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Original Article

Laparoscopic surgery for subfertility related to endometriosis: A meta-analysis

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ABSTRACT

Objective: Endometriosis is the presence of an endometrial gland or stroma in sites other than the uterine cavity and it is frequently diagnosed in infertile women. It has not been well established whether laparoscopic surgery improves fertility. The objective of this study was to assess the effectiveness of laparoscopic surgery for subfertility related to endometriosis.

Materials and methods: Main electronic databases were searched for randomized and nonrandomized controlled trials. Trials were included if they were randomized or nonrandomized controlled trials that compared the effectiveness of laparoscopic surgery in the treatment of subfertility associated with endometriosis versus other treatment methods or diagnostic laparoscopy only. Six studies were included in this meta-analysis. Outcomes analyzed included live birth rate, pregnancy rate, fetal losses, and surgical complications.

Results: An overall advantage of laparoscopic surgery was demonstrated when analyzing live birth rate [relative risk (RR) 1.52, 95% confidence interval (CI) 1.26–1.84, $p < 0.01$]. An increase in pregnancy rate after laparoscopic surgery was seen (RR of 1.44, 95% CI 1.24–1.68, $p < 0.01$). No significant difference in foetal losses.

Conclusion: The use of laparoscopic surgery in the treatment of subfertility related to minimal endometriosis may increase the chances of future pregnancy and live birth.

Introduction

Endometriosis is one of the most common gynecological problems that affect women in their reproductive years. Endometriosis is characterized by the presence of endometrial tissue outside the lining of the uterine cavity, such as the fallopian tubes, ovaries, and pelvis. The ectopic endometrial tissue is morphologically similar to normal endometrium and responds to ovarian hormones undergoing cyclical changes similar to eutopic endometrium.

The prevalence of endometriosis in women without symptoms is 2–50%, depending on the diagnostic criteria used and the populations studied. The incidence is 40–60% in women with dysmenorrhoea and 20–30% in women with subfertility [1]. Nevertheless, the current gold standard for diagnosis of endometriosis is direct visualization of typical or subtle lesions under laparoscopy or laparotomy. Other diagnostic methods, which include serum markers and radiological imaging, are less reliable. There is no reliable test that can be applied to national screening [2]. Thus, the exact scale of influence of endometriosis will remain unknown until a simple trustworthy screening test is developed.

Endometriosis is associated with dysmenorrhoea, dyspareunia, pelvic pain, and subfertility. Severe pelvic pain may occur in minimal or mild endometriosis identified under laparoscopy, whereas minimal or no symptoms may be associated with severe endometriosis [3].

The cause of endometriosis is unclear. There are several theories postulated to explain its pathogenesis. These include retrograde menstruation and implantation, the metaplasia theory, lymphatic and vascular spreading, and genetic predisposition [4–6].

The Revised American Fertility Society (R-AFS) classification system is used and four anatomical areas (peritoneum, fallopian tubes, ovaries, and pouch of Douglas) are examined for the presence of endometriosis and adhesions [7]. This system provides a numerical score of severity, dividing endometriosis into minimal, mild, moderate, and severe. This classification relates well with the chance of spontaneous conception. The fecundity of women with minimal or mild endometriosis is nearly normal, whereas women with moderate or severe disease have reduced conception rates.

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The role of medical therapies, as hormonal manipulation of ovarian cycles, in infertility treatments has been analyzed in a Cochrane review, which concluded that their use does not improve fertility [8].

If fertility is the priority, laparoscopic surgery can be considered. The aim of the surgery is to remove the deposits of endometriosis tissue and to divide peritubal or periovarian adhesions, restoring normal anatomy where possible. Various treatment modalities are available including excision, electrodiathermy, or laser. In addition, cystectomy of ovarian endometriomas may facilitate the successful response to *in vitro* fertilization (IVF). Drawbacks of surgery include postoperative adhesion formation and incomplete removal of the disease [9].

