National Institute for Health and Care Excellence

Final

Endometriosis

Evidence review A: Treatment of endometriosis when fertility is a priority

NICE guideline NG73 (update)

Evidence review underpinning recommendations 1.11.2 to 1.11.4 and recommendation for research 5 in the NICE guideline

April 2024

FINAL

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Treatment of endometriosis when fertility is a priority

Review question

What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis:

- hormonal medical treatments
- surgery
- non-pharmacological therapies
- combination treatment (hormonal treatment and surgery)

Introduction

Endometriosis is a chronic inflammatory disease affecting up to 10% of women and is defined as the presence of endometrium-like tissue outside the uterus. Endometriosis can cause chronic pain affecting daily activities and quality of life, particularly on a cyclical basis. It can also cause heavy periods and urinary or gastrointestinal symptoms. It may also impact on fertility. Treatment can include hormonal and surgical options, but some hormonal treatments such as contraceptive pills are not suitable in women or people with endometriosis wishing to become pregnant. For women or people living with endometriosis where fertility is a priority there is a need for treatment options that improve pregnancy rates and are suitable for different sites and stages of endometriosis.

The aim of this review is to determine the optimum treatment for endometriosis in women who wish to improve their fertility, including improving pregnancy and live birth rates.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	**Inclusion** • Subfertile women desiring pregnancy, between menarche and menopause with endometriosis of any stage or severity. • Women with a suspected diagnosis of endometriosis desiring pregnancy • Recurrent and asymptomatic endometriosis. • Both primary and secondary infertility. **Exclusion** • Women with chronic pelvic pain known to be due to causes other than endometriosis • Those suspected based solely on a CA-125 test with no other contributing factor • Women receiving additional fertility treatments • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months

Intervention	**Hormonal medical treatments** Contraceptives • Combined hormonal contraceptive (pill, patch, ring) • Progestogen only pill • Implant (Nexplanon / Implanon) • Injection (depot medroxyprogesterone acetate) • Levonorgestrel-releasing intrauterine system (LNG-IUS) Other hormonal treatments • Progestogens (high dose) • Danazol • Gonadotrophin-releasing hormone analogues (agonists and antagonists) • Combined treatment (GnRH agonist with "add back" HRT/Tibolone) • Aromatase inhibitors (anastrozole, lanastrozole, letrozole and exemestane) • Selective oestrogen receptor modulators (tamoxifen, raloxifene) • Selective progesterone receptor modulators (ulipristal, mifepristone) • Dienogest **Surgical interventions** • Ablation/sclerotherapy • Excision of endometriosis or excision of ovarian endometrioma • Total peritoneal excision • Stripping (only used in endometrioma) • Laparoscopy (robotic assisted) • Laparoscopy (normal) • Ovarian cystectomy • Drainage of endometrioma • Unilateral oophorectomy • Unilateral salpingectomy Specific techniques: • Laser (laser vaporisation, helium coagulation, plasmajet, argan, carbon dioxide, diathermy) • Bi-polar and mono polar (types of electrical energy) • Ultrasonic energy or a combination i.e., ultrasonic with bi-polar **Combinations of treatments** • Any hormonal medical treatment administered before, after or both before & after any surgical treatment **Non-pharmacological management** • Behavioural medicine (such as psychological and physiotherapy techniques): • Cognitive behavioural therapy • Mindfulness • Relaxation techniques • Expert patient programme • Exercise (for example yoga and pilates) • Hypnosis • Psychosexual therapy • Biofeedback Physical methods: • Acupuncture • Transcutaneous electrical nerve stimulation (TENS) • Manual and Physical therapy • Massage (e.g., shiatsu)

	• Osteopathy • Chiropractic treatment • Reflexology • Other: • Herbal medicine • Naturopathy • Homeopathic therapy • Nutrition (gluten free, dairy free, vegetarian, endo diet)
Comparison	**For hormonal medical treatments** • Hormonal medical treatment vs no treatment, usual care or placebo • Hormonal medical treatment A vs Hormonal medical treatment B • Hormonal medical treatment vs other medical treatment • Hormonal medical treatment vs. surgery • Hormonal medical treatment vs. combinations of hormonal medical and surgical treatment **For surgical interventions** • Surgery compared to diagnostic laparoscopy. • Different types of surgery compared to each other. **For combinations of treatments** • Hormonal medical treatment before surgery vs no treatment/placebo • Hormonal medical treatment after surgery vs no treatment/placebo • Hormonal medical treatment before vs after surgery • Hormonal medical treatment before and after surgery vs no treatment/usual care **For non-pharmacological management specific to pain** • Non-pharmacological management vs no treatment, usual care, or placebo • Non-pharmacological management A vs non-pharmacological management B • Non-pharmacological management vs pharmacological treatment (hormonal medical treatment, analgesics, and neuromodulators) • Non-pharmacological management vs surgical interventions
Outcome	**Critical** • Live birth • Clinical pregnancy (spontaneous) • Miscarriage • Ectopic pregnancy **Important** • Time from intervention to conception • Ovarian reserve as measured by antral follicle count (AFC) or ovarian volume • Anti-mullerian hormone (AMH)

CA-125 test: Cancer antigen 125, RCT: Randomised control trial, Gonadotrophin-releasing hormone analogues: GnRHa

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and below.

The quality of the evidence was assessed using GRADE methodology. Imprecision was assessed using default minimally important differences (MIDs) (0.8 and 1.25) for all dichotomous outcomes. The evidence was downgraded for imprecision by one level when

the confidence interval around the point estimate crossed one of the thresholds for minimally important difference [0.8 and 1.25 for dichotomous outcomes, for continuous outcomes either 0.5x the SD of the control group or 0.5x the mean of the SD of both groups (if there was no control group i.e., head-to-head comparison of interventions) was used] and downgraded by two levels when the confidence interval around the point estimate crossed both thresholds.

The approach of this review was to meta-analyse studies where possible and investigate heterogeneity where needed. If the I^2 value was greater than 80% this would be considered as very significant heterogeneity among studies and would be explored through sub-group analyses (where there were sufficient studies to conduct these analyses). If these analyses could not explain the heterogeneity, we would not pool the study estimates but instead keep them separate with the understanding the studies were too different to combine. However, there was insufficient evidence in this review to conduct any meta-analyses.

Minimally important differences (MID) were used to assess clinically important differences. Cut-offs of confidence intervals of 0.8 and 1.25 were used for dichotomous outcomes and for continuous outcomes either 0.5x the SD of the control group or 0.5x the mean of the SD of both groups (if there was no control group i.e., head-to-head comparison of interventions) was used. Outcomes were considered to have an important benefit or harm, no evidence of an important difference, or no important difference using the following approach:

- point estimate (PE) > +MID, 95% CI do not cross line of no effect = important benefit
- point estimate (PE) > +MID, 95% CI cross the line of no effect = no evidence of an important difference.
- point estimate (PE) between two MIDs = no important difference.
- point estimate (PE) < -MID, 95% CI cross the line of no effect = no evidence of an important. Difference
- point estimate (PE) < -MID, 95% CI do not cross line of no effect = important harm

This review is an update of the review conducted in guideline NG73. The evidence identified from this review update was not pooled with evidence from previous review versions. This is due to the following:

- the protocol for this update stratifies the population based on severity of endometriosis which differs from the previous protocol (no population strata)
- the subgroups identified for investigating heterogeneity differ
- it has not been possible to locate information on the included studies for the previously conducted pairwise review

The previous review included an NMA which was not updated in this review due to the scarcity of the new evidence identified (7 new studies with NMA outcomes of interest). It was agreed that pairwise comparisons would be sufficient for the committee to assess the impact of the new evidence on the existing recommendations.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Twelve randomised control trials were included in this review (Acien 2021, Bala 2022, Candiani 2018, Ghasemi-Tehrani 2022, Muraoka 2021, Muzii 2016, Rius 2020, Shaltout 2019, Sweed 2019, Xue 2018, Yang 2019, Zhao 2020).

The included studies were from China, Egypt Iran, Italy and Poland, Italy, Japan, Pakistan, and Spain.

The studies compared surgery to surgery plus hormonal medication (Acien 2021, Bala 2022, Xue 2018, Yang 2018), different surgical techniques to one another (Candiani 2018, Ghasemi-Tehrani 2022, Muzii 2016, Rius 2020, Shaltout 2019, Sweed 2019), surgery to surgery plus Chinese herbal medicine (Zhao 2020) and surgery plus hormonal medication A to surgery plus hormonal medication B (Muraoka 2021).

Data was not available for the outcome time from intervention to conception.

The evidence was stratified by stage and site of endometriosis.

The included studies are summarised in Table 2

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Acien 2021 RCT Spain	N= 31 Anastrozole + LNG-IUD + Surgery (Laparoscopy + cystectomy): N=8 Anastrozole + LNG-IUD + Drainage: N=7 LNG-IUD + Surgery (Laparoscopy + cystectomy): N=9 LNG-IUD + Drainage: N=7 Strata: Deep not involving other structures	Anastrozole + LNG-IUD + surgery (Laparoscopy + cystectomy) Anastrozole + LNG-IUD + Drainage LNG-IUD + surgery (Laparoscopy + cystectomy) LNG-IUD + Drainage	Interventions compared to each other	• Pregnancy	• Anastrozole 1 mg tablet/day for 6 months, from the start of menstruation • LNG-IUD (Mirena) for 6 months, inserted during the same menstruation as anastrozole administration started • Laparoscopy and cystectomy or drainage (TUGPA) performed at least 1 month after start of anastrozole administration
Bala 2022 RCT Pakistan	N= 360 GnRHa: n= 120	GnRHa group (3.75mg leuprorelin acetate subcutaneous monthly	Interventions compared to each other	• Pregnancy • Live birth • Ectopic pregnancy	

Study	Population	Intervention	Comparison	Outcomes	Comments
	Laparoscopic excision: n= 120 Laparoscopic excision + GnRHa: n= 120 Strata: Mixed	injection for 3 months) Laparoscopic excision Laparoscopic excision + GnRHa (as above for 3 months after laparoscopic excision)			
Candiani 2018 RCT Italy and Poland	N= 60 Laparoscopic cystectomy: n=30 Laparoscopic drainage + ablation (laser vaporisation): n=30 Strata: Ovarian 3 – 8cm	Laparoscopic cystectomy Laparoscopic drainage + ablation (laser vaporisation)	Interventions compared to each other	• Pregnancy rate • Anti-mullerian hormone • Antral follicle count	
Ghasemi-Tehrani 2022 RCT Iran	N= 70 Sclerotherapy: n=36 Laparoscopic cystectomy: n=37 Strata: Ovarian 4 – 10cm	Sclerotherapy Laparoscopic cystectomy	Interventions compared to each other	• Anti-mullerian hormone at 12 months	
Muraoka 2021 RCT Japan	N= 57 Laparoscopic cystectomy + GnRHa: n= 25 Laparoscopic cystectomy + Dienogest: n= 32 Strata: Ovarian > 4cm	Laparoscopic cystectomy + GnRHa (Buserelin acetate at 1.8 mg/month total 2 months before and after surgery) Laparoscopic cystectomy + Dienogest (Dienogest at 2 mg/day for 2 months before and after surgery)	Interventions compared to each other	• Pregnancy • Serum Anti-mullerian hormone 1 year post operatively	

Study	Population	Intervention	Comparison	Outcomes	Comments
Muzii 2016 RCT Italy	N= 102 ovaries Laparoscopic stripping n= 51 Laparoscopic excision and ablation n= 51 Strata: Ovarian > 3cm	Laparoscopic stripping Laparoscopic excision and ablation	Interventions compared to each other	• Antral follicle count at 6 months • Ovarian reserve at 6 months	
Rius 2020 RCT Spain	N= 32 ovaries Stripping: n= 16 Laparoscopic drainage and ablation (laser vaporisation): n= 16 Strata: Ovarian > 3cm	Stripping Laparoscopic drainage and ablation (laser vaporisation)	Interventions compared to each other	• Antral Follicle Count at 6 months • Ovarian volume at 6 months	
Shaltout 2019 RCT Egypt	N= 107 Laparoscopic drainage: n= 53 Laparoscopic cystectomy: n= 54 Strata: Ovarian > 5cm	Laparoscopic drainage Laparoscopic cystectomy	Interventions compared to each other	• Pregnancy rate • Post-treatment Anti-mullerian hormone percentage change • Post-treatment total Antral follicle count percentage change	
Sweed 2019 RCT Egypt	N = 122 Laparoscopic cystectomy: n= 61 Laparoscopic drainage: n= 61 Strata: Ovarian > 3cm	Laparoscopic cystectomy Laparoscopic drainage	Interventions compared to each other	• Postoperative Anti-mullerian hormone level • Postoperative Antral follicle count • Postoperative ovarian volume	
Xue 2018 RCT China	N = 150 Adhesion lysis + Triptorelin: n= 50	Adhesion lysis + Triptorelin (3.75 mg of Triptorelin acetate was injected monthly for	Interventions compared to each other	• Clinical pregnancy • Live birth • Ectopic pregnancy • Miscarriage	

Study	Population	Intervention	Comparison	Outcomes	Comments
	Adhesion lysis + Gestrinone: n= 50 Adhesion lysis + Mifepristone: n= 50 Strata: Mixed	three months post-surgery) Adhesion lysis + Gestrinone (2.5 mg of Gestrinone was taken orally twice a week for six months post-surgery) Adhesion lysis + Mifepristone (25 mg of Mifepristone was taken orally twice a day for three months post-surgery)			
Yang 2019 RCT China	N = 130 Laparoscopic surgery: n= 65 Laparoscopic surgery and GnRHa: n= 65 Strata: Ovarian 3 – 10cm	Laparoscopic surgery Laparoscopic surgery and GnRHa (six months of subcutaneous injections of 3.75 mg of gonadotropin-releasing hormone agonist (GnRHa) triptorelin acetate injection post surgery)	Interventions compared to each other	• Pregnancy rate	
Zhao 2020 RCT China	N= 204 Laparoscopy + Chinese medicine: n= 102 Laparoscopy + placebo: n= 102 Strata: Unclear	Laparoscopy + Chinese medicine (Chinese medicine given post surgery for 6 months)	Laparoscopy + placebo (Placebo granules given post surgery for 6 months)	• Clinical pregnancy • Live birth • Ectopic pregnancy • Miscarriage	Chinese medicine: treatment before ovulation with, Huoxue Xiaoyi Granule with Radix Bupleuri 10 g, Cyperus 10 g, Salvia Miltiorrhizae 20 g, Rhizoma Curcuma 10 g, and Radix Paeoniae rubra 10 g being the main medicines.

Study	Population	Intervention	Comparison	Outcomes	Comments
					After ovulation, they were treated with Bushen Zhuyun Granule, with Radix Bupleuri 10 g, Poria 15 g, Ligustrum lucidum 15 g, Eclipta 15 g, Rhizoma Atractylodes 15 g, and Radix dipsaci 30 g. being the main medicines. The chinese medicine was given at 1–5 days after surgery. The therapy lasted for 6 menstrual cycles

RCT: randomised control trial, LNG-IUD: Levonorgestrel-releasing intrauterine device, GnRHa: Gonadotrophin releasing hormone agonist.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see 'The committee's discussion and interpretation of the evidence' section.

The evidence was assessed as being very low to high quality. Downgrading the evidence was due to risk of bias arising from lack of information on randomisation methods, deviations from intended interventions, and missing outcome data, and imprecision (95% confidence intervals crossing decision making thresholds or low event rates). See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The evidence included in this report is from single studies, mainly showing no evidence of important difference. Limited evidence of important benefits was observed for some combined and single interventions. The outcome of time from intervention to conception included in the protocol was not reported by any studies.

Surgical interventions, Strata: site: ovarian, depth: unspecified

Low to moderate quality evidence from a single study showed an important benefit for the outcomes postoperative anti-mullerian hormone level (low quality), postoperative antral follicle count (moderate quality) and postoperative ovarian volume (moderate quality) from laparoscopic drainage when compared to laparoscopic cystectomy.

Low quality evidence from a single study showed no evidence of an important difference for pregnancy rate for laparoscopic cystectomy when compared to laparoscopic drainage. Median and range percentage changes were also reported for post treatment anti mullerian

hormone level and antral follicle count however statistical significance could not be determined as p values for the comparisons were not provided.

Low quality evidence from a single study showed no evidence of an important difference for anti-mullerian hormone level for sclerotherapy when compared to laparoscopic cystectomy.

Combination of interventions, Strata: site: ovarian, depth: unspecified

Low quality evidence from a single study a showed an important benefit for pregnancy rate from laparoscopic cystectomy and ablation plus GnRHa when compared to laparoscopic cystectomy and ablation alone.

Moderate quality evidence from a single study a showed an important benefit for ovarian volume and antral follicle count from laparoscopic drainage and ablation when compared to laparoscopic stripping.

Very low quality evidence from a single study showed no evidence of an important difference for pregnancy rate from laparoscopic cystectomy and GnRHa compared to laparoscopic cystectomy and dienogest. Median and interquartile range values were reported for anti-mullerian hormone level at one year which showed no statistical significance (p value = 0.1)).

Moderate quality evidence from a single study showed laparoscopic stripping to have a benefit on ovarian volume but no evidence of an important difference for antral follicle count when compared to laparoscopic excision plus ablation.

Very low quality evidence from a single study showed no evidence of an important difference between laparoscopic drainage plus ablation and laparoscopic cystectomy on pregnancy rate or anti-mullerian hormone levels but did show the combination of laparoscopic drainage and ablation to have a benefit on antral follicle count.

Combination interventions, Strata: site: ovarian, depth: deep not involving other structures

Very low quality evidence from a single 4-arm study reported number of pregnancies for the following interventions: 1) Anastrozole, LNG-IUD and Laparoscopy plus cystectomy, 2) Anastrozole, LNG-IUD and Drainage, 3) LNG-IUD and Laparoscopy plus cystectomy, 4) LNG-IUD and Drainage. No evidence of an important difference was found for any of the comparisons when assessing differences in number of pregnancies.

Combination interventions, Strata: site: mixed (ovarian/peritoneum), depth: deep involving other structures

Very low to low quality evidence from a single study showed an important benefit for clinical pregnancy (very low quality) and live birth (low quality) from adhesion lysis and triptorelin compared to adhesion lysis and gestrinone. This comparison demonstrated no evidence of an important difference for ectopic pregnancy (very low quality) and miscarriage (very low quality). The same study also showed an important benefit for clinical pregnancy (very low quality) and live birth (low quality) for adhesion lysis and triptorelin compared to adhesion lysis and mifepristone. This comparison demonstrated no evidence of an important difference for ectopic pregnancy (very low quality) and miscarriage (very low quality). The final comparison from this study adhesion lysis and gestrinone versus adhesion lysis and mifepristone demonstrated no evidence of an important difference for all reported outcomes: clinical pregnancy (very low quality), live birth (low quality), ectopic pregnancy (very low quality) and miscarriage (very low quality).

Very low quality evidence from a single 3-arm study comparing the following interventions: 1) GnRHa, 2) Laparoscopic excision, 3) Laparoscopic excision + GnRHa, found no evidence of an important difference when assessing number of pregnancies, live births or ectopic pregnancies.

Combination interventions, Strata: unspecified

Very low to low quality evidence from a single study showed an important benefit for clinical pregnancy (very low quality) and live birth (very low quality) from laparoscopy and Chinese medicine when compared to laparoscopy and placebo, however, no evidence of an important difference was seen for ectopic pregnancy (low quality) and miscarriage (low quality) outcomes.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because, after reviewing the evidence, the committee agreed that substantive changes to the existing recommendations would not be required.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The aim of this review was to determine the effectiveness of hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving fertility in endometriosis, including recurrent and asymptomatic endometriosis. The committee agreed that live birth and clinical pregnancy were critical outcomes for this review, as they would show the effectiveness of the interventions in improving fertility. The committee also prioritised miscarriage, and ectopic pregnancy as critical outcomes because they wanted to understand if any of the interventions led to a pregnancy which did not proceed to term as this may indicate the effectiveness and safety of interventions. The committee also chose the time from intervention to conception as an important outcome to help understand if some interventions were effective in a shorter time period than others. Finally, ovarian reserve measured using antral follicle count, ovarian volume and anti-mullerian hormone were important outcomes, as they provide an indication of ovarian function, which may be reduced by some surgical interventions and which can have an impact on future fertility.

The quality of the evidence

The quality of the evidence ranged from very low to moderate with the majority being very low quality. There were concerns over risk of bias due to included studies not reporting enough information on randomisation methods, deviations from intended interventions, and missing outcome data. There were also concerns over imprecision for some of the evidence. The committee took into account the quality of the evidence in their interpretation of the evidence.

Benefits and harms

The committee's discussion initially focused on the predominance of head-to-head comparisons or combination comparisons in the evidence and therefore the lack of comparisons where there was an intervention compared to no intervention or placebo. They

specifically noted that most of the available evidence focussed on the comparison between different types of surgical interventions.

The committee then discussed that the evidence around the different surgical methods for the treatment of endometriosis compared to each other, and in particular the evidence for the treatment of ovarian endometriosis and endometriomas. For the comparison of cystectomy compared to laparoscopic drainage with/without ablation, 2 studies showed no evidence of an important difference in pregnancy rates and 3 studies showed an increase in anti-mullerian hormone, ovarian volume and/or antral follicle count with laparoscopic drainage with/without ablation compared to laparoscopic cystectomy or stripping (which equates to cystectomy). This indicated that drainage with/without ablation may preserve ovarian reserve better than cystectomy. The committee were aware however, based on their knowledge and experience, that using ablation with laparoscopic drainage may reduce the risk of recurrence and that ablation would be needed to control bleeding, thus they agreed laparoscopic drainage and ablation was preferable over laparoscopic drainage alone. They discussed the evidence from a single study of low quality that showed no difference in pregnancy rates between cystectomy and drainage, and that drainage led to a smaller percentage reduction in anti-mullerian hormone level when compared to cystectomy, again suggesting that drainage may be as effective as cystectomy in terms of pregnancy rate but may have less of an impact on ovarian reserve. However, the same study also showed that drainage led to a greater percentage reduction in antral follicle count when compared to cystectomy. Unfortunately, because anti-mullerian hormone and antral follicle count in this study were reported using median and range percentage change values with no reported p values, the committee were unable to assess the significance of these changes. The committee discussed that the evidence suggested that techniques such as drainage and ablation of endometriomas may be less harmful to ovarian reserve than cystectomy and therefore may be a more appropriate choice for a person whose priority is to preserve their future fertility, and so included this in the recommendations. They noted that recommending laparoscopic draining and ablation as well as laparoscopic cystectomy provided more intraoperative options. They also emphasised that the choice of treatment would depend on the priorities of the person with endometriosis and therefore the choice of techniques would need to be discussed with them.

The committee discussed the complexities of how the type and stage of the person's endometriosis influences the most appropriate choice of surgery for fertility preservation. They discussed that, in their experience, surgical treatment is likely to be beneficial for fertility outcomes in a person with American Society of Reproductive Medicine (ASRM) stage 1 or 2 endometriosis, and that people with ASRM stage 3 or 4 would usually be referred for fertility treatment as surgery alone would be unlikely to improve their fertility. The committee noted that the evidence included in the review comparing different surgical techniques with each other had been for ovarian disease and therefore they did not amend the existing recommendations on the surgical management of deep endometriosis, although they clarified that the recommendations applied to deep endometriosis at all sites, and not just involving bowel, bladder or ureter. They also added that the possible impact of deep endometriosis on pregnancy outcomes should be discussed to enable a broader consideration of the benefits and risks of surgery.

The committee discussed the evidence for the use of hormonal treatments in combination with laparoscopic surgery compared to laparoscopic surgery alone in ovarian disease. Evidence from a single study suggested an increased pregnancy rate favouring laparoscopic surgery plus GnRHa when compared to laparoscopic surgery alone, however this was in a small population and of low quality. There was very low quality evidence for laparoscopic cystectomy plus GnRHa compared to laparoscopic cystectomy plus dienogest in ovarian disease. This showed no difference in the pregnancy rate and the difference between the two groups in anti-mullerian hormone at one year was a not significant as the reported p value was 0.1. There was some evidence for anastrazole and LNG-IUD in combination with different surgical techniques compared to surgery alone in deep ovarian endometriosis, but

there was no difference in pregnancy rates for any of the comparisons. However, evidence for mixed ovarian and peritoneal disease comparing triptorelin and gestrinone (both in combination with surgery) found an increase in pregnancy rates and live birth with triptorelin. There was also evidence for the same mixed strata (ovarian and peritoneal disease) that showed no difference in pregnancy rate or live birth for GnRHA compared to laparoscopic excision, GnRHa compared to laparoscopic excision plus GnRHa and laparoscopic excision compared to laparoscopic excision plus GnRHa. As the evidence was limited and contradictory the committee agreed not to make a recommendation for hormonal treatment to be used in combination surgery, as the benefit of hormonal treatment with surgery was inconclusive. The committee also noted that recommending hormonal treatment in this context would be a large change in practice to make based on such inconclusive evidence and would also have resource implications due to the cost of gonadotrophins.

The committee also noted that the previous recommendation stating not to use hormonal treatment was made within the section on surgery. The committee therefore clarified that this recommendation applied to hormonal treatment alone or in combination with surgery.

The committee noted that most of the evidence that compared surgery to a hormonal treatment involved administering the hormone after surgery. The committee discussed that there may, theoretically, be benefits to administering hormonal treatment before surgery as this would then not impair ovarian function after surgery and may increase the chances of pregnancy. However, the committee agreed that the lack of evidence on pre-surgery use did not allow them to recommend this. The committee also noted the variation in the duration of hormonal treatments in the evidence, which varied from 2 to 6 months. Considering all these uncertainties, and the limited evidence available for the different hormonal treatments given in combination with surgery, the committee agreed a research recommendation was needed in this area. They proposed the need to investigate the effect of different doses and durations of hormones (for example GnRHa) given either before, after, or both before and after surgery on fertility outcomes in people with endometriosis where fertility is a priority. The full research recommendation is in appendix K.

The committee discussed the evidence for the use of Chinese medicine in combination with laparoscopy. Although the evidence showed a benefit for the use of Chinese medicine for the only reported outcome of pregnancy, the committee were concerned about the very low quality of the evidence which was a result of selective reporting and lack of clarity on method of randomisation. The committee noted that a network meta-analysis undertaken for the previous guideline had not shown any benefit for Chinese medicine over placebo. They also discussed the unavailability of the Chinese medicines on the NHS, thus chose not to make a recommendation for its use as a treatment for improving fertility outcomes in this population.

