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Title:

When to do surgery and when not to do surgery for endometriosis: a systematic review and meta-analysis

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Abstract

Objective

We performed a systematic review and meta-analysis with the aim to answer whether operative laparoscopy is an effective treatment in a woman with demonstrated endometriosis as compared to alternative treatments. We also aimed to assess the risks of operative laparoscopy as compared to alternatives. In addition, we aimed to systematically review the literature on the impact of patient preference on decision-making around surgery.

Data Sources

We searched MEDLINE, EMBASE, PsycINFO, ClinicalTrials.gov, CINAHL, Scopus, OpenGrey and Web of Science from inception through May 2019. Additionally, a manual search of reference lists of relevant studies was also conducted**.**

Methods of Study Selection

Published and unpublished randomized controlled trials (RCT) in any language describing a comparison between surgery and any other intervention were included, with particular reference to timing and its impact on pain and fertility. Studies reporting on keywords including, but not limited to, endometriosis, laparoscopy, pelvic pain, infertility were included. In the anticipated absence of RCTs on patient preference, all original research on this topic was considered eligible.

Tabulation, Integration, and Results

In total, 1990 studies were reviewed. Twelve studies were identified as being eligible for inclusion to assess outcomes of pain (*n* = 6), fertility (*n* = 7), quality of life (*n* = 1), and disease progression (*n* = 3). Seven studies were identified as being of interest to evaluate patient preferences. There is evidence that operative laparoscopy may improve overall pain levels at

six months compared to diagnostic laparoscopy (relative risk (RR), 2.65; 95% confidence interval (CI), 1.61–4.34; p < .001; 2 RCTs, 102 participants; low quality evidence). Since the quality of the evidence was very low, it is uncertain if operative laparoscopy improves live birth rates. Operative laparoscopy probably yields little or no difference on clinical pregnancy rates compared to diagnostic laparoscopy (RR, 1.29; 95% CI, 0.99–1.92; p = .06; 4 RCTs, 624 participants; moderate quality evidence). It is uncertain if operative laparoscopy yields a difference in adverse outcomes when compared to diagnostic laparoscopy (RR, 1.98; 95% CI, 0.84–4.65; p = .12; 5 RCTs, 554 participants; very low quality evidence). No studies reported on progression of endometriosis to a symptomatic state or progression of extent of disease in terms of volume of lesions and/or locations in asymptomatic women with endometriosis. We found no studies that reported on the timing of surgery. No quantitative or qualitative studies specifically aimed at elucidating the factors informing a woman's choice for surgery were identified.

Conclusion

Operative laparoscopy may improve overall pain levels, but may have little or no difference for fertility-related or adverse outcomes when compared to diagnostic laparoscopy. Additional high quality RCTs, including comparing surgery to medical management, are needed and these should also report adverse events as an outcome. Studies on patient preference in surgical decision-making are needed.

PROSPERO

Our systematic review was prospectively registered with PROSPERO (CRD42019135167).

Keywords

Laparoscopy; endometriosis; pelvic pain; infertility; quality of life; patient preference; randomized controlled trial, evidence, systematic review.

Introduction

Endometriosis is an inflammatory disease process, characterized by lesions of endometrial-like tissue outside the uterus, commonly affecting women of reproductive age [1]. Worldwide, endometriosis was estimated to impact 176 million women in 2010 [2], usually in the form of pelvic pain and/or infertility. The umbrella term endometriosis-associated pelvic pain encompasses a myriad of more specific symptoms, including but not limited to dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, dyschezia, and chronic pelvic pain [3–5].

We are still very limited in our understanding of the disease. For example, there is poor correlation between the severity of a patient's symptoms and disease state, with some patients being asymptomatic despite advanced endometriosis [6,7]. Similarly, fertility is impacted in some patients with endometriosis but not others [8]. Though we are learning more about non-invasive diagnosis, we have yet to grasp the origins and progression of the disease [9,10], which may be exacerbated by the well-known delay in diagnosis that patients experience[11].

Whilst navigating many questions about endometriosis etiology and diagnosis, the key question is how to treat patients with the disease. Though medical management consisting of agents such as hormonal contraceptives, progestins, and gonadotropin-releasing hormone agonists (GnRHa) or antagonists is recommended in many circumstances [12], laparoscopic surgery is frequently a part of the treatment, consisting of excision and/or ablation [13]. The complexity in therapeutic decision-making is in part due to the heterogenous population of patients with endometriosis and the various phenotypes patients may harbour. Patient preference and the setting in which care takes place (encompassing accessibility to and costs of healthcare) also play large roles in treatment decisions. Patient-reported outcomes measures (PROM), which likely go far beyond issues such as pain and infertility, should be prioritized. Fatigue, for example, has recently been recognized as an important outcome of endometriosis [14].

For now, we must base our patient counselling regarding surgery on the available evidence and expert consensus [12,15]. This systematic review aims to evaluate the effectiveness of surgery on improving symptomatology, fecundity, recurrence of disease, and/or reoperation

rates compared to alternative therapies. We will also assess adverse events of the therapies. Secondarily, we aimed to understand whether the timing of surgery impacts these outcomes.

Methodology

Our systematic review was prospectively registered with PROSPERO (CRD42019135167). The review is reported according to PRISMA guidelines [16].

To fulfil the study aims, four individual objectives were formulated to best assess unique outcomes and timing-specific queries (Table 1). A narrative review on the role of patient preference on surgical decision-making was done.

Search strategies

The following databases were searched from inception until May 2019: MEDLINE and Embase via OvidSP, PsycINFO, CINAHL, Web of Science Core Collection, Scopus, and ClinicalTrials.gov. OpenGrey was used to search for grey literature. The electronic search algorithm consisted of terms relating to key concepts of “endometriosis”, “surgery”, “medical management”, “fertility therapy”, and “randomized controlled trials (RCT)”, customized for each objective (Appendix 1). For the patient preference component, terms related to the concept of “patient preference” were added.

Reference lists of relevant articles and related reviews were manually searched to identify papers not captured by the electronic searches. There were no language restrictions in the search or selection of papers. Studies were uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia).

Selection of studies

All studies, published and unpublished in any language at any time, were considered for inclusion. Eligible studies were selected if the focus of the paper was the comparison of

surgery to an alternative therapy (expectant or medical management) in patients with endometriosis. The selection of studies for each individual objective was done separately, each with unique inclusion and exclusion criteria based on the specific patient population. Only studies that were RCTs (including crossover RCTs) were considered eligible. Quasi-randomized trials were not eligible. Where participants were included in more than one publication, the data were combined so as to not duplicate the effect of a single study group.

For the patient preference component, search terms relating to “RCTs” were removed and all study types were eligible for inclusion, though reviews were excluded.

Quality Assessment

The Cochrane bias risk tools for RCT studies were used to assign a judgment of high, low, or unclear risk of material bias for each study. For each objective, this was completed independently by two individual authors (RH, EG, TG, ML). The level of evidence for particular interventions’ effect on each outcome was summarized and scored according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [17] by MA and ML.

Data Extracted

For each objective, two authors (RH, EG, AC, JO, TG, ML) independently screened titles/abstracts and selected full-texts. When discrepancies arose after the screening of titles/abstracts of full-texts, a separate third author (NPJ, MA, GC) was consulted to resolve the conflict. Data were independently extracted from each study meeting the inclusion criteria by the same two authors who completed study selection. Data extracted included study characteristics and outcome data.

Outcomes Measured

The primary and secondary outcomes for all objectives are described in Table 1.

Statistical Analysis

Data were analyzed using RevMan v5.3 (Cochrane Collaboration, Oxford, UK). A random-effects model was used, which incorporates an assumption that the different studies are estimating different, yet related, intervention effects. It was felt to be an appropriate choice in the setting of surgical RCTs where there was likely to be clinical heterogeneity. Where there is heterogeneity, confidence intervals (CIs) for the average intervention effect will be wider if the random-effects method is used rather than a fixed-effect method, and corresponding claims of statistical significance will be more conservative [18]. For continuous data, we report MDs and relevant 95% CIs. For dichotomous outcomes, we report risk ratios (RRs) and 95% CIs. Statistical heterogeneity between studies was quantified using the I^2 statistic, which provides an estimate of the degree of heterogeneity resulting from between-study variance, rather than by chance[18]. An I^2 of more than 75% was considered to indicate high level heterogeneity, I^2 of 50–75% as indicative of substantial heterogeneity, and an I^2 of less than 40% as low heterogeneity.

Patient and Public Involvement

We included active involvement of an anonymous patient representative (one who has undergone laparoscopic excision of endometriosis) throughout all stages of study development, with particular emphasis on the section on *patient preference*.

Results

Number of retrieved papers

The systematic searches for each objective are depicted in Figures 1A-E. Overall, 12 studies published between 1994 and 2013 were included for objectives *one* to *four* (Table 2A) [19,20, 29,30,21–28]. Excluded studies after full-text retrieval are included in Table S1. No studies directly assessing the timing of surgery for endometriosis or patient preference as a variable in surgical decision-making were identified. Seven studies of interest dealing with some element of preference were identified and included (Table 2B) [31–37].

Characteristics and summary findings of included studies

Summary of findings for each objective can be found in Table 3, along with the GRADE level of evidence, stratified by outcome.

Objective one

To assess the effectiveness and safety of laparoscopic surgery in the treatment of endometriosis-associated infertility.

The search yielded 324 publications (Figure 1A). Five studies fulfilled the eligibility criteria and these are presented in Table 2A with key characteristics of each of these trials highlighted [21,22,25–27]. Four studies were reported as full-text publications and one as a conference abstract. Publication dates ranged from 1997 to 2012, with two studies being within the last ten years. The studies were conducted in various countries, with one study from Canada, Egypt, Italy, Iran, and Turkey, and all were reported in English.

Four of the included studies compared operative (treatment) laparoscopy with diagnostic laparoscopy [22,25–27]. The remaining included study, Demirol *et al*. 2006, compared surgical treatment of endometrioma (cystectomy) versus no surgery in the setting of all participants undergoing intracytoplasmic sperm injection (ICSI) [21]. The Demirol *et al*. study had no

extractable data suitable for inclusion in the meta-analysis as their reported percentages could not be converted to absolute raw numbers [21].

Only one study reported on live birth rate as an outcome [27]. The one-year live birth rate was comparable at 10/51 women (20%) in the operative laparoscopy group and 10/45 (22%) in the diagnostic laparoscopy group [27]. Four studies assessed clinical pregnancy rate [22,25–27] with a total of 624 participants. Combining data, there is moderate quality evidence that operative laparoscopy probably yields little or no difference on clinical pregnancy rates compared to diagnostic laparoscopy. (*n* = 624; risk ratio (RR), 1.29; 95% confidence interval (CI), 0.99–1.92; p = .06, four RCTs, I^2 = 43%) (Figure 2). Two studies assessed miscarriage [25,27]. Combining data, there is low quality evidence that operative laparoscopy may have little or no difference on the rate of miscarriages compared to diagnostic laparoscopy. (*n* = 437; RR, 1.31; 95% CI, 0.60–2.86; p = .50, two RCTs, I^2 = 2%).