The efficacy of laparoscopic surgery in the treatment of subfertility associated with endometriosis has been assessed in a Cochrane review [10]. However, there are several limitations of the review. The review was published in July 2010 and has not been updated since, which included only two randomized controlled trials (RCTs) the results are inconclusive.

Given the limited number of RCTs in this field and the restriction in observation of long-term outcomes, a systematic review is proposed of both randomized and nonrandomized controlled trials (NCTs) to reassess the efficacy of laparoscopic surgery for subfertility in endometriosis. As laparoscopy is a surgical intervention, NCTs are study designs that are relatively more feasible and common than RCTs [11].

The aim of this review is to assess the effectiveness of laparoscopic surgery in treating infertility related to endometriosis with the most current evidence, in order to provide the most updated knowledge of evidence to help women experiencing fertility issues associated with endometriosis and their clinicians to make optimized decisions in terms of treatment options.

The objective of this study was to assess the efficacy of laparoscopic surgery in the treatment of infertility associated with endometriosis.

Materials and methods

Eligible studies for this review were randomized/nonrandomized controlled trials that compared laparoscopic surgery as therapeutic management of infertility associated with endometriosis, against at least one of the following comparative options: (1) no treatment; (2) placebo; (3) medical therapy; and (4) nonlaparoscopic surgical treatment. Other study types were regarded as ineligible. There was no limitation on language or study population.

Participants were women with endometriosis diagnosed either by laparoscopy or laparotomy, and infertility diagnosed by the study.

Types of interventions included: (1) laparoscopic surgeries (including peritoneal excision, cauterisation, laser); (2) medical therapies designated for endometriosis or infertility; (3) placebo (e.g., diagnostic laparoscopy); and (4) no treatment.

Outcome measures included: (1) live birth rate (the number of couples achieving a live birth divided by the number of couples assigned); (2) clinical pregnancy rate (the number of couples with a pregnancy confirmed by ultrasound divided by the number of couples assigned); (3) fetal losses; and (4) events of surgical complications (e.g., organ injury, internal bleeding).

Search methods for identification of studies are outlined in Table 1. Studies identified were published in March 2011.

Data collection and analysis

Two reviewers (J.X. and J.R.B.) were assigned to screen the titles and abstracts in order to discard studies that were clearly ineligible and were assigned to independently assess whether the rest of identified studies met the inclusion criteria in this review. The eligibility appraisal was in accordance with the criteria for including studies for this review, which have been described above. Discrepancy between two reviewers was settled by discussion, (Fig. 1).

Table 1
Electronic databases and trial registers searched.

Cochrane Controlled Trials Register (CCTR)
Cochrane Database of Systematic Reviews (CDSR)
EMBASE
Medline
Database of Abstracts of Reviews of Effectiveness (DARE)
ACP Journal Club
Conference Papers index
Conference Proceedings Citation Index Science
Australian and New Zealand Clinical Trial Registry
United States National Institutes of Health ongoing trials register
Reference lists

Data from the included trials were entered in a standard extraction form including the following categories and items. (1) *General information:* study design, publishing status, language,

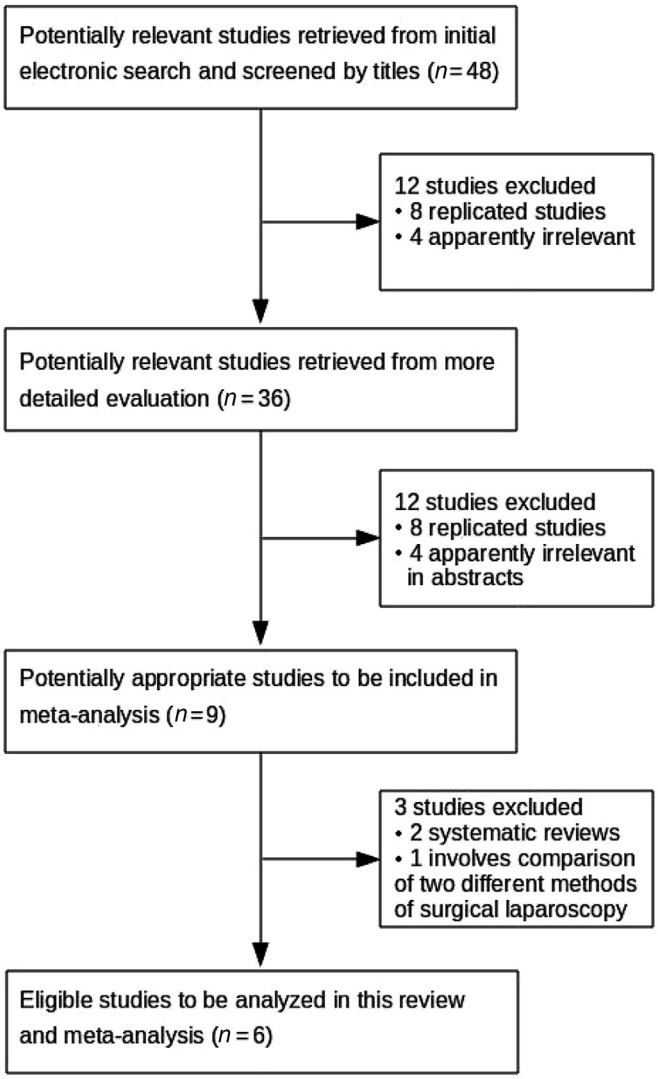

Fig. 1. Flow chart of the included studies.

Table 2
Characteristics and methodology of included studies.

Study	No. of participants	Age (y), mean (SD)	Stage of disease	Duration of infertility (y), mean (SD)	Randomization
Marcoux et al [15]	341	31.0 (3.0)	Minimal/mild	2.6 (1.3)	Randomized
Parazzini [16]	101	30.6 (3.6)	Minimal/mild	3.9 (2.7)	Randomized
Chang et al [17]	176	28.7 (3.5)	Minimal/mild	3.5 (2.5)	Quasi-randomized
Nowroozi et al [18]	123	Not specified	Mild	2.3	Quasi-randomized
Seiler et al [19]	90	29	Moderate	3.4	Quasi-randomized
Milingos et al [20]	102	31.8 (3.9)	Moderate/severe	3.5 (1.9)	Quasi-randomized

authors, article title, journal title and year, volume, issue, page, and funding source. (2) *Participants:* diagnostic criteria, total number and number in comparison groups, baseline characteristics, age, inclusion criteria, exclusion criteria, and study setting (Table 2). (3) *Intervention:* type of preparation, dose, regimen, cointervention, withdrawals, loss to follow up. (4) *Outcome:* primary outcomes, secondary outcomes, and other outcomes at the end of treatment and/or the end of follow up. The adverse events recorded were also extracted. (5) *Data analysis:* study data in detail, statistical methods for data analysis.

Two reviewers (J.X. and J.R.B.) independently assessed the quality of all studies included (Table 1). A scale developed by Downs and Black [12] was used to assess methodological quality both of randomized and nonrandomized trials.

Data synthesis

Analysis was performed on the Review Manager (RevMan Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The number of events in the intervention and control group of each study was used to calculate relative risk (RR) by Mantel–Haenzel statistical method. A 95% confidence interval (CI) was used to measure the effect of random variability. A fixed effect model was used to calculate a summary statistic for each outcome. The synthesis of effect of interventions for each outcome was illustrated in a forest plot. The outcomes of pregnancy and live birth were considered as positive consequences of the interventions, whereas the outcomes of fetal losses and surgical complications were considered as negative consequences of the treatments. These were individually labelled in the forest plot so as to indicate whether the outcome favors treatment or control.