Cost effectiveness and resource use

Only minor changes were made to the existing recommendations, and these are not expected to have a significant resource impact to the NHS. An addition to the recommendations related to laparoscopic surgery for women or people who have endometriomas. This now noted that ablation and drainage may preserve ovarian reserve more than cystectomy. Whilst this may have some impact on the type of procedures undertaken, the committee believed the two procedures required the same type of equipment and therefore there would be no cost impact from offering ablation/drainage as an additional option.

Other factors the committee took into account

The committee noted that their recommendations were in-line with the recent European Society of Human Reproduction and Embryology (ESHRE) guidelines on endometriosis which recommends laparoscopic surgery without additional hormonal treatment.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.2 to 1.11.4 and a research recommendation on combination therapy with surgery and hormonal treatment.

References – included studies

Effectiveness

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Other

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42023433813
Review title	Hormonal medical treatments, surgery, combination treatments (hormonal treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis.
Review question	What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis: • Hormonal medical treatments • Surgery • Non-pharmacological therapies • Combination treatment (hormonal treatment and surgery)
Objective	The aim of is to determine the clinical efficacy of hormonal medical treatment, surgery and non-pharmacological therapies to improve fertility in women with endometriosis. This evidence review will allow the committee to consider the evidence to update recs in Section 1.11 (Surgical management when fertility is a priority) in Endometriosis: diagnosis and management (NICE Guideline NG73).

Searches	The following databases will be searched: Clinical Searches: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE All Epistemonikos Searches will be restricted by: English language Human studies Date limit: 29/11/2016 (last date searched) The full search strategies will be published in the final review.
Condition or domain being studied	Endometriosis
Population	Inclusions: • Sub fertile women desiring pregnancy, between menarche and menopause with endometriosis of any stage or severity. (Subfertility definition: failure to conceive after ≥ 2 months of unprotected intercourse) - • Women with a suspected diagnosis of endometriosis desiring pregnancy (definition: suspected diagnosis based on the history of the patient, pelvic examination and other tests such as ultrasound, MRI and the CA-125 blood test) Include women with • Recurrent and asymptomatic endometriosis. • Both primary and secondary infertility. Studies with indirect populations (such as women with dysmenorrhea, women with non-confirmed pelvic pain, or post-menopausal women) will not be considered.

	Exclusions: • Women with chronic pelvic pain which was known to be due to causes other than endometriosis • Those suspected based solely on a CA-125 test with no other contributing factor (CA-125 should be used in combination with other evaluative measures) • Women receiving additional fertility treatments (e.g. IVF, clomiphene citrate) • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months Setting: No particular setting specified
Intervention	**Hormonal medical treatments** Hormonal medical treatments of any type and administered at any dose, frequency, treatment duration recommended in the BNF, or by any route of administration: <u>Contraceptives:</u> • Combined hormonal contraceptive (pill, patch, ring) • Progestogen only pill • Implant (Nexplanon / Implanon) • Injection (depot medroxyprogesterone acetate) • Levonorgestrel-releasing intrauterine system (LNG-IUS) <u>Other hormonal treatments:</u> • Progestogens (high dose) • Danazol • Gonadotrophin-releasing hormone analogues (GnRHa) [sub-categories: agonists and antagonists] • Combined treatment (GnRH agonist with "add back" HRT/Tibolone) • Aromatase inhibitors (for example anastrazole, lanastrozole, letrazole and exemestane) • Selective oestrogen receptor modulators (SERMs) (tamoxifen, raloxifene) • Selective progesterone receptor modulators (SPRMs) (ulipristal, mifepristone) • Dienogest

	Surgical interventions • Ablation/sclerotherapy • Excision of endometriosis or excision of ovarian endometrioma • Total peritoneal excision • Stripping (only used in endometrioma) • Laparoscopy (robotic assisted) • Laparoscopy (normal) Specific techniques: • Laser (includes laser vaporisation, helium coagulation, plasmajet, argan, carbon dioxide, diathermy) • Bi-polar and mono polar (types of electrical energy) • Ultrasonic energy or a combination i.e., ultrasonic with bi-polar Surgery also includes: • Ovarian cystectomy • Drainage of endometrioma • Unilateral oophorectomy - • Unilateral salpingectomy Keep robotic and normal laparoscopy separate. **Combinations of treatments** (hormonal treatment and surgery) • Any hormonal medical treatment administered before, after or both before & after any surgical treatment **Non-pharmacological management** • Behavioural medicine (such as psychological and physiotherapy techniques): • Cognitive behavioural therapy • Mindfulness • Relaxation techniques

	• Expert patient programme • Exercise (for example yoga and pilates) • Hypnosis • Psychosexual therapy • Biofeedback Physical methods: • Acupuncture • (TENS) • Manual and Physical therapy • Massage (e.g., shiatsu) • Osteopathy • Chiropractic treatment • Reflexology • Other: • Herbal medicine • Naturopathy • Homeopathic therapy • Nutrition (gluten free, dairy free, vegetarian, endo diet)
Comparator/Reference standard/Confounding factors	**For hormonal medical treatments:** • Hormonal medical treatment vs no treatment, usual care or placebo • Hormonal medical treatment A vs Hormonal medical treatment B • Hormonal medical treatment vs other medical treatment • Hormonal medical treatment vs. surgery • Hormonal medical treatment vs. combinations of hormonal medical and surgical treatment **For surgical interventions:** • Surgery compared to diagnostic laparoscopy. • Different types of surgery compared to each other. **For combinations of treatments:** • Hormonal medical treatment before surgery vs no treatment/placebo

	• Hormonal medical treatment after surgery vs no treatment/placebo • Hormonal medical treatment before vs after surgery • Hormonal medical treatment before and after surgery vs no treatment/usual care **For non-pharmacological management specific to pain:** • Non-pharmacological management vs no treatment, usual care, or placebo • Non-pharmacological management A vs non-pharmacological management B • Non-pharmacological management vs pharmacological treatment (hormonal medical treatment, analgesics, and neuromodulators) • Non-pharmacological management vs surgical interventions
Types of study to be included	For intervention reviews: Include published full-text papers: • Systematic reviews of RCTs • RCTs Only RCTS will be considered for inclusion. For crossover trials, only data from the first period of the study will be included. Note: Do not exclude any studies based on duration of treatment.
Other exclusion criteria	Conference abstracts will not be included. Non-English language studies. Quasi-randomised trials will be excluded. For NMA: Active interventions that are not part of the decision problem will not be considered in the analysis unless they act as the sole connectors of the interventions of interest in the network.
Context	The population of this guideline may overlap with the population of women included in NICE guideline on Fertility problems: assessment and treatment (CG 156).
Primary outcomes (critical outcomes)	Pair-wise outcomes: • Live birth • Clinical pregnancy (spontaneous) • Miscarriage • Ectopic pregnancy

	NMA outcomes: • Live birth • Clinical pregnancy Follow-up times: Where multiple time-points are reported, data for baseline measures (where provided) and last follow-up will be extracted
Secondary outcomes (important outcomes)	• Time from intervention to conception • Ovarian reserve as measured by antral follicle count/ovarian volumes [this only relevant for ovarian endometriosis] • Anti-Mullerian Hormone (AMH) test– [this is another way of measuring ovarian reserve. This is used in all women with endometriosis]. Where multiple time-points are reported, data for baseline measures and last follow-up will be extracted
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.

Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	**Method of analysis** Network meta-analysis (NMA) Network meta-analysis will be conducted within a Bayesian framework using WinBUGS. The exact model structure will be agreed with the NICE Technical Support Unit (TSU) following the review of available clinical evidence. Fixed and random effects NMA models will be fitted to the data and compared based on the posterior mean residual deviance and DIC. The model with the best fit and meaningfully lower DIC will be selected. Differences of at least 3 will be considered meaningful. For dichotomous outcomes, posterior median ORs and 95% credible intervals (CrIs) will be used to report the results. For continuous outcomes, mean differences will be used to report the results. Ranking of treatments will be provided (i.e. posterior median ranks and 95% CrIs, rankograms, probability being best). Inconsistency checks will be conducted by comparing the posterior mean residual deviance, DIC, and where appropriate (i.e., random effects models), posterior median between study standard deviation, of the base case NMA model and unrelated mean effects (UME) model. Plots of contributions to the residual deviance for the UME vs the NMA model will be inspected to identify lack of consistency for particular studies/comparisons. If these checks indicate potential inconsistency, further checks will be conducted using node splitting analysis. Pairwise estimates will be obtained from the UME model to aid comparison of the direct estimates with the NMA estimates. Threshold analysis will also be conducted if a clear decision rule between linking the recommendations to the NMA estimates can be identified. Pairwise meta-analysis Standard pair-wise meta-analysis will be conducted using Cochrane Review Manager. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and

	confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. Please note, this is an update of NG73. The novel evidence identified from this review update will not be pooled with evidence from previous review versions. This is due to the following: • The protocol for this update stratifies the population based on severity of endometriosis which differs from the previous protocol (no population strata) • The subgroups for investigating heterogeneity differ
Analysis of sub-groups	Evidence will be stratified by: Population strata: Strata (surgery treatment/hormonal treatments): • Superficial endometriosis (stage 1 or stage 2) • Ovarian (stage 2, 3 or 4) – depending on the size of the cyst – endometrioma • Deep not involving other structures (stage 2, 3 or 4) • Deep involving other structures- bladder, recto vaginal, bowel involvement, ureter (Stage 3 or 4) Note: Treatment could be different for different stages of endometriosis. Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes. Age • adolescents (24 years and under) • adults (25-34 years) • adults (35-51years) Ethnicity • White • Asian/Asian British • Black/African/Caribbean/Black British

	• Mixed/Multiple ethnic groups • Other ethnic group Where evidence is stratified or sub-grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others. Sub-group analyses NMA: Networks will be examined separately if study populations for separate groups of treatments are substantially different: • Hormonal treatments • Surgical treatments • Non-pharmacological treatments Covariates (NMA): Covariates can sometimes be included to reduce heterogeneity instead of running subgroup analyses, where data is available. In order of importance: • Stage of endometriosis • Prior surgery within the last 6 months: • Not including diagnostic surgery if separately defined by study Not including surgery immediately (within 4 weeks) prior (combined surgery + hormonal therapy)	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic

	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	June 2023		
Anticipated completion date	To add		
Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
	Preliminary searches	☒	☒
	Piloting of the study selection process	☒	☒
	Formal screening of search results against eligibility criteria	☒	☒
	Data extraction	☒	☒
	Risk of bias (quality) assessment	☒	☒
	Data analysis	☒	☒
Named contact	5a. **Named contact** National Guideline Alliance development team at NICE 5b **Named contact e-mail** Endosurgmgmt@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance development team at NICE		
Funding sources/sponsor	This systematic review is being completed by NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the		

	start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10392/documents	
Other registration details		
Reference/URL for published protocol	Prospero registration number: CRD42023433813	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	[Give words or phrases that best describe the review.]	
Details of existing review of same topic by same authors	Update of review from NICE guidance NG73	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CA-125: cancer antigen-125; MRI: magnetic resonance imaging; IVF: In vitro fertilisation; BNF: British National Formulary; LNG-IUS: Levonorgestrel Intrauterine System; GnRHa: Gonadotropin-releasing hormone analogues; SERMs: Selective oestrogen receptor modulators; SPRMs: Selective progesterone receptor modulators; TENS: transcutaneous electrical nerve stimulation; RCT: randomised control trial; NMA: Network meta-analysis; AMH: Anti-mullerian hormone; ROBIS: Risk of Bias in Systematic Reviews; RoB: Risk of Bias; TSU: Technical Support unit; OR: Odds ratio; CrIs: credible intervals; UME: unrelated mean effects; PROSPERO: The International Prospective Register of Systematic Reviews.

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Database: Ovid MEDLINE

Date of last search: 27/06/2023

#	Searches
1	Endometriosis/
2	(endometrios* or endometrioma*).ti,ab,kf.
3	1 or 2
4	Contraception/ or Hormonal Contraception/ or Long-Acting Reversible Contraception/ or Ovulation Inhibition/
5	exp Contraceptive Agents, Female/
6	Contraceptive Devices, Female/ or Intrauterine Devices, Medicated/
7	exp Estradiol Congeners/
8	exp Norpregnanes/
9	exp Pregnanes/
10	exp Progesterone Congeners/
11	contracept*.ti,ab,kf.
12	(intrauter* adj3 (homon* or medicat*) adj3 (device* or iud?)).ti,ab,kf.
13	(cyproterone acetate or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen? or estrone or ethinyl?estradiol or ethyl?estrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or nomegestrol acetate or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen? or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone).ti,ab,kf.
14	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press).ti,ab,kf.
15	Chorionic Gonadotropin/tu
16	exp Estrogen Antagonists/
17	exp Estrogen Receptor Modulators/
18	exp Gonadotropin-Releasing Hormone/
19	Hormone Antagonists/
20	(gonadotrop?in* or GnRH or GnRHa or Gn RH or Gn RHa).ti,ab,kf.
21	(buserelin or goserelin or leuporelin or triptorelin).ti,ab,kf.
22	exp Aromatase Inhibitors/
23	(aromatase inhibit* or aminoglutethimide or anastr?zole or exemestane or lanastr?zole or letr?zole).ti,ab,kf.
24	Luteolytic Agents/
25	Selective Estrogen Receptor Modulators/
26	Mifepristone/ or Raloxifene Hydrochloride/ or Tamoxifen/
27	(antiestrogen? or antioestrogen? or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or RU 486 or SERM? or SPRM?).ti,ab,kf.
28	Gynecologic Surgical Procedures/ or Surgical Procedures, Operative/
29	exp Ablation Techniques/
30	Argon/
31	Carbon Dioxide/
32	Cystectomy/
33	Cysts/su
34	Cytoreduction Surgical Procedures/
35	exp Diathermy/
36	exp Drainage/
37	exp Electrocoagulation/
38	Electrosurgery/
39	Fallopian Tubes/su
40	exp Laparoscopy/
41	Laparotomy/
42	Laser Coagulation/
43	Laser Therapy/
44	Lasers, Gas/
45	Microsurgery/

#	Searches
46	exp Minimally Invasive Surgical Procedures/
47	Ovarian Cysts/su
48	exp Ovariectomy/
49	exp Ovary/su
50	Robotic Surgical Procedures/
51	exp Salpingectomy/
52	Sclerotherapy/
53	Surgery, Computer-Assisted/
54	Ultrasonic Surgical Procedures/
55	exp Uterus/su
56	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapo?r* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapo?r* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* adj (energy or therap* or treat*)) or vapoenucleat* or vapo?ri* or videolaparoscop* or videolaparotom*).ti,ab,kf.
57	(((laser* or argon or bipolar or bi polar or carbon dioxide or helium or monopolar or mono polar or plasma*) adj3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*).ti,ab,kf.
58	(minimal* adj3 (access* or invasive or surg*)).ti,ab,kf.
59	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) adj5 remov*)).ti,ab,kf.
60	(salpingectom* or tubectom* or (fallopian adj3 remov*)).ti,ab,kf.
61	Behavioral Medicine/
62	exp Cognitive Behavioral Therapy/
63	exp Complementary Therapies/
64	exp Diet/ or exp Diet Therapy/ or Nutrition Therapy/
65	Herbal Medicine/ or exp Plant Extracts/ or Plants, Medicinal/
66	exp Exercise/
67	Patient Participation/ or Peer Group/ or Self Care/ or Social Support/
68	Physical Fitness/
69	exp Physical Therapy Modalities/
70	exp Postural Balance/
71	exp Psychotherapy/
72	exp Counseling/
73	Transcutaneous Electric Nerve Stimulation/
74	((non med* or nonmed* or non pharm* or nonpharm*) adj3 (intervention* or manag* or therap* or treat*)).ti,ab,kf.
75	(((behavi* or cognit*) adj3 (intervention* or technique? or therap* or treatment*)) or CBT).ti,ab,kf.
76	(psychotherap* or psycho therap* or logotherap* or logo therap*).ti,ab,kf.
77	(cope? or coping or meditat* or mind body or mindfulness or relax*).ti,ab,kf.
78	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) adj1 (intervention* or program* or therap* or treatment*))).ti,ab,kf.
79	((balance* or balancing* or breathing* or movement* or posture* or postural*) adj3 (exercise* or intervention* or program* or therap* or training*)).ti,ab,kf.
80	(((alternative or compl?ment* or folk or herb* or holistic or plant* or traditional* or non Western or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) adj (extract? or medicine? or therap* or remed*)) or Ayurveda or Shaman*).ti,ab,kf.
81	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) adj (therap* or treatment*))).ti,ab,kf.
82	((diet* adj2 (endo* or keto* or low carb* or low fat or gluten free or paleo* or protein or raw food or restrict* or vegetarian or vegan)) or endodiet* or nutrition*).ti,ab,kf.
83	(exercis* or pilates or tai chi or tai ji or yoga).ti,ab,kf.
84	(manipulat* adj1 (medicine or therap* or treatment?)).ti,ab,kf.
85	(chiropra* or osteopath* or (musculoskelet* adj (manipulat* or therap*))).ti,ab,kf.
86	(acupressure or massag* or reflexolog* or shiatsu or tui na).ti,ab,kf.
87	(acupoint? or acupuncture or electroacupuncture or meridian? or mox?bust* or acu* point? or needling or shu).ti,ab,kf.
88	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) adj2 (electrostimulat* or electro stimulat* or nerve stimulat*)) or electroanalges* or electro analges* or TENS).ti,ab,kf.
89	(expert* adj3 patient*).ti,ab,kf.
90	(peer* adj3 counsel*).ti,ab,kf.
91	(((peer or social) adj3 support*) or support group?).ti,ab,kf.
92	(biofeedback or bio feedback or bio feed back or psychophysiolog* or psycho physiolog*).ti,ab,kf.
93	(autogenic* or hypno* or mesmeris*).ti,ab,kf.
94	((psychosex* or sex*) adj3 (counsel* or intervention* or therap* or treatment*)).ti,ab,kf.
95	or/4-94
96	3 and 95
97	letter/
98	editorial/
99	news/
100	exp historical article/
101	Anecdotes as topic/

#	Searches
102	comment/
103	case reports/
104	(letter or comment*).ti.
105	or/97-104
106	randomized controlled trial/ or random*.ti,ab.
107	105 not 106
108	animals/ not humans/
109	exp Animals, Laboratory/
110	exp Animal Experimentation/
111	exp Models, Animal/
112	exp Rodentia/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/107-113
115	96 not 114
116	limit 115 to english language
117	meta-analysis/
118	meta-analysis as topic/
119	(meta analy* or metanaly* or metaanaly*).ti,ab.
120	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
121	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
122	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
123	(search* adj4 literature).ab.
124	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
125	cochrane.jw.
126	or/117-125
127	randomized controlled trial.pt.
128	controlled clinical trial.pt.
129	pragmatic clinical trial.pt.
130	randomi#ed.ab.
131	placebo.ab.
132	drug therapy.fs.
133	randomly.ab.
134	trial.ab.
135	groups.ab.
136	or/127-135
137	116 and 126
138	116 and 136
139	137 or 138
140	limit 139 to dt=20160101-20230627
141	limit 139 to ed=20160101-20230627
142	140 or 141

Database: Ovid Embase

Date of last search: 27/06/2023

#	Searches
1	exp endometriosis/
2	(endometrios* or endometrioma*).ti,ab,kf.
3	1 or 2
4	contraception/ or hormonal contraception/ or long-acting reversible contraception/ or oral contraception/ or ovulation inhibition/
5	exp hormonal contraceptive agent/
6	exp female contraceptive device/
7	exp estradiol derivative/
8	exp pregnane derivative/
9	exp progesterone derivative/
10	contracept*.ti,ab,kf.
11	(intrauter* adj3 (homon* or medicat*) adj3 (device* or iud?)).ti,ab,kf.
12	(cyproterone acetate or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen? or estrone or ethinyl?estradiol or ethyl?estrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or nomegestrol acetate or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen? or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone).ti,ab,kf.
13	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press).ti,ab,kf.

#	Searches
14	chorionic gonadotropin/dt
15	exp antiestrogen/
16	exp gonadotropin derivative/ or exp gonadorelin agonist/ or gonadorelin derivative/
17	hormone antagonist/
18	(gonadotrop?in* or GnRH or GnRHa or Gn RH or Gn RHa).ti,ab,kf.
19	(buserelin or goserelin or leuporelin or triptorelin).ti,ab,kf.
20	exp aromatase inhibitor/
21	(aromatase inhibit* or aminoglutethimide or anastr?zole or exemestane or lanastr?zole or letr?zole).ti,ab,kf.
22	luteolytic agent/
23	selective estrogen receptor modulator/
24	exp progesterone receptor modulator/
25	mifepristone/ or tibolone/ or ulipristal/
26	(antiestrogen? or antioestrogen? or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or RU 486 or SERM? or SPRM?).ti,ab,kf.
27	gynecologic surgery/ or surgery/
28	exp ablation therapy/
29	exp argon laser/
30	exp carbon dioxide laser/
31	computer assisted surgery/
32	exp coagulation surgery/
33	cystectomy/
34	cyst/su
35	cytoreductive surgery/
36	exp diathermy/
37	surgical drainage/
38	electrosurgery/
39	endometrial disease/dt, su, th
40	exp endometrium/su
41	exp fallopian tube/ and su.fs.
42	gas laser/
43	helium laser/
44	exp laparoscopy/
45	laparotomy/
46	laser therapy/
47	microsurgery/
48	minimally invasive surgery/
49	exp ovary cyst/su
50	exp ovariectomy/
51	exp ovary/su
52	robot assisted surgery/
53	salpingectomy/
54	exp sclerotherapy/
55	ultrasound surgery/
56	exp uterus/su
57	vaginal cyst/su
58	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapo?r* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapo?r* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* adj (energy or therap* or treat*)) or vapoenucleat* or vapo?ri* or videolaparoscop* or videolaparotom*).ti,ab,kf.
59	(((laser* or argon or bipolar or bi polar or carbon dioxide or helium or monopolar or mono polar or plasma*) adj3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*).ti,ab,kf.
60	(minimal* adj3 (access* or invasive or surg*)).ti,ab,kf.
61	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) adj5 remov*)).ti,ab,kf.
62	(salpingectom* or tubectom* or (fallopian adj3 remov*)).ti,ab,kf.
63	behavioral medicine/
64	exp cognitive behavioral therapy/
65	exp alternative medicine/
66	exp diet/ or exp diet therapy/
67	herbaceous agent/ or exp medicinal plant/ or exp plant extract/ or exp traditional medicine/
68	exp exercise/ or exp kinesiotherapy/
69	patient participation/ or exp peer group/ or exp self care/ or exp social support/
70	fitness/
71	exp physiotherapy/
72	exp body equilibrium/
73	exp psychotherapy/
74	exp counseling/
75	transcutaneous electrical nerve stimulation/
76	((non med* or nonmed* or non pharm* or nonpharm*) adj3 (intervention* or manag* or therap* or treat*)).ti,ab,kf.