Marcoux *et al*. reported raw data of adverse effects of surgery [25]. Four women had minor intraoperative complications (three in operative laparoscopy versus one in diagnostic laparoscopy) but none required laparotomy or transfusion. Sixteen women (5.8% in the operative laparoscopy group and 3.6% in the diagnostic laparoscopy group, *p* = .46) reported minor postoperative complications [25]. Moini *et al*. reported no surgical complications in either group [26].

With respect to *timing*, Moini *et al.* and Marcoux *et al.* recruited patients with unexplained infertility of at least one year [25,26], whereas Parazzini *et al*. included patients with infertility of at least two years [27]. The mean duration of infertility in the Marcoux *et al*. study was 31 +/- 16 months in both groups [25]. Demirol *et al.* recruited patients who were pending in-vitro fertilization (IVF) treatment, largely due to male factor infertility necessitating ICSI. They do not specify the proportion of those with female infertility nor its duration before treatment, but they

do plan ovarian stimulation at an interval of 3 months post-operatively [21]. Gad *et al.* do not elaborate on the details of infertility history [22].

Objective two

To assess the effectiveness and safety of laparoscopic surgery for endometriosis on future fertility in patients with a desire for fertility but not currently trying to conceive.

The search yielded 367 publications (Figure 1B). Two studies fulfilled the eligibility criteria and are presented in Table 2A with key characteristics [19,20]. The trials were conducted in Germany and the United Kingdom (UK), reported in English, and published as full-texts in 2004 and 2013.

Alkatout *et al*. compared groups: (1) operative laparoscopy, (2) operative laparoscopy plus the gonadotropin-releasing hormone agonist (GnRHa) Leuprorelin and (3) Leuprorelin. The participants did not have a history of surgical or medical treatment for endometriosis and all patients with bladder or rectal deep endometriosis were excluded [20]. When comparing operative laparoscopy plus Leuprorelin to Leuprorelin (*n* = 273), there did not seem to be an effect from undergoing surgery for live birth (RR, 0.91; 95% CI, 0.72–1.14; p = .39), clinical pregnancy (RR, 0.93; 95% CI, 0.77–1.12, p = .12), or miscarriage (RR, 1.10; 95% CI 0.50–2.42; p = .82). When comparing operative laparoscopy to Leuprorelin (*n* = 262), there did not seem to be an effect from undergoing surgery for live birth (RR, 0.82; 95% CI, 0.64–1.04; p = .11), clinical pregnancy (RR, 0.84; 95% CI, 0.69–1.03; p = .10), or miscarriage (RR, 1.09; 95% CI 0.49–2.45; p = .82).

Abbott *et al*. compared immediate operative laparoscopy and delayed operative laparoscopy (control), with the controls first undergoing diagnostic laparoscopy followed by operative laparoscopy 6 months later. Fifty-one percent of women had previous medical treatment and 17% had previous surgical treatment for endometriosis [19]. Of the 12 participants trying to

conceive, 6/12 (50.0%) conceived and went on to have a live birth. All occurred in the period following excisional surgery and 5/6 occurred within 6 months of surgery. However, the randomization group of these patients is not clearly discussed [19].

Only Abbott *et al.* reported raw data of adverse effects of surgery [19]. Two complications occurred in two patients belonging to the immediate operative laparoscopy group (conversion to laparotomy and post-operative blood transfusion). Alkatout *et al*. did not report adverse effects of surgery or Leuprorelin [20].

With respect to *timing*, there is no information provided on the duration of patient symptomatology (including, if present, infertility) prior to interventions in either study. The crossover design of Abbott *et al*. does have the possibility of highlighting value in immediate operative laparoscopy for clinical pregnancy/live birth rate (i.e. as close to the time of presentation to the gynecologist as possible), but as fertility-related outcomes were not the primary aim of the study, insufficient information was published to fully evaluate this effect.

Objective three

To assess the impact and safety of laparoscopic surgery on the progression of disease state or patient symptomatology in patients who are asymptomatic from a pain perspective.

There were no eligible RCTs identified that met inclusion/exclusion criteria for this objective (Figure 1C). The outcomes 1) progression of disease to a symptomatic state and 2) progression of disease size and/or locations in an asymptomatic population of women with endometriosis are unanswerable based on current literature.

Objective four

To assess the effectiveness and safety of laparoscopic surgery in the treatment of endometriosis-associated pain problems.

The search yielded 527 publications (Figure 1D). Seven studies fulfilled the eligibility criteria and these are presented in Table 2A with key characteristics of each of this trial highlighted [19,20, 23,24,28–30]. The Sutton *et al*. 1997 [29] study was a follow-up on their 1994 study [28]; data from these studies were combined. All seven studies were reported as full-text publications. Publications dates ranged from 1994 to 2013, with only one study being within the last ten years. The studies were conducted in various countries (Canada, China, Germany, UK) and all were reported in English. A duplicate publication of Wu *et al.* was identified in Chinese, published two years earlier in 2000 [38]. The Tutunaru *et al.* conference abstract [39] describing an RCT that would likely meet inclusion criteria based on its inclusion in the Duffy *et al.* meta-analysis [40] could not be retrieved and was thus not included.

Of the included studies, three compared operative laparoscopy to diagnostic laparoscopy [19, 23,28]. Alkatout *et al*. and Lalchandani *et al.* compared operative laparoscopy (with and without GnRHa in the case of Alkatout *et al*.) to GnRHa, respectively [20,24]. Wu *et al*. however, compared combination therapy (operative laparoscopic surgery plus traditional Chinese herbal medicine (CHM) to medical management, either with CHM or danazol for patients with endometriomas [30]. Outcome measures were heterogenous and not well reported. Abbott *et al*. used a 100 mm visual analogue scale (VAS) [19], Sutton *et al.* presented scores as a range from 0 to 10, possibly representing a composite of dysmenorrhea, dyspareunia, and pelvic pain) [28], while Jarrell *et al.* [23] and Lalchandani *et al.* [24] did not provide details on what tools were used to measure their outcomes. For the secondary pain outcomes, Abbott *et al*. reported on dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and dyschezia using a VAS 6 months after surgery 1 and again 6 months after surgery 2 [19]. They also reported quality of life outcomes using the EQ-5D and SF-12 [19]. Alkatout *et al.* reported on

dysmenorrhea, dyspareunia, and abdominal pain using an extensive questionnaire 12 months after treatment [20]. Wu *et al*. reported on dysmenorrhea but did not describe how this was quantified [30]. Fertility-related secondary outcomes were reported by four studies [19,20, 24,30]. Progression of disease was assessed by four studies [19,20, 28,30]. Alkatout *et al*. assessed the changes to the Endoscopic Endometriosis Classification (EEC) stage from the primary to second-look laparoscopy [20]. Abbott *et al*. assessed the changes to the revised American Fertility Society (rAFS) *stage* and *scores* from surgery one to surgery two [19]. Sutton *et al.* assessed the changes to the rAFS *score* in patients who underwent a second-look laparoscopy following their initial diagnostic laparoscopy [28,29]. Wu *et al*. assessed the volume alteration of endometriomas using ultrasound [30]. Recurrence of pain symptoms was reported by Alkatout *et al.* and Sutton *et al.* [20,28,29].

A planned subgroup analysis on the special populations of *adolescent women* and *women who are done family building* for any outcome was not possible as no studies or individual study subgroup analyses were done on these populations

With respect to *timing*, the crossover study design of Abbott *et al*. provides insight into changes in pain and quality of life measures when surgery is done immediately versus a delay of 6 months in women who are diagnosed with endometriosis intraoperatively [19]. There is no information on the timing of surgical intervention from the onset of symptoms, time of presentation to a gynecologist, or point at which endometriosis was clinically or radiographically diagnosed in any of the studies included in objective *four.*

Combining data, operative laparoscopy is deemed more effective than diagnostic laparoscopy (that is, expectant management) at improving overall pain at 6 months following surgical intervention (n = 102; RR, 2.65; 95% CI, 1.61–4.34; $p < .001$, two RCTs, $I^2 = 0\%$) (Figure 3) [19,28]. When using a 10-point VAS, Jarrell *et al*. demonstrated an overall decrease in pain over 12 months for participants who underwent operative and diagnostic laparoscopy ($p < .05$)

compared to pre-operative pain, but no significant difference in the MD of pain scores between groups (no numerical data reported in publication) [23]. Lalchandani *et al.* demonstrated that operative laparoscopy (ablation) was associated with decreased overall pain at 12 months compared to diagnostic laparoscopy and Goserelin with add-back therapy (measured as symptom-free at 12 months) (*n* = 35; RR, 3.18; 95% CI 1.03–9.79; p = .04).

For dysmenorrhea specifically, Abbott *et al.* demonstrated no significant difference in the MD of dysmenorrhea VAS scores between groups (*n* = 39; MD, -10.80; 95% CI -27.46–5.86; p = .20) [19]. Alkatout *et al*. demonstrated that operative laparoscopy plus GnRHa is more effective than GnRHa at improving dysmenorrhea at 12 months (*n* = 273; RR, 0.58; 95% CI, 0.37–0.92; p = .02), but there did not seem to be an effect between operative laparoscopy and GnRHa (*n* = 262, RR, 0.70; 95% CI, 0.45–1.09, p = .12) [20]. Wu *et al.* detected high rates of improvement in dysmenorrhea across all intervention groups, but did not seem to detect any effect difference between any of their interventions [30].

For dyspareunia, Abbott *et al.* demonstrated no significant difference in the MD of dyspareunia VAS scores between groups (*n* = 39; MD, 6.40; 95% CI -15.20–28.00; p = .56) [19]. Alkatout *et al*. demonstrated that operative laparoscopy plus GnRHa is more effective than GnRHa at improving dyspareunia at 12 months (*n* = 273; RR, 0.36; 95% CI, 0.19–0.68; p = .002), but there did not seem to be an effect between operative laparoscopy and GnRHa (*n* = 262, RR, 0.68; 95% CI, 0.41–1.14, p = .15) [20].

For dyschezia, Abbott *et al.* demonstrated no significant difference in the MD of dyschezia VAS scores between groups (*n* = 39; MD, -2.60; 95% CI -24.40–19.20; p = .82) [19].

For fertility-related secondary outcomes, Alkatout *et al*. and Abbott *et al.* findings are noted above under the heading "*objective two*" [19,20]. Lalchandani *et al*. report three pregnancies in the GnRH-a plus add-back group and none in the surgical group (*n* =35; RR, 0.15; 95% CI,

0.01–2.72; p = .20). Wu *et al*. reported no significant difference in clinical pregnancy between operative laparoscopy plus CHM and CHM (*n* = 38; RR, 1.41; 95% CI, 0.69–2.89; p = .34), but there was evidence of a statistically significant difference (though questionably not clinically relevant) between operative laparoscopy plus CHM and danazol (*n* = 36; RR 3.67; 95% CI, 0.98–13.81; p = .05) [30]. Only one pregnancy was documented by Sutton *et al.* in the operative laparoscopy group at the 12 month interval and none in the diagnostic laparoscopy group (of which, 24/31 went on to have operative laparoscopy after 6 months of expectant management following diagnostic laparoscopy) [29].