Heterogeneity among included studies was assessed by two methods. Firstly, the existence of heterogeneity was estimated by inspection on the forest plot. Secondly, Chi-square test and I^2 test were performed to determine the significance and the extent of heterogeneity. A result of Chi-square > 25% and $p < 0.10$ was defined as evidence of statistically significant heterogeneity across included studies. I^2 test with a value >30% represents moderate heterogeneity and a value >50% indicated substantial heterogeneity. Identified factors, which may contribute to heterogeneity across studies, were explored further in a sensitivity analysis and a subgroup analysis (Fig. 2).

Subgroup analysis comparing the following aspects were carried out to assess the influence of identified confounding factors. (1) Severity or stage of endometriosis (e.g., minimal, mild, moderate, and severe). (2) Comparison of different control (e.g., diagnostic laparoscopy only, medical treatments, and open surgery). (3) Comparison of specific laparoscopic techniques (e.g., diathermy and laser).

Results

A search of the electronic databases yielded 36 relevant studies that were eligible for further assessment for inclusion in this review. No relevant ongoing trial was found from the clinical trials registers. Nine of these studies were found to be potentially eligible and were subsequently scrutinized in the full text (Fig. 1).

Three studies were further excluded from this systematic review after thorough scrutiny of the full text [10,13,14].

Six studies met the inclusion criteria and were included in this meta-analysis (Table 2). They were two multi-centered randomized controlled trials, three quasi-randomized controlled trials, and one nonrandomized controlled trial [15–20]. All of them involved women with different levels of infertility associated with endometriosis and had postoperative pregnancy rates as an endpoint measurement with different lengths of follow up.

With the exception of one study, the other five studies involved women that had a mean age between 25 years and 35 years and had a varied duration of infertility from 12 months to 36 months [18]. All studies recruited women who were diagnosed with endometriosis as their primary cause of infertility. All participants were prescribed with a thorough infertility evaluation prior to laparoscopy, including ovarian function assessment, hysterosalpingography, postcoital test, and semen analysis. Participants with any abnormalities in these tests were excluded from studies, except one in which patients with correctable problems were included [19]. All six studies confirmed the diagnosis under laparoscopy or laparotomy. In four studies, participants were classified to have minimal to mild endometriosis according to the Revised American Fertility Society (R-AFS) classification system. [15–18] In a study by Seiler et al [19] in 1986, patients with moderate endometriosis were included yet the study used Acosta classification because it was conducted prior to when R-AFS classification was published. In a study by Milingos et al [20] in 1999, all patients had moderate or severe disease with large endometrioma >3 cm.

Three studies directly compared the efficacy of laparoscopic resection of all visible endometriotic implants against diagnostic laparoscopy only [15,16,18]. In the study by Parazzini [16] in 1999, gonadotrophin releasing hormone (GnRH) analogue treatment (tryptorelin 3.75 mg/month for 3 months) was allowed after

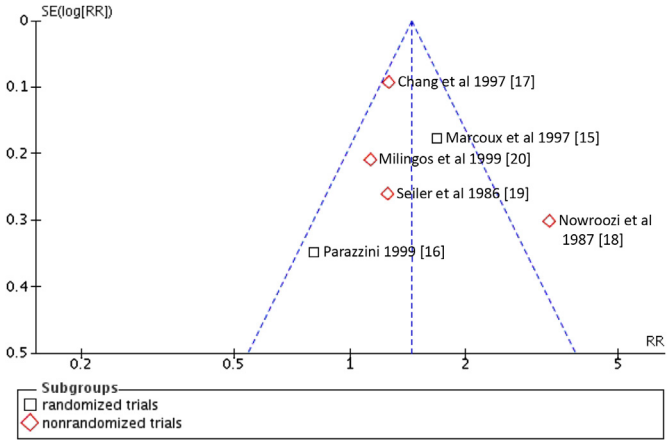

Fig. 2. Heterogeneity of studies. SE = standard error; RR = relative risk.

laparoscopy according to the physician's judgment. In one study eligible patients were assigned to four treatment arms, including laser laparoscopy, electrocautery laparoscopy, diagnostic laparoscopy, and medical treatment (danazol 800 mg/day for 3 months). [17] Two studies compared operative laparoscopy with danazol 800 mg/day for 6 months and open laparotomy with a microsurgical technique, respectively [19,20].

