

Research Draft Protocol

# Uterine-Preserving Interventions for the Management of Symptomatic Uterine Fibroids: A Systematic Review of Clinical and Cost-Effectiveness

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**CADTH**

## CONTEXT AND POLICY ISSUES

Uterine fibroids (or leiomyoma) are the most common pelvic tumours and the most common benign tumours in women. Their prevalence increases with age until menopause. They are usually diagnosed in a woman's late reproductive period and are present in up to 40% of women after the age of 40. Approximately 25% of the fibroids are symptomatic (abnormal uterine bleeding, infertility, recurrent pregnancy loss, and the impact of the enlarged uterus on adjacent structures in the pelvis) and often lead to a significant reduction in patient's quality of life as a result of pelvic and abdominal pain, heavy menstrual bleeding, and fertility issues.<sup>1-3</sup> Their appearance and growth are not fully understood but are known to be driven by hormonal factors.<sup>2</sup> Because of their prevalence, fibroids impose a significant burden on affected women and society.

Asymptomatic fibroids can be discovered on routine pelvic examination and verified with an ultrasound. Treatment is generally reserved for women experiencing symptoms and for those who want to become pregnant but have large, disruptive fibroids that impede fertility.

Removal of the uterus (hysterectomy) can be the ultimate solution for many affected women. In the US and Canada, fibroids are responsible for the majority of hysterectomies.<sup>4</sup> However, many patients seek alternatives to such a definitive intervention, to preserve fertility and avoid invasive surgery. Less drastic approaches can now be offered to women with symptomatic fibroids, with a lower level of invasiveness and the ability to preserve the integrity of the uterus. These include myomectomy (surgical removal of the fibroid), uterine artery embolization (disruption of the blood supply to the fibroid with small particles), myolysis (disruption of the blood supply to the fibroid with an electrical current or other methods), and endometrial ablation (destruction of the uterine lining). Various methods are used in these approaches.<sup>5-12</sup> Each technology carries a specific safety and effectiveness profile; therefore, the best candidates for one technology may not be for another. In addition, the technologies all vary significantly in cost. The applicability of a technology may be limited by its accessibility in clinical settings, such as magnetic resonance-guided focused ultrasound. The choice of the intervention is influenced by patient preferences, as well.

The objective of this study is to conduct a systematic review of the clinical and cost-effectiveness evidence of interventions available in Canada for symptomatic uterine fibroids to help select the optimal fibroid management in clinical practice. The optimal strategy may differ depending on various fibroid- or patient-related factors and this will be considered using subgroup analysis when data are available.

## RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of uterine-preserving interventions for the treatment of symptomatic uterine fibroids?
2. What is the cost-effectiveness of uterine-preserving interventions for the treatment of symptomatic uterine fibroids?

Subgroup analyses will be conducted, where appropriate, based on fibroid or patient factors.

# METHODS

## Literature search strategy

A peer-reviewed literature search will be conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, The Cochrane Library, and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine>). Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, cohort studies, and economic studies and guidelines. Where possible, retrieval will be limited to the human population. The search will also be limited to English- or French-language documents. Conference abstracts will be excluded from the search results. The search for randomized controlled trials, controlled clinical trials, cohort studies, and economic studies will not be limited by publication year. The search for health technology assessments, systematic reviews, meta-analyses, and guidelines will be limited to documents published since January 1, 2005. Regular alerts will be established to update all searches until project completion. Two independent reviewers will screen articles using predefined criteria.

## Article selection

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen included/excluded studies. Disagreements will be resolved through discussion until consensus is reached. Duplicate publications of the same trial will be excluded unless they provide additional outcome information of interest. The study inclusion/exclusion form is provided in Appendix 1. The study selection process will be presented in a PRISMA flowchart.

Selection criteria are outlined in Table 1.

