Evidence Report/Technology Assessment: Number 34

Management of Uterine Fibroids

Summary

Under its Evidence-based Practice Program (http://www.ahrq.gov/clinic/epc/), the Agency for Healthcare Research and Quality (AHRQ) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools. Contractor institutions review all relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities.

Overview / Reporting the Evidence / Methodology / Findings / Future Research / Availability of Full Report

Overview

Uterine leiomyomata, or fibroids, are benign tumors of the uterus made up of smooth muscle and the extracellular matrix proteins collagen and elastin. They are exceptionally common; the cumulative incidence of a diagnosis of fibroids in women aged 25 to 45 is approximately 30 percent. The incidence of fibroids is higher in black women than in white women, and black women appear to have larger and more numerous fibroids at diagnosis. Data do not exist to estimate the total prevalence of fibroids in the population, since it is unclear what proportion of all fibroids are asymptomatic.

Fibroids represent the most common indication for hysterectomy, accounting for 30 percent of hysterectomies in white women and over 50 percent of hysterectomies in black women. The cumulative risk of a hysterectomy for fibroids for all women between ages 25 and 45 is 7 percent; for black women, the risk is as high as 20 percent.

Fibroids can cause abnormal uterine bleeding, dysmenorrhea, and non-cyclic pelvic pain. They also can contribute to symptoms related to an enlarging pelvic mass (e.g., urinary frequency or constipation).

Fibroids are also associated with an increased risk of complications of pregnancy, and with infertility, although it is unclear whether this association is causative. Symptoms associated with fibroids can have a significant impact on quality of life, with scores on standard measures that are comparable to those for other major chronic diseases.

Although there are few data on the nonmedical or outpatient costs associated with symptomatic fibroids, the estimated annual charges for inpatient care for fibroids (primarily surgical) totaled more than $2 billion in 1997.

Despite the frequency with which fibroids are diagnosed and their significant impact on quality of life and use of health resources, there continues to be considerable practice variation and controversy about appropriate treatments for fibroids, especially about the use of hysterectomy. New nonsurgical treatments, such as uterine artery embolization, have received a considerable amount of attention in the lay press and on the World Wide Web.

Researchers at the Duke University Evidence-based Practice Center (EPC) (http://www.ahrq.gov/clinic/epc/dukeepc.htm) reviewed the available evidence on the benefits, risks, and costs of commonly used medical and invasive therapies for uterine fibroids, primarily those treatments currently available in the United States. They also formulated recommendations for future research and developed the framework for a decision model that may be useful in synthesizing evidence about the management of fibroids. The EPC detailed their work in an evidence report prepared for the Agency for Healthcare Research and Quality.

The primary audience for the report is practicing obstetricians and gynecologists (ob-gyns) who represent the majority of physicians providing care for women with symptomatic fibroids. Secondary audiences include:

- Other primary care providers.
- Interventional radiologists.
- Policymakers at the government, payer, integrated delivery system, and hospital levels.
- Patients with uterine fibroids.

Reporting the Evidence

Key Research Questions

The EPC addressed nine key research questions:

1. What are the risks and benefits of hysterectomy and myomectomy in the treatment of symptomatic and asymptomatic fibroids?
2. What are the risks associated with single vs. multiple myomectomies? (i.e., Do women with a solitary clinically apparent fibroid have different outcomes after surgical management than women with multiple fibroids?)
3. Who are appropriate candidates for each procedure?
4. What is the incidence of need for additional treatment after myomectomy or other uterus-sparing interventions?
5. Does additional treatment result in significantly increased morbidity? (i.e., Is the overall risk of adverse outcomes greater with uterus-conserving therapy because of recurrence or persistence resulting in additional therapy with associated risks, compared with immediate definitive therapy such as hysterectomy?)
6. What are the risks and benefits of nonsurgical treatment?

7. What are the costs associated with effective surgical and nonsurgical treatments? (This question was expanded to include other invasive therapies such as uterine artery embolization.)
8. Do risks and benefits differ by race, ethnicity, age, interest in future childbearing, etc.?
9. What are the effects of surgical management of uterine fibroids, especially hysterectomy, on the aging process?

