Interventions for endometriosis-related infertility: a systematic review and network meta-analysis

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Objective: To compare the effectiveness of different treatments for women with endometriosis-related infertility.
Design: A systematic review and network meta-analysis of randomized controlled trials (RCTs).
Setting: Not applicable.
Patient(s): Women with endometriosis confirmed by laparoscopy with associated infertility.
Intervention(s): An extensive electronic search of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, ClinicalTrials.gov, and Embase.
Main Outcome Measure(s): Clinical pregnancy, live birth rate, miscarriage, and adverse events.
Result(s): A total of 4,252 trials/abstracts were identified through the literature search, of which we included 36 trials in the systematic review and 26 trials reporting on 2,245 women with endometriosis-related infertility in the network meta-analysis. Network meta-analysis showed that compared with placebo, surgical laparoscopy alone (odds ratio = 1.63; 95% confidence interval, 1.13–2.35) or GnRH agonist alone (odds ratio = 1.68; 95% confidence interval, 1.07–2.46) results in higher odds of pregnancy. The evidence on the other interventions versus placebo or on the secondary outcomes including live birth, miscarriage, and adverse events is insufficient.
Conclusion(s): The most important conclusion is that more RCTs are needed to clarify the relative effectiveness of treatments for endometriosis-related infertility, ideally comparing interventions to existing recommended interventions such as surgical laparoscopy. In addition, further RCTs comparing IVF and IUI to other treatments are essential.
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El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, infertility, interventions

Endometriosis is a common gynecological condition, an inflammatory disease process characterized by endometrium-like tissue outside the uterus that is associated with pelvic pain and/or infertility (1). Although it has been over 300 years since endometriosis was first described, there is still much that is unknown about the disease (2). It affects women of reproductive age and has a prevalence of up to 10% of the general population (3). There is an association between endometriosis and infertility, with the disorder being a contributing cause of a couple's inability to become pregnant in approximately 25%–40% of cases (3, 4), and it is estimated that 30%–50% of women with endometriosis will have difficulty conceiving (5). Although this strong link between endometriosis and infertility is well established, the exact mechanism by which this occurs is unclear, and it is likely that a number of processes are in play (6, 7). An effect on the quality and quantity of oocytes in women

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with endometriosis is becoming more evident (8), with this further compounded by the disease-related inflammation that alters the pelvic environment and may be leading to poorer egg quality and hence embryo development, impaired implantation receptivity (9), and possibly even impaired sperm performance (6). In addition, with more severe endometriosis there may be anatomical damage to ovaries (including impact on ovarian reserve) and fallopian tubes that may block the transport of gametes and embryos (2).

Much work has been done in the field of endometriosis management with the development of treatment interventions, both alone and in conjunction with medically assisted reproduction aimed at improving a woman's fertility (10). Fertility treatment options include laparoscopic surgery and medical treatments, sometimes in combination, in addition to medically assisted reproduction, with a number of other potential emerging fertility treatment options identified (11).

It is difficult to advise women on their best approach to treatment as many of the therapies have not been directly compared in randomized controlled trials (RCTs), and therefore there is no direct evidence to identify the optimum treatment strategy. Multiple treatment comparison meta-analysis, or network meta-analysis, compares multiple treatments in one statistical model (12–14). This method makes it possible to guide treatment decision-making through the provision of a hierarchy of effectiveness of the treatment options. This model will often allow selection of the most optimal therapy for women with a clinical problem where there are numerous treatment options and where comparative effectiveness of treatments is unclear.

A systematic review and network meta-analysis was undertaken to compare the effectiveness of different treatment options for women with laparoscopic proven endometriosis experiencing infertility. The aim of this review was to best identify the ideal strategy for first-line treatment.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for network meta-analysis for conducting and reporting the study (15). An extensive electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, ClinicalTrials.gov, and Embase was undertaken for RCTs. The search strategies were based on combinations of endometriosis and any intervention, using both free words and index terms (Supplemental App. 1, available online). The search strategy was developed by a clinician experienced in performing systematic reviews and meta-analysis. If indicated, we sought additional trial details or trial protocols to establish potential studies' eligibilities. A search of previously published Cochrane systematic reviews on endometriosis was also performed to detect any additional studies. There were no language restrictions applied. Our most recent search was performed on March 30, 2019.

We included published and unpublished RCTs comparing one or more surgical or medical treatment options with placebo, with no treatment, or with each other for endometriosis in the setting of infertility.

Studies were excluded if the diagnosis of endometriosis was not confirmed by laparoscopy, if they only included women with endometriomas, if they only made comparisons of different ways of undertaking the same treatment intervention (such as comparing different stimulation protocols for IVF), or if they failed to report on fertility outcomes. The decision to exclude trials that examined only women with infertility and endometriomas was made as we considered that this clinical situation justified a systematic review and network meta-analysis as a stand-alone topic, as the clinical management around this particularly takes into account the concern and question of ovarian reserve and success in the setting of fertility treatment.

Women in the included studies were classified as laparoscopically treated previously, not laparoscopically treated previously, combination of laparoscopically treated and not laparoscopically treated previously, and treatment status unknown/unspecified. Crossover trials were included only if precrossover data were available. Study authors were contacted for further information if required. Unfortunately, the definition used and duration of infertility were not always defined in the studies.