#	Searches
77	(((behavi* or cognit*) adj3 (intervention* or technique? or therap* or treatment*)) or CBT).ti,ab,kf.
78	(psychotherap* or psycho therap* or logotherap* or logo therap*).ti,ab,kf.
79	(cope? or coping or meditat* or mind body or mindfulness or relax*).ti,ab,kf.
80	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) adj1 (intervention* or program* or therap* or treatment*))).ti,ab,kf.
81	((balance* or balancing* or breathing* or movement* or posture* or postural*) adj3 (exercise* or intervention* or program* or therap* or training*)).ti,ab,kf.
82	(((alternative or compl?ment* or folk or herb* or holistic or plant* or traditional* or non Western or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) adj (extract? or medicine? or therap* or remed*)) or Ayurveda or Shaman*).ti,ab,kf.
83	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) adj (therap* or treatment*))).ti,ab,kf.
84	((diet* adj2 (endo* or keto* or low carb* or low fat or gluten free or paleo* or protein or raw food or restrict* or vegetarian or vegan)) or endodiet* or nutrition*).ti,ab,kf.
85	(exercis* or pilates or tai chi or tai ji or yoga).ti,ab,kf.
86	(manipulat* adj1 (medicine or therap* or treatment?)).ti,ab,kf.
87	(chiropra* or osteopath* or (musculoskelet* adj (manipulat* or therap*))).ti,ab,kf.
88	(acupressure or massag* or reflexolog* or shiatsu or tui na).ti,ab,kf.
89	(acupoint? or acupuncture or electroacupuncture or meridian? or mox?bust* or acu* point? or needling or shu).ti,ab,kf.
90	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) adj2 (electrostimulat* or electro stimulat* or nerve stimulat*)) or electroanalges* or electro analges* or TENS).ti,ab,kf.
91	(expert* adj3 patient*).ti,ab,kf.
92	(peer* adj3 counsel*).ti,ab,kf.
93	(((peer or social) adj3 support*) or support group?).ti,ab,kf.
94	(biofeedback or bio feedback or bio feed back or psychophysiolog* or psycho physiolog*).ti,ab,kf.
95	(autogenic* or hypno* or mesmeris*).ti,ab,kf.
96	((psychosex* or sex*) adj3 (counsel* or intervention* or therap* or treatment*)).ti,ab,kf.
97	or/4-96
98	3 and 97
99	letter.pt. or letter/
100	note.pt.
101	editorial.pt.
102	case report/ or case study/
103	(letter or comment*).ti.
104	or/99-103
105	randomized controlled trial/ or random*.ti,ab.
106	104 not 105
107	animal/ not human/
108	nonhuman/
109	exp Animal Experiment/
110	exp Experimental Animal/
111	animal model/
112	exp Rodent/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/106-113
115	98 not 114
116	limit 115 to english language
117	systematic review/
118	meta-analysis/
119	(meta analy* or metanaly* or metaanaly*).ti,ab.
120	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
121	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
122	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
123	(search* adj4 literature).ab.
124	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
125	((pool* or combined) adj2 (data or trials or studies or results)).ab.
126	cochrane.jw.
127	or/117-126
128	random*.ti,ab.
129	factorial*.ti,ab.
130	(crossover* or cross over*).ti,ab.
131	((doubl* or singl*) adj blind*).ti,ab.
132	(assign* or allocat* or volunteer* or placebo*).ti,ab.
133	crossover procedure/
134	single blind procedure/
135	randomized controlled trial/
136	double blind procedure/
137	or/128-136

#	Searches
138	116 and 127
139	116 and 137
140	138 or 139
141	limit 140 to dc=20160101-20230627
142	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
143	141 not 142

Database: Cochrane Database of Systematic Reviews (CDSR) - Wiley

Date of last search: 27/06/2023

ID	Search
#1	MeSH descriptor: [Endometriosis] this term only
#2	(endometrios* or endometrioma*):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Contraception] this term only
#5	MeSH descriptor: [Hormonal Contraception] this term only
#6	MeSH descriptor: [Long-Acting Reversible Contraception] this term only
#7	MeSH descriptor: [Ovulation Inhibition] this term only
#8	MeSH descriptor: [Contraceptive Agents, Female] explode all trees
#9	MeSH descriptor: [Contraceptive Devices, Female] this term only
#10	MeSH descriptor: [Intrauterine Devices, Medicated] this term only
#11	MeSH descriptor: [Estradiol Congeners] explode all trees
#12	MeSH descriptor: [Norpregnanes] explode all trees
#13	MeSH descriptor: [Pregnanes] explode all trees
#14	MeSH descriptor: [Progesterone Congeners] explode all trees
#15	contracept*:ti,ab,kw
#16	(intrauter* near/3 (homon* or medicat*) near/3 (device* or iud*)):ti,ab,kw
#17	("cyproterone acetate" or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen* or estrone or ethinylestradiol or ethylestrenol or ethinyloestradiol or ethyloestrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or "nomegestrol acetate" or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen* or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone):ti,ab,kw
#18	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press):ti,ab,kw
#19	MeSH descriptor: [Chorionic Gonadotropin] this term only and with qualifier(s): [therapeutic use - TU]
#20	MeSH descriptor: [Estrogen Antagonists] explode all trees
#21	MeSH descriptor: [Estrogen Receptor Modulators] explode all trees
#22	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#23	MeSH descriptor: [Hormone Antagonists] this term only
#24	(gonadotrophin* or gonadotropin* GnRH or GnRHa or "Gn RH" or "Gn RHa"):ti,ab,kw
#25	(buserelin or goserelin or leuporelin or triptorelin):ti,ab,kw
#26	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#27	("aromatase inhibiter" or "aromatase inhibiters" or aminoglutethimide or anastrazole or anastrozole or exemestane or lanastrazole or lanastrozole or letrazole or letrozole):ti,ab,kw
#28	MeSH descriptor: [Luteolytic Agents] this term only
#29	MeSH descriptor: [Selective Estrogen Receptor Modulators] this term only
#30	MeSH descriptor: [Mifepristone] this term only
#31	MeSH descriptor: [Raloxifene Hydrochloride] this term only
#32	MeSH descriptor: [Tamoxifen] this term only
#33	(antiestrogen* or antioestrogen* or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or "RU 486" or SERM or SPRM):ti,ab,kw
#34	MeSH descriptor: [Gynecologic Surgical Procedures] this term only
#35	MeSH descriptor: [Surgical Procedures, Operative] this term only
#36	MeSH descriptor: [Ablation Techniques] explode all trees
#37	MeSH descriptor: [Argon] this term only
#38	MeSH descriptor: [Carbon Dioxide] this term only
#39	MeSH descriptor: [Cystectomy] this term only
#40	MeSH descriptor: [Cysts] this term only and with qualifier(s): [surgery - SU]
#41	MeSH descriptor: [Cytoreduction Surgical Procedures] this term only
#42	MeSH descriptor: [Diathermy] explode all trees
#43	MeSH descriptor: [Drainage] explode all trees
#44	MeSH descriptor: [Electrocoagulation] explode all trees
#45	MeSH descriptor: [Electrosurgery] this term only
#46	MeSH descriptor: [Fallopian Tubes] this term only and with qualifier(s): [surgery - SU]
#47	MeSH descriptor: [Laparoscopy] explode all trees
#48	MeSH descriptor: [Laparotomy] explode all trees

ID	Search
#49	MeSH descriptor: [Laser Coagulation] this term only
#50	MeSH descriptor: [Laser Therapy] this term only
#51	MeSH descriptor: [Lasers, Gas] this term only
#52	MeSH descriptor: [Microsurgery] this term only
#53	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
#54	MeSH descriptor: [Ovarian Cysts] this term only and with qualifier(s): [surgery - SU]
#55	MeSH descriptor: [Ovariectomy] explode all trees
#56	MeSH descriptor: [Ovary] explode all trees and with qualifier(s): [surgery - SU]
#57	MeSH descriptor: [Robotic Surgical Procedures] this term only
#58	MeSH descriptor: [Salpingectomy] explode all trees
#59	MeSH descriptor: [Sclerotherapy] this term only
#60	MeSH descriptor: [Surgery, Computer-Assisted] this term only
#61	MeSH descriptor: [Ultrasonic Surgical Procedures] this term only
#62	MeSH descriptor: [Uterus] explode all trees and with qualifier(s): [surgery - SU]
#63	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapor* or electrovapour* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapor* or photovapour* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* near (energy or therap* or treat*)) or vapoenucleat* or vapori* or vapouri* or videolaparoscop* or videolaparotom*):ti,ab,kw
#64	(((laser* or argon or bipolar or "bi polar" or "carbon dioxide" or helium or monopolar or "mono polar" or plasma*) near/3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*):ti,ab,kw
#65	(minimal* near/3 (access* or invasive or surg*)):ti,ab,kw
#66	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) near/5 remov*)):ti,ab,kw
#67	(salpingectom* or tubectom* or (fallopian near/3 remov*)):ti,ab,kw
#68	MeSH descriptor: [Behavioral Medicine] this term only
#69	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
#70	MeSH descriptor: [Complementary Therapies] explode all trees
#71	MeSH descriptor: [Diet] explode all trees
#72	MeSH descriptor: [Diet Therapy] explode all trees
#73	MeSH descriptor: [Nutrition Therapy] this term only
#74	MeSH descriptor: [Plant Extracts] explode all trees
#75	MeSH descriptor: [Herbal Medicine] this term only
#76	MeSH descriptor: [Plants, Medicinal] this term only
#77	MeSH descriptor: [Exercise] explode all trees
#78	MeSH descriptor: [Patient Participation] this term only
#79	MeSH descriptor: [Peer Group] this term only
#80	MeSH descriptor: [Self Care] this term only
#81	MeSH descriptor: [Social Support] this term only
#82	MeSH descriptor: [Physical Fitness] this term only
#83	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#84	MeSH descriptor: [Postural Balance] explode all trees
#85	MeSH descriptor: [Psychotherapy] explode all trees
#86	MeSH descriptor: [Counseling] explode all trees
#87	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] this term only
#88	(("non medical" or "non medicine" or nonmed* or (non next pharm*) or nonpharm*) near/3 (intervention* or manag* or therap* or treat*)):ti,ab,kw
#89	(((behavi* or cognit*) near/3 (intervention* or technique* or therap* or treatment*)) or CBT):ti,ab,kw
#90	(psychotherap* or (psycho next therap*) or logotherap* or (logo next therap*)):ti,ab,kw
#91	(cope or coped or coping or meditat* or "mind body" or mindfulness or relax*):ti,ab,kw
#92	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) near/1 (intervention* or program* or therap* or treatment*))):ti,ab,kw
#93	((balance* or balancing* or breathing* or movement* or posture* or postural*) near/3 (exercise* or intervention* or program* or therap* or training*)):ti,ab,kw
#94	(((alternative or complement* or compliment* or folk or herb* or holistic or plant* or traditional* or "non Western" or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) next (extract* or medicine* or therap* or remed*)) or Ayurveda or Shaman*):ti,ab,kw
#95	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) next (therap* or treatment*))):ti,ab,kw
#96	((diet* near/2 (endo* or keto* or (low next carb*) or "low fat" or "gluten free" or paleo* or protein or "raw food" or restrict* or vegetarian or vegan)) or endodiet* or nutrition*):ti,ab,kw
#97	(exercis* or pilates or "tai chi" or "tai ji" or yoga):ti,ab,kw
#98	(manipulat* near (medicine or therap* or treatment*)):ti,ab,kw
#99	(chiropra* or osteopath* or (musculoskelet* next (manipulat* or therap*))):ti,ab,kw
#100	(acupressure or massag* or reflexolog* or shiatsu or "tui na"):ti,ab,kw
#101	(acupoint* or acupuncture or electroacupuncture or meridian* or moxibust* or (acu* next point*) or needling or shu):ti,ab,kw
#102	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) near/2 (electrostimulat* or (electro next stimulat*) or (nerve next stimulat*))) or electroanalges* or (electro next analges*) or TENS):ti,ab,kw

ID	Search
#103	(expert* near/3 patient*):ti,ab,kw
#104	(peer* near/3 counsel*):ti,ab,kw
#105	(((peer or social) near/3 support*) or "support group" or "support groups"):ti,ab,kw
#106	(biofeedback or "bio feedback" or "bio feed back" or psychophysiolog* or (psycho next physiolog*)):ti,ab,kw
#107	(autogenic* or hypno* or mesmeris*):ti,ab,kw
#108	((psychosex* or sex*) near/3 (counsel* or intervention* or therap* or treatment*)):ti,ab,kw
#109	{or #4-#108}
#110	#3 and #109 with Cochrane Library publication date Between Jan 2016 and Jun 2016, in Cochrane Reviews, Cochrane Protocols

Database Cochrane Central Register of Controlled Trials (CENTRAL) - Wiley

Date of last search: 27/06/2023

ID	Search
#1	MeSH descriptor: [Endometriosis] this term only
#2	(endometrios* or endometrioma*):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Contraception] this term only
#5	MeSH descriptor: [Hormonal Contraception] this term only
#6	MeSH descriptor: [Long-Acting Reversible Contraception] this term only
#7	MeSH descriptor: [Ovulation Inhibition] this term only
#8	MeSH descriptor: [Contraceptive Agents, Female] explode all trees
#9	MeSH descriptor: [Contraceptive Devices, Female] this term only
#10	MeSH descriptor: [Intrauterine Devices, Medicated] this term only
#11	MeSH descriptor: [Estradiol Congeners] explode all trees
#12	MeSH descriptor: [Norpregnanes] explode all trees
#13	MeSH descriptor: [Pregnanes] explode all trees
#14	MeSH descriptor: [Progesterone Congeners] explode all trees
#15	contracept*:ti,ab,kw
#16	(intrauter* near/3 (homon* or medicat*) near/3 (device* or iud*)):ti,ab,kw
#17	("cyproterone acetate" or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen* or estrone or ethinylestradiol or ethylestrenol or ethinyloestradiol or ethyloestrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or "nomegestrol acetate" or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen* or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone):ti,ab,kw
#18	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press):ti,ab,kw
#19	MeSH descriptor: [Chorionic Gonadotropin] this term only and with qualifier(s): [therapeutic use - TU]
#20	MeSH descriptor: [Estrogen Antagonists] explode all trees
#21	MeSH descriptor: [Estrogen Receptor Modulators] explode all trees
#22	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#23	MeSH descriptor: [Hormone Antagonists] this term only
#24	(gonadotrophin* or gonadotropin* GnRH or GnRHa or "Gn RH" or "Gn RHa"):ti,ab,kw
#25	(buserelin or goserelin or leuporelin or triptorelin):ti,ab,kw
#26	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#27	("aromatase inhibiter" or "aromatase inhibiters" or aminoglutethimide or anastrazole or anastrozole or exemestane or lanastrazole or lanastrozole or letrazole or letrozole):ti,ab,kw
#28	MeSH descriptor: [Luteolytic Agents] this term only
#29	MeSH descriptor: [Selective Estrogen Receptor Modulators] this term only
#30	MeSH descriptor: [Mifepristone] this term only
#31	MeSH descriptor: [Raloxifene Hydrochloride] this term only
#32	MeSH descriptor: [Tamoxifen] this term only
#33	(antiestrogen* or antioestrogen* or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or "RU 486" or SERM or SPRM):ti,ab,kw
#34	MeSH descriptor: [Gynecologic Surgical Procedures] this term only
#35	MeSH descriptor: [Surgical Procedures, Operative] this term only
#36	MeSH descriptor: [Ablation Techniques] explode all trees
#37	MeSH descriptor: [Argon] this term only
#38	MeSH descriptor: [Carbon Dioxide] this term only
#39	MeSH descriptor: [Cystectomy] this term only
#40	MeSH descriptor: [Cysts] this term only and with qualifier(s): [surgery - SU]
#41	MeSH descriptor: [Cytoreduction Surgical Procedures] this term only
#42	MeSH descriptor: [Diathermy] explode all trees
#43	MeSH descriptor: [Drainage] explode all trees
#44	MeSH descriptor: [Electrocoagulation] explode all trees
#45	MeSH descriptor: [Electrosurgery] this term only
#46	MeSH descriptor: [Fallopian Tubes] this term only and with qualifier(s): [surgery - SU]

ID	Search
#47	MeSH descriptor: [Laparoscopy] explode all trees
#48	MeSH descriptor: [Laparotomy] explode all trees
#49	MeSH descriptor: [Laser Coagulation] this term only
#50	MeSH descriptor: [Laser Therapy] this term only
#51	MeSH descriptor: [Lasers, Gas] this term only
#52	MeSH descriptor: [Microsurgery] this term only
#53	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
#54	MeSH descriptor: [Ovarian Cysts] this term only and with qualifier(s): [surgery - SU]
#55	MeSH descriptor: [Ovariectomy] explode all trees
#56	MeSH descriptor: [Ovary] explode all trees and with qualifier(s): [surgery - SU]
#57	MeSH descriptor: [Robotic Surgical Procedures] this term only
#58	MeSH descriptor: [Salpingectomy] explode all trees
#59	MeSH descriptor: [Sclerotherapy] this term only
#60	MeSH descriptor: [Surgery, Computer-Assisted] this term only
#61	MeSH descriptor: [Ultrasonic Surgical Procedures] this term only
#62	MeSH descriptor: [Uterus] explode all trees and with qualifier(s): [surgery - SU]
#63	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapor* or electrovapour* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapor* or photovapour* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* near (energy or therap* or treat*)) or vapoenucleat* or vapori* or vapouri* or videolaparoscop* or videolaparotom*):ti,ab,kw
#64	(((laser* or argon or bipolar or "bi polar" or "carbon dioxide" or helium or monopolar or "mono polar" or plasma*) near/3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*):ti,ab,kw
#65	(minimal* near/3 (access* or invasive or surg*)):ti,ab,kw
#66	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) near/5 remov*)):ti,ab,kw
#67	(salpingectom* or tubectom* or (fallopian near/3 remov*)):ti,ab,kw
#68	MeSH descriptor: [Behavioral Medicine] this term only
#69	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
#70	MeSH descriptor: [Complementary Therapies] explode all trees
#71	MeSH descriptor: [Diet] explode all trees
#72	MeSH descriptor: [Diet Therapy] explode all trees
#73	MeSH descriptor: [Nutrition Therapy] this term only
#74	MeSH descriptor: [Plant Extracts] explode all trees
#75	MeSH descriptor: [Herbal Medicine] this term only
#76	MeSH descriptor: [Plants, Medicinal] this term only
#77	MeSH descriptor: [Exercise] explode all trees
#78	MeSH descriptor: [Patient Participation] this term only
#79	MeSH descriptor: [Peer Group] this term only
#80	MeSH descriptor: [Self Care] this term only
#81	MeSH descriptor: [Social Support] this term only
#82	MeSH descriptor: [Physical Fitness] this term only
#83	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#84	MeSH descriptor: [Postural Balance] explode all trees
#85	MeSH descriptor: [Psychotherapy] explode all trees
#86	MeSH descriptor: [Counseling] explode all trees
#87	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] this term only
#88	(("non medical" or "non medicine" or nonmed* or (non next pharm*) or nonpharm*) near/3 (intervention* or manag* or therap* or treat*)):ti,ab,kw
#89	(((behavi* or cognit*) near/3 (intervention* or technique* or therap* or treatment*)) or CBT):ti,ab,kw
#90	(psychotherap* or (psycho next therap*) or logotherap* or (logo next therap*)):ti,ab,kw
#91	(cope or coped or coping or meditat* or "mind body" or mindfulness or relax*):ti,ab,kw
#92	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) near/1 (intervention* or program* or therap* or treatment*))):ti,ab,kw
#93	((balance* or balancing* or breathing* or movement* or posture* or postural*) near/3 (exercise* or intervention* or program* or therap* or training*)):ti,ab,kw
#94	(((alternative or complement* or compliment* or folk or herb* or holistic or plant* or traditional* or "non Western" or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) next (extract* or medicine* or therap* or remed*)) or Ayurveda or Shaman*):ti,ab,kw
#95	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) next (therap* or treatment*))):ti,ab,kw
#96	((diet* near/2 (endo* or keto* or (low next carb*) or "low fat" or "gluten free" or paleo* or protein or "raw food" or restrict* or vegetarian or vegan)) or endodiet* or nutrition*):ti,ab,kw
#97	(exercis* or pilates or "tai chi" or "tai ji" or yoga):ti,ab,kw
#98	(manipulat* near (medicine or therap* or treatment*)):ti,ab,kw
#99	(chiropra* or osteopath* or (musculoskelet* next (manipulat* or therap*))):ti,ab,kw
#100	(acupressure or massag* or reflexolog* or shiatsu or "tui na"):ti,ab,kw
#101	(acupoint* or acupuncture or electroacupuncture or meridian* or moxibust* or (acu* next point*) or needling or shu):ti,ab,kw

ID	Search
#102	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) near/2 (electrostimulat* or (electro next stimulat*) or (nerve next stimulat*))) or electroanalges* or (electro next analges*) or TENS):ti,ab,kw
#103	(expert* near/3 patient*):ti,ab,kw
#104	(peer* near/3 counsel*):ti,ab,kw
#105	(((peer or social) near/3 support*) or "support group" or "support groups"):ti,ab,kw
#106	(biofeedback or "bio feedback" or "bio feed back" or psychophysiolog* or (psycho next physiolog*)):ti,ab,kw
#107	(autogenic* or hypno* or mesmeris*):ti,ab,kw
#108	((psychosex* or sex*) near/3 (counsel* or intervention* or therap* or treatment*)):ti,ab,kw
#109	{or #4-#108}
#110	#3 and #109
#111	"conference":pt or (clinicaltrials or trialsearch):so
#112	#110 not #111 with Publication Year from 2016 to 2023, in Trials

Database: Epistemonikos

Date of last search: 27/06/2023

ID	Search
1	endometrios* OR endometrioma*)
2	[Filters: min_date=20160101, max_date=20230627; Publication type=Systematic Reviews; Systematic Review Question=Interventions
3	1 and 2

Economics search strategies:

Database: Ovid MEDLINE

Date of last search: 27/06/2023

#	Searches
1	Endometriosis/
2	(endometrios* or endometrioma*).ti,ab,kf.
3	1 or 2
4	Contraception/ or Hormonal Contraception/ or Long-Acting Reversible Contraception/ or Ovulation Inhibition/
5	exp Contraceptive Agents, Female/
6	Contraceptive Devices, Female/ or Intrauterine Devices, Medicated/
7	exp Estradiol Congeners/
8	exp Norpregnanes/
9	exp Pregnanes/
10	exp Progesterone Congeners/
11	contracept*.ti,ab,kf.
12	(intrauter* adj3 (homon* or medicat*) adj3 (device* or iud?)).ti,ab,kf.
13	(cyproterone acetate or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen? or estrone or ethinyl?estradiol or ethyl?estrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or nomegestrol acetate or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen? or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone).ti,ab,kf.
14	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press).ti,ab,kf.
15	Chorionic Gonadotropin/tu
16	exp Estrogen Antagonists/
17	exp Estrogen Receptor Modulators/
18	exp Gonadotropin-Releasing Hormone/
19	Hormone Antagonists/
20	(gonadotrop?in* or GnRH or GnRHa or Gn RH or Gn RHa).ti,ab,kf.
21	(buserelin or goserelin or leuporelin or triptorelin).ti,ab,kf.
22	exp Aromatase Inhibitors/
23	(aromatase inhibit* or aminoglutethimide or anastr?zole or exemestane or lanastr?zole or letr?zole).ti,ab,kf.
24	Luteolytic Agents/
25	Selective Estrogen Receptor Modulators/
26	Mifepristone/ or Raloxifene Hydrochloride/ or Tamoxifen/
27	(antiestrogen? or antioestrogen? or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or RU 486 or SERM? or SPRM?).ti,ab,kf.
28	Gynecologic Surgical Procedures/ or Surgical Procedures, Operative/
29	exp Ablation Techniques/
30	Argon/
31	Carbon Dioxide/

#	Searches
32	Cystectomy/
33	Cysts/su
34	Cytoreduction Surgical Procedures/
35	exp Diathermy/
36	exp Drainage/
37	exp Electrocoagulation/
38	Electrosurgery/
39	Fallopian Tubes/su
40	exp Laparoscopy/
41	Laparotomy/
42	Laser Coagulation/
43	Laser Therapy/
44	Lasers, Gas/
45	Microsurgery/
46	exp Minimally Invasive Surgical Procedures/
47	Ovarian Cysts/su
48	exp Ovariectomy/
49	exp Ovary/su
50	Robotic Surgical Procedures/
51	exp Salpingectomy/
52	Sclerotherapy/
53	Surgery, Computer-Assisted/
54	Ultrasonic Surgical Procedures/
55	exp Uterus/su
56	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapo?r* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapo?r* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* adj (energy or therap* or treat*)) or vapoenucleat* or vapo?ri* or videolaparoscop* or videolaparotom*).ti,ab,kf.
57	(((laser* or argon or bipolar or bi polar or carbon dioxide or helium or monopolar or mono polar or plasma*) adj3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*).ti,ab,kf.
58	(minimal* adj3 (access* or invasive or surg*)).ti,ab,kf.
59	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) adj5 remov*)).ti,ab,kf.
60	(salpingectom* or tubectom* or (fallopian adj3 remov*)).ti,ab,kf.
61	Behavioral Medicine/
62	exp Cognitive Behavioral Therapy/
63	exp Complementary Therapies/
64	exp Diet/ or exp Diet Therapy/ or Nutrition Therapy/
65	Herbal Medicine/ or exp Plant Extracts/ or Plants, Medicinal/
66	exp Exercise/
67	Patient Participation/ or Peer Group/ or Self Care/ or Social Support/
68	Physical Fitness/
69	exp Physical Therapy Modalities/
70	exp Postural Balance/
71	exp Psychotherapy/
72	exp Counseling/
73	Transcutaneous Electric Nerve Stimulation/
74	((non med* or nonmed* or non pharm* or nonpharm*) adj3 (intervention* or manag* or therap* or treat*)).ti,ab,kf.
75	(((behavi* or cognit*) adj3 (intervention* or technique? or therap* or treatment*)) or CBT).ti,ab,kf.
76	(psychotherap* or psycho therap* or logotherap* or logo therap*).ti,ab,kf.
77	(cope? or coping or meditat* or mind body or mindfulness or relax*).ti,ab,kf.
78	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) adj1 (intervention* or program* or therap* or treatment*))).ti,ab,kf.
79	((balance* or balancing* or breathing* or movement* or posture* or postural*) adj3 (exercise* or intervention* or program* or therap* or training*)).ti,ab,kf.
80	(((alternative or compl?ment* or folk or herb* or holistic or plant* or traditional* or non Western or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) adj (extract? or medicine? or therap* or remed*)) or Ayurveda or Shaman*).ti,ab,kf.
81	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) adj (therap* or treatment*))).ti,ab,kf.
82	((diet* adj2 (endo* or keto* or low carb* or low fat or gluten free or paleo* or protein or raw food or restrict* or vegetarian or vegan)) or endodiet* or nutrition*).ti,ab,kf.
83	(exercis* or pilates or tai chi or tai ji or yoga).ti,ab,kf.
84	(manipulat* adj1 (medicine or therap* or treatment?)).ti,ab,kf.
85	(chiropra* or osteopath* or (musculoskelet* adj (manipulat* or therap*))).ti,ab,kf.
86	(acupressure or massag* or reflexolog* or shiatsu or tui na).ti,ab,kf.
87	(acupoint? or acupuncture or electroacupuncture or meridian? or mox?bust* or acu* point? or needling or shu).ti,ab,kf.