<b>Population</b>	Women with symptomatic uterine fibroids  Possible subgroups: <ul style="list-style-type: none"><li>• age</li><li>• size of uterus or fibroid, number of fibroids, location of fibroids</li><li>• types of symptoms (e.g., heavy menstrual bleeding, pain, pressure)</li><li>• previous treatment for uterine fibroids</li><li>• anemia</li><li>• body mass index</li></ul>
<b>Intervention</b>	Uterine-preserving interventions to eliminate or specifically alleviate fibroid-related health problems: <ul style="list-style-type: none"><li>• myomectomy (laparotomy, laparoscopy, or hysteroscopy)</li><li>• myolysis (ultrasound, laser, cryotherapy, radiofrequency, or other methods)</li><li>• uterine artery embolization</li><li>• endometrial ablation (electrosurgery, heat, laser, radiofrequency, or other methods)</li></ul>

	<ul style="list-style-type: none"> <li>• magnetic resonance-guided focused ultrasound ablation</li> <li>• uterine artery occlusion</li> <li>• uterine artery ligation</li> </ul>
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Other uterine-preserving interventions such as those previously listed</li> <li>• Watchful waiting and monitoring</li> <li>• Placebo</li> <li>• Drug therapy (selective progesterone receptor modulators, GnRH agonists)</li> <li>• Hysterectomy</li> </ul>
<b>Outcome Measures</b>	<p>Clinical effectiveness:</p> <ul style="list-style-type: none"> <li>• change in abnormal uterine bleeding</li> <li>• change in pelvic pressure (pain, bladder pressure painful sexual intercourse, urinary frequency, incontinence, nocturia, or constipation)</li> <li>• change in fibroid size</li> <li>• health-related quality of life</li> <li>• pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)</li> <li>• relapse/re-intervention rate</li> <li>• length of hospital stay</li> <li>• patient satisfaction</li> </ul> <p>Cost-effectiveness:</p> <ul style="list-style-type: none"> <li>• incremental cost-effectiveness ratio</li> <li>• quality-adjusted life-year</li> <li>• incremental net monetary benefit</li> <li>• incremental net health benefit</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (operation complications, pregnancy complications, etc.)</li> </ul>
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• Randomized controlled trials and non-randomized studies with a control group</li> <li>• Economic evaluations</li> </ul>

GnRH = gonadotropin-releasing hormone.

## Exclusion criteria

Articles will be excluded if they do not meet the selection criteria in Table 1, or if they are duplicate publications of the same study. Studies of infertile women who are asymptomatic will be excluded.

## Data extraction and critical appraisal

A data extraction form for the clinical effectiveness review will be designed a priori to document and tabulate relevant study characteristics. Data will be extracted by one reviewer, and will be verified by a second reviewer for accuracy and completeness. Any disagreements will be resolved through discussion until consensus is reached. The validated Downs and Black checklist<sup>13</sup> will be used to assess the study quality of randomized controlled trials and non-randomized studies based on the quality of reporting, external validity, and risk of bias. The quality of the economic evaluations will be assessed using the Drummond checklist.<sup>14</sup> A draft of the data extraction form for the clinical studies is provided in Appendix 2.

## Data analysis methods

If trials are available, results will be pooled, where applicable. If meta-analysis is deemed inappropriate because of heterogeneity of the clinical or methodological characteristics of included studies, a narrative synthesis and summary of study findings will instead be conducted.

If meta-analysis is deemed appropriate, meta-analyses will be carried out using Cochrane Review Manager (RevMan) software<sup>15</sup> to derive pooled estimates of interest. If sufficient homogeneity is found across trials such that it is reasonable to assume that all studies are estimating an identical effect, all meta-analyses performed will consider a fixed-effects model; if not, a random-effects model will be used. Forest plots will be presented for all evidence syntheses to supplement reported estimates. Analyses of dichotomous outcomes will be summarized using relative risks and 95% confidence intervals (CI), and analyses of continuous outcomes will be summarized using differences in means and 95% CIs. The chi-square test will be used to assess variations in effects estimates across studies, with  $P < 0.10$  indicating significant heterogeneity across trials. When significant heterogeneity is identified and sufficient data are available, subgroup analyses will be conducted to identify the primary sources of heterogeneity, such as patient characteristics and intervention procedure. Additional sensitivity analyses dealing with outlying data points, study quality, study size, and other factors will also be considered to establish the robustness of findings. If required, and measures of variance are found to be missing from a relevant article, the study's authors will be contacted to determine if the measure can be provided for the purposes of this investigation. If relevant data are not available, variances will be imputed, where possible, based on the available data such as the number of patients in each treatment group, between-group difference, and  $P$  values.