Data Extraction and Assessment of Risk of Bias

Two reviewers (R.M.H. and H.L.L.) independently assessed the eligibility of all identified citations and extracted data from original trial reports using a specifically designed form that captured information on study design, trial setting, patient characteristics (including inclusion criteria, age, body mass index, duration of infertility, stage of endometriosis, previous treatments), sample sizes, and details of endometriosis treatment options and outcomes. Disagreements were referred to a third reviewer (N.J.) to reach consensus.

The primary outcome was clinical pregnancy. Clinical pregnancy was defined as either pregnancy visualized at ultrasonography of one or more gestational sacs or definitive clinical proof of pregnancy (positive blood or urine test for hCG). For the network meta-analysis we looked only at spontaneous pregnancy (excluding the assisted reproduction trials). Secondary outcomes were live birth, miscarriage, and adverse events. Live birth was defined as delivery of a live fetus after 20 weeks of completed gestation. We had initially planned for live birth to be a primary outcome (as per the PROSPERO registration), but due to the lack of reporting, it was decided to change this to a secondary outcome.

Study quality was assessed by two reviewers (R.M.H. and H.L.L.) using methodology and categories described in the Cochrane Collaboration Handbook. Again, in case of disagreement, a third reviewer (N.J.) was consulted to reach consensus. The tool used for assessing risk of bias addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain is assigned a judgment relating to the risk of bias for that study classified as low risk, high risk, or unclear.

Data Synthesis and Statistical Analysis

A network meta-analysis was conducted to simultaneously compare 14 treatment options for endometriosis versus placebo or no treatment for each outcome. Network plots were constructed to illustrate the geometry of the network (16). Diagnostic laparoscopy, placebo, and no treatment were considered as the same node in network meta-analysis, while laparoscopic ablation and resection were considered as laparoscopic surgery. All network meta-analyses were conducted with a random effects multivariate meta-analysis model using the "network" suite in Stata software (ver. 15.0, Stata Corp.) (16, 17). Where direct data were available, pairwise meta-analyses in random effects model were also performed. Network inconsistency was evaluated in a design-by-treatment interaction test (18) and side-splitting approach (19).

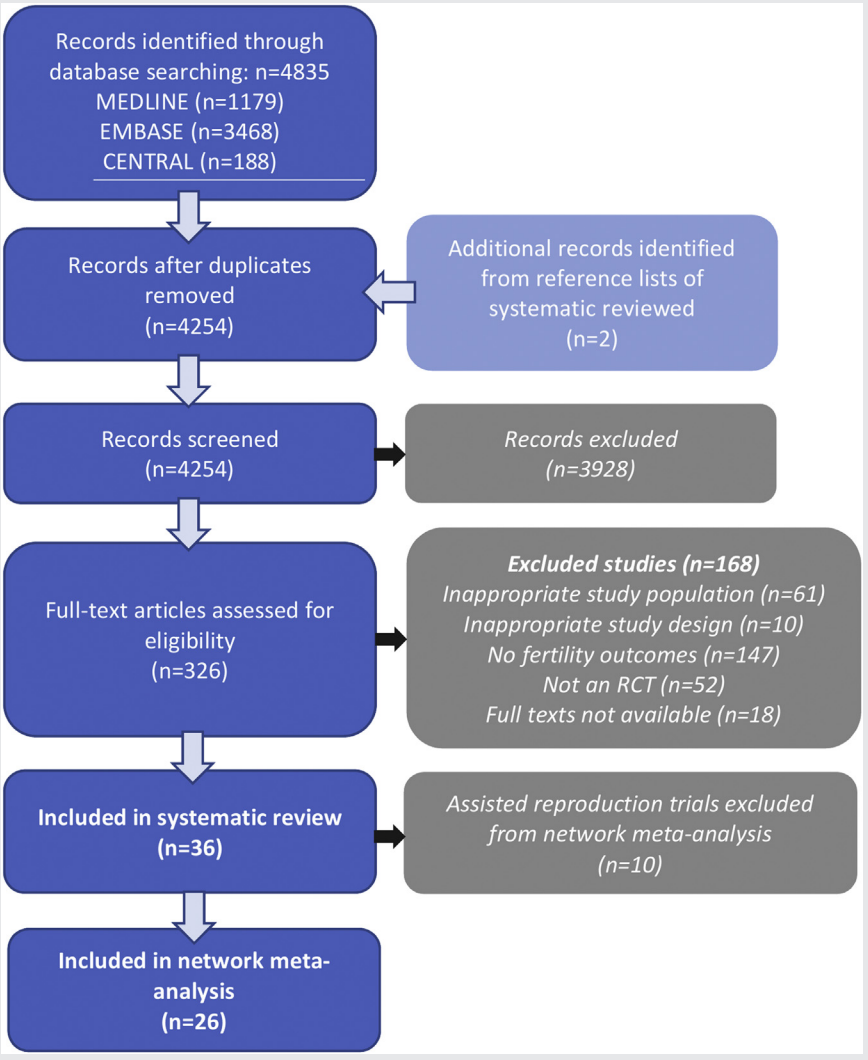
For network meta-analysis, we presented summary treatment effects (odds ratios [ORs]) with corresponding 95% confidence intervals (CIs) for each intervention as compared with placebo. We used the surface under the cumulative ranking curve to rank the treatments (16, 20).