#	Searches
88	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) adj2 (electrostimulat* or electro stimulat* or nerve stimulat*)) or electroanalges* or electro analges* or TENS).ti,ab,kf.
89	(expert* adj3 patient*).ti,ab,kf.
90	(peer* adj3 counsel*).ti,ab,kf.
91	(((peer or social) adj3 support*) or support group?).ti,ab,kf.
92	(biofeedback or bio feedback or bio feed back or psychophysiolog* or psycho physiolog*).ti,ab,kf.
93	(autogenic* or hypno* or mesmeris*).ti,ab,kf.
94	((psychosex* or sex*) adj3 (counsel* or intervention* or therap* or treatment*)).ti,ab,kf.
95	or/4-94
96	3 and 95
97	letter/
98	editorial/
99	news/
100	exp historical article/
101	Anecdotes as topic/
102	comment/
103	case reports/
104	(letter or comment*).ti.
105	or/97-104
106	randomized controlled trial/ or random*.ti,ab.
107	105 not 106
108	animals/ not humans/
109	exp Animals, Laboratory/
110	exp Animal Experimentation/
111	exp Models, Animal/
112	exp Rodentia/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/107-113
115	96 not 114
116	limit 115 to english language
117	Economics/
118	Value of life/
119	exp "Costs and Cost Analysis"/
120	exp Economics, Hospital/
121	exp Economics, Medical/
122	exp Resource Allocation/
123	Economics, Nursing/
124	Economics, Pharmaceutical/
125	exp "Fees and Charges"/
126	exp Budgets/
127	budget*.ti,ab.
128	cost*.ti,ab.
129	(economic* or pharmaco?economic*).ti,ab.
130	(price* or pricing*).ti,ab.
131	(financ* or fee or fees or expenditure* or saving*).ti,ab.
132	(value adj2 (money or monetary)).ti,ab.
133	resourc* allocat*.ti,ab.
134	(fund or funds or funding* or funded).ti,ab.
135	(ration or rations or rationing* or rationed).ti,ab.
136	ec.fs.
137	or/117-136
138	116 and 137
139	limit 138 to dt=20160101-20230627
140	limit 138 to ed=20160101-20230627
141	139 or 140

Database: Ovid Embase

Date of last search: 27/06/2023

#	Searches
1	exp endometriosis/
2	(endometrios* or endometrioma*).ti,ab,kf.
3	1 or 2
4	contraception/ or hormonal contraception/ or long-acting reversible contraception/ or oral contraception/ or ovulation inhibition/
5	exp hormonal contraceptive agent/
6	exp female contraceptive device/
7	exp estradiol derivative/

#	Searches
8	exp pregnane derivative/
9	exp progesterone derivative/
10	contracept*.ti,ab,kf.
11	(intrauter* adj3 (homon* or medicat*) adj3 (device* or iud?)).ti,ab,kf.
12	(cyproterone acetate or danazol or desogestrel or dienogest or drospirenone or equilenin or equalin or estetrol or estradiol or estriol or estrogen? or estrone or ethinyl?estradiol or ethyl?estrenol or etonogestrel or fulvestrant or gestodene or gestrinone* or hydroxyestrone* or levonorgestrel or lynestrenol or medroxyprogesterone or mestranol or methoxyestradiol or nomegestrol acetate or norelgestromin or norethandrolone or norethindrone or norethisterone or norethynodrel or norgestimate or norgestrel or norgestrienone* or norpregn* or norprogesteron* or oestetrol or oestradiol or oestriol or oestrogen? or oestrone or pregnenolone* or progest* or promegestone* or quinestrol or tibolone).ti,ab,kf.
13	(LNG-IUS or implanon or jaydess or mirena or nexplanon or noristerat or provera or sayana press).ti,ab,kf.
14	chorionic gonadotropin/dt
15	exp antiestrogen/
16	exp gonadotropin derivative/ or exp gonadorelin agonist/ or gonadorelin derivative/
17	hormone antagonist/
18	(gonadotrop?in* or GnRH or GnRHa or Gn RH or Gn RHa).ti,ab,kf.
19	(buserelin or goserelin or leuporelin or triptorelin).ti,ab,kf.
20	exp aromatase inhibitor/
21	(aromatase inhibit* or aminoglutethimide or anastr?zole or exemestane or lanastr?zole or letr?zole).ti,ab,kf.
22	luteolytic agent/
23	selective estrogen receptor modulator/
24	exp progesterone receptor modulator/
25	mifepristone/ or tibolone/ or ulipristal/
26	(antiestrogen? or antioestrogen? or antiprogest* or luteoly* or mifepristone or raloxifene or tamoxifen or ulipristal or RU 486 or SERM? or SPRM?).ti,ab,kf.
27	gynecologic surgery/ or surgery/
28	exp ablation therapy/
29	exp argon laser/
30	exp carbon dioxide laser/
31	computer assisted surgery/
32	exp coagulation surgery/
33	cystectomy/
34	cyst/su
35	cytoreductive surgery/
36	exp diathermy/
37	surgical drainage/
38	electrosurgery/
39	endometrial disease/dt, su, th
40	exp endometrium/su
41	exp fallopian tube/ and su.fs.
42	gas laser/
43	helium laser/
44	exp laparoscopy/
45	laparotomy/
46	laser therapy/
47	microsurgery/
48	minimally invasive surgery/
49	exp ovary cyst/su
50	exp ovariectomy/
51	exp ovary/su
52	robot assisted surgery/
53	salpingectomy/
54	exp sclerotherapy/
55	ultrasound surgery/
56	exp uterus/su
57	vaginal cyst/su
58	(ablat* or aspirat* or cauter* or coagulat* or colectom* or colpectom* or cystectom* or diatherm* or drain* or electrocauter* or electrocoagulat* or electroresect* or electrosurg* or electrovapo?r* or enucleat* or enucleoresect* or excis* or fenestrat* or fulgarat* or incise* or incision or keyhole* or laparoscop* or laparotom* or microlaparoscop* or microlaparotom* or microsurg* or minilaparoscop* or minilaparotom* or needl* or photovapo?r* or peritoneo* or resect* or sclerotherap* or shav* or strip* or surg* or thermocoagulat* or thermotherap* or (ultraso* adj (energy or therap* or treat*)) or vapoenucleat* or vapo?ri* or videolaparoscop* or videolaparotom*).ti,ab,kf.
59	(((laser* or argon or bipolar or bi polar or carbon dioxide or helium or monopolar or mono polar or plasma*) adj3 (intervention* or therap* or treatment*)) or laseroscop* or videolaseroscop*).ti,ab,kf.
60	(minimal* adj3 (access* or invasive or surg*)).ti,ab,kf.
61	(oophorectom* or oophorotom* or ovariectom* or ovariotom* or ((ovary or ovaries) adj5 remov*)).ti,ab,kf.
62	(salpingectom* or tubectom* or (fallopian adj3 remov*)).ti,ab,kf.
63	behavioral medicine/
64	exp cognitive behavioral therapy/

#	Searches
65	exp alternative medicine/
66	exp diet/ or exp diet therapy/
67	herbaceous agent/ or exp medicinal plant/ or exp plant extract/ or exp traditional medicine/
68	exp exercise/ or exp kinesiotherapy/
69	patient participation/ or exp peer group/ or exp self care/ or exp social support/
70	fitness/
71	exp physiotherapy/
72	exp body equilibrium/
73	exp psychotherapy/
74	exp counseling/
75	transcutaneous electrical nerve stimulation/
76	((non med* or nonmed* or non pharm* or nonpharm*) adj3 (intervention* or manag* or therap* or treat*)).ti,ab,kf.
77	(((behavi* or cognit*) adj3 (intervention* or technique? or therap* or treatment*)) or CBT).ti,ab,kf.
78	(psychotherap* or psycho therap* or logotherap* or logo therap*).ti,ab,kf.
79	(cope? or coping or meditat* or mind body or mindfulness or relax*).ti,ab,kf.
80	(physiotherap* or kinesiotherap* or ((kinesio or manual or physical or physio) adj1 (intervention* or program* or therap* or treatment*))).ti,ab,kf.
81	((balance* or balancing* or breathing* or movement* or posture* or postural*) adj3 (exercise* or intervention* or program* or therap* or training*)).ti,ab,kf.
82	(((alternative or compl?ment* or folk or herb* or holistic or plant* or traditional* or non Western or nonWestern or African or Arabic or Asian or Ayurvedic or Chinese or Indian or Hindu or Oriental) adj (extract? or medicine? or therap* or remed*)) or Ayurveda or Shaman*).ti,ab,kf.
83	(homeopath* or homeotherap* or naturopath* or naturotherap* or phytopharma* or phytotherap* or ((homeo or naturo or phyto) adj (therap* or treatment*))).ti,ab,kf.
84	((diet* adj2 (endo* or keto* or low carb* or low fat or gluten free or paleo* or protein or raw food or restrict* or vegetarian or vegan)) or endodiet* or nutrition*).ti,ab,kf.
85	(exercis* or pilates or tai chi or tai ji or yoga).ti,ab,kf.
86	(manipulat* adj1 (medicine or therap* or treatment?)).ti,ab,kf.
87	(chiropra* or osteopath* or (musculoskelet* adj (manipulat* or therap*))).ti,ab,kf.
88	(acupressure or massag* or reflexolog* or shiatsu or tui na).ti,ab,kf.
89	(acupoint? or acupuncture or electroacupuncture or meridian? or mox?bust* or acu* point? or needling or shu).ti,ab,kf.
90	(((cutaneous or dermal or percutaneous or transcutaneous or transdermal) adj2 (electrostimulat* or electro stimulat* or nerve stimulat*)) or electroanalges* or electro analges* or TENS).ti,ab,kf.
91	(expert* adj3 patient*).ti,ab,kf.
92	(peer* adj3 counsel*).ti,ab,kf.
93	(((peer or social) adj3 support*) or support group?).ti,ab,kf.
94	(biofeedback or bio feedback or bio feed back or psychophysiolog* or psycho physiolog*).ti,ab,kf.
95	(autogenic* or hypno* or mesmeris*).ti,ab,kf.
96	((psychosex* or sex*) adj3 (counsel* or intervention* or therap* or treatment*)).ti,ab,kf.
97	or/4-96
98	3 and 97
99	letter.pt. or letter/
100	note.pt.
101	editorial.pt.
102	case report/ or case study/
103	(letter or comment*).ti.
104	or/99-103
105	randomized controlled trial/ or random*.ti,ab.
106	104 not 105
107	animal/ not human/
108	nonhuman/
109	exp Animal Experiment/
110	exp Experimental Animal/
111	animal model/
112	exp Rodent/
113	(rat or rats or rodent* or mouse or mice).ti.
114	or/106-113
115	98 not 114
116	limit 115 to english language
117	health economics/
118	exp economic evaluation/
119	exp health care cost/
120	exp fee/
121	budget/
122	funding/
123	resource allocation/
124	budget*.ti,ab.
125	cost*.ti,ab.
126	(economic* or pharmaco?economic*).ti,ab.

#	Searches
127	(price* or pricing*).ti,ab.
128	(financ* or fee or fees or expenditure* or saving*).ti,ab.
129	(value adj2 (money or monetary)).ti,ab.
130	resourc* allocat*.ti,ab.
131	(fund or funds or funding* or funded).ti,ab.
132	(ration or rations or rationing* or rationed).ti,ab.
133	or/117-132
134	116 and 133
135	limit 134 to dc=20160101-20230627
136	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
137	135 not 136

Database: Health Technology Assessment (HTA) - CRD

Date of last search: 27/06/2023

#	Searches
1	MeSH DESCRIPTOR Endometriosis
2	((endometrios* OR endometrioma*))
3	#1 OR #2
4	* WHERE LPD FROM 01/01/2016 TO 27/06/2023
5	* IN HTA
6	#3 AND #4 AND #5

Database: INAHTA International HTA Database

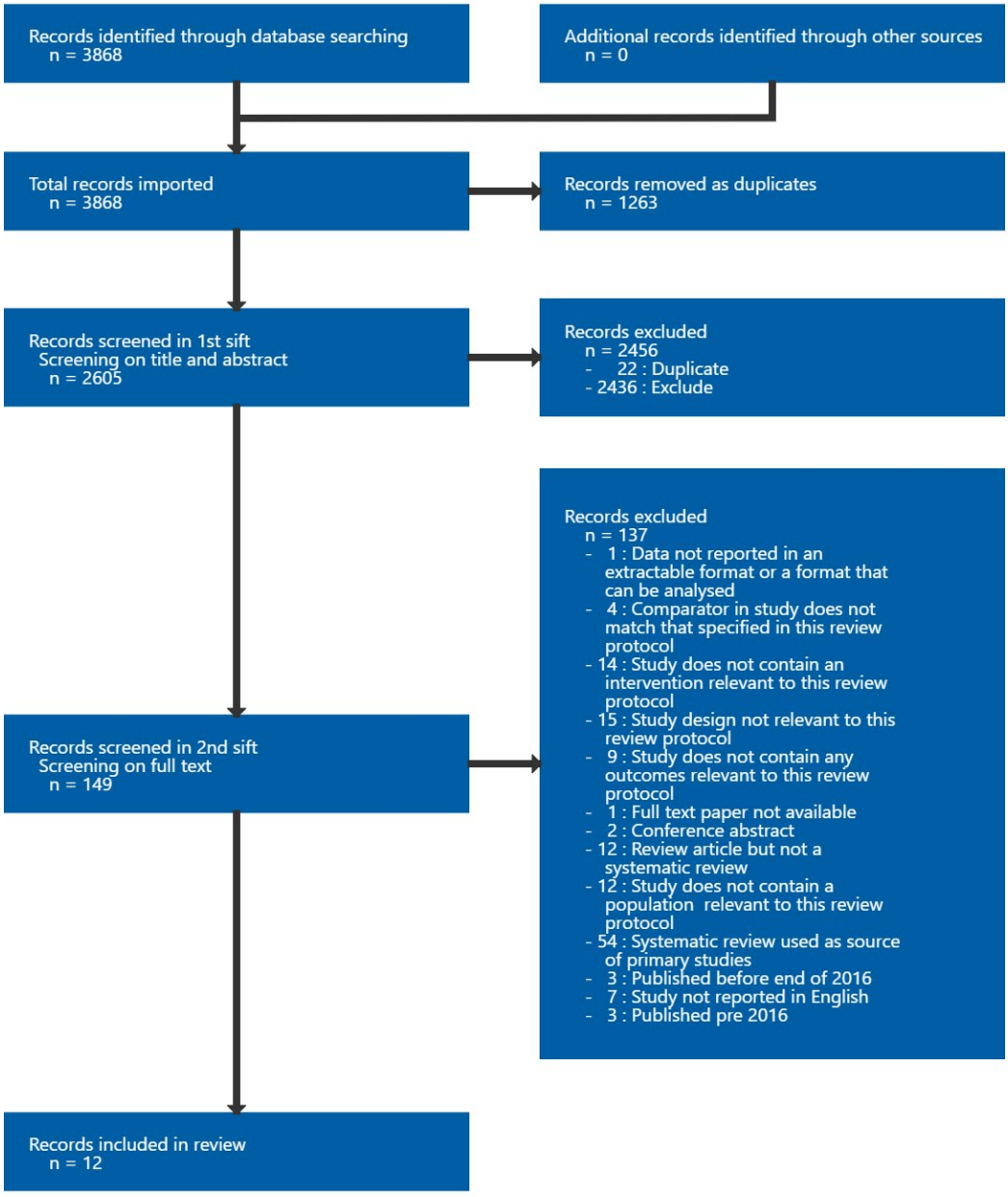
Date of last search: 27/06/2023

Line	Query
3	#1 or #2 FROM 2016 TO 2023 AND (English)[Language]
2	((endometrios* OR endometrioma*))
1	"Endometriosis"[mh]

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non- pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Acien, 2021

Bibliographic Reference	Acien, Pedro; Velasco, Irene; Acien, Maribel; Anastrozole and levonorgrestrel-releasing intrauterine device in the treatment of endometriosis: a randomized clinical trial.; BMC women's health; 2021; vol. 21 (no. 1); 211

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	January 2009 – March 2015
Inclusion criteria	Young (<41 years) premenopausal women with a transvaginal ultrasound suggestive of endometriomas >3 × 4 cm, CA-125 levels ≥35 U/mL and significant clinical endometriosis symptoms. The women had been advised for conservative surgery, did not desire pregnancy, and accepted randomisation and any intrauterine device insertion or surgery that that would entail. The patients could not have received medical treatment in the last 3 months. A previous diagnosis or treatment of endometriosis is not an exclusion criterion. Mixture of primary and secondary infertility. Significant endometriosis symptoms were defined as a score of visual analogue scale (VAS) of 4 or greater. The VAS scale had a maximum of 10 points, with dysmenorrhea (0–3 points), deep dyspareunia (0–3 points), chronic pelvic pain (0–3 points), and other symptoms (0–1 point). The endometriomas also had to appear on the ultrasound with ground glass echogenicity and no papillary structures with detectable blood flow.
Exclusion criteria	Women who were pregnant; or infertile and wanted to get pregnant; or who had had no previous sexual intercourse and/or who did not want/accept levonorgestrel-releasing intrauterine device (LNG-IUD) insertion; or who had acute or recurrent pelvic inflammatory disease, genital tract infection, uterine malformations, leiomyomas, or any medical pathology contraindicating aromatase inhibitor treatment or LNG-IUD insertion

Patient characteristics	Age, mean (SD), years: Anastrozole, LNG-IUD and Laparoscopy plus cystectomy: 30.7 (7.3) Anastrozole, LNG-IUD and Drainage: 31.0 (5.6) LNG-IUD and Laparoscopy plus cystectomy: 33.6 (4.0) LNG-IUD and Drainage: 30.4 (8.2) Ethnicity (N): Not reported Type of endometriosis: Stage not reported, moderate to severe endometriosis Setting: University hospital
Intervention(s)/control	Anastrozole (aromatase inhibitor), oral administration of 1 mg tablet/day for 6 months, starting at the beginning of menstruation and levonorgestrel-releasing intrauterine device (LNG-IUD; Mirena) for 6 months, inserted during the same menstruation as anastrozole administration started and Laparoscopy plus cystectomy, ovarian and fertility sparing laparoscopy (or laparotomy 24% of participants) and cystectomy performed at least 1 month after start of anastrozole administration and calcium carbonate and cholecalciferol (no further details reported, e.g., unclear daily dose) to counteract bone loss associated with anastrozole administration. versus Anastrozole (as group above), LNG-IUD (as group above) and Drainage (transvaginal ultrasound-guided puncture-aspiration) of endometriomas performed at least 1 month after start of anastrozole administration and calcium carbonate and cholecalciferol (as group above). versus LNG-IUD and Laparoscopy plus cystectomy (both interventions as outlined for the first group above) versus LNG-IUD and Drainage (both interventions as outlined for the second group above)
Duration of follow-up	Mean (SD), years: 4.2 (1.7)
Sources of funding	Ministry of Health, Madrid, Spain and Fondo de Investigaciones Sanitarias (FIS) PI07/0417
Sample size	Randomised: n= 31 Anastrozole, LNG-IUD and Laparoscopy plus cystectomy: N=8 Anastrozole, LNG-IUD and Drainage: N=7 LNG-IUD and Laparoscopy plus cystectomy: N=9 LNG-IUD and Drainage: N=7

Outcomes

Study timepoints

- 4.2 year (Group with AI were followed up for Mean (SD) years: 4.67 (1.63) years Groups without AI were followed up for Mean (SD) years: 3.78 (1.77) years)

Primary and secondary outcomes

Outcome	Anastrozole, LNG-IUD and Laparoscopy plus cystectomy**, 4.2 year, N = 8**	Anastrozole, LNG-IUD and Drainage**, 4.2 year, N = 7**	LNG-IUD and Laparoscopy plus cystectomy**, 4.2 year, N = 9**	LNG-IUD and Drainage**, 4.2 year, N = 7**
Pregnancies/deliveries No of events	n = 0	n = 1	n = 1	n = 1

Critical appraisal

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Although all the study reported was that "Participants were randomized by computer, determined at the Hospital Pharmacy after a telephone call from the Endometriosis Consultation." (p. 2) both the randomisation sequence and allocation concealment were probably adequate)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Patients and researchers were not blinded. An appropriate statistical analysis was used and there were no deviations from the intended interventions. However, knowledge of which group patients were in could have impacted results. Analysis is intention to treat)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome (pregnancy rate) measurement was not reported but it is unlikely to be influenced by the knowledge of assigned intervention as it is an objective outcome)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Analysis intentions are reported and detail is given on analysis method. Reported data is unlikely to have been selected from multiple analyses due to the limited objective outcomes measured at different timepoints)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Bala, 2022

Bibliographic Reference	Bala, M.; Tahir, H.; Soomro, P.; Maqsood, S.; Nawaz, N.; Baloch, P.; A Randomized Control Trial of Combined Surgical and Hormonal Therapy of Endometriosis; Pakistan Journal of Medical and Health Sciences; 2022; vol. 6 (no. 1); 1020-1023

Study details

Country/ies where study was carried out	Pakistan
Study type	Randomised controlled trial (RCT)
Study dates	June 2020 – June 2021
Inclusion criteria	Women who had been diagnosed with genital endometriosis ranging from 18 – 45 years in age who had not had surgical intervention before. Primary or secondary infertility not reported. Type of endometriosis was symptomatic.
Exclusion criteria	Women who had surgery for endometriosis; or had undergone hormonal therapy to treat endometriosis.
Patient characteristics	Age, range, years: 18-45 (mean and SD not reported, age per group not given) Ethnicity: not reported Type of endometriosis:

	EEC (Endoscopic Endometriosis Classification) (higher stages are more severe): EEC Stage 0 (N) GnRHa group: n= 0 Laparoscopic excision group: n= 0 Laparoscopic excision plus GnRHa group: n= 0 EEC Stage 1 (N) GnRHa group: n= 48 Laparoscopic excision group: n= 60 Laparoscopic excision plus GnRHa group: n= 63 EEC Stage 2 (N) GnRHa group: n= 46 Laparoscopic excision group: n= 38 Laparoscopic excision plus GnRHa group: n= 29 EEC Stage 3 (N) GnRHa group: n= 26 Laparoscopic excision group: n= 22 Laparoscopic excision plus GnRHa group: n= 28 Setting: Hospital
Intervention(s)/control	GnRHa group: 3.75mg leuprorelin acetate (GnRH agonist) subcutaneous monthly injection for 3 months Before hormonal therapy, the women underwent surgical laparoscopy for diagnostic purposes and a second-look laparoscopy was conducted after 1-2 months of hormonal therapy; it is unclear whether this laparoscopy was diagnostic or surgical. versus Laparoscopic excision group: adhesion removal, and endometriosis foci excision. The normal anatomy of the reproductive organs was also corrected. Patients complaining of infertility were also checked for tubal patency. “In Group 2, the follow-up laparoscopy was performed 5 to 6 months followed by the surgical treatment.” (p. 1021; no further information provided) During the second-look laparoscopy, patients complaining of infertility were given chromopertubation; it is unclear whether this laparoscopy was diagnostic or surgical (The study reported “In Group 2, the follow-up laparoscopy was performed 5 to 6 months followed by the surgical treatment.”, p. 1021). No further therapy (medical or hormonal) given versus

	Laparoscopic excision plus GnRHa group: Laparoscopic excision (performed in the same manner as the surgical laparoscopy group) followed by GnRHa therapy according to the same schedule as outlined above for the GnRHa group A second-look laparoscopy was conducted after 1-2 months of GnRHa therapy; it is unclear whether this laparoscopy was diagnostic or surgical.
Duration of follow-up	2 years
Sources of funding	None
Sample size	Randomised: n= 360 GnRHa group: n= 120 Laparoscopic excision group: n= 120 Laparoscopic excision plus GnRHa group: n= 120
Other information	

Outcomes

Primary and secondary outcomes

Outcome	GnRHa group, , N = 120	Laparoscopic excision group, , N = 120	Laparoscopic excision plus GnRHa group, , N = 120
Pregnancies No of events	n = 77	n = 64	n = 70
Live births No of events	n = 66	n = 54	n = 60
Ectopic pregnancies No of events	n = 3	n = 1	n = 2

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Study only states 'patients were randomly allocated into three groups of treatment'. No information given on who randomised the participants and allocation concealment)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No blinding. No deviations from interventions. Knowledge of participant's groups may have impacted results)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate and the same between the groups. The assessment of the outcomes is unlikely to have been influenced by knowledge of the groups because they are objective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Reported results unlikely to have been selected from multiple analyses at different time points as the reported time points and method of analysis are what would be expected for the target outcomes. Pregnancy outcomes were evaluated within the first 3-6 months and then at delivery)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Candiani, 2018

Bibliographic Reference	Candiani, M; Ottolina, J; Posadzka, E; Ferrari, S; Castellano, L M; Tandoi, I; Pagliardini, L; Nocun, A; Jach, R; Assessment of ovarian reserve after cystectomy versus 'one-step' laser vaporization in the treatment of ovarian endometrioma: a small randomized clinical trial.; Human reproduction (Oxford, England); 2018; vol. 33 (no. 12); 2205-2211

Study details

Country/ies where study was carried out	Italy and Poland
Study type	Randomised controlled trial (RCT)
Study dates	July 2017 – February 2018
Inclusion criteria	Women of reproductive age with symptomatic (including pelvic pain or infertility) primary unilateral or bilateral endometriomas (between 3 and 8 cm diameter). Some patients had infertility, but type of infertility was not reported.
Exclusion criteria	Patients aged 40 years or above, or with deep infiltrating endometriosis, or with adenomyosis (on ultrasound), or prior ovarian surgery, or with unilateral oophorectomy, or with previous salpingectomy or hysterectomy, or with other endocrine diseases (e.g., thyroid disease), or hormonal treatment within 3 months of ovarian reserve assessment.
Patient characteristics	Age, mean (SD), years: Laparoscopic cystectomy group: 30.3 (5.2) Laparoscopic drainage plus ablation (laser vaporisation) group: 32.1(4.8) Ethnicity: not reported Type of endometriosis: site Bilateral endometrioma: N Laparoscopic cystectomy group: 3 Laparoscopic drainage plus ablation (laser vaporisation) group: 6 Endometriomas in right ovary: N Laparoscopic cystectomy group: 15 Laparoscopic drainage plus ablation (laser vaporisation) group: 15 Endometriomas in left ovary: N

	Laparoscopic cystectomy group: 18 Laparoscopic drainage plus ablation (laser vaporisation) group: 21 Setting: Scientific Institute and University Medical College
Intervention(s)/control	Laparoscopic cystectomy technique to treat endometriomas. Versus Laparoscopic drainage plus ablation (laser vaporisation) group consisted of drainage of the cyst content, biopsy and vaporisation of the cystic lining with a CO2 fibre laser (radially, from centre to periphery, using a power density of 13 W/cm2) and no subsequent suture. Operative laparoscopy was performed during the proliferative phase of the menstrual cycle.
Duration of follow-up	Mean (SD) in months: Laparoscopic cystectomy group: 7.8 (1.5) Laparoscopic drainage plus ablation (laser vaporisation) group: 8.1 (1.4)
Sources of funding	None
Sample size	Randomised: n= 60 Laparoscopic cystectomy group: n=30 Laparoscopic drainage plus ablation (laser vaporisation) group: n=30

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic cystectomy group, , N = 30	Laparoscopic drainage plusablation (laser vaporisation) group, , N = 30
Pregnancy rate Out of the 25 women who wished to become pregnant, Laparoscopic cystectomy n=13, CO2 laser vaporisation n=12 No of events	n = 2	n = 3
Anti-mullerian hormone Mean change over 3 months (95% CI) Mean (95% CI)	-0.8 (-1.3 to -0.2)	-0.4 (-1 to -0.2)
Antral follicle count Mean change over 3 months (95% CI) Mean (95% CI)	2.2 (0.9 to 4)	5 (2.8 to 7.1)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation sequence was generated by a computer, allocation concealment was done with sealed, numbered and opaque envelopes and baseline characteristics were balanced between the groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(The ultrasonographer was blinded but no information of blinding of patients. No deviations from the intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants for Antral follicle count and Anti-mullerian hormone values. However, only 25/60 patients wanted to become pregnant so data only available for this subsection of participants for this outcome)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods of outcome measurement were not reported but it is unlikely to be influenced by the knowledge of assigned intervention as they are objective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Low (Antral follicle count and Anti-mullerian hormone) (Antral follicle count and Anti-mullerian hormone were unlikely to have been selected from multiple outcome measures and analyses) Some concerns (Pregnancy rate was not an outcome set out beforehand so could have been selected on the basis of the results))*
Overall bias and Directness	Risk of bias judgement	High *(Some concerns for antral follicle count and anti-Mullerian hormone. High for pregnancy rate)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Not all women were infertile or desired pregnancy)*
Overall bias and Directness	Risk of bias variation across outcomes	Risk of variation across outcomes

Ghasemi Tehrani, 2022

Bibliographic Reference	Ghasemi Tehrani, Hatav; Tavakoli, Raheleh; Hashemi, Maryam; Haghighat, Somayeh; Ethanol Sclerotherapy versus Laparoscopic Surgery in Management of Ovarian Endometrioma; a Randomized Clinical Trial.; Archives of academic emergency medicine; 2022; vol. 10 (no. 1); e55

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	December 2020 – January 2022
Inclusion criteria	Infertile (≥ 1 year of failing to become clinically pregnant) women aged 18-40 years with US or MRI-confirmed ovarian endometrioma, chronic pelvic pain, CA125 levels <200 IU/mL and ovarian endometrioma cysts with a diameter of 4 to 10 cm. It was not reported whether the infertility of the included women was primary or secondary.
Exclusion criteria	Women with missing information; non-endometrial ovarian masses or previous malignancy.
Patient characteristics	Age, mean (SD), years: Sclerotherapy: 32.17 (4.76) Laparoscopic cystectomy: 30.80 (4.63) Ethnicity: not reported Type of endometriosis site: (N) Location of cyst: right Sclerotherapy: 7 Laparoscopic cystectomy: 11 Location of cyst: left Sclerotherapy: 22 Laparoscopic cystectomy: 17 Location of cyst: bilateral Sclerotherapy: 6

	Laparoscopic cystectomy: 7 Setting: Hospital
Intervention(s)/control	Sclerotherapy with a puncture needle: While the patient was sedated, ultrasound-guided transvaginal sclerotherapy was undertaken in the lithotomic position, using different sized needles to aspirate the cyst after confirmation of the endometria lesion About 80% of the cyst volume was replaced with ethanol for 20 minutes. The ethanol was 95% and up to 100 ml. Following this, complete aspiration was done to avoid side effects of ethanol. versus Laparoscopic cystectomy: Laparoscopic cystectomy was done under general anaesthesia. The contents of the cyst were aspirated after incising the cyst wall. The endometria was stripped from the healthy ovarian parenchyma.
Duration of follow-up	12 months
Sources of funding	Isfahan University of Medical Sciences
Sample size	Randomised: n= 70 Sclerotherapy: n=36 Laparoscopic cystectomy: n=37

Outcomes

Primary and secondary outcomes

Outcome	Sclerotherapy, , N = 35	Laparoscopic cystectomy, , N = 35
Anti-mullerian hormone level at baseline Mean (SD)	2.12 (1.05)	2.48 (1.34)
Anti-mullerian hormone level at 12 months Mean (SD)	2.09 (1.01)	1.62 (1.22)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation concealment was done using identical, sealed and sequentially-numbered envelopes, randomisation sequence was generated by a computer and baseline characteristics are similar between the groups)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Patients were blinded and an appropriate analysis was used. It was not reported if personnel were blinded, therefore this could have impacted the results. One patient did require extra surgery because of complications)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(1/36 patient was lost to follow-up in the sclerotherapy group and 2/37 were lost to follow-up in the laparoscopy group, and these patients were not included in the analysis)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcomes was appropriate and did not differ between the groups. Assessment of outcome is unlikely to have been influenced by knowledge of the intervention received because the outcomes were objective)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Analysis method was appropriate. Reported results unlikely to have been selected form multiple analyses at different time points as the reported time points and method of analysis are what would be expected for the target outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Muraoka, 2021

Bibliographic Reference	Muraoka, Ayako; Osuka, Satoko; Yabuki, Atsushi; Bayasula; Yoshihara, Masato; Tanaka, Hideaki; Sonehara, Reina; Miyake, Natsuki; Murakami, Mayuko; Yoshita, Sayako; Nakanishi, Natsuki; Nakamura, Tomoko; Goto, Maki; Iwase, Akira; Kajiyama, Hiroaki; Impact of perioperative use of GnRH agonist or dienogest on ovarian reserve after cystectomy for endometriomas: a randomized controlled trial.; Reproductive biology and endocrinology : RB&E; 2021; vol. 19 (no. 1); 179

Study details

Country/ies where study was carried out	Japan
Study type	Randomised controlled trial (RCT)
Study dates	June 2016 - May 2020
Inclusion criteria	The inclusion criteria for this trial were women between the ages of 20 and 42 years who had transvaginal ultrasound and MRI diagnosed ovarian endometrioma of >4 cm and a regular menstrual cycle of between 25 and 35 days.
Exclusion criteria	Women were excluded from the trial if they had suspicious findings of malignant ovarian diseases, or evidence of any other endocrine disorders and a history of ovarian or adnexal surgery.
Patient characteristics	Age, mean (SD), years: Laparoscopic cystectomy plus Gonadotropin-releasing hormone agonist (GnRHa): 33.0 (5.7) Laparoscopic cystectomy plus Dienogest (DNG) group: 33.0 (5.5) Ethnicity (N): Not reported Type of endometriosis: Unilateral endometrioma (N): Laparoscopic cystectomy plus GnRHa group: 12 Laparoscopic cystectomy plus DNG group: 17 Bilateral endometrioma (N): Laparoscopic cystectomy plus GnRHa group: 10 Laparoscopic cystectomy plus DNG group: 10 revised American Society for Reproductive Medicine (rASRM) score (median (IQR): Laparoscopic cystectomy plus GnRHa group: 48 (37-64)

	Laparoscopic cystectomy plus DNG group: 63 (37-85) Setting: Department of Obstetrics and Gynecology of Nagoya University Hospital in Nagoya, Japan
Intervention(s)/control	All participants had laparoscopic surgery. (Cysts were removed from normal ovarian tissue, hemostasis was achieved with bipolar forceps if necessary) Laparoscopic cystectomy plus GnRHa group: participants received GnRHa (buserelin acetate) at 1.8 mg/month total 2 months before and after surgery versus Laparoscopic cystectomy plus Dienogest group: participants received Dienogest at 2 mg/day for 2 months before and after surgery
Duration of follow-up	1 year
Sources of funding	Grants from Mochida Pharmaceutical Co., Ltd
Sample size	Randomised: n= 57 Laparoscopic cystectomy plus GnRHa group: n= 25 Laparoscopic cystectomy plus Dienogest group: n= 32
Other information	Serum Anti-mullerian hormone was measured by an enzyme immunoassay kit Elecsys AMH Plus; Roche Measuring range: - 23 ng/mL (0.071 - 164.2 pmol/L) Imprecision: 5% Pre-treatment AMH LS plus GnRHa: 2.3 [1.1-4.0] LS plus Dienogest: 2.2 [1.1-3.2] P Value: 0.54 AMH 1 year post operative p value: 0.10

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic cystectomy plus GnRHa group, , N = 22	Laparoscopic cystectomy plus Dienogest group, , N = 27
Serum Anti-mullerian hormone pre-treatment (ng/mL)	2.3 (1.1 to 4)	2.2 (1.1 to 3.2)

Outcome	Laparoscopic cystectomy plus GnRHa group, , N = 22	Laparoscopic cystectomy plus Dienogest group, , N = 27
Median (IQR)		
Serum Anti-mullerian hormone 1 year postoperatively Median (IQR)	0.79 (0.48 to 2.2)	1.3 (0.64 to 2.7)
Pregnancy GnRH (n=15) DNG (n=17) No of events	n = 6	n = 4

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised using a computer generated randomisation software. Differences at baseline do not suggest an issue with randomisation but the groups are not of equal size immediately post randomisation which suggests some issue)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(No information on whether participants or personnel delivering the intervention were aware of assigned intervention but the GnRHa and Dienogest interventions were different so they could have been..)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data available for 22/25 and 27/32 participants in the surgery plus GnRHa group and surgery plus dienogest group respectively. Reasons for missing data provided and in the DNG group are unrelated to the outcome (missing blood tests, limit of quantification, emergency surgery before end point, did not meet eligibility criteria - not endometrioma))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(*Anti-mullerian hormone *level was measured by an enzyme immunoassay kit so is deemed an objective outcome. No information on how pregnancy was assessed)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Pre specified protocol available (jRCTs041180140).Insufficient detail in protocol. Reported results unlikely to have been selected form multiple analyses at different time points as the*

Section	Question	Answer
		reported time points and method of analysis are what would be expected for the target outcomes)
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Some risk of variation across outcomes

Muzii, 2016

Bibliographic Reference	Muzii, Ludovico; Achilli, Chiara; Bergamini, Valentino; Candiani, Massimo; Garavaglia, Elisabetta; Lazzeri, Lucia; Lecce, Francesca; Maiorana, Antonio; Maneschi, Francesco; Marana, Riccardo; Perandini, Alessio; Porpora, Maria Grazia; Seracchioli, Renato; Spagnolo, Emanuela; Vignali, Michele; Benedetti Panici, Pierluigi; Comparison between the stripping technique and the combined excisional/ablative technique for the treatment of bilateral ovarian endometriomas: a multicentre RCT.; Human reproduction (Oxford, England); 2016; vol. 31 (no. 2); 339-44

Study details

Country/ies where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	January 2013 - April 2014
Inclusion criteria	Diagnosis by two separate ultrasounds more than 8 weeks apart of single endometrioma on both ovaries greater than 3cm, indicated for surgery due to pain and/or infertility and did not currently have or have a history of major chronic illness, were between 18 and 40 years and had a regular menstrual cycle. Type of infertility was not specified.
Exclusion criteria	People were excluded I at enrolment phase if in the previous 3 months they had received any treatment for endometriosis. People were excluded post first consultation if a bilateral endometrioma was not confirmed by the second ultrasound. People were excluded post randomisation if the endometriotic nature of the bilateral cysts was not confirmed by histology, if there was deviation from the planned

	surgical procedure. In addition, the presence of multiples of the same type of cyst on either ovary at surgery was a reason for exclusion.
Patient characteristics	Patient characteristics not reported split by intervention group as intervention groups were the same participants Age, mean (SD), years: 32.9 (5.7) Ethnicity (N): Not reported Setting: Multicentre‘
Intervention(s)/control	All participants underwent the stripping technique on one endometrioma on one ovary and the combined excision/ablation technique on one endometrioma on the opposite ovary. Laparoscopic stripping technique consisted of the cyst capsule being detached from the ovarian tissue by repeated diverging tractions applied using two atraumatic grasping forceps. versus Laparoscopic excision plus ablation technique. This was a combined procedure that included use of the stripping technique to treat 80-90% of the cysts surface from the adhesion site to the mesovarium and then bipolar coagulation to treat the remaining 10-20% that was attached to the ovarian hilus.
Duration of follow-up	Participants were followed up on day 2 to 4 of their menstrual cycle at 1, 3 and 6 months post-surgery
Sources of funding	None
Sample size	Randomised: n= 102 ovaries Laparoscopic stripping n= 51 Laparoscopic excision plus ablation n= 51
Other information	Antral follicle count of each ovary was assessed by transvaginal ultrasound between day 2 and day 4 of the participant’s menstrual cycle. Antral follicle count was defined as the number of follicles between 2 and 10 mm in diameter, observed on each side. Ovarian volume (OV) was calculated using the prolate ellipsoid formula (length × width × height × 0.523).

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic stripping group, , N = 40	Laparoscopic excision plus ablation group, , N = 40
Antral Follicle Count at 6 months Mean (SD)	4.8 (2.9)	4.4 (2.3)
Ovarian volume at 6 months Mean (SD)	8.4 (5)	6.5 (3.3)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants ovaries were randomised by a computer generated system. Allocation was concealed in sealed opaque envelopes which were opened when a participant's eligibility was confirmed by the laparoscopic findings)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(The participants and personnel involved in the follow up were blinded to which ovary had received which treatment. The surgical team were unable to be blinded but this did not lead to any deviations from intended intervention. Analysis assumed ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 40/51 participants. All 51 participants attended the follow-ups, but Antral follicle count and OV data was not considered for 11 participants at 6 months due to pregnancy (n= 4) or starting medical treatment for pain recurrence not responsive to NSAIDs (n=7))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome measurement for both outcomes was appropriate. Antral follicle count of each ovary was assessed by transvaginal ultrasound between day 2 and day 4 of the participant's menstrual cycle. Antral follicle count was defined as the number of follicles between 2 and 10 mm in diameter, observed on each side. Ovarian volume (OV) was calculated using the prolate ellipsoid formula (length × width × height × 0.523). The outcome assessor was blinded to the intervention each ovary received)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Protocol is available (ACTRN12614000653662). Analysis were in accordance with the protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Rius, 2020

Bibliographic Reference	Rius, Mariona; Gracia, Meritxell; Ros, Cristina; Martinez-Zamora, Maria-Angeles; deGuirior, Cristian; Quintas, Lara; Carmona, Francisco; Impact of endometrioma surgery on ovarian reserve: a prospective, randomized, pilot study comparing stripping with CO2 laser vaporization in patients with bilateral endometriomas.; The Journal of international medical research; 2020; vol. 48 (no. 6); 300060520927627

Study details

Country/ies where study was carried out	Spain
Study type	Randomised controlled trial (RCT)
Study dates	January 2017 - December 2017
Inclusion criteria	18 and 45 years who are indicated for surgical treatment due to pain and/or infertility had bilateral symptomatic endometriomas of greater than or equal to 3 cm and were in premenopausal status.
Exclusion criteria	If there was either a surgical suspicion of or evidence of premature ovarian failure. They were also excluded if they were suspected of having or had a history of cancer.
Patient characteristics	Patient characteristics not reported split by intervention group Age, mean (SD), years: 32.13 (6.56)

	Type of endometriosis Mixed population, presence of deep infiltrating endometriosis: n=10 Ethnicity (N): Not reported Setting: Hospital Clinic of Barcelona
Intervention(s)/control	Stripping group (laparoscopic decapsulation): the cleavage plane was identified, the cyst wall was stripped from the surrounding healthy ovarian tissue and sent for histologic examination. versus Laparoscopic drainage and ablation (laser vaporisation) group: drainage of the cyst contents followed by irrigation and inner wall inspection. The cyst was turned inside out, and the internal wall was vapourised using CO2 laser from the centre to the periphery at 12 W/cm3. A biopsy of the cyst wall was sent for histologic examination to confirm endometriosis. For cases of deep infiltrating endometriosis, the nodules were excised as usual practice.
Duration of follow-up	6 months
Sources of funding	Partial grant funding from Lumenis Ltd.
Sample size	Randomised: n= 32 ovaries Stripping group: n= 16 Laparoscopic drainage and ablation (laser vaporisation) group: n= 16

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic stripping group, , N = 16	Laparoscopic drainage plus ablation (laser vaporisation) group, , N = 16
Antral Follicle Count at baseline Mean (SD)	6.75 (4.1)	6.67 (6.3)
Antral Follicle Count at 6 months Mean (SD)	4.38 (3.3)	9.33 (6.2)
Ovarian volume at baseline Mean (SD)	98.51 (30.9)	67.33 (16.7)
Ovarian volume at 6 months Mean (SD)	19.98 (3.5)	27.1 (9.1)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was done via computer generated randomisation list. Allocation was concealed from participants and personnel involved in the study apart from the surgical team)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and personnel delivering the intervention (bar the surgical team) were blinded to the intervention. Analysis assumed ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Antral follicle count and ovarian volume were assessed by a transvaginal ultrasound by a sonographer who was blinded to the treatment allocation. Antral follicle count: the total number of antral follicles with a mean diameter of 2–9 mm. Ovarian volume was calculated using the prolate ellipsoid formula (length x width x height x 0.523))*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Reported results unlikely to have been selected form multiple analyses at different time points as the reported time points and method of analysis are what would be expected for the target outcomes)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of variation across outcomes

Shaltout, 2019

Bibliographic Reference	Shaltout, Mohamed F; Elsheikhah, Ahmad; Maged, Ahmed M; Elsherbini, Moutaz M; Zaki, Sherif S; Dahab, Sherif; Elkomy, Rasha O; A randomized controlled trial of a new technique for laparoscopic management of ovarian endometriosis preventing recurrence and keeping ovarian reserve.; Journal of ovarian research; 2019; vol. 12 (no. 1); 66

Study details

Country/ies where study was carried out	Egypt
Study type	Randomised controlled trial (RCT)
Study dates	October 2016 - January 2019
Inclusion criteria	Wwho were considered a candidate for treatment of ovarian endometriomas via conservative laparoscopic drainage or cyst wall excision, who between the ages of 20 and 35 years, who had unilateral and unilocular endometrioma greater than or equal to 5cm, endometriosis related pelvic pain, infertility or pelvic mass. Women with endometrioma that were developing rapidly and ovarian reserve of greater than 1 ng/ml anti mullerian hormone and an antral follicular count greater than 4. The trial also includes both primary and secondary infertility.
Exclusion criteria	Women were excluded from the trial if they had any contraindications for laparoscopic surgery or were unfit for surgery. They were also excluded if they had recurrent and bilateral endometrioma or suffered chronic diseases.
Patient characteristics	Age, mean (SD), years: Laparoscopic drainage: 28.2 (4.1) Laparoscopic cystectomy: 26.6 (4.4) Ethnicity (N): Not reported Type of endometriosis: Not reported Setting: Kasr El Aini hospital
Intervention(s)/control	Laparoscopic drainage: the contents of the cyst were removed by puncturing the cyst wall, the cyst was then washed with saline until all contents were removed. Cyst wall drainage was done via creating a small hole in the cyst wall followed by removal of the chocolate material and then the cyst cavity was flushed with saline solution. versus Laparoscopic cystectomy: Laparoscopic excision of the endometrioma cyst wall was done via creating a small hole in the cyst wall followed by content removal then separating the wall of the cyst from the ovary and washing the ovarian tissue with saline.
Duration of follow-up	2 years
Sources of funding	Self-funded

Sample size	Randomised n= 107 Laparoscopic drainage: n= 53 Laparoscopic cystectomy: n= 54
Other information	Serum anti-mullerian hormone was checked by ELISA (enzyme linked immunosorbent assay) technique, using Anti-mullerian hormone Gen II ELISA kits. Transvaginal ultrasound was done using a 7.5 MHz vaginal probe to assess the Antral follicle count (Number of visible follicles from 2 to 10 mm) in both the affected and healthy ovary. AMH Gen II ELISA kits Studies expected values : 0.9–9.5 ng/ml Minimum sensitivity detection limit: 0.08 ng/ml Range for this assay is 0.14 – 22.0 ng/ml. P value <0.001 AFC P value 0.007

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic drainage , , N = 50	Laparoscopic cystectomy, , N = 50
Pregnancy rate (n) No of events	n = 2	n = 5
Post-treatment Anti-Mullerian hormone percentage change Median (Range)	-33.5% (-65.3% to -23.6%)	-54.1% (-75.8% to -36.1%)
Post-treatment total Antral follicle count percentage change Median (Range)	-9.1% (-33.3% to 33.3%)	0% (-37.5% to 28.6%)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised using computer generated random numbers, no information on allocation concealment. Baseline differences did not suggest a problem with randomisation)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information as to whether participants were aware of their assigned intervention. Personnel delivering the intervention were aware of assigned intervention as they needed to be to perform the correct surgery. Analysis assumed ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 50/53 and 50/54 participants for drainage only and cystectomy only respectively. Those not included were lost during follow up or failed laparoscopy. Drainage only: n= 3 (failed laparoscopy n= 2, lost during follow up n= 1)Cystectomy only: n= 4 (failed laparoscopy n= 1, lost during follow up n= 3))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome measurement was appropriate. Serum Anti-mullerian hormone was measured by ELISA (enzyme linked immunosorbent assay) technique, using Gen II ELISA kits. Antral follicle count (Number of visible follicles from 2 to 10 mm) was measured via transvaginal ultrasound. pregnancy measurement not specified)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified protocol available (NCT02947724). Analyses were in accordance with the protocol reported data is unlikely to have been selected from multiple analyses due to the objective outcomes measured at different timepoints))*
Overall bias and Directness	Risk of bias judgement	*Some concerns*
Overall bias and Directness	Overall Directness	*Directly applicable*
Overall bias and Directness	Risk of bias variation across outcomes	*Some risk of bias across outcomes*

Sweed, 2019

Bibliographic Reference	Sweed, Mohamed S; Makled, Ahmed K; El-Sayed, Medhat A; Shawky, Mohamed E; Abd-Elhady, Hamdy A; Mansour, Ahmed M; Mohamed, Radwa M; Hemeda, Hossam; Nasr-Eldin, Eman A; Attia, Neveen S; Eltaieb, Ebtihal; Allam, Heba; Hussein, Ahmed; Ovarian Reserve Following Laparoscopic Ovarian Cystectomy vs Cyst Deroofing for Endometriomas.; Journal of minimally invasive gynecology; 2019; vol. 26 (no. 5); 877-882

Study details

Country/ies where study was carried out	Egypt
Study type	Randomised controlled trial (RCT)
Study dates	June 2013 - March 2017
Inclusion criteria	The inclusion criteria for this trial were people diagnosed by ultrasound with unilateral or bilateral endometriomas of greater than or equal to 3 cm diameter and aged between 18 and 35 years.
Exclusion criteria	People were excluded from the trial if they had evidence of polycystic ovary syndrome, premature ovarian failure (follicle stimulating hormone level greater than or equal to 40 IU/L), endocrine disorders that could affect ovarian function, presence of ascites, transvaginal ultrasound diagnosis of ovarian malignant disease and doppler ultrasound diagnosis of increase vascularity. They were also excluded if they used hormonal medications less than three months before surgery. People were also excluded if they had had previous ovarian surgery and had any contraindications to surgery.
Patient characteristics	Age, mean (SD), years: Laparoscopic cystectomy group: 27.1 (4.6) Laparoscopic drainage group: 25.5 (3.6) Ethnicity (N): not reported Type of endometriosis: stage/site/extent of involvement: (N): Not reported Setting: Ain Shams University Maternity Hospital
Intervention(s)/control	Laparoscopic cystectomy: The ovary and cyst wall were pulled gently in opposite directions using 2 nontraumatic grasping forceps. After the cyst wall was removed, selective minimal (15 W) bipolar coagulation of bleeding was performed. Versus

	Laparoscopic drainage: Part of the cyst wall was removed, the contents of the cyst were removed, and the cavity was flushed. If an active bleeding was identified the inner cyst wall was coagulated by the touch technique using 30 W bipolar coagulating forceps. Bipolar electrocoagulation (15 W) was used to control bleeding from small blood vessels in the ovarian bed and ovarian hilum.
Duration of follow-up	At 1 month and 1 year
Sources of funding	Not reported
Sample size	Randomised: n= 122 Laparoscopic cystectomy group: n= 61 Laparoscopic drainage group: n= 61
Other information	Anti-mullerian hormone serum samples were stored at −20˚C until being checked using commercially available ELISA kits. Antral follicle count was measured as the total number of identified follicles of 2 to 9 mm in diameter. Ovarian volume was calculated using the prolate ellipsoid formula: volume (cm3) = 0.5233 x anteroposterior diameter (cm) x transverse diameter (cm) x longitudinal diameter (cm).

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic cystectomy group, , N = 61	Laparoscopic drainage group, , N = 61
Preoperative Anti-mullerian hormone level (ng/mL) Mean (SD)	4.25 (0.87)	4.2 (1.69)
Preoperative Antral follicle count Mean (SD)	8.9 (2.6)	7.3 (2.8)
Preoperative ovarian volume (cm^3) Mean (SD)	8.3 (2)	7.4 (2.6)
Postoperative anti-mullerian hormone level (ng/mL) At 1 year. (Cystectomy n = 54, Cyst deroofing: n = 53) Mean (SD)	1.39 (0.76)	2.07 (1.49)
Postoperative Antral follicle count At 1 year. (Cystectomy n = 54, Cyst deroofing: n = 53) Mean (SD)	3.17 (1.36)	5.42 (2.68)
Postoperative ovarian volume (cm^3) At 1 year. (Cystectomy n = 54, Cyst deroofing: n = 53)	2.89 (1.5)	5.6 (2.56)

Outcome	Laparoscopic cystectomy group, , N = 61	Laparoscopic drainage group, , N = 61
Mean (SD)		

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participants were randomised using MedCalc version 13.2.2. No information on allocation concealment. Differences at baseline do not suggest a problem with randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Personnel delivering the intervention were aware of assigned intervention as it determined which type of surgery the participants received. It is not stated whether the participants were aware of their assigned intervention but as the groups had different surgery then it is possible that they were. Analysis assumed ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants at 1 month follow up. Data available for 54/61 and 53/61 Laparoscopic ovarian cystectomy and Laparoscopic cyst deroofing respectively at 1 year. Reasons for loss to follow up were becoming pregnant and generic loss to follow up. Laparoscopic ovarian cystectomy: n= 7 (lost to follow up n= 6, pregnant n=1) Laparoscopic cyst deroofing: n= 8 (lost to follow up n= 5, pregnant n=3))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome(s) measurement was objective. Anti-mullerian hormone was measured via venous blood samples, Antral follicle count was measured by the total number of follicles of 2-9mm in diameter identified and ovarian volume was calculated by the prolate ellipsoid formula. These are objective measurements so variation due to knowledge of assigned intervention is low)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified protocol available (NCT01808170) Insufficient analysis information in the protocol so reported results unlikely to have been selected form multiple analyses at different time points as the reported time points and method of analysis are what would be expected for the target outcomes)*
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of variation across outcomes

Xue, 2018

Bibliographic Reference	Xue, Huiling; Liu, Meiyun; Hao, Wanjiao; Li, Ye; Clinical evaluation of laparoscopic surgery combined with triptorelin acetate in patients with endometriosis and infertility.; Pakistan journal of medical sciences; 2018; vol. 34 (no. 5); 1064-1069

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	January 2013 - January 2016
Inclusion criteria	The inclusion criteria for this trial were people diagnosed with endometriosis by laparoscopy and pathological biopsy, they met the diagnostic criteria, and their family members sign informed consent. They had experienced infertility for over 1 year despite a normal sexual life. Type of endometriosis was symptomatic. Type of infertility not reported.
Exclusion criteria	People were excluded from the trial if they had malformations of the genitals, pelvic inflammatory masses, combined malignant ovarian tumours, previous pelvic surgery, adenomyosis, haemorrhagic disease, vital organ dysfunction and pregnant breastfeeding women. They have either experienced infertility caused by immune factors, semen abnormalities or other factors of the body. Additional exclusion criteria included participants who denied to participate, or the use of drugs viewed as a taboo and incomplete clinical data
Patient characteristics	Mean age in years (SD): Adhesion lysis plus Triptorelin: 26.71 (4.82) Adhesion lysis plus Gestrinone: 27.51 (5.12) Adhesion lysis plus Mifepristone: 26.12 (4.90) Ethnicity: Not reported

	Type of endometriosis: r-AFS stage I: (N) Adhesion lysis plus Triptorelin: 15 Adhesion lysis plus Gestrinone: 16 Adhesion lysis plus Mifepristone: 16 Type of endometriosis: r-AFS stage II: (N) Adhesion lysis plus Triptorelin: 20 Adhesion lysis plus Gestrinone: 21 Adhesion lysis plus Mifepristone: 20 Type of endometriosis: r-AFS stage III: (N) Adhesion lysis plus Triptorelin: 8 Adhesion lysis plus Gestrinone: 8 Adhesion lysis plus Mifepristone: 8 Type of endometriosis: r-AFS stage IV: (N) Adhesion lysis plus Triptorelin: 7 Adhesion lysis plus Gestrinone: 5 Adhesion lysis plus Mifepristone: 6 Setting: University hospital
Intervention(s)/control	All participants had a combination of Adhesion lysis surgery followed by laparoscopic drugs. Adhesion lysis: The surgery was performed under general anaesthesia: • Pneumoperitoneum was established • Pelvic cavity was inspected • Adhesion lysis was performed • Normal pelvic anatomy was then re-established • Sodium carbonate was used to prevent adhesion Adhesion lysis plus Triptorelin: 3.75 mg of Triptorelin acetate was injected monthly for three months. This began on day 5 of the first menstrual cycle post-surgery. versus Adhesion lysis plus Gestrinone: 2.5 mg of Gestrinone was taken orally twice a week for six months. This began on day 5 of the first menstrual cycle post-surgery.