For the progression of endometriosis as determined by surgery, Abbott *et al*. demonstrated a clinically relevant and statistically significant difference between operative laparoscopy and diagnostic laparoscopy, whereby operative laparoscopy results in an improvement in r-AFS stage between surgery one and two (*n* = 34; RR, 3.94; 95% CI, 1.63–9.53; p = .002) [19]. Abbott *et al*. take care to report specific patient changes, whilst Alkatout *et al*. report overall rates of EEC stage in the second-look laparoscopy, irrespective of the staging in the first laparoscopy. Overall, Alkatout *et al*. demonstrated no significant difference between operative laparoscopy plus GnRHa and GnRHa at achieving a “cure” (i.e. no evidence of endometriosis at second-look laparoscopy (EEC score of 0) at 12 months) (*n* = 273; RR, 1.53; 95% CI, 0.95–2.48; p = .08); similarly, there was no significant difference in effect between operative laparoscopy and GnRHa (*n* = 262, RR, 1.23; 95% CI, 0.76–2.00, p = .41) [20]. Sutton *et al.* performed a second-look laparoscopy in 24/31 participants who initially underwent diagnostic laparoscopy, demonstrating an unchanged rAFS score in 10 (42%), a greater score in 7 (29%), and a lesser score in 7 (29%) [29]. They did not perform routine second-look laparoscopies in the group that was randomized to laser operative laparoscopy, so it is not possible to compare the progression of disease between groups. Wu *et al*. demonstrated a higher rate of resolution of endometriomas in the group who underwent combined operative laparoscopy (drainage of endometriomas) and CHM compared to those who received medical management with CHM

(*n* = 112; RR, 3.00; 95% CI, 1.17–7.70; p = .02) and danazol (*n* = 112; RR, 4.45; 95% CI, 1.56–12.73; p = .005) [30].

The quality-of-life analyses reported by Abbott *et al.* were the only of the kind. This study demonstrates statistically significant improvements over baseline for both immediate and delayed operative laparoscopy groups in all measures except the mental component of the SF-12 for the delayed laparoscopy group. When compared to a baseline population without endometriosis, scores for both groups were not significantly different at 12 months. The group that underwent immediate surgery reached equivalent scores for the EQ-5D VAS and the mental component of the SF-12 at 6 months [19].

With respect to adverse outcomes, documented findings for Abbott *et al*. and Alkatout *et al*. can be found above under the "*objective two*" heading. Jarrell *et al.* do not report adverse outcomes in either intervention group [23]. Lalchandani *et al*. report no surgical complications and do not report side effects from medical management; however, 12/18 (66.7%) of those randomized to the GnRHa group ultimately proceeded to surgical treatment [24]. Sutton *et al*. report no surgical complications [28]. Wu *et al*. reported one minor surgical complication in the operative laparoscopy plus CHM group (umbilical infection), one side effect from the CHM group (heavy menstrual bleeding), and a number of side effects experienced in the danazol group (acne: 10, weight gain: 15, hot flushes/sweating: 11, irregular vaginal bleeding: 14, abnormal liver function tests (normalized after cessation): 8). It is not clear whether these were individual patients experiencing the side effect or simply a count of the side effects experienced across the study.

Adverse Outcomes

Overall, five studies reported on adverse outcomes related to surgery [19, 24–26,28]. Combining data, there no significant evidence of a difference between operative laparoscopy and diagnostic laparoscopy for surgical complications (*n* = 554; RR, 1.98; 95% CI, 0.84–4.65; p

= .19, 5 RCTs, I^2 = 0%), though the quality was deemed to be "very low" (Figure 4). Three of the studies reported no adverse surgical outcomes in either operative or diagnostic laparoscopy group, so whilst they contribute to the total number of participants, they do not contribute to the RR [24, 26,28].

Quality assessment

The risk of bias classification for the included RCTs is depicted in Figure 5A and B.

Patient preference

A prospective study followed a cohort of 157 endometriosis patients through a self-elected, step-wise management pathway where surgery represented the final step [41]. Whilst they did not specifically aim to identify reasons for self-electing surgical management, pain and lack of efficacy of medical management, as well as intolerance of side effects were noted to be reasons for those who escalated to surgery. However, it was also noted in their discussion that of the 38 of patients who stated they were dissatisfied with medical management, only two elected to proceed to surgery, with the majority preferring to tolerate the reduced but persistent pain and symptoms/side effects [41]. Another study examined a group of women who were initially referred for surgical intervention for endometriosis involving colorectal disease (generally planned as a laparotomy and bowel resection), of whom half elected for medical management after counselling in the shared decision-making model [42]. The reasons for changing management were not documented. Of the women who initially chose medical management, six later elected for surgery, with the reason was documented as drug inefficacy or intolerance. Another seven reported dissatisfaction with management but were unwilling to pursue surgery – the reasons for this were not explored. It was suggested if more surgeries had been offered laparoscopically, results may have differed; this suggests that fear of perceived increased risk may be a barrier for women considering surgery.

This idea that fear may be a strong negative motivator is echoed by the works of qualitative researcher Seear, who examined barriers to compliance with medical intervention in endometriosis. She found that the reasons for non-compliance to treatment are complex and interwoven with fear and mistrust acquired along the long road to diagnosis, compounded by failed treatments [43]. This is reaffirmed by the qualitative findings of Chen and Manderson, who independently conclude that patients' perceptions that pelvic pain is seen in society as "not a real issue" is a barrier to women seeking treatment [32,34]. These fears may well result in presentation of the patient with what Barlow refers to as the "hit list" of treatments they are not prepared to undertake [44]; compounded by the accessibility (and overwhelming array) of testimonials and information on the internet.

Finally, it is worth noting that some 30-50% of endometriosis patients do not present with pain but primary infertility [45]. Culley *et al*. suggest that infertility may, in some women, override symptomatology as indication for desiring surgery [33]. Dyspareunia, sexual dysfunction and associated guilt are also highlighted as potential strong motivators influencing the women's choice of treatment [31,33].

Discussion

Main findings

We found operative laparoscopy may improve overall pain levels, but may have little or no difference for fertility-related outcomes when compared to diagnostic laparoscopy. The quality of the studies ranged from moderate to very low using GRADE classification.

Operative laparoscopy (with or without a GnRHa) appears to yield little or no difference in pregnancy and/or live birth rates when compared with diagnostic laparoscopy or a GnRHa. These findings differ from that published in the previous Cochrane review on laparoscopic surgery for endometriosis [40]. The difference in clinical pregnancy rate can be explained by a few factors: first, the addition of the Parazzini *et al*. study to our meta-analysis, which was

excluded by the Duffy *et al.* group because of the use of GnRHa post-operatively [27,40]. Interestingly, the Marcoux *et al*. study was still included by Duffy *et al.* despite a portion of both groups receiving cointerventions (including therapies such as IVF and ovulation induction) [25]. Second, our meta-analysis was performed using the random-effects model, rather than the fixed-effects model, which was utilized by Duffy *et al.* Given the individualized nature of surgical interventions, a random-effects model is more appropriate. The difference in live birth is also partly explained by the inclusion/exclusion of Parazzini *et al.* More interestingly, Duffy *et al*. bundled "ongoing pregnancy" with live birth and included Marcoux *et al*. and Gad *et al.* We did not believe that either of these studies were appropriate for assessment of live birth; Marcoux *et al*. specifically states their "follow-up ended at 20 weeks because fetal losses are rare after that time" [25]. This assumption is challenged by a recent meta-analysis demonstrating the increased risk of stillbirth and neonatal death for fetuses of women with endometriosis [46]. Gad *et al*. similarly report pregnancy outcomes "up to 20 weeks" and makes no reference to live birth as an outcome [22].

For overall pain, operative laparoscopy may improve women's pain at 6 months post-operatively when compared to diagnostic laparoscopy. A three-month course of GnRHa may improve dysmenorrhea and dyspareunia at 12 months post-operatively when compared to use of GnRHa alone. Quality of life, as determined by the EQ-5D VAS and the mental component of the SF-12, was seen to be improved by operative laparoscopy when compared to diagnostic laparoscopy at 6 months and had a sustained effect at 12 months [19]. Beyond the Abbott *et al*. study, which included a group having immediate laparoscopy and a group having delayed laparoscopy, no studies included data that could inform the optimal timing of surgery. A glaring gap in the evidence is the assessment of longer term pain outcomes following surgery.

Abbott *et al*., randomizing to immediate versus delayed laparoscopic excision of endometriosis, provided the only RCT data that begin to address the appropriate timing of surgery. This RCT also nicely demonstrated how endometriosis might change/progress over a 6 month period

with their crossover RCT design [19]. Not surprisingly, operative laparoscopy yields an improvement in rAFS score compared to diagnostic laparoscopy [19]. The study by Alkatout *et al.* attempted to demonstrate the same improvement in endometriosis state (using EEC) by comparing operative laparoscopy plus GnRHa with operative laparoscopy and diagnostic laparoscopy plus GnRHa [20]; though they did demonstrate the highest "cure" rate amongst those who underwent operative laparoscopy and GnRHa use, they did not quantify the state of change by individual patient, which makes it difficult to understand how the disease progresses.

Strengths and limitations

A novel strength of this study was that our objectives were developed with the aim of highlighting the importance of timing surgery. For example, objective three, for which no studies were identified, aimed to understand whether prophylactic surgery for endometriosis in the absence of symptoms alters disease progression, either in the form of symptom onset or a change in the physical nature of the disease. Might superficial endometriosis progress to deep endometriosis or are these different entities? A planned subgroup analysis, which could not be completed due to the absence of studies, was on adolescent patients and how surgery might have utility (compared to no surgery or medical management). Another subgroup which we hoped to evaluate was women with endometriosis who no longer/do not seek fertility; what is the utility of surgery (possibly including hysterectomy) in this special population? The main weakness is that, unfortunately, in spite of our study aim, no studies yielded conclusive information on when to have surgery and when not to have surgery. At present, expert consensus suggests medical management should be utilized until either medical management fails or fertility is sought (necessitating the cessation of contraceptive agents) [12,47]. One striking finding of this study is the lack of high quality (i.e. RCT) evidence comparing typical contraceptive or hormonal agents to operative laparoscopy. We would suggest the development of a RCT that compares surgery to alternatives in the setting of failed medical

management, in which the time from diagnosis and duration of medical management should be included.

Interpretation

Consistent with other RCTs on laparoscopic surgery for other indications, there is a significant lack of reporting of adverse outcomes. The occurrence of surgical complications is rare, hence RCTs of these sizes would likely be underpowered anyway to provide interpretable data regarding surgical complications, even via a meta-analysis of operative complications of laparoscopy, which has been demonstrated with our meta-analysis. Adverse outcomes are also not exclusively relevant to surgery. All possible comparison groups (e.g. oral contraceptive pill, selective progestin receptor modulators, ovulation induction, IVF, GnRHa) carry their own set of risks and knowledge of these outcomes is extremely relevant to clinicians and patients. Patients may in fact define medical management failure as their inability to tolerate side effects more than the inability of the medication to treat their problem. At odds with previous evidence and guideline recommendations [15, 40,48], we did not find fertility benefit from laparoscopic surgery in this systematic review. The main reason for this discrepancy is that the Marcoux *et al*. study has been the RCT on which inferences regarding a positive impact of laparoscopic removal of endometriosis was based [25], however more recent RCTs have not confirmed this benefit. Hence, we are far from certain about the fertility benefit of operative laparoscopy for women with endometriosis and this requires further evaluation by a well-designed and appropriately-powered RCT as a matter of priority.