RESULTS

Characteristics of Included Studies

The literature search yielded 4,254 publications (Fig. 1). Twenty-six trials fulfilled the eligibility criteria. The key characteristics of each of these trials are presented in Supplemental Table 1 (available online). One study was reported in a conference abstract (21), and the remaining 25 studies were reported as full-text publications. Publication dates ranged from 1982 to 2014, with seven studies published within the last 10 years. The studies were conducted in various countries, with 25 of the studies reported in English and one study reported in Polish (22). The list of included studies is presented

FIGURE 1



PRISMA flow diagram of literature search for randomized controlled trials comparing treatments for infertility in women with endometriosis. *Full-text articles include abstract-only publications.

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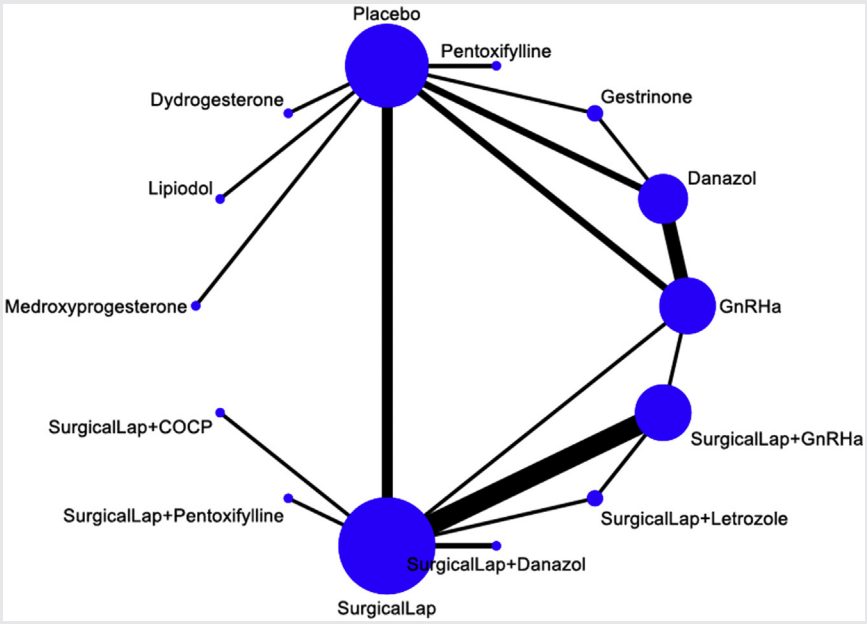
FIGURE 2



Network plot for clinical pregnancy.

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in Supplemental Appendix 2 and the list of excluded studies is presented in Supplemental Appendix 3 (available online).

It is important to note the wide range of publication dates of the included studies (32 years from 1982 to 2014) and the possible impact of this, as advancements, particularly in the setting of surgical technique and treatment, have been made over this time. Detailed evaluation of this, however, is difficult, as there is a significant lack of high-volume, good-quality randomized trials in this field.

Ten trials that examined ovarian stimulation, IUI, or IVF/intracytoplasmic sperm injection were included in our systematic review but were not included in the network meta-analysis as these had not been compared with other medical or surgical interventions. These included trials are presented in Supplemental Table 2 (available online).

The other 26 RCTs compared at least two of the 14 treatments: surgical laparoscopy, surgical laparoscopy plus GnRH agonist, surgical laparoscopy plus letrozole, surgical laparoscopy plus danazol, surgical laparoscopy plus pentoxifylline, surgical laparoscopy plus combined oral contraception pill, GnRH agonist, danazol, pentoxifylline, gestrinone, medroxyprogesterone, dydrogesterone, lipiodol, and placebo. Three RCTs (23–25) had three comparisons, while the remaining 23 trials all had two. In relation to patient treatment status, 20 studies were classified as treatment status unknown/unspecified, two studies were classified as laparoscopically treated previously, and two studies were classified as not laparoscopically treated previously.

Risk of Bias Assessment Results

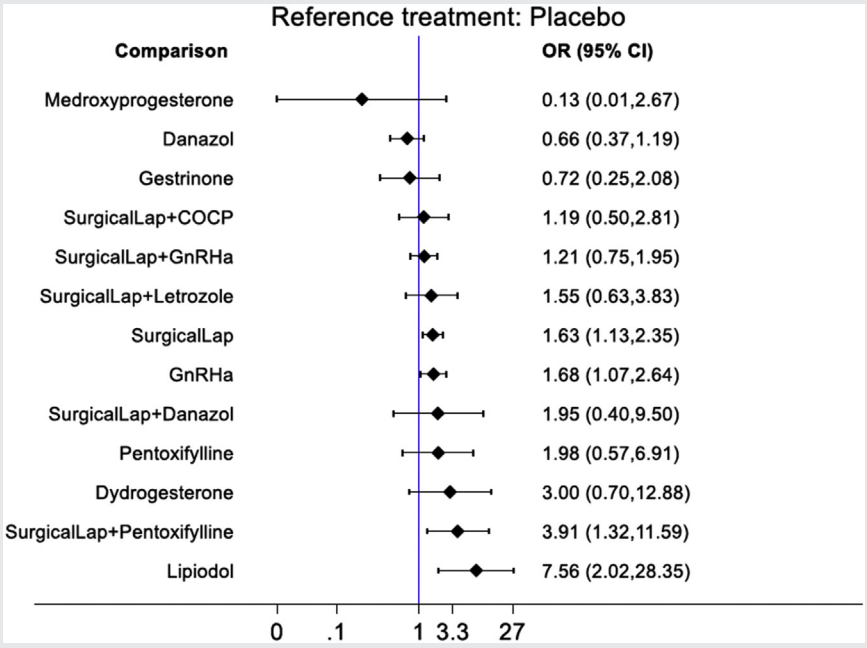
There were 16 (61.5%) RCTs with low risk of bias on random sequence generation and eight 30.8%) RCTs with low risk of bias on allocation concealment. Only one trial had low risk of bias on both blinding of personnel and outcome assessment. Supplemental Figure 1A and 1B (available online) shows results from the risk of bias assessment.