All six studies observed the incidence of pregnancy after interventions. Most studies had follow-up periods between 24 months and 36 months. In only one study, both miscarriage and live birth data were collected [16]. Incidence of abortion was reported in two studies [15,18]. Clinical pregnancy was defined as a positive pregnancy test and ongoing pregnancy was confirmed by ultrasonography at 20 gestation weeks. Surgical characteristics were compared and monthly fecundity was calculated in two studies [15,20].

Quality assessment of included studies

All six studies aimed to address the question of whether laparoscopic surgery for endometriosis improved pregnancy rate in women with unexplained infertility. Overall, most included studies clearly described the inclusion/exclusion criteria of eligible patients and the procedure details of interventions. Characteristics of patients were reported in all included studies but one [18]. Adverse events of surgery were reported and compared in two studies [15,20].

Patients in each study were representative of women with infertility associated with endometriosis. All included studies confirmed and staged the diagnosis of endometriosis by laparoscopy, which is the "gold standard" of diagnosing this disease. Five studies used the R-AFS classification whereas one study adopted the Acosta classification [19,21]. The surgical technique of laparoscopy used across all included studies was monopolar electrocauterization, with one study comparing the utility of laser laparoscopy and nonlaser laparoscopy [17].

It was not clear whether patients and assessors were blinded to the intervention group in the included studies. Given the difficulties of executing blinding in research that involve surgical treatments, it was assumed blinding was not made. Each arm had an identical follow-up period in all included studies. In the Parazzini [16] study, three participants in the treatment group and two participants in the control group withdrew from the study, therefore the data of these patients were excluded in the statistical analysis. In the Marcoux et al [15] study, seven women were assigned to a group but had no follow-up. These patients were removed from the analysis. Another nine women in the treatment group and 12 women in the control group withdrew after operation; however, data of these women were included in the final analysis.

Both randomized studies employed a computer-generated system and a randomization center stratified patients. Allocation of patients into groups was notified by telephone calls to the randomization center. Three quasi-randomized controlled trials used alternate allocation either based on social digit number or by swapping choices of therapy on a regular course. Known confounders, such as age, duration of infertility, and disease stage were sorted to be comparable in each arm at the baseline of the studies.

Only one study performed a calculation of power [16]. The sample size of this study was estimated to be able to detect an increase of 2.5 times in pregnancies in the treatment group, with a baseline pregnancy rate of 25% in the control group.

Effects of interventions

Four studies were eligible to assess the live birth rate influenced by surgical laparoscopy as an endometriosis treatment [15–18]. With a combined total of 741 participants, this meta-analysis demonstrated an overall advantage of laparoscopic surgery when compared to diagnostic laparoscopy only with a combined RR of 1.52 (95% CI 1.26–1.84, $p < 0.01$) favoring laparoscopic surgery. Both statistics from randomized controlled trials and nonrandomized controlled trials yielded similar results, with a RR of 1.47 (95% CI 1.03–2.11, $p = 0.03$) and 1.55 (95% CI 1.25–1.92, $p < 0.01$), respectively. Parazzini [16] reported a small negative effect whereas the other three studies reported positive effects. This may be explained by the small sample size of the study and unpredictable random error. This is supported by the 95% CI of the study crossing the value of 1 when those of the other three studies are unambiguous and larger than 1.

All six studies reported pregnancy rates with a combined total of 933 participants. The combined result was statistically significant with a pooled RR of 1.44 (95% CI 1.24–1.68, $p < 0.01$). The statistic suggests that laparoscopic surgery improves pregnancy rates in subfertile women with endometriosis when compared to controls, including diagnostic laparoscopy only, danazol treatment, and open laparotomy. The data pulled from RCTs gave a less significant effect with a RR of 1.44 (95% CI 1.06–1.95, $p = 0.02$), compared to nonrandomized trials with a RR of 1.45 (95% CI 1.45–1.71, $p < 0.01$). This is probably caused by the contradictory results of two randomized trials (Fig. 3).

