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REVIEW

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Impact of treatment interventions of endometriomas prior to in vitro fertilization: a systematic review and meta-analysis

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Abstract

Background Treatment of endometrioma before in vitro fertilization (IVF) is challenging as it may affect ovarian response to induction.

Objective A systematic review to search for the available optimal management of ovarian endometrioma before ovulation induction in IVF.

Search strategy Screening of the MEDLINE, Web of Science, EMBASE, Cochrane database, and the clinical trial registration sites, covering the period from their inception up to June 2023 was done by two reviewers independently using the keywords ovarian endometrioma, ovarian endometriosis, endometrioma/surgery, endometrioma/hormonal treatment, randomized controlled trial(s), case-controlled studies, and cohort studies.

Selection criteria All types of studies were included. Participants included were women with unilateral or bilateral ovarian endometriomas candidate for IVF/ICSI. We included 18 studies in the review. Three studies were randomized controlled parallel studies, six were prospective cohort, and nine were retrospective cohort studies.

Data collection and analysis Data from all included studies were extracted by two authors (A. M., A. O.) independently. Data extracted included sample size, population characteristics including age, BMI, duration of infertility, ovarian reserve markers, cyst size, and bilaterality and induction protocol used.

Main results We found 18 studies. Women with untreated endometrioma had significantly higher numbers of MII oocytes (the mean difference (MD) effect estimate was −0.53 with [−1.04, −0.01] 95% CI and 0.04 *P*-value), higher number of obtained embryos (MD effect estimate was −0.25 with [−0.38, −0.11] 95%CI and < 0.001 *P*-value), and required lower doses of gonadotropins for induction (MD effect estimate was 361.14 with [168.13, 5554.15] 95% CI and < 0.001 *P*-value) compared to those who had undergone surgical management of endometrioma. However, live birth (OR effect estimate was 0.79 with [0.54, 1.18] 95% CI and 0.25 *P*-value), clinical pregnancy (OR effect estimate was 0.95 with [0.72, 1.26] 95% CI and 0.73 *P*-value), miscarriage (OR effect estimate was 0.74 with [0.33, 1.63] 95% CI and 0.45 *P*-value), cancellation rates (OR effect estimate was 1.62 with [0.57, 4.66] 95% CI and 0.37 *P*-value), and the duration of stimulation (MD effect estimate was 0.19 with [−0.42, −0.81] 95% CI and 0.54 *P*-value) did not show any significant difference between the two groups of women. Hormonal treatment of endometrioma was associated with higher ongoing pregnancy rate (OR effect estimate was 3.39 with [1.83, 6.26] 95% CI and < 0.001 *P*-value), higher clinical pregnancy rate (OR effect estimate was 3.36 with [2.01, 5.63] 95% CI and < 0.001 *P*-value), and higher numbers of MII oocytes (MD effect estimate was 2.04 with [0.72, 3.36] 95% CI and 0.003 *P*-value)

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when compared to women who did not receive such therapy. These effects were evident in treatment with GnRH agonists, OCPs (oral contraceptive pills), and dienogest, while the miscarriage and cycle cancellation rates did not show these differences.

Conclusions The optimal approach for treating endometrioma prior to IVF is not clear yet due to lack of well-designed randomized controlled trials.

Registration number CRD42020151736.

Keywords Ovarian endometrioma, Ovarian endometriosis, Endometrioma/surgery, Endometrioma/hormonal treatment, Endometrioma/GnRH agonist, Endometrioma/aspiration, Endometrioma/laparoscopy, IVF outcome

Introduction

Endometriosis is a benign gynecological pathology characterized by the existence of endometrium outside the uterine cavity and was commonly diagnosed by surgery [1]. Recently, ESHRE in 2022 stated that diagnosis of endometriosis with laparoscopy showed to be restricted to only to those with negative different imaging findings, and women with failed empirical treatment and the group stated that laparoscopy is no longer considered as the gold standard for diagnosis of endometriosis [2]. Endometriosis is an estrogen-dependent chronic inflammatory pathology that affects between 10 and 15% of women during their childbearing period. It is commonly associated with pain, infertility [3, 4], chronic stress, and anxiety [5]. Difficult conception is observed in 30 to 50% of women diagnosed with endometriosis [6], and many of them are trying to conceive through different assisted reproductive techniques [7].