Network Meta-Analysis Results

Overall, 2,245 women with endometriosis were randomized to 14 different treatment options including placebo or no treatment (presented in Supplemental Fig. 2, available online). Figure 2 presents the network plot for clinical pregnancy. The most frequent comparisons were surgical laparoscopy versus surgical laparoscopy plus GnRH agonist (six RCTs; 666 women), surgical laparoscopy versus placebo (three RCTs; 533), GnRH agonist versus danazol (four RCTs; 127) and surgical laparoscopy versus placebo (three RCTs; 533). As shown in Figure 2, the comparisons between pentoxifylline, dydrogesterine, lipiodol, medroxyprogesterone, surgical laparoscopy plus combined oral contraception pill, surgical laparoscopy plus pentoxifylline, and surgical laparoscopy plus danazole were compared in open loops.

Network meta-analysis (Fig. 3) showed that compared with placebo, surgical laparoscopy alone (OR = 1.63; 95% CI, 1.13–2.35) or GnRH agonist alone (OR = 1.68; 95% CI, 1.07–2.46) resulted in higher odds of clinical pregnancy. Compared with placebo/no intervention, lipiodol (OR = 7.56; 95% CI, 2.02–29.37) or surgical laparoscopy plus pentoxifylline (OR = 3.91; 95% CI, 1.08–10.93) led to higher odds of clinical pregnancy, but the results of these comparisons should be considered with caution given that they were based on open-loop networks and had large CIs. There was insufficient evidence of a difference for any other interventions versus placebo. The results of pairwise meta-analyses

FIGURE 3



Forest plot showing the results of the network meta-analysis.

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were in agreement with those of network meta-analyses (Table 1). Inconsistency tests showed no evidence of global or local inconsistencies.

In relation to lipiodol hysterosalpingogram, this treatment was compared with no intervention rather than a placebo hysterosalpingogram. Included participants had infertility and endometriosis that did not have an impact on the fallopian tubes or ovaries and were randomized to lipiodol tubal flushing (hysterosalpingogram) or no flush (no intervention).

The surface under the cumulative ranking curve was used to provide a hierarchical ranking of the different treatments. The efficacy of every intervention, expressed as a percentage, was considered in relation to an imaginary intervention assumed to be the best. Higher surface under the cumulative ranking curve values therefore correspond to more effective treatments. The surface under the cumulative ranking curve values for the 14 interventions were 95%, 85%, 75%, 62%, 61%, 61%, 59%, 54%, 41%, 40%, 28%, 20%, 14% and 7% for lipiodol, surgical laparoscopy plus pentoxifylline, dydrogesterone, pentoxifylline, surgical laparoscopy plus danazol, GnRH agonist, surgical laparoscopy only, surgical laparoscopy plus letrozole, surgical laparoscopy plus combined oral contraceptive pill, surgical laparoscopy plus GnRH agonist, placebo/no treatment, gestrinone, danazol, and medroxyprogesterone, respectively (Supplemental Fig. 2).

TABLE 1

Results of the network meta-analysis.

Interventions vs. placebo	Network meta-analysis	Pairwise meta-analysis
Medroxyprogesterone	0.13 (0.01–2.67)	0.13 (0.01–2.67), 1 RCT
Danazol	0.66 (0.37–1.19)	0.36 (0.15–1.44), 2 RCTs
Gestrinone	0.72 (0.25–2.08)	1.08 (0.24–4.90), 1 RCT
Surgical laparoscopy + COCP	1.19 (0.50–2.81)	NA
Surgical laparoscopy + GnRH agonist	1.21 (0.75–1.95)	NA
Surgical laparoscopy + letrozole	1.55 (0.63–3.83)	NA
Surgical laparoscopy	1.63 (1.13–2.35)	1.83 (1.21–2.77), 3 RCTs
GnRH agonist	1.68 (1.07–2.46)	2.10 (0.35–12.67), 2 RCTs
Surgical laparoscopy + danazol	1.95 (0.40–9.50)	NA
Pentoxifylline	1.98 (0.57–6.91)	1.98 (0.57–6.91), 1 RCT
Dydrogesterone	3.00 (0.70–12.88)	3.00 (0.70–12.88), 1 RCT
Surgical laparoscopy + pentoxifylline	3.91 (1.32–11.59)	NA
Lipiodol	7.56 (2.02–28.35)	7.56 (2.02–28.35), 1 RCT

Note: Data are reported as odds ratio and (95% confidence interval). COCP = combined oral contraception pill; NA = not available; RCT = randomized controlled trial.