Four studies reported incidence of spontaneous abortion or fetal losses. The rate of fetal losses was calculated by dividing the number of fetal losses by the number of pregnancies received after interventions [15–18]. There was no difference between laparoscopic surgery and diagnostic laparoscopy, with a RR of 1.01 (95% CI 0.56–1.79, $p = 0.98$). Both randomized and nonrandomized trials demonstrated similar results in the events of fetal losses after interventions, with a slight benefit favoring laparoscopic surgery in randomized trials but a slightly harmful effect of laparoscopic surgery in nonrandomized trials (Fig. 4).

Only one study reported incidence of intraoperative complications and postoperative complications [15]. Three cases of intraoperative complications were reported in the surgical laparoscopy group whereas only one case was in the diagnostic laparoscopy group. Similarly, surgical laparoscopy had a higher incidence rate in terms of postoperative complications than diagnostic laparoscopy only. Seven patients experienced wound infection or hematoma and three patients had urinary tract infection in the surgical laparoscopy group, compared to five patients and one patient, respectively, in the diagnostic laparoscopy group. The difference in postoperative complications rate can be attributable to the extended operation period in surgical laparoscopy (Fig. 5).

Subgroup analyses were conducted in order to investigate the potential influence of other factors, such as disease stage, different control, and specific laparoscopic techniques, on the effectiveness of laparoscopic surgery in improving pregnancy rate.

One study used the Acosta classification whereas the other studies used R-AFS classification; therefore it was excluded from this subgroup analysis [19]. Based on this result, laparoscopic surgery appeared to be more effective in treating infertility associated with minimal and mild endometriosis (RR 1.52, 95% CI 1.29–1.81, $p < 0.01$). Such benefit was reduced and became insignificant when treating those with moderate and severe endometriosis (RR 1.13, 95% CI 0.75–1.70, $p = 0.57$). The insignificant effect of laparoscopic surgery in these cases could be a result of use of different controls.

Removing endometriotic implants by surgical laparoscopy yielded a positive effect of increasing pregnancy rate when compared to diagnostic laparoscopy only (RR 1.50, 95% CI 1.25–1.80, $p < 0.01$) or danazol therapy (RR 1.40, 95% CI 1.08–1.80, $p = 0.01$). The insignificant effect found of laparoscopy when

