Age (yr)				
Mean (SD)	41.8 (3.6)	45.1 (3.5)	44.6 (6.0)	43.9 (4.6)
Min-Max	37–48	39–50	35–52	35–52
Weight (kg)				
Mean (SD)	73.4 (11.7)	73.8 (17.7)	75.9 (11.8)	74.4 (13.8)
Min-Max	54–89	45–105	60–96	45–105
Height (cm)				
Mean (SD)	165.3 (6.4)	164.3 (4.7)	165.6 (7.3)	165.1 (6.0)
Min-Max	158–177	156–172	157–178	156–178

Race, age, weight, and height distribution across the three treatment groups. Max, Maximum; Min, minimum.

Effects on uterine bleeding

Treatment with asoprisnil led to a substantial decrease in uterine bleeding. There was a large mean reduction in blood loss in the final month compared with baseline in both asoprisnil groups, which was statistically significantly different from the mean increase in the placebo group (Table 3). These decreases were already apparent during the first 4 wk of treatment.

Patients treated with 10 and 25 mg asoprisnil had bleeding of 7.0 and 8.0 d on average at baseline, which decreased to 1.2 and 0.2 d in the final month, respectively. The placebo group had a mean number of 7.3 bleeding days at baseline and the final month. The difference between asoprisnil groups and placebo was statistically significant ($P < 0.001$). The decrease in the asoprisnil groups was evident during the first month and continued throughout the treatment period. Suppression of uterine bleeding was experienced by 33% of patients treated with 10 mg asoprisnil and 91% treated with 25 mg, compared with none of the patients in the placebo group. The difference between the 25-mg asoprisnil and placebo groups was statistically significant ($P < 0.001$).

UFS-QOL

Results of the UFS-QOL total score, and in particular the subscales of concern, activities, control, and self-consciousness, showed statistically significant improvement from baseline to final visit for both asoprisnil groups compared with placebo, indicating an effect on quality of life. Reduced symptom severity was observed in both asoprisnil groups but was statistically significant only with 25 mg asoprisnil compared with placebo (Fig. 2).

TABLE 2. Analysis of RI and PI

	Treatment group			Between-groups *P* value[a]	
	Placebo (n = 10) mean ± SD	Asoprisnil 10 mg (n = 12) mean ± SD	Asoprisnil 25 mg (n = 11) mean ± SD	Asoprisnil 10 mg *vs.* placebo	Asoprisnil 25 mg *vs.* placebo
RI					
Baseline	0.73 ± 0.10	0.76 ± 0.09	0.71 ± 0.08	NA	NA
Final visit	0.71 ± 0.17	0.75 ± 0.10	0.77 ± 0.08	NA	NA
Change from baseline	−0.02 ± 0.13	−0.01 ± 0.06	0.06 ± 0.08	0.756	0.146
Within-group *P* value[b] (change from baseline)	0.629	0.689	0.034[c]	NA	NA
PI					
Baseline	1.69 ± 0.60	1.80 ± 0.72	1.52 ± 0.44	NA	NA
Final visit	1.27 ± 0.33	1.81 ± 0.67	1.81 ± 0.48	NA	NA
Change from baseline	−0.42 ± 0.42	0.01 ± 0.56	0.30 ± 0.54	0.019[d]	0.005[d]
Within-group *P* value[b] (change from baseline)	0.012[c]	0.956	0.099	NA	NA

Mean changes of RI and PI (impedance indices to quantify uterine artery blood flow as determined by color Doppler imaging) from baseline to final visit in the three treatment groups (placebo, 10 mg asoprisnil, and 25 mg asoprisnil). NA, Not applicable.

[a] From ANCOVA model for change from baseline to final visit including fixed effects of treatment and investigator and baseline mean RI/PI as a covariate.

[b] A *t* test was performed on change from baseline to final visit for each treatment group.

[c] Statistical significance at 0.05 level.

[d] Statistical significance at 0.05 level using Hochberg's multiple-comparison procedure.