Interventions Assessed

Interventions considered include:

- No intervention ("watchful waiting").
- Medical therapies:
  - Nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Oral contraceptive pills (OCPs).
  - Progestational agents.
  - Other oral agents identified in a literature search (e.g., mifepristone, tibolone, herbal preparations).
  - Gonadotropin-releasing hormone (GnRH) agonists (both as primary therapy and as an adjunct to myomectomy or hysterectomy).
- Invasive therapies:
  - Uterine artery embolization.
  - Coagulation using cautery or laser.
  - Myomectomy.
  - Hysterectomy.

In addition, the EPC reviewed the available evidence on the following strategies for managing asymptomatic fibroids:

- No intervention.
- Prophylactic myomectomy.
- Prophylactic hysterectomy.

The EPC did not attempt to evaluate systematically the evidence on the relative benefits, risks, and costs of different technical approaches to either the diagnosis and followup of fibroids (such as clinical examination, ultrasound, or magnetic resonance imaging) or surgical procedures (e.g., comparing a laparoscopic to an abdominal myomectomy). Although these questions are clearly important, each topic in itself is large and complex enough to warrant a formal systematic review.

*Patient Population and Setting*s

The primary population of interest is women between the ages of 20 and 55 years with symptomatic or asymptomatic uterine fibroids. Separate reviews were performed for women of different racial and ethnic backgrounds, ages (especially perimenopausal women), and plans for future childbearing.

The principal practice settings considered were offices of ob-gyns, offices of other primary care providers, ambulatory surgical centers, interventional radiology suites, and acute care hospitals (for inpatient surgical procedures).

Outcomes Considered

Outcomes considered varied depending on the study and the question being addressed. Data recorded on the abstraction forms included:

- Anatomical/physiological outcomes (change in uterine size, fibroid size, hemoglobin, or hematocrit).
- Symptomatic outcomes (change in symptoms of bleeding, cyclic pain, or non-cyclic pain).
- Pregnancy-related outcomes (pregnancy rates, live-birth rates, pregnancy complications).
- Quality-of-life measures.
- Adverse outcomes (side effects and complications of treatment, development of new symptoms).
- Need for additional treatment after uterus-conserving therapy.
- Resource use (length of stay, medical costs, time lost from work or usual activities).

Methodology

Literature Sources

The primary sources of literature were the following databases (with search years shown in parentheses): MEDLINE (1975-February 2000), HealthSTAR (1975-February 2000), CINAHL (1983-February 2000), CancerLit (1983-February 2000), the Cochrane Library (Issue 3 1999), and EMBASE (1980-January 2000). Searches of these databases were supplemented by secondary searches that included E-mail subscriptions for announcements of newly published journal articles and thorough searching of the reference lists of all included articles and review articles.

The initial search was performed in MEDLINE (and then duplicated in the other databases) and limited to articles in the English language and with human subjects. A previously validated search strategy was used that identifies three subsets:

1. High specificity for randomized controlled trials (RCTs), using terms like "randomized."
2. Moderate specificity, using terms like "blinding."
3. Low specificity, using terms such as "followup studies."

All searches included:

- The MeSH terms "uterine neoplasms," "leiomyoma," "hysterectomy," "hysterectomy, vaginal," and "surgical procedures, laparoscopic."
- Text terms (truncated) for "fibroid," "uterine and leiomyoma)," "hysterectomy," and "myomectomy."

The overwhelming majority of RCTs identified by this initial search examined the use of gonadotropin-releasing hormone (GnRH) agonists, frequently as adjunctive treatment prior to surgery. The remainder of the citations identified were either uncontrolled case series, case series with historical or nonrandomized controls, case-control studies, or in a few instances, prospective cohort studies. A subsequent search (performed initially in EMBASE and then duplicated in MEDLINE and the other databases) was targeted to surgical interventions and included other, less robust study designs. Finally, because few of the targeted articles on hysterectomy and fibroids provided data relevant to question 9 (on the effects of hysterectomy on the aging process), the EPC performed an additional search on hysterectomy without limiting studies to those including patients with fibroids.