Unfortunately, the pathogenesis of endometriosis associated with infertility remains unclear. Endometriosis causes infertility through various mechanisms: distortion of the normal pelvic anatomy, scarring of the fallopian tubes, inflammation of different pelvic organs with adhesion formation, alteration of immune response and hormonal environment of ova, impairment of implantation of a pregnancy, and alteration of oocytes quality [8]. Various inflammatory changes have been proposed to be the reasons behind endometriosis-associated infertility including alteration of macrophages proliferation and its phagocytic activity, increasing the numbers of malfunctioning natural killer cells and T lymphocytes with enhancement of proinflammatory and angiogenic cytokines release [9, 10]. Ovarian endometrioma decreases the volume of functioning ovarian tissue through its space-occupying action and/or the local inflammatory and immune reactions or both. This reduction in functioning ovarian tissue is aggravated by surgery. Clinical examination has low sensitivity and specificity for diagnosis of endometriosis, and laparoscopy remains the gold standard for diagnosis; however, recent studies look promising for new sonographic and magnetic resonance imaging (MRI) techniques [11].

Endometrioma could be managed by either medical or surgical modalities, and both affect the reproductive potential of the women. Women should be counselled about behavioral changes that creates optimum patients' characteristics and healthy lifestyle before they started medical and/or surgical treatments. One of these is the maintenance of ideal body weight to decrease the endometriosis cancer risk and to improve the success of IVF [2]. The best management of endometriomas before starting IVF/ICSI trial is unknown. Medical treatment for endometrioma includes mainly hormonal therapy with progestogens, combined oral contraceptives, aromatase enzyme inhibitors, and gonadotropin-releasing hormone analogues. Their mode of action depends on their ability to decrease ovarian activity [12]. Surgical treatment includes cyst aspiration, laparoscopic ovarian cystectomy, ovarian cystectomy via laparotomy, or robotic surgery. Laparoscopic management is currently the most accepted approach being associated with lower costs and faster recovery compared to other approaches [13]. The aim of current review is to evaluate the impact of medical and surgical interventions to endometriomas prior to IVF-ET as there was no similar review to assess the effects of different treatment modalities of ovarian endometriomas on IVF outcomes.

Methodology

This study protocol was prospectively registered following the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) with CRD42020151736 number.

Research question

- Population: Women with unilateral or bilateral ovarian endometrioma
- Intervention: Surgical (including cystectomy and aspiration) and medical (including GnRH, progester-

one, and aromatase inhibitors) management of endometrioma before IVF
- Comparison: Surgical treatment and medical treatment compared to no intervention
- Outcome: Outcomes of IVF cycles

In this systematic review, the following databases: MEDLINE, Web of Science, Embase, Cochrane Library, and the clinical trial registry were searched from inception up to June 2023. The search used the keywords as follows: endometriosis; endometrioma, ovarian endometriosis, and ovarian endometrioma; ovarian endometriosis; endometriotic ovarian cyst; endometrioma/surgery; endometrioma/hormonal treatment, GnRH agonist, letrozole, aromatase inhibitors, OCPs (oral contraceptive pills)), IVF/ICSI, and in vitro fertilization; intracytoplasmic sperm injection; assisted reproductive technologies; ART; oocytes; live birth; fertilization; and live birth rate, pregnancy rate, miscarriage rate, number of oocytes, cancellation rate, randomized controlled trial(s), case-controlled studies, and cohort studies. As only few randomized controlled trials were available, the authors agreed to include other types of studies as case controlled and cohort studies whether prospective or retrospective. Review articles and case reports, editorial opinion, and commentary were excluded. We analyzed the references and citations of all available studies (both primary and secondary), narrative and systematic reviews, abstracts of gynecology, and infertility seminars. We emailed the authors directly for any missing or unclear information. If necessary, all studies written in English comparing different surgical and medical modalities against no treatment or other modalities were included. Surgical modalities include laparoscopic cystectomy, open cystectomy, or cyst aspiration. Medical modalities include progestogens, aromatase inhibitors, GnRH agonists, or oral contraceptive pills (OCPs).

Cystectomy is the stripping of the cyst wall away from the healthy ovarian tissues through either laparoscopy or laparotomy. Aspiration procedure is the transvaginal aspiration of the cyst content guided by ultrasound. Medical treatment acts through antagonizing estrogen secretion and/or action.

Two authors (A. O. and A. M.) independently assessed the titles, abstracts, and the full articles and then extracted the data of the included studies, and disagreements were discussed further with other authors. Extracted data included study type, settings, participants characteristics, details of intervention, and outcome parameters.

The risk of bias was assessed using the Cochrane Handbook of Systematic Reviews recommendations for the 3 RCTs [14]. These recommendations include random sequence generation, allocation concealment, participants and outcome assessors blinding, incomplete data of outcomes, selective reporting, and other biases.

The outcome parameters of this review included live birth, clinical pregnancy, miscarriage, cancellation rates, number of MII follicles, duration of stimulation, total dose of gonadotropin used for induction, and number of obtained embryos.

Statistical analysis

For analysis of continuous and dichotomous data, the mean difference and odd ratio with 95% confidence interval (CI) analysis were used, respectively. The random effect model was used to calculate the effect size, and I^2 statistic and Cochran's Q test were calculated to evaluate the studies heterogeneity. Significant P-value was considered when < 0.05, and significant I^2 was considered when $> 40\%$. Analyses were done using the Review Manager (RevMan) version 5.4.1 (The Nordic Cochrane Centre, Cochrane Collaboration, 2020, Copenhagen, Denmark).

Results

The PRISMA flow chart is shown in Fig. 1.

Study characteristics

Table 1 describes the characteristics of the included studies.

Eighteen studies were included in this review [15–32]. Five were conducted in Turkey [15, 16, 18, 25, 26], 3 in Japan [19, 27, 28], and 1 in each of the following countries: Canada [31], China [21], Denmark [22], Egypt [23], France [32], Italy [30], Russia [24], Spain [17], South Korea [20], and the USA [29]. Three studies were RCTs [16, 23, 26], six were prospective cohort [21, 22, 24, 25, 30, 32], and nine were retrospective cohort studies [15, 17–20, 27–29, 31]. All were single center except three trials [17, 31, 32] that were conducted in two centers. Six studies compared laparoscopic surgery to no treatment [16–19, 21, 27], five compared surgery to no treatment [15, 20, 25, 26, 29], and three compared cyst aspiration to no treatment [20, 25, 27]. Medical treatment was GnRH in two studies [23, 24], OCPs in one study [15], and dienogest in one study [24], while aromatase inhibitors were studied in two trials [22, 31].

Risk of *bias* of included studies

Risk of bias in the three RCTs is described in Table 2. The risk of bias for non-RCTs was evaluated using the Newcastle–Ottawa scale (Table 3).

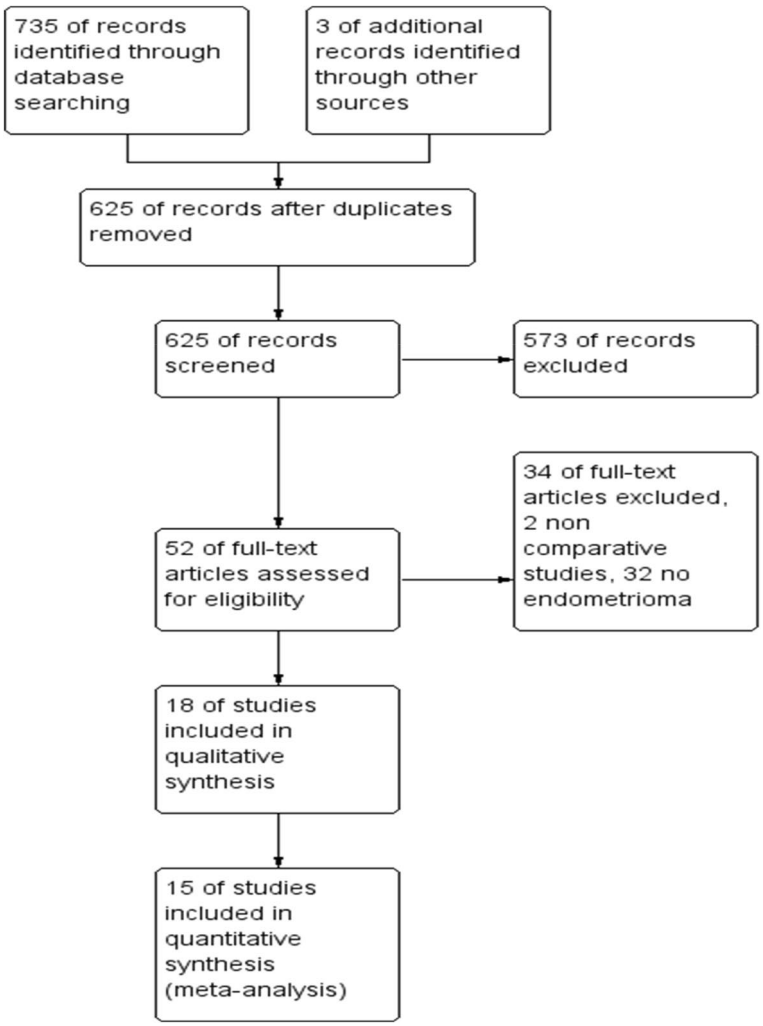

Fig. 1 Prisma flow chart

Synthesis of results

Eighteen studies with 3063 participants were included in our review.

Surgical intervention versus no treatment

Live birth rate was evaluated in 4 studies (565 participants). The OR effect estimate was 0.79 with [0.54, 1.18] 95% CI and 0.25 *P*-value (Fig. 2).

Clinical pregnancy rate was evaluated in 11 studies (1447 participants). The OR effect estimate was 0.95 with [0.72, 1.26] 95% CI and 0.73 *P*-value (Fig. 3).

Miscarriage rate was evaluated in 6 studies (333 participants). The OR effect estimate was 0.74 with [0.33, 1.63] 95% CI and 0.45 *P*-value (Figure S1).

Cycle cancellation rate was evaluated in 4 studies (551 participants). The OR effect estimate was 1.62 with [0.57, 4.66] 95% CI and 0.37 *P*-value (Figure S2).

Number of MII oocytes was evaluated in 11 studies (1475 participants). The mean difference (MD) effect estimate was −0.53 with [−1.04, −0.01] 95% CI and 0.04 *P*-value (Figure S3).

Number of obtained embryos was evaluated in 4 studies (569 participants). The MD effect estimate was −0.25 with [−0.38, −0.11] 95% CI and < 0.001 *P*-value (Figure S4).

Duration of stimulation was evaluated in 6 studies (881 participants). The MD effect estimate was 0.19 with [−0.42, 0.81] 95% CI and 0.54 *P*-value (Figure S5).

The total dose of gonadotropins was evaluated in 9 studies (1255 participants). The MD effect estimate was 361.14 with [168.13, 554.15] 95% CI and < 0.001 *P*-value (Figure S6).

Table 1 Characteristics of the included studies

Study	Settings	Design	Size	Participants	Intervention	Outcome
Candiani (2020)	Single center, Italy	Prospective cohort	142	Inclusion criteria ○ Previous surgery for unilateral or bilateral endometriomas > 3 cm Exclusion criteria • Age ≥ 40 years • Previous bilateral ovarian surgery or more at the time of surgery • Previous salpingectomy or hysterectomy • Follow-up < 12 months	2 arms group 1: patients underwent a standardized laparoscopic stripping technique group 2: patients underwent cyst co2 laser vaporization	Postoperative pregnancy rate (spontaneous or assisted) Identification of independent predictors of pregnancy
Canton (2018)	2 centers, Canada	Retrospective cohort	126	Inclusion criteria • Age 21–39 years • Ground-glass cysts persistent for at least 3 months and not enlarging • Previous IVF failed cycle with frozen embryo transfers Exclusion criteria • Hydrosalpinges • Intracavitary lesion • Severe male factor • Previous surgery for endometriosis • First IVF cycle • Lack of an endometrioma	2 arms • Group 1 received 3.75-mg intramuscular depo-leuprolide treatment alone for 60 days • Group 2 received 5 mg of oral letrozole daily beside leuprolide with the same regimen and duration	CPR LBR AFC Largest mean endometrioma diameter Total Gn dose No. of mature oocytes retrieved No. of pronuclear (2PN) embryos No. of blastocysts
Demirdag (2021) [15]	Single center, Turkey	Retrospective cohort	179 P 259 C	Inclusion criteria • History of ovarian endometrioma before the IVF/ICSI cycle Exclusion criteria • Polycystic ovarian syndrome • Male factor infertility • Thaw cycles	3 arms • Group 1 ($n=81$): Previous endometrioma surgery • Group 2 ($n=98$): Non-operated endometrioma • Group 3 ($n=1757$): Other infertility causes as unexplained and tubal factor infertility without endometrioma	CPR LBR AFC, NOR E2 levels on the day of hCG trigger Total Gn dose Cancellation rates
Demirol (2006) [16]	Single center, Turkey	RCT	99	Inclusion criteria • Single or multiple • Unilateral ovarian endometriomas between • 3 and 6 cm referred to ICSI Exclusion criteria • Bilateral endometrioma • Patients with laparoscopic suturing	2 arms ○ Group 1 ($n=49$) underwent conservative ○ ovarian surgery before ICSI • Group 2 ($n=50$) underwent ICSI directly	Stimulation duration Peak E2 level No. of mature oocytes retrieved FR IR CPR

Table 1 (continued)

Study	Settings	Design	Size	Participants	Intervention	Outcome
DeZiegler (2010)	2 centers, France	Prospective cohort	60	Endometriosis was diagnosed either surgically or by ultrasound	4 arms • Group 1 ($n=540$) received OCP0 .03 mg of EE and 0.125 mg of LNG before ART for 6 to 8 weeks subdivided to endometriosis ($n=114$, 29 endometrioma) and control ($n=426$) • Group 1 ($n=255$) received no OC pretreatment subdivided to endometriosis ($n=172$, 31 endometrioma) and control ($n=83$)	CPR No. of mature oocytes retrieved No. of embryos
Garcia-Velasco (2004) [17]	2 centers, Spain	Retrospective cohort	189 P 210 C	Inclusion criteria • Ovarian endometriomas underwent IVF-ET cycles Exclusion criteria • Any other known infertility factor besides endometriosis	2 arms • Study group ($n=133$ women, 147 cycles): Previous laparoscopic cystectomy for an ovarian endometrioma • Control group ($n=56$ women, 63 cycles): Non-operated ovarian endometrioma(s)	No. of oocytes retrieved No. of mature oocytes No. of embryos FR IR CPR MPR ChPR Miscarriage rate Cancellation rate
Guler (2017) [18]	Single center, Turkey	Retrospective ohort	150 P 257 C	Exclusion criteria Unexplained infertility without endometriosis, endometriosis-related tubal factor, male factor infertility • Previous laparotomy or oophorectomy for endometrioma • Recurrent endometrioma	4 arms 257 ICSI cycles of 150 patients • Group 1 ($n=84$ women, 91 cycles): Minimal endometriosis • Group 2 ($n=25$ women, 57 cycles): Endometrioma removal • Group 3 ($n=53$ women, 65 cycles): Non-operated endometrioma Group 4 ($n=24$ women, 44 cycles): Tubal factor infertility	CPR LBR Total Gn dose No. of oocytes retrieved Stimulation duration
Kuroda (2009)[19]	Single center, Japan	Retrospective cohort	61 P 97 C	Inclusion criteria • Women with endometriosis or endometrioma Exclusion criteria Women with more than 4 IVF/ICSI cycles	4 arms • Group A ($n=31$ cycles): Unoperated endometrioma • Group B ($n=51$ cycles): Postoperative • endometrioma • Group C ($n=15$ cycles): No endometrioma Group D ($n=27$ cycles): Tubal infertility	No. of oocytes retrieved FR Cancellation rate IR CPR LBR Miscarriage rate

Table 1 (continued)

Study	Settings	Design	Size	Participants	Intervention	Outcome
Lee (2014) [20]	Single center, Korea	Retrospective cohort	101	*Inclusion criteria* • Women with pathologically confirmed previous or current endometrioma(s) > 3 cm • Age: 20–45 years • Normal: 24–35-day ovulatory cycles • BMI: 18–25 kg/m^2 *Exclusion criteria* • Endocrine abnormalities as diabetes mellitus, PCOS, hyperprolactinemia • Previous severe OHSS • Abnormalities interfering with stimulation Previous (within 12 months) or current drug or alcohol abuse	3 arms • Resection group (n = 36): Surgical resection of endometrioma • Aspiration group (n = 29): Transvaginal endometrioma aspiration Control group (n = 36): No surgical intervention	No. of oocytes retrieved No. of mature oocytes No. of embryos Total Gn dose CPR LBR MPR Miscarriage rate
Liang (2019) [21]	Single center, China	Prospective cohort	41	Inclusion criteria O Infertility due to stages III or IV endometriosis • Normal semen analysis Exclusion criteria • Age: ≥ 40 years • BMI: ≥ 30 kg/m^2 • FSH: ≥ 12 mIU/mL • PCOS • Endocrinal disorders (thyroiddisease, diabetes mellitus, and Cushing's syndrome) Cycles with contaminated dominant FF with blood cycles with the dominant FF not yielding oocytes	2 arms • Surgery group (n = 13): Surgery to remove the endometrioma Surgery group (n = 28): Untreated before IVF	Total Gn dose No. of oocytes retrieved No. of MII oocytes FR IR CPR

Table 1 (continued)

Study	Settings	Design	Size	Participants	Intervention	Outcome
Lossl (2009) [22]	Single center, Denmark	Prospective ohort	20	Inclusion criteria O Ultrasonographic diagnosedendometrