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Add-back therapy with GnRH analogues for uterine fibroids (Review)

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[Intervention Review]

Add-back therapy with GnRH analogues for uterine fibroids

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ABSTRACT

Background

Uterine fibroids (also known as leiomyomas) are the most common benign pelvic tumours among women. They may be asymptomatic, or may be associated with pelvic symptoms such as bleeding and pain. Medical treatment of this condition is limited and gonadotropin-releasing hormone (GnRH) analogues are the most effective agents. Long-term treatment with such agents, however, is restricted due to their adverse effects. The addition of other medications during treatment with GnRH analogues, a strategy known as add-back therapy, may limit these side effects. There is concern, however, that add-back therapy may also limit the efficacy of the GnRH analogues and that it may not be able to completely prevent their adverse effects.

Objectives

To assess the short-term (within 12 months) effectiveness and safety of add-back therapy for women using GnRH analogues for uterine fibroids associated with excessive uterine bleeding, pelvic pain, or urinary symptoms.

Search methods

We searched electronic databases including the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, CENTRAL, MEDLINE, PubMed, EMBASE, LILACS, CINAHL, PsycINFO; and electronic registries of ongoing trials including ClinicalTrials.gov, Current Controlled Trials, World Health Organization (WHO) International Clinical Trials Registry Platform. All searches were from database inception to 16 June 2014.

Selection criteria

Randomized controlled trials (RCTs) that included women with uterine fibroids experiencing irregular or intense uterine bleeding, cyclic or non-cyclic pelvic pain, or urinary symptoms, and that compared treatment with a GnRH analogue plus add-back therapy versus a GnRH analogue alone or combined with placebo were eligible for inclusion.

Data collection and analysis

Two authors independently reviewed the identified titles and abstracts for potentially eligible records. Two review authors reviewed eligible studies and independently extracted data. Two authors independently assessed the studies' risk of bias. They assessed the quality of the evidence using GRADE criteria.

Main results

Fourteen RCTs were included in the review. Data were extracted from 12 studies (622 women). The primary outcome was quality of life (QoL).

Add-back therapy with GnRH analogues for uterine fibroids (Review)

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Add-back therapy with medroxyprogesterone (MPA): no studies reported QoL or uterine bleeding. There was no evidence of effect in relation to bone mass (standardized mean difference (SMD) 0.38, 95% confidence interval (CI) -0.62 to 1.38, 1 study, 16 women, $P = 0.45$, low quality evidence) and MPA was associated with a larger uterine volume (mean difference (MD) 342.19 cm³, 95% CI 77.58 to 606.80, 2 studies, 32 women, $I^2 = 0\%$, low quality evidence).

Tibolone: this was associated with a higher QoL but the estimate was imprecise and the effect could be clinically insignificant, small or large (SMD 0.47, 95% CI 0.09 to 0.85, 1 study, 110 women, $P = 0.02$, low quality evidence). It was also associated with a decreased loss of bone mass, which could be insignificant, small or moderate (SMD 0.36, 95% CI 0.03 to 0.7, 3 studies, 160 women, $I^2 = 7\%$, moderate quality evidence). Tibolone may, however, have been associated with larger uterine volumes (MD 23.89 cm³, 95% CI= 8.13 to 39.66, 6 studies, 365 women, $I^2 = 0\%$, moderate quality evidence) and more uterine bleeding (results were not combined but three studies demonstrated greater bleeding with tibolone while two other studies demonstrated no bleeding in either group). Four studies (268 women; not pooled owing to extreme heterogeneity) reported a large benefit on vasomotor symptoms in the tibolone group.

Raloxifene: there was no evidence of an effect on QoL (SMD 0.11, 95% CI -0.57 to 0.34, 1 study, 74 women, $P = 0.62$, low quality evidence), while there was a beneficial impact on bone mass (SMD 1.01, 95% CI 0.57 to 1.45, 1 study, 91 women, $P < 0.00001$, low quality evidence). There was no clear evidence of effect on uterine volume (MD 27.1 cm³, 95% CI -17.94 to 72.14, 1 study, 91 women, $P = 0.24$, low quality evidence), uterine bleeding or severity of vasomotor symptoms (MD 0.2 hot flushes/day, 95% CI -0.34 to 0.74, 1 study, 91 women, $P = 0.46$, low quality evidence).

Estriol: no studies reported QoL, uterine size, uterine bleeding or vasomotor symptoms. Add-back with estriol may have led to decreased loss of bone mass, from results of a single study (SMD 3.93, 95% CI 1.7 to 6.16, 1 study, 12 women, $P = 0.0005$, low quality evidence).

Ipriflavone: no studies reported QoL, uterine size or uterine bleeding. Ipriflavone was associated with decreased loss of bone mass in a single study (SMD 2.71, 95% CI 2.14 to 3.27, 1 study, 95 women, $P < 0.00001$, low quality evidence); there was no evidence of an effect on the rate of vasomotor symptoms (RR 0.67, 95% CI 0.44 to 1.02, 1 study, 95 women, $P = 0.06$, low quality evidence).

Conjugated estrogens: no studies reported QoL, uterine size, uterine bleeding or vasomotor symptoms. One study suggested that adding conjugated estrogens to GnRH analogues resulted in a larger decrease in uterine volume in the placebo group (MD 105.2 cm³, 95% CI 27.65 to 182.75, 1 study, 27 women, $P = 0.008$, very low quality evidence).

Nine of 12 studies were at high risk of bias in at least one domain, most commonly lack of blinding. All studies followed participants for a maximum of six months. This short-term follow-up is usually insufficient to observe any significant effect of the treatment on bone health (such as the occurrence of fractures), limiting the findings.

Authors' conclusions

There was low or moderate quality evidence that tibolone, raloxifene, estriol and ipriflavone help to preserve bone density and that MPA and tibolone may reduce vasomotor symptoms. Larger uterine volume was an adverse effect associated with some add-back therapies (MPA, tibolone and conjugated estrogens). For other comparisons, outcomes of interest were not reported or study findings were inconclusive.

PLAIN LANGUAGE SUMMARY

Combined treatment with GnRH analogues and add-back therapy for women with uterine fibroids

Review question

Uterine fibroids may be shrunk with gonadotropin-releasing hormone (GnRH) analogues but commonly cause hot flushes. Combining GnRHa with other drugs may decrease hot flushes (a strategy known as add-back therapy) but cause other problems such as low bone mineral density. The efficacy and safety of this approach is controversial.

Background

Uterine fibroids are benign tumours that arise from the wall of the uterus. Although they are mostly asymptomatic, women with associated symptoms may require treatment. Medical options for treating the condition are limited and, among them, a class of drugs named GnRH analogues is considered effective for decreasing the size of the tumour and for controlling symptoms such as uterine bleeding and pelvic pressure. This class of drugs, however, is limited by its adverse effects, mainly a rise in the incidence of hot flashes and reduced bone mass. Therefore, prolonged treatment is usually not recommended.

Study characteristics

In June 2014, Cochrane authors performed computer searches of the medical literature to locate all relevant studies about this subject, in any language. We found 14 eligible randomized controlled trials. We analysed their data, assessed them for the quality of their methods

and precision of their results, and communicated with their authors to obtain additional information and to clarify any doubts about the information.

Key results

Quality of life

Available evidence from 110 women suggested that tibolone may have a very small to large benefit with respect to quality of life when compared with the use of GnRH analogues alone. There was no evidence that raloxifene had an effect on quality of life (data from 74 women). The effect of other add-back agents on quality of life had not been studied.

Bone mass

Evidence from 91 women suggested that raloxifene may have a moderate to large benefit for preserving bone mass when used for up to six months, while tibolone may have a small to moderate bone mass-preserving effect, based on data from 160 women. Estriol (studied in 12 women) and ipriflavone (studied in 95 women) may have had a large effect in decreasing the loss of bone mass associated with the use of GnRH analogues. The effect of medroxyprogesterone (MPA) on bone mass was uncertain.

Vasomotor symptoms

Tibolone may have had a large effect in decreasing vasomotor symptoms (data from 268 women) when compared with the use of GnRH analogues without add-back therapy. MPA may also have decreased vasomotor symptoms (840 to 137 fewer women with vasomotor symptoms per 1000 women, data from 16 women).

Adverse effects

Tibolone could lead to a greater uterine size (increased by 8 cm³ to 39 cm³, data from 365 women) and increased bleeding (data not pooled but studied in 310 patients). MPA may also have resulted in a increased uterine size (by 77 cm³ to 606 cm³, data from 32 women). Conjugated estrogens could also result in greater uterine size (data from 27 women).

Evidence regarding this subject was generally of low quality and higher quality studies are necessary for more robust conclusions to be achieved.

Quality of the evidence

Evidence ranged from very low to moderate quality and the main limitations were risk of bias in the primary studies and imprecision of the estimates. For quality of life, evidence was of low quality for both tibolone and raloxifene. For bone mass, evidence was of moderate quality for tibolone and of low quality for all the other treatments studied.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. GnRH-a + medroxyprogesterone acetate compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + medroxyprogesterone acetate compared to GnRH-a ± placebo for uterine fibroids

Patient or population: patients with uterine fibroids
Intervention: GnRH-a + medroxyprogesterone acetate (MPA)
Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + medroxyprogesterone acetate				
Quality of life	This primary review outcome was not reported in any of the included studies		Not estimable			
Bone density (SMD) - Follow-up: 6 months	The mean bone density was 0.74 g/cm ²	The mean bone density in the MPA add-back group was 0.38 SDs higher (0.62 lower to 1.38 higher)		16 (1 study)	⊕⊕⊕⊕ low ¹	
Uterine size (cm ³) - Follow-up: 3 to 6 months	The mean uterine volume ranged from 294 to 937 cm ³	The mean uterine size in the MPA add-back group was 342.19 cm³ higher (77.58 to 606.8 cm ³ higher)		32 (2 studies)	⊕⊕⊕⊕ low ¹	
Uterine bleeding	This secondary review outcome was not reported in any of the included studies.		Not estimable			
Severity of vasomotor symptoms	This secondary review outcome was not reported in any of the included studies.		Not estimable			
Rate of vasomotor symptoms - Follow-up: 6 months	857 per 1000	111 per 1000 (17 to 720)	RR 0.13 (0.02 to 0.84)	16 (1 study)	⊕⊕⊕⊕ low 1	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SD:** Standard deviation

MPA: medroxyprogesterone acetate; **SMD:** standardized mean difference. **For interpretation, a SMD between 0.2 and 0.5 was considered a small effect; between 0.5 and 0.8 was considered a moderate effect; and higher than 0.8 was considered a large effect.**

Interpretation: Based on the interpretation of the SMDs, MPA add-back had a clinically meaningful effect in decreasing the rate of patients with vasomotor symptoms, but the protection of bone density was not meaningful. It also had a clinically meaningful and harmful effect on uterine size, leading to its increase.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded two levels for inadequate reporting of study methods and imprecision of the estimates

Summary of findings 2. GnRH-a + tibolone compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + tibolone compared to GnRH-a ± placebo for uterine fibroids

Patient or population: patients with uterine fibroids

Intervention: GnRH-a + tibolone

Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + tibolone				
Quality of life (SMD) - Follow-up: 6 months	The mean SF-36 score was 78.5	The mean quality of life (SF-36 scores) in the tibolone add-back group was 0.47 SDs higher (0.09 to 0.85 higher)		110 (1 study)	⊕⊕⊕⊕ low ¹	
Bone density (SMD) - Follow-up: 4 to 6 months	The mean bone density ranged from 1.002 to 1.08 g/cm ²	The mean bone density in the tibolone add-back group was 0.36 SDs higher		160 (3 studies)	⊕⊕⊕⊖ moderate ²	

	(0.03 to 0.7 higher)				
Uterine size (cm³) - Follow-up: 2 to 6 months	The mean uterine volume ranged from 337 to 1,794 cm ³	The mean uterine size in the tibolone add-back group was 23.89 cm³ higher (8.13 to 39.66 cm ³ higher)	365 (6 studies)	⊕⊕⊕⊖	moderate ²
Uterine bleeding	These results were not meta-analysed due to inconsistency among studies and elevated heterogeneity. In two studies, there was no difference in bleeding, while in three studies, there was higher bleeding in the tibolone groups.				
Severity of vasomotor symptoms (SMD) - Follow-up: 2 to 6 months	These results were not meta-analysed due to extreme heterogeneity. The studies used three different measures. All studies reported a large benefit in the tibolone group.		268 (4 studies)		
Rate of vasomotor symptoms - Follow-up: 6 months	800 per 1000	304 per 1000 (112 to 816)	RR 0.38 (0.14 to 1.02)	20 (1 study)	⊕⊕⊖⊖ low ¹

*The basis for the **assumed risk** is the mean control group risk.. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SD:** Standard deviation.

SMD: standardized mean difference. **For interpretation, a SMD between 0.2 and 0.5 was considered a small effect; between 0.5 and 0.8 was considered a moderate effect; and higher than 0.8 was considered a large effect.**

Interpretation: Based on the interpretation of the SMDs, tibolone add-back had a beneficial effect on quality of life, leading to an increase that spanned from small and clinically non-significant to large and clinically meaningful (results from a single study). The effect on bone density was similar, being beneficial, but spanning from a small and clinically non-significant to a moderate and clinically meaningful effect. Intensity of vasomotor symptoms was meaningfully decreased by a large effect of tibolone add-back. There was no evidence of effect on rates of vasomotor symptoms, based on a single study.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for quality of the included studies and one additional level for imprecision of the estimates.

² Downgraded one level for quality of included studies

Summary of findings 3. GnRH-a + raloxifene compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + raloxifene compared to GnRH-a ± placebo for uterine fibroids

Patient or population: patients with uterine fibroids

Intervention: GnRH-a + raloxifene

Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + raloxifene				
Quality of life (SMD) - Follow-up: 6 months	The mean SF-36 score was 81.7	The mean quality of life (SF-36 scores) in the raloxifene add-back group was 0.11 SDs lower (0.57 lower to 0.34 higher)		74 (1 study)	⊕⊕⊕⊕ low ¹	
Bone density (SMD) - Follow-up: 6 months	The mean bone density was 1.015 g/cm ²	The mean bone density in the raloxifene add-back group was 1.01 SDs higher (0.57 to 1.45 higher)		91 (1 study)	⊕⊕⊕⊕ low ¹	
Uterine size (cm³) - Follow-up: 6 months	The mean uterine volume was 421.5	The mean uterine size in the raloxifene add-back group was 27.1 higher (17.94 lower to 72.14 higher)		91 (1 study)	⊕⊕⊕⊕ low ¹	
Uterine bleeding (VAS) - Follow-up: 6 months	The mean uterine bleeding in the control group was 0	The mean uterine bleeding in the raloxifene add-back group was 0 (no measurable difference between groups)		91 (1 study)	⊕⊕⊕⊕ low ¹	
Severity of vasomotor symptoms (no. of hot flushes per day) - Follow-up: 6 months	The mean severity of vasomotor symptoms - add-back with raloxifene in the control groups was 3.2 hot flushes per day	The mean severity of vasomotor symptoms in the raloxifene add-back group was 0.20 hot flushes higher (0.34 lower to 0.74 hot flushes higher)		91 (1 study)	⊕⊕⊕⊕ low ¹	

Rate of vasomotor symptoms

This secondary review outcome was not reported in the only included study

Not estimable

*The basis for the **assumed risk** is the mean control group risk.. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SD:** Standard deviation; **VAS:** visual analogue scale.

SMD: standardized mean difference. **For interpretation, a SMD between 0.2 and 0.5 was considered a small effect; between 0.5 and 0.8 was considered a moderate effect; and higher than 0.8 was considered a large effect.**

Interpretation: Based on the interpretation of the SMDs, raloxifene had no significant effect on quality of life, while its effect on bone density was beneficial, spanning from a moderate to a large effect. There was no evidence of effect on uterine sizes, severity of vasomotor symptoms and uterine bleeding.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for quality of the included studies and one additional level for imprecision of the estimates

Summary of findings 4. GnRH-a + estriol compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + estriol compared to GnRH-a ± placebo for uterine fibroids

Patient or population: patients with uterine fibroids

Intervention: GnRH-a + estriol

Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + estriol				
Quality of life	The primary review outcome was not reported in the only included study		Not estimable			
Bone density (SMD) - Follow-up: 6 months	The mean bone density was 1.11 g/cm ²	The mean bone density in the estriol add-back group was 3.93 SDs higher (1.7 to 6.16 higher)		12 (1 study)	⊕⊕⊕⊕ low ¹	

Uterine Size	This secondary review outcome was not reported in the only included study	Not estimable
Uterine bleeding	This secondary review outcome was not reported in the only included study	Not estimable
Severity of vasomotor symptoms	This secondary review outcome was not reported in the only included study	Not estimable
Rate of vasomotor symptoms	This secondary review outcome was not reported in the only included study	Not estimable

*The basis for the **assumed risk** is the mean control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SD:** Standard deviation.

SMD: standardized mean difference. **For interpretation, a SMD between 0.2 and 0.5 was considered a small effect; between 0.5 and 0.8 was considered a moderate effect; and higher than 0.8 was considered a large effect.**

Interpretation: Based on the interpretation of the SMD, estriol add-back had a large and beneficial effect on bone density (based on a single study).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded one level for quality of the included study and one additional level for imprecision of the estimates

Summary of findings 5. GnRH-a + ipriflavone compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + ipriflavone compared to GnRH-a ± placebo for uterine fibroids

Patient or population: patients with uterine fibroids

Intervention: GnRH-a + ipriflavone

Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + ipriflavone				

Quality of life	The primary review outcome was not reported in the only included study		Not estimable		
Bone density (SMD) - Follow-up: 6 months	The mean bone density was 5.24% less than baseline values	The mean bone density in the ipriflavone add-back group was 2.71 SDs higher (2.14 to 3.27 higher)	95 (1 study)	⊕⊕⊕⊕ low ¹	
Uterine size	This secondary review outcome was not reported in the only included study		Not estimable		
Uterine bleeding	This secondary review outcome was not reported in the only included study		Not estimable		
Severity of vasomotor symptoms	This secondary review outcome was not reported in the only included study		Not estimable		
Rate of vasomotor symptoms - Follow-up: 6 months	600 per 1000	402 per 1000 (264 to 612)	RR 0.67 (0.44 to 1.02)	95 (1 study)	⊕⊕⊕⊕ low ¹

*The basis for the **assumed risk** is the mean control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

Interpretation: Based on the interpretation of the SMD, ipriflavone add-back had a large and beneficial effect on bone density (based on a single study). There was no evidence of effect on the rate of vasomotor symptoms.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded one level for quality of the included study and one additional level for imprecision of the estimates

Summary of findings 6. GnRH-a + conjugated estrogens compared to GnRH-a ± placebo for uterine fibroids

GnRH-a + conjugated estrogens compared to GnRH-a ± placebo for uterine fibroids

Population: women with uterine fibroids

Intervention: GnRH-a + conjugated estrogens

Comparison: GnRH-a ± placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GnRH-a ± placebo	GnRH-a + conjugated estrogens				
Reduction in uterine size	The mean reduction in uterine volume was 151.9 cm ³	The mean reduction in uterine size was 105.2 cm³ less in the add-back group (27.65 less to 182.75 cm ³ less)	Not estimable	27 (1 study)	⊕○○○ very low	

*The basis for the **assumed risk** is the mean control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

Interpretation: Based on the interpretation of the SMD, estrogen add-back had a large and beneficial effect on bone density (based on a single study). There was no evidence of effect on the rate of vasomotor symptoms.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded two levels for serious risk of bias in the included study (32% attrition rate) and one additional level for imprecision

BACKGROUND

Description of the condition

Uterine leiomyomas, or fibroids, are benign tumours arising from smooth muscle cells of the myometrium. It is largely accepted that they are monoclonal tumours, stemming from the mutation of a single myometrial cell (Flake 2002). Various risk factors have been described, including early menarche, nulliparity, obesity and black ethnicity. Prolonged exposure to unopposed estrogen is one of the proposed mechanisms through which these factors increase the risk of fibroids (Flake 2002).

Fibroids are the most common benign pelvic tumours among women, although their exact prevalence is unknown and depends on the diagnostic method used (Borgfeldt 2000). Ultrasound estimates indicate a prevalence of up to 60% among white women and 80% among black women (Day Baird 2003). The association between fibroids and symptoms, however, is largely based on uncontrolled trials that reported symptomatic improvement after fibroid treatment (Lumsden 1998). According to these estimates, around 30% of women with fibroids have abnormal uterine bleeding, with longer menstrual periods, more intense bleeding during periods and the need for a higher number of tampons (Wegienka 2003). Pelvic pain occurs in about 34% of women with fibroids, in the form of dyspareunia, dysmenorrhoea and non-cyclic pelvic pain, although some studies have demonstrated only a slightly higher probability of affected women reporting moderate to severe pelvic pain (Lippman 2003). Urinary frequency and urgency may occur in some cases, probably due to bladder compression by the tumours, but the prevalence of such symptoms is largely unknown and has only been reported by small studies, estimating around 48% with lower urinary tract symptoms among these women (Cheung 2011). Fibroids may also interfere with fertility, in around 27% of women, depending on the characteristics of the tumour such as when leading to distortion of the uterine cavity (Sunkara 2010).

Description of the intervention

Gonadotropin-releasing hormone (GnRH) is a decapeptide produced in the hypothalamus and released in a pulsatile fashion, reaching the anterior pituitary and stimulating the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Islam 2013). GnRH analogues have higher potency and longer half-life than GnRH. The use of GnRH analogues in a repetitive or continuous fashion produces prolonged binding to the GnRH receptor, which leads to an initial stimulation of gonadotropin secretion (flare-up effect) but ultimately resulting in the suppression of FSH and LH secretion.

GnRH analogues are an established class of drugs for the medical treatment of uterine fibroids, with their therapeutic benefit stemming from an induced state of hypoestrogenism (Sankaran 2008). Even though GnRH analogues are effective in the treatment of uterine fibroids, their long-term use is not recommended due to several adverse effects. Short-term treatment has been tried, usually for up to six months, but after treatment discontinuation fibroid volumes have systematically returned to their previous pre-treatment state in multiple trials (Costantini 1990; Friedman 1987; Schlaff 1989; Williams 1990).

The use of hormone replacement therapy (HRT) or selective estrogen receptor modulators (SERMs) with GnRH analogues, a strategy known as add-back therapy, has been studied as an alternative to the use of GnRH analogues alone in the treatment of uterine fibroids (Sankaran 2008). Various regimens have been described, including combination with estrogen, progestogens, estrogen-progestogen therapy, tibolone, and raloxifene (Caird 1997; Gocmen 2002; Palomba 2002). It is still unknown, however, whether this strategy is safe and efficacious.

How the intervention might work

After administration of GnRH analogues, the resulting blockade of the hypothalamic-pituitary-ovarian axis leads to a state of profound hypoestrogenism (Islam 2013). Fibroid tissue is rich in sex steroid receptors, and these agents act as stimulators of tumour growth (Islam 2013). The state of estrogen deprivation induced by GnRH analogues thus has therapeutic benefit in women with fibroids, resulting in tumour volume reduction and symptomatic improvement. Studies evaluating multiple GnRH analogues have demonstrated volume reductions of around 40% after six months of treatment (Costantini 1990; Bozzini 2004), and up to 97% of women complaining of abnormal bleeding reported improvement of this symptom after six months (Friedman 1991). This estrogen deprivation, however, is also associated with various adverse effects in around 95% of treated women (Friedman 1991). Vasomotor symptoms are estimated to occur in about 90% of women (Perry 1996) and loss of bone mass occurs in from 2.5% to 5% of women after four to six months of treatment (Perry 1996). Atrophic vaginitis, insomnia, peripheral edema and nervousness have also been reported, although with an unknown prevalence (Friedman 1991). These effects limit the use of these agents and make them unfeasible as long-term medical treatments for uterine fibroids. The rationale for adding add-back therapy to GnRH analogues in the treatment of uterine fibroids is an attempt to limit the state of estrogen deprivation induced by these agents and decrease the adverse effects that are usually observed. However, since the therapeutic benefit on fibroids is based, at least partly, on the hypoestrogenism there is concern about diminished treatment efficacy.

Why it is important to do this review

The use of GnRH analogues with add-back therapy has been studied in the treatment of uterine fibroids, but results have varied between studies and multiple available regimens have not been properly compared. There is still debate on whether treatment efficacy is maintained and whether adverse effects are consistently controlled by the different add-back regimens.

OBJECTIVES

To assess the short-term (within 12 months) effectiveness and safety of add-back therapy for women using GnRH analogues for leiomyomas (uterine fibroids) associated with excessive uterine bleeding, pelvic pain, or urinary symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (for example studies with evidence of inadequate sequence generation such as alternate days or patient numbers) as they are associated with a high risk of bias. Cross-over trials were included but only data from the first phase were considered in meta-analyses as the cross-over is not a valid design in this context.

Types of participants

Women with uterine fibroids experiencing irregular or intense uterine bleeding, cyclic or non-cyclic pelvic pain, or urinary symptoms were eligible for inclusion.

Types of interventions

The experimental treatment analysed was the combination of any GnRH analogue (goserelin, leuprolide, triptorelin, buserelin, nafarelin) with some form of add-back therapy: estrogen, progestin, estrogen-progestin, tibolone, or any selective estrogen receptor modulators (SERMs, for example raloxifene, tamoxifen, ospemifene). Sequential interventions (treatment with a GnRH analogue followed by separate treatment with another agent, such as a progestin) were not considered add-back therapy and, therefore, were not eligible for inclusion.

The comparator was any GnRH analogue alone or combined with placebo.

There were no restrictions on dose, frequency, route of administration or duration of the treatment. Studies that compared treatments in the pre-operative phase (that is, treating women with fibroids using GnRH analogues with or without add-back therapy before proceeding with surgical treatment) were still considered eligible, as long as all the data available were related to the medical treatment alone, before any surgical intervention.

Types of outcome measures

Primary outcomes

Quality of life (QoL): defined by scores measured with any validated questionnaire. When multiple questionnaires were reported in studies, preference was given to the Short Form 36 (SF-36), followed by any generic questionnaires and condition-specific questionnaires.

Secondary outcomes

Bone density: change in bone mineral density (BMD) measured by any method. Preference was given to Dual X-Ray Absorptiometry (DEXA), followed by calcaneal quantitative ultrasound and by other ultrasound methods.

Uterine size (adverse effect): measured by ultrasound or other imaging methods. Preference was given to uterine volume, followed by any uterine diameter.

Uterine bleeding (adverse effect): change in uterine bleeding intensity measured by any scale. When multiple scales were encountered in different studies, preference was given to the

Pictorial Blood Assessment Chart (PBAC) (Higham 1990), followed by other visual analogue scales, the alkaline haematin method (Shaw 1972), and data from menstrual diaries.

Severity of vasomotor symptoms: measured by any scale. Preference was given to the Menopausal Vasomotor Symptoms Survey (MVS), followed by the Greene Climacteric Scale, the Women's Health Questionnaire, the Menopause-Specific Quality of Life Questionnaire, the Blatt-Kupperman Index, and by customised questionnaires used by individual studies.

Rate of vasomotor symptoms: measured by the number of participants reporting vasomotor symptoms, disregarding the number or the intensity of such episodes.

For all continuous outcomes, we preferred reporting change from baseline whenever it was available. When change from baseline values were not available, and a mix of change and final values was extracted, we combined these change and final values in a single outcome measure as long as they were reported in the same scale and mean differences were used. When change from baseline values were reported in per cent values and final values were reported in an outcome-specific scale, these values were not combined.

Reporting any specific outcome measure was not required for study inclusion. When studies reported multiple time-specific analyses, we considered the outcome values obtained in the evaluation performed closest to six months for the outcomes related to symptoms and tumour size (intensity and rate of vasomotor symptoms, quality of life and uterine size), and the last evaluation performed during the treatment period for bone mineral density.

Search methods for identification of studies

We searched for trials meeting the inclusion criteria, without language restriction and in consultation with the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

We searched for RCTs in the following electronic databases, from inception to 16 June 2014:

- MDSG Specialised Register (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2);
- MEDLINE (Appendix 3), this search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials (Higgins 2011);
- EMBASE (Appendix 4), this search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html);
- LILACS (regional.bvsalud.org/php/index.php?lang=en) (Appendix 5);
- CINAHL (www.ebscohost.com/cinahl/) (Appendix 6);
- PubMed, starting in 2012, to pick up studies that had not yet been indexed in MEDLINE (Appendix 7); and
- PsycINFO (Appendix 8).

We searched for study protocols and ongoing trials in the following trials registers:

- ClinicalTrials.gov (www.clinicaltrials.gov) ([Appendix 9](#));
- Current Controlled Trials (www.controlled-trials.com/isrctn/) ([Appendix 10](#)); and
- World Health Organization International Clinical Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx) ([Appendix 11](#)).

We searched for conference abstracts in the Web of Knowledge (<http://wokinfo.com>) ([Appendix 12](#)).

We searched for grey literature in Open Grey (www.opengrey.eu/) ([Appendix 13](#)).

We searched for similar reviews in the Database of Abstracts of Reviews of Effects (DARE) in *The Cochrane Library*) ([Appendix 14](#)).

Searching other resources

We handsearched the reference lists of articles and similar reviews retrieved by the search for any additional relevant studies.

Data collection and analysis

Selection of studies

Titles and abstracts were reviewed independently by two review authors (LGB and RMM), checking for duplicates and using the pre-established criteria for inclusion (see [Criteria for considering studies for this review](#)). The same review authors further evaluated all potentially eligible records for inclusion; disagreements were resolved by consulting another review author (WPM). Authors attempted to correspond with study investigators to clarify study eligibility when required. There were no limitations regarding language, publication date or publication status.

Data extraction and management

Two review authors (LGB and RMM) independently extracted data from included studies using a data extraction form designed and pilot-tested by the authors. Any disagreements were resolved by discussion or by a third review author (WPM). Data extracted included study characteristics and outcome data. Where studies had multiple publications, the authors collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review, and such studies had a single study ID with multiple references. We corresponded with study investigators for further data on methods and results, as required.

Assessment of risk of bias in included studies

Two review authors (LGB and RMM) independently assessed the risk of bias in included studies using the Cochrane 'risk of bias' assessment tool ([Higgins 2011](#)). We assessed: allocation (random sequence generation and allocation concealment); blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective reporting; and other bias. Disagreements were resolved by discussion. We described all judgements fully and presented the conclusions in the 'Risk of bias' table, which were incorporated into the interpretation of review findings by means of sensitivity analyses.

We took care to search for within-trial selective reporting, such as trials failing to report obvious outcomes or reporting them in insufficient detail to allow inclusion. We sought published protocols

and compared the outcomes between the protocol and the final published study.

Measures of treatment effect

For continuous data (for example uterine sizes) we calculated the mean difference (MD) or, if similar outcomes were reported in different scales, the standardized mean difference (SMD). SMDs were also used for some continuous outcomes (quality of life, bone density) even though all studies reported them on the same scale, because the original scale was difficult to interpret clinically. For outcomes reported as dichotomous data (for example rate of vasomotor symptoms) we calculated the risk ratio (RR).

Wherever studies presented two groups with the same intervention (for example two different dosages), they were combined to create a single pair-wise comparison to prevent loss of information and avoid results-related choices ([Higgins 2011](#)). We reversed the direction of effect of individual studies, if required, to ensure consistency across trials. Ordinal data (for example uterine bleeding scores; QoL scores) were treated as continuous data. We presented the 95% confidence intervals (CIs) for all outcomes. If data to calculate MDs, SMDs or RRs were not available, we had planned to utilise the most detailed numerical data available that might facilitate a similar analysis of included studies (for example P values, percentages). When studies reported sufficient detail to calculate the MD but gave no information on the associated standard deviation (SD), it was assumed that the outcome had an SD equal to the highest SD from other studies using the same assessment scale. We compared the magnitude and direction of effects reported by studies with how they were presented in the review, taking account of legitimate differences.

For the purpose of interpretation, a SMD between 0.2 and 0.5 was considered a small effect; between 0.5 and 0.8 was considered a moderate effect; and higher than 0.8 was considered a large effect ([Cohen 1988](#)). We considered the clinical relevance of all comparisons taking into account the precision of the estimates.

Unit of analysis issues

The primary analysis was per randomised woman.

Dealing with missing data

The data were analysed on an available case basis, but we attempted to obtain missing data from the original trialists. When there was still an excessive proportion of missing data (> 5% and < 10% of allocated women were not analysed) we considered the study to be at unclear risk of attrition bias. If more than 10% of allocated women were not analysed the study was judged as being at a high risk of attrition bias.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the I^2 statistic. An I^2 value greater than 50% was taken to indicate substantial heterogeneity ([Higgins 2011](#)).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the authors tried to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. If there were 10 or more studies in an analysis, a funnel plot would have been used to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

When the studies were considered to be sufficiently similar, the data from primary studies were combined comparing GnRH analogue plus add-back therapy versus GnRH analogue alone or combined with placebo. An increase in the MD, SMD or RR of a particular outcome associated with the GnRH analogue (GnRH-a) plus add-back therapy, which may be beneficial (for example QoL) or detrimental (for example bleeding), was displayed graphically in the meta-analyses to the right of the centre line.

We grouped the results depending on the medication used as add-back therapy:

- GnRH-a + medroxyprogesterone acetate versus GnRH-a alone or combined with placebo;
- GnRH-a + tibolone versus GnRH-a alone or combined with placebo;
- GnRH-a + raloxifene versus GnRH-a alone or combined with placebo;
- GnRH-a + estriol versus GnRH-a alone or combined with placebo;
- GnRH-a + ipriflavone versus GnRH-a alone or combined with placebo.

We did not combine the results of studies using different add-back strategies because the effects of different treatments on some outcomes may be substantially different, and a global pooled estimate would not be clinically meaningful.

Subgroup analysis and investigation of heterogeneity

We did not plan to perform any subgroup analysis. Where substantial heterogeneity was observed ($I^2 > 50\%$) we planned to

address it by: (1) rechecking data; (2) excluding studies at high risk of bias; (3) performing a random-effects model meta-analysis. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses to determine whether the conclusions were robust to arbitrary decisions made regarding inclusion and analysis, particularly to evaluate whether the review conclusions would have differed if eligibility had been restricted to studies without high risk of bias. We also checked the effects of using odds ratios (ORs) as measures for dichotomous outcomes when only RRs were reported in the results.

Overall quality of the body of evidence: 'Summary of findings' tables

We prepared 'Summary of findings' tables using GRADEpro software. The tables evaluated the overall quality of the body of evidence for the review outcomes using GRADE criteria (study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The electronic searches for this review were performed on 16 June 2014, retrieving a total of 546 records from the electronic databases. An additional 294 records were retrieved from searching the trials registers for protocols and ongoing trials. After excluding duplicates and applying the predefined criteria for inclusion, 35 records were considered potentially eligible and were fully examined for eligibility. None of the protocols from trials registers were considered eligible. Fourteen trials (from 25 records) met the inclusion criteria, while seven studies (from eight records) were excluded. Two studies are awaiting classification.

The study flow diagram is shown in [Figure 1](#).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Study design and setting

Fourteen RCTs were included in the review. Thirteen were parallel design and one was a cross-over study, from which data from the first phase only were extracted (Carr 1993). They were all single-centre studies conducted at the gynaecology departments from university hospitals in seven countries: Canada (Sherwin 1996),

Italy (DiLierto 2005; Palomba 1998; Palomba 2001; Palomba 2002; Palomba 2008), Japan (Nakayama 1999; Somekawa 2001), Spain (Espejo 1999), Turkey (Gocmen 2002), United States (Carr 1993; Friedman 1988; Daniels 2002) and United Kingdom (Morris 2008). We were able to extract data for the quantitative analyses from 12 of 14 eligible trials. In two trials (Daniels 2002; Sherwin 1996) there was insufficient information in the published reports and the authors did not provide any additional information, although they

answered our e-mails. Authors of the [Daniels 2002](#) study informed us that it was never published and that they would try to gather the data to send to us but did not succeed in doing so. Authors of the [Sherwin 1996](#) study also answered our e-mails but informed us they no longer had any additional data for that study.

Participants

Twelve RCTs included 622 women with fibroids, 328 in the intervention groups receiving some form of add-back therapy, and 294 in the control groups receiving GnRH-a alone or combined with placebo. The two RCTs excluded from the quantitative analyses ([Daniels 2002](#); [Sherwin 1996](#)) enrolled another 245 women but the distribution among the intervention and control groups was not clear. All the studies included only women with uterine fibroids.

Interventions

The included studies used different GnRH-a combined with various regimens of add-back therapy. The doses and treatment durations also varied across studies.

Medroxyprogesterone acetate (MPA)

- Leuprolide acetate (LA) 1 mg/day + medroxyprogesterone acetate (MPA) 20 mg/day compared with LA 1 mg/day + placebo for 3 months, followed by cross-over between treatment arms and three more months of treatment ([Carr 1993](#))
- LA 0.5 mg/day + MPA 20 mg/day compared with LA 0.5 mg/day + placebo daily for 6 months ([Friedman 1988](#))

Tibolone

- LA 3.75 mg/month + tibolone 2.5 mg/d for 4 months compared to LA 3.75 mg/month for 4 months ([DiLieto 2005](#))
- LA 3.75 mg/month + tibolone 2.5 mg/d for 6 months compared with LA 3.75 mg/month + placebo for 6 months ([Palomba 1998](#))
- LA 3.75 mg/month + tibolone 2.5 mg/d for 2 months compared with LA 3.75 mg/month + placebo for 2 months ([Palomba 2001](#))
- LA 11.25 mg/3 months + tibolone 2.5 mg/d for 6 months compared with LA 11.25 mg/3 months + placebo for 6 months ([Palomba 2008](#))
- Goserelin 3.6 mg/month + tibolone 2.5 mg/day for 3 months, goserelin 3.6 mg/month for 3 months + tibolone 2.5 mg/day in the last 2 months, goserelin 3.6 mg/month for 2 months + tibolone 2.5 mg in the last month, goserelin 3.6 mg/month + conjugated estrogens 0.625 mg/day for 3 months, and goserelin 3.6 mg/month for 3 months ([Espejo 1999](#)); results for the two arms which treated patients for three months and used tibolone have been combined and compared with the GnRH-a only group; results for the third tibolone group, which only used tibolone for a single month, were individually reported
- Goserelin 3.6 mg/month for 6 months + placebo in the first 3 months and tibolone 2.5 mg/day in the last 3 months, goserelin 3.6 mg/month + tibolone 2.5 mg/d for 6 months and goserelin 3.6 mg/month + placebo for 6 months ([Morris 2008](#)); results from the two intervention groups with tibolone were combined and compared with the placebo control group
- Triptorelin 3.75 mg/month + tibolone 2.5 mg/d for 6 months compared with triptorelin 3.75 mg/month for 6 months ([Gocmen 2002](#))

Raloxifene

- LA 3.75 mg/month + raloxifene 60 mg/day for 6 months compared with LA 3.75 mg/month + placebo for 6 months ([Palomba 2002](#))

Estrogens

- Deslorelin (D) 1 mg + estradiol (E2) 75 g, D 1 mg + E2 50 g, D 1 mg + E 2 25 g, D 1 mg + placebo and placebo only, all regimens compared during 6 months of treatment ([Daniels 2002](#))
- LA 3.75 mg/month for 5 months + conjugated estrogens 0.625 mg in the last 2 months compared with LA 3.75 mg/month for 5 months with placebo in the last 2 months ([Sherwin 1996](#))
- LA 3.75 mg/month for 6 months + estriol 4 mg/d from the third to sixth month compared with LA 3.75 mg/month for 6 months ([Nakayama 1999](#))
- Goserelin 3.6 mg/month for 3 months + conjugated estrogens 0.625 mg/day for 3 months, compared with goserelin 3.6 mg/month for 3 months – one of the arms (group 5) in a multi-arm study ([Espejo 1999](#))

Ipriflavone

- LA 1.88 mg/month + ipriflavone 600 mg/day for 6 months compared with LA 1.88 mg/month for 6 months ([Somekawa 2001](#))

Outcomes

Two out of 14 trials reported quality of life through the SF-36 questionnaire

Six out of 14 trials reported bone density

Nine out of 14 trials reported uterine size

Six out of 14 trials reported uterine bleeding

Five out of 14 trials reported severity of vasomotor symptoms

Three out of 14 trials reported the rate of vasomotor symptoms

Excluded studies

Eleven studies were excluded from the review and the reasons for exclusion are explained in the 'Characteristics of excluded studies' table. Two studies ([Alfonso 1998](#); [Caird 1997](#)) included patients with both fibroids and idiopathic abnormal uterine bleeding; three studies included patients with fibroids and endometriosis ([Lindsay 1996](#); [Mukherjee 1996](#); [Somekawa 1999](#)); three studies were not randomized ([Ishimaru 1995](#); [Ivanov 1998](#); [Maheux 1992](#)); two studies used sequential interventions instead of simultaneous add-back therapy ([Benagiano 1990](#); [Scialli 1995](#)); one study compared two different add-back regimens instead of comparing add-back therapy with placebo or isolated GnRH analogues ([Friedman 1994](#))

Studies awaiting classification

Two studies, one of them an abstract from a conference proceeding ([Opala 1997](#)) and the other a published full text article ([Ingrassia 1994](#)), were considered potentially eligible during the screening phase. However, we were unable to obtain the conference proceedings for the first study or the full text for the second study and the authors did not answer our request for these texts or for

additional details. Therefore, both studies were kept as 'awaiting classification'.

of bias' graph is shown in [Figure 2](#), and the 'Risk of bias' summary in [Figure 3](#).

Risk of bias in included studies

Detailed information about the risk of bias of the included studies is reported in the 'Characteristics of included studies' table. The 'Risk

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Carr 1993	+	?	+	+	+	+	+
Daniels 2002	?	?	+	+	-	?	-
DiLieto 2005	?	?	-	?	?	+	-
Espejo 1999	?	?	-	-	-	+	+
Friedman 1988	?	?	+	+	+	+	+
Gocmen 2002	?	?	-	-	+	+	+
Morris 2008	+	+	+	+	+	+	+
Nakayama 1999	?	?	-	-	+	+	+

Figure 3. (Continued)

Palomba 1998	+	+	+	+	?	+	+
Palomba 2001	+	+	-	-	+	+	+
Palomba 2002	+	+	-	+	+	+	+
Palomba 2008	+	+	-	-	+	+	+
Sherwin 1996	?	?	+	+	+	+	+
Somekawa 2001	?	?	-	-	?	+	+

Allocation

Adequate methods were used for generating the randomization list and for maintaining allocation concealment in five studies (Morris 2008; Palomba 1998; Palomba 2001; Palomba 2002; Palomba 2008), which were considered as being at a low risk of selection bias. In the other nine studies, methods for sequence generation or allocation concealment were not described and these were considered as being at unclear risk of selection bias.

Blinding

In six studies (Carr 1993; Daniels 2002; Friedman 1988; Morris 2008; Palomba 1998; Sherwin 1996) patients, providers and outcome assessors were blinded to treatment allocation, assessed at low risk of performance and detection bias. In the other eight studies, there was no adequate blinding of participants, healthcare providers or outcome assessors and these studies were considered as being at high risk of bias.

Incomplete outcome data

In six studies, there were no losses to follow-up after randomization and these studies were considered as being at low risk of attrition bias. In another three studies (Morris 2008; Palomba 2001; Palomba 2002) there were losses after randomization but they were well distributed among the study groups and were unlikely to result in bias. Two studies were at high risk of bias due to high attrition rates (Daniels 2002; Espejo 1999). Three studies were considered at unclear risk of attrition bias due to attrition rates of less than 10%.

Selective reporting

One study (Daniels 2002) was considered as at unclear risk of bias because it did not report a comparison between groups taking GnRH-a combined with add-back treatment or with placebo.

Other potential sources of bias

We considered one study to be at high risk of bias because it was sponsored by a pharmaceutical company and the final results were never published; moreover, the authors did not send us any additional data, although they answered our initial e-mails (Daniels

2002). Another study was also considered to be at high risk of bias because it was apparently published along with three separate publications or reports with different information regarding the number of patients randomized and lost to follow-up in each of these reports (DiLieto 2005).

Effects of interventions

See: **Summary of findings for the main comparison** GnRH-a + medroxyprogesterone acetate compared to GnRH-a ± placebo for uterine fibroids; **Summary of findings 2** GnRH-a + tibolone compared to GnRH-a ± placebo for uterine fibroids; **Summary of findings 3** GnRH-a + raloxifene compared to GnRH-a ± placebo for uterine fibroids; **Summary of findings 4** GnRH-a + estriol compared to GnRH-a ± placebo for uterine fibroids; **Summary of findings 5** GnRH-a + ipriflavone compared to GnRH-a ± placebo for uterine fibroids; **Summary of findings 6** GnRH-a + conjugated estrogens compared to GnRH-a ± placebo for uterine fibroids

1. GnRH-a + medroxyprogesterone acetate versus GnRH-a alone or combined with placebo

Primary outcome

1.1 Quality of life

No study making this comparison reported this outcome.

Secondary outcomes

1.2 Bone density

One study (Friedman 1988) reported this outcome and its estimate was too imprecise to indicate whether the treatment was harmful, beneficial or ineffective in relation to bone density (SMD 0.38, 95% CI -0.62 to 1.38, 1 study, 16 women, P = 0.45, low quality evidence, [Analysis 1.1](#)).

1.3 Uterine size

Two studies reported this outcome (Friedman 1988, Carr 1993) and the pooled estimate was sufficiently precise to suggest that adding MPA to GnRH-a had a harmful effect (larger uterine volumes) (MD

342.19 cm³, 95% CI 77.58 to 606.80, 2 studies, 32 women, $I^2 = 0\%$, low quality evidence, [Analysis 1.2](#)).

Both studies were judged as being at low risk of bias but only one of them treated patients for six months or more ([Friedman 1988](#)); sensitivity analysis considering the result of this single study still indicated a harmful effect (MD 394 cm³, 95% CI 78.99 to 709.01, 1 study, 16 women, low quality evidence).

1.4 Uterine bleeding

No study making this comparison reported this outcome.

1.5 Severity of vasomotor symptoms

No study making this comparison reported this outcome.

1.6 Rate of vasomotor symptoms

According to one study ([Friedman 1988](#)), add-back therapy with MPA had a beneficial effect in relation to the proportion of women

that developed vasomotor symptoms (RR 0.13, 95% CI 0.02 to 0.84, 1 study, 16 women, $P = 0.03$, moderate quality evidence, [Analysis 1.3](#)).

2. GnRH-a + tibolone versus GnRH-a alone or combined with placebo

Primary outcome

2.1 Quality of life

One study reported this outcome ([Palomba 2008](#)), measuring it using the SF-36 questionnaire, and its estimate was sufficiently precise to suggest that adding tibolone to GnRH-a had a beneficial effect in relation to quality of life (higher scores on a quality of life scale) (SMD 0.47, 95% CI 0.09 to 0.85, 1 study, 110 women, $P = 0.02$, low quality evidence, [Figure 4](#)).

Figure 4. Forest plot of comparison: 2 GnRH-a + tibolone versus GnRH-a ± placebo, outcome: 2.1 Quality of life.

Secondary outcomes

2.2 Bone density

Three studies reported this outcome ([DiLieto 2005](#); [Morris 2008](#); [Palomba 1998](#)) and the pooled estimate was sufficiently precise to suggest that using tibolone as add-back therapy had a beneficial effect in relation to bone density, varying from a very weak benefit to a moderate benefit (SMD 0.36, 95% CI 0.03 to 0.7, 3 studies, 160 women, $I^2 = 0\%$, moderate quality evidence, [Analysis 2.2](#)).

Sensitivity analyses considering only the studies which treated patients for a minimum of six months ([Morris 2008](#); [Palomba 1998](#)), and studies with a low risk of bias (the same two studies), made the estimate imprecise in indicating whether add-back tibolone had a beneficial effect or no effect in relation to bone density (SMD 0.27, 95% CI -0.16 to 0.71, 2 studies, 118 women, $I^2 = 23\%$, moderate quality evidence).

2.3 Uterine size

Six studies reported this outcome ([DiLieto 2005](#); [Espejo 1999](#); [Morris 2008](#); [Palomba 1998](#); [Palomba 2001](#); [Palomba 2008](#)) and the pooled estimate was sufficiently precise to suggest that add-back tibolone had a harmful effect in relation to uterine volumes (MD 23.89 cm³, 95% CI 8.13 to 39.66, 6 studies, 365 women, $I^2 = 0\%$, moderate quality evidence, [Analysis 2.3](#)).

In one multi-arm study ([Espejo 1999](#)), one of the arms received treatment with GnRH-a for two months and received add-back with tibolone for a single month. This arm was not combined with the other arms, which used tibolone for a longer period. In this arm, mean uterine volume was 9.7 ± 58.2 cm³ less than baseline values in 15 women (compared with 151.9 ± 159.7 cm³ less in the GnRH-

a group (20 women) and 93.33 ± 115.98 cm³ less in the other two tibolone groups combined (35 women)).

Sensitivity analyses including only trials which treated participants for a minimum of six months ([Morris 2008](#); [Palomba 1998](#); [Palomba 2008](#)) were performed and the estimate became imprecise for detecting a difference between a harmful effect and no effect with add-back tibolone (MD 18.07 cm³, 95% CI -2.01 to 38.15, 3 studies, 228 women, $I^2 = 0\%$, low quality evidence). Considering only the trials at low risk of bias ([Morris 2008](#); [Palomba 1998](#)), the estimate was also imprecise in indicating whether the effect was harmful, beneficial or if there was no effect (MD 27.18 cm³, 95% CI -26.67 to 81.03, 2 studies, 118 women, $I^2 = 0\%$, moderate quality evidence).

2.4 Uterine bleeding

Five studies using tibolone reported uterine bleeding, but two studies reported no events in either group ([DiLieto 2005](#); [Palomba 2008](#)). We chose not to combine the results of the trials because there was great inconsistency among the results of these studies using the same add-back agent ($I^2 = 93\%$), and meta-analysing them would result in a combined estimate that reflected only the results from studies in which tibolone was associated with increased bleeding without considering the two studies in which there was no evidence of effect due to absence of bleeding in both groups.

Results of the individual studies were as follows. In the studies reporting events ([Morris 2008](#); [Palomba 1998](#); [Palomba 2001](#)) add-back therapy was associated with more uterine bleeding compared to the control group: 28.33 ± 9.66 versus 17.1 ± 3.7 mean days with uterine bleeding during the study period ([Morris 2008](#)); 2.5 ± 0.7 versus 0 points on a visual analogue scale (VAS) for bleeding

(Palomba 1998); and 3.5 ± 0.7 versus 1.8 ± 1.1 points on a VAS for bleeding (Palomba 2001).

2.5 Severity of vasomotor symptoms

This outcome was reported by four trials (268 women). Two studies measured it through the mean number of hot flushes per day (Palomba 1998; Palomba 2001), one measured it through the Blatt-Kupperman Index (Palomba 2008) and the other used the Greene Climacteric Scale (Morris 2008).

All four studies showed a benefit with the addition of tibolone as add-back therapy, with large effect sizes. However, the studies were not pooled due to extreme heterogeneity ($I^2 = 98\%$).

2.6 Rate of vasomotor symptoms

One study that reported the proportion of patients that developed vasomotor symptoms employed tibolone as add-back therapy

(Gocmen 2002), but its estimate was not sufficiently precise to indicate whether such treatment was harmful, beneficial or had no effect in relation to this outcome (RR 0.38, 95% CI 0.14 to 1.02, 1 study, 20 women, $P = 0.05$, low quality evidence, Analysis 2.6).

3. GnRH-a + raloxifene versus GnRH-a alone or combined with placebo

Primary outcome

3.1 Quality of life

The only study which used raloxifene as add-back therapy (Palomba 2002) measured quality of life through the SF-36 questionnaire, and its estimate was not sufficiently precise to indicate if adding such an agent had a beneficial, harmful or no effect in relation to quality of life scores (SMD -0.11, 95% CI -0.57 to 0.34, 1 study, 74 women, $P = 0.62$, low quality evidence, Figure 5).

Figure 5. Forest plot of comparison: 3 GnRH-a + raloxifene versus GnRH-a ± placebo, outcome: 3.1 Quality of life.

Secondary outcomes

3.2 Bone density

The estimate from a single study (Palomba 2002) suggested that adding raloxifene as add-back therapy had a beneficial effect, resulting in a decreased loss of bone mass (SMD 1.01, 95% CI 0.57 to 1.45, 1 study, 91 women, $P < 0.00001$, low quality evidence, Analysis 3.2). Although add-back therapy may have had a beneficial effect, the magnitude of the effect was uncertain due to imprecision in the effect size.

3.3 Uterine size

The estimate for uterine size from one single study (Palomba 2002) was not sufficiently precise to indicate whether the addition of raloxifene had a beneficial, harmful or no effect in relation to uterine size (MD 27.1 cm³, 95% CI -17.94 to 72.14, 1 study, 91 women, $P = 0.24$, low quality evidence, Analysis 3.3).

3.4 Uterine bleeding

In the only study which employed raloxifene as add-back therapy (Palomba 2002), both the control and the add-back groups had a mean VAS score for bleeding of 0, with no measurable difference between groups for this outcome (low quality evidence, Analysis 3.4).

3.5 Severity of vasomotor symptoms

In the only trial which used raloxifene (Palomba 2002), there was insufficient evidence of a difference when using this regimen of add-back therapy in relation to the severity of vasomotor symptoms (MD 0.2 hot flushes/day, 95% CI -0.34 to 0.74, 1 study, 91 women, $P = 0.46$, low quality evidence, Analysis 3.5).

3.6 Rate of vasomotor symptoms

No study making this comparison reported this outcome.

4. GnRH-a + estriol versus GnRH alone or combined with placebo

Primary outcome

4.1 Quality of life

No study making this comparison reported this outcome.

Secondary outcomes

4.2 Bone density

The estimate from the only study which made this comparison and reported this outcome (Nakayama 1999) was sufficiently precise to suggest that the addition of estriol had a beneficial effect in relation to bone density (SMD 3.93, 95% CI 1.7 to 6.16, 1 study, 12 women, $P = 0.0005$, low quality evidence, Analysis 4.1).

4.3 Uterine size

No study making this comparison reported this outcome.

4.4 Uterine bleeding

No study making this comparison reported this outcome.

4.5 Severity of vasomotor symptoms

No study making this comparison reported this outcome.

4.6 Rate of vasomotor symptoms

No study making this comparison reported this outcome.

5. GnRH-a + ipriflavone versus GnRH-a alone or combined with placebo

Primary outcome

5.1 Quality of life

No study making this comparison reported this outcome.

Secondary outcomes

5.2 Bone density

This outcome was reported by one study ([Somekawa 2001](#)) in per cent changes from baseline bone density, and its estimate was sufficiently precise to suggest that add-back ipriflavone had a beneficial effect, resulting in decreased loss of bone mass (SMD 2.71, 95% CI 2.14 to 3.27, 1 study, 95 women, $P < 0.00001$, low quality evidence, [Analysis 5.1](#)).

5.3 Uterine size

No study making this comparison reported this outcome.

5.4 Uterine bleeding

No study making this comparison reported this outcome.

5.5 Severity of vasomotor symptoms

No study making this comparison reported this outcome.

5.6 Rate of vasomotor symptoms

The estimate from one study ([Somekawa 2001](#)) was not sufficiently precise to indicate whether the addition of ipriflavone had a harmful, beneficial or no effect in relation to the proportion of treated patients that developed vasomotor symptoms (RR 0.67, 95% CI 0.44 to 1.02, 1 study, 95 women, $P = 0.06$, low quality evidence, [Analysis 5.2](#)).

6. GnRH + conjugated estrogens versus GnRH-a alone

Primary outcome

6.1 Quality of life

No study making this comparison reported this outcome.

Secondary outcomes

6.2 Bone density

No study making this comparison reported this outcome.

6.3 Uterine size

This outcome was reported in one of the arms of a single study ([Espejo 1999](#)) and the estimate suggested that adding conjugated estrogens to GnRH-a resulted in a larger decrease in uterine volume in the placebo group (MD 105.2 cm³, 95% CI 27.65 to 182.75, 1 study, 27 women, $P = 0.008$, very low quality evidence, [Analysis 6.1](#)).

6.4 Uterine bleeding

No study making this comparison reported this outcome.

6.5 Severity of vasomotor symptoms

No study making this comparison reported this outcome.

6.6 Rate of vasomotor symptoms

No study making this comparison reported this outcome.

DISCUSSION

Summary of main results

The use of tibolone add-back combined with a GnRH-a seems to achieve a higher quality of life after treatment, but this effect varied from a clinically insignificant to a large and clinically meaningful

one. Tibolone may also result in weak to moderate protection of bone mass when compared with the use GnRH-a alone. While it effectively decreases vasomotor symptoms, however, such add-back therapy has been associated with a decrease in the efficacy of the GnRH-a in reducing uterine volumes, although the final volumes were not greatly increased. It might also cause increased vaginal bleeding. We could not locate long-term evidence that supports the prolonged use of tibolone as add-back therapy, but it was effective in the short term for preserving bone mass.

Evidence for using MPA, raloxifene, estriol, conjugated estrogens and ipriflavone is limited to small studies, with very few participants.

There was insufficient evidence that use of raloxifene as add-back therapy improved quality of life, but it may preserve bone mineral density (BMD) during treatment for up to six months with a GnRH-a. While it had no impact on the efficacy of the analogue in reducing uterine bleeding or decreasing uterine volumes, such an agent was not able to decrease the severity of vasomotor symptoms when compared to the use of GnRH-a alone. Similarly to tibolone, the long-term efficacy of this agent on bone densities was not studied compared to GnRH-a alone.

There was no good evidence that add-back therapy with MPA is effective in preserving bone mass during treatment with GnRH-a, and its impact on quality of life is unknown. It may decrease the proportion of treated women that develop vasomotor symptoms but is also associated with significantly increased uterine volumes.

Estriol and ipriflavone may preserve bone densities but have an unknown effect on quality of life, while conjugated estrogens may lead to larger uterine volumes. Additionally, their effects on uterine bleeding and the intensity of vasomotor symptoms are unknown.

Limitations

Nine out of 12 studies in the quantitative analysis were at high risk of bias in at least one domain; most commonly this related to lack of blinding. We could not extract any quantitative data from the reports of two eligible studies ([Daniels 2002](#); [Sherwin 1996](#)) and although the authors answered our e-mails they did not provide any additional data. We could not pool data from multiple studies for one of the secondary outcomes, uterine bleeding, because there was great inconsistency among the results of different studies using the same add-back agent (tibolone); and in two of these studies it was not possible to estimate the mean difference in bleeding because both groups had zero bleeding at the end of the study. For another secondary outcome, severity of vasomotor symptoms, high levels of heterogeneity across studies were present, even though we stratified the results according to the type of add-back therapy. In all eligible studies, the maximum treatment duration was six months with some studies evaluating their outcomes after only two to four months. This fact was justified by the use of GnRH-a alone in the control groups (which could not be submitted to prolonged treatment with these agents) but resulted in no studies reporting bone fractures, which is a major adverse event that would only be observed after treatment for longer durations. Assessment of publication bias was suboptimal because we could not perform a funnel plot analysis due to the small number of included studies.

Overall completeness and applicability of evidence

There are two main clinical questions to be considered when deciding about using add-back therapy during GnRH-a treatment for fibroids.

1. What is the impact of add-back therapy on quality of life, considering its efficacy in decreasing the adverse effects related to hypoestrogenism, and the possibility of also decreasing the therapeutic effect of GnRH-a on fibroid-related symptoms?
2. What is the impact of add-back therapy in relation to bone health?

We believe that quality of life after treatment reflects the balance between improvement of the initial, fibroid-related symptoms and the occurrence of new bothersome complaints related to the treatment itself. We observed moderate quality evidence that tibolone add-back therapy may improve the quality of life of these women, while low quality evidence indicates that raloxifene does not seem to have a beneficial impact on quality of life, although these findings were based on single trials for each agent. There was no evidence available on the effects of other add-back agents in relation to this outcome. Failure of most studies to report the impact of treatment on quality of life limited the review's conclusion regarding this most important outcome.

Regarding the impact on bone health, we found moderate quality evidence that tibolone decreases the loss of bone mass; and low quality evidence that raloxifene, estriol and ipriflavone, each one studied by a single trial, are also capable of providing such benefit. Conversely, we observed moderate quality evidence from a single study that MPA is not able to reduce the bone mass loss induced by GnRH-a. It must be stressed, however, that all these studies have only treated patients for up to six months. This time frame is already considered safe for the use of isolated GnRH-a regarding their deleterious effect on bone mass, and is probably insufficient to detect the impact such treatment has in relation to a more clinically meaningful outcomes, such as bone fractures.

Quality of the evidence

The evidence quality ranged from very low to moderate and the main limitations, which resulted in downgrading according to the GRADE criteria, were risk of bias in the primary studies and imprecision of the estimates.

Details regarding quality of evidence for all comparisons and outcomes can be found in the 'Summary of findings' tables.

Potential biases in the review process

The authors took care to perform a comprehensive search across electronic databases of published and unpublished trials, databases of study protocols and unfinished studies; and the reference lists of included studies and of other related reviews in order to minimize the risk of having a relevant study not identified. Although every effort was made to contact the authors of all studies to clarify any doubts about the published results, or to obtain additional study data, we could not obtain the full text of a published study (Ingrassia 1994) nor the conference proceedings containing the abstract for another study (Opala 1997), and our efforts to contact the authors of these studies were not successful.

Agreements and disagreements with other studies or reviews

We located a non-Cochrane systematic review of multiple treatment modalities for uterine fibroids by Lethaby et al (Lethaby 2011), which included GnRH-a with and without add-back therapy but did not pool the studies' results. This review reported the results of all the included individual studies, and its results are in agreement with the findings of our review because the included studies were essentially the same. Regarding the use of tibolone as add-back therapy, the study by Lethaby et al concluded that the addition of such an agent may decrease some of the adverse effects caused by GnRH-a, such as cognitive impairment, vasomotor symptoms and loss of bone mass; it also concluded that such an agent may not reduce uterine and fibroid volumes. Both findings are in agreement with the findings in the present review. As for the effects of raloxifene as add-back therapy, the review by Lethaby et al concluded that such an agent may decrease the loss of bone mass after six months of treatment, and may also contribute with a reduction in fibroid volumes. Regarding the use of MPA, the Lethaby et al review concluded that this agent may decrease the proportion of patients with vasomotor symptoms but it did not make any remark regarding the potential for compromising the efficacy of the GnRH-a in decreasing uterine volumes.

Palomba et al performed a cohort trial of leuprolide with tibolone add-back for two years among women with uterine fibroids (Palomba 1999), and reported no significant change in lumbar BMD after this period of treatment. Another long-term cohort study by Palomba et al (Palomba 2004) followed women with uterine fibroids who were treated with leuprolide and raloxifene for 18 months, and again demonstrated no difference in BMD after this treatment length.

AUTHORS' CONCLUSIONS

Implications for practice

Quality of life was reported in only two studies. One reported low quality evidence that tibolone add-back therapy may improve quality of life, but the estimate was imprecise and the effect size could range from clinically insignificant to large. The other found no evidence of effect from raloxifene add-back therapy. There was low or moderate quality evidence that tibolone, raloxifene, estriol and ipriflavone help to preserve bone density, and that MPA and tibolone may reduce vasomotor symptoms. A larger uterine volume was an adverse effect associated with some add-back therapies (MPA, tibolone and conjugated estrogens). For other comparisons, outcomes of interest were not reported or else study findings were inconclusive.

Implications for research

Quality of life, which we considered the primary outcome of interest, to reflect both the efficacy of the GnRH analogues over fibroid symptoms and of the add-back regimens over symptoms of hypoestrogenism was only reported by two studies. Future trials should give more attention to quality of life measurements. Another important limitation of this review was that most included studies were at high risk of bias. Also limiting was the short length of follow-up employed by all studies, which limits the conclusions that can be drawn regarding the effects of different treatments on bone health (we did not locate any report of bone fractures, for

example). However, it is unrealistic to expect that studies using isolated GnRH analogues as comparators will be conducted for longer durations due to these agents' adverse effects. Evidence for long-term combined treatment may only be available through cohorts, the comparison of different add-back regimens, or through comparison with other treatment modalities such as surgical treatment, endometrial ablation or other medical agents that may be used for a prolonged period.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Carr 1993

Methods	Cross-over randomized controlled trial; treatment for 6 months; only the first 3 months of data were analysed
Participants	University hospital; United States; Premenopausal women aged 29 to 47 years with uterine leiomyomata greater than 12 weeks gestational size; 16 participants included, 8 in the add-back group and 8 in the control group
Interventions	Leuprolide 1 mg/d subcutaneously + medroxyprogesterone acetate 20 mg/d orally versus leuprolide 1 mg/d subcutaneously + placebo orally for three months, followed by a cross-over and treatment for 3 more months
Outcomes	Uterine size, measured by ultrasound volume in cm ³
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors responded that randomization was done by randomly drawn pieces of paper
Allocation concealment (selection bias)	Unclear risk	Authors did not clear whether allocation concealment was preserved or not
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All of the women and examiners were blinded with regard to treatment and protocol group..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...MRI studies were performed and measured by one of the investigators, who was blinded to which protocol..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study does not report any patients being lost to follow-up until the final measurements were made
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Daniels 2002

Methods	Parallel designed randomized controlled trial; treatment for 12 months
Participants	University hospital; United States; women with menorrhagia secondary to uterine fibroids; mean age was 38.6, 38.2 and 37.5 years in the three studied group; 265 participants included, with numbers allocated to each study group not informed.
Interventions	Deslorelin (D) 1 mg nasal spray + E2 75 g transdermally; D 1 mg nasal spray + E2 50 g; D 1 mg nasal spray + E2 25 g; D 1 mg nasal spray + placebo transdermally; placebo nasal spray and placebo transdermally only
Outcomes	Uterine bleeding assessed by weight of sanitary pads (no objective results reported); uterine size measured by ultrasound volume (no objective results reported); bone density, measured by DEXA at the lumbar spine (L1 to L4) in g/cm ² . Outcomes reported at 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is reported as being 'double-blind'; control groups used placebo via the same route as the experimental arms (transdermal and nasal spray). The researchers were apparently careful in maintaining blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although it is not explicitly stated in the report whether the outcome assessors were blinded or not, there is no reason to believe they were not, since both patients and providers were blinded and the authors appeared to be careful in maintaining allocation blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 265 women randomized, while the results reported refer to only 185 women completing six months of treatment - an attrition rate of about 30%
Selective reporting (reporting bias)	Unclear risk	Uterine bleeding is stated as significantly reduced in patients taking active treatment, in comparison with those taking placebo. However, no comparison is made regarding uterine bleeding in patients taking active treatment combined with active add-back or with placebo add-back. Since only a conference proceeding was available, data reporting was restricted
Other bias	High risk	The study was sponsored by a pharmaceutical company, final results were never published and, although we succeeded in contacting the authors, they did not send any supplementary data

DiLieto 2005

Methods	Parallel designed randomized controlled trial; treatment for 4 months
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DiLieto 2005 (Continued)

Participants	University hospital; Italy; premenopausal women with symptomatic uterine leiomyomata; mean age was 36.8 and 37.2 years in each of the groups; 45 participants included in the treatment arms, 22 in the add back group and 23 in the control group
Interventions	Leuporelin 3.75 mg/month subcutaneously + tibolone 2.5 mg/d orally versus leuporelin 3.75 mg/month subcutaneously versus no medical treatment
Outcomes	Uterine bleeding reported through a visual analogue scale from 0 to 10; vasomotor symptoms reported as mean number of vasomotor symptoms per day; Uterine size reported as ultrasound volume in cm ³ ; bone density, measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² . Outcomes reported at 4 months

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not stated in the report whether the patients or the providers were blinded to the allocated treatment arm. However, since one group received a depot injection plus a pill, and another one received only a depot injection, without a placebo pill, it is probable that patients and care providers could know which treatment was being provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although patients and providers could probably know the treatment allocated to each patient, the report suggests that outcome assessors did not know each participant's allocation. "Clinical and laboratory tests were repeated after medical therapy. In each case, they were performed without previous knowledge of the therapy..."; "In all the cases, sections were examined and immunostaining was graded without previous knowledge of the clinical data of the patients." It is possible that outcome providers did not know each patient's allocation, but because the strategies used to maintain blinding of these personnel were not reported, and both patients and researchers could be aware of the treatment being offered, the risk of detection bias is unclear at best
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 out of 73 patients were lost to follow-up after randomization. Since an attrition rate of less than 10% was observed, the study was considered as being at unclear risk of attrition bias
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	High risk	The study was apparently published along with the separate publications and reports, with different information regarding the number of patients randomized and lost to follow-up in each of these reports. The authors did not clarify these inconsistencies. The report with the highest number of participants randomized, and disclosing the highest number of patents being lost to follow-up, was chosen as the main source of data

Espejo 1999

Methods	Parallel designed randomized controlled trial; treatment for 3 months
Participants	University hospital; Spain; premenopausal women with uterine leiomyomata; mean age was not given; 113 participants included
Interventions	Goserelin 3.6 mg/month subcutaneously for 3 months + tibolone 2.5 mg/d immediately; goserelin 3.6 mg/month subcutaneously for 3 months + tibolone in the last 2 months; goserelin 3.6 mg/month subcutaneously for 2 months + tibolone 2.5 mg in the second month; goserelin 3.6 mg/month subcutaneously for 3 months + conjugated estrogens 0.625 mg/d immediately; goserelin 3.6 mg/month subcutaneously for 3 months without add-back
Outcomes	Uterine size measured by ultrasound volume in cm ³ ; outcomes reported at 3 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not stated in the report whether the patients or the providers were blinded to the allocated treatment arm. However, since treatment arms received oral medications through different regimens, allocation could have easily been known to patients and providers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Since both patients and providers could know the allocated treatment, there is no reason to believe the outcome assessors were blinded to allocation. Also, there is no mention of blinding of this personnel in the report
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 113 participants randomized, but data were presented for only 77 patients, a 32% attrition rate
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Friedman 1988

Methods	Parallel designed randomized controlled trial; treatment for 6 months
Participants	University hospital; United States; premenopausal women with no desire for future pregnancy, at least one fibroid equal to or larger than 2.5 cm, uterus increased in size for at least 6 months without significant growth in this period, BMD no more than 1 SD below the mean for the age group and with no suspicion of malignancy in the genital tract; 16 participants included, 9 in the add-back group and 7 in the control group
Interventions	Leuprolide 0.5 mg/day subcutaneously + medroxyprogesterone acetate 20 mg/d orally versus leuprolide 0.5 mg/d subcutaneously + placebo orally

Add-back therapy with GnRH analogues for uterine fibroids (Review)

Friedman 1988 (Continued)

Outcomes	Uterine size measured by ultrasound volume in cm ³ ; bone density measured by single photon absorptiometry at the radius in g/cm ² . Outcomes reported at 6 months	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is described as a double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Since neither patients nor providers knew the allocated treatments, there is no reason to suspect that outcome assessors were knowledgeable of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients in both groups completed the 24-week treatment period"
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Gocmen 2002

Methods	Parallel designed randomized controlled trial; treatment for 6 months	
Participants	University hospital; Turkey; women with uterine leiomyomata; mean ages were 33.5 and 33.4 years in each group; 20 participants included, 10 in the add-back group and 10 in the control group	
Interventions	Triptorelin 3.75 mg/month intramuscularly + tibolone 2.5 mg/d orally; triptorelin 3.75 mg/month intramuscularly	
Outcomes	Leiomyoma size measured by ultrasound in cm ³ ; number of patients with vasomotor symptoms in each group. Outcomes reported at 6 months	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list

Add-back therapy with GnRH analogues for uterine fibroids (Review)

Gocmen 2002 (Continued)

Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study is described as double-blind, however, one of the groups is allocated to an injectable treatment plus an oral pill, while the other is allocated to an injectable treatment alone, with no placebo pills. Therefore, the allocation may be known to both patients and providers
Blinding of outcome assessment (detection bias) All outcomes	High risk	There is no mention of blinding of the outcome assessors. However, since both patients and providers could easily break the blinding allocation due to characteristics of the treatment scheme, so could the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no mention of patients being lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect of other sources of bias

Morris 2008

Methods	Parallel designed randomized controlled trial; treatment for 6 months
Participants	University hospital; United Kingdom; women of reproductive age, experiencing regular periods, and suffering from symptomatic uterine fibroids; mean ages were 38.6, 38.2 and 37.5 years in each group; 75 participants included, 50 in the add-back groups and 25 in the control group
Interventions	Goserelin 3.6 mg/month subcutaneously for 6 months + placebo orally in the first 3 months and tibolone 2.5 mg/d orally in the last 3 months; goserelin 3.6 mg/month subcutaneously for 6 months + tibolone 2.5 mg/d for 6 months; goserelin 3.6 mg/month subcutaneously for 6 months + placebo for 6 months
Outcomes	Uterine bleeding measured by mean number of bleeding days by study period (1-3 months / 4-6 months / whole study); vasomotor symptoms measured by the Greene climacteric scale; uterine size measured by ultrasound volumes in cm ³ ; bone density measured by DEXA at the lumbar spine and at the neck of the femur in g/cm ² ; outcomes reported at 6 months (under treatment), and 12 months (post-treatment follow-up)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	75 pieces of paper with A, B, or C written on them (25 each) were sequentially shuffled and inserted into opaque, sealed, sequentially numbered envelopes
Allocation concealment (selection bias)	Low risk	Sealed, opaque, sequentially numbered envelopes were opened according to the numbered sequence and the patient received its allocation
Blinding of participants and personnel (performance bias)	Low risk	The study is described as a double-blind trial

Add-back therapy with GnRH analogues for uterine fibroids (Review)

Morris 2008 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The report does not explicitly state that the outcome assessors (the ones performing the ultrasounds, applying the questionnaires and performing the bone scans) were blinded to allocation, but since neither the investigators nor the patients were aware of allocation there is no reason to believe the outcome assessors were knowledgeable
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were six losses, which were equally distributed among the groups (2, 2, 2), resulting in an 8% attrition rate. Although this rate is in the 5% to 10%, range, usually considered at least at unclear risk of bias, the risk was considered low in this case because the losses were evenly distributed
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Nakayama 1999

Methods	Parallel designed randomized controlled trial; treatment for 6 months
Participants	University hospital; Japan; premenopausal women with uterine leiomyomata and ovulatory cycles; mean ages were 47.3 and 46.3 years; 12 participants included, 6 in the add-back group and 6 in the control group
Interventions	Leuprolide 3.75 mg/month subcutaneously for 6 months + estriol 4 mg/day orally starting in the third month; leuprolide 3.75 mg/month subcutaneously for 6 months
Outcomes	Leiomyoma size measured by ultrasound volume in cm ³ ; bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² . Outcomes were reported at 6 months (under treatment), and at 18 months (12 months after treatment withdrawal for non-add back group only)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list.
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not stated whether the patients or providers were blinded or not, but because one of the groups used an injectable and oral treatment, while the other used an injectable treatment only, the allocation was probably known by patients and providers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was probably open
Incomplete outcome data (attrition bias)	Low risk	There are no statement of patients being lost to follow-up

Add-back therapy with GnRH analogues for uterine fibroids (Review)

Nakayama 1999 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Palomba 1998

Methods	Parallel designed randomized controlled trial; treatment for 6 months	
Participants	University hospital; Italy; premenopausal women with symptomatic uterine leiomyomata; mean age was 44.5 years in both groups; 50 participants included, 25 in the add-back group and 25 in the control group	
Interventions	Leuprolide 3.75 mg/month subcutaneously for 6 months + tibolone 2.5 mg/d orally; leuprolide 3.75 mg/month subcutaneously for 6 months	
Outcomes	Uterine bleeding measured by a visual analogue scale from 0 to 10; vasomotor symptoms measured by the number of hot flushes per day; uterine size measured by ultrasound volume in cm ³ ; bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² . Outcomes reported at 6 months	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors stated: "The randomization was performed by using computer software that generated a random allocation sequence (a single sequence of random assignment). The random allocation sequence was created by using the single blocks as a method of restriction"
Allocation concealment (selection bias)	Low risk	Allocation concealment was not clearly described by the authors, but in other studies by the same authors, allocation concealment was performed. This study has probably received the same treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All subjects and examiners were blinded with regard to treatment and protocol group during the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The report does not explicitly state that the outcome assessors (the ones performing the ultrasounds, applying the questionnaires and performing the bone scans) were blinded to allocation, but since neither the investigators nor the patients were aware of allocation, there is no reason to believe the outcome assessors were knowledgeable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was one loss only, in the add-back group, due to persistent bleeding, with an attrition rate of 2%. Per protocol, this is considered as at unclear risk of bias (< 10%)
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section

Palomba 1998 (Continued)

Other bias	Low risk	We did not suspect other sources of bias
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Palomba 2001

Methods	Parallel designed randomized controlled trial; treatment for 2 months
Participants	University hospital; Italy; premenopausal women with symptomatic uterine leiomyomata; mean age was 26.7 years among all included patients; 44 participants included in the treatment groups, 22 in the add-back group and 22 in the control group
Interventions	Leuprolide 3.75 mg/month intramuscularly for 2 months + tibolone 2.5 mg/d orally for 2 months + iron tablets orally; leuprolide 3.75 mg/month intramuscularly for 2 months + placebo orally + iron tablets orally; iron tablets orally only
Outcomes	Uterine bleeding measured by a visual analogue scale from 0 to 10; vasomotor symptoms measured by the number of hot flushes per day; uterine size measured by ultrasound volume in cm ³ ; bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² . Outcomes reported at 2 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By using a computer-generated randomization table, patients were allocated in equal numbers to one of three groups
Allocation concealment (selection bias)	Low risk	Authors stated: "By using a computer-generated randomization table, patients were allocated in equal numbers (1:1:1) to one of three groups. Treatment allocation was concealed in dark envelopes until the interventions were performed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although there were 5 losses among all three groups, and 4 losses considering only the comparison add-back versus GnRH-a alone, these 4 losses were evenly distributed (2, 2) in the add-back and GnRH-a groups
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Palomba 2002

Methods	Parallel designed randomized controlled trial; treatment for 6 months
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Add-back therapy with GnRH analogues for uterine fibroids (Review)

Palomba 2002 (Continued)

Participants	University hospital; Italy; premenopausal women affected by symptomatic uterine leiomyomas; mean ages were 49.1 and 48.6 years in each group; 100 participants included, 50 in the add-back group and 50 in the control group (for the quality of life analyses, only 38 patients were included in the add-back group and 36 patients in the control group)
Interventions	Leuprolide 3.75 mg/month intramuscularly for 6 months + raloxifene 60 mg/d orally for 6 months; leuprolide 3.75 mg/month intramuscularly for 6 months + placebo orally for 6 months
Outcomes	Uterine bleeding measured by a visual analogue scale from 0 to 10; vasomotor symptoms measured by the number of hot flushes per day; uterine size measured by ultrasound volume in cm ³ ; bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² ; quality of life measured by the SF-36 scale. Outcomes reported at 6 months

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random allocation sequences."
Allocation concealment (selection bias)	Low risk	Authors stated: "At the entry, all subjects were randomized in single blocks. The random allocation sequence was created by using the single blocks as a method of restriction. Allocation was concealed in dark envelopes until the interventions."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study is described as single-blind, meaning that patients did not know their allocated treatment, but care providers did. Since the study had subjective outcomes of interest (menopausal symptoms questionnaire; quality of life questionnaire), these outcomes could have been biased by the health providers' knowledge of the allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (personnel performing the ultrasonographic scans; personnel who read and interpreted the BMD measurements) were blinded to patient allocation. "The operator was unaware of treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although there were losses to follow-up, these occurred in a well distributed fashion among the two study groups. Since the losses were balanced, it is unlikely that they could bias the results, although an ITT analysis was not performed by the authors
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Palomba 2008

Methods	Parallel designed randomized controlled trial; treatment for 6 months
Participants	University hospital; Italy; premenopausal women affected by symptomatic uterine leiomyomas; mean ages were 44.5 and 45.1 years in each group; 110 participants included, 55 in the add-back group and 55 in the control group

Palomba 2008 (Continued)

Interventions	Leuprolide 11.25 mg intramuscularly every 3 months for 6 months + tibolone 2.5 mg/d orally; leuprolide 11.25 mg intramuscularly every 3 months for 6 months + placebo orally
Outcomes	Uterine bleeding measured by a visual analogue scale from 0 to 10; vasomotor symptoms measured by the Blatt-Kupperman Index; uterine size measured by ultrasound volume in cm ³ ; bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² ; quality of life measured by the SF-36 scale. Outcomes reported at 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequences
Allocation concealment (selection bias)	Low risk	The allocation sequence was concealed in opaque envelopes until intervention assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study is described as single-blind, meaning that patients did not know their allocated treatment, but care providers did. Since the study had mostly subjective outcomes of interest (menopausal symptoms questionnaire; quality of life questionnaire), these outcomes could have been biased by the health providers' knowledge of the allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were unblinded and mostly subjective outcomes were measured
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect of other sources of bias

Sherwin 1996

Methods	Parallel designed randomized controlled trial; treatment for 5 months
Participants	University hospital; Canada; women with regular menses, without current or past history of acute or chronic psychiatric illnesses, not taking any medications. All included women had infertility due to the presence of uterine leiomyomata; mean ages were 34.2 and 35.8 years in each group; 20 participants included, 10 in the add-back group and 10 in the control group
Interventions	Leuprolide 3.75 mg/month intramuscularly for 5 months + conjugated estrogens 0.625 mg/d orally in the fourth and fifth months; leuprolide 3.75 mg/month intramuscularly for 5 months + placebo orally in the fourth and fifth months
Outcomes	No outcomes of interest for the review were reported, although the study meets the inclusion criteria. Uterine volume reduction was reported, however only mean reduction for all patients, without group-specific stratification, was reported

Add-back therapy with GnRH analogues for uterine fibroids (Review)

Sherwin 1996 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list
Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The add-back treatment phase of the study was double-blinded; neither the investigator nor the patient knew whether conjugated estrogens or placebo were being administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Because neither patients nor investigators were knowledgeable of treatment allocation, it is probable that the personnel assessing the outcomes were also blinded, but this is not stated explicitly in the report
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient that was initially enrolled withdrew from the study. However, withdrawal occurred after 4 weeks of study, and the patients were only randomized after 3 weeks, for the final two months of study
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Somekawa 2001

Methods	Parallel designed randomized controlled trial; treatment for 6 months
Participants	Gynecology department of a general hospital; Japan; women aged 24 to 52 years, with uterine leiomyomata, who met the criteria for leuprolide treatment; mean ages were 45.1 and 46.1 years in each group; 102 participants included, 51 in the add-back group and 51 in the control group
Interventions	Leuprolide 1.88 mg/month for 6 months + ipriflavone 600 mg/d orally; leuprolide 1.88 mg/month for 6 months
Outcomes	Leiomyoma volume presented as per cent reduction (did not present baseline values); bone density measured by DEXA at the lumbar spine (L2 to L4) in g/cm ² ; number of patients with vasomotor symptoms

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report does not specify the methods used to generate the randomization list

Somekawa 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The report does not specify how the randomization list was handled and if there was allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of patients or providers
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Seven patients, out of 102, were stated as having vasomotor symptoms severe enough to stop them from completing the treatment with leuprolide - an attrition rate around 7%, which is considered as at unclear risk of bias, per review protocol
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section were provided in the results section
Other bias	Low risk	We did not suspect other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alfonso 1998	Authors included both patients with leiomyoma-related bleeding and dysfunctional bleeding. Results were not stratified according to pathology
Benagiano 1990	Authors studied sequential interventions (i.e. patients were treated with a GnRH analogue, and after such treatment was suspended, they were treated with a second agent, medroxyprogesterone acetate). There was no simultaneous use of a GnRH analogue and a second 'add-back' agent.
Caird 1997	Authors included both patients with leiomyoma-related bleeding and patients with idiopathic abnormal uterine bleeding. Results were not stratified according to pathology
Friedman 1994	The study assessed add-back therapy, but compared treatment with leuprolide acetate using one of two different add-back regimens - oestropipate + cyclic norethindrone versus continuous norethindrone. None of the groups were treated with a GnRH analogue alone or combined only with placebo.
Ishimaru 1995	The study was an observational cohort study including four patients with leiomyomata treated with buserelin + estrogen-progestin add-back
Ivanov 1998	Authors compared treatment with goserelin + add-back with vaginal estrogen versus goserelin alone for women with fibroids, but the study was not randomized.
Lindsay 1996	The majority of patients included had endometriosis only, and not UF (28 out of 33); three had UF only and another two had both conditions. Since the number of patients with UF was so small, the authors did not report any fibroid-specific outcomes, like uterine or leiomyoma volume, or uterine bleeding intensity. For almost all the included subjects, inclusion criteria do not apply (one of the fibroid patients was also withdrawn from the study, with only four subjects with UF included in the analysis)

Study	Reason for exclusion
Maheux 1992	The study was not randomized. It also did not compare the use of an isolated GnRH analogue versus a GnRH analogue with an add-back regimen, but compared two groups of patients using different regimens of GnRH analogue + add-back therapy
Mukherjee 1996	Included leiomyoma and endometriosis patients and did not stratify the results according to these two pathologies
Scialli 1995	Authors studied sequential interventions (i.e. patients were treated with a GnRH analogue, and after such treatment was suspended, they were randomized to receive treatment with medroxy-pogesterone acetate or placebo). There was no simultaneous use of a GnRH analogue and a second 'add-back' agent.
Somekawa 1999	Included leiomyoma and endometriosis patients and did not stratify the results according to these two pathologies

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Ingrassia 1994](#)

Methods	Parallel designed prospective trial. Insufficient information in the abstract to conclude if it was a randomized trial or not
Participants	Setting, not informed; Italy; women aged 30 to 45 years with uterine leiomyomata
Interventions	Triptorelin 3.75 mg/month + oral contraceptive with desogestrel 150 µg and ethinylestradiol 20 µg for 6 months; triptorelin 3.75 mg/month for 6 months
Outcomes	The studied outcomes are not clearly stated in the abstract
Notes	The study was not included nor excluded because it was potentially eligible, based on the inclusion criteria, but eligibility could not be confirmed due to lack of data in the abstract. Also, we could not obtain the full text of the paper, and the authors did not respond to our making contact

[Opala 1997](#)

Methods	Unknown
Participants	Unknown
Interventions	Unknown. The title refers to GnRH analogue associated with "Mercilon add-back therapy"
Outcomes	Unknown
Notes	Potential eligibility of this trial was determined based on its title. However, there was no abstract available and we could not locate the study's full text, nor did the authors respond to our making contact

UF = Uterine fibroids

DATA AND ANALYSES

Comparison 1. GnRH-a + medroxyprogesterone acetate versus GnRH-a ± placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone Density	1	16	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.62, 1.38]
2 Uterine Size	2	32	Mean Difference (IV, Random, 95% CI)	342.19 [77.58, 606.80]
3 Rate of Vasomotor Symptoms	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.84]

Analysis 1.1. Comparison 1 GnRH-a + medroxyprogesterone acetate versus GnRH-a ± placebo, Outcome 1 Bone Density.

Analysis 1.2. Comparison 1 GnRH-a + medroxyprogesterone acetate versus GnRH-a ± placebo, Outcome 2 Uterine Size.

Analysis 1.3. Comparison 1 GnRH-a + medroxyprogesterone acetate versus GnRH-a ± placebo, Outcome 3 Rate of Vasomotor Symptoms.

Comparison 2. GnRH-a + tibolone versus GnRH-a ± placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of Life	1	110	Std. Mean Difference (IV, Fixed, 95% CI)	0.47 [0.09, 0.85]
2 Bone Density	3	160	Std. Mean Difference (IV, Random, 95% CI)	0.36 [0.03, 0.70]
3 Uterine Size	6	365	Mean Difference (IV, Random, 95% CI)	23.89 [8.13, 39.66]
4 Uterine Bleeding	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Severity of Vasomotor Symptoms	4		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Rate of Vasomotor Symptoms	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.02]

Analysis 2.1. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 1 Quality of Life.

Analysis 2.2. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 2 Bone Density.

Analysis 2.3. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 3 Uterine Size.

Analysis 2.4. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 4 Uterine Bleeding.

Analysis 2.5. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 5 Severity of Vasomotor Symptoms.

Analysis 2.6. Comparison 2 GnRH-a + tibolone versus GnRH-a ± placebo, Outcome 6 Rate of Vasomotor Symptoms.

Comparison 3. GnRH-a + raloxifene versus GnRH-a ± placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of Life	1	74	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.57, 0.34]
2 Bone Density	1	91	Std. Mean Difference (IV, Fixed, 95% CI)	1.01 [0.57, 1.45]
3 Uterine Size	1	91	Mean Difference (IV, Fixed, 95% CI)	27.10 [-17.94, 72.14]
4 Uterine Bleeding	1	91	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Severity of Vasomotor Symptoms (No. of hot flashes per day)	1	91	Mean Difference (IV, Random, 95% CI)	0.20 [-0.34, 0.74]

Analysis 3.1. Comparison 3 GnRH-a + raloxifene versus GnRH-a ± placebo, Outcome 1 Quality of Life.

Analysis 3.2. Comparison 3 GnRH-a + raloxifene versus GnRH-a ± placebo, Outcome 2 Bone Density.

Analysis 3.3. Comparison 3 GnRH-a + raloxifene versus GnRH-a ± placebo, Outcome 3 Uterine Size.

Analysis 3.4. Comparison 3 GnRH-a + raloxifene versus GnRH-a ± placebo, Outcome 4 Uterine Bleeding.

Analysis 3.5. Comparison 3 GnRH-a + raloxifene versus GnRH-a ± placebo, Outcome 5 Severity of Vasomotor Symptoms (No. of hot flashes per day).

Comparison 4. GnRH-a + estriol versus GnRH-a ± placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone Density	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	3.93 [1.70, 6.16]

Analysis 4.1. Comparison 4 GnRH-a + estriol versus GnRH-a ± placebo, Outcome 1 Bone Density.

Comparison 5. GnRH-a + ipriflavone versus GnRH-a ± placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone Density	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	2.71 [2.14, 3.27]
2 Rate of Vasomotor Symptoms	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.44, 1.02]

Analysis 5.1. Comparison 5 GnRH-a + ipriflavone versus GnRH-a ± placebo, Outcome 1 Bone Density.

Analysis 5.2. Comparison 5 GnRH-a + ipriflavone versus GnRH-a ± placebo, Outcome 2 Rate of Vasomotor Symptoms. **Comparison 6. GnRH-a + conjugated estrogens versus GnRH-a ± placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine size	1	27	Mean Difference (IV, Fixed, 95% CI)	105.4 [27.65, 183.15]

Analysis 6.1. Comparison 6 GnRH-a + conjugated estrogens versus GnRH-a ± placebo, Outcome 1 Uterine size. **APPENDICES****Appendix 1. MDSG Specialised Register search strategy**

Keywords CONTAINS "Leiomyoma" or "leiomyomata" or "fibroids" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "myoma" or "myomas" or Title CONTAINS "Leiomyoma" or "leiomyomata" or "fibroids" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "myoma" or "myomas"

AND

Keywords CONTAINS "Gonadorelin" or "GnRH analogue" or "GnRH analog" or "GnRh" or "GnRHa" or "GnRHa-gonadotropin" or "gonadotrophin" or "gonadotropin" or "gonadotropin-releasing hormone" or "Goserelin" or "Gosereline" or "LHRH" or "luteinizing hormone" or "leuprolide" or "leuprorelin" or "leuprolin" or "Zoladex" or "Lupron" or "decapetyl" or "buserelin" or "busereline" or "nafarelin" or "triptorelin" or "triptoreline" or "triptorelyn" or "triptrolein" or "triptoielin" or "ganirelix" or "degarelix" or Title CONTAINS "Gonadorelin" or "GnRH analogue" or "GnRH analog" or "GnRh" or "GnRHa" or "GnRHa-gonadotropin" or "gonadotrophin" or "gonadotropin" or "gonadotropin-releasing hormone" or "Goserelin" or "Gosereline" or "LHRH" or "luteinizing hormone" or "leuprolide" or "leuprorelin" or "leuprolin" or "Zoladex" or "Lupron" or "decapetyl" or "buserelin" or "busereline" or "nafarelin" or "triptorelin" or "triptoreline" or "triptorelyn" or "triptrolein" or "triptoielin" or "ganirelix" or "degarelix"

AND

Keywords CONTAINS "add back therapy" or "estrogen" or "estrogen-progestogen" or "estrogen replacement therapy" or "*Estrogens" or "ethinyl estradiol" or "ethinyl estradiol-cyproterone acetate" or "ethinylestradiol" or "oestrogen" or "progestagen" or "progesterone" or "progestin" or "progestins" or "progestogen" or "progestogens" or "tibolone" or "SERM" or "selective estrogen receptor modulator" or "Raloxifene" or "Tamoxifen" or "*Medrogestone" or "Medroxyprogesterone" or "toremifen" or "toremifene" or "hormonal add-back therapy" or "*Hormone Substitution" or "hormone therapy" or "estradiol" or "Estriol" or "norethisterone" or "Norethindrone" or "Norethisterone" or "*Gestagen" or Title CONTAINS "add back therapy" or "estrogen" or "estrogen-progestogen" or "estrogen replacement therapy" or "*Estrogens" or "ethinyl estradiol" or "ethinyl estradiol-cyproterone acetate" or "ethinylestradiol" or "oestrogen" or "progestagen" or "progesterone" or "progestin" or "progestins" or "progestogen" or "progestogens" or "hormonal add-back therapy" or "Medroxyprogesterone" or "toremifen" or "toremifene" or "SERM" or "selective estrogen receptor modulator" or "Raloxifene" or "Tamoxifen"

Appendix 2. CENTRAL search strategy

(The Cochrane Library search - trials)

- 1 leiomyoma/ or myoma/ (334)
- 2 leiomyom\$.tw. (197)
- 3 myoma\$.tw. (202)
- 4 fibroid\$.tw. (224)
- 5 hysteromyoma\$.tw. (12)
- 6 fibromyoma\$.tw. (11)
- 7 or/1-6 (594)
- 8 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin pamoate/ (1800)
- 9 gonadotropin-releasing hormone\$.tw. (713)
- 10 gonadotrophin-releasing hormone\$.tw. (299)
- 11 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (1186)
- 12 GnRH\$.tw. (1653)
- 13 luteinizing hormone releasing hormone\$.tw. (242)
- 14 LHRH\$.tw. (342)
- 15 suprefact.tw. (9)
- 16 synarel.tw. (3)
- 17 decapeptyl.tw. (53)
- 18 Gonadorelin.tw. (6)
- 19 Cetrorelix.tw. (112)
- 20 Degarelix.tw. (16)
- 21 Ganirelix.tw. (72)
- 22 lupron.tw. (32)
- 23 zoladex.tw. (219)
- 24 or/8-23 (3291)
- 25 "add back".tw. (77)
- 26 exp Estrogens/ (5696)
- 27 exp Estradiol/ (3241)
- 28 Estradiol.tw. (3843)
- 29 exp Estriol/ (188)
- 30 Estriol.tw. (178)
- 31 estrogen\$.tw. (4853)
- 32 oestrogen\$.tw. (1179)
- 33 progestin\$.tw. (852)
- 34 tibolone.tw. (396)
- 35 selective estrogen receptor modulator\$.tw. (179)
- 36 SERM\$.tw. (80)
- 37 raloxifene.tw. (499)
- 38 tamoxifen\$.tw. (2594)
- 39 ospemifene.tw. (15)
- 40 estroprogestin\$.tw. (16)
- 41 exp Progestins/ (1754)
- 42 Medroxyprogesterone\$.tw. (1263)
- 43 exp Medroxyprogesterone/ (998)
- 44 oestroprogestin\$.tw. (1)
- 45 exp Norethindrone/ (669)
- 46 Norethindrone.tw. (219)

47 norethisterone.tw. (552)
48 exp selective estrogen receptor modulators/ or clomiphene/ or raloxifene/ or tamoxifen/ or toremifene/ (2037)
49 or/25-48 (13815)
50 7 and 24 and 49 (89)

Appendix 3. MEDLINE search strategy

(OvidSP)

1 leiomyoma/ or myoma/ (16413)
2 leiomyom\$.tw. (10484)
3 myoma\$.tw. (4462)
4 fibroid\$.tw. (4097)
5 hysteromyoma\$.tw. (49)
6 fibromyoma\$.tw. (632)
7 or/1-6 (22725)
8 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin pamoate/ (29776)
9 gonadotropin-releasing hormone\$.tw. (11556)
10 gonadotrophin-releasing hormone\$.tw. (2721)
11 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (4237)
12 GnRH\$.tw. (19166)
13 luteinizing hormone releasing hormone\$.tw. (5274)
14 LHRH\$.tw. (6176)
15 suprefact.tw. (24)
16 synarel.tw. (14)
17 decapeptyl.tw. (211)
18 Gonadorelin.tw. (162)
19 Cetrorelix.tw. (752)
20 Degarelix.tw. (104)
21 Ganirelix.tw. (158)
22 lupron.tw. (157)
23 zoladex.tw. (375)
24 or/8-23 (40201)
25 "add back".tw. (469)
26 exp Estrogens/ (147632)
27 exp Estradiol/ (78130)
28 Estradiol.tw. (69348)
29 exp Estriol/ (5750)
30 Estriol.tw. (3783)
31 estrogen\$.tw. (113940)
32 oestrogen\$.tw. (19477)
33 progestin\$.tw. (10329)
34 tibolone.tw. (896)
35 selective estrogen receptor modulator\$.tw. (2367)
36 SERM\$.tw. (1963)
37 raloxifene.tw. (2845)
38 tamoxifen\$.tw. (19436)
39 ospemifene.tw. (83)
40 estroprogestin\$.tw. (129)
41 exp Progestins/ (61649)
42 Medroxyprogesterone\$.tw. (5510)
43 exp Medroxyprogesterone/ (6692)
44 oestroprogestin\$.tw. (25)
45 exp Norethindrone/ (4085)
46 Norethindrone.tw. (1219)
47 norethisterone.tw. (1909)
48 exp selective estrogen receptor modulators/ or clomiphene/ or raloxifene/ or tamoxifen/ or toremifene/ (25868)
49 or/25-48 (276393)
50 7 and 24 and 49 (374)
51 randomized controlled trial.pt. (389747)
52 controlled clinical trial.pt. (89891)

53 randomized.ab. (305362)
54 randomised.ab. (67126)
55 placebo.tw. (168007)
56 clinical trials as topic.sh. (175327)
57 randomly.ab. (216021)
58 trial.ti. (131667)
59 (crossover or cross-over or cross over).tw. (62991)
60 or/51-59 (978015)
61 exp animals/ not humans.sh. (4057880)
62 60 not 61 (903656)
63 50 and 62 (102)

Appendix 4. EMBASE search strategy

(Ovid)

