Systematic review of mifepristone for the treatment of uterine leiomyomata

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CRD summary
This review assessed the effects of mifepristone on the size and symptoms of uterine leiomyomata. The authors concluded that mifepristone reduced the size of and symptoms from leiomyoma, but increased endometrial hyperplasia. This was generally a well-conducted review, but a more cautious conclusion might have been appropriate given the limited information from small observational studies.

Authors’ objectives
To assess the effects and safety of mifepristone on the size and symptoms of uterine leiomyomata.

Searching
MEDLINE, EMBASE, LILACS and the Cochrane CENTRAL Register were searched from 1985 to 2002; the search terms were stated. Conference proceedings of four named relevant European and American societies were handsearched from 1995 to 2002. No language restrictions were applied. Reference lists were checked.

Study selection
Study designs of evaluations included in the review
Clinical trials were eligible for inclusion. All of the included studies were before-and-after clinical trials, with three employing randomisation.

Specific interventions included in the review
Studies of daily mifepristone were eligible for inclusion. The included studies used 5 to 50 mg mifepristone for 3 to 6 months. Control interventions, when present, were gonadotropin-releasing hormone (GnRH) agonists and different doses of mifepristone.

Participants included in the review
Studies of women with uterine leiomyomata were included. The included studies were conducted in premenopausal women with symptomatic uterine leiomyomata (5 studies) and women scheduled for myomectomy or hysterectomy (1 study). The age of the participants ranged from 18 to 53 years and all participants had spontaneous menstrual cycles at baseline. Baseline average uterine volumes ranged from 314 to 859 cm3 and leiomyoma volumes ranged from 124 to 169 cm3. Three studies did not report baseline volumes.

Outcomes assessed in the review
Studies that measured uterine or leiomyoma volume before and after treatment were eligible for inclusion. The review also assessed symptoms of leiomyoma and adverse effects. The included studies used ultrasonography to measure volumes. All of the studies questioned participants about adverse effects. Two studies followed patients for up to 9 months post-treatment.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and agreed on the selection.

Assessment of study quality
The authors did not state that they assessed validity. However, they did comment on blinding, the use of placebo control, study design and sample size.

Data extraction
Two reviewers independently extracted the data and reached consensus with the aid of a third reviewer.

**Methods of synthesis**

**How were the studies combined?**
The studies were generally combined in a narrative. The range of percentage decrease in volumes across the individual studies was reported, and the mean percentage reduction in symptoms and rates of adverse effects were calculated.

**How were differences between studies investigated?**
Differences between the studies were discussed in the text.

**Results of the review**
Six studies (n=166) were included: 3 randomised controlled studies (n=73 randomised plus 20 women who were not randomised) and 3 non-randomised before-and-after studies (n=73).

Uterine and leiomyoma volumes.

Mifepristone (all doses combined) reduced uterine volumes by 27 to 49% and reduced leiomyoma volumes by 26 to 74%. Two studies showed greater reductions in leiomyoma volume with increased duration of treatment: a reduction of 21% at 2 months versus 48% at 6 months in one study, and 24% at 1 month versus 56% at 3 months in the other. Studies showed large variations in individual responses to treatment.

Follow-up studies.

One study (n=20) found no change in leiomyoma volume 3 to 9 months after stopping treatment. Another study (n=45) found no increase in uterine volume at 3 months, but found leiomyoma growth in 8 (18%) of 45 women 6 months after stopping treatment.

Controlled trials.

One randomised controlled trial found similar reductions in leiomyoma volume for mifepristone and GnRH agonist, while another found no statistically significant difference in uterine volume between mifepristone and GnRH agonist.

Symptoms.

Mifepristone reduced dysmenorrhoea and pelvic pain in 46 (75%) of 61 women and improved pelvic pressure in 35 (70%) of 50 women. The rates of amenorrhoea ranged from 63% (1 study) to 100% (4 studies, n=118). All patients resumed menstruation 2 to 6 weeks after stopping treatment.

Adverse effects.

Hot flushes were reported by 38% of women. Other adverse events reported were joint pain, fatigue, dizziness, nervousness and loss of appetite.

Endometrial hyperplasia was found in 10 of 36 women (28%) screened after 6 months using endometrial biopsy (1 study). After re-evaluation of the histology, 5 specimens were downgraded from hyperplasia. No cases of complex or atypical hyperplasia were found.

Transaminases were raised transiently in 7 (4%) of 164 women.

**Authors' conclusions**
The studies showed that mifepristone reduced the size of and symptoms from leiomyoma, but increased the development of endometrial hyperplasia.
CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention and outcomes. Given the small number of identified studies, the broad inclusion criteria for study design were appropriate. Several relevant sources were searched and attempts were made to minimise language and publication bias. Two reviewers independently selected studies and extracted the data, thus reducing the potential for bias and errors. Although validity was not formally assessed, several aspects of study quality were discussed.

The authors presented adequate information on the included studies, either in tables or in the text. Given the small number of diverse studies identified, the narrative synthesis was appropriate. Evidence was based on before-and-after data from a small number of patients in a small number of studies and, therefore, is limited. A more cautious conclusion might have been more appropriate given the limitations of the evidence.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that blinded, randomised controlled trials are required to compare the efficacy and safety of mifepristone with placebo and GnRH agonists. They stated that future randomised controlled trials should carefully monitor liver transaminases and endometrial histology.

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