TABLE 3. MP scores

	Treatment group			*P* value[a]	
	Placebo (n = 10) mean ± SD	Asoprisnil 10 mg (n = 12) mean ± SD	Asoprisnil 25 mg (n = 11) mean ± SD	Asoprisnil 10 mg *vs.* placebo	Asoprisnil 25 mg *vs.* placebo
Baseline	213.0 ± 128.0	156.7 ± 103.8	217.9 ± 115.4	NA	NA
Final month	225.6 ± 232.7	2.4 ± 4.9	2.5 ± 8.1	NA	NA
Change from baseline to final month	12.6 ± 150.6	−154.3 ± 105.2	−215.4 ± 114.1	0.001[b]	<0.001[b]

Mean changes of MP scores (in milliliters) from baseline to final month in the three treatment groups (placebo, 10 mg asoprisnil, and 25 mg asoprisnil). NA, Not applicable.

[a] From ANCOVA model for change from baseline to final month with fixed effect of treatment and baseline score as a covariate.

[b] Statistical significance at 0.05 level using Hochberg's multiple-comparison procedure.

Ovarian activity

Urinary PdG levels (Table 4) were used to calculate luteal activity for three different time periods during treatment. In the 25-mg asoprisnil group, 70–80% of patients showed NELA during wk 9–12 of treatment compared with up to 20% in the placebo group. Dose-dependent suppression of luteal activity was apparent during wk 1–4 of treatment with 10–20% of patients showing NELA in the placebo group compared with 33% in the 10-mg asoprisnil and 80–90% in the 25-mg asoprisnil group.

Follicular activity indicated by urinary E_1G levels (Table 4) was partially or totally suppressed in 22% of patients on placebo compared with 33% on 10 mg asoprisnil and 60% on 25 mg asoprisnil. Continued follicular activity was seen in 78% of patients in the placebo group *vs.* 67 and 40% in the 10- and 25-mg asoprisnil groups, respectively. These results suggest a dose-dependent suppressive effect of asoprisnil on follicular activity.

Safety parameters

No asoprisnil-treated patient had a serious AE. No AEs led to discontinuation of study drug. The most common AEs reported by at least four patients in any group during treatment were headache, nasopharyngitis, nausea, back pain, perioperative complications, and abdominal pain. AEs exhibited no drug-related or dose-dependent pattern. There were no clinically meaningful mean changes from baseline in hematology, chemistry, and urinalysis laboratory values.

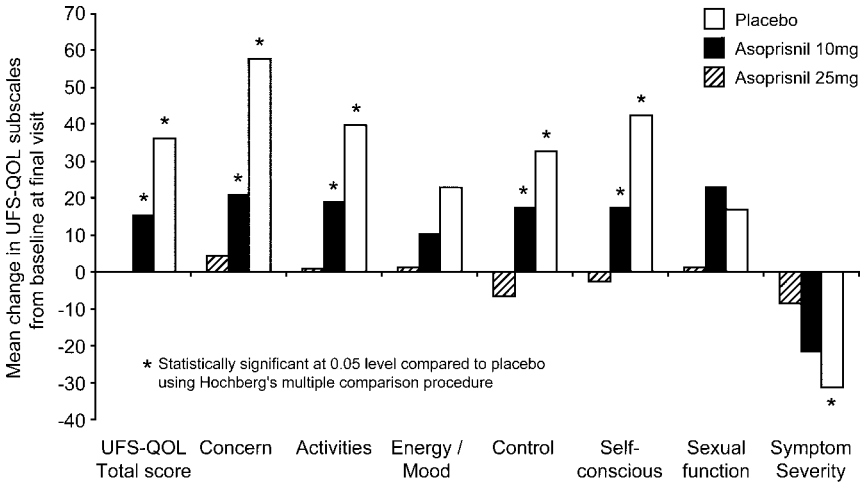

FIG. 2. Analysis of UFS-QOL questionnaires. Mean changes in UFS-QOL total score and subscales (concern, activities, energy/mood, control, self-consciousness, sexual function, and symptom severity) from baseline to final visit in the three treatment groups (placebo, 10 mg asoprisnil, and 25 mg asoprisnil) are shown. The significance of the difference of change from baseline between placebo and asoprisnil groups was determined using Hochberg's multiple-comparison procedure at 0.05 level. For symptom severity, a lower score corresponds to a lower severity; for other scales, a higher score indicates a better quality of life.