1 exp leiomyoma/ (14021)
2 exp uterus myoma/ or exp myoma/ (10880)
3 myoma\$.tw. (5754)
4 fibroid\$.tw. (5768)
5 hysteromyoma\$.tw. (95)
6 fibromyoma\$.tw. (566)
7 leiomyom\$.tw. (12320)
8 or/1-7 (29645)
9 exp gonadorelin/ (28438)
10 exp buserelin acetate/ or exp buserelin/ (4649)
11 exp goserelin/ (5657)
12 exp leuprorelin/ (8452)
13 exp nafarelin acetate/ or exp nafarelin/ (1326)
14 exp triptorelin/ (3973)
15 gonadotropin-releasing hormone\$.tw. (11841)
16 gonadotrophin-releasing hormone\$.tw. (2737)
17 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (5362)
18 GnRH\$.tw. (21574)
19 luteinizing hormone releasing hormone\$.tw. (4876)
20 LHRH\$.tw. (6881)
21 Gonadorelin.tw. (249)
22 Cetrorelix.tw. (641)
23 Degarelix.tw. (171)
24 Ganirelix.tw. (293)
25 lupron.tw. (1596)
26 zoladex.tw. (1947)
27 suprefact.tw. (920)
28 synarel.tw. (314)
29 decapeptyl.tw. (1613)
30 or/9-29 (55322)
31 "add back".tw. (554)
32 exp gestagen/ (136323)
33 gestagen.tw. (944)
34 exp estrogen/ (212322)
35 estrogen\$.tw. (123493)
36 oestrogen\$.tw. (20319)
37 exp Estradiol/ (94176)
38 Estradiol.tw. (72396)
39 exp Estriol/ (7418)
40 Estriol.tw. (3601)
41 exp Norethindrone/ (6526)
42 norethisterone.tw. (1877)
43 Norethindrone.tw. (944)
44 progestin\$.tw. (10771)
45 exp medroxyprogesterone acetate/ or exp medroxyprogesterone/ (17437)
46 Medroxyprogest\$.tw. (5904)

47 oestroprogesterin\$.tw. (33)
 48 tibolone.tw. (1207)
 49 exp tamoxifen/ or exp selective estrogen receptor modulator/ or exp raloxifene/ or exp ethinylestradiol/ (67781)
 50 selective estrogen receptor modulator\$.tw. (2781)
 51 SERM\$.tw. (2689)
 52 raloxifene.tw. (3575)
 53 tamoxifen\$.tw. (23221)
 54 ospemifene.tw. (78)
 55 estroprogesterin\$.tw. (162)
 56 exp ospemifene/ (141)
 57 exp toremifene/ (1770)
 58 or/31-57 (368163)
 59 8 and 30 and 58 (686)
 60 Clinical Trial/ (889560)
 61 Randomized Controlled Trial/ (359225)
 62 exp randomization/ (63800)
 63 Single Blind Procedure/ (18456)
 64 Double Blind Procedure/ (118442)
 65 Crossover Procedure/ (38843)
 66 Placebo/ (228016)
 67 Randomized controlled trial\$.tw. (95753)
 68 Rct.tw. (12868)
 69 random allocation.tw. (1304)
 70 randomly allocated.tw. (19876)
 71 allocated randomly.tw. (1936)
 72 (allocated adj2 random).tw. (736)
 73 Single blind\$.tw. (14032)
 74 Double blind\$.tw. (141298)
 75 ((treble or triple) adj blind\$.tw. (337)
 76 placebo\$.tw. (196657)
 77 prospective study/ (253689)
 78 or/60-77 (1385959)
 79 case study/ (22072)
 80 case report.tw. (255080)
 81 abstract report/ or letter/ (891087)
 82 or/79-81 (1162800)
 83 78 not 82 (1348726)
 84 59 and 83 (216)

Appendix 5. LILACS search strategy

#1

(tw:GnRH OR mh:"Gonadotropin-Releasing Hormone" OR tw:goserelin OR mh:goserelin OR tw:zadex OR tw:buserelin OR mh:buserelin
 OR tw:suprefact OR tw:nafarelin OR mh:nafarelin OR tw:synarel OR tw:leuprolide OR mh:leuprolide OR tw:lupron OR tw:triptorelin OR
 mh:"triptorelin pamoate" OR tw:decapeptyl)

#2

(tw:leiomyoma OR mh:leiomyoma OR leiomyom* OR fibroid*)

#3

(tw:"add-back" OR tw:estradiol OR mh:estradiol OR tw:estriol OR mh:estriol OR mh:"Estrogen Replacement Therapy" OR
 tw:progestins OR mh:progestins OR tw:medroxyprogesterone OR mh:medroxyprogesterone OR tw:"medroxyprogesterone acetate" OR
 mh:"medroxyprogesterone acetate" OR tw:norethindrone OR mh:norethindrone OR tw:SERM OR mh:"Estrogen Receptor Modulators" OR
 tw:raloxifene OR mh:raloxifene OR tw:tamoxifen OR mh:tamoxifen OR tw:ospemifene OR tw:tibolone)

#4

pt:clinical trial

Search: (#1) AND (#2) AND (#3) AND (#4)

Appendix 6. CINAHL search strategy

S40	S25 AND S39	28
S39	S26 OR S27 or S28 or S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	878,348
S38	TX allocat* random*	3,845
S37	(MH "Quantitative Studies")	11,691
S36	(MH "Placebos")	8,664
S35	TX placebo*	31,178
S34	TX random* allocat*	3,845
S33	(MH "Random Assignment")	36,861
S32	TX randomi* control* trial*	70,325
S31	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	706,365
S30	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	102
S29	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	0
S28	TX clinic* n1 trial*	161,662
S27	PT Clinical trial	75,618
S26	(MH "Clinical Trials+")	172,600
S25	S8 AND S24	88
S24	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	1,497
S23	TX zoladex	27
S22	TX Gonadorelin	725
S21	TX LHRH*	78
S20	(MM "Luteinizing Hormone") OR "luteinizing hormone releasing hormone"	214
S19	TX GnRH	278
S18	TX triptorelin	31
S17	TX nafarelin	17
S16	(MM "Nafarelin")	6

(Continued)

S15	TX leuprolide	258
S14	(MM "Leuprolide")	114
S13	TX goserelin	216
S12	TX buserelin	8
S11	TX gonadotrophin-releasing hormone*	75
S10	TX gonadotropin-releasing hormone*	313
S9	(MH "Gonadorelin+") OR "gonadotropin-releasing hormone"	1,167
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	2,340
S7	TX fibromyoma*	5
S6	TX hysteromyoma*	3
S5	TX fibroid*	811
S4	TX leiomyoma*	1,984
S3	TX myoma*	276
S2	(MM "Leiomyoma") OR "leiomyoma"	1,914
S1	(MH "Myoma+") OR "myoma"	251

Appendix 7. PubMed search strategy

(Search start - 2012)

#1

(GnRH OR goserelin OR zoladex OR buserelin OR suprefact OR nafarelin OR synarel OR leuprolide OR lupron OR triptorelin OR decapeptyl)

#2

(leiomyoma OR leiomyom* OR fibroid*)

#3

(add-back OR estradiol OR estriol OR Estrogen Replacement Therapy OR progestins OR medroxyprogesterone OR medroxyprogesterone acetate OR norethindrone OR serm OR raloxifene OR tamoxifen OR ospemifene OR tibolone)

#4

((((((((randomized controlled trial [pt]) OR randomized controlled trial) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab])) NOT ((animals [mh] NOT humans [mh]))

Search: (#1) AND (#2) AND (#3) AND (#4)

Appendix 8. PsycINFO search strategy

(Ovid)

1 myoma\$.tw. (22)

2 leiomyoma\$.tw. (11)

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3 fibroid\$.tw. (36)
4 hysteromyoma\$.tw. (2)
5 fibromyoma\$.tw. (1)
6 or/1-5 (69)
7 exp Gonadotropic Hormones/ or exp Luteinizing Hormone/ (3639)
8 gonadotropin-releasing hormone\$.tw. (511)
9 gonadotrophin-releasing hormone\$.tw. (168)
10 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw. (107)
11 GnRH\$.tw. (650)
12 luteinizing hormone releasing hormone\$.tw. (189)
13 Gonadorelin.tw. (2)
14 Cetrorelix.tw. (5)
15 Degarelix.tw. (3)
16 Ganirelix.tw. (0)
17 lupron.tw. (14)
18 zoladex.tw. (4)
19 or/7-18 (4018)
20 6 and 19 (3)

Appendix 9. ClinicalTrials.gov search strategy

#1

(GnRH OR goserelin OR buserelin OR nafarelin OR leuprolide OR triptorelin)

#2

(leiomyoma OR fibroid)

#3

("add-back" OR estradiol OR estriol OR "replacement therapy" OR progestins OR raloxifene OR tamoxifen OR ospemifene OR tibolone)

Search: (#1) AND (#2) AND (#3)

Appendix 10. Current Controlled Trials search strategy

#1

(GnRH OR goserelin OR buserelin OR nafarelin OR leuprolide OR triptorelin)

#2

(leiomyoma OR fibroid)

#3

("add-back" OR estradiol OR estriol OR "replacement therapy" OR progestins OR raloxifene OR tamoxifen OR ospemifene OR tibolone)

Search: (#1) AND (#2) AND (#3)

Appendix 11. World Health Organization International Clinical Trials Registry Platform search strategy

Separate lines in simple search (i.e. 3 individual searches)

1- "add back"

2- Fibroid*

3- Leiomyom*

Appendix 12. Web Of Knowledge Conference Reports search strategy

#1 - Databases=CPCI-S, CPCI-SSH Timespan=All years

TS=(GnRH OR gonadorelin OR goserelin OR zoladex OR buserelin OR suprefact OR nafarelin OR synarel OR leuprolide OR lupron OR triptorelin OR decapeptyl)

#2 – Databases=CPCI-S, CPCI-SSH Timespan=All years

TS=(leiomyom* OR fibroid*)

#3 – Databases=CPCI-S, CPCI-SSH Timespan=All years

TS=("add-back" OR estrogens OR estradiol OR estriol OR hrt OR (hormone SAME replacement SAME therapy) OR progestins OR medroxyprogesterone OR "medroxyprogesterone acetate" OR norethindrone OR serm OR "estrogen receptor modulator" OR raloxifene OR tamoxifen OR ospemifene OR tibolone)

Search: (#1) AND (#2) AND (#3)

Appendix 13. OpenGrey search strategy

#1

(GnRH OR gonadorelin OR goserelin OR zoladex OR buserelin OR suprefact OR nafarelin OR synarel OR leuprolide OR lupron OR triptorelin OR decapeptyl)

#2

(leiomyom* OR fibroid*)

#3

("add-back" OR estrogens OR estradiol OR estriol OR hrt OR (hormone SAME replacement SAME therapy) OR progestins OR medroxyprogesterone OR "medroxyprogesterone acetate" OR norethindrone OR serm OR "estrogen receptor modulator" OR raloxifene OR tamoxifen OR ospemifene OR tibolone)

Search: (#1) AND (#2) AND (#3)

Appendix 14. DARE search strategy

(The Cochrane Library search - other reviews)

#1 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees

#2 zoladex

#3 synarel

#4 decapeptyl

#5 lupron

#6 suprefact

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Leiomyoma] explode all trees

#9 leiomyom*

#10 fibroid*

#11 #8 or #9 or #10

#12 "add back"

#13 MeSH descriptor: [Estrogens] explode all trees

#14 estriol

#15 MeSH descriptor: [Progestins] explode all trees

#16 MeSH descriptor: [Estrogen Replacement Therapy] explode all trees

#17 MeSH descriptor: [Medroxyprogesterone] explode all trees

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#18 MeSH descriptor: [Norethindrone] explode all trees

#19 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees

#20 raloxifene

#21 tamoxifen

#22 ospemifene

#23 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 #7 and #11 and #23

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: Luiz Gustavo Brito; Rui A. Ferriani
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- Developing the search strategies: Luiz Gustavo Brito; Rafael M Moroni; Wellington P Martins; Carolina O Nastri
- Reviewing the protocol and commenting on it critically: Wellington P Martins; Carolina S Vieira; Francisco José Candido Dos Reis; Luiz Gustavo Brito
- Undertaking searches: Rafael M Moroni
- Screening search results: Rafael M Moroni, Luiz Gustavo Brito
- Screening retrieved papers against eligibility criteria: Rafael M Moroni, Luiz Gustavo Brito
- Extracting data from papers: Rafael M Moroni, Luiz Gustavo Brito
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DECLARATIONS OF INTEREST

The authors declare no conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had initially planned to avoid combining the results of studies using different add-back strategies only when such combinations resulted in significant heterogeneity. However, such planning was discarded and, instead, we decided we would not combine any results of studies using different add-back strategies due to potentially different effects among these interventions, which could lead to clinically non-significant estimates.

We removed the plan to use Peto OR from our Methods section due to the fact that the dichotomous outcome that remained in the review was 'patients with vasomotor symptoms', and we did not expect to find zero or near-zero values for such an outcome in any of the groups.

We decided to change the primary outcomes from 'uterine bleeding' and 'intensity of vasomotor symptoms' to 'quality of life'. This change was made to reflect our perception that quality of life relates both to symptomatic improvement (reflecting maintained treatment efficacy) and to limited adverse effects (reflecting tolerability, the efficacy of the add-back agents in avoiding the bothersome symptoms

of hypoestrogenism, especially vasomotor symptoms). Evaluation of each specific consequence of using GnRH analogues with or without add-back therapy (impact on bone density, uterine volumes, uterine bleeding, rise of vasomotor symptoms and the intensity of these symptoms) was considered to be secondary.

We excluded one of our initially planned outcomes, bone fractures. Such an outcome was excluded because studies comparing the use of GnRH analogues with or without add-back therapy were limited to six months of follow-up. This short-term follow-up is intentionally chosen to avoid exposing patients in the control groups to the risks related to prolonged hypoestrogenism, including bone fractures. Therefore, seeking a consequence of long-term hypoestrogenism in studies with short-term use of GnRH analogues would not make sense. In accordance with this decision, we also excluded from our Methods section the planning to perform subgroup analyses according to treatment length regarding the effects of treatment on bone-related outcomes, including fractures.

For quality of life and for bone density, we decided to express our estimates as SMDs, even though all the studies expressed their results in the same scale. This decision was made to facilitate interpretation because the meaning of the changes in bone mass expressed in g/cm², and in quality of life expressed in number of points in the SF-36 questionnaire, may not be so straightforward. By using SMDs we provide standardized values that allow the reader to interpret whether the effect of the intervention was small, moderate or large.

INDEX TERMS

Medical Subject Headings (MeSH)

*Quality of Life; Antineoplastic Agents, Hormonal [adverse effects] [therapeutic use]; Bone Density [*drug effects]; Bone Density Conservation Agents [adverse effects] [therapeutic use]; Drug Therapy, Combination [methods]; Estriol [adverse effects] [therapeutic use]; Gonadotropin-Releasing Hormone [*analogs & derivatives]; Isoflavones [adverse effects] [therapeutic use]; Leiomyoma [*drug therapy]; Medroxyprogesterone [adverse effects] [therapeutic use]; Norpregnenes [adverse effects] [therapeutic use]; Raloxifene Hydrochloride [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Uterine Hemorrhage [chemically induced] [drug therapy]; Uterine Neoplasms [*drug therapy]

MeSH check words

Female; Humans