Original Article

Low-dose mifepristone in treatment of uterine leiomyoma: A randomised double-blind placebo-controlled clinical trial

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Aims: To evaluate the effect of low-dose mifepristone on leiomyoma-related symptoms, uterine and leiomyoma in women with symptomatic leiomyomata.

Methods: In a double-blind placebo-controlled trial, 40 patients with symptomatic leiomyoma and normal endometrial histology were randomised to receive 10 mg mifepristone (group 1) or placebo (group 2) daily for three months. Leiomyoma-related symptoms, uterine, leiomyoma and largest leiomyoma volumes were assessed at baseline and every month for three months. Endometrial biopsy was repeated at the end of therapy.

Results: Significant change was noticed between the two groups for mean menstrual blood loss (MBL) by first month. Menstrual blood loss declined by 94.8% in group 1 at three months and 84.2% patients attained amenorrhoea in this group. In group 1 complete relief of dysmenorrhoea occurred in significant number of women (80%) but only 33% patients got rid of pelvic pain. There was no change in these symptoms in group 1 Backache, urinary complaints and dyspareunia were not relieved in either group. Uterine, leiomyoma and largest leiomyoma volume declined by 26–32% in group 1 as compared to none in group 2, and this difference was statistically significant only by the end of the third month of therapy. Mean haemoglobin increased from 9.5 to 11.2 g/dL in group 1. In group 1, at the end of therapy, 63.1% of patients had endometrial hyperplasia without atypia.

Conclusions: Ten milligrams mifepristone for three months is effective in reducing MBL, increasing haemoglobin and reducing uterine and leiomyoma volume with side-effect of endometrial hyperplasia.

Key words: largest leiomyoma volume, leiomyoma volume, mifepristone, uterine leiomyoma, uterine volume.

Introduction

Uterine fibroids are common benign pelvic tumours that incapacitate women due to menorrhagia, pain and other symptoms. This often calls for treatment and absence of effective medical therapeutic options accounts for 30% of all hysterectomies.[1] However, interest has grown in developing measures for cost containment, use of conservative and where possible non-surgical techniques.[2] Attempts at medical treatment with progesterone, danazol and gestrinone and *GnRH* agonists have been disappointing.[3–5]

Observational data suggest that mifepristone or RU486, a synthetic steroid with antiprogesterone and antiglucocorticoid activity, is effective in treating leiomyomata producing relief in symptoms and in reduction of their size.[6] The first study demonstrating the decrease in leiomyoma volume in response to progesterone antagonist was conducted by Murphy *et al.* [7]

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Received 13 December 2007; accepted 23 June 2008.

Seven other clinical trials using mifepristone in doses of 5–50 mg were conducted for varying periods between three to 12 months.[1,6,8–12] Of these, only one was a randomised double-blind placebo-controlled trial[6] which used the drug in dose of 5 mg. Search in the literature has shown a relative lack of randomised controlled trials to confirm the benefits of mifepristone. Furthermore, the exact dose and the duration of the drug are yet to be determined by conducting randomised trials in different doses.

Methods

The present study, a double-blind placebo-controlled clinical trial, was conducted to evaluate the effect of low-dose (10 mg) mifepristone on leiomyoma-related symptoms and uterine/leiomyoma volume. Forty premenopausal women with symptomatic uterine leiomyoma were recruited from the gynaecological outpatient department of University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India between March 2005 to March 2006. A preliminary power analysis suggested that a sample of 20 women in each group would provide greater than 80% power to detect a difference of 30% change in uterine and leiomyoma volume (initial and after three months) at 5% significance.

The present study was approved by the ethical committee of the institution. The exclusion criteria included presence of pregnancy or lactation, suspicion or documented evidence of ovarian, cervical or uterine malignancy, history of hormonal treatment in the past three months, histopathological evidence of endometrial hyperplasia, presence of liver, respiratory (asthma), renal, heart disease, pelvic inflammatory disease or any other adnexal pathology and patient necessitating early surgical intervention for uterine leiomyoma.

