

RESEARCH ARTICLE

Medical Therapies for Uterine Fibroids – A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials

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Abstract

Background

Uterine fibroids are common, often symptomatic and a third of women need repeated time off work. Consequently 25% to 50% of women with fibroids receive surgical treatment, namely myomectomy or hysterectomy. Hysterectomy is the definitive treatment as fibroids are hormone dependent and frequently recurrent. Medical treatment aims to control symptoms in order to replace or delay surgery. This may improve the outcome of surgery and prevent recurrence.

Purpose

To determine whether any medical treatment can be recommended in the treatment of women with fibroids about to undergo surgery and in those for whom surgery is not planned based on currently available evidence.

Study Selection

Two authors independently identified randomised controlled trials (RCT) of all pharmacological treatments aimed at the treatment of fibroids from a list of references obtained by formal search of MEDLINE, EMBASE, Cochrane library, Science Citation Index, and ClinicalTrials.gov until December 2013.

Data Extraction

Two authors independently extracted data from identified studies.

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Data Synthesis

A Bayesian network meta-analysis was performed following the National Institute for Health and Care Excellence—Decision Support Unit guidelines. Odds ratios, rate ratios, or mean differences with 95% credible intervals (CrI) were calculated.

Results and Limitations

A total of 75 RCT met the inclusion criteria, 47 of which were included in the network meta-analysis. The overall quality of evidence was very low. The network meta-analysis showed differing results for different outcomes.

Conclusions

There is currently insufficient evidence to recommend any medical treatment in the management of fibroids. Certain treatments have future promise however further, well designed RCTs are needed.

Introduction

Uterine fibroids are benign tumours of the uterus known as leiomyomas. Malignant transformation is rare. The prevalence of uterine fibroids varies between 5% and 65% depending on age, ethnicity, geographical region and quality of imaging techniques [1–5]. They can occur as single or multiple focal fibroids or can be diffuse [5, 6]. The mechanism for development of uterine fibroids is poorly understood. Both genetic factors such as mutations and environmental factors such as obesity have been implicated in the development of fibroids [7]. Additionally they can be estrogen and progesterone dependent [8]. Symptoms related to fibroids include bleeding irregularities such as heavy, prolonged or irregular periods which may result in iron deficiency, anaemia, subfertility and preterm birth [4, 9–11]. Enlargement of the tumor may cause a mass effect such as pressure on the urinary bladder depending on the anatomical location of the fibroids, or may experience chronic pelvic pain, and pain during sexual intercourse. The proportion of women with fibroids who are symptomatic varies with the size and location of the fibroids with at least 60% of women suffering from one or more symptoms [4, 10, 11]. Classification and subclassification by fibroid position and size is important. Such factors have clinical and research implications. The FIGO PALM-COEIN classification listed eight types of leiomyoma however there is ongoing debate regarding interpretation [12]. Approximately 25% to 50% require treatment [5]. It is suggested that these symptoms and sequelae may decrease the health-related quality of life [13, 14], with 30% suffering symptoms severe enough to miss work [14].

Fibroid treatment includes medical and surgical management. In the USA, between 22 and 63% of women who seek medical help for symptoms related to uterine fibroids undergo surgical management while the remaining women undergo short-term medical treatment with hormonal agonists and antagonists [15]. Of the women who undergo surgical treatment, 84–94% undergo hysterectomy (mostly open or vaginal hysterectomies), 5–9% undergo myomectomy (removal of fibroids; mostly open), 1–4% undergo endometrial ablation (removal or destruction of the endometrium), and 1–3% undergo uterine artery embolization (obstruction of blood flow to uterine artery). The direct treatment costs (including the costs of medical treatments involved in surgery) in US have been estimated to be between US \$6,000 and \$12,000 for hysterectomy, between \$7,000 and \$15,000 for myomectomy, between US \$7,000 and \$13,000

for uterine artery embolization, US\$5,000 for endometrial ablation, and between US \$6,000 and \$9,000 for non-surgical treatment [15, 16]. Thus, uterine fibroids cause a large socio-economic burden.

Although hysterectomy is generally considered a safe operation, complications occur in a significant proportion of patients [15]. These include intra-operative bleeding (about 5% of people undergoing hysterectomy), post-operative fever (about 40% of people undergoing hysterectomy), post-operative surgical site infection (20%), deep vein thrombosis (symptomatic in <1%), vaginal cuff dehiscence (<1%), lower urinary tract injury (5%), gastrointestinal injury (<1%), and femoral or sciatic neuropathy (1% to 2%) [17]. There are alternative medical treatments. A variety of treatments have been used for uterine fibroids which take advantage of their hormonal dependence. These include gonadotropin releasing hormone (GnRH) analogues such as buserelin and, goserelin, selective estrogen receptor modulators (SERM) such as raloxifene, selective progesterone receptor modulators (SPRM) such as ulipristal, and progesterone antagonists such as mifepristone [18–21]. These drugs shrink the size of the fibroid and uterine volume [22] and hence have the potential to provide relief from symptoms in patients who undergo medical treatment. These drugs also provide symptomatic relief in patients waiting for surgery and enable vaginal or laparoscopic surgery, allowing a shorter hospital stay and quicker return to normal activities compared with open surgery [23]. Many of these drugs have a significant adverse event profile which limit the duration of administration. For example, GnRH analogues cause hypoestrogenism which leads to hot flushes and bone loss, limiting the treatment to a maximum of 3 to 6 months. These drugs are also associated with significant costs. While several meta-analyses have been performed comparing different medical treatments used in the management of fibroids [18–20], there has been no multiple treatment comparison meta-analysis or network meta-analysis. Such an analysis allows comparison of multiple treatments simultaneously and a Bayesian analysis allows ranking of treatments based on probability of being the best treatment [24]. The aim of this research is to determine whether any medical treatment is useful in the treatment of women with fibroids about to undergo surgery and in those for whom surgery is not planned.

Methods

The systematic review was conducted following the PRISMA (Transparent Reporting of Systematic Reviews and Meta-analyses) reporting standards, those of the Cochrane collaboration, and the National Institute for Health Research and Clinical Excellence Decision Support Unit (NICE DSU) guidelines [25–27]. The detailed process is described in [S1 Appendix](#). In short, randomised controlled trials which addressed one of the following comparisons were included.

1. Medical versus surgical treatments for fibroids.
2. Different medical treatments for fibroids (studies that compared different doses of the same drug were excluded unless the different drugs were compared with another drug or inactive control).
3. Different medical treatments prior to surgical treatment of fibroids (as before, studies that compared different doses of the same drug were excluded unless the different drugs were compared with another drug or inactive control).

The outcomes assessed for the first comparison included proportion requiring hysterectomy, quality of life, successful pregnancies, and costs.

The outcomes assessed for the second and third comparisons included proportion requiring subsequent surgery, treatment related adverse events, quality of life, blood transfusion

requirements (proportion transfused and amount transfused), haemoglobin levels, successful pregnancies, length of hospital stay, and costs. In the comparison between different medical treatments prior to surgical treatment, the outcomes assessed included mortality, proportion undergoing laparoscopic or vaginal hysterectomy and laparoscopic or hysteroscopic myomectomy as applicable, treatment related adverse events, quality of life, blood transfusion requirements, haemoglobin levels, successful pregnancies (in only those in reproductive age group undergoing myomectomy), and resource measures such as length of hospital stay, operating time, and overall costs. The Cochrane library, MEDLINE, EMBASE, Science Citation Index Expanded, and ClinicalTrials.gov were searched until December 2013. The search strategies are available in [S1 Appendix](#). The references of the included trials were searched to identify further trials. Two authors (KG and JV), independently identified the trials for inclusion and extracted data related to the outcomes mentioned above and assessed the risk of bias (according to Cochrane tools) in the trials. All differences in opinion were resolved by discussion until consensus was reached.

The software Winbugs 1.4 was used to perform the network meta-analysis using a Bayesian framework. The models used for analysis were based on those available from NICE DSU. Binomial likelihood was used for binary outcomes such as proportion of people with successful pregnancies, poisson likelihood for count outcomes such as number of adverse events and for binary outcomes with too many zeros that did not allow the analysis by binomial likelihood, and normal likelihood for continuous outcomes to calculate the odds ratio, rate ratio, and mean difference (MD) with 95% credible intervals (CrI) respectively. We used normal distribution with large variance (10,000) (non-informative priors) for treatment effects to ensure that the choice of prior does not influence the posterior probabilities [27]. Three different starting points (initial values) (three chains) were used and a burn-in of 30,000 iterations to ensure that the final results were not dependent on the starting point. A further 30,000 iterations were run to obtain the effect estimates. The probability of being the best treatment, the probability of being one of the best two treatments, best three treatments and so on [24] was calculated for each outcome to generate a cumulative ranking probability.

Exploration of publication bias and other reporting bias by funnel plot asymmetry and Egger's regression method of exploration of publication bias [28] was planned but not performed because there were less than 10 trials for comparing the same intervention and control.

Summary of findings tables providing the number of studies and participants included in the network meta-analysis, quality of the evidence based on GRADE methodology [29], the relative effect (odds ratio or rate ratio) or the mean difference for each pairwise comparison, and illustrative absolute effect for odds ratio or rate ratio were created for each outcome based on the mean control group proportion or rate (for odds ratio and rate ratio respectively) and control group mean for mean difference and are available in [S3 Appendix](#).

Results

A total of 4237 references were identified by searching the electronic databases and the other sources. A total of 146 full texts were sought and 86 references [30–115] of 75 randomised controlled trials were included for this systematic review. Forty seven trials contributed to the network meta-analysis. The reference flow is shown in [Fig 1](#). The characteristics of included studies are given in tables 1 and 11 in [S3 Appendix](#) for medical treatment and surgical treatment respectively.