	versus Adhesion lysis plus Mifepristone: 25 mg of Mifepristone was taken orally twice a day for three months. This began on day 5 of the first menstrual cycle post-surgery.
Duration of follow-up	2 years postoperatively
Sources of funding	Not funded
Sample size	Randomised n= 150 Adhesion lysis plus Triptorelin group: n= 50 Adhesion lysis plus Gestrinone group: n= 50 Adhesion lysis plusMifepristone group: n= 50
Other information	

Outcomes

Primary and secondary outcomes

Outcome	Adhesion lysis plus Triptorelin group, , N = 50	Adhesion lysis plus Gestrinone group, , N = 50	Adhesion lysis plus Mifepristone group, , N = 50
Clinical pregnancy No of events	n = 40	n = 24	n = 16
Live birth Vaginal and caesarean birth No of events	n = 38	n = 18	n = 10
Ectopic pregnancy No of events	n = 0	n = 1	n = 1
Miscarriage Reported as spontaneous abortion No of events	n = 2	n = 5	n = 5

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Study only states that a randomised single blind method was used, no information reported on allocation concealment, there were no differences at baseline that suggested a problem with randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(The study was single blinded so the participants were unlikely to be aware of their assigned intervention but as the interventions are different it is possible that they were, and this may have resulted in different between group behaviours. The personnel delivering the intervention were aware of the assigned intervention. Analysis assumed ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(All reported outcomes (clinical pregnancy, live birth (vaginal and caesarean birth), ectopic pregnancy and miscarriage) are objective outcomes, but are not defined or have method of measurement reported.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No pre specified protocol available. Reported results unlikely to have been selected form multiple analyses at different time points as the reported time points and method of analysis are what would be expected for the target outcomes)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

Yang, 2019

Bibliographic Reference	Yang, Yu; Zhu, Weidong; Chen, Shuqiu; Zhang, Guangyuan; Chen, Ming; Zhuang, Yuhong; Laparoscopic Surgery Combined with GnRH Agonist in Endometriosis.; Journal of the College of Physicians and Surgeons--Pakistan : JCPSP; 2019; vol. 29 (no. 4); 313-316

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	January 2015 - March 2016
Inclusion criteria	The inclusion criteria for this trial were people who were 25 to 35 years old, were eligible for laparoscopic surgery, not taking any contraception with a normal sexual life, but failed to conceive for over 1 year. They needed to have undergone laparoscopy or B-ultrasound to confirm endometriosis and had had a postoperative biopsy. Endometrioma cyst 3-10 cm.
Exclusion criteria	People were excluded from the trial if they had abnormal activity or function of the pelvic floor musculature, severe cardiovascular, hepatic or renal disease, recent use of hormones, painful or abnormal menstruation from other causes and were allergic to any of the medications administered in this study. They were also excluded for seminal abnormality or sexual dysfunction of their spouse.
Patient characteristics	Patient characteristics not reported split by intervention group Age, mean (SD), years: 28.73 (1.92) Ethnicity (N): Not reported Type of endometriosis: stage/site/extent of involvement: (N): Mixed population Endometriosis stage III: 80, Endometriosis stage IV: 50 Setting: Department of Urology, Zhongda Hospital
Intervention(s)/control	Laparoscopic surgery group: Laparoscopic surgery under anaesthesia using the three-hole method ectopic lesions were peeled off after cysts adhesions were removed under microscopy, and small lesions were electrocauterised. Where ovarian endometriosis was present ovarian cysts were removed. Laparoscopic surgery was performed three to seven days post menstruation. versus Laparoscopic surgery plusand GnRHa group: Laparoscopic surgery (as above) followed by six months of subcutaneous injections of 3.75 mg of gonadotropin-releasing hormone agonist (GnRHa) triptorelin acetate injection.
Duration of follow-up	2 years
Sources of funding	Medical Science and Technology Development Project of Nanjing City in China
Sample size	Randomised: n= 130

	Laparoscopic surgery group: n= 65 Laparoscopic surgery and GnRHa group: n= 65

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopic surgery group, , N = 65	Laparoscopic surgery plus GnRHa group, , N = 65
Pregnancy rate (n) No of events	n = 6	n = 20

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Study only states 'patients were randomly divided into the control group and the observation group'. No information given on who randomised the participants, so allocation concealment is unclear. Baseline characteristics are reported for the whole population, so it is unclear if there were any differences at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(No information on whether the participants were aware of their assigned intervention. Trialists delivering the intervention were likely to be aware of assigned intervention as the observation group received injections for 6 months after surgery and the rate of adverse reactions was higher in the control group (5 cases) compared to the observation group (4 cases). Analysis is assumed to be intention to treat)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome (pregnancy rate) measurement was not reported but it is unlikely to be influenced by the knowledge of assigned intervention as it is an objective outcome)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(The study does not provide evidence of a trial protocol, analysis intentions are not reported, and minimal detail is given on analysis method. Reported data is unlikely to have*

Section	Question	Answer
		been selected from multiple analyses due to the objective outcomes measured at different timepoints)
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Zhao, 2020

Bibliographic Reference	Zhao, Rui-Hua; Liu, Yong; Lu, Dan; Wu, Ying; Wang, Xiao-Yun; Li, Wei-Li; Zeng, Cheng; Meng, Qing-Wei; Lian, Feng-Mei; Zhou, Jun; Shi, Yun; Sun, Wei-Wei; Han, Qian; Tang, Yi; Shi, Guang; Chinese Medicine Sequential Therapy Improves Pregnancy Outcomes after Surgery for Endometriosis-Associated Infertility: A Multicenter Randomized Double-blind Placebo Parallel Controlled Clinical Trial.; Chinese journal of integrative medicine; 2020; vol. 26 (no. 2); 92-99

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	May 2014 - September 2017
Inclusion criteria	The inclusion criteria for this trial were people between the ages of 20 and 35 years who have laparoscopy confirmed endometriosis, give consent for randomisation to either of the trial interventions; Chinese medicine or placebo, and followed-up. They have either experienced infertility for a year or have not used contraception for more than 1 year. They have a 28 day (+/- 7 days) menstrual cycle, either none or mild bilateral obstruction of their fallopian tubes and an endometriosis fertility index score of greater than four. The measurement of their baseline follicle stimulating hormone is less than or equal to 10 mIU/L. Both primary and secondary infertility were included.
Exclusion criteria	People were excluded from the trial if they had adenomyosis, intrauterine adhesions, hyperprolactinemia, pelvic tuberculosis, endometrial tuberculosis, polycystic ovary syndrome, male factor infertility and abnormal thyroid function. They were also excluded if they had hysteromyoma of greater than four centimetres in diameter, history of severe drug allergy and if they were going through couple separation.

Patient characteristics	Age, mean (SD), years: Laparoscopy plusChinese medicine group: 29.2 (3.2) Laparoscopy plus placebo group: 29.7 (3.1) Ethnicity (N): Not reported Type of endometriosis: stage/site/extent of involvement: (N): Not reported Setting: Multicenter - 6 level III Grade A hospitals
Intervention(s)/control	Laparoscopy plus Chinese medicine group: All patients had undergone laparoscopic surgery and then went onto receive Chinese herbal medicine as part of their combination treatment. Before ovulation, they were treated Huoxue Xiaoyi Granule with Radix Bupleuri 10 g, Cyperus 10 g, Salvia Miltiorrhizae 20 g, Rhizoma Curcuma 10 g, and Radix Paeoniae rubra 10 g being the main medicines. After ovulation, they were treated with Bushen Zhuyun Granule, with Radix Bupleuri 10 g, Poria 15 g, Ligustrum lucidum 15 g, Eclipta 15 g, Rhizoma Atractylodes 15 g, and Radix dipsaci 30 g. being the main medicines. The Chinese medicine was given at 1–5 days after surgery. versus Laparoscopy plus placebo group: After surgery, this group was treated with placebo; granule medicines and placebo granule which in appearance, smell and taste were similar to the Chinese medicines given to the other group. The placebo granule was given one to five days post-surgery. Placebo was then given at a dose of two bags of granules, twice a day, 1 hour after meals. For both groups the therapy lasted for 6 menstrual cycles. The Chinese medicine or placebo were discontinued in the event of pregnancy. Drugs that were prohibited during this trial were, GnRH-a, clomiphene, gestrinone, human chorionic gonadotropin (HCG), human menopausal gonadotropin (HMG), danazol, other ovulation-promoting drugs and other hormone drugs.
Duration of follow-up	Not reported Study states patients were treated for 6 menstrual cycles or until pregnancy, pregnant patients were follow-up until delivery.
Sources of funding	Key Projects of the National Science and Technology Pillar Program during the 12th Five-Year Plan Period (No. 2014BAI10B08)
Sample size	Randomised: n= 204 Laparoscopy plus Chinese medicine group: n= 102 Laparoscopy plus placebo group: n= 102

Outcomes

Primary and secondary outcomes

Outcome	Laparoscopy plus Chinese medicine group, , N = 101	Laparoscopy plus placebo group, , N = 101
Clinical pregnancy	n = 45	n = 30

Outcome	Laparoscopy plus Chinese medicine group, , N = 101	Laparoscopy plus placebo group, , N = 101
No of events		
Live birth No of events	n = 35	n = 21
Ectopic pregnancy No of events	n = 1	n = 2
Miscarriage Reported as spontaneous abortion No of events	n = 4	n = 2

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomly assigned to the Laparoscopic surgery plus Chinese herbal medicine group or Laparoscopic surgery plus placebo group at a ratio of 1:1 using a central block randomization. Random numbers, based on the allocation sequence were generated using SAS statistical software. Allocation was concealed until the end of outcome assessment. The differences at baseline did not suggest a problem with randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Neither participant nor those delivering the intervention were aware of the assigned intervention as the trial was double blind. Analysis was ITT)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 202/204 participants. Analysis was ITT. Number of participants that did not receive the intervention/discontinued the intervention/lost to follow up in each group: Laparoscopic surgery plus Chinese herbal medicine group: 1/4/6, laparoscopic surgery plus Placebo group: 1/7/7)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Clinical pregnancy was measured by ultrasound. Live birth measurement method not reported but participants were followed until delivery. Ectopic pregnancy and miscarriage measurement method not reported. Live birth and clinical pregnancy outcome measurements*

Section	Question	Answer
		are objective so unlikely that assessment would have differed across groups however the use of assisted reproductive techniques may have increased the occurrence of those outcomes)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Trial protocol was registered (NCT02676713), analyses was in accordance with the protocol)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	The outcomes ectopic pregnancy and miscarriage are at low risk. There is evidence of the use of assisted reproductive treatment in the study (based on biochemical pregnancy and embryo arrest outcomes within the trial) but no details of this. Therefore, the outcomes of live birth and clinical pregnancy are at a high risk of bias as it is unclear how many of these were due to the spontaneous pregnancies post study interventions or assisted reproductive treatment.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

It was not possible to conduct any meta-analysis for this review question.

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Surgical interventions, Strata: Ovarian

Table 7: Evidence profile for comparison 1: Laparoscopic drainage versus Laparoscopic cystectomy; STRATA: Site: Ovarian (>3cm), depth: unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic drainage	Laparoscopic cystectomy	Relative (95% CI)	Absolute		
Post-operative Anti-mullerian hormone level (follow up 1 year) (better indicated by higher values)												
1 (Sweed 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	53	-	MD 0.68 higher (0.23 to 1.13 higher)	LOW **IMP BENEFIT (favouring drainage)**	IMPORTANT
Post-operative ovarian volume (follow up 1 year)(better indicated by higher values)												
1 (Sweed 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	54	53	-	MD 2.71 higher (1.91 to 3.51 higher)	MODERATE **IMP BENEFIT (favouring drainage)**	IMPORTANT
Post-operative Antral follicle count (follow up 1 year) (better indicated by higher values)												
1 (Sweed 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	54	53	-	MD 2.25 higher (1.44 to 3.06 higher)	MODERATE **IMP BENEFIT (favouring drainage)**	IMPORTANT

CI: confidence interval; RR: risk ratio; MD: mean difference
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (0.5x of the mean of the SD of both groups, for Post operative Anti-mullerian hormone = 0.56)

Table 8: Evidence profile for comparison 2: Laparoscopic cystectomy versus Laparoscopic drainage; STRATA: Site: Ovarian (>5cm), depth: unspecified

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laparoscopic cystectomy**	**Laparoscopic drainage**	**Relative (95% CI)**	**Absolute**		
Pregnancy rate (n) (follow up 1 year) (better indicated by higher values)												
1 (Shaltout 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/50 (10%)	2/50 (4%)	RR 2.5 (0.51 to 12.29)	60 more per 1000 (from 20 fewer to 452 more)	LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Post-treatment Anti-mullerian hormone percentage change (better indicated by higher values)												
1 (Shaltout 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	50	50	-	Median in Laparoscopic drainage -33.5 (-65.3 to -23.6), Median in Laparoscopic cystectomy -54.1 (-75.8 to -36.1)[3,4]	LOW	IMPORTANT
Post-treatment Antral follicle count percentage change (better indicated by higher values)												
1 (Shaltout 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	50	50	-	Median in Laparoscopic drainage -9.1 (-33.3 to 33.3), Median in Laparoscopic cystectomy 0 (-37.5 to 28.6)[3,4]	LOW	IMPORTANT

CI: confidence interval; n: number; RR: risk ratio
[1] 95% CI crosses 2 MIDs (0.8 and 1.25)
[2] Sample size <200
[3] Kruskal Wallis test was used due to non-normal distribution followed by pair wise analysis. All tests used <0.05 as their p-value. Laparoscopic drainage was the reference group.
[4] P values and significance between groups not reported

Table 9: Evidence profile for comparison 3: Sclerotherapy versus Laparoscopic cystectomy; STRATA: site: Ovarian (4-10cm), depth: unspecified

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sclerotherapy**	**Laparoscopic cystectomy**	**Relative (95% CI)**	**Absolute**		
Anti-mullerian hormone level (follow up 12 months) (better indicated by higher values)												
1 (Ghasemi-Tehrani 2022)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	35	-	MD 0.47 higher (0.05 lower to 0.99 higher)	LOW **NO EV. OF IMP. DIFF.**	IMPORTANT

CI: confidence interval; MD: mean difference
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for Anti-mullerian hormone at 12 months = 0.56)

Combination interventions, Strata: Ovarian

Table 10: Evidence profile for comparison 4: Laparoscopic cystectomy plus ablation and GnRHa versus Laparoscopic cystectomy plus ablation; STRATA: site: Ovarian (3-10cm), depth: unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic cystectomy plus ablation and GnRHa	Laparoscopic cystectomy plus ablation	Relative (95% CI)	Absolute		
Pregnancy rate (n) (follow up 2 years)(better indicated by higher values)												
1 (Yang 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/65 (30.8%)	6/65 (9.2%)	RR 3.33 (1.43 to 7.76)	215 more per 1000 (from 40 more to 624 more)	LOW **IMP BENEFIT (favouring cystectomy + ablation + GnRHa)**	CRITICAL

CI: confidence interval; n: number; RR: risk ratio; GnRHa: Gonadotrophin-releasing hormone analogue
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 11: Evidence profile for comparison 5: Laparoscopic drainage plus ablation (laser vaporisation) versus Laparoscopic stripping; STRATA: site: Ovarian (>3cm), depth: unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic drainage plus ablation (laser vaporisation)	Laparoscopic stripping	Relative (95% CI)	Absolute		
Antral follicle count (follow up 6 months) (better indicated by higher values)												
1 (Ruis 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16	16	-	MD 4.5 higher (1.12 to 7.88 higher)	MODERATE **IMP. BENEFIT (favouring drainage + ablation)**	IMPORTANT
Ovarian volume (follow up 6 months) (better indicated by higher values)												
1 (Ruis 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	16	16	-	MD 7.12 higher (2.34 to 11.9 higher)	MODERATE **IMP BENEFIT (favouring drainage + ablation)**	IMPORTANT

CI: confidence interval; MD: mean difference

[1] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for Antral follicle count at 6 months = 2.38)
[2] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for ovarian volume at 6 months = 3.15)

Table 12: Evidence profile for comparison 6: Laparoscopic cystectomy plus GnRHa versus Laparoscopic cystectomy plus Dienogest; STRATA: site: Ovarian (>4cm), depth: unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic cystectomy plus GnRHa	Laparoscopic cystectomy plus Dienogest	Relative (95% CI)	Absolute		
Pregnancy rate (n) (better indicated by higher values)												
1 (Muraoka, 2021)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/15 (40%)	4/17 (23.5%)	RR 1.7 (0.59 to 4.9)	165 more per 1000 (from 96 fewer to 918 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Anti-mullerian hormone serum 1 year post operatively (better indicated by higher values)												
1 (Muraoka, 2021)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	22	27	-	Median in Laparoscopic cystectomy + GnRHa 0.79 (0.48 to 2.2), Median in Laparoscopic cystectomy + Dienogest 1.3 (0.64 to 2.7)[4,5]	VERY LOW	IMPORTANT

CI: confidence interval; n: number; RR: risk ratio; GnRHa: Gonadotrophin-releasing hormone analogue
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)
[3] Sample size <200
[4] Students' t-test or Mann-Whitney. P-values of <0.05 was used.
[5] Non-significant result, p value = 0.1

Table 13: Evidence profile for comparison 7: Laparoscopic stripping versus Laparoscopic excision plus ablation; STRATA: site: Ovarian (>3cm), depth:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic stripping	Laparoscopic excision plus ablation	Relative (95% CI)	Absolute		
Antral follicle count (follow up 6 months) (better indicated by higher values)												
1 (Muzii, 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	40	-	MD 0.4 higher (0.75 lower to 1.55 higher)	MODERATE **NO EV. OF IMP. DIFF.**	IMPORTANT

Ovarian volume (follow up 6 months) (better indicated by higher values)												
1 (Muzii, 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	MD 1.9 higher (0.04 to 3.76 higher)	MODERATE NO EV. OF IMP. DIFF.	IMPORTANT

CI: confidence interval; MD: mean difference
[1] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for Antral follicle count at 6 months = 1.3)
[2] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for ovarian volume at 6 months = 2.07)

Table 14: Evidence profile for comparison 8: Laparoscopic drainage plus ablation (laser vaporisation) versus Laparoscopic cystectomy; STRATA: site: Ovarian (3-8 cm), depth: unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laparoscopic drainage plus ablation (laser vaporisation)**	**Laparoscopic cystectomy**	**Relative (95% CI)**	**Absolute**		
Pregnancy rate (n) (follow up mean 5.3 months) (better indicated by higher values)												
1 (Candiani 2018)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/30 (6.7%)	3/30 (10%)	RR 1.5 (0.27 to 8.34)	33 more per 1000 (from 49 fewer to 489 more)	VERY LOW NO EV. OF IMP. DIFF.	CRITICAL
Anti-mullerian hormone (follow up 3 months) (better indicated by higher values)												
1 (Candiani 2018)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	30	30	-	MD 0.1 higher (0.33 lower to 0.53 higher)	VERY LOW NO EV. OF IMP. DIFF.	IMPORTANT
Antral follicle count (follow up 3 months) (better indicated by higher values)												
1 (Candiani 2018)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	30	30	-	MD 2.3 higher (0.34 to 4.26 higher)	VERY LOW IMP BENEFIT (favouring drainage + ablation)	IMPORTANT

CI: confidence interval; n: number; RR: risk ratio; MD: mean difference
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to not all women desired pregnancy
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)
[4] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for Anti-mullerian hormone change over 3 months = 0.0.43)
[5] 95% CI crosses 1 MID (0.5x the mean of the SD of both groups, for Antral follicle count change over 3 months = 1.9)

Combination interventions, Strata: Deep not involving other structures

Table 15: Evidence profile for comparison 9: Anastrozole, LNG-IUD and Laparoscopy plus cystectomy versus Anastrozole, LNG-IUD and Drainage; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anastrozole, LNG-IUD and Laparoscopy plus cystectomy**	**Anastrozole, LNG-IUD and Drainage**	**Relative (95% CI)**	**Absolute**		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												
1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/8 (0%)	1/7 (14.3%)	POR 0.12 (0 to 5.96)	123 fewer per 1000 (from 143 fewer to 355 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; POR: Peto odds ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 16: Evidence profile for comparison 10: Anastrozole, LNG-IUD and Laparoscopy plus cystectomy versus LNG-IUD and Laparoscopy plus cystectomy; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anastrozole, LNG-IUD and Laparoscopy plus cystectomy**	**LNG-IUD and Laparoscopy plus cystectomy**	**Relative (95% CI)**	**Absolute**		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												
1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/8 (0%)	1/9 (11.1%)	POR 0.15 (0 to 7.67)	93 fewer per 1000 (from 111 fewer to 378 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; POR: Peto odds ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 17: Evidence profile for comparison 11: Anastrozole, LNG-IUD and Laparoscopy plus cystectomy versus LNG-IUD and Drainage; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anastrozole, LNG-IUD and Laparoscopy plus cystectomy**	**LNG-IUD and Drainage**	**Relative (95% CI)**	**Absolute**		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												

1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/8 (0%)	1/7 (14.3%)	POR 0.12 (0 to 5.96)	123 fewer per 1000 (from 143 fewer to 355 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; POR: Peto odds ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 18: Evidence profile for comparison 12: Anastrozole, LNG-IUD and Drainage versus LNG-IUD and Laparoscopy plus cystectomy; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anastrozole, LNG-IUD and Drainage versus LNG-IUD**	**LNG-IUD and Laparoscopy plus cystectomy**	**Relative (95% CI)**	**Absolute**		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												
1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/7 (14.3%)	1/9 (11.1%)	RR 1.29 (0.1 to 17.14)	32 more per 1000 (from 100 fewer to 1000 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 19: Evidence profile for comparison 13: Anastrozole, LNG-IUD and Drainage versus LNG-IUD and Drainage; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anastrozole, LNG-IUD and Drainage**	**LNG-IUD and Drainage**	**Relative (95% CI)**	**Absolute**		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												
1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/7 (14.3%)	1/7 (14.3%)	RR 1 (0.08 to 13.02)	0 fewer per 1000 (from 131 fewer to 1000 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 20: Evidence profile for comparison 14: LNG-IUD and Laparoscopy plus cystectomy versus LNG-IUD and Drainage; STRATA: site: Ovarian, depth: Deep not involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG-IUD and Laparoscopy plus cystectomy	LNG-IUD and Drainage	Relative (95% CI)	Absolute		
Pregnancies/deliveries (follow up mean 4.2 years) (better indicated by higher values)												
1 (Acien 2021)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/9 (11.1%)	1/7 (14.3%)	RR 0.78 (0.06 to 10.37)	31 fewer per 1000 (from 134 fewer to 1000 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio; LNG-IUD: Levonorgestrel-releasing intrauterine device
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CL crosses 2 MIDs (0.8 and 1.25)

Combination interventions, Strata: Mixed

Table 21: Evidence profile for comparison 15: Adhesion lysis plus Triptorelin versus Adhesion lysis plus Gestrinone; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adhesion lysis plus Triptorelin	Adhesion lysis plus Gestrinone	Relative (95% CI)	Absolute		
Clinical Pregnancy (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/50 (80%)	24/50 (48%)	RR 1.67 (1.21 to 2.3)	322 more per 1000 (from 101 more to 624 more)	VERY LOW **IMP. BENEFIT (favouring lysis + triptorelin)**	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/50 (76%)	18/50 (36%)	RR 2.11 (1.41 to 3.15)	400 more per 1000 (from 148 more to 774 more)	LOW **IMP. BENEFIT (favouring lysis + triptorelin)**	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/50 (0%)	1/50 (2%)	POR 7.39 (0.15 to 372.38)	20 more per 1000 (from 3 fewer to 70 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Miscarriage (follow up 2 years) (better indicated by lower values)												

1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/50 (4%)	5/50 (10%)	RR 0.4 (0.08 to 1.97)	60 fewer per 1000 (from 92 fewer to 97 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (1.25)
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 22: Evidence profile for comparison 16: Adhesion lysis plus Triptorelin versus Adhesion lysis plus Mifepristone; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adhesion lysis plus Triptorelin**	**Adhesion lysis plus Mifepristone**	**Relative (95% CI)**	**Absolute**		
Clinical Pregnancy (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/50 (80%)	16/50 (32%)	RR 2.5 (1.63 to 3.83)	480 more per 1000 (from 202 more to 906 more)	LOW **IMP. BENEFIT (favouring lysis + triptorelin)**	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/50 (76%)	10/50 (20%)	RR 3.8 (2.14 to 6.76)	560 more per 1000 (from 228 more to 1000 more)	LOW **IMP. BENEFIT (favouring lysis + triptorelin)**	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/50 (0%)	1/50 (2%)	POR 7.39 (0.15 to 372.38)	20 more per 1000 (from 3 fewer to 70 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Miscarriage (follow up 2 years) (better indicated by lower values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/50 (4%)	5/50 (10%)	RR 0.4 (0.08 to 1.97)	60 fewer per 1000 (from 92 fewer to 97 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 23: Evidence profile for comparison 17: Adhesion lysis plus Gestrinone versus Adhesion lysis plus Mifepristone; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adhesion lysis plus Gestrinone**	**Adhesion lysis plus Mifepristone**	**Relative (95% CI)**	**Absolute**		
Clinical Pregnancy (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/50 (48%)	16/50 (32%)	RR 1.5 (0.91 to 2.46)	160 more per 1000 (from 29 fewer to 467 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/50 (36%)	10/50 (20%)	RR 1.8 (0.92 to 3.5)	160 more per 1000 (from 16 fewer to 500 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/50 (2%)	1/50 (2%)	RR 1 (0.06 to 15.55)	0 fewer per 1000 (from 19 fewer to 291 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Miscarriage (follow up 2 years) (better indicated by lower values)												
1 (Xue 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/50 (10%)	5/50 (10%)	RR 1 (0.31 to 3.24)	0 fewer per 1000 (from 69 fewer to 224 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (1.25)
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 24: Evidence profile for comparison 18: GnRHa versus Laparoscopic excision; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GnRHa**	**Laparoscopic excision**	**Relative (95% CI)**	**Absolute**		
Pregnancies (follow up 2 years) (better indicated by higher values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77/120 (64.2%)	64/120 (53.3%)	RR 1.2 (0.97 to 1.49)	107 more per 1000 (from 16 fewer to 261 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/120 (55%)	54/120 (45%)	RR 1.22 (0.95 to 1.58)	99 more per 1000 (from 23 fewer to 261 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/120 (2.5%)	1/120 (0.83%)	RR 3 (0.32 to 28.43)	17 more per 1000 (from 6 fewer to 229 more)	VERY LOW	CRITICAL

											NO EV. OF IMP. DIFF.	

CI: confidence interval; RR: risk ratio; GnRHa: Gonadotrophin-releasing hormone analogue
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (1.25)
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 25: Evidence profile for comparison 19: GnRHa versus Laparoscopic excision plus GnRHa; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GnRHa	Laparoscopic excision plus GnRHa	Relative (95% CI)	Absolute		
Pregnancies (follow up 2 years) (better indicated by higher values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77/120 (64.2%)	70/120 (58.3%)	RR 1.1 (0.9 to 1.35)	58 more per 1000 (from 58 fewer to 204 more)	VERY LOW NO EV. OF IMP. DIFF.	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/120 (55%)	60/120 (50%)	RR 1.1 (0.86 to 1.4)	50 more per 1000 (from 70 fewer to 200 more)	VERY LOW NO EV. OF IMP. DIFF.	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/120 (2.5%)	2/120 (1.7%)	RR 1.50 (0.26 to 8.82)	8 more per 1000 (from 12 fewer to 130 more)	VERY LOW NO EV. OF IMP. DIFF.	CRITICAL

CI: confidence interval; RR: risk ratio; GnRHa: Gonadotrophin-releasing hormone analogue
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI cross 1 MID (1.25)
[3] 95% CI cross 2 MIDs (0.8 and 1.25)

Table 26: Evidence profile for comparison 20: Laparoscopic excision versus Laparoscopic excision plus GnRHa; STRATA: Site: Mixed (ovarian/peritoneum), depth: Deep involving other structures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic excision	Laparoscopic excision plus GnRHa	Relative (95% CI)	Absolute		
Pregnancies (follow up 2 years) (better indicated by higher values)												

1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[12]	none	64/120 (53.3%)	70/120 (58.3%)	RR 0.91 (0.73 to 1.15)	52 fewer per 1000 (from 157 fewer to 87 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Live Birth (follow up 2 years) (better indicated by higher values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/120 (45%)	60/120 (50%)	RR 0.9 (0.69 to 1.18)	50 fewer per 1000 (from 155 fewer to 90 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Ectopic Pregnancy (follow up 2 years) (better indicated by lower values)												
1 (Bala 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/120 (0.83%)	2/120 (1.7%)	RR 0.5 (0.05 to 5.44)	8 fewer per 1000 (from 16 fewer to 74 more)	VERY LOW **NO EV. OF IMP. DIFF.**	CRITICAL

CI: confidence interval; RR: risk ratio; GnRHa: Gonadotrophin-releasing hormone analogue
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (0.8)
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Combination interventions, Strata: Unspecified

Table 27: Evidence profile for comparison 21: Laparoscopy plus Chinese medicine versus Laparoscopy plus placebo; STRATA: Unspecified

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laparoscopy plus Chinese medicine**	**Laparoscopy plus placebo**	**Relative (95% CI)**	**Absolute**		
Clinical Pregnancy (better indicated by higher values)												
1 (Zhao 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/101 (44.6%)	30/101 (29.7%)	RR 1.5 (1.04 to 2.17)	149 more per 1000 (from 12 more to 348 more)	VERY LOW **IMP. BENEFIT (favouring laparoscopy + Chinese medicine)**	CRITICAL
Live Birth (better indicated by higher values)												
1 (Zhao 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35/101 (34.7%)	21/101 (20.8%)	RR 1.67 (1.05 to 2.65)	139 more per 1000 (from 10 more to 343 more)	VERY LOW **IMP. BENEFIT (favouring laparoscopy + Chinese medicine)**	CRITICAL
Ectopic Pregnancy (better indicated by lower values)												
1 (Zhao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/101 (0.99%)	2/101 (2%)	RR 0.5 (0.05 to 5.43)	10 fewer per 1000 (from 19 fewer to 88 more)	LOW **NO EV. OF IMP. DIFF.**	CRITICAL
Miscarriage (better indicated by lower values)												

1 (Zhao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/101 (4%)	2/101 (2%)	RR 2 (0.37 to 10.68)	20 more per 1000 (from 12 fewer to 192 more)	LOW **NO EV. OF IMP. DIFF.**	CRITICAL

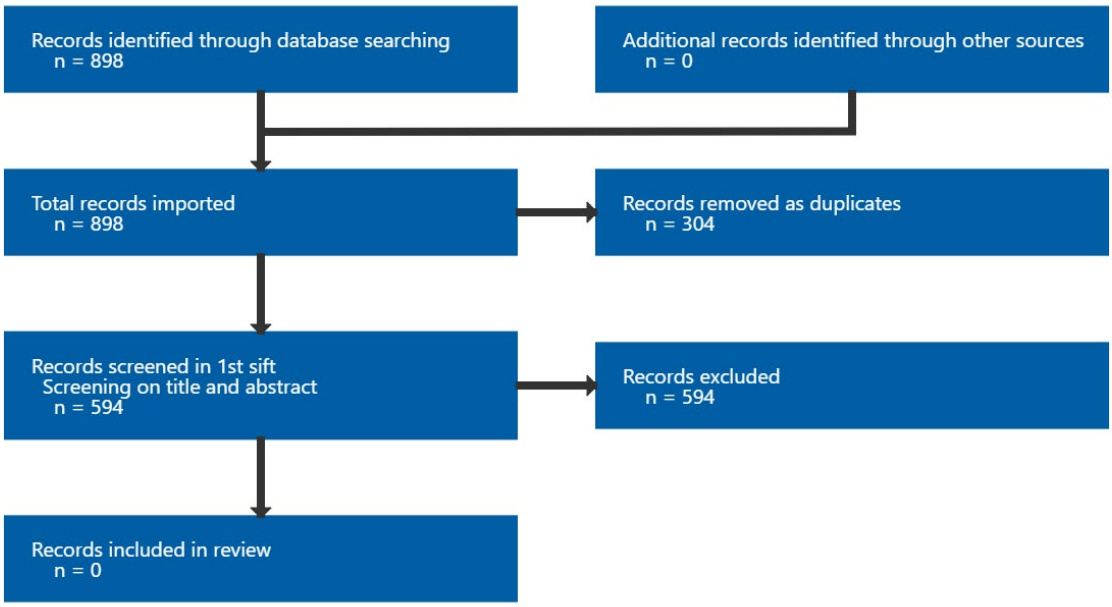
CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (1.25)
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

No economic evidence was identified which was applicable to this review question.

Figure 2: Study selection flowchart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

Excluded effectiveness studies

Study	Code [Reason]
Abu Hashim, Hatem (2016) Aromatase Inhibitors for Endometriosis-Associated Infertility; Do We Have Sufficient Evidence?. International journal of fertility & sterility 10(3): 270-277	- Non-systematic review
Adamyan, Leila, Kasyan, Victoria, Pivazyan, Laura et al. (2023) Laser vaporization compared with other surgical techniques in women with ovarian endometrioma: a systematic review and meta-analysis. Archives of gynecology and obstetrics 308(2): 413-425	- Systematic review, included studies checked for relevance
Akbaribazm, Mohsen; Goodarzi, Nader; Rahimi, Mohsen (2021) Female infertility and herbal medicine: An overview of the new findings. Food science & nutrition 9(10): 5869-5882	- Study design not relevant to this review protocol *Qualitative synthesis with no relevant references to endometriosis*
Akhkubekova, NK, Kaysinova, AS, Fedorov, AA et al. (2018) The role of the combined balneotherapeutic treatment as the 'add-back therapy' against the background of the anti-hormonal effects of the agonists of gonadotropin-releasing hormone in the women suffering from endometriosis genitalis externa. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury 95(5): 31-39	- Study not reported in English
Alborzi, Saeed, Poordast, Tahereh, Askary, Elham et al. (2022) The effect of vasopressin injection on ovarian reserve in patients with ovarian endometrioma: a randomized controlled trial. Reproductive biomedicine online 44(4): 651-658	- Study does not contain an intervention relevant to this review protocol *Vasopressin injection was not included in the protocol*
Alborzi, Saeed, Zahiri Sorouri, Ziba, Askari, Elham et al. (2019) The success of various endometrioma treatments in infertility: A systematic review and meta-analysis of prospective studies. Reproductive medicine and biology 18(4): 312-322	- Systematic review, included studies checked for relevance

Study	Code [Reason]
Ansaripour, S., Tamizi, N., Sadeghi, M.R. et al. (2022) Comparison of Triggering Final Oocyte Maturation with Follicle Stimulating Hormone Plus Human Chorionic Gonadotropin, versus Human Chorionic Gonadotropin Alonein Normoresponder Women Undergoing Intracytoplasmic Sperm Injection: A Randomized Clinical Trial. International Journal of Fertility and Sterility 16(3): 162-166	- Study does not contain a population relevant to this review protocol *Study does not state that the participants have or are suspected to have endometriosis and it excludes endometriosis grade 3 and 4*
Araujo, Raquel Silveira da Cunha, Maia, Sabina Bastos, Baracat, Clara Micalli Ferruzzi et al. (2022) Ovarian function following use of various hemostatic techniques during treatment for unilateral endometrioma: A randomized controlled trial. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 157(3): 549-556	- Comparator in study does not match that specified in this review protocol *Different hemostatic methods are not relevant to this review question*
Artymuk, NV; Danilova, LN; Tachkova, OA (2019) Possibilities of a combined approach to treating endometriosis-associated infertility. Akusherstvo i ginekologiya (russian federation) 2019(10): 148-156	- Study not reported in English
Asgari, Zahra, Rouholamin, Safoura, Hosseini, Reihaneh et al. (2016) Comparing ovarian reserve after laparoscopic excision of endometriotic cysts and hemostasis achieved either by bipolar coagulation or suturing: a randomized clinical trial. Archives of gynecology and obstetrics 293(5): 1015-22	- Published pre 2016 *EPPI stated 2016 but actual article states published in 2015*
Bafort, Celine, Beebeejaun, Yusuf, Tomassetti, Carla et al. (2020) Laparoscopic surgery for endometriosis. The Cochrane database of systematic reviews 10: cd011031	- Systematic review , included studies checked for relevance
Balan, Andreea, Moga, Marius Alexandru, Dima, Lorena et al. (2021) An Overview on the Conservative Management of Endometriosis from a Naturopathic Perspective: Phytochemicals and Medicinal Plants. Plants (Basel, Switzerland) 10(3)	- Non-systematic review
Bansal, Piyush, Khoiwal, Kavita, Malhotra, Neena et al. (2018) The Role of GnRH Analogues in Improving Outcome in Women Undergoing Superovulation and Intrauterine Insemination after Surgical Correction of Mild Endometriosis: A Randomized Controlled Trial. The Eurasian journal of medicine 50(2): 105-110	- Study does not contain an intervention relevant to this review protocol *The ART was not identical in both arms so therefore the impact of the endometriosis treatment on fertility outcomes cannot be separated from the ART*

Study	Code [Reason]
Barbara, G, Facchin, F, Meschia, M et al. (2017) When love hurts. A systematic review on the effects of endometriosis surgical and pharmacological treatments on female sexual functioning. Acta obstetricia et gynecologica Scandinavica	- Systematic review, included studies checked for relevance
Barra, Fabio, Scala, Carolina, Biscaldi, Ennio et al. (2018) Ureteral endometriosis: a systematic review of epidemiology, pathogenesis, diagnosis, treatment, risk of malignant transformation and fertility. Human reproduction update 24(6): 710-730	- Systematic review, included studies checked for relevance
Bavarsadkarimi, M., Omidi, S., Shahmoradi, F. et al. (2022) Comparison of two ovarian stimulation protocols among women with poor response: A randomized clinical trial. European Journal of Translational Myology 32(3): 10634	- Study does not contain a population relevant to this review protocol *Less than 20% of the participants had endometriosis*
Behbehani, S., Suarez-Salvador, E., Yi, J. et al. (2022) Pregnancy Rates after Surgical Resection of Deep Infiltrating Endometriosis in Patients with Infertility: A Systematic Review and Meta-Analysis. Journal of Gynecologic Surgery 38(1): 24-32	- Systematic review , included studies checked for relevance
Bila, Jovan, Dotlic, Jelena, Radjenovic, Svetlana Spremovic et al. (2022) Predictive Value of Basal Serum Progesterone for Successful IVF in Endometriosis Patients: The Need for a Personalized Approach. Journal of personalized medicine 12(10)	- Study design not relevant to this review protocol *Observational study (REporting of studies Conducted using Observational Routinely-collected health Data (RECORD))*
Brink Laursen, Jacob, Schroll, Jeppe B, Macklon, Kirsten T et al. (2017) Surgery versus conservative management of endometriomas in subfertile women. A systematic review. Acta obstetricia et gynecologica Scandinavica 96(6): 727-735	- Systematic review , included studies checked for relevance
Candiani, Massimo, Ottolina, Jessica, Salmeri, Noemi et al. (2023) Minimally invasive surgery for ovarian endometriosis as a mean of improving fertility: Cystectomy vs. CO2 fiber laser ablation what do we know so far?. Frontiers in surgery 10: 1147877	- Non-systematic review
Cantineau, Astrid Ep; Rutten, Anouk Gh; Cohlen, Ben J (2021) Agents for ovarian stimulation for intrauterine insemination (IUI) in	- Systematic review , included studies checked for relevance

Study	Code [Reason]
ovulatory women with infertility. The Cochrane database of systematic reviews 11: cd005356	
Cao, Xue, Chang, Hong-Yang, Xu, Jun-Yan et al. (2020) The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis. Reproductive biology and endocrinology : RB&E 18(1): 16	- Systematic review , included studies checked for relevance
Ceccaroni, Marcello, Clarizia, Roberto, Liverani, Stefano et al. (2021) Dienogest vs GnRH agonists as postoperative therapy after laparoscopic eradication of deep infiltrating endometriosis with bowel and parametrial surgery: a randomized controlled trial. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 37(10): 930-933	- Study does not contain any outcomes relevant to this review protocol *Study states that pregnancy rate was a secondary outcome but does not report any data*
Celik, Onder, Acet, Mustafa, Kucuk, Tansu et al. (2017) Surgery for Benign Gynecological Disorders Improve Endometrium Receptivity. Reproductive sciences (Thousand Oaks, Calif.) 24(2): 174-192	- Non-systematic review
Chang, Jui-Chun, Yi, Yu-Chiao, Chen, Ya-Fang et al. (2023) Presence of endometrioma decreased blastocyst formation rate but not impair Assisted Reproductive Technology (ART) outcome. Archives of gynecology and obstetrics 307(6): 2011-2020	- Study design not relevant to this review protocol *Retrospective study*
Chen, Innie, Veth, Veerle B, Choudhry, Abdul J et al. (2020) Pre- and postsurgical medical therapy for endometriosis surgery. The Cochrane database of systematic reviews 11: cd003678	- Systematic review , included studies checked for relevance
Chen, Yan, Wang, Hua, Wang, Saili et al. (2019) Efficacy of ten interventions for endometriosis: A network meta-analysis. Journal of cellular biochemistry 120(8): 13076-13084	- Systematic review , included studies checked for relevance
Choi, Chahien, Kim, Woo Young, Lee, Dong Hee et al. (2018) Usefulness of hemostatic sealants for minimizing ovarian damage during laparoscopic cystectomy for endometriosis. The journal of obstetrics and gynaecology research 44(3): 532-539	- Study design not relevant to this review protocol Comparison not in PICO

Study	Code [Reason]
Chung, Jacqueline Pui Wah, Law, Tracy Sze Man, Mak, Jennifer Sze Man et al. (2021) Ovarian reserve and recurrence 1 year post-operatively after using haemostatic sealant and bipolar diathermy for haemostasis during laparoscopic ovarian cystectomy. Reproductive biomedicine online 43(2): 310-318	- Study design not relevant to this review protocol *Randomisation broken*
Chung, Jpw, Law, Tsm, Chung, Chs et al. (2019) Impact of haemostatic sealant versus electrocoagulation on ovarian reserve after laparoscopic ovarian cystectomy of ovarian endometriomas: a randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 126(10): 1267-1275	- Comparator in study does not match that specified in this review protocol *Different hemostasis methods are not relevant to this protocol*
Cohen, Aviad; Almog, Benny; Tulandi, Togas (2017) Sclerotherapy in the management of ovarian endometrioma: systematic review and meta-analysis. Fertility and sterility 108(1): 117-124e5	- Systematic review , included studies checked for relevance
Cong, J., Sun, L., Zhuang, L. et al. (2019) Effects of high quality nursing on the immunological and psychological states of perioperative patients with endometriosis undergoing laparoscopic surgery. International Journal of Clinical and Experimental Medicine 12(7): 9082-9089	- Study does not contain any outcomes relevant to this review protocol
Cunha, Fernando Lorenzetti da, Arcoverde, Fernanda Vieira Lins, Andres, Marina Paula et al. (2021) Laparoscopic Treatment of Ureteral Endometriosis: A Systematic Review. Journal of minimally invasive gynecology 28(4): 779-787	- Systematic review, included studies checked for relevance
Darai, Emile; Cohen, Jonathan; Ballester, Marcos (2017) Colorectal endometriosis and fertility. European journal of obstetrics, gynecology, and reproductive biology 209: 86-94	Non-systematic review
Davar, R.; Neghab, N.; Naghshineh, E. (2018) Pregnancy outcome in delayed start antagonist versus microdose flare GnRH agonist protocol in poor responders undergoing IVF/ICSI: An RCT. International Journal of Reproductive BioMedicine 16(4): 255-260	- Study does not contain a population relevant to this review protocol *Study does not explicitly state that it included participants with endometriosis and it excluded participants with severe endometriosis*
de Souza Pinto, Luiz Paulo, Ferrari, Gustavo, Dos Santos, Isis Kelly et al. (2023) Evaluation of safety and effectiveness of gestrinone in the	- Systematic review , included studies checked for relevance

Study	Code [Reason]
treatment of endometriosis: a systematic review and meta-analysis. Archives of gynecology and obstetrics 307(1): 21-37	
Deckers, Paula, Ribeiro, Sergio Conti, Simoes, Ricardo Dos Santos et al. (2018) Systematic review and meta-analysis of the effect of bipolar electrocoagulation during laparoscopic ovarian endometrioma stripping on ovarian reserve. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 140(1): 11-17	- Systematic review , included studies checked for relevance
Decleer, W, Osmanagaoglu, K, Verschueren, K et al. (2016) RCT to evaluate the influence of adjuvant medical treatment of peritoneal endometriosis on the outcome of IVF. Human reproduction (Oxford, England) 31(9): 2017-23	- Published before end of 2016
Donatti, Lilian, Malvezzi, Helena, Azevedo, Bruna Cestari de et al. (2022) Cognitive Behavioral Therapy in Endometriosis, Psychological Based Intervention: A Systematic Review. Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia 44(3): 295-303	- Systematic review , included studies checked for relevance
Dong, Panpan; Ling, Lin; Hu, Lanyawen (2021) Systematic review and meta-analysis of traditional Chinese medicine compound in treating infertility caused by endometriosis. Annals of palliative medicine 10(12): 12631-12642	- Systematic review , included studies checked for relevance
Dong, Zhenzhu, An, Jian, Xie, Xi et al. (2019) Preoperative serum anti-Mullerian hormone level is a potential predictor of ovarian endometrioma severity and postoperative fertility. European journal of obstetrics, gynecology, and reproductive biology 240: 113-120	- Study design not relevant to this review protocol *Not randomised - participants were grouped based on pathological confirmation after surgery*
Ebrahimi, Mahbod, Akbari Asbagh, Firoozeh, Davari Tanha, Fatemeh et al. (2022) Co-treatment of gonadotropin and letrozole in infertile women with endometriosis: A double-blind randomized clinical trial. International journal of reproductive biomedicine 20(6): 483-490	- Comparator in study does not match that specified in this review protocol *Compares 2 different fertility treatments for women with endometriosis*

Study	Code [Reason]
Espejo-Catena, M.; Bano, I.; Puertos, J. (2016) Effectiveness of gonadotropin-releasing hormone antagonists in the management of multifollicular recruitment in intrauterine insemination cycles. Acta Medica International 3(1): 13-18	- Study does not contain a population relevant to this review protocol *Women with endometriosis were excluded*
Farag, Sara, Padilla, Pamela Frazzini, Smith, Katherine A et al. (2018) Management, Prevention, and Sequelae of Adhesions in Women Undergoing Laparoscopic Gynecologic Surgery: A Systematic Review. Journal of minimally invasive gynecology 25(7): 1194-1216	- Systematic review , included studies checked for relevance
Fenghua, Yu, Rong, Shao, Juan, Song et al. (2022) Effect of Mirena intrauterine device combined with GNRH-A on endometriosis, sex hormone level and carbohydrate antigen 125. Cellular and molecular biology (Noisy-le-Grand, France) 68(7): 22-26	- Study does not contain any outcomes relevant to this review protocol
Gao, Qiang, Shen, Lei, Jiang, Bei et al. (2022) Salvia miltiorrhiza-Containing Chinese Herbal Medicine Combined With GnRH Agonist for Postoperative Treatment of Endometriosis: A Systematic Review and meta-Analysis. Frontiers in pharmacology 13: 831850	- Systematic review , included studies checked for relevance
Gao, Xinyan, Zhang, Yousheng, Xu, Xinxin et al. (2022) Effects of ovarian endometrioma aspiration on in vitro fertilization-intracytoplasmic sperm injection and embryo transfer outcomes: a systematic review and meta-analysis. Archives of gynecology and obstetrics 306(1): 17-28	- Systematic review , included studies checked for relevance
Georgiou, Ektoras X, Melo, Pedro, Baker, Philip E et al. (2019) Long-term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis. The Cochrane database of systematic reviews 2019(11)	- Systematic review , included studies checked for relevance
Ghorbani, M.; Ashrafizaveh, A.; Azmoude, E. (2021) Effects of progestin contraceptive methods on sexual function in reproductive age women: a meta-analysis. Journal of Psychosomatic Obstetrics and Gynecology 42(1): 3-14	- Systematic review , included studies checked for relevance
Giannini, Andrea, Tebache, Linda, Noti, Giacomo et al. (2022) Impact on ovarian reserve and fertility using carbon dioxide laser for	- Non-systematic review

Study	Code [Reason]
endometriosis treatment: a systematic review. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 38(8): 617-622	
Grammatis, Alexandros Loukas; Georgiou, Ektoras X; Becker, Christian M (2021) Pentoxifylline for the treatment of endometriosis-associated pain and infertility. The Cochrane database of systematic reviews 8: cd007677	- Systematic review , included studies checked for relevance
Harris, A. and Tsaltas, J. (2017) Endometriosis and infertility: A systematic review. Journal of Endometriosis and Pelvic Pain Disorders 9(3): 139-149	- Non-systematic review
Hirsch, Martin, Duffy, James M N, Farquhar, Cindy M et al. (2022) Re: A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 158(1): 230-231	- Conference abstract
Hodgson, Ruth Mary, Lee, Hui Linn, Wang, Rui et al. (2020) Interventions for endometriosis-related infertility: a systematic review and network meta-analysis. Fertility and sterility 113(2): 374-382e2	- Systematic review , included studies checked for relevance
Huang, Y., Zhao, X., Chen, Y. et al. (2020) Miscarriage on Endometriosis and Adenomyosis in Women by Assisted Reproductive Technology or with Spontaneous Conception: A Systematic Review and Meta-Analysis. BioMed Research International 2020: 4381346	- Systematic review , included studies checked for relevance
Iwase, Akira, Nakamura, Tomoko, Kato, Nao et al. (2016) Anti-Mullerian hormone levels after laparoscopic cystectomy for endometriomas as a possible predictor for pregnancy in infertility treatments. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 32(4): 293-7	- Published Pre 2016 Article states published in 2015
Javaheri, Atiye, Ashkezar, Samane Kabirpour, Eftekhar, Maryam et al. (2021) Ovarian reserve in women with endometriosis under total cystectomy compared to partial cystectomy: A randomized clinical trial. International journal of reproductive biomedicine 19(7): 619-624	- Study does not contain an intervention relevant to this review protocol *Compares the same method with itself*

Study	Code [Reason]
Jiang, Meng; Hou, Wenxiao; Yu, Tao (2022) Clinical efficacy of laparoscopic surgery combined with drug therapy for endometriosis: A meta-analysis. Medical engineering & physics 107: 103866	- Systematic review, included studies checked for relevance
Kaponis, Apostolos, Chatzopoulos, Grigoris, Paschopoulos, Minas et al. (2020) Ultralong administration of gonadotropin-releasing hormone agonists before in vitro fertilization improves fertilization rate but not clinical pregnancy rate in women with mild endometriosis: a prospective, randomized, controlled trial. Fertility and sterility 113(4): 828-835	- Study does not contain an intervention relevant to this review protocol *Not receiving identical ART therefore cannot assume that fertility outcomes are as a result of the endometriosis treatment*
Karadag, Cihan, Yoldemir, Tevfik, Demircan Karadag, Sinem et al. (2020) The effects of endometrioma size and bilaterality on ovarian reserve. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 40(4): 531-536	- Study design not relevant to this review protocol *Participants were allocated to groups based on the type of Endometriomas (OMA)*
Kashani, L., Mohamadi, M., Fattah-Ravandi, B.-H. et al. (2018) Impact of prolonged versus OCP plus long protocol on IVF-ET outcomes in patients with grade III-IV endometriosis: A randomized clinical trial. Acta Medica Iranica 56(5): 308-313	- Study does not contain an intervention relevant to this review protocol *ART versus ART not treatment for endometriosis*
Khalifa, Eissa, Mohammad, Hashem, Abdullah, Ameer et al. (2021) Role of suppression of endometriosis with progestins before IVF-ET: a non-inferiority randomized controlled trial. BMC pregnancy and childbirth 21(1): 264	- Study does not contain an intervention relevant to this review protocol *Not receiving identical ART therefore cannot assume that fertility outcomes are as a result of the endometriosis treatment*
Khodarahmian, Mahshad, Amidi, Fardin, Moini, Ashraf et al. (2021) A randomized exploratory trial to assess the effects of resveratrol on VEGF and TNF-alpha 2 expression in endometriosis women. Journal of reproductive immunology 143: 103248	- Study does not contain any outcomes relevant to this review protocol *None of the outcomes included in the protocol are reported*
Kim, Gun Ha, Kim, Pyeong Hwa, Shin, Ji Hoon et al. (2022) Ultrasound-guided sclerotherapy for the treatment of ovarian endometrioma: an updated systematic review and meta-analysis. European radiology 32(3): 1726-1737	- Systematic review, included studies checked for relevance
Kitagawa, Yoshiyasu, Ishigaki, Asuka, Nishii, Rino et al. (2022) Randomized study of two	- Study does not contain a population relevant to this review protocol