Discussion

The primary outcome of this study was evaluation of the effects of 3 months treatment with asoprisnil on uterine artery blood flow. Furthermore, effects of asoprisnil on uterine bleeding and quality of life measures were assessed in patients scheduled for hysterectomy due to symptomatic leiomyomata.

Asoprisnil treatment was associated with a moderately decreased uterine artery blood flow. There was a rapid reduction in uterine bleeding, evidenced by MP scores, and an improvement in quality of life measures.

Previous clinical studies suggested uterine artery blood flow to be important for leiomyoma growth (25). Pharmacological agents such as GnRH analogs (26) and danazol (27), which reduce leiomyoma volume, have been shown to reduce uterine artery blood flow. Furthermore, the progesterone antagonist mifepristone has been demonstrated to decrease uterine artery blood flow and reduce the size of the leiomyomatous uterus (10).

The effect of asoprisnil on uterine artery blood flow was assessed in this study to investigate a possible mechanism of action in patients with uterine leiomyomata. RI and PI were measured in uterine arteries to show a statistically significant effect on PI in both groups treated with asoprisnil and a trend toward increased RI compared with placebo. These findings suggest a moderate inhibitory effect of asoprisnil on uterine artery blood flow.

Asoprisnil has previously been shown to reduce leiomyoma volumes (15) with direct

TABLE 4. Urinary E_1G and PdG levels

	Treatment group		
	Placebo (n = 10) Mean ± SD	Asoprisnil 10 mg (n = 12) Mean ± SD	Asoprisnil 25 mg (n = 11) Mean ± SD
E_1G (μmol/mol)			
Screening	11.5 ± 4.0	18.0 ± 7.2	15.0 ± 5.5
wk 1–4	12.0 ± 4.9	16.2 ± 4.5	11.6 ± 3.3
wk 5–8	13.3 ± 3.4	17.5 ± 6.6	12.5 ± 5.4
wk 9–12	12.0 ± 4.0	21.0 ± 4.4	10.7 ± 2.0
PdG (mmol/mol)			
Screening	0.42 ± 0.15	0.37 ± 0.15	0.39 ± 0.22
wk 1–4	0.39 ± 0.17	0.45 ± 0.26	0.17 ± 0.11
wk 5–8	0.50 ± 0.25	0.45 ± 0.33	0.23 ± 0.19
wk 9–12	0.45 ± 0.19	0.46 ± 0.27	0.15 ± 0.10

Mean levels of urinary E_1G and PdG collected twice weekly over 4-wk intervals during the screening cycle and during treatment with placebo, 10 mg asoprisnil, 25 mg or asoprisnil. E_1G and PdG levels were measured using ELISA and hormone concentrations corrected for creatinine excretion. levels are expressed as ratios of the creatinine concentration (E_1G in micromoles per mole and PdG in millimoles per mole).

and indirect mechanisms likely to be involved. With the recognition that progesterone stimulates fibroid development and growth (6, 7), antiproliferative properties would be expected in a compound with partial progesterone antagonist effects. There is growing evidence from *in vitro* studies that asoprisnil suppresses proliferation and induces apoptosis in cultured leiomyoma cells while failing to show a similar effect on myometrial cells (28, 29). Evidence to date suggests that asoprisnil has selective antiproliferative effects on leiomyoma cells via down-regulation of growth factors and their receptors and induction of apoptosis (29) mediated by the PR. This is in contrast to the mode of action of GnRH analogs, which down-regulate ovarian estrogen and progesterone secretion via the pituitary gland to achieve a reduction in total uterine volume (30), whereas asoprisnil specifically decreases leiomyoma size. The present and previous studies have shown the antiproliferative effects of asoprisnil to occur in the presence of circulating follicular-phase estrogen concentrations (15).

Asoprisnil induces a constellation of endometrial morphological changes, which have been described as a nonphysiological secretory effect. In particular, administration of asoprisnil is associated with profound vascular changes with increased numbers of thick-walled stromal arterioles specific to the endometrium (16). These changes are associated with low levels of mitotic activity in endometrial glands and stroma, and no adverse endometrial findings such as endometrial hyperplasia or atypia have been demonstrated.