Most trials included premenopausal women with symptomatic fibroids. The size of the fibroids varied between the studies. The details of size of the fibroids, menstrual status of the women, and the type of surgery, if any, that the women underwent are available in [S2 Appendix](#) and [S3 Appendix](#).

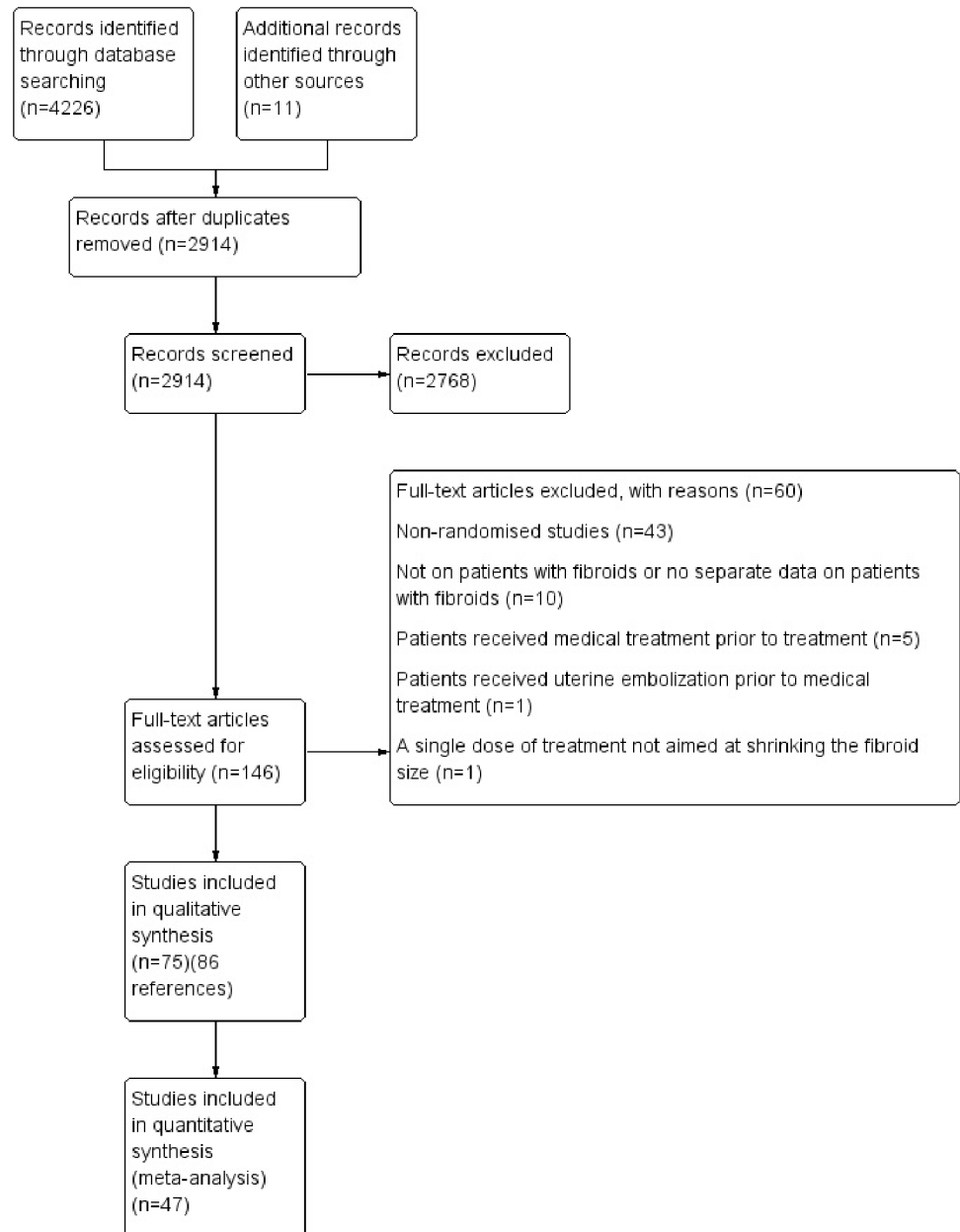


Fig 1. Reference flow diagram.

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Effect estimates

Results are summarised in [Table 1](#). The detailed results are available in [S2 Appendix](#) and [S3 Appendix](#). There was no evidence of inconsistency for any of the analyses.

Medical versus surgical treatment. Two trials compared medical versus surgical treatment [64] [77]. In one trial, the control group received surgery immediately [64] and in another trial, the control group underwent medical treatment and endometrial resection routinely [77]. The randomised participants were followed up for 3 years in the first trial [64] which included 72 premenopausal women with > 10 cm fibroids randomised to medical and surgical treatment and for 1 year in the second trial which included 25 premenopausal women

Table 1. Summary of results.

Outcome	Statistically significant comparisons	Effect estimate of statistically significant comparisons (95% CrI) (non-significant comparisons are not shown)
Medical versus surgical treatment		
Proportion undergoing hysterectomy	Medical treatment versus routine hysterectomy	RR 0.41; 95% CrI 0.29 to 0.57
Medical treatment in women not scheduled to undergo surgery^a		
Proportion undergoing surgery	Tibolone/leuprolide versus placebo	OR 0.08; 95% CrI 0.01 to 0.47
Proportion with adverse events	No statistically significant differences between any of the pairwise comparisons	Not applicable
Number of adverse events	Leuprolide versus placebo	OR 5.57; 95% CrI 3.63 to 8.57
	Mifepristone versus placebo	OR 1.51; 95% CrI 1.09 to 2.08
Haemoglobin	Medroxyprogesterone/leuprolide versus placebo	OR 3.33; 95% CrI 1.1 to 10.03
	Raloxiphene/leuprolide versus placebo	OR 3.78; 95% CrI 1.07 to 13.41
	Leuprolide versus asoprisnil	OR 3.87; 95% CrI 2.16 to 6.92
	Mifepristone versus leuprolide	OR 0.27; 95% CrI 0.16 to 0.46
	Leuprolide versus placebo	MD 0.77; 95% CrI 0.37 to 1.17
Haemoglobin	Mifepristone versus placebo	MD 1.88; 95% CrI 1.06 to 2.69
	Raloxiphene/leuprolide versus placebo	MD 0.97; 95% CrI 0.23 to 1.70
	Ulipristal versus placebo	MD 0.96; 95% CrI 0.61 to 1.31
Haemoglobin	Mifepristone versus Leuprolide	MD 1.11; 95% CrI 0.2 to 2.02
	Medical treatment prior to planned surgery^b	
Proportion with adverse events	Goserelin versus placebo	OR 6.35; 95% CrI 3.33 to 12.10
Number with adverse events	Goserelin versus no active treatment	OR 1.66; 95% CrI 1.33 to 2.06
	Leuprolide versus no active treatment	OR 1.38; 95% CrI 1.17 to 1.62
Proportion undergoing abdominal hysterectomy	Leuprolide versus no active treatment	OR 0.55; 95% CrI 0.4 to 0.75
Proportion undergoing blood transfusion	Goserelin versus no active treatment	OR 0.40; 95% CrI 0.22 to 0.75
	Leuprolide versus no active treatment	OR 0.38; 95% CrI 0.2 to 0.71
Hospital stay	No statistically significant differences between any of the pairwise comparisons	Not applicable
Operating time	Leuprolide versus no active treatment	MD -8.56; 95% CrI -15.28 to -1.84
Haemoglobin	Leuprolide versus no active treatment	MD 1.28; 95% CrI 0.93 to 1.63
	Mifepristone versus no active treatment	MD 1.10; 95% CrI 0.04 to 2.15
	Tibolone/leuprolide versus no active treatment	MD 1.16; 95% CrI 0.65 to 1.66

OR = odds ratio. RaR = rate ratio. MD = mean difference. CrI = credible interval

^a Proportion of people who underwent blood transfusion or amount of blood transfused, proportion of people with successful pregnancies, length of hospital stays, and costs were not reported in any of the trials. Meta-analysis of quality of life outcomes was not performed because of incompatibility of reporting methods. A narrative summary can be found in [S2 Appendix](#).

^b Quality of life, amount of blood transfused, cost of treatment, proportion with a successful pregnancy and proportion undergoing abdominal myomectomy did not provide data for meta-analysis

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with symptomatic fibroids with uterine size between 12 weeks and 16 weeks gestation randomised to medical and surgical treatment [77]. Both trials were at unclear or high risk of bias in most domains. The risk ratio of undergoing hysterectomy at 3 years in the first trial [64] was statistically significantly lower in the medical treatment group than direct surgery group (RR 0.41; 95% CrI 0.29 to 0.57; $P < 0.00001$). The proportion of people who underwent hysterectomy at 12 months was not statistically significant between the medical treatment and medical

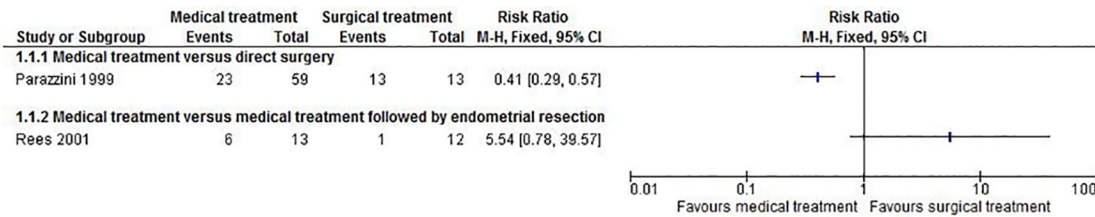


Fig 2. Medical treatment versus surgical treatments for uterine fibroids—proportion undergoing abdominal hysterectomy—forest plot.

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treatment followed by endometrial resection groups in the second trial (RR 5.54; 95% CrI 0.78 to 39.57; $P = 0.09$) [77]. However, neither of these trials reported any other outcome and so we were unable to determine whether there was any significant difference in mortality, number of successful pregnancies or the overall quality of life between medical and surgical treatment. These results are shown in Fig 2.

Medical treatment in women not scheduled to undergo surgery. Outcomes investigated were: proportion requiring surgery; treatment related adverse events; quality of life; blood transfusion requirements (proportion and amount transfused); haemoglobin levels; successful pregnancies; length of hospital stay and costs.)

The proportion of women requiring surgery in the short-term was statistically significantly lower in the tibolone/leuprolide group compared to no treatment (OR 0.08; 95% CrI 0.01 to 0.47). There were no statistically significant differences in the proportion of people with adverse events between any of the treatments and the placebo. Leuprolide (OR 5.57; 95% CrI 3.63 to 8.57), mifepristone (OR 1.51; 95% CrI 1.09 to 2.08), medroxyprogesterone/leuprolide (OR 3.33; 95% CrI 1.1 to 10.03) and raloxifene/leuprolide (OR 3.78; 95% CrI 1.07 to 13.41) had statistically significant more adverse events than the placebo group. Leuprolide had statistically significantly more adverse events than asoprisnil (OR 3.87; 95% CrI 2.16 to 6.92) and mifepristone had significantly fewer adverse events than leuprolide (OR 0.27; 95% CrI 0.16 to 0.46). All six studies reporting quality of life as an outcome found an increased quality of life scores with medical treatments, because of incompatibility of different reporting methods used meta-analysis is not appropriate. A more detailed narrative summary can be found in S2 App. Four treatments were found to statistically significantly increase haemoglobin levels compared to a group receiving placebo. These included: leuprolide (MD 0.77; 95% CrI 0.37 to 1.17), mifepristone (MD 1.88; 95% CrI 1.06 to 2.69), raloxifene/leuprolide (MD 0.97; 95% CrI 0.23 to 1.7) and ulipristal (MD 0.96; 95% CrI 0.61 to 1.31). Mifepristone was found to cause significantly higher haemoglobin levels than leuprolide (MD 1.11; 95% CrI 0.20 to 2.02). These results are summarised in Fig 3. More detailed results are described in S2–S17 Figs, including forest plots and cumulative probability rankings.

The effect estimates of each pairwise comparison are available in tables 3–10 in S3 Appendix. The proportion of people with successful pregnancies, proportion of people who underwent blood transfusion or amount of blood transfused, length of hospital days, and costs were not reported in any of the trials.

Medical treatment in women prior to planned surgery. Outcomes investigated were: proportion undergoing abdominal myomectomy; proportion undergoing abdominal hysterectomy; treatment related adverse events; quality of life; blood transfusion requirements (proportion and amount transfused); haemoglobin levels; successful pregnancies; length of hospital stay; operating time and costs

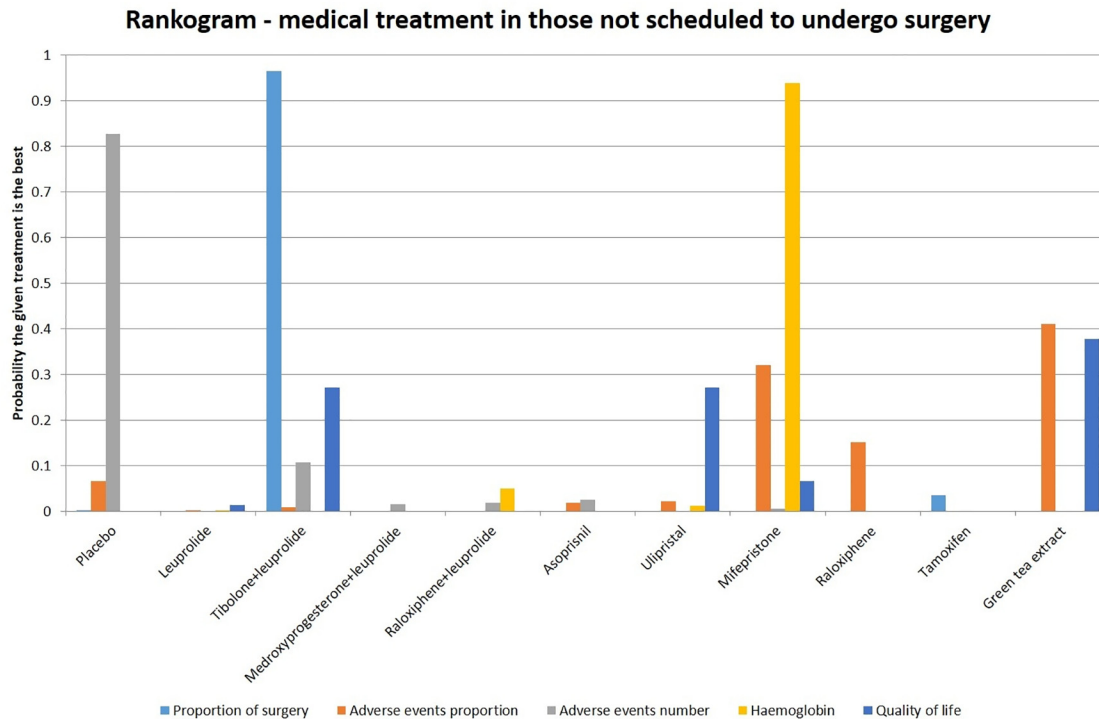


Fig 3. Different medical treatments in those not scheduled to undergo surgery—rankogram.

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The proportion of women with adverse events was statistically significantly higher in the goserelin group compared to those receiving placebo (OR 6.35; 95% CrI 3.33 to 12.10). Goserelin also caused a statistically significant increase in the number of women with adverse events compared to the group with no active treatment (OR 1.66; 95% CrI 1.33 to 2.06), as did leuprolide (OR 1.38; 95% CrI 1.17 to 1.62). Leuprolide did significantly reduce the proportion of women undergoing abdominal hysterectomy in the short-term compared to women receiving no active treatment (OR 0.55; 95% CrI 0.40 to 0.75). Both goserelin (OR 0.40; 95% CrI 0.22 to 0.75) and leuprolide (OR 0.38; 95% CrI 0.20 to 0.71) significantly reduced the proportion of women undergoing blood transfusion. There were no statistically significant differences in hospital stay between any of the treatments and no active treatment. Leuprolide reduced the operating time compared to the group receiving no active treatment (MD -8.56; 95% CrI -15.28 to -1.84). Three treatments were found to statistically increase haemoglobin levels compared to the group receiving no active treatment. These were: leuprolide (MD 1.28; 95% CrI 0.93 to 1.63), mifepristone (MD 1.10; 95% CrI 0.04 to 2.15) and tibolone/leuprolide (MD 1.16; 95% CrI 0.65 to 1.66). These results are summarised in Fig 4. More detailed results are described in S18–S45 Figs, including forest plots and cumulative probability rankings.

The effect estimates of each pairwise comparison are available in tables 13–26 in S3 Appendix. Quality of life, amount of blood transfused, cost of treatment, proportion with a successful pregnancy and proportion undergoing abdominal myomectomy did not have available data for meta-analysis.

Discussion

This is the first network meta-analysis assessing the effect of different pharmacological interventions in the treatment of uterine fibroids.

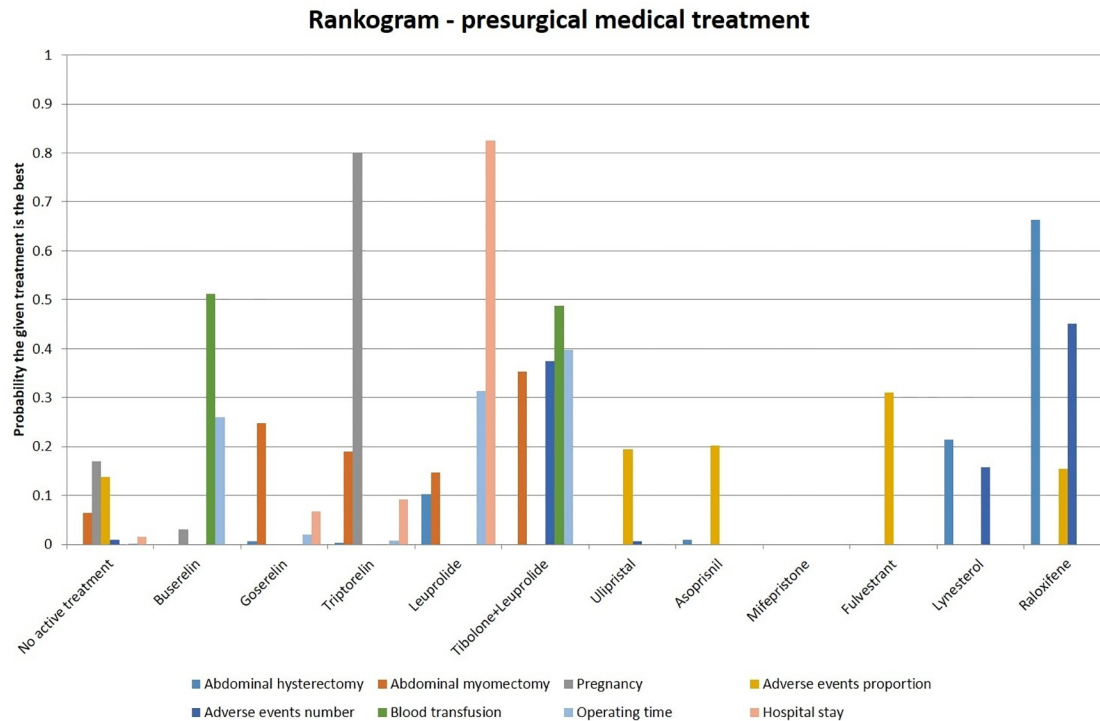


Fig 4. Different presurgical medical treatments—rankogram.

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Medical versus surgical treatment

Only two trials compared medical with surgical treatment. Network meta-analysis could not be performed because of differences in the treatments in the two trials. The trials were at unclear or high risk of bias for most domains and the overall quality of evidence was poor. The only outcome of interest reported was the proportion that underwent hysterectomy. The two trials reported different results and so there is currently no evidence to recommend medical treatment as a substitute for surgical treatment.

Medical treatment in women not scheduled to undergo surgery

The network meta-analyses showed different results for different outcomes. In the ranking of treatments for different outcomes, more than 80% probability of one treatment being the best treatment was noted only in the proportion undergoing surgery in which Tibolone/leuprolide combination was the best treatment, the number of adverse events for which placebo was the best treatment, and haemoglobin for which mifepristone was the best treatment. The number of adverse events included disease-related and treatment-related adverse events. The severity of the adverse events was not reported but most of the adverse events reported appeared to be mild. In addition, there is currently no evidence to suggest that patients consider one type of adverse event to be worse than another type. Until the relative importance and the variability in the relative importance that patients assign to these adverse events is obtained in relation to the benefits seen in avoiding or postponing surgery, one cannot advocate medical treatment for the control of symptoms. This may be captured in quality of life instruments. In addition, the treatment can be given only for short periods of time because of the long-term risks, such as increased rate of bone loss for GnRH analogues, and it is not clear whether medical

treatment only delays the inevitable at significant costs and adverse events without any major advantages. Approximately, 45% of patients who received no active treatment had surgery during the follow-up period. A minimum sample size of 932 participants will be required to detect a 20% reduction in the proportion of patients who require surgery with an alpha error of 0.05 and power of 0.8. The final haemoglobin level is higher for a number of interventions compared to no active treatment but the clinical significance of this difference in haemoglobin is not known since the trials did not report the blood transfusion requirements. Iron deficiency itself may be relevant for the treatment of fibroids with associated heavy menstrual bleeding and post-surgically where it may be slow to correct. Short-term quality of life appears to be improved for a number of treatments compared to placebo despite the increase in adverse events. However, long-term follow-up is necessary to determine whether this improvement in short-term quality of life and reduction in the proportion of people who undergo hysterectomy persists in the long run. The same reporting methodology must be used in future trials to allow for meta-analysis of results. Clinically long term assessment is crucial because fibroids are a long term condition. Short-term trials are of limited value to a gynaecologist deciding treatment for a given patient. A well designed randomised controlled trial with cost-effectiveness analysis is necessary before medical treatment can be routinely recommended for women with fibroids who are not scheduled to undergo hysterectomy.

Medical treatment in women prior to planned surgery

The network meta-analyses again showed different results for different outcomes. In the ranking of treatments for different outcomes, more than 80% probability of one treatment being the best treatment was noted only in the length of hospital stay in which leuprolide was the best treatment. The trials were at high risk of bias and overall quality of evidence was low. A number of treatments had more adverse events than inactive treatment. As mentioned earlier, until the relative importance that patients ascribe to these adverse events is determined, one cannot advocate medical treatment for the control of symptoms during the waiting time. Although leuprolide appears to show benefit in a number of outcomes such as reduction in the proportion of women requiring abdominal hysterectomy, blood transfusion requirement, and length of hospital stay, the trials were at high risk of bias and the overall quality of evidence was low. So, no medical treatment can be recommended currently during the waiting time for surgery. Approximately, 75% of patients who received no active treatment had abdominal hysterectomy. A minimum sample size of 304 participants will be required to detect a 20% reduction in the proportion of patients who require hysterectomy with an alpha error of 0.05 and power of 0.8. Again, a well-designed randomised controlled trial with cost-effectiveness analysis is necessary before medical treatment can be routinely recommended for women waiting for surgery for fibroids.

The major strengths of this review were that we followed the PRISMA guidance for reporting and included all randomized controlled trials on the topic without any restriction on the language of publication. We also selected studies and extracted data independently, which decreases the errors. We chose non-informative priors and used three different chains of initial values which decreases the risk of error due to the choice of prior and initial values. The major weaknesses of the review are the risk of bias in the included trials and the sparse data for many of the outcomes despite the number of trials included in this review.

This is the first network meta-analysis on this topic. Some previous head-to-head comparisons found insufficient evidence to support medical treatment for fibroids [18] [20] while one review advocated the use of pre-operative GnRH analogues [22]. The differences in the conclusion between our review and the review that advocated the use of medical treatment may be

because of new trials conducted in this field in the last 15 years and the use of clinical outcomes rather than surrogate outcomes such as decrease in fibroid size.

There is currently no evidence to support the routine use of medical treatment in women with uterine fibroids. Several treatments appear promising but the efficacy of these drugs should be assessed in low risk of bias trials powered to measure differences in clinical outcomes. Ideally these would be both large scale and long term. Ultimately medical treatment may involve continued treatment over a period of time to prevent surgery.

Supporting Information

S1 Appendix. Methods.

(DOCX)

S2 Appendix. Detailed results.

(DOCX)

S3 Appendix. Tables.

(DOCX)

S1 Fig. Medical treatment versus surgical treatment for uterine fibroids-proportion undergoing abdominal hysterectomy-forest plot.

(JPG)

S2 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion undergoing surgery-forest plot.

(JPG)

S3 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion undergoing surgery-network plot.

(JPG)

S4 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion undergoing surgery-probability of best treatment.

(JPG)

S5 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion undergoing surgery-cumulative ranking probability.

(JPG)

S6 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion with adverse events-forest plot.

(JPG)

S7 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion with adverse events-network plot.

(JPG)

S8 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion with adverse events-probability of best treatment.

(JPG)

S9 Fig. Medical treatment in women not scheduled to undergo surgery-Proportion with adverse events-cumulative ranking probability.

(JPG)

S10 Fig. Medical treatment in women not scheduled to undergo surgery-Number of adverse events-forest plot.

(JPG)

S11 Fig. Medical treatment in women not scheduled to undergo surgery-Number of adverse events-network plot.

(JPG)

S12 Fig. Medical treatment in women not scheduled to undergo surgery-Number of adverse events-probability of best treatment.

(JPG)

S13 Fig. Medical treatment in women not scheduled to undergo surgery-Number of adverse events-cumulative ranking probability.

(JPG)

S14 Fig. Medical treatment in women not scheduled to undergo surgery-Haemoglobin-forest plot.

(JPG)

S15 Fig. Medical treatment in women not scheduled to undergo surgery-Haemoglobin-network plot.

(JPG)

S16 Fig. Medical treatment in women not scheduled to undergo surgery-Haemoglobin-probability of best treatment.

(JPG)

S17 Fig. Medical treatment in women not scheduled to undergo surgery-Haemoglobin-cumulative ranking probability.

(JPG)

S18 Fig. Presurgical medical treatment-Proportion with adverse events-forest plot.

(JPG)

S19 Fig. Presurgical medical treatment-proportion with adverse events-network plot.

(JPG)

S20 Fig. Presurgical medical treatment-proportion with adverse events-probability of best treatment.

(JPG)

S21 Fig. Presurgical medical treatment-proportion with adverse events-cumulative ranking probability.

(JPG)

S22 Fig. Presurgical medical treatment-number with adverse events-forest plot.

(JPG)

S23 Fig. Presurgical medical treatment-number with adverse events-network plot.

(JPG)

S24 Fig. Presurgical medical treatment-number with adverse events-probability of best treatment.

(JPG)

S25 Fig. Presurgical medical treatment-number with adverse events-cumulative ranking probability.

(JPG)

S26 Fig. Presurgical medical treatment-proportion undergoing abdominal hysterectomy-forest plot.

(JPG)

S27 Fig. Presurgical medical treatment-proportion undergoing abdominal hysterectomy-network plot.

(JPG)

S28 Fig. Presurgical medical treatment-proportion undergoing abdominal hysterectomy-probability of best treatment.

(JPG)

S29 Fig. Presurgical medical treatment-proportion undergoing abdominal hysterectomy-cumulative ranking probability.

(JPG)

S30 Fig. Presurgical medical treatment-proportion undergoing blood transfusion-forest plot.

(JPG)

S31 Fig. Presurgical medical treatment-proportion undergoing blood transfusion-network plot.

(JPG)

S32 Fig. Presurgical medical treatment-proportion undergoing blood transfusion-probability of best treatment.

(JPG)

S33 Fig. Presurgical medical treatment-proportion undergoing blood transfusion-cumulative ranking probability.

(JPG)

S34 Fig. Presurgical medical treatment-hospital stay-forest plot.

(JPG)

S35 Fig. Presurgical medical treatment-hospital stay-network plot.

(JPG)

S36 Fig. Presurgical medical treatment-hospital stay-probability of best treatment.

(JPG)

S37 Fig. Presurgical medical treatment-hospital stay-cumulative ranking probability.

(JPG)

S38 Fig. Presurgical medical treatment-operating time-forest plot.

(JPG)

S39 Fig. Presurgical medical treatment-operating time-network plot.

(JPG)

S40 Fig. Presurgical medical treatment-operating time-probability of best treatment.

(JPG)

S41 Fig. Presurgical medical treatment-operating time-cumulative ranking probability.
(JPG)

S42 Fig. Presurgical medical treatment-haemoglobin-forest plot.
(JPG)

S43 Fig. Presurgical medical treatment-haemoglobin-network plot.
(JPG)

S44 Fig. Presurgical medical treatment-haemoglobin-probability of best treatment.
(JPG)

S45 Fig. Presurgical medical treatment-haemoglobin-cumulative ranking probability.
(JPG)

S1 PRISMA Checklist. Completed PRISMA Checklist for meta-analyses.
(DOC)

Author Contributions

Conceived and designed the experiments: IF TR. Performed the experiments: KG JV TR. Analyzed the data: KG JV LB. Contributed reagents/materials/analysis tools: KG. Wrote the paper: KG JV IF LB TR. Revisions: LB KG.

References

1. Baird DD, Hill MC, Schectman JM, Hollis BW. Vitamin d and the risk of uterine fibroids. *Epidemiology*. 2013; 24(3):447–53. doi: [10.1097/EDE.0b013e31828acca0](https://doi.org/10.1097/EDE.0b013e31828acca0) PMID: [23493030](https://pubmed.ncbi.nlm.nih.gov/23493030/).
2. Marsh EE, Ekpo GE, Cardozo ER, Brocks M, Dune T, Cohen LS. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18–30 years old): a pilot study. *Fertility and sterility*. 2013; 99(7):1951–7. doi: [10.1016/j.fertnstert.2013.02.017](https://doi.org/10.1016/j.fertnstert.2013.02.017) PMID: [23498888](https://pubmed.ncbi.nlm.nih.gov/23498888/).
3. Myers SL, Baird DD, Olshan AF, Herring AH, Schroeder JC, Nylander-French LA, et al. Self-report versus ultrasound measurement of uterine fibroid status. *Journal of women's health*. 2012; 21(3):285–93. doi: [10.1089/jwh.2011.3008](https://doi.org/10.1089/jwh.2011.3008) PMID: [22044079](https://pubmed.ncbi.nlm.nih.gov/22044079/); PubMed Central PMCID: PMC3298676.
4. Zimmermann A, Bernuit D, Gerlinger C, Schaefer M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC women's health*. 2012; 12:6. doi: [10.1186/1472-6874-12-6](https://doi.org/10.1186/1472-6874-12-6) PMID: [22448610](https://pubmed.ncbi.nlm.nih.gov/22448610/); PubMed Central PMCID: PMC3342149.
5. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *American journal of obstetrics and gynecology*. 2003; 188(1):100–7. PMID: [12548202](https://pubmed.ncbi.nlm.nih.gov/12548202/).
6. Moorman PG, Leppert P, Myers ER, Wang F. Comparison of characteristics of fibroids in African American and white women undergoing premenopausal hysterectomy. *Fertility and sterility*. 2013; 99(3):768–76.e1. doi: [10.1016/j.fertnstert.2012.10.039](https://doi.org/10.1016/j.fertnstert.2012.10.039) PMID: [23199610](https://pubmed.ncbi.nlm.nih.gov/23199610/); PubMed Central PMCID: PMC3632655.
7. Segars JH, Parrott EC, Nagel JD, Guo XC, Gao X, Birnbaum LS, et al. Proceedings from the Third National Institutes of Health International Congress on Advances in Uterine Leiomyoma Research: comprehensive review, conference summary and future recommendations. *Human reproduction update*. 2014. doi: [10.1093/humupd/dmt058](https://doi.org/10.1093/humupd/dmt058) PMID: [24401287](https://pubmed.ncbi.nlm.nih.gov/24401287/).
8. Bulun SE. Uterine fibroids. *The New England journal of medicine*. 2013; 369(14):1344–55. doi: [10.1056/NEJMr1209993](https://doi.org/10.1056/NEJMr1209993) PMID: [24088094](https://pubmed.ncbi.nlm.nih.gov/24088094/).
9. Moshesh M, Olshan AF, Saldana T, Baird D. Examining the relationship between uterine fibroids and dyspareunia among premenopausal women in the United States. *The journal of sexual medicine*. 2014; 11(3):800–8. PMID: [24467730](https://pubmed.ncbi.nlm.nih.gov/24467730/)
10. Puri K, Famuyide AO, Erwin PJ, Stewart EA, Laughlin-Tommaso SK. Submucosal fibroids and the relation to heavy menstrual bleeding and anemia. *American journal of obstetrics and gynecology*. 2014; 210(1):38.e1–7. doi: [10.1016/j.ajog.2013.09.038](https://doi.org/10.1016/j.ajog.2013.09.038) PMID: [24080304](https://pubmed.ncbi.nlm.nih.gov/24080304/).

11. Kroon B, Johnson N, Chapman M, Yazdani A, Hart R, Australasian CCEPoTeg. Fibroids in infertility—consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence). *The Australian & New Zealand journal of obstetrics & gynaecology*. 2011; 51(4):289–95. doi: [10.1111/j.1479-828X.2011.01300.x](https://doi.org/10.1111/j.1479-828X.2011.01300.x) PMID: [21806566](https://pubmed.ncbi.nlm.nih.gov/21806566/).
12. Munro MG, Critchley HO, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? *American journal of obstetrics and gynecology*. 2012; 207(4):259–65. doi: [10.1016/j.ajog.2012.01.046](https://doi.org/10.1016/j.ajog.2012.01.046) PMID: [22386064](https://pubmed.ncbi.nlm.nih.gov/22386064/).
13. Arleo EK, Masheb RM, Pollak J, McCarthy S, Tal MG. Fibroid volume, location and symptoms in women undergoing uterine artery embolization: does size or position matter? *International journal of fertility and women's medicine*. 2007; 52(2–3):111–20. PMID: [18320870](https://pubmed.ncbi.nlm.nih.gov/18320870/).
14. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. *American journal of obstetrics and gynecology*. 2013; 209(4):319 e1–e20. doi: [10.1016/j.ajog.2013.07.017](https://doi.org/10.1016/j.ajog.2013.07.017) PMID: [23891629](https://pubmed.ncbi.nlm.nih.gov/23891629/).
15. Carls GS, Lee DW, Ozminkowski RJ, Wang S, Gibson TB, Stewart E. What are the total costs of surgical treatment for uterine fibroids? *Journal of women's health*. 2008; 17(7):1119–32. doi: [10.1089/jwh.2008.0456](https://doi.org/10.1089/jwh.2008.0456) PMID: [18687032](https://pubmed.ncbi.nlm.nih.gov/18687032/).
16. Cardozo ERC, A.D.; Banks N.K.; Henne M.B.; Stegmann B.J.; Segars J.H.;. The estimated annual cost of uterine leiomyomata in the United States. *American journal of obstetrics and gynecology*. 2012; 206(3):211 e1–9. doi: [10.1016/j.ajog.2011.12.002](https://doi.org/10.1016/j.ajog.2011.12.002) PubMed Central PMCID: [PMC3292655](https://pubmed.ncbi.nlm.nih.gov/PMC3292655/). PMID: [22244472](https://pubmed.ncbi.nlm.nih.gov/22244472/)
17. Hodges KR, Davis BR, Swaim LS. Prevention and management of hysterectomy complications. *Clinical obstetrics and gynecology*. 2014; 57(1):43–57. doi: [10.1097/GRF.000000000000004](https://doi.org/10.1097/GRF.000000000000004) PMID: [24488052](https://pubmed.ncbi.nlm.nih.gov/24488052/).
18. Song H, Lu D, Navaratnam K, Shi G. Aromatase inhibitors for uterine fibroids. *The Cochrane database of systematic reviews*. 2013; 10:CD009505. doi: [10.1002/14651858.CD009505.pub2](https://doi.org/10.1002/14651858.CD009505.pub2) PMID: [24151065](https://pubmed.ncbi.nlm.nih.gov/24151065/).
19. Deng L, Wu T, Chen XY, Xie L, Yang J. Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. *The Cochrane database of systematic reviews*. 2012; 10:CD005287. doi: [10.1002/14651858.CD005287.pub4](https://doi.org/10.1002/14651858.CD005287.pub4) PMID: [23076912](https://pubmed.ncbi.nlm.nih.gov/23076912/).
20. Tristan M, Orozco LJ, Steed A, Ramirez-Morera A, Stone P. Mifepristone for uterine fibroids. *The Cochrane database of systematic reviews*. 2012; 8:CD007687. doi: [10.1002/14651858.CD007687.pub2](https://doi.org/10.1002/14651858.CD007687.pub2) PMID: [22895965](https://pubmed.ncbi.nlm.nih.gov/22895965/).
21. Biglia N, Carinelli S, Maiorana A, D'Alonzo M, Lo Monte G, Marci R. Ulipristal acetate: a novel pharmacological approach for the treatment of uterine fibroids. *Drug design, development and therapy*. 2014; 8:285–92. doi: [10.2147/DDDT.S54565](https://doi.org/10.2147/DDDT.S54565) PMID: [24591818](https://pubmed.ncbi.nlm.nih.gov/24591818/); PubMed Central PMCID: [PMC3934585](https://pubmed.ncbi.nlm.nih.gov/PMC3934585/).
22. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. *The Cochrane database of systematic reviews*. 2001;(2:): CD000547. doi: [10.1002/14651858.CD000547](https://doi.org/10.1002/14651858.CD000547) PMID: [11405968](https://pubmed.ncbi.nlm.nih.gov/11405968/).
23. Johnson N, Barlow D, Lethaby A, Tavender E, Curr L, Garry R. Methods of hysterectomy: systematic review and meta-analysis of randomised controlled trials. *Bmj*. 2005; 330(7506):1478. doi: [10.1136/bmj.330.7506.1478](https://doi.org/10.1136/bmj.330.7506.1478) PMID: [15976422](https://pubmed.ncbi.nlm.nih.gov/15976422/); PubMed Central PMCID: [PMC558455](https://pubmed.ncbi.nlm.nih.gov/PMC558455/).
24. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of clinical epidemiology*. 2011; 64(2):163–71. doi: [10.1016/j.jclinepi.2010.03.016](https://doi.org/10.1016/j.jclinepi.2010.03.016) PMID: [20688472](https://pubmed.ncbi.nlm.nih.gov/20688472/).
25. Higgins J, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
26. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*. 2009; 6(7):e1000097. doi: [10.1371/journal.pmed.1000097](https://doi.org/10.1371/journal.pmed.1000097) PMID: [19621072](https://pubmed.ncbi.nlm.nih.gov/19621072/)
27. Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. Available: <http://www.nicedsuorg.uk/TSD1%20Introductionfinal080512.pdf>. 2012 (Accessed 11 March 2014).
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997; 315(7109):629–34. PMID: [9310563](https://pubmed.ncbi.nlm.nih.gov/9310563/); PubMed Central PMCID: [PMC2127453](https://pubmed.ncbi.nlm.nih.gov/PMC2127453/).
29. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *Journal of clinical epidemiology*. 2011; 64(4):380–2. doi: [10.1016/j.jclinepi.2010.09.011](https://doi.org/10.1016/j.jclinepi.2010.09.011) PMID: [21185693](https://pubmed.ncbi.nlm.nih.gov/21185693/).

30. Palomba S, Orio F, Russo T, Falbo A, Tolino A, Lombardi G, et al. Antiproliferative and proapoptotic effects of raloxifene on uterine leiomyomas in postmenopausal women. *Fertility and sterility*. 2005; 84(1):154–61. WOS:000230544800026. PMID: [16009171](#)
31. De Aloysio D, Altieri P, Penacchioni P, Salgarello M, Ventura V. Bleeding patterns in recent postmenopausal outpatients with uterine myomas: Comparison between two regimens of HRT. *Maturitas*. 1998; 29(3):261–4. doi: [10.1016/S0378-5122%2898%2900014-0](#)
32. Levens ED, Potlog-Nahari C, Armstrong AY, Wesley R, Premkumar A, Bliethe DL, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. *Obstetrics and gynecology*. 2008; 111(5):1129–36. Epub 2008/05/02. doi: [10.1097/AOG.0b013e3181705d0e](#) PMID: [18448745](#); PubMed Central PMCID: PMC2742990.
33. Palomba S, Affinito P, Tommaselli GA, Nappi C. A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertility and sterility*. 1998; 70(1):111–8. doi: [10.1016/s0015-0282\(98\)00128-9](#) WOS:000074479600020. PMID: [9660431](#)
34. Baytur YB, Ozbilgin K, Cilaker S, Lacin S, Kurtul O, Oruc S, et al. A comparative study of the effect of raloxifene and gosereline on uterine leiomyoma volume changes and estrogen receptor, progesterone receptor, bcl-2 and p53 expression immunohistochemically in premenopausal women. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2007; 135(1):94–103. doi: [10.1016/j.ejogrb.2006.07.042](#) WOS:000251485700016.
35. Sayyah-Melli M, Tehrani-Gadim S, Dastranj-Tabrizi A, Gatrehsamani F, Morteza G, Ouladesahebmadarek E, et al. Comparison of the effect of gonadotropin-releasing hormone agonist and dopamine receptor agonist on uterine myoma growth Histologic, sonographic, and intra-operative changes. *Saudi Med J*. 2009; 30(8):1024–33. WOS:000270844200007. PMID: [19668882](#)
36. Melli MS, Farzadi L, Madarek EO. Comparison of the effect of gonadotropin-releasing hormone analog (Diphereline) and Cabergoline (Dostinex) treatment on uterine myoma regression. *Saudi Med J*. 2007; 28(3):445–50. CN-00609303. PMID: [17334477](#)
37. Audebert AJ, Madenelat P, Querleu D, Pontonnier G, Racinet C, Renaud R, et al. Deferred versus immediate surgery for uterine fibroids: clinical trial results. *British journal of obstetrics and gynaecology*. 1994; 101 Suppl 10:29–32. CN-00101771. PMID: [8199102](#)
38. van de Ven J, Donker TH, Blankenstein MA, Thijssen JH. Differential effect of gonadotropin-releasing hormone analogue treatment on estrogen levels and sulfatase activity in uterine leiomyoma and myometrium. *Fertility and sterility*. 2002; 77(6):1227–32. doi: [10.1016/s0015-0282\(02\)03093-5](#) WOS:000176176000022. PMID: [12057733](#)
39. Levy G, Avila N, Armstrong AY, Nieman L. Does the selective progesterone receptor modulator ulipristal normalize the uterine cavity in women with leiomyoma. *Reproductive Sciences*. 2011; 1):95A.
40. Hudecek R, Ivanova Z, Smerdova M, Pankova S, Krajcovicova R. Effect of GnRH analogues pre-treatment on myomectomy outcomes in reproductive age women. [Czech] Vliv aplikace GnRH analogu na peroperacni a postoperacni vysledky myomektomie u zen v reprodukcnim veku. *Ceska Gynekologie*. 2012; 77(2):109–17. PMID: [22702067](#).
41. Varun N, Kumar A, Prasad S. Effect of low dose mifepristone on uterine leiomyoma in reproductive age group. *Fertility and sterility*. 2013; 1):S78. doi: [10.1016/j.fertnstert.2013.07.1924](#)
42. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. *Obstetrics and gynecology*. 2006; 108(6):1381–7. doi: [10.1097/01.AOG.0000243776.23391.7b](#) CN-00574102. PMID: [17138770](#)
43. Gregoriou O, Vitoratos N, Papadias C, Konidaris S, Costomenos D, Chryssikopoulos A. Effect of tibolone on postmenopausal women with myomas. *Maturitas*. 1997; 27(2):187–91. doi: [10.1016/s0378-5122\(97\)00036-4](#) WOS:A1997XL50900012. PMID: [9255754](#)
44. Armstrong A, Nieman LK. Effect of ulipristal acetate, a selective progesterone receptor modulator (SPRM), on fibroid size in women with symptomatic uterine fibroids. *Human Reproduction*. 2010; 25:i90–i1. doi: [10.1093/humrep/de.25.s1.58](#)
45. Palomba S, Russo T, Orio F Jr., Tauchmanova L, Zupi E, Panici PL, et al. Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas: a prospective, randomized, single-blind, placebo-controlled clinical trial. *Human reproduction (Oxford, England)*. 2002; 17(12):3213–9. Epub 2002/11/29. PMID: [12456626](#).
46. Palomba S, Pellicano M, Affinito P, Carlo C, Zullo F, Nappi C. Effectiveness of short-term administration of tibolone plus gonadotropin-releasing hormone analogue on the surgical outcome of laparoscopic myomectomy. *Fertility and sterility*. 2001; 75(2):429–33. CN-00329050. PMID: [11172852](#)
47. Orsini G, Pinto V, Biase S, D'Altorio C, Lanzilotti G. Effects of hormone replacement therapy on postmenopausal women with uterine fibroids. *Minerva Ginecologica*. 1999; 51(11):421–5. CN-00295054.

48. Reinsch RC, Murphy AA, Morales AJ, Yen SS. The effects of RU 486 and leuprolide acetate on uterine artery blood flow in the fibroid uterus: a prospective, randomized study. *American journal of obstetrics and gynecology*. 1994; 170(6):1623–7; discussion 7–8. CN-00101922. PMID: [8203418](#)
49. Williams AR, Critchley HO, Osei J, Ingamells S, Cameron IT, Han C, et al. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata. *Human reproduction (Oxford, England)*. 2007; 22(6):1696–704. doi: [10.1093/humrep/dem026](#) CN-00587138.
50. Wilkens J, Chwalisz K, Han C, Walker J, Cameron IT, Ingamells S, et al. 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. *The Journal of clinical endocrinology and metabolism*. 2008; 93(12):4664–71. doi: [10.1210/jc.2008-1104](#) CN-00665611. PMID: [18765509](#)
51. Nieman LK, Blocker W, Nansel T, Mahoney S, Reynolds J, Blithe D, et al. Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study. *Fertility and sterility*. 2011; 95(2):767–U9. doi: [10.1016/j.fertnstert.2010.09.059](#) WOS:000286419000071. PMID: [21055739](#)
52. Morris EP, Rymer J, Robinson J, Fogelman I. Efficacy of tibolone as "add-back therapy" in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. *Fertility and sterility*. 2008; 89(2):421–8. doi: [10.1016/j.fertnstert.2007.02.064](#) WOS:000253246100024. PMID: [17572410](#)
53. Green LJ, Levy G, Wesley R, Nieman L, Armstrong A. Efficacy of ulipristal acetate for the treatment of symptomatic uterine leiomyomas in African Americans. *Fertility and sterility*. 2012; 1):S96. doi: [10.1016/j.fertnstert.2012.07.351](#)
54. Williams AR, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. *International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists*. 2012; 31(6):556–69. Epub 2012/09/29. doi: [10.1097/PGP.0b013e318251035b](#) PMID: [23018219](#).
55. Friedman AJ, Rein MS, Pandian MR, Barbieri RL. Fasting serum growth hormone and insulin-like growth factor-I and -II concentrations in women with leiomyomata uteri treated with leuprolide acetate or placebo. *Fertility and sterility*. 1990; 53(2):250–3. CN-00065156. PMID: [2105242](#)
56. Stovall TG, Muneyyirci-Delale O, Summitt RL Jr, Scialli AR. GnRH agonist and iron versus placebo and iron in the anemic patient before surgery for leiomyomas: A randomized controlled trial. *Obstetrics and Gynecology*. 1995; 86(1):65–71. doi: [10.1016/0029-7844\(95\)2895-2900102-W](#)
57. Seracchioli R, Venturoli S, Colombo FM, Bagnoli A, Vianello F, Govoni F, et al. GnRH agonist treatment before total laparoscopic hysterectomy for large uteri. *J Am Assoc Gynecol Laparoscopists*. 2003; 10(3):316–9. doi: [10.1016/s1074-3804\(05\)60254-x](#) WOS:000188064600003.
58. Muzii L, Boni T, Bellati F, Marana R, Ruggiero A, Zullo MA, et al. GnRH analogue treatment before hysteroscopic resection of submucous myomas: a prospective, randomized, multicenter study. *Fertility and sterility*. 2010; 94(4):1496–9. doi: [10.1016/j.fertnstert.2009.05.070](#) WOS:000281674600057. PMID: [19541299](#)
59. Zullo E, Pellicano M, De SR, Zupi E, Mastrantonio P, Nappi C, et al. GnRH analogues and laparoscopic myomectomy. *Italian Journal of Gynaecology and Obstetrics*. 1997; 9(2):63–7. CN-00199155.
60. Coddington CC, Grow DR, Ahmed MS, Toner JP, Cook E, Diamond MP. Gonadotropin-releasing hormone agonist pretreatment did not decrease postoperative adhesion formation after abdominal myomectomy in a randomized control trial. *Fertility and sterility*. 2009; 91(5):1909–13. doi: [10.1016/j.fertnstert.2008.02.128](#) WOS:000265969200049. PMID: [18439584](#)
61. Vercellini P, Trespidi L, Zaina B, Vicentini S, Stellato G, Crosignani PG. Gonadotropin-releasing hormone agonist treatment before abdominal myomectomy: A controlled trial. *Fertility and sterility*. 2003; 79(6):1390–5. doi: [10.1016/S0015-0282\(03\)2803-2900362-5](#)
62. Stovall TG, Summitt RL Jr, Washburn SA, Ling FW. Gonadotropin-releasing hormone agonist use before hysterectomy. *American journal of obstetrics and gynecology*. 1994; 170(6):1744–51.
63. Muneyyirci-Delale O, Richard-Davis G, Morris T, Armstrong J. Goserelin acetate 10.8 mg plus iron versus iron monotherapy prior to surgery in premenopausal women with iron-deficiency anemia due to uterine leiomyomas: Results from a phase III, randomized, multicenter, double-blind, controlled trial. *Clin Ther*. 2007; 29(8):1682–91. doi: [10.1016/j.clinthera.2007.08.024](#) WOS:000249682900013. PMID: [17919549](#)
64. Parazzini F, Bortolotti A, Chiantera V, Scollo P, Del Monaco D, Bianchi M, et al. Goserelin acetate to avoid hysterectomy in pre-menopausal women with fibroids requiring surgery. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 1999; 87(1):31–3. doi: [10.1016/s0301-2115\(99\)00089-5](#) WOS:000083143900005.

65. Lim SS, Sockalingam JK, Tan PC. Goserelin versus leuprolide before hysterectomy for uterine fibroids. *Int J Gynecol Obstet*. 2008; 101(2):178–83. doi: [10.1016/j.ijgo.2007.10.020](https://doi.org/10.1016/j.ijgo.2007.10.020) WOS:000255816700013.
66. Simsek T, Karakus C, Trak B. Impact of different hormone replacement therapy regimens on the size of myoma uteri in postmenopausal period: tibolone versus transdermal hormonal replacement system. *Maturitas*. 2002; 42(3):243–6. CN-00405090. PMID: [12161049](https://pubmed.ncbi.nlm.nih.gov/12161049/)
67. Fedele L, Bianchi S, Baglioni A, Arcaini L, Marchini M, Bocciolone L. Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. *Eur J Obstet Gynecol Reprod Biol*. 1990; 38(1):53–7. CN-00195993.
68. Campo S, Garcea N. Laparoscopic myomectomy in premenopausal women with and without preoperative treatment using gonadotrophin-releasing hormone analogues. *Human Reproduction*. 1999; 14(1):44–8. doi: [10.1093/humrep/14.1.44](https://doi.org/10.1093/humrep/14.1.44) WOS:000078341300011. PMID: [10374092](https://pubmed.ncbi.nlm.nih.gov/10374092/)
69. De Falco M, Staibano S, Mascolo M, Mignogna C, Improda L, Ciociola F, et al. Leiomyoma pseudocapsule after pre-surgical treatment with gonadotropin-releasing hormone agonists: Relationship between clinical features and immunohistochemical changes. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2009; 144(1):44–7. doi: [10.1016/j.ejogrb.2009.02.006](https://doi.org/10.1016/j.ejogrb.2009.02.006)
70. Barbieri RL, Dilena M, Chumas J, Rein MS, Friedman AJ. Leuprolide acetate depot decreases the number of nucleolar organizer regions in uterine leiomyomata. *Fertility and sterility*. 1993; 60(3):569–70. CN-00095809. PMID: [8375543](https://pubmed.ncbi.nlm.nih.gov/8375543/)
71. Rutgers JL, Spong CY, Sinow R, Heiner J. Leuprolide acetate treatment and myoma arterial size. *Obstetrics and Gynecology*. 1995; 86(3):386–8. doi: [10.1016/0029-7844\(95\)00191-s](https://doi.org/10.1016/0029-7844(95)00191-s) WOS: A1995RQ63700013. PMID: [7651647](https://pubmed.ncbi.nlm.nih.gov/7651647/)
72. Verspyck E, Marpeau L, Lucas C. Leuprorelin depot 3.75 mg versus lynestrenol in the preoperative treatment of symptomatic uterine myomas: a multicentre randomised trial. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 2000; 89(1):7–13. doi: [10.1016/s0301-2115\(99\)00168-2](https://doi.org/10.1016/s0301-2115(99)00168-2) WOS:000085843800002.
73. van de Ven J, Sprong M, Donker GH, Thijssen JH, Mak-Kregar S, Blankenstein MA. Levels of estrogen and progesterone receptors in the myometrium and leiomyoma tissue after suppression of estrogens with gonadotropin releasing hormone analogs. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology*. 2001; 15 Suppl 6:61–8. PMID: [12227888](https://pubmed.ncbi.nlm.nih.gov/12227888/).
74. Palomba S, Russo T, Orio F, Sammartino A, Sbrano FM, Nappi C, et al. Lipid, glucose and homocysteine metabolism in women treated with a GnRH agonist with or without raloxifene. *Human Reproduction*. 2004; 19(2):415–21. doi: [10.1093/humrep/deh053](https://doi.org/10.1093/humrep/deh053) WOS:000188800300033. PMID: [14747190](https://pubmed.ncbi.nlm.nih.gov/14747190/)
75. Bagaria M, Suneja A, Vaid NB, Guleria K, Mishra K. Low-dose mifepristone in treatment of uterine leiomyoma: A randomised double-blind placebo-controlled clinical trial. *Aust N Z J Obstet Gynaecol*. 2009; 49(1):77–83. doi: [10.1111/j.1479-828X.2008.00931.x](https://doi.org/10.1111/j.1479-828X.2008.00931.x) WOS:000263855900016. PMID: [19281585](https://pubmed.ncbi.nlm.nih.gov/19281585/)
76. Constantini S, Anserini P, Valenzano M, Remorgida V, Venturini PL, De Cecco L. Luteinizing hormone-releasing hormone analog therapy of uterine fibroid: Analysis of results obtained with buserelin administered intranasally and goserelin administered subcutaneously as a monthly depot. *European Journal of Obstetrics Gynecology and Reproductive Biology*. 1990; 37(1):63–9.
77. Rees M, Chamberlain P, Gillmer M. Management of uterine fibroids with goserelin acetate alone or goserelin acetate plus endometrial resection. *Gynaecological Endoscopy*. 2001; 10(1):33–5. doi: [10.1046/j.1365-2508.2001.00396.x](https://doi.org/10.1046/j.1365-2508.2001.00396.x) WOS:000168262200008.
78. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. *Human reproduction (Oxford, England)*. 2009; 24(8):1870–9. doi: [10.1093/humrep/dep100](https://doi.org/10.1093/humrep/dep100) CN-00720560.
79. Jo Varghese S, Engman M, Brett G, Gemzell K, Lalitkumar PGL. Mifepristone induces myoma volume reduction by regulating genes in the Integrin and Ephrin pathways. *Human Reproduction*. 2011; 26:i70–i1. doi: [10.1093/humrep/26.s1.47](https://doi.org/10.1093/humrep/26.s1.47)
80. Esteve JL, Acosta R, Perez Y, Rodriguez B, Seigler I, Sanchez C, et al. Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. *International journal of women's health*. 2013; 5:361–9. Epub 2013/07/12. doi: [10.2147/ijwh.s42770](https://doi.org/10.2147/ijwh.s42770) PMID: [23843709](https://pubmed.ncbi.nlm.nih.gov/23843709/); PubMed Central PMCID: PMC3702243.
81. Gerris J, Deguelde M, Peters AA, Romao F, Stjernquist M, al-Taher H. The place of Zoladex in deferred surgery for uterine fibroids. Zoladex Myoma Study Group. *Hormone research*. 1996; 45(6):279–84. CN-00129653. PMID: [8793522](https://pubmed.ncbi.nlm.nih.gov/8793522/)

82. Shaw RW, Trabant H. Placebo-controlled comparison of the effectiveness of buserelin depot formulation in the preoperative management of patients with uterine fibroids. *Gynaecological Endoscopy*. 1997; 6(Suppl 1):1. CN-00363521.
83. Schlaff WD, Zerhouni EA, Huth JA, Chen J, Damewood MD, Rock JA. A placebo-controlled trial of a depot gonadotropin-releasing hormone analogue (leuprolide) in the treatment of uterine leiomyomata. *Obstetrics and gynecology*. 1989; 74(6):856–62. CN-00063914. PMID: [2511532](#)
84. Lieto A, Falco M, Mansueto G, Rosa G, Pollio F, Staibano S. Preoperative administration of GnRH-a plus tibolone to premenopausal women with uterine fibroids: evaluation of the clinical response, the immunohistochemical expression of PDGF, bFGF and VEGF and the vascular pattern. *Steroids*. 2005; 70(2):95–102. doi: [10.1016/j.steroids.2004.10.008](#) CN-00513680. PMID: [15631865](#)
85. Golan A, Bukovsky I, Pansky M, Schneider D, Weinraub Z, Caspi E. Pre-operative gonadotrophin-releasing hormone agonist treatment in surgery for uterine leiomyomata. *Human reproduction (Oxford, England)*. 1993; 8(3):450–2. CN-00092526.
86. Bustos Lopez HH, Miranda Rodriguez JA, Kably Ambe A, Serviere Zaragoza C, Espinoza de los Monteros A, Alvarado Duran A. Preoperative management of uterine leiomyomatosis using pituitary gonadotropin-releasing hormone analogues. [Spanish] *Tratamiento medico preoperatorio de leiomiomatosis uterina con analogos de hormona liberadora de gonadotropinas hipofisarias*. *Ginecologia y obstetricia de Mexico*. 1995; 63:356–64. PMID: [7672654](#).
87. Engel JB, Audebert A, Frydman R, Zivny J, Diedrich K. Presurgical short term treatment of uterine fibroids with different doses of cetrorelix acetate: a double-blind, placebo-controlled multicenter study. *European journal of obstetrics, gynecology, and reproductive biology*. 2007; 134(2):225–32. doi: [10.1016/j.ejogrb.2006.07.018](#) CN-00617443. PMID: [16930803](#)
88. Zullo F, Pellicano M, De Stefano R, Zupi E, Mastrantonio P. A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: Efficacy and ultrasonographic predictors. *American journal of obstetrics and gynecology*. 1998; 178(1):108–12. doi: [10.1016/s0002-9378\(98\)70635-0](#) WOS:000071776100019. PMID: [9465812](#)
89. Palomba S, Orio F Jr, Morelli M, Russo T, Pellicano M, Zupi E, et al. Raloxifene administration in premenopausal women with uterine leiomyomas: A pilot study. *Journal of Clinical Endocrinology and Metabolism*. 2002; 87(8):3603–8. doi: [10.1210/jc.87.8.3603](#)
90. Palomba S, Orio F Jr, Morelli M, Russo T, Pellicano M, Nappi C, et al. Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *The Journal of clinical endocrinology and metabolism*. 2002; 87(10):4476–81. Epub 2002/10/05. PMID: [12364422](#).
91. Jirecek S, Lee A, Pavo I, Crans G, Eppel W, Wenzl R. Raloxifene prevents the growth of uterine leiomyomas in premenopausal women. *Fertility and sterility*. 2004; 81(1):132–6. Epub 2004/01/09. PMID: [14711556](#).
92. Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia. *Int J Gynecol Obstet*. 2011; 112(2):126–30. doi: [10.1016/j.ijgo.2010.08.009](#) WOS:000286704100011.
93. Fedele L, Bianchi S, Raffaelli R, Zanconato G. A randomized study of the effects of tibolone and transdermal estrogen replacement therapy in postmenopausal women with uterine myomas. *European journal of obstetrics, gynecology, and reproductive biology*. 2000; 88(1):91–4. CN-00274902. PMID: [10659924](#)
94. Stovall TG, Ling FW, Henry LC, Woodruff MR. A randomized trial evaluating leuprolide acetate before hysterectomy as treatment for leiomyomas. *American journal of obstetrics and gynecology*. 1991; 164(6):1420–5. WOS:A1991FR47000003. PMID: [1904681](#)
95. Parsanezhad ME, Azmoon M, Alborzi S, Rajaeefard A, Zarei A, Kazerooni T, et al. A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status. *Fertility and sterility*. 2010; 93(1):192–8. doi: [10.1016/j.fertnstert.2008.09.064](#) WOS:000273601200029. PMID: [19135657](#)
96. Chwalisz K, Larsen L, Mattia-Goldberg C, Edmonds A, Elger W, Winkel CA. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. *Fertility and sterility*. 2007; 87(6):1399–412. doi: [10.1016/j.fertnstert.2006.11.094](#) WOS:000247150100024. PMID: [17307170](#)
97. Friedman AJ, Barbieri RL, Doubilet PM, Fine C, Schiff I. A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. *Fertility and sterility*. 1988; 49(3):404–9. WOS:A1988M343000004. PMID: [2963759](#)

98. Donnez J, Hervais Vivancos B, Kudela M, Audebert A, Jadoul P. A randomized, placebo-controlled, dose-ranging trial comparing fulvestrant with goserelin in premenopausal patients with uterine fibroids awaiting hysterectomy. *Fertility and sterility*. 2003; 79(6):1380–9. CN-00438263. PMID: [12798886](#)
99. Friedman AJ, Rein MS, Harrison-Atlas D, Garfield JM, Doubilet PM. A randomized, placebo-controlled, double-blind study evaluating leuprolide acetate depot treatment before myomectomy. *Fertility and sterility*. 1989; 52(5):728–33. CN-00063303. PMID: [2509250](#)
100. Sadan O, Ginath S, Sofer D, Rotmensch S, Debby A, Glezerman M, et al. The role of tamoxifen in the treatment of symptomatic uterine leiomyomata—a pilot study. *European journal of obstetrics, gynecology, and reproductive biology*. 2001; 96(2):183–6. CN-00348348. PMID: [11384804](#)
101. D'Anna R, Palmara V, Lo RC, Scilipoti A, Leonardi I. Short treatment with leuprolide acetate depot before hysterectomy for uterine leiomyomata. *Minerva Ginecol*. 1994; 46(6):343–6. CN-00188320. PMID: [7936386](#)
102. Palomba S, Morelli M, Noia R, Santagata M, Oliverio A, Sena T, et al. Short-term administration of tibolone plus GnRH analog before laparoscopic myomectomy. *J Am Assoc Gynecol Laparoscopists*. 2002; 9(2):170–4. doi: [10.1016/s1074-3804\(05\)60126-0](#) WOS:000175442800012.
103. Palomba S, Orio F Jr, Falbo A, Oppedisano R, Tolino A, Zullo F. Tibolone reverses the cognitive effects caused by leuprolide acetate administration, improving mood and quality of life in patients with symptomatic uterine leiomyomas. *Fertility and sterility*. 2008; 90(1):165–73. doi: [10.1016/j.fertnstert.2007.05.061](#)
104. Fernandez-Mentoli ME, Diez-Gibert O, Samaniego JM, Balaguero L, Navarro MA. Total and unbound cytosolic estrogen and progesterone receptors in myometrium and fibroid after gonadotropin-releasing hormone agonist treatment. *Fertility and sterility*. 1995; 63(3):522–7.
105. Friedman AJ, Hoffman DI, Comite F, Browneller RW, Miller JD. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group. *Obstetrics and gynecology*. 1991; 77(5):720–5. CN-00074529.
106. Roshdy E, Rajaratnam V, Maitra S, Sabry M, Ait Allah AS, Al-Hendy A. Treatment of symptomatic Uterine fibroids with green tea extract: A pilot randomized controlled clinical study. *International Journal of Women's Health*. 2013; 5(1):477–86. doi: [10.2147/IJWH.S41021](#)
107. Fedele L, Vercellini P, Bianchi S, Brioschi D, Dorta M. Treatment with GnRH agonists before myomectomy and the risk of short-term myoma recurrence. *British journal of obstetrics and gynaecology*. 1990; 97(5):393–6. CN-00069033. PMID: [2115379](#)
108. Daniels A, Pike M, Daniels J, Spicer D. Treatment with the GnRH agonist (GnRHa) deslorelin (D) and low-dose add-back estradiol (E2) is effective in reducing pain, bleeding and uterine volume(UV) while maintaining bone mineral density (BMD) in women with symptomatic uterine fibroids (UF). *Fertility & Sterility*. 2002; Vol 78(3 Suppl 1):S65–6, Abstract no: O-170. CN-00404980.
109. Lumsden MA, West CP, Thomas E, Coutts J, Hillier H, Thomas N, et al. Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *British journal of obstetrics and gynaecology*. 1994; 101(5):438–42. CN-00102553. PMID: [8018618](#)
110. Balasch J, Manau D, Mimo J, Duran M, Puerto B, Vanrell JA. Trial of routine gonadotropin releasing hormone agonist treatment before abdominal hysterectomy for leiomyoma. *Acta Obstetrica et Gynecologica Scandinavica*. 1995; 74(7):562–5.
111. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *New England Journal of Medicine*. 2012; 366(5):421–32. doi: [10.1056/NEJMoa1103180](#)
112. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *The New England journal of medicine*. 2012; 366(5):409–20. doi: [10.1056/NEJMoa1103182](#) CN-00804100. PMID: [22296075](#)
113. Zullo F, Pellicano M, Carlo C, Stefano R, Marconi D, Zupi E. Ultrasonographic prediction of the efficacy of GnRH agonist therapy before laparoscopic myomectomy. *The Journal of the American Association of Gynecologic Laparoscopists*. 1998; 5(4):361–6. CN-00155984. PMID: [9782139](#)
114. Polatti F, Viazzo F, Colleoni R, Nappi RE. Uterine myoma in postmenopause: a comparison between two therapeutic schedules of HRT. *Maturitas*. 2000; 37(1):27–32. doi: [10.1016/s0378-5122\(00\)00159-6](#) WOS:000165650900003.
115. Mavrellos D, Ben-Nagi J, Davies A, Lee C, Salim R, Jurkovic D. The value of pre-operative treatment with GnRH analogues in women with submucous fibroids: a double-blind, placebo-controlled randomized trial. *Human reproduction (Oxford, England)*. 2010; 25(9):2264–9. doi: [10.1093/humrep/deq188](#) CN-00768479.