Endometriosis remains a challenging disease to diagnose. Though non-invasive imaging has come a long way and many more patients are being diagnosed in a non-operative setting [9], these studies are quite dated and likely relied on surgical diagnosis. Most studies excluded any patients that had previous medical or surgical treatment for endometriosis. Alkatout *et al*. actually state that patients with pre-operatively diagnosed deep endometriosis of bowel or bladder were excluded from their study [20]. For many women, the *diagnosis* of endometriosis

itself may be therapeutic, or at least validating. This may not only be a factor in decision-making to undergo surgery for some patients, but the diagnosis may amplify the therapeutic value of the placebo effect [19], thus diminishing the effect difference (at least from a pain/quality of life perspective) in some studies. The other major limitation of relying on a surgical diagnosis is the occasional inability to completely excise/ablate the disease due to limited surgeon skill or inadequate informed consent [49]. Moini *et al*. specifically state that "in difficult anatomic positions, implants were cauterized with the fulguration method without complete resection" [26]. An ideal study design would involve a diagnosis of endometriosis that does not happen at the same time as planned therapy. This could either be a diagnosis using imaging or a diagnosis by diagnostic laparoscopy, both of which still have limitations in understanding the full extent of disease. This type of true diagnosis would allow patients to be referred to appropriately-trained endometriosis surgeons and be fully consented for whatever study intervention is being investigated.

Patient preference

Whilst there is consensus in the literature regarding shared decision-making and tailoring treatment options to suit the woman's individual goals, we lack research and data on the priorities and decision-making processes of our patients. A review of the literature found no quantitative or qualitative studies specifically aimed at elucidating the factors informing a woman's choice for surgery. Whilst several studies suggest that factors such as reduction in symptomatology (most commonly dysmenorrhea, dyschezia, dyspareunia), age, desire for fertility, and treatment intolerance or failure of more conservative measures [44,50] are important, these observations appear to be subjective and derived from clinicians rather than objective patient data.

There are sparse data suggesting that fear of perceived risk, fertility, dyspareunia, sexual functioning and failure of medical treatment are important factors to patients considering surgery, potentially more so than pain alone. There is also evidence that a societal perception

that their pain is “not serious”, delayed or misdiagnosis and poor communication of information significantly undermine confidence in medical professionals and may contribute to biases against treatments, and development of what Barlow refers to as the “hit list” – a list of treatments that patients are not prepared to even consider due to previous experiences [44].

The tide, however, is turning and there is an increased focus on patient-centred care across endometriosis research. Poulos *et al*. performed a discrete choice experiment in women with endometriosis, reporting that respondents placed the greatest weight on hot flashes associated with treatment, dyspareunia, pelvic pain and dysmenorrhoea, compared to risk of bone fracture and risk of associated pregnancy problems [51]. However, no conclusions can be made with regards to patient preference and decision-making for surgery. Geukens *et al*. recently published an article recommending the use of patient-centred assessment measures such as ENDOCARE to guide management [52]. Guideline groups are actively involving patients and patient advocacy groups and decision tools are being developed to guide the patient’s decisions with regards to medical management [53]. Given this, it is all the more crucial to fund research investigating the patient decisions, and barriers thereof, to surgery. The work of Chen and Bucher highlights that research into understanding patient reasons for decision is both possible and pertinent to patient care and shared decision-making [32,57].

Conclusion

There are genuine concerns about the overall quality of research identified in this field. These concerns translate to a difficulty in making strong statements and recommendations from the published literature. There does appear to be evidence for an improvement in pain-related symptoms when operative laparoscopy is done, but there may be little or no effect for fertility-related outcomes. Due to the very low quality of the evidence, it is uncertain if operative laparoscopy has an effect on the rate of surgical complications compared to diagnostic laparoscopy. If we are asking *when* is it definitely indicated to have operative laparoscopic surgery, one really good indication would be the participation in a randomized trial, especially if

pregnancy or birth is one of the primary outcomes. Yet more good quality randomized trials are required to further investigate the timing of surgery.

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Table 1: Overall review aim and specific objectives based on various populations and outcomes

Aim	
To assess the impact and safety of laparoscopic surgery on symptomatology, fecundity, recurrence of disease, and/or reoperation rates compared to alternative therapies.	
	Objective	**Outcome**

1	To assess the effectiveness and safety of laparoscopic surgery in the treatment of endometriosis-associated infertility.	▪ Primary outcome: live birth rate
		▪ Secondary outcome:
		  ▪ Clinical pregnancy/miscarriage
		  ▪ Risks of (a) surgery, (b) medical treatment, (c) no intervention

2	To assess the effectiveness and safety of laparoscopic surgery for endometriosis on future fertility in patients with a desire for fertility but not currently trying to conceive.	▪ Primary outcome: live birth rate
		▪ Secondary outcome:
		  ▪ Clinical pregnancy/miscarriage
		  ▪ Risks of (a) surgery, (b) medical treatment, (c) no intervention

3	To assess the impact and safety of laparoscopic surgery on the progression of disease state or patient symptomatology in patients who are asymptomatic from a pain perspective.	▪ Primary outcome: progression of disease to a symptomatic state
		▪ Secondary outcome:
		  ▪ Progression of endometriosis lesion size and/or locations
		  ▪ Risks of (a) surgery, (b) medical treatment, (c) no intervention

4	To assess the effectiveness and safety of laparoscopic surgery in the treatment of endometriosis-associated pain problems.
	
	Subgroup populations:
	adolescents (menarche-19 years)
	▪ patients who are done family building
		▪ Primary outcome: overall pain; mean difference or standard mean pain difference measured by a pain scale at different time intervals or as specified in the individual study
		▪ Secondary outcome:
		  ▪ Specific types of pain: self-reported pain relief measured by a pain scale at different time intervals or as specified in the individual study measuring:
		  ▪ Pelvic pain, dysmenorrhea, dyspareunia, dyschezia
		  ▪ Fertility-related
		  ▪ Live birth rate
		  ▪ Clinical pregnancy/miscarriage
		  ▪ Progression of endometriosis lesion size and/or locations
		  ▪ Recurrence of endometriosis-associated pain symptoms: self-reported pain presence measured by a pain scale at different time intervals or as specified in the individual study (after intervention/comparison versus a later point in time)
		  ▪ Risks of (a) surgery, (b) medical treatment, (c) no intervention

Table 2A: Characteristics of studies included in the systematic review

Author	Objective	Country	Full-text	Sample size	Intervention		Mean Age (Years±SD)		Stage of endometriosis (cases)	Characteristics of controls
					Cases	Control	Cases	Control		
Abbott *et al.* 2004 [19]	2, 4	United Kingdom	Yes	Intervention: 20 Control: 19	Operative laparoscopy (excision)	Diagnostic laparoscopy + Delayed operative laparoscopy	32.1± 5.8	32.1± 5.8	Laparoscopy: Surgical group rAFS stage I (1/20); II (9/20); III (2/20); IV (8/20)	Median rAFS score; 27 in the control compared with 16 in surgical group (p = .84) Control group rAFS stage II (8/19); III (2/19); IV (9/19)
Alkatout *et al*. 2013 [20]	2, 4	Germany	Yes	Intervention 1: 137 Intervention 2: 148 Control: 125	Cases 1: Operative laparoscopy (excision) Cases 2: Operative laparoscopy (excision) + Leuprorelin acetate	Leuprorelin acetate	18-44 (range)		Laparoscopy: Surgical group EEC stage: I (59/137); II (44/137); III (24/137) Combined surgery + GnRH group EEC stage: I (79/148); II (36/148); III (33/148)	Greater proportion of patients reported initial symptoms of pain (dysmenorrhea, dyspareunia and abdominal pain) Control group EEC stage I (50/125); II (47/125); III (28/125)
Demirol *et al.* 2006 [21]	1	Turkey	Yes	Intervention: 49 Control: 50	Operative laparoscopy (cystectomy) + ICSI	ICSI	35.2± 0.3	34.9± 0.2	Ultrasound: Unilateral endometrioma size 3-6cm	Unilateral endometrioma size 3-6cm; Similar with respect to BMI, male factor infertility, treatment with ICSI
Gad *et al*. 2012 [22]	1	Egypt	No. Abstract only	Intervention: 20 Control: 21	Laparoscopic resection or ablation	Diagnostic laparoscopy	n/a	n/a	Laparoscopy: rAFS stage I or II	Control group: rAFS stage I or II
Jarrell *et al*. 2005 [23]	4	Canada	Yes	Intervention: 9 Control: 7	Operative laparoscopy (excision)	Diagnostic laparoscopy + expectant management	28.9	29.4	Laparoscopy: Excision group rAFS stage I (2/15); II (10/15); III (3/15)	Control group rAFS stage I (4/14); II (10/14) Lower proportions of nodular endometriotic disease at time of surgery (p < .025)
Lalchandani *et al.* 2005 [24]	4	Republic of Ireland	Yes	Intervention: 17 Control: 18	Operative laparoscopy (helium thermal coagulator therapy)	Diagnostic laparoscopy + Goserelin + add back therapy	32.8	20-45	Laparoscopy: Surgical group rAFS mean score = 6 (range 2-12)	Control group rAFS mean score = 5 (range 2-12)

Marcoux *et al.* 1997 [25]	1	Canada	Yes	Intervention: 172 Control: 169	Operative laparoscopy (excision or ablation)	Diagnostic laparoscopy + expectant management	31.0± 3.0	30.0± 4.0	Laparoscopy: rAFS stages I-II; Median rAFS score = 4	Greater proportion of younger women (<30) in control group (45 vs 35); Median rAFS score = 4
Moini *et al.* 2012 [26]	1	Iran	Yes	Intervention: 38 Control: 38	Operative laparoscopy (ablation)	Diagnostic laparoscopy	27.8± 3.3	27.7± 3.1	Laparoscopy: rAFS stage I (52.6%); rAFS stage II (47.4%)	rAFS stage I (57.9%); rAFS stage II (42.1%)
Parazzini *et al.* 1999 [27]	1	Italy	Yes	Intervention: 51 Control: 45	Operative laparoscopy (excision or ablation)	Diagnostic laparoscopy + expectant management	30.6± 3.6	30.3± 3.8	Laparoscopy: rAFS stage I (20/51); II (31/51)	Control group rAFS stage I (20/45); II (25/45)
Sutton *et al*. 1994/1997 [28,29]	4	United Kingdom	Yes	Intervention: 32 Control: 31	Operative laparoscopy (laser vaporization, adhesiolysis, and uterine nerve transection)	Diagnostic laparoscopy + expectant management	29.0 18-42 (range)	29.5 18-42 (range)	Laparoscopy: Laser group rAFS stage I (13/32); II (16/32); III (3/32)	Control group rAFS stage I (16/31); II (12/31); III (3/31) Lower initial median visual analogue pain score; 7.5 compared with 8.5
Wu *et al*. 2002 [30]	4	China	Yes	Intervention: 72 Control 1: 40 Control 2: 40	Operative laparoscopy or laparotomy (drainage of cyst) + Chinese herbal medicine	Control 1: Chinese herbal medicine Control 2: Danazol	33.1± 4.1 22-45 (range)	33.4± 4.7 21-44 (range)	Laparoscopy or laparotomy: Combination group moderate* (33/72); advanced* (39/72)	Lower proportion of patients in an advanced stage of endometriosis; 21 compared with 39; lower number of patients with bilateral cysts; 11 compared with 21; lower number of patients with infertility; 13 compared with 23 Control group moderate* (19/40); advanced* (21/40)