Study	Code [Reason]
endo-knives for the traction-assisted endoscopic submucosal dissection of early esophageal squamous cell carcinoma. Scientific reports 12(1): 4619	*Population with histologically diagnosed or suspected squamous cell carcinoma*
Kostrzewa, Marta, Wilczynski, Jacek R, Glowacka, Ewa et al. (2019) One-year follow-up of ovarian reserve by three methods in women after laparoscopic cystectomy for endometrioma and benign ovarian cysts. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 146(3): 350-356	- Study design not relevant to this review protocol *Not a randomised trial participants were divided into two groups according to histopathological results*
Kramer, B., Andress, J., Neis, F. et al. (2023) Improvement in Fertility and Pain after Endometriosis Resection and Adhesion Prevention with 4DryField PH: Follow-up of a Randomized Controlled Clinical Trial. Journal of Clinical Medicine 12(10): 3597	- Study does not contain an intervention relevant to this review protocol *Adhesion prevention using a PH gel not endometriosis treatment*
Kumbasar, Serkan; Gul, Ozer; Sik, Aytek (2017) Evaluation of the effect of indomethacin and piroxicam administration before embryo transfer on pregnancy rate. The journal of obstetrics and gynaecology research 43(3): 536-542	- Study does not contain a population relevant to this review protocol *Participants with Endometriosis only made up 6.66% of the study population*
Lang, Jinghe, Yu, Qi, Zhang, Shulan et al. (2018) Dienogest for Treatment of Endometriosis in Chinese Women: A Placebo-Controlled, Randomized, Double-Blind Phase 3 Study. Journal of women's health (2002) 27(2): 148-155	- Study does not contain any outcomes relevant to this review protocol *None of the outcomes in the protocol are reported*
Lapointe, Mathilde, Pontvianne, Mary, Faller, Emilie et al. (2022) Impact of surgery for colorectal endometriosis on postoperative fertility and pregnancy outcomes. Journal of gynecology obstetrics and human reproduction 51(4): 102348	- Study design not relevant to this review protocol *Retrospective observational study*
Leonardi, Mathew, Gibbons, Tatjana, Armour, Mike et al. (2020) When to Do Surgery and When Not to Do Surgery for Endometriosis: A Systematic Review and Meta-analysis. Journal of minimally invasive gynecology 27(2): 390-407e3	- Systematic review, included studies checked for relevance
Li, Xueying, Lin, Jinli, Zhang, Linhao et al. (2023) Pretreatment of Dienogest for women with endometriosis in in vitro Fertilization: a	- Systematic review, included studies checked for relevance

Study	Code [Reason]
systematic review and meta-analysis. Gynecologic and obstetric investigation	
Li, Yantao; Li, Te; Song, Shilin (2017) Evaluation of Efficacy and Safety of Dan'e-Fukang Soft Extract in the Treatment of Endometriosis: A Meta-Analysis of 39 Randomized Controlled Trials Enrolling 5442 Patients. Evidence-based complementary and alternative medicine : eCAM 2017: 9767391	- Systematic review , included studies checked for relevance
Lier, M C I, Ozcan, H, Schreurs, A M F et al. (2020) Uterine bathing with sonography gel prior to IVF/ICSI-treatment in patients with endometriosis, a multicentre randomised controlled trial. Human reproduction open 2020(4): hoaa054	- Study does not contain an intervention relevant to this review protocol *Uterine bath is an add on to the fertility treatment not treatment for endometriosis*
Liu, Yijun, Gong, Han, Gou, Jinhai et al. (2021) Dienogest as a Maintenance Treatment for Endometriosis Following Surgery: A Systematic Review and Meta-Analysis. Frontiers in medicine 8: 652505	- Systematic review , included studies checked for relevance
Maged, Ahmed Mohamed, Rashwan, Hamsa, Mahmoud, Maryam et al. (2018) Effect of Prolonged GnRH Agonist Downregulation on ICSI Outcome in Patients With Endometriomas of Less Than 5 cm: A Randomized Controlled Trial. Reproductive sciences (Thousand Oaks, Calif.) 25(10): 1509-1514	- Study does not contain an intervention relevant to this review protocol *ART versus ART and not treatment for endometriosis*
Mehdizadehkashi, Abolfazl, Chaichian, Shahla, Rokhgireh, Samaneh et al. (2023) Does laparoscopic treatment of deep endometriosis improve sexual dysfunction. Caspian journal of internal medicine 14(2): 349-355	- Study does not contain any outcomes relevant to this review protocol *Study does not report any of the outcomes specified in the protocol*
Meng, Wenbin; Ta, Na; Wang, Fei (2019) Add-on effect of Guizhi Fuling formula to mifepristone for endometriosis: A meta-analysis of randomized controlled trials. Medicine 98(33): e16878	- Systematic review , included studies checked for relevance
Meresman, Gabriela F; Gotte, Martin; Laschke, Matthias W (2021) Plants as source of new therapies for endometriosis: a review of preclinical and clinical studies. Human reproduction update 27(2): 367-392	- Non-systematic review
Miller, Charles E (2021) The Endometrioma Treatment Paradigm when Fertility Is Desired: A	- Non-systematic review

Study	Code [Reason]
Systematic Review. Journal of minimally invasive gynecology 28(3): 575-586	
Miller, P B, Savaris, R F, Forstein, D A et al. (2016) Laparoscopic surgery improves pregnancy outcomes in women with suspected endometriosis with or without pathological confirmation. Clinical and experimental obstetrics & gynecology 43(1): 31-6	- Study design not relevant to this review protocol *Cohort study*
Mira, Ticiana A A, Yela, Daniela A, Podgaec, Sergio et al. (2020) Hormonal treatment isolated versus hormonal treatment associated with electrotherapy for pelvic pain control in deep endometriosis: Randomized clinical trial. European journal of obstetrics, gynecology, and reproductive biology 255: 134-141	- Study does not contain any outcomes relevant to this review protocol
Mojtahedi, M.F., Aref, S., Moini, A. et al. (2022) Natural cycle versus modified natural cycle for endometrial preparation in women undergoing frozen-thawed embryo transfer: An RCT. International Journal of Reproductive BioMedicine 20(11): 923-930	- Study does not contain a population relevant to this review protocol *Less than 10% of the population have endometriosis and the study excluded severe endometriosis (Stage 3 or more according to American Fertility Society)*
Moreno-Sepulveda, Jose, Romeral, Carolina, Nino, Geraldine et al. (2022) The Effect of Laparoscopic Endometrioma Surgery on Anti-Mullerian Hormone: A Systematic Review of the Literature and Meta-Analysis. JBRA assisted reproduction 26(1): 88-104	- Systematic review , included studies checked for relevance
Nankali, Anisodowleh, Kazeminia, Mohsen, Jamshidi, Parnian Kord et al. (2020) The effect of unilateral and bilateral laparoscopic surgery for endometriosis on Anti-Mullerian Hormone (AMH) level after 3 and 6 months: a systematic review and meta-analysis. Health and quality of life outcomes 18(1): 314	- Systematic review , included studies checked for relevance
Nickkho-Amiry, M, Savant, R, Majumder, K et al. (2018) The effect of surgical management of endometrioma on the IVF/ICSI outcomes when compared with no treatment? A systematic review and meta-analysis. Archives of gynecology and obstetrics 297(4): 1043-1057	- Systematic review , included studies checked for relevance
Ottolina, J, Posadzka, E, Ferrari, S et al. (2017) The impact on ovarian reserve of ovarian cystectomy versus laser vaporization in the treatment of ovarian endometrioma: a	- Conference abstract

Study	Code [Reason]
randomized clinical trial. Journal of minimally invasive gynecology 24suppl1(7): 34	
Park, Soo Jin, Seol, Aeran, Lee, Nara et al. (2021) A randomized controlled trial of ovarian reserve preservation and hemostasis during ovarian cystectomy. Scientific reports 11(1): 8495	- Comparator in study does not match that specified in this review protocol *Hemostasis sealant method post-laparoscopy not included in the protocol*
Peitsidis, Panagiotis, Tsikouras, Panagiotis, Lagana, Antonio Simone et al. (2023) A Systematic Review of Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The Evidence to Date. Drug design, development and therapy 17: 1329-1346	- Systematic review of systematic reviews, included studies checked for relevance
Peng, Chao; Huang, Yan; Zhou, Yingfang (2021) Dydrogesterone in the treatment of endometriosis: evidence mapping and meta-analysis. Archives of gynecology and obstetrics 304(1): 231-252	- Systematic review , included studies checked for relevance
Pirog, M., Kacalska-Janssen, O., Jach, R. et al. (2022) GnRH Antagonist Protocol Enhances Coagulation During Controlled Ovarian Stimulation for IVF. Reproductive Sciences 29(12): 3521-3531	- Study design not relevant to this review protocol *Case control study*
Pluchino, Nicola, Wenger, Jean-Marie, Petignat, Patrick et al. (2016) Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment. Human reproduction update 22(6): 762-774	- Non-systematic review
Reilly, S.J., Glanville, E.J., Dhorepatil, B. et al. (2019) The IVF-LUBE trial - a randomized trial to assess Lipiodol uterine bathing effect in women with endometriosis or repeat implantation failure undergoing IVF. Reproductive BioMedicine Online 38(3): 380-386	- Study does not contain an intervention relevant to this review protocol *IVF and lipiodol is not specified in the protocol*
Richard, Evelyne, Morin, Jessica, Murji, Ally et al. (2022) Effect of Postoperative Hormonal Suppression on Fertility in Patients With Endometriosis After Conservative Surgery: A Systematic Review and Meta-analysis. Obstetrics and gynecology 139(6): 1169-1179	- Systematic review , included studies checked for relevance
Riemma, Gaetano, De Franciscis, Pasquale, La Verde, Marco et al. (2023) Impact of the hemostatic approach after laparoscopic	- Systematic review , included studies checked for relevance

Study	Code [Reason]
endometrioma excision on ovarian reserve: Systematic review and network meta-analysis of randomized controlled trials. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 162(1): 222-232	
Rodriguez-Tarrega, Elisabet, Monzo, Ana M, Quiroga, Ramiro et al. (2020) Effect of GnRH agonist before IVF on outcomes in infertile endometriosis patients: a randomized controlled trial. Reproductive biomedicine online 41(4): 653-662	- Study does not contain an intervention relevant to this review protocol *The endometriosis treatment is part of the ART*
Roman, Horace, Bubenheim, Michael, Huet, Emmanuel et al. (2018) Conservative surgery versus colorectal resection in deep endometriosis infiltrating the rectum: a randomized trial. Human reproduction (Oxford, England) 33(1): 47-57	- Study does not contain any outcomes relevant to this review protocol *No outcomes in the protocol are reported*
Roman, Horace, Chanavaz-Lacheray, Isabella, Ballester, Marcos et al. (2018) High postoperative fertility rate following surgical management of colorectal endometriosis. Human reproduction (Oxford, England) 33(9): 1669-1676	- Study design not relevant to this review protocol *Randomisation broken - only uses a selected subset of population*
Roman, Horace, Huet, Emmanuel, Bridoux, Valerie et al. (2022) Long-term Outcomes Following Surgical Management of Rectal Endometriosis: Seven-year Follow-up of Patients Enrolled in a Randomized Trial. Journal of minimally invasive gynecology 29(6): 767-775	- Study design not relevant to this review protocol *Randomisation broken - only uses a selected subset of population*
Rossi, A Cristina and Prefumo, Federico (2016) The effects of surgery for endometriosis on pregnancy outcomes following in vitro fertilization and embryo transfer: a systematic review and meta-analysis. Archives of gynecology and obstetrics 294(3): 647-55	- Systematic review , included studies checked for relevance
Rouholamin, S and Ahmadpour-Ghazvini, F (2019) Evaluation of ovarian reserve after laparoscopic cystectomy for endometrioma with or without vasopressin injection: a randomized clinical trial study. Journal of isfahan medical school 37(514): 48-54	- Study not reported in English
Ruan, J.-Y., Zheng, Y.-X., Tian, Q. et al. (2021) Efficacy and safety of sanjiezhentong capsules, a traditional chinese patent medicine, on long-term management of endometriosis: A	- Study does not contain any outcomes relevant to this review protocol

Study	Code [Reason]
randomized controlled trial. Reproductive and Developmental Medicine 5(1): 15-22	
Seyedoshohadaei, F, Rezaie, M, Shahgheibi, S et al. (2020) Effect of surgery of endometrioma>=4 cm on fertility rate and pregnancy outcome in women with infertility: a randomized clinical trial. Iranian journal of obstetrics, gynecology and infertility 23(5): 10-17	- Study not reported in English
Shan, Jing, Cheng, Wen, Zhai, Dong-Xia et al. (2017) Meta-Analysis of Chinese Traditional Medicine Bushen Huoxue Prescription for Endometriosis Treatment. Evidence-based complementary and alternative medicine : eCAM 2017: 5416423	- Systematic review , included studies checked for relevance
Song, J.-Y., Gao, D.-D., Cao, X.-L. et al. (2021) The Role of Traditional Chinese Formula Ding-Kun Pill (DKP) in Expected Poor Ovarian Response Women (POSEIDON Group 4) Undergoing In Vitro Fertilization-Embryo Transfer: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Frontiers in Endocrinology 12: 675997	- Study does not contain a population relevant to this review protocol *Women were undergoing IVF treatment during the intervention*
Stojkovska, S., Dimitrov, G., Stojkovski, J. et al. (2020) The impact of laparoscopic treated endometrioma on the live birth rate in IVF/ICSI cycles compared with unexplained infertility: A prospective randomized study. Open Access Macedonian Journal of Medical Sciences 8: 160-165	- Study does not contain a population relevant to this review protocol *people with endometriosis versus people without*
Tamura, Hiroshi, Yoshida, Hiroaki, Kikuchi, Hiroyuki et al. (2019) The clinical outcome of Dienogest treatment followed by in vitro fertilization and embryo transfer in infertile women with endometriosis. Journal of ovarian research 12(1): 123	- Study does not contain an intervention relevant to this review protocol *Not receiving identical ART therefore cannot assume that fertility outcomes are as a result of the endometriosis treatment*
Tao, Xin, Chen, Lei, Ge, Shuqi et al. (2017) Weigh the pros and cons to ovarian reserve before stripping ovarian endometriomas prior to IVF/ICSI: A meta-analysis. PloS one 12(6): e0177426	- Non-systematic review
Tennfjord, Merete Kolberg; Gabrielsen, Rakel; Tellum, Tina (2021) Effect of physical activity and exercise on endometriosis-associated symptoms: a systematic review. BMC women's health 21(1): 355	- Systematic review , included studies checked for relevance

Study	Code [Reason]
Thomas, S, Sebastian, T, Karthikeyan, M et al. (2019) Effectiveness of spontaneous ovulation as monitored by urinary luteinising hormone versus induced ovulation by administration of human chorionic gonadotrophin in couples undergoing gonadotrophin-stimulated intrauterine insemination: a randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 126suppl4: 58-65	- Study does not contain a population relevant to this review protocol *only a subset of the people (less than 20%) had endometriosis*
Tian, Yizheng, Zhang, Lixia, Qi, Dan et al. (2023) Efficacy of long-term pituitary down-regulation pretreatment prior to in vitro fertilization in infertile patients with endometriosis: A meta-analysis. Journal of gynecology obstetrics and human reproduction 52(3): 102541	- Systematic review , included studies checked for relevance
Tomassetti, C, Beukeleirs, T, Conforti, A et al. (2021) The ultra-long study: a randomized controlled trial evaluating long-term GnRH downregulation prior to ART in women with endometriosis. Human reproduction (Oxford, England) 36(10): 2676-2686	- Study does not contain an intervention relevant to this review protocol *ART versus ART not treatment for endometriosis*
Touboul, Cyril, Ballester, Marcos, Dubernard, Gil et al. (2015) Long-term symptoms, quality of life, and fertility after colorectal resection for endometriosis: extended analysis of a randomized controlled trial comparing laparoscopically assisted to open surgery. Surgical endoscopy 29(7): 1879-87	- Published pre 2016
Tsiampa, Eleni, Spartalis, Eleftherios, Tsourouflis, Gerasimos et al. (2021) Impact on ovarian reserve after minimally invasive single-port laparoscopic ovarian cystectomy in patients with benign ovarian cysts: A systematic review and meta-analysis. International journal of clinical practice 75(12): e14875	- Systematic review , included studies checked for relevance
van Hoesel, Maaike Ht, Chen, Ya Li, Zheng, Ai et al. (2021) Selective oestrogen receptor modulators (SERMs) for endometriosis. The Cochrane database of systematic reviews 5: cd011169	- Systematic review , included studies checked for relevance
van Kessel, M., Tros, R., van Kuijk, S. et al. (2021) Transvaginal hydrolaparoscopy versus hysterosalpingography in the work-up for subfertility: a randomized controlled trial. Reproductive BioMedicine Online 43(2): 239-245	- Study does not contain a population relevant to this review protocol *Study excluded participants with endometriosis*

Study	Code [Reason]
Van Niekerk, Leesa; Weaver-Pirie, Bronwyn; Matthewson, Mandy (2019) Psychological interventions for endometriosis-related symptoms: a systematic review with narrative data synthesis. Archives of women's mental health 22(6): 723-735	- Systematic review , included studies checked for relevance
Vesali, S, Razavi, M, Rezaeinejad, M et al. (2020) Endometriosis fertility index for predicting non-assisted reproductive technology pregnancy after endometriosis surgery: a systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology 127(7): 800-809	- Systematic review , included studies checked for relevance
Vitagliano, A., Noventa, M., Saccone, G. et al. (2018) Endometrial scratch injury before intrauterine insemination: is it time to re-evaluate its value? Evidence from a systematic review and meta-analysis of randomized controlled trials. Fertility and Sterility 109(1): 84-96e4	- *Systematic review, included studies checked for relevance*
Wu, Clara Q, Albert, Arianne, Alfaraj, Sukainah et al. (2019) Live Birth Rate after Surgical and Expectant Management of Endometriomas after In Vitro Fertilization: A Systematic Review, Meta-Analysis, and Critical Appraisal of Current Guidelines and Previous Meta-Analyses. Journal of minimally invasive gynecology 26(2): 299-311e3	- Systematic review , included studies checked for relevance
Xia, Ju-Feng, Inagaki, Yoshinori, Zhang, Jian-Feng et al. (2017) Chinese medicine as complementary therapy for female infertility. Chinese journal of integrative medicine 23(4): 245-252	- Non-systematic review
Xu, Zhihui, Chen, Wenming, Chen, Chune et al. (2019) Effect of intrauterine injection of human chorionic gonadotropin before frozen-thawed embryo transfer on pregnancy outcomes in women with endometriosis. The Journal of international medical research 47(7): 2873-2880	- Study design not relevant to this review protocol *Retrospective cohort study*
Xue, Hui-Ling, Yu, Ning, Wang, Jing et al. (2016) Therapeutic effects of mifepristone combined with Gestrinone on patients with endometriosis. Pakistan journal of medical sciences 32(5): 1268-1272	- Published before end of 2016

Study	Code [Reason]
Yin, W Q (2016) Treating 49 cases of endometriosis with laparoscopy in combination with chinese medicine. Western journal of traditional chinese medicine [xi bu zhong yi yao za zhi] 29(8): 115-117	- Study not reported in English
Yin, Wei-Wei, Huang, Chang-Chang, Chen, Yi-Ru et al. (2022) The effect of medication on serum anti-mullerian hormone (AMH) levels in women of reproductive age: a meta-analysis. BMC endocrine disorders 22(1): 158	- Systematic review included studies checked for relevance -
Younis, Johnny S, Shapso, Nora, Fleming, Richard et al. (2019) Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: a systematic review and meta-analysis. Human reproduction update 25(3): 375-391	- Systematic review , included studies checked for relevance
Yu, Lu; Sun, Yunming; Fang, Qiongyan (2022) Efficacy of Laparoscopic Surgery Combined With Leuprorelin in the Treatment of Endometriosis Associated With Infertility and Analysis of Influencing Factors for Recurrence. Frontiers in surgery 9: 873698	- Data not reported in an extractable format or a format that can be analysed *Data reported in graphs with axis' without precise scales*
Zahiri, Z., Sarrafzadeh, Y., Leili, E.K.N. et al. (2021) Success Rate of Hysteroscopy and Endometrial Scratching in Repeated Implantation Failure: A Randomized Controlled Clinical Trial. Galen Medical Journal 10: e1399	- Study does not contain a population relevant to this review protocol *Population was participants with a history of ICSI failure*
Zhang, Chun-Hua; Wu, Ling; Li, Pei-Quan (2016) Clinical study of the impact on ovarian reserve by different hemostasis methods in laparoscopic cystectomy for ovarian endometrioma. Taiwanese journal of obstetrics & gynecology 55(4): 507-11	- Systematic review , included studies checked for relevance
Zhang, Kemei, Huang, Shisi, Xu, Haiyan et al. (2022) Effectiveness of gonadotrophin-releasing hormone agonist therapy to improve the outcomes of intrauterine insemination in patients suffering from stage I-II endometriosis. Annals of medicine 54(1): 1330-1338	- Study design not relevant to this review protocol *Study is a retrospective cohort*
Zhang, Y C (2016) Clinical effect observation of Chinese medicine periodic therapeutic in the treatment of endometriosis infertility. Chinese community doctors[zhong guo she qu yi shi] 32(13): 99101	- Study not reported in English

Study	Code [Reason]
Zhang, Y X (2016) Effect of mifepristone in the different treatments of endometriosis. Clinical and experimental obstetrics & gynecology 43(3): 350-3	- Published before end of 2016
Zhang, Yanxia, Li, Meiqing, Li, Lian et al. (2021) Randomized Controlled Study of the Effects of DHEA on the Outcome of IVF in Endometriosis. Evidence-based complementary and alternative medicine : eCAM 2021: 3569697	- Full text paper not available *Article has been Retracted*
Zhang, Ying, Zhang, Shiqian, Zhao, Zeyi et al. (2022) Impact of cystectomy versus ablation for endometrioma on ovarian reserve: a systematic review and meta-analysis. Fertility and sterility 118(6): 1172-1182	- Systematic review , included studies checked for relevance
Zhao, C Y; Yu, L L; Wang, H (2016) Analysis on clinical effect of laparoscopy combined with Dingkundan in treatment of endometriosis-induced infertility. Maternal and child health care of china [zhong guo fu you bao jian] 31(4): 796-798	- Study not reported in English
Zheng, X., Wang, F., Liu, C. et al. (2022) Effects of Chinese Herbal Medicine on ovarian functions in the patients with endometriosis: A systematic review and meta-analysis of randomized controlled trials. European Journal of Integrative Medicine 51: 102125	- Systematic review , included studies checked for relevance
Zhou, Lu, Fu, Jing, Liu, Dong et al. (2022) Ovulation induction with clomiphene citrate or letrozole following laparoscopy in infertile women with minimal to mild endometriosis: a prospective randomised controlled trial. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 42(2): 316-321	- Study does not contain an intervention relevant to this review protocol *ART versus ART not treatment for endometriosis*

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of the following hormonal medical treatments, surgery, combination treatments (hormonal medical treatment and surgery) and non-pharmacological treatments for improving pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis

B.1.1 Research recommendation

What is the effect of different doses and durations of hormonal treatments given either before, after, or both before and after surgery on fertility outcomes in people with endometriosis where fertility is a priority?

B.1.2 Why this is important

Endometriosis is known to impair fertility and therefore treatments which not only reduce the symptomatic disease but also increase fertility would be very valuable in the management of endometriosis. Surgery is known to improve fertility in endometriosis but the addition of hormonal treatments has led to mixed results, and there are also unknown factors relating to the dose, duration of therapy and timing in relation to surgery. Since the evidence in this area is limited, and the effectiveness is varied, there is a need for more evidence of high quality to assess the impact of hormonal treatments and surgery as a combined intervention for improving pregnancy rates in people with endometriosis.

B.1.3 Rationale for research recommendation

Table 4: Research recommendation rationale

Importance to 'patients' or the population	Endometriosis affects up to 10% of women, and up to 50% of women with fertility problems may have endometriosis. Any treatment which improves fertility would therefore benefit a large number of women.
Relevance to NICE guidance	Use of hormones have been considered in this review but there is a lack of high quality data and inconclusive effectiveness. Evidence in this area would allow clearer recommendations to be made.
Relevance to the NHS	The outcome would affect the types of treatment available on the NHS to people with endometriosis where fertility is a priority and surgery is being considered. This may prevent people needing to seek more expensive fertility treatments such as IVF.
National priorities	Treatment of endometriosis is a priority in the Woman's Health Strategy.
Current evidence base	Minimal and conflicting evidence
Equality considerations	None identified.

B.1.4 Modified PICO table

Table 5: Research recommendation modified PICO table

Population	Inclusion:

	• Sub fertile women desiring pregnancy, between menarche and menopause with endometriosis of any stage or severity. • Women with a suspected diagnosis of endometriosis desiring pregnancy • Recurrent and asymptomatic endometriosis. • Both primary and secondary infertility. Exclusion: • Women with chronic pelvic pain known to be due to causes other than endometriosis • Those suspected based solely on a CA-125 test with no other contributing factor • Women receiving additional fertility treatments • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months
Intervention	• Any hormonal medical treatment administered before, after or both before and after any surgical treatment
Comparator	**Hormonal medical treatments** • Hormonal treatment before and/or after surgery vs placebo before and/or after surgery • Hormonal treatment before and/or after surgery vs hormonal treatment alone • Hormonal treatment before and/or after surgery vs surgery alone • Hormonal medical treatment A before and/ or after surgery vs hormonal medical treatment B before and/or after surgery • Hormonal treatment before and/or after surgery vs no treatment
Outcome	• Live birth • Clinical pregnancy (spontaneous) • Miscarriage • Ectopic pregnancy • Time from intervention to conception • Ovarian reserve as measured by antral follicle count (AFC)/ovarian volumes • Anti-mullerian hormone (AMH)
Study design	• Systematic reviews of RCTs • RCTs
Timeframe	• Follow up for minimum 2 years
Additional information	• Dose-ranging studies would be useful