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Secondary Outcomes

All our secondary outcomes were infrequently reported. Four RCTs reported on live birth in different comparisons, and therefore network meta-analyses were not performed. Miscarriage and adverse events were reported only in 10 and eight out of the 26 studies, respectively. Due to the low number of studies in each comparison, we did not perform a network meta-analysis on any of the secondary outcomes. Results of pairwise meta-analyses are presented in Supplemental Table 3 (available online). There was insufficient evidence of a difference in most comparisons for live birth and miscarriage.

DISCUSSION

Summary of Findings

In women with infertility and surgically confirmed endometriosis, surgical laparoscopy alone or GnRH agonist alone increased the odds of clinical pregnancy compared with placebo. Lipiodol or surgical laparoscopy plus pentoxifylline potentially increases the odds of clinical pregnancy, but the results should be interpreted with caution given that they were based on open-loop networks. There was insufficient evidence of a difference for any other interventions versus placebo for clinical pregnancy. Live birth and miscarriage were poorly reported outcomes in RCTs. Most of the body of evidence in endometriosis had overall low to very low certainty due to imprecision and concerns of risk of bias.

Strengths and Limitations

Our systematic review provided a unique overview of available evidence on the treatments of endometriosis-related infertility, including assisted reproductive technology (ART) and non-ART treatments. The search included non-English papers as well as conference abstracts. Network meta-analysis provided extra confidence of evidence by using evidence from indirect comparisons. There were also limitations to our study. First, most of the included studies did not report live birth. The analyses on live birth were based on single studies in different comparisons and the evidence for live birth suffers from imprecision. Second, the comparisons in the included studies were so diverse that there was no common comparator in the published RCTs. Such diversity results in a small number of studies in most comparisons and open loops in more than half of the interventions assessed in the network meta-analysis, and ART-related interventions were not able to be incorporated in the network meta-analysis. Third, different stages of endometriosis may affect fertility outcomes, but only 60% of the trials reported the severity of endometriosis. Therefore, we are not able to explore the treatment effects in women with different stages of endometriosis. In addition, there were deficiencies in the studies for establishing what definition of infertility was used, as well as the duration of infertility. Of the studies included in the network meta-analysis, only 12 (46%) stated whether an infertility duration criteria (months) was used. In relation to the exclusion of other causes of infertility (and investigations undertaken to establish this), only 11 of the included studies (42%) commented on having addressed this issue. This does have an impact on the ability to interpret the studies' findings from a clinical perspective, as it is important to have all the required clinical knowledge when undertaking treatment recommendations for an individual or couple.

Interpretation and Implications

Women with endometriosis and infertility could benefit from surgical laparoscopy alone or GnRH agonist alone to improve fertility outcomes. The beneficial effect of surgical laparoscopy agrees with the existing evidence (26) as well as the guidelines (10, 27). However, the effectiveness of GnRH agonist was not supported by published systematic reviews (28) or clinical guidelines (10, 27). Such a different conclusion is very likely due to the use of indirect evidence. Previous reviews pooled GnRH agonist with other ovulation suppression interventions and concluded that there was no evidence of benefit in the use of ovulation suppression in infertile women with endometriosis (28, 29). This conclusion has been used in subsequent recommendations (10, 27). However, the direct evidence comparing GnRH agonist alone and placebo is very limited. A recent moderate-quality RCT including 450 women with endometriosis showed comparable fertility outcomes among GnRH agonist alone, surgical laparoscopy alone, and the combination of the two (24). This RCT was not included in previous evidence syntheses, and the inclusion of this RCT will add indirect evidence favoring GnRH agonist.

GnRH agonists are effective at treating endometriosis by inducing a hypogonadal state, which stops the estrogen support to the disease already present and reduces new disease formation (30). This mechanism of endometriosis treatment may be one of the ways GnRH agonists increase pregnancy rates as there will be a temporary improvement in disease burden, with a potential improvement in distorted anatomy and adhesions that affect oocyte release or transport (31). Additionally, it has been demonstrated that women with endometriosis who receive treatment with GnRH analogues will express higher levels of endometrial integrins that are typically lacking in eutopic endometrium of women with endometriosis (32). It is important to point out that outside of an RCT, a clinician's decision-making in relation to treatment options (e.g., surgical laparoscopy vs. GnRH agonist) may be guided by a number of patient factors, such as surgical risk, medical comorbidities, and the extent of expected anatomical disease. We must acknowledge that the CI of GnRH agonist alone was wide (95% CI, 0.35–12.67), and these findings should be interpreted with caution. This again highlights the need for further careful and well-designed research to investigate this clinical question.

There is also the question of the surgical laparoscopy technique. Unfortunately, there is no strong evidence to support a difference in relation to the method of removal of endometriosis (i.e., excision vs. ablation). Because of this, the surgical laparoscopy group includes both surgical methods. A benefit of excision, in addition to disease treatment, is to provide histologic diagnosis (avoiding the possibility of a false-positive diagnosis), but this is counterbalanced with the less

technically demanding, faster, and easier method of ablation, although ablation may result in incomplete lesion removal (e.g., in the setting of deep infiltrating endometriosis) (31).

Lipiodol or surgical laparoscopy plus pentoxifylline also showed higher pregnancy rates than no intervention/placebo. The top-ranking interventions were for lipiodol, surgical laparoscopy plus pentoxifylline, dydrogesterone, pentoxifylline, and surgical laparoscopy plus danazol. But the results of these interventions should be interpreted with caution, given that all these results are based on open-loop networks and the direct comparisons are based on single small studies. The effectiveness of these interventions needs to be confirmed in future trials.

Although we were able to report reproductive outcomes, we were unable to include other relevant factors, such as adverse events, as these were reported in only seven of the 26 studies, with a very varied range of how and what was reported. This is important, as some of these interventions have renowned adverse effects; for example, GnRH analogues classically cause hypoestrogenic side effects such as vasomotor symptoms, while, on the other hand, there are also risks and complications associated with surgical treatment (although these were not reported in most studies addressing surgery as an intervention).

We also found that not all of the included studies excluded other causes for infertility, with only 11 of the studies stating that they excluded other contributing causes for infertility. Further information in relation to this is present in Supplemental Table 1.

For future infertility trials, a consensus process is underway to define core outcomes in infertility trials in women with endometriosis (33). Until this guidance is available, we would recommend that the Harbin consensus on reporting of outcomes be followed (34).

Further RCTs of both medical and surgical treatments for women with endometriosis-related infertility are required to clarify the relative effectiveness of treatments for endometriosis-related infertility, in particular, trials comparing IVF and IUI to other treatments. Ideally, future trials should compare other interventions to existing recommended interventions such as surgical laparoscopy.

Conclusion

In the setting of women with surgically confirmed endometriosis and infertility, when compared to placebo, surgical laparoscopy alone or GnRH agonist alone increase the odds of clinical pregnancy. Lipiodol or surgical laparoscopy plus pentoxifylline potentially increases the odds of clinical pregnancy, but the results should be interpreted with caution given that they were based on single small studies. Evidence on the other comparisons and outcomes was insufficient.

As highlighted, there is a lack of good-quality research in the field of infertility and endometriosis, and targeted, well-designed RCTs need to be undertaken to further clarify and provide clear direction on the optimal patient management.

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REFERENCES

1. Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, Abrao MS, et al. for the World Endometriosis Society Sao Paulo Consortium. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod 2017;32:315–24.
2. Yazdani A. Surgery or in vitro fertilisation: the simplicity of this question belies its complexity. Aust N Z J Obstet Gynaecol 2017;57:676–8.
3. Ozkan S, Murk W, Arici A. Endometriosis and infertility. Epidemiology and evidence based treatments. Ann N Y Acad Sci 2008;1127:92–100.
4. Prentice A, Ingamells S. Endometriosis and infertility. J Br Fertil Soc 1996;1:51–5.
5. Missmer SA, Hankison SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 2004;160:784–96.
6. Koch J, Rowan K, Rombauts L, Yazdani A, Chapman M, Johnson N. Endometriosis and infertility—a consensus statement from ACCEPT (Australasian CREI Concensus Expert Panel on Trial evidence). Aust N Z J Obstet Gynaecol 2012;52:513–22.
7. The Practice Committee of the American Society of Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril 2012;98:591–8.
8. Sanchez AM, Vanni VS, Bartiromo L, Papaleo E, Zilberberg E, Candiani M, et al. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res 2017;10:43.
9. Johnson NP. A review of lipiodol treatment for infertility—an innovative treatment for endometriosis-related infertility? Aust N Z J Obstet Gynaecol 2014;54:9–12.
10. National Institute for Health and Care Excellence. Endometriosis: diagnosis and management (NICE guideline 73). Manchester: National Institute for Health and Care Excellence; 2017. https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315. Accessed December 15, 2018.
11. Johnson NP, Hummelshoj L, and the World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. Hum Reprod 2013;28:1552–68.
12. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. Br Med J 2013;346:f2914.
13. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: a survey of published systematic reviews. Br Med J 2009;338:b1147.
14. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. J Am Stat Assoc 2006;101:447–59.
15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
16. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STRATA. PLoS One 2013;8:e76654.
17. White IR. Network meta-analysis. Stata J 2015;15:951–85.
18. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98–110.
19. Dias S, Welton NJ, Caldwell DM, Ades AE. 2010. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932–44.
20. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
21. Gad MS, Badroui MHH. Evidence-based therapy for infertility associated with early stage endometriosis. Int J Gynecol Obstet 2012;119:548.

22. Skrzypulec V, Walaszek A, Drosdzol A, Nowosielski K, Piela B, Rozmus-Warcholinska W. [Influence of GnRH analogue on the intensification of endometriosis symptoms and infertility treatment]. Wiadomosci Lekarskie 2004;57:301–4.
23. Alborzi S, Hamedi B, Omidvar A, Dehbashi S, Alborzi S, Alborzi M. A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. Arch Gynecol Obstet 2011;284:105–10.
24. Alkatout I, Mettler L, Beteta C, Hedderich J, Jonat W, Schollmeyer T, et al. Combined surgical and hormone therapy for endometriosis is the most effective treatment: prospective, randomized, controlled trial. J Minim Invasive Gynecol 2013;20:473–81.
25. Overton CE, Lindsay PC, Johal B, Collins SA, Siddle NC, Shaw RW, et al. A randomized, double-blind, placebo-controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosis. Fertil Steril 1994;62:701–7.
26. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, et al. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev 2014; CD011031.
27. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.
28. Brown J, Farquhar C. Endometriosis: an overview of Cochrane reviews. Cochrane Database Syst Rev 2014;CD009590.
29. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2007;CD000155.
30. Magon N. Gonadotropin releasing hormone agonist: expanding vistas. Indian J Endocrinol Metab 2011;15:261–7.
31. Lam A, Hengrasmee P, Paz M. To excise or ablate. O&G Mag 2014;16.
32. Lessey B. Medical management of endometriosis and infertility. Fertil Steril 2000;73:1089–96.
33. Hirsch M, Duffy JMN, Barker C, Hummelsjoj L, Johnson NP, Mol B, et al. for the International Collaboration to Harmonize Outcomes and Measures for Endometriosis (iHOME). Protocol for developing, disseminating and implementing a core outcome set for endometriosis. Br Med J Open 2016;6:e013998.
34. Harbin Consensus Conference Workshop Group. Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT); modifying the CONSORT statement. Fertil Steril 2014;102:952–9.e15. pmid:25225072.

Intervenciones para la infertilidad asociada a endometriosis: una revisión sistemática y meta-análisis de la red

Objetivo: Comparar la eficacia de diferentes tratamientos en mujeres con infertilidad asociada a endometriosis.

Diseño: Una revisión sistemática y meta-análisis de la red de los estudios controlados aleatorizados (RCTs).

Lugar: No aplica.

Paciente(s): Mujeres con endometriosis confirmada por laparoscopia con esterilidad asociada.

Intervención(es): Una investigación electrónica extensa de las siguientes bases de datos: registro central Cochrane de estudios controlados (CENTRAL), MEDLINE, clinicaltrials.gov, y Embase.

Medida(s) principal(es) de resultado: Embarazo clínico, tasa de nacido vivo, tasa de aborto y eventos adversos.

Resultado(s): Del total de 4252 estudios/abstracts, 36 de ellos se analizaron en la revisión sistemática y 26 estudios en el meta-análisis, que incluyeron 2245 mujeres con esterilidad asociada a endometriosis. El meta-análisis de red, demostró que comparado con placebo la cirugía laparoscópica sola (Odds Ratio=1.63; intervalo de confianza 95%, 1.13-2.35) o el uso sólo de agonistas de GnRH (Odds Ratio= 1.68; intervalo de confianza de 95%, 1.07-2.4) resultó en mayores probabilidades de embarazo. La evidencia en otras intervenciones comparado con placebo o en resultados secundarios como la tasa de nacido vivo, abortos o eventos adversos es insuficiente.

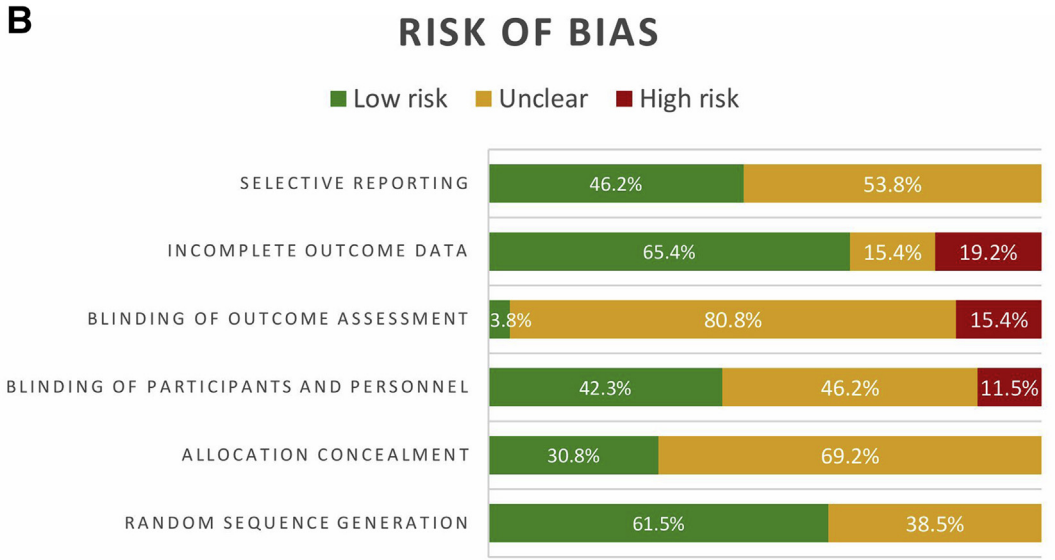
Conclusión(es): La conclusión más importante es que se necesitan más RCTs para aclarar la relativa efectividad de los tratamientos de la esterilidad asociada a endometriosis, idealmente comparando intervenciones con las actuaciones recomendadas existentes como la laparoscopia quirúrgica. Además, es esencial comparar FIV e inseminación intrauterina con otros tratamientos mediante más RCTs.

SUPPLEMENTAL FIGURE 1

A

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Abd Rabbo 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk
Abu Hashim 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Alborzi 2011	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk
Alkatout 2013	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk
Anonymous 1996	Unclear	Unclear	Unclear	Unclear	High risk	Low risk
Balasch 1997	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear
Bayer 1988	Low risk	Unclear	Low risk	Unclear	High risk	Unclear
Bianchi 1999	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear
Busacca 2001	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk
Creus 2008	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear
Fedele, May 1989	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Fedele, Oct 1989	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Fedele, May 1992	Low risk	Low risk	Low risk	High risk	Unclear	Unclear
Fedele, Jul 1992	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk
Fraser 1991	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk
Gad 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Harrison 2000	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Johnson 2004	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Kim 1996	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear
Loverro 2003	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear
Marcoux 1997	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk
Moini 2012	Unclear	Low risk	High risk	High risk	High risk	Unclear
Nadir-Ciray 2005	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk
Overton 1994	Low risk	Unclear	Low risk	Unclear	High risk	Low risk
Parazzini 1994	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Rickes 2002	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk
Seibel 1982	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Skrypulec 2004	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear
Surrey 2002	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk
Tei 1998	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear
Thomas 1987	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Tummon 1989	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Tummon 1997	Unclear	Low risk	High risk	Unclear	Low risk	Low risk
Vercellini 1999	Low risk	Low risk	High risk	Unclear	Low risk	Low risk
Ye He 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhu 2014	Low risk	Low risk	High risk	High risk	Low risk	Low risk

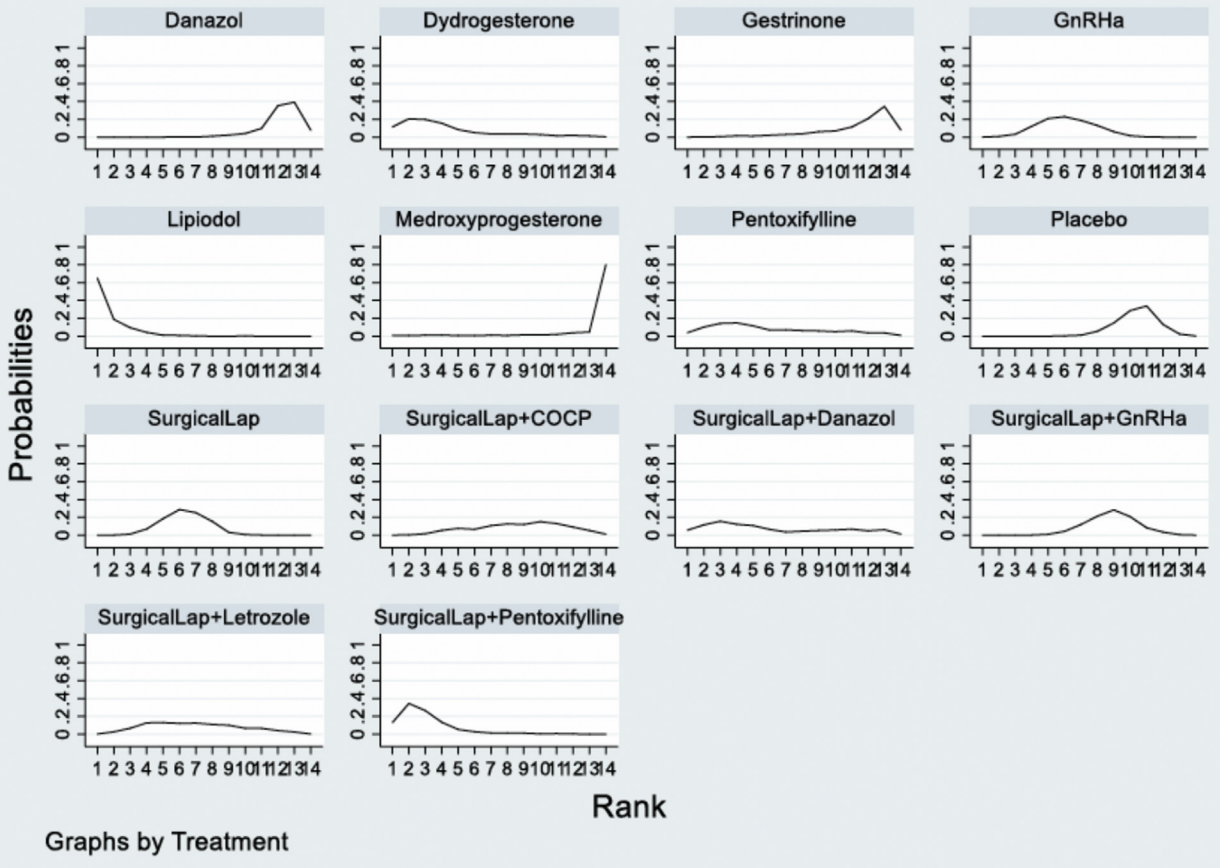
B



(A) Risk of bias summary: review of authors' judgments about risk of bias for each included study. (B) Risk of bias graph: judgments presented as percentages across all included studies.

Hodgson. Endometriosis, infertility, intervention? Fertil Steril 2019.

SUPPLEMENTAL FIGURE 2



Ranking of treatments for endometriosis-related infertility.
The rankograms below illustrate the probability per rank (the best intervention, second best, third best, etc.) for each treatment in terms of clinical pregnancy.

Hodgson. Endometriosis, infertility, intervention? Fertil Steril 2019.