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# Appendix 1: Clinical Study Inclusion/Exclusion Form

## Interventions for the Management of Symptomatic Uterine Fibroids

**Title:**

**First author and year:**

Reviewer:

### Inclusion criteria:

1. **Population:** Yes \_\_\_\_\_ no \_\_\_\_\_ can't tell \_\_\_\_\_

Women with symptomatic uterine fibroids

2. **Intervention:** Yes \_\_\_\_\_ no \_\_\_\_\_ can't tell \_\_\_\_\_

Uterine-preserving interventions to eliminate or specifically alleviate fibroid-related health problems:

- myomectomy (laparotomy, laparoscopy, or hysteroscopy)
- myolysis (ultrasound, laser, cryotherapy, radiofrequency, or other methods)
- uterine artery embolization
- endometrial ablation (electrosurgery, heat, laser, radiofrequency, or other methods)
- magnetic resonance-guided focused ultrasound ablation
- uterine artery occlusion
- uterine artery ligation

3. **Comparator:** Yes \_\_\_\_\_ no \_\_\_\_\_ can't tell \_\_\_\_\_

- Other uterine-preserving interventions such as those previously listed
- Watchful waiting and monitoring
- Placebo
- Drug therapy (selective progesterone receptor modulators, gonadotropin-releasing hormone [GnRH] agonists)
- Hysterectomy

4. **Outcome Measures** (any of): Yes \_\_\_\_\_ no \_\_\_\_\_ can't tell \_\_\_\_\_

- change in bleeding
- change in pelvic pressure (pain, bladder pressure painful sexual intercourse, urinary frequency, incontinence, nocturia, or constipation)
- fibroid size
- health-related quality of life
- pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery, etc.)
- relapse/re-intervention rate
- length of hospital stay
- patient satisfaction
- cost-effectiveness (incremental cost-effectiveness ratio, quality-adjusted life-year, incremental net monetary benefit, incremental net health benefit)
- adverse events (operation complications, pregnancy complications, etc.)

5. **Study Design:** Yes\_\_\_\_\_ no\_\_\_\_\_ can't tell\_\_\_\_\_

Randomized controlled trials, non-randomized studies with a control group, economic evaluations

**Include or exclude:**

- "Yes" (1 to 5 inclusively): Include study and order full paper\_\_\_\_\_
- At least one "can't tell" and others "yes" for 1 to 5: Order full paper for further review\_\_\_\_\_
- "No" (any 1 to 5): Exclude study

## Appendix 2: Clinical Study Data Extraction Form (Draft)

### Interventions for the Management of Symptomatic Uterine Fibroids

Reviewer:

Study title:		
Author:		
ID #: Year:		
<b>Methods</b>		
Study design		
Study duration		
Population <ul style="list-style-type: none"> <li>• Number of patients randomized</li> <li>• Number of patients completing the study</li> </ul>		
Diagnosis (location, size, and number of fibroids)		
Eligibility criteria		
Country of origin		
Industry sponsorship	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	
<b>Baseline Characteristics of Study Participants</b>		
<ul style="list-style-type: none"> <li>• Demographic characteristics (age, BMI, parity, etc.)</li> <li>• Diagnosis (number/location/size of fibroids, size of uterus)</li> <li>• Previous treatment (medical, surgical, etc.)</li> <li>• Anemia</li> <li>• Others</li> </ul>		
<b>Outcomes</b>	<b>Intervention</b>	<b>Comparator</b>
Change in bleeding		
Change in pelvic pressure: <ul style="list-style-type: none"> <li>• bladder pressure</li> <li>• pelvic pain</li> <li>• painful sexual intercourse</li> </ul>		

<ul style="list-style-type: none"> <li>• urinary frequency</li> <li>• incontinence</li> <li>• nocturia</li> <li>• constipation</li> </ul> <p>Fibroid size post-intervention</p> <p>Health-related quality of life</p> <p>Fertility</p> <p>Pregnancy outcomes:</p> <ul style="list-style-type: none"> <li>• infertility</li> <li>• miscarriage</li> <li>• bleeding during pregnancy</li> <li>• full-term delivery</li> </ul> <p>Relapse/re-intervention rate</p> <p>Length of hospital stay</p> <p>Patient satisfaction</p> <p>Adverse events:</p> <ul style="list-style-type: none"> <li>• operation-related complications</li> <li>• pregnancy-related complications</li> </ul>		
<b>Comments</b>		