Screening of Articles

Empirical study designs considered included controlled trials, prospective trials with historical controls, prospective or retrospective cohort studies, case-control studies, and medium to large case series (n = 20). Studies of these types and review articles were included if they met the following criteria:

- The study population included women with uterine fibroids.
- Data were relevant to one or more of the key questions described above.
- Information was presented on health outcomes, health services use, and/or health care costs for the management of uterine fibroids.

Exclusion criteria were as follows:

- The article was not original research or relevant review.
- The patient population did not include women with uterine fibroids.
- The study design was a single case report.
- The study design was a small case series with fewer than 20 subjects.

For studies on the effects of hysterectomy on aging (question 9), the EPC expanded the inclusion criteria to include studies of all hysterectomies for benign disease, even if the patient population did not include women with fibroids or results were not reported separately for patients with fibroids.

The searches yielded 1,084 articles. Abstracts from these articles were reviewed against the inclusion/exclusion criteria by five physician investigators. A team of two physicians reviewed each abstract; when no abstract was available, the title, source, and MeSH words were reviewed. Articles were included if requested by one member of the review

team. At the full-text screening stage, each article was independently reviewed by two physicians, and disagreements were resolved through discussion. Articles on the effects of hysterectomy on aging were identified by a separate search and were reviewed by a single reviewer with a special interest in gynecological surgery and the aging process.

Data Abstraction Process

Teams of two physicians performed the data abstraction for articles identified by the main searches. For each included article, one physician completed the data abstraction form, and the other served as over-reader. The physician responsible for the primary abstraction also entered data on relevant outcomes and results into a Microsoft¤ Word¤ document. The information from the data abstraction form and the corresponding outcomes and results data were then merged into the evidence table format. The data abstraction assignments were made based on the physicians' clinical interests and expertise.

Again, data on outcomes of hysterectomy that did not explicitly focus on patients with fibroids were not subject to the same level of review. A single reviewer was responsible for selecting articles and assessing their relevance. Because the majority of these articles did not explicitly focus on women with fibroids, they were not abstracted into the evidence tables.

Criteria for Evaluating Article Quality

The majority of the evidence was not of the highest quality according to published grading systems, such as that used by the U.S. Preventive Services Task Force in its evaluation of preventive services or by the American College of Obstetricians and Gynecologists (ACOG) in its Practice Bulletins. In these and most other systems, randomized trials done with rigorous methodology are judged to be of the highest quality, followed by prospective cohort studies. Very few of the identified articles were of these types.

Dismissing this literature entirely would have severely limited the investigators' ability to make any inferences at all. In fact, some study designs, such as large cohort studies or retrospective reviews of administrative data, may be better suited to certain questions, such as those concerning disease incidence or resource use. On the other hand, the quality of these studies clearly varies widely. Therefore, each study was evaluated for factors affecting internal and external validity.

For internal validity, these criteria were:

Randomized allocation to treatment, and appropriate methods for randomization.
Adequate description of patients and controls.
Adequate description of length of followup, loss to followup, and dropout rates.
Recognition and discussion of important statistical issues.

For external validity, these criteria were:

Information about age, racial/ethnic background, pregnancy history, and prior surgical history.
Adequate description of uterine or fibroid size, fibroid location, and fibroid number.
Adequate description of baseline symptoms.
Adequate description of timing of outcomes measurement.
Adequate description of methods used for outcomes measurement.
Description of the validity and reliability of outcomes measures.
Adequate description or reference to clinical care provided to subjects.
Use of standard, validated measures.

Additional Data Sources

The EPC used two additional data sources, primarily to address questions of costs and racial differences:

1. The Nationwide Inpatient Sample (NIS) (http://www.ahrq.gov/data/hcup/hcupnis.htm). The NIS is maintained by the Agency for Healthcare Research and Quality (AHRQ). This database contains administrative discharge data from over 1,000 hospitals in 22 States, representing a stratified sample of 20 percent of U.S. hospitals. The NIS provided supplemental data on frequency and resource use for hysterectomy and myomectomy by age and race (question 7, on cost and question 8, on age and race). These data from the sampled hospitals were converted to national estimates using the weighting variables provided by AHRQ. To assess differences in the proportion of white and black women undergoing each procedure, logistic regression was performed using myomectomy versus hysterectomy as the dependent variable and race as the main independent variable and controlling for age, payer type, and median income.
2. Data from Duke University Medical Center. Data on hospital costs and clinical characteristics affecting cost and complications of patients undergoing myomectomy were obtained from Duke University Medical Center. Records for patients undergoing abdominal myomectomy at Duke University Medical Center between July 1, 1993, and June 30, 1998, were identified using the hospital's cost-accounting system. Data on each patient's age, race, length of stay, insurance status, ZIP code, attending physician, and hospital costs were available from the abstracted discharge data. After the appropriate records were identified, trained abstractors reviewed the charts to collect additional clinical information. Multivariate analysis was used to determine the effects of multiple patient characteristics on outcomes using linear regression for continuous outcomes (length of stay and costs) and logistic regression for dichotomous outcomes (transfusions and complications).

Decision Model

The EPC constructed a Markov model incorporating 11 possible health states:

1. Asymptomatic fibroids, defined as having clinically detectable fibroids, but without symptoms attributable to their presence.
2. Symptomatic fibroids, without side effects/complications of therapy.
3. Symptomatic fibroids, with side effects/complications of therapy.
4. Improved symptoms, with no side effects/complications.
5. Improved symptoms, with side effects/complications.
6. No symptoms, without side effects/complications, defined as having symptoms prior to treatment but experiencing complete relief after treatment with no side effects or complications attributable to therapy.
7. No symptoms, with side effects/complications, defined as having symptoms prior to treatment with complete relief after treatment but with side effects or complications attributable to therapy.
8. Uncomplicated pregnancy (no complications attributable to fibroids).
9. Complicated pregnancy (complications attributable to fibroids).
10. Menopause.
11. Death.

Data needed to estimate transition probabilities were identified. Because data on many of the probabilities were unavailable, a simplified analysis comparing outcomes of hysterectomy, myomectomy, and no treatment in women of different ages was performed.

Findings

The principal findings presented in the report are summarized here:

- The majority of the articles identified by the EPC on management of uterine fibroids do not provide sufficient information to allow determination of either internal or external validity.
- Data were sparse on the natural history of fibroids.
- Data to allow direct comparison of the risks and benefits of myomectomy and hysterectomy are lacking. Data are limited on the effect of myomectomy on long-term symptomatic relief. Hysterectomy appears to result in favorable outcomes in most patients up to 2 years after surgery, based on prospective cohort studies.
- Differences in complication rates between the two procedures may be attributable in part to differences in uterine size, based on multivariate analyses of retrospective series.
- There are no data supporting the use of prophylactic hysterectomy or myomectomy in women with asymptomatic fibroids. There are clear data from multiple study designs that these procedures do have a risk of complications.
- Complications of myomectomy appear to increase with increasing number of fibroids removed, but the exact relationship is unclear, based on retrospective series. Risk of recurrence may be lower when only one fibroid is present and removed, based on case series.

Data are insufficient to allow conclusions about the most appropriate therapy for a given symptomatic patient.

Data are insufficient to allow estimation of the cumulative incidence of recurrent symptoms after conservative management of fibroids. Reported recurrence rates (which may represent either recurrence of incompletely removed fibroids or the development of new fibroids) range up to 50 percent at 5 years after myomectomy, with up to 8 percent of patients undergoing hysterectomy, based on case series.

There are no data addressing the issue of increased morbidity associated with treatment for recurrent or persistent symptoms; i.e., there are no data to allow estimation of the overall relative risk of morbidity associated with immediate definitive surgical therapy, such as hysterectomy, compared with conservative therapy with a subsequent need for additional therapy.

With the exception of trials of GnRH agonist therapy as an adjunct to surgery, there is a remarkable lack of randomized trial data demonstrating the effectiveness of medical therapies (non-steroidals, progestins, or oral contraceptives) in the management of women with symptomatic fibroids.

There is good evidence based on randomized trials that use of GnRH agonists prior to myomectomy or hysterectomy reduces estimated blood loss and may facilitate certain surgical approaches (use of laparoscopic or vaginal approaches and use of transverse abdominal incisions as opposed to vertical incisions). There are no data on the long-term clinical significance of these effects.