Legend: SD – standard deviation; EEC – Endoscopic Endometriosis Classification; rAFS – revised American Fertility Society classification of endometriosis; BMI – body mass index; ICSI – intracytoplasmic sperm injection; *as per Third Academic

Conference of Gynecology-Obstetrics Specialty Committee of Chinese Association of Integration of Traditional and Western Medicine

Table 2B: Characteristics of studies included in the patient preference narrative review

Author	Country	Study Design	Full-text	Sample size	Mean Age (Years)	Stage of endometriosis
Adamson 1999	United States of America	Case Report	Yes	1	36	Unspecified
Chen *et al*. 2018	United States of America	Cross-sectional survey study; Qualitative thematic analysis	Yes	225	35± 6.8 18-57 (range)	Women with dysmenorrhea, 5% confirmed endometriosis
Culley *et al*. 2013	United Kingdom	Qualitative trial	No, Conference Abstract	44	Unspecified	Unspecified
Manderson *et al*. 2008	Australia	Qualitative trial	Yes	40	46 20-78 (range)	Unspecified
Seear 2009	Australia	Qualitative trial	Yes	20	34 24-55 (range)	Unspecified
Vercellini *et al*. 2018	Italy	Prospective single-arm self-controlled study	Yes	157	33 ± 5.7	Unstaged; included both surgically and non-surgically confirmed diagnoses. 41% deep endometriotic lesions, 41% ovarian endometriomas, 21% adenomyosis
Vercellini *et al*. 2018	Italy	Parallel cohort study	Yes	87	45 30-67 (range)	Unstaged; symptomatic deep bowel endometriosis infiltrating the sigmoid colon, the rectosigmoid junction or the proximal rectum, confirmed by ultrasound.

Table 3: Summary of findings

Operative laparoscopic surgery versus alternative therapy for endometriosis										
					Number of patients		Effect			
RQ	Outcomes	*n* studies	Operative laparoscopy + ____	Alternative therapy	Operative laparoscopy	Alternative	Relative (95% CI)	Absolute per 1,000 (95% CI)	Certainty (GRADE)	Importance
1	Live birth rate	1	N/A	Diagnostic laparoscopy	10/51 (19.6%)	10/45 22.2%)	RR 0.88 (0.40-1.92)	27 fewer (from 133 fewer to 204 more)	⊕◯◯◯ VERY LOW[1,2]	Due to the very low quality of the evidence, it is uncertain if operative laparoscopy improves live birth rates.
	Clinical pregnancy	4			91/316 (28.8%)	62/308 (20.1%)	RR 1.38 (0.99-1.92)	76 more (from 2 fewer to 185 more)	⊕⊕⊕◯ MODERATE[3]	There is moderate quality evidence that operative laparoscopy probably yields little or no difference on clinical pregnancy rates compared to diagnostic laparoscopy.
	Miscarriage	2			15/223 (6.7%)	11/214 (5.1%)	RR 1.31 (0.60-2.86)	16 more (from 21 fewer to 96 more)	⊕⊕◯◯ LOW[4,5]	There is low quality evidence that operative laparoscopy may have little or no difference on the rate of miscarriages compared to diagnostic laparoscopy.
2	Live birth rate	2	N/A	Diagnostic laparoscopy + GnRHa	62/137 (45.3%)	69/125 (55.2%)	RR 0.82 (0.64-1.04)	99 fewer (from 199 fewer to 22 more)	⊕⊕⊕◯ MODERATE[6]	There is moderate quality evidence that operative laparoscopy (with/without GnRHa) probably yields little or no difference on clinical
	Clinical pregnancy				75/137 (54.7%)	81/125 (64.8%)	RR 0.84 (0.69-1.03)	104 fewer (from 201 fewer to 19 more)	⊕⊕⊕◯ MODERATE[6]	
	Live birth		GnRHa		74/148	69/125	RR	50	⊕⊕⊕◯	

	rate				(50.0%)	(55.2%)	0.91 (0.72-1.14)	fewer (from 155 fewer to 77 more)	MODERATE[6]	pregnancy or live birth rates compared to treatment with GnRHa.
	Clinical pregnancy				89/148 (60.1%)	81/125 (64.8%)	RR 0.93 (0.77-1.12)	45 fewer (from 149 fewer to 78 more)	⊕⊕⊕◯ MODERATE[6]	
3	Progression of disease to a symptomatic state	0	-	-	-	-	-	-	-	No studies were found that looked at these outcomes.
	Progression of disease size and/or locations									
4	Overall pain better or improved at 6 months*	2	N/A	Diagnostic laparoscopy	36/52 (69.2%)	13/50 (26.0%)	RR 2.65 (1.61-4.34)	429 more (from 159 more to 868 more)	⊕⊕◯◯ LOW[7]	There is low quality evidence that operative laparoscopy may improve overall pain levels at 6 months compared to diagnostic laparoscopy.
All	Adverse outcomes	5	-	Diagnostic laparoscopy	15/279 (5.4%)	7/275 (2.5%)	RR 1.98 (0.84-4.65)	25 more (from 4 fewer to 93 more)	⊕◯◯◯ VERY LOW[8,9]	Due to the very low quality of the evidence, it is uncertain if operative laparoscopy has an effect on the rate of surgical complications compared to diagnostic laparoscopy.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes:
[1] Downgraded two levels for imprecision: very small sample size for relatively rare events, 95% CI crosses both benefit and harm.
[2] Downgraded one level for risk of bias: single included study rated unclear in four domains.
[3] Downgraded one level for risk of bias: one of the three included studies are at high risk of bias in selection bias and attrition bias, with both the remaining two studies both having unclear risk of bias relating to blinding.

[4] Downgraded one level for inconsistency: results are not consistent across studies (though have overlapping confidence intervals).
[5] Downgraded one level for imprecision: very small sample size for relatively rare events, 95% CI crosses both benefit and harm.
[6] Downgraded one level for risk of bias: single included study rated unclear in four domains.
[7] Downgraded two levels for imprecision: small sample size with very wide CI.
[8] Downgraded two levels for imprecision: small sample size for relatively rare events, with very wide CI.
[9] Downgraded one level for risk of bias: one of the five included studies are at high risk of bias in selection bias and attrition bias; one of five are at high risk for detection bias; two of five are at high risk for performance bias. The study contributing greatest weight has unclear risk of bias relating to performance, detection and attrition.

Legend: n – number; RR – relative risk; CI – confidence interval; N/A – not applicable; GnRHa – gonadotropin-releasing hormone agonist

*As measured by the proportion of women reporting overall improvement in pain using a visual analogue scale.