After the written informed consent; history pertaining to leiomyoma-related symptoms like menorrhagia, dysmenorrhoea, pelvic pressure, pelvic pain, low backache, rectal pressure, urinary frequency and dyspareunia was obtained. Severity of the symptoms was graded according to the visual analog scale while quantification of blood loss was done using pictorial blood loss assessment chart (PBAC).[13]

Ultrasound evaluation (transabdominal or transvaginal) involved measurement of uterine volume, leiomyoma volume and largest leiomyoma volume. Viscosmi formula was used for the uterine volume, that is, $4/3\ \pi\ W/2 \times L/2 \times T/2$, where W is uterine width on transverse section passing through the uterine fundus; *L* is uterine length, measured on sagittal section from internal cervical os to fundus. *T* is uterine thickness measured on sagittal section between the anterior and posterior walls.[14]

Assessment of leiomyoma volume (average leiomyoma volume)[15] was done by the formula $4/3\ \pi$ abc, where abc represent radii of the sphere in three dimensions. In cases of multiple fibroids, average volume of all the leiomyoma was taken. Volume of the largest leiomyoma calculated as above was also taken as an index parameter. Endometrium was biopsied in premenstrual phase at the start of the therapy.

Drug capsules in strength of 10 mg each were prepared from 200 mg tablet at the start of the study using lactose as filler along with the placebo capsules. Forty identical-looking packets of 90 capsules each were made and were numbered from 1–40 by a third party. These packets were randomised to contain either the drugs or the placebo by the computer-generated random tables. Participants as they were enrolled in the trial were assigned number 1–40 and received either the drug or the placebo accordingly starting from D1–D3 of the cycle. They received the same drug packet every month for three months by a third party. Thus both the patients and the investigator were not aware of the drug being dispensed. For the analysis of the data, the packets were decoded at the end of therapy and the participants receiving mifepristone were allocated to group 1 and those receiving placebo were allocated to group 2.

Patients in both groups were followed monthly in postmenstrual phase or on a fixed day of each month if they became amenorrhoeic for a period of three months. Patients were enquired regarding their blood loss by PBAC and leiomyoma-related symptoms. Measurements including uterine volume, leiomyoma volume and largest leiomyoma volume were repeated each month. Note of serum biochemistry, that is, haemoglobin, liver function tests and kidney function tests and side-effects, such as nausea, vomiting, diarrhoea, headache, fatigue, hot flushes and loss of libido was also made. Endometrial biopsy was repeated on completion of the therapy.

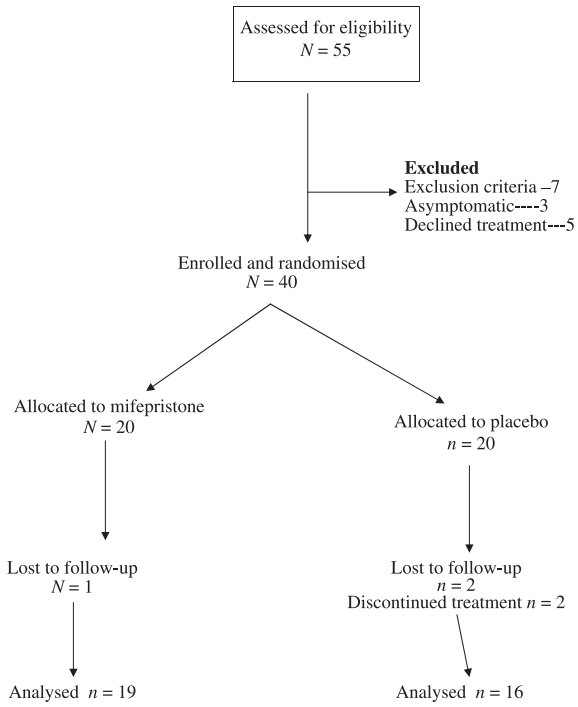

Figure 1 Participant flow through the study.

Data analysis

Unpaired *t*-test and χ^2 test were used to compare the baseline parameters between the interventional versus placebo groups. The severity of symptoms between and within the groups, the percentage change in various symptoms score and ultrasound parameters at different time points were evaluated by using multiple measures ANOVA. If on comparison by multiple measures ANOVA the difference at different time points was found to be significant, the level of significance was determined by using the Tukey's test at 5% level of significance. *P*-value of < 0.05 was taken as significant.

Results

Participant flow through the study is shown in Figure 1. Of the 40 women, one in group 1 (mifepristone) and four in group 2 (placebo) were lost to follow-up during the study period. Baseline parameters of the patients with respect to their demographic profile, symptoms and ultrasound parameters were comparable in both groups (Table 1, Table 2).

Menstrual blood loss (MBL) index declined by 94.8% (188.8 to 9.8) in mifepristone group. This change was significant between the two groups as early as first month (Fig. 2) and this was reflected in the improvement of anaemia in group 1. Mean haemoglobin level increased from 9.5 to 11.2 g/dL (17.8% increase) in group 1 at the end of

three months. In the placebo group it decreased from 10.4 to 9.5 g/dL (8.3% decrease) (Fig. 3).

Among the treated women 84.2% of patients had cessation of menstruation versus none in the placebo group (Table 3) at the end of therapy. Correspondingly, significant number of women was completely relieved of dysmenorrhoea in group 1. About a third of women in group 1 were relieved of pelvic pain (statistically insignificant) while backache, urinary complaints and dyspareunia were not relieved in either group (Table 3). Monthly reports of the severity of these symptoms by visual analog score showed improvement in study group for dysmenorrhoea and pelvic pain only. This change reached statistical significance by the end of second month of therapy (Fig. 4).

Significant reduction in uterine volume was observed in mifepristone-treated women from 256.2 to 188.0 cm^3 (26.6% reduction) at the end of three months of therapy as compared to placebo-treated women (Table 4).

Similarly significant reduction was seen in group 1 for leiomyoma volume from 137.3 to 95.8 cm^3 (30.2%), and largest leiomyoma volume from 140.4 to 97.5 cm^3 (30.0% reduction) at the end of therapy (Table 4). It was noticed that this volume change between the two groups reached significance only at the end of third month, although the effect started as early as the first month of therapy (Fig. 5).

Biochemical parameters like serum bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, blood urea and serum creatinine checked monthly throughout the study period did

Table 1 Demographic characteristics of the patients in both groups

Demographic Characteristics	Group 1 Mifepristone $n = 20$	Group 2 Placebo $n = 20$	*P*-value
Mean ± SD age (years)	40.3 ± 6.8	41.1 ± 9.3	0.7 NS
Parity			
Nulliparous	0	1	
1	4	2	0.6
2	2	4	NS
≥ 3	14	13	
Mean ± SD BMI	24.4 ± 3.1	24.7 ± 3.0	0.7 NS

Values other than mean represent number of patients.
BMI, body mass index; NS, not significant; SD, standard deviation.

Table 2 Characteristics of the patients in both groups

Characteristics Symptoms	Group 1 Mifepristone $n = 20$ *n* (%)	Group 2 Placebo $n = 20$ *n* (%)	*P*-value
Dysmenorrhoea	15 (75)	11 (55)	0.3 NS
Pelvic pain	15 (75)	11 (55)	0.3 NS
Backache	7 (35)	7 (35)	1.0 NS
Urinary complaints	4 (20)	4 (20)	1.0 NS
Dyspareunia	3 (15)	0 (0)	0.2 NS
Volume	Mean ± SD (mL) (after log base 10)⋆	Mean ± SD (mL) (after log base 10)⋆	
Uterine volume	256.2 ± 235.6 (2.2 ± 0.3)	281.7 ± 417.5 (2.1 ± 0.4)	0.6 NS
Leiomyoma volume	137.4 ± 217.8 (1.6 ± 0.7)	117.8 ± 243.5 (1.3 ± 0.7)	0.9 NS
Largest leiomyoma volume	140.5 ± 216.5 (1.6 ± 0.6)	118.1 ± 243.3 (1.3 ± 0.7)	0.9 NS

⋆As SD was greater than the mean, log base 10 has been used. NS, not significant; SD, standard deviation.

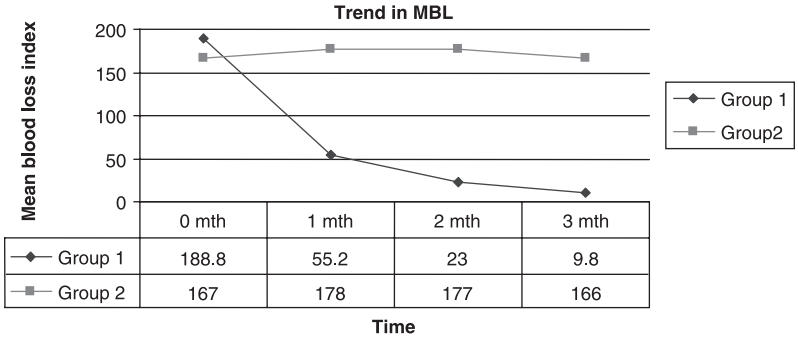

Figure 2 Change in mean menstrual blood loss (MBL) as calculated by pictorial blood loss chart.