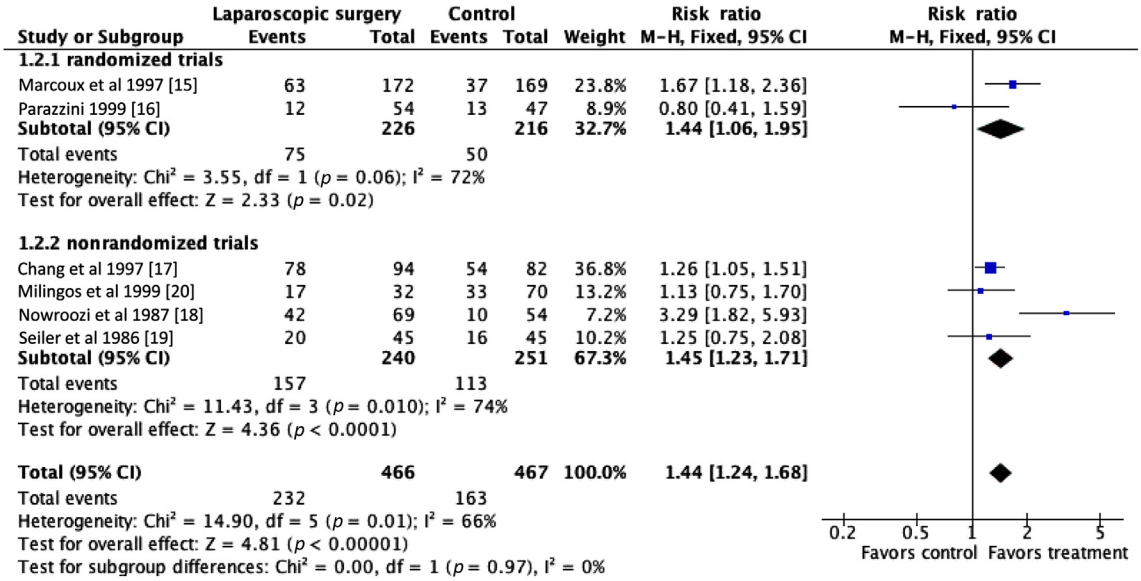

Fig. 3. Forest plot of comparison between laparoscopic surgery and control on clinical pregnancy rate. df = degree of freedom.

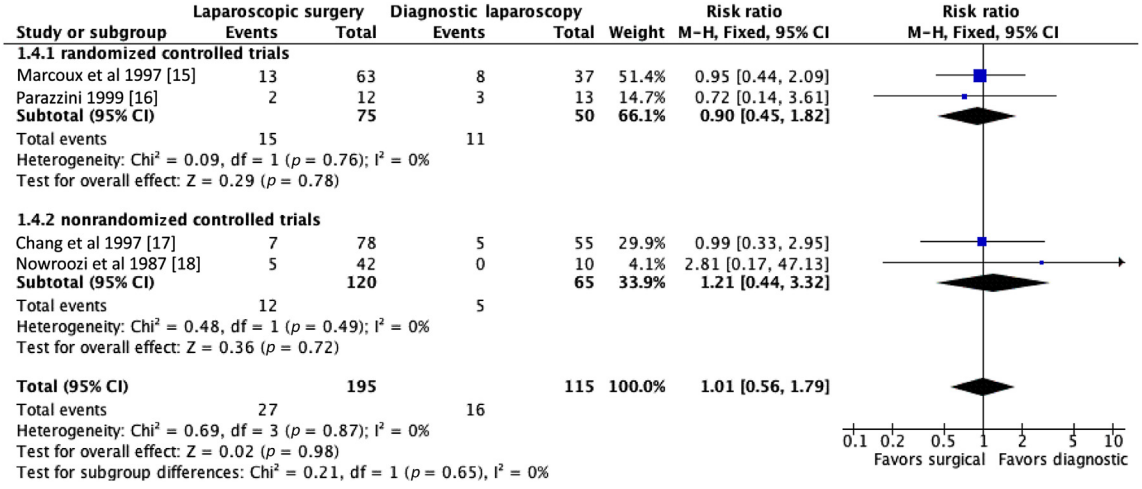

Fig. 4. Comparison of fetal losses between laparoscopic surgery and diagnostic laparoscopy.

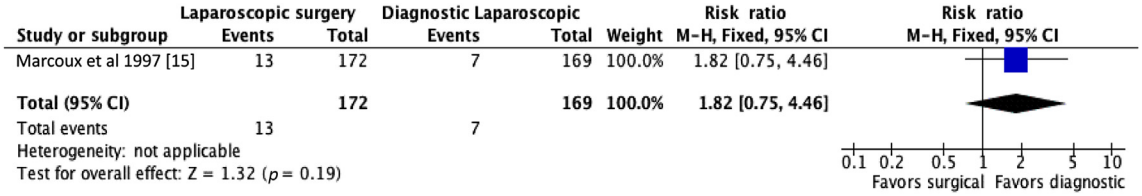

Fig. 5. Comparison of surgical laparoscopy versus control on surgical complication.

compared to laparotomy may be confounded by the fact that women with advanced stage of endometriosis were recruited [20].

Comparison in terms of cumulative pregnancy rate was made between the use of isotype CO_2 laser and the use of conventional electrodiathermy in one study [17]. The difference was statistically insignificant between two techniques with a RR of 1.07 (95% CI 0.89–1.29, $p = 0.47$).