There are no data on the non-medical costs associated with symptomatic fibroids.

There also are no data on costs associated with outpatient management apart from wholesale drug prices, which are lowest for non-steroidals (less than $60 for 3 months of therapy), intermediate for progestins and oral contraceptives ($90-120 for 3 months of therapy), and highest for GnRH agonists ($1,500 for 3 months of therapy).

Mean hospital costs for myomectomy are approximately $800 less than mean costs for hysterectomy for fibroids, based on a national sample of hospital discharges.

Black women are more likely than white women to develop fibroids and appear to have larger and more numerous fibroids at treatment, based on both prospective and retrospective cohort studies. Black women are more likely to have in-hospital complications of surgical therapy, which can be attributed at least in part to having larger and more numerous fibroids. Based on the EPC's analysis of NIS data, black women are more likely to undergo both myomectomy and hysterectomy at younger ages than white women. At any given age, black women are more likely to undergo myomectomy than hysterectomy.

Uterus-conserving treatments such as GnRH agonists, uterine artery embolization, and myomectomy may be more effective in perimenopausal women than in premenopausal women, based on case series and subgroup analyses; however, additional studies are needed.

Fibroids are associated with an increased risk of pregnancy complications, including preterm labor, placental abruption, cesarean section, and breech presentation. The degree to which this association reflects causation rather than confounding by factors such as race and age or detection bias is unclear.

- Hysterectomy may result in changes in ovarian steroid levels even when both ovaries are preserved; however, there is a lack of prospective data confirming this.
- Hysterectomy does not appear to adversely affect sexual function in most women. In women with significant symptoms prior to surgery, there may be improvement in sexual functioning.
- Data were insufficient to allow use of the decision model to compare strategies for management of fibroids in terms of effectiveness and cost-effectiveness. The EPC researchers were able to model the likelihood of spontaneous menopause with age, and preliminary work suggests that the model can generate qualitatively reasonable estimates of relative effectiveness.

In general, there was a remarkable lack of high quality evidence supporting the effectiveness of most interventions for symptomatic fibroids. Lack of evidence is not equivalent to evidence of no benefit or of harm. It is possible that some of these interventions are effective in at least some patients. However, the current state of the literature does not permit definitive conclusions about benefit or harm.

Future Research

The lack of high quality evidence for the management of such a common and important condition creates numerous opportunities for researchers.

- Studies into the basic mechanisms of fibroid growth and regulation are needed. Observed differences in the epidemiology of fibroids between racial groups imply that research into the genetics of fibroids would be fruitful.
- More data on the natural history of fibroids, especially the prevalence and biology of asymptomatic fibroids, are needed. Further studies are needed to explore epidemiological and socioeconomic factors that might explain observed differences in the occurrence of fibroids among women of different ethnic groups. The effects of fibroids and their treatment on menopausal women are unknown.
- Meaningful comparison of studies would be significantly enhanced by the development and adaptation of standard methods for assessing and reporting baseline symptoms, uterine anatomy, and responses to treatment. Such standardization also would have the potential to improve clinical practice by allowing comparisons of outcomes between providers and institutions.
- High priority should be given to performing randomized trials of the effectiveness of commonly used medical treatments compared with placebo and with each other for the treatment of specific symptoms. Ideally, trials comparing medical and surgical treatments also should be performed.
- Basic data on the non-medical costs associated with symptomatic fibroids are needed. Additionally, more information on the frequency and nature of outpatient management is needed.
- Finally, longer term prospective studies on the outcomes of hysterectomy, preferably targeted to surgeries performed on women with fibroids, are needed to help determine the type and risk of any long-term adverse consequences.

Availability of Full Report

The full evidence report from which this summary was derived was prepared for the Agency for Healthcare Research and Quality by the Duke University Evidence-based Practice Center under contract 290-97-0014. Publication of the report is anticipated in spring 2001. At that time, printed copies will be available free from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 34, Management of Uterine Fibroids (AHRQ Publication No. 01-E052).

The report will be available online at http://www.ahrq.gov/clinic/epcix.htm.

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