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Table 3 Number of patients with complete resolution of symptoms at the end of three months

Symptoms	Group 1 Mifepristone $n = 19$ n (%)	Group 2 Placebo $n = 16$ n (%)	P-value
Cessation of menstruation	16 of 19 (84.2)	0 (0)	0.0 S
Dysmenorrhoea	12 of 15 (80)	2 of 11 (18.2)	0.0 S
Pelvic pain	5 of 15 (33.3)	2 of 11 (18.2)	0.6 NS
Backache	0 of 7 (0)	2 of 7 (28.5)	0.4 NS
Urinary complaints	0 of 4 (0)	0 of 4 (0)	0 NS
Dyspareunia	0 of 3 (0)	0*	0 NS

*None of the patients in group 2 had dyspareunia at the time of recruitment. NS, not significant; S, significant.

Table 4 Effect on ultrasound volume changes

Parameters	Group 1 Mifepristone $n = 19$ Baseline (mean) (after log base 10)	3 months (mean) (after log base 10) (% change)	P-value	Group 2 Placebo $n = 16$ Baseline (mean) (after log base 10)	3 months (mean) (after log base 10) (% change)	P-value
Uterine volume (mL)	256.2 ± 235.6 (2.2 ± 0.3)	188.0 ± 203.5 (2.0 ± 0.3) (–26.6)	0.0 S	281.6 ± 417.5 (2.1 ± 0.4)	281.1 ± 417.2 (2.2 ± 0.4) 0.2	(–0.2) NS
Leiomyoma volume (mL)	137.3 ± 217.8 (1.6 ± 0.7)	95.8 ± 181 (1.3 ± 0.7) (–30.2)	0.0 S	117.7 ± 243.4 (1.3 ± 0.7)	118.3 ± 243.4 (1.3 ± 0.8) (+ 0.5)	0.2 NS
Largest leiomyoma volume (mL)	140.4 ± 216.5 (1.6 ± 0.6)	97.5 ± 180.3 (1.4 ± 0.7) (–30.0)	0.0 S	118.1 ± 243.4 (1.3 ± 0.7)	118.7 ± 243.4 (1.4 ± 0.7) (+ 0.5)	0.7 NS

NS, not significant; S, significant.

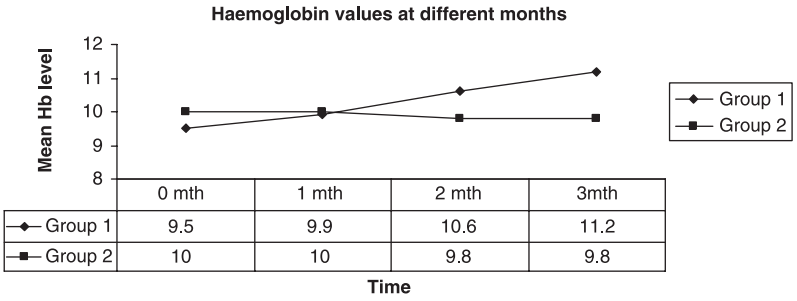

Figure 3 Change in the mean Haemoglobin level.

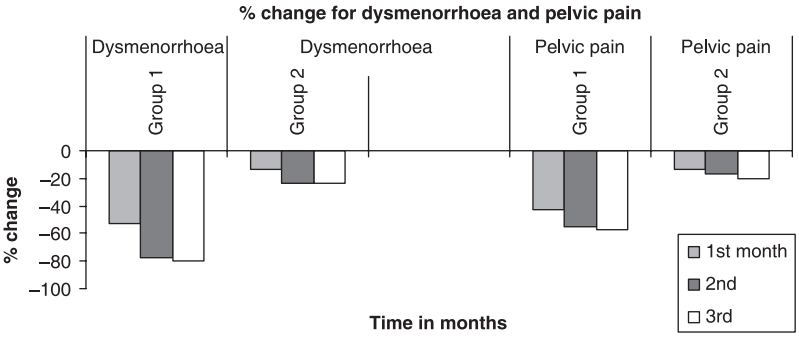

Figure 4 Percentage change for dysmenorrhoea and pelvic pain.