There was noticeable heterogeneity across the included studies. Several factors that could become the sources of heterogeneity had been identified, including confounding factors (e.g., disease stage, different controls, and surgical techniques) and methodological issues (e.g., randomization). We tried to explore the impacts of these factors by subgroup analyses and sensitivity analyses. One nonrandomized study was found notably responsible for the heterogeneity [18]. The study reported a large positive effect of laparoscopic surgery, which was not seen in other studies. When this study was taken off the meta-analysis, the heterogeneity was resolved.

Discussion

The meta-analysis in this review demonstrated a statistically significant benefit of laparoscopic surgery in improving both pregnancy rates and live birth rates in women with endometriosis. This benefit was mostly demonstrated in the women whose infertilities were primarily caused by minimal and mild endometriosis (R-AFS stage I/II). Electro-cauterization of visible endometriotic implants during laparoscopy was also demonstrated to be more effective than medical treatments in terms of better pregnancy rates. There was only one study that investigated surgical treatments for endometriosis of advanced stages but the results were apparently affected by confounding factors. Therefore, no conclusion could be drawn with respect to the effectiveness of laparoscopic surgery for moderate and severe endometriosis. The choice of laser or electrodiathermy for surgical laparoscopy appeared to exert no difference to the benefit of laparoscopic treatment.

The positive effects demonstrated by randomized and nonrandomized trials were both statistically significant. Despite noticeable heterogeneity among included studies, most of the studies demonstrated consistent benefits of surgical laparoscopy to fertility outcomes. Participants and outcome measurers were not blinded during follow-up in all included studies. Considering the objective of pregnancy and live birth, we believe blinding the assessors would not profoundly alter the outcomes. Unfortunately, the definition of pregnancy was not specified in the majority of included studies in this review.

Jacobson et al [10] conducted a review based on two RCTs, which concluded that laparoscopic treatment of minimal and mild endometriosis may improve the ongoing pregnancy rate and live birth rate in couples with otherwise unexplained infertility. The conclusion of that review needs to be interpreted with caution as one RCT reported a larger positive effect of laparoscopic surgery whereas the other one had a small negative effect. In our review, the positive effect of laparoscopic surgery for minimal and mild endometriosis was confirmed in our meta-analysis including both randomized and nonrandomized trials. Adamson and Pasta [22] conducted a meta-analysis of all uncontrolled studies concerning the efficacy of surgery for subfertility associated with endometriosis. The results indicated that surgical intervention to treat subfertility associated with endometriosis was estimated to produce pregnancy rates that were 38% (95% CI 28–48%) higher in the surgical group when compared to the control nonsurgical group. However, based on the results of meta-analysis of this review, the enhancement of pregnancy rates was estimated to be lower than the one suggested by Adamson and Pasta [22]. Based on the background pregnancy rate in an infertile population, which is 19.9% after 12 months, our review estimates that an overall 12-month cumulative pregnancy rate is 28.7% (95% CI 24.7–33.4%) after laparoscopic treatment for endometriosis [23]. This estimate is in agreement with a recent literature review based on the results of observational and NCTs, which concluded an increase of 10–25% in pregnancy rate after surgery for endometriosis [24].

This systematic review suggests that the use of laparoscopic surgery in the treatment of subfertility related to minimal and mild endometriosis may increase chances of future pregnancy and live birth. However, it is uncertain regarding possible fertility benefits of laparoscopic surgery when treating more severe endometriosis. These implications are in agreement with several national and international guidelines concerning the management of subfertile women with endometriosis [24–26].

The advantage of this systematic review is the inclusion of both randomized and NCTs. Considering the fact that very few RCTs were done in this field, inclusion of nonrandomized controlled trials helps to provide a broader picture for the use of laparoscopic surgery for infertility related to endometriosis. However, future randomized controlled trials in this area are still required. Further data from high quality randomized controlled trials are needed for undertaking further evaluation of the efficacy of laparoscopic surgery, especially focusing on R-AFS stage III/IV endometriosis and endometrioma.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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