A further novel feature of this study is measurement of ovarian activity by assessing urinary PdG and E_1G twice weekly throughout the treatment period. There was an apparent dose-dependent suppression of luteal activity in asoprisnil-treated patients. Most patients experienced continued or only partially suppressed follicular activity on treatment with asoprisnil.

It should be stressed that luteinization in this study was defined based on urinary PdG concentrations typical for the normal luteal phase. Hence, luteal phase PdG may be indicative of either ovulation or a luteinized unruptured follicle. Serial ultrasound examinations of the dominant follicle and more frequent measurement of ovarian and pituitary hormones would be needed to determine the effects of asoprisnil on ovulation.

Previous studies have consistently reported asoprisnil to exert its clinical effects including suppression of menstruation in the presence of follicular-phase estrogen concentrations (15, 31). The risk of hypoestrogenism is the main limiting factor for the long-term use of GnRH analogs (32), which are currently often the only option for symptom control in patients with uterine fibroids seeking to avoid surgery.

The clinical effects of asoprisnil administered for 12 wk during this double-blind, placebo-controlled study are consistent with previous reports (15). A profound effect on menstrual bleeding was clearly demonstrated accompanied by a reduction in the severity of fibroid-related symptoms. Asoprisnil has previously been shown to dramatically reduce menstrual bleeding in women with (15) and without (31) fibroids. In this study, the effect of asoprisnil on endometrial bleeding was quantified using the MP. Consistent use of standardized sanitary products and provision of visual analogs on the pictogram allowed for quantification of menstrual blood loss, as previously described (20). Significant reductions were already apparent after the first month, highlighting a rapid effect of asoprisnil on uterine bleeding. Number of days with bleeding also markedly decreased in asoprisnil groups in a dose-related manner. Similarly, there was a dose response in the percentage of patients experiencing suppression of uterine bleeding. Treatment with 25 mg asoprisnil achieved suppression of uterine bleeding in 91% of patients, some of whom presented with MP scores of over 200 ml (definition of HMB is blood loss over 80 ml) (33). HMB is commonly difficult to manage in the presence of fibroids and frequent indication for hysterectomy. In this and previous studies (14, 15), asoprisnil has been shown to control uterine bleeding independent of size and location of uterine fibroids.

The mechanism of suppression of menstrual bleeding during asoprisnil treatment is not understood. Asoprisnil has previously been shown to reversibly suppress menstruation at doses of 10 mg/d or higher in women with regular menses. This effect was irrespective of the impact on luteal-phase progesterone concentrations indicative of luteinization (31). The results of the present study are consistent with these findings. Collectively, these observations strongly suggest that asoprisnil suppresses menstrual bleeding primarily via an endometrial effect. Asoprisnil induces

unique morphological changes in endometrial arterioles and stroma (16), and these changes are likely to contribute to the suppression of menstrual bleeding.

Asoprisnil-treated patients demonstrated statistically significantly greater improvements than placebo patients in most of the disease-specific UFS-QOL domains. Responses to the UFS-QOL questionnaire were grouped into subscales, as previously described (21). The mean change from baseline to the final visit indicated improvement in both asoprisnil groups compared with placebo on all subscales. These quality of life measures indicate a significant impact of asoprisnil on patients' perception of the severity of their symptoms and their quality of life. Every patient in this study had experienced symptoms significant enough to consent to major surgery for benign disease. In this study, treatment with asoprisnil was well tolerated. There were no premature terminations, and all patients completed the study with good compliance.

In conclusion, we have made the novel observations that asoprisnil reduces uterine artery blood flow while substantially decreasing menstrual blood loss and improving quality of life measures in patients with symptomatic uterine leiomyomata scheduled for hysterectomy. A moderate reduction in uterine artery blood flow was demonstrated by change in resistance and pulsatility indices. This effect may contribute to leiomyoma volume reduction, even though it is unlikely to be the primary mechanism. Decreased blood loss was evidenced by MP evaluation and improvement of quality of life by responses to the UFS-QOL. All these effects were observed in the presence of continued or only partially suppressed ovarian follicular activity in the majority of patients. The 10- and 25-mg doses of asoprisnil were safe and effective when administered daily for a 12-wk period. Further studies are needed to determine safety and efficacy profiles of asoprisnil when administered beyond 12 wk.

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