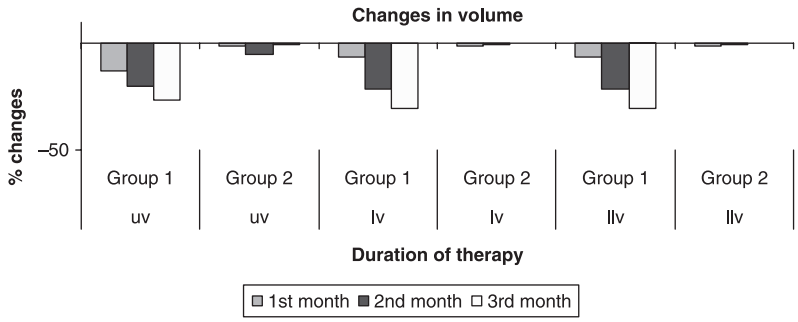

Figure 5 Percentage change for uterine volume (uv), leiomyoma volume (lv), largest leiomyoma volume (llv).

Table 5 Effect on endometrial histopathology at the end of three months

Endometrium type	Group 1 Mifepristone $n = 19$ n (%)	Group 2 Placebo $n = 16$ n (%)	Tukey's test at 5% significance
Normal	4 (21.0)	16 (100)	0.0 S
Atrophic endometrium	1 (5.2)	0 (0)	0.5 NS
Disordered endometrium	2 (10.2)	0 (0)	0.2 NS
Hyperplasia	12 (63.1)	0 (0)	
Simple hyperplasia without atypia	11 (57.8)	0 (0)	0.0 S
Complex hyperplasia without atypia	1 (5.2)	0 (0)	

not show any alteration in either group and remained within normal range.

No side-effects like nausea, vomiting, fatigue, diarrhoea, headache, weakness, hot flashes and loss of libido were seen in either group.

All participants had normal endometrium (proliferative or secretory) at the time of recruitment. At the end of the therapy, 12 of the 19 patients (63.1%) in the mifepristone group had endometrial hyperplasia compared to none in the placebo group. This difference was highly significant. Of these 12 patients, one had complex hyperplasia, while rest developed simple hyperplasia (Table 5). However, none demonstrated atypia. The hyperplasia noted in the participants, however, reverted back to normal as observed upon histopathology when these women had to undergo surgical therapy (hysterectomy or dilation and curettage (D&C) with myomectomy/polypectomy) upon the return of their symptoms or persistence of the lump abdomen following the cessation of the therapy.

Discussion

In the present double-blind placebo-controlled clinical trial, 10 mg mifepristone has been used as other studies have shown that 10 mg is as effective as 25 mg and 50 mg doses with minimal side-effects.[6–12] The drug was started from D1–D3 of cycle, that is, in the early follicular phase so that it starts acting before the development of the dominant follicle. Of note, earlier studies have shown that if the drug is given in late follicular phase it leads to collapse of the dominant follicle and withdrawal bleeding.[16]

Mifepristone caused significant improvement in leiomyoma-related symptoms. MBL declined by 94.8% in group 1 as compared to none in the placebo group at the end of therapy. MBL index as determined by the PBAC had certain limitations. Though women have quite an accurate perception of the degree to which the sanitary towels are soiled over a wide range of menstrual loss, but the extent to which items are soiled is determined partly by the rate of flow and the tolerance of soaked items.[13] Further the passage of clots cannot be assessed in the same manner by the patient and the investigator. To increase the accuracy of our study, we supplied towels made in our hospital of approximately uniform size and absorbency. The reduction in MBL was due to the induction of amenorrhoea and it occurred in 84.2% of patients in group 1 (Table 3). Eisinger *et al.*[1] using the same dose and for similar duration of therapy as ours had similar rate of amenorrhoea (85%). A study by Eisinger *et al.*, by prolonging the duration of therapy to six and 12 months, reported amenorrhoea in only 65% and 70% of patients, respectively.[12] This might indicate that as the duration of treatment increases, the prevalence of amenorrhoea decreases. Similar levels of improvement were seen in symptoms like dysmenorrhoea and pelvic pain with mifepristone in our study which again could be due to amenorrhoea. Improvement in these symptoms and MBL was noticed as early as first month of therapy. However, the difference was significant only after the second month of therapy.

In the present study, the change in uterine and leiomyoma volume showed a significant reduction of 26–30% by the end of the therapy. Different studies using drug in doses of 5–25 mg for varying periods (three to 12 months) have also shown reduction in uterine volume by 27–52% at the end of therapy (Table 6). In a non-randomised trial with therapy lasting for three months, Yang *et al.*[10] using 10 mg dose regimen showed 27% reduction in uterine volume similar to

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Table 6 Effect on uterine volume with different doses and different time periods

Authors	Dose of drug	Treatment length	% reduction in uterine volume	Endometrial hyperplasia
Reinsch *et al.* (1994)	25 mg	3 months	32%	–
Yang *et al.* (1996)	10 mg	3 months	27%	–
	20 mg		33%	–
Eisinger *et al.* (2003)	5 mg	6 months	48%	–
	10 mg		49%	13.9%
Eisiniger *et al.* (2005)	5 mg	12 months	52%	–
	10 mg		53%	4.8%
Fiscella *et al.* (2006)	5 mg	6 months	47%	–
Present study	10 mg	3 months	26.6%	63.2%

our study. However, their study did not take leiomyoma volume into account. Eisinger *et al.*, using 10 mg dose and while prolonging the duration of therapy to six and 12 months, observed 47% and 53% reduction in uterine volume respectively.[12] It is possible that the trend continues further on prolonging the therapy.

Most of the studies with mifepristone have either taken uterine volume or leiomyoma volume as their study parameter. However, studies with GnRH analogs have included both of these parameters in their study. Schlaff *et al.*,[17] using magnetic resonance imaging in their study, have shown that GnRH acts more on the non-myoma volume (42.7% reduction) than on myoma volume (30.4% reduction), and the reduction in uterine volume (35%) is mainly due to its action on the non-myoma volume. In the present study both of these parameters were included, and it is observed that reduction in uterine volume (26%) is almost parallel to reduction in leiomyoma volume (32%), thereby suggesting that mifepristone reduces the uterine volume by acting on leiomyoma and not on non-myoma tissue. The mechanism for the action of mifepristone is unclear. There is evidence that mifepristone decreases the number of progesterone receptors in myometrium and leiomyoma directly. In addition it maintains the hormonal milieu similar to early follicular phase and inhibits the growth of steroid-dependent leiomyoma. The drug also alters the blood flow to leiomyomata by a direct vascular effect.[18]

This study has also shown that reduction in leiomyoma volume (average leiomyoma volume) and the largest leiomyoma volume go hand in hand. Technically measurement of largest leiomyoma volume is easier, less time-consuming and more reproducible than leiomyoma volume. Thus, measurement of largest leiomyoma volume can be a reliable yardstick to monitor the response to therapy.

The drug was well tolerated as evidenced by the low dropout rates and absence of any side-effects. However, 63% patients in mifepristone group had endometrial hyperplasia compared to none in the placebo group. All the patients had simple hyperplasia except one that exhibited complex hyperplasia. However, none of the patients had atypia. Presumably the antiprogesterone effect of mifepristone results in unopposed oestrogen acting on the endometrium resulting in hyperplasia. With higher doses, activation of the hypothalamic pituitary axis may play a role. It has been shown that with higher doses drug-induced rise in plasma ACTH is followed by an increase in not only plasma cortisol but also adrenal androgen and oestradiol. The peripheral aromatisation of adrenal androgen may lead to increased oestradiol level and contribute to the proliferation of the endometrium. So far no case of endometrial carcinoma has been reported in relation to long-term treatment with mifepristone.[19] Newfield *et al.*, also reported regression of endometrial hyperplasia on cessation of therapy when 400 mg/day was used intermittently for treating an adolescent female with cushingoid features.[20] It is noteworthy that in our study all the patients with endometrial hyperplasia (12 patients) showed normal endometrium on histopathology specimens when they underwent surgical intervention in form of hysterectomies and D&C with myomectomy/polypectomy. This indicates that the drug-induced endometrial changes are reversible. Eisinger *et al.*[12] while using two dosage schedules of 5 mg and 10 mg reported endometrial hyperplasia without atypia in only the group receiving 10 mg. In their study hyperplasia was seen in five of 36 (13.9%) of patients at six months and only one of 21 (4.8%) at the end of 12 months. Resumption of menses on prolonging the therapy might have been responsible for the regression of endometrial hyperplasia. Similarly, Fiscella *et al.*,[6] using 5 mg dose for six months, did not observe any incidence of endometrial hyperplasia. However, they did observe a higher rate of characteristic pattern of cystic glandular dilatation among endometrium of treated women.

To conclude three months therapy of 10 mg of mifepristone is efficacious and acceptable for the treatment of symptomatic leiomyoma. Because of the associated risk of endometrial hyperplasia, clinical safety of the drug has yet to be determined by larger sample size with longer periods of treatment.

Acknowledgements

We wish to thank Professor K. K. Sharma (Department of Pharmacology, UCMS and GTB Hospital) for his contribution in preparing the drug in 10 mg strength and placebo.

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