Figures Legends

Figure 1A: Flow diagram for study selection for objective 1

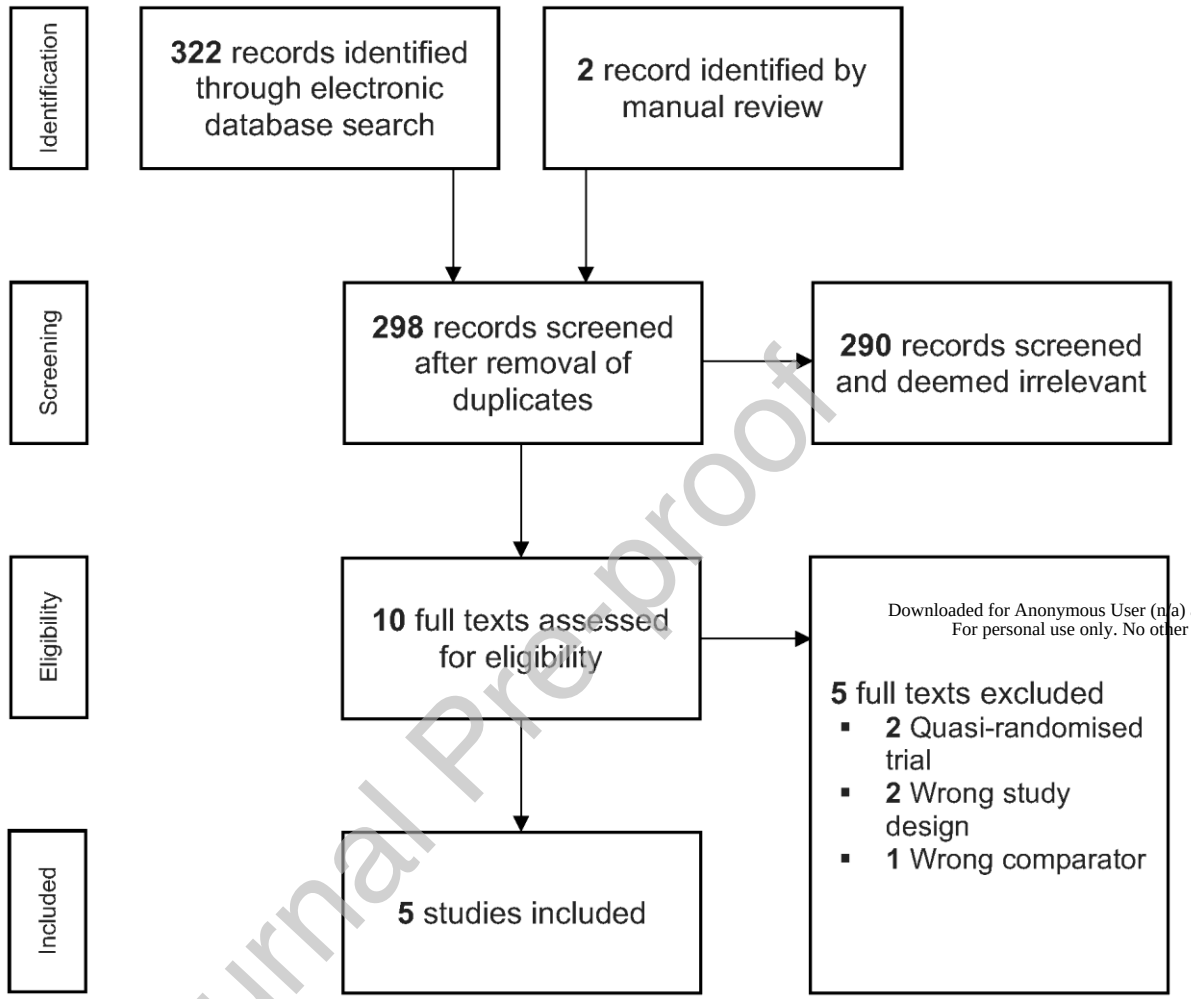


Figure 1B: Flow diagram for study selection for objective 2

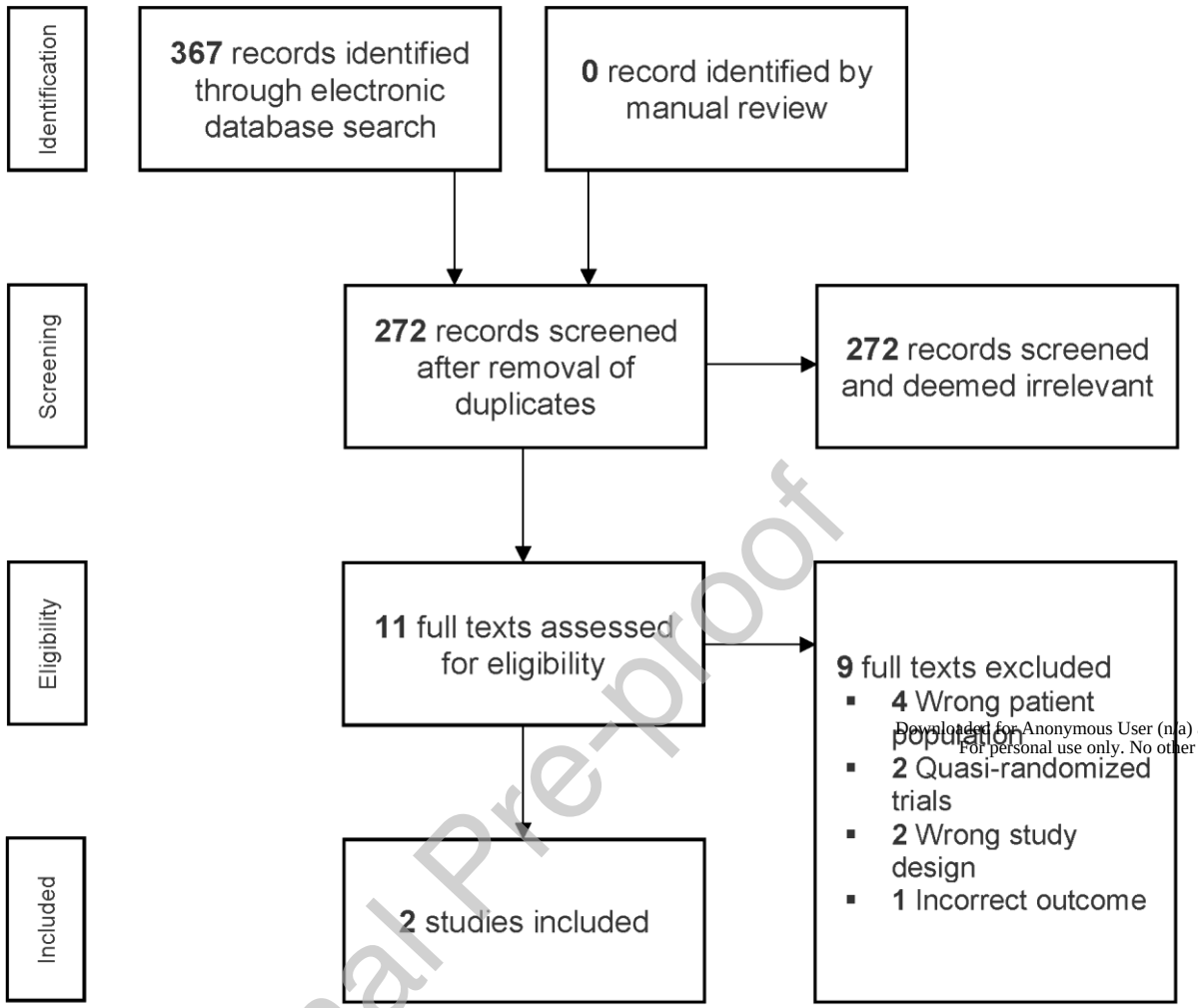


Figure 1C: Flow diagram for study selection for objective 3

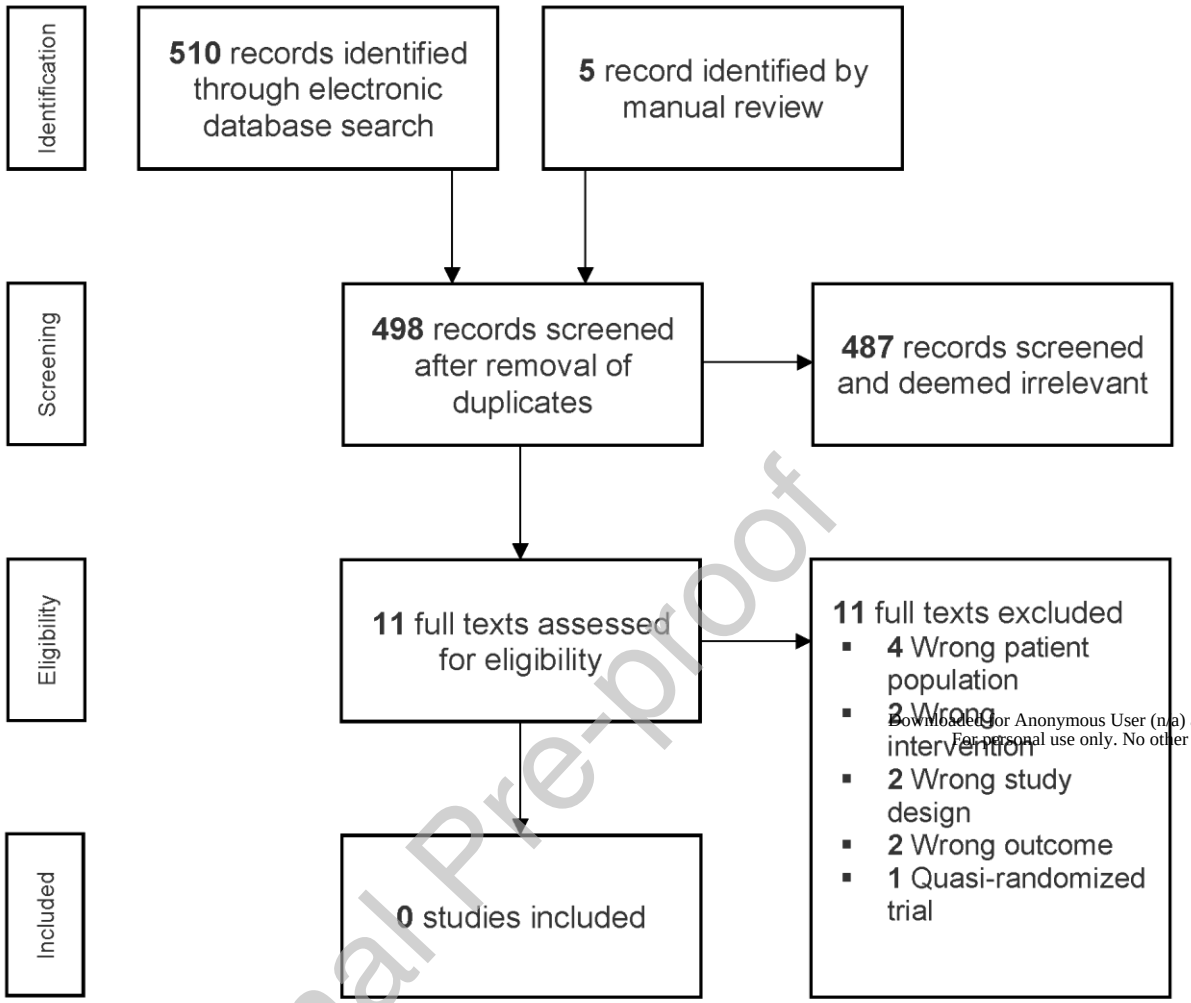


Figure 1D: Flow diagram for study selection for objective 4

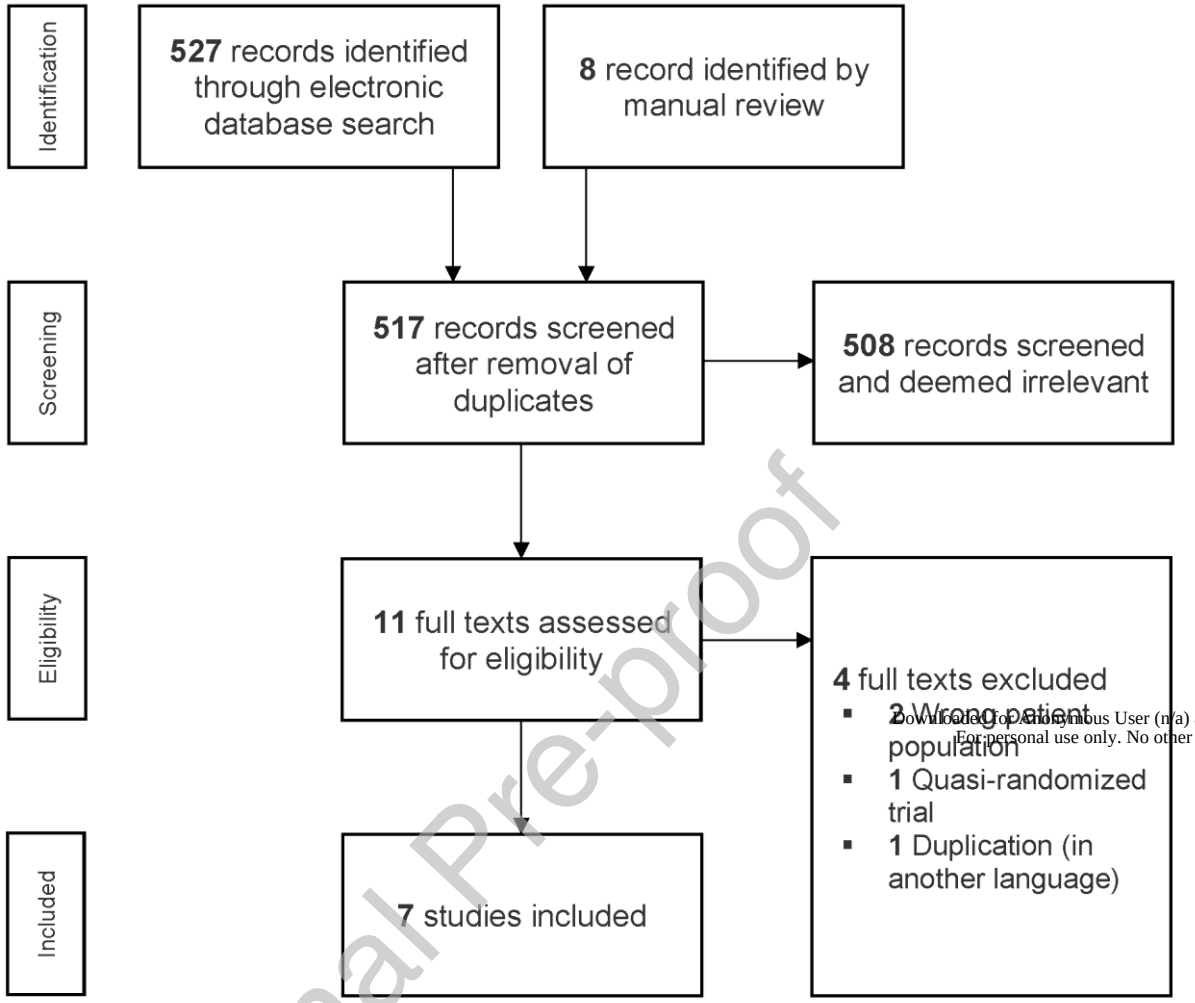


Figure 1E: Flow diagram for study selection for patient preference objective

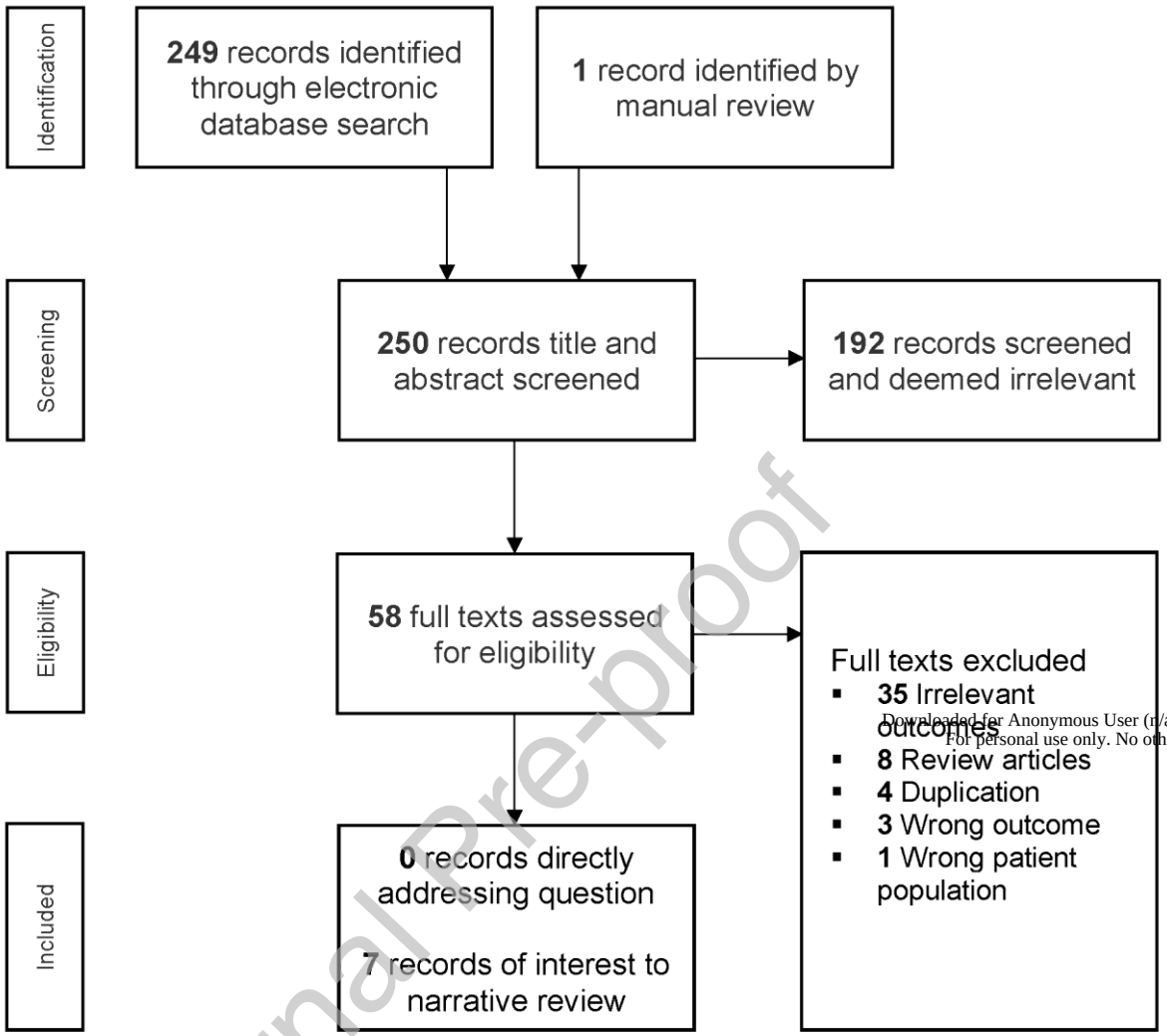


Figure 2: Forest plot for meta-analysis of operative laparoscopy versus diagnostic laparoscopy for clinical pregnancy

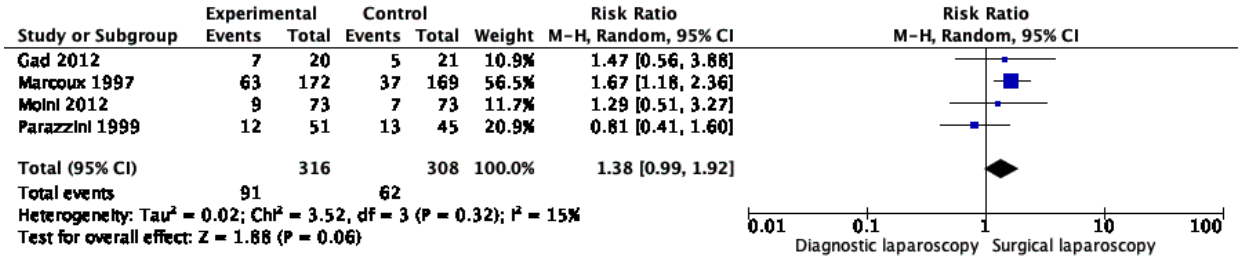


Figure 3: Forest plot for meta-analysis of operative laparoscopy versus diagnostic laparoscopy for overall pain 6 months post-operatively

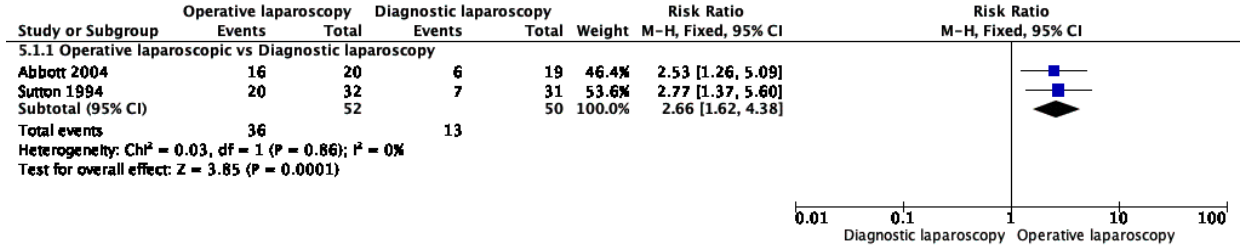


Figure 4: Forest plot for meta-analysis of operative laparoscopy versus diagnostic laparoscopy for adverse surgical outcomes

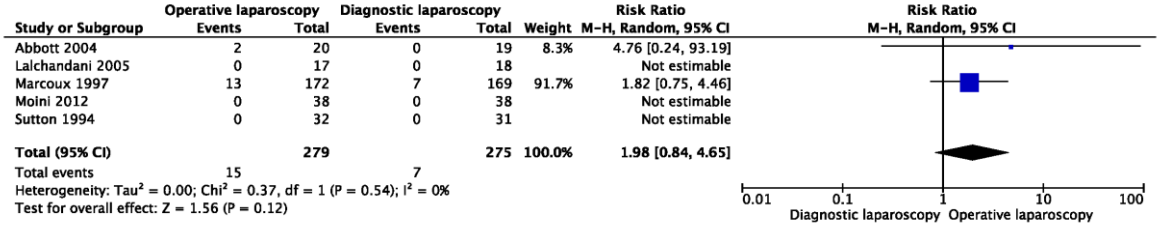


Figure 5A: Risk of bias summary

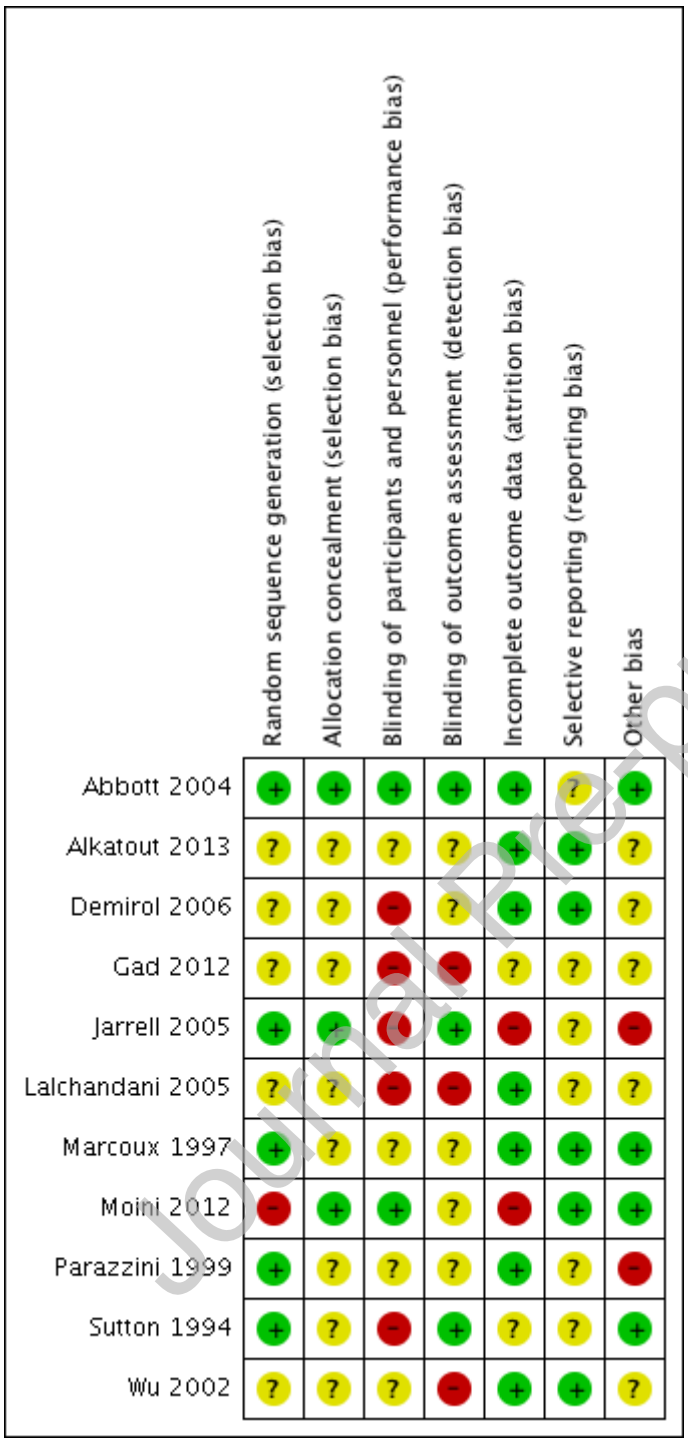
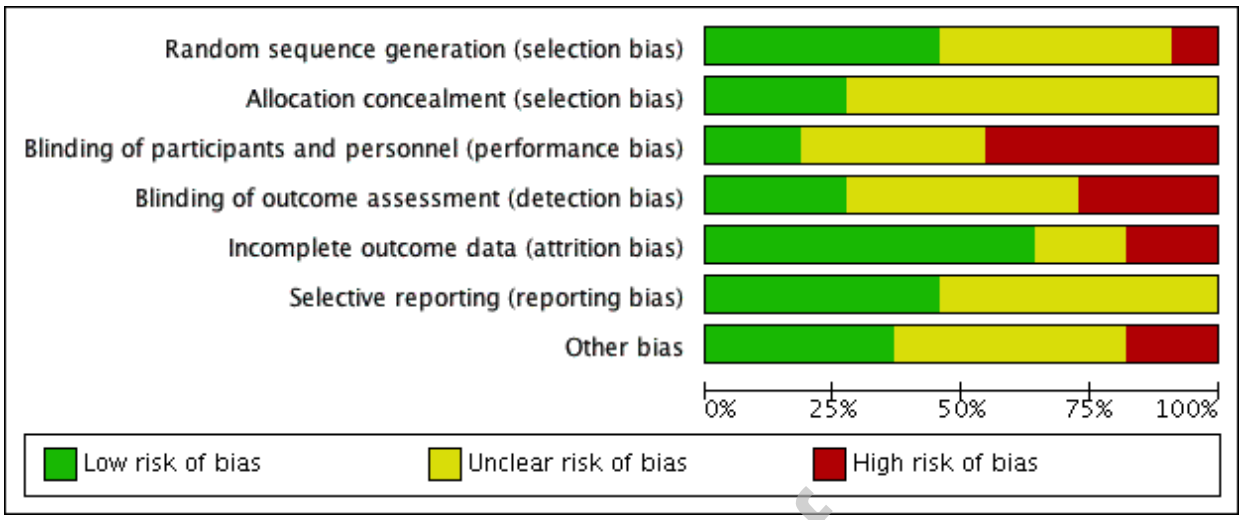


Figure 5B: Risk of bias graph



Appendix 1
Search Strategy Example for Objective 1
Embase Classic+Embase

1 exp Laparoscopy/ (151043)

2 Laparoscop$.ti,ab,sh.(222494)

3 Laparoscop$.tw. (189963)

4 celioscop$.tw. (580)

5 peritoneoscop$.tw. (1179)

6 exp Surgical Procedures, Minimally Invasive/ (38372)

7 minimally invasive.tw. (88105)

8 Lasers/ (65751)

9 exp laser/(126909)

10 exp diathermy/ (126909)

11 Diathermy.tw.(5037)

12 LUNA.tw. (1432)

13 presacral neurectom$.tw. (177)

14 laser$.tw. (177)

15 plasmajet.tw. (78)

16 plasma jet.tw. (370)

17 microlaparoscop$.tw. (199)

18 minilaparoscop$.tw. (352)

19 exp robotics/ (35592)

20 exp computer assisted surgery/ (11)561)

21 Computer Assisted Surg$.tw.(1278)

22 da vinci.tw. (4940)

23 (keyhole adj3 surg$).tw.(202)

24 Robot$.tw. (59216)

25 remote surg$.tw. (158)

26 microsurg$.tw. (30612)

27 uterine nerve ablation$.tw. (40)

28 excision.tw. (157362)

29 (ablation or ablative).tw. (140959)

30 (minimal$ adj5 surg$).tw. (37046)

31 exp hand assisted laparoscopy/ (726)

32 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (916027)

33 exp Endometriosis/ (37726)

34 endometrio$.tw. (43998)

35 33 or 34 (50971)

36 32 and 35 (13427)

37 exp anti-inflammatory agents, non-steroidal/ or exp aspirin/ or exp diclofenac/ or exp flurbiprofen/ or exp ibuprofen/ or exp indomethacin/ or exp ketoprofen/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp naproxen/ or exp piroxicam/ or exp cyclooxygenase inhibitors/ or exp cyclooxygenase 2 inhibitors/ (758155)

38 nonsteroidal$.tw. (28247)

39 non-steroidal$.tw. (26540)

40 nsaid$.tw. (40655)

41 (COX 2 or COX-2 or COX2).tw. (42623)

42 (diclofenac or flurbiprofen or ibuprofen or meclofenamic acid or mefenamic acid or naproxen or aspirin).tw. (152429)

43 (etoricoxib$ or lumiracoxib$ or parecoxib$).tw. (2071)

44 (rofecoxib$ or valdecoxib$).tw. (3099)

45 (acemetacin or celecoxib or dexibuprofen or dexketoprofen or indometacin or ketoprofen).tw. (15620)

46 (ponstan or voltaren).tw. (3181)

47 (cyclooxygenase inhibitor$ or cyclooxygenase 2 inhibitor$).tw. (7614)

48 (sulphonanilide$ or flufenamic or nimesulide).tw. (3559)

49 (salicylate$ or sulindac or acetylsalicylic).tw. (30065)

50 piroxicam.tw. (30065)

51 CONTRACEPTIVES, ORAL/ (47360)

52 CONTRACEPTIVES, ORAL, SYNTHETIC/ (47360)

53 CONTRACEPTIVES, ORAL, COMBINED/ (47360)

54 (combin$ adj3 (oral$ or hormon$) adj3 (pill$ or contracept$)).tw. (4921)

55 CONTRACEPTIVES, ORAL, HORMONAL/ (47360)

56 contraceptive ring.tw. (138)

57 VAGINAL RING/ (1921)

58 vaginal ring.tw. (1147)

59 CONTRACEPTIVE PATCH/ (240)

60 contraceptive patch$.tw. (291)

61 PROGESTERONE/ (101514)

62 PROGESTERONE CONGENERS/ (3488

63 progesterone$.tw. (105321)

64 PROGESTINS/ (26740)

65 (progestin$ or progestogen$ or gestagen$).tw. (22799)

66 DYDROGESTERONE/ (1928)

67 dydrogesterone$.tw. (681)

68 NORETHINDRONE/ (8766)

69 (norethindrone$ or norethisterone$).tw. (3954)

70 LEVONORGESTREL/ (11483)

71 levonorgestrel$.tw. (5801)

72 MEDROXYPROGESTERONE 17-ACETATE/ (17528)

73 medroxyprogesterone$.tw. (7608)

74 depo.tw. (3646)

75 dmpa.tw. (1456)

76 DIENOGEST/ (1196)

77 dienogest.tw. (805)

78 INTRAUTERINE DEVICES, MEDICATED/ (18314)

79 lng-ius.tw. (1082)

80 ((intrauterine$ or intra uterine$) adj3 levonorgestrel$).tw. (2123)

81 DANAZOL/ (8495)

82 danazol$.tw. (3379)

83 GONADOTROPINS/ (34981)

84 gonadotrop?in$.tw. (79556)

85 GnRH$.tw. (28648)

86 GONADORELIN/ (37052)

87 gonadorelin$.tw. (360)

88 BUSERELIN/ (4427)

89 buserelin$.tw. (1678)

90 GnRH/ (37052)

91 GOSERELIN/ (6915)

92 goserelin$.tw. (1446)

93 LEUPROLIDE/ (10868)

94 (leuprolide$ or leuprorelin$).tw. (3415)

95 NAFARELIN/ (992)

96 nafarelin$.tw. (341)

97 TRIPTORELIN/ (5207)

98 triptorelin$.tw.(1237)

99 ELAGOLIX/ (126)

100 elagolix.tw. (92)

101 DEGARELIX/ (723)

102 degarelix.tw. (409)

103 PROGESTERONE RECEPTOR MODULATOR/ (603)

104 SELECTIVE PROGESTERONE RECEPTOR MODULATOR/ (603)

105 PRM$.tw. (6219)

106 SPRM$.tw.(283)

107 PRM/ (1)

108 progesterone receptor modulat$.tw. (627)

109 selective progesterone receptor modulat$.tw. (427)

110 PROGESTERONE RECEPTOR ANTAGONIST/(6)

111 progesterone receptor antagonist$.tw.(371)

112 ULIPRISTAL ACETATE/ (964)

113 ULIPRISTAL/ (1073)

114 ulipristal acetate.tw. (676)

115 ulipristal.tw. (760)

116 TELAPRISTONE/ (16)

117 telapristone.tw. (28)

118 MIFEPRISTONE/ (12421)

119 mifepristone.tw. (4471)

120 AROMATASE INHIBITORS/ (12833)

121 aromatase inhibitor$.tw. (11029)

122 aromatase inhibit$.tw. (11309)

123 ANASTROZOLE/ (9218)

124 anastrozole.tw. (2862)

125 LETROZOLE/ (11227)

126 letrozole.tw. (4897)

127 EXEMESTANE/ (5856)

128 exemestane.tw. (2287)

129 ESTROGEN RECEPTOR MODULATOR/ (7)

130 estrogen receptor modulat$.tw. (4208)

131 oestrogen receptor modulat$.tw.(414)

132 SELECTIVE ESTROGEN RECEPTOR MODULATOR/ (7578)

133 SERM$.tw.(3901)

134 selective estrogen receptor modulat$.tw.(3951)

135 selective oestrogen receptor modulat$.tw.(390)

136 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 (1185320)

137 32 or 136 (2071915)

138 35 and 137 (22052)

139 36 and 136 (2861)

140 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp zygote intrafallopian transfer/(67931)

141 (in Vitro adj2 fertili$).tw. (31400)

142 (ivf or icsi or ZIFT).tw.(45060)

143 (intracytoplas$ adj2 sperm).tw. (9411)

144 zygote intrafallopian transfer$.tw.(100)

145 (embryo transfer$ or ET).tw. (657126)

146 invitro fertili$.tw.(179)

147 exp Clomiphene/ (7568)

148 clomi$.tw. (12427)

149 exp insemination, artificial/ or exp insemination, artificial, homologous/ (19716)

150 (intrauter$ adj5 inseminat$).tw. (3759)

151 (artificial adj2 inseminat$).tw. (7075)

152 IUI.tw. (3183)

153 fertili?ation.tw. (71455)

154 ivf et.tw.(3099)

155 ivf.tw.(38423)

156 (blastocyst adj2 transfer$).tw.(2217)

157 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (99665)

158 exp reproductive technology/ (0)

159 assisted reproduct$.tw.(21298)

160 ovulation induc$.tw. (5937)

161 (ovari$ adj2 stimulat$).tw. (10902)

162 superovulat$.tw. (4096)

163 ovarian hyperstimulation.tw. (7292)

164 (ovari$ adj2 induction).tw. (401)

165 exp Oocyte Retrieval/ (6368)

166 Oocyte Retrieval$.tw. (4533)

167 oocyte$ pick up$.tw.(421)

168 (semen adj5 injection$).tw.(176)

169 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 (809197)

170 36 and 169 (1519)

171 randomized controlled trial.pt. (0)

172 controlled clinical trial.pt.(0)

173 placebo.tw.(293444)

174 clinical trials as topic.sh. (2)

175 randomly.ab. (414067)

176 trial.ti. (279951)

177 (crossover or cross-over or cross over).tw. (99901)

178 randomized.ab. (640600)

179 Clinical Trial/ (979059)

180 Randomized Controlled Trial/ (555431)

181 exp randomization/ (83096)

182 Single Blind Procedure/ (35390)

183 Double Blind Procedure/ (163867)

184 Crossover Procedure/(59779)

185 Placebo/(34562)

186 Randomi?ed controlled trial$.tw. (203790)

187 Rct.tw. (32703)

188 random allocation.tw.(1970)

189 randomly allocated.tw.(32871)

190 allocated randomly.tw.(2477)

191 (allocated adj2 random).tw.(966)

192 Single blind$.tw. (23172)

193 Double blind$.tw. (203938)

194 ((treble or triple) adj blind$).tw. (998)

195 prospective study/(527264)

196 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 (2559069)

197 exp animals/ not humans.sh. (26305229)

198 196 not 197(171623)

199 139 and 198 (23)

200 138 and 198(150)

201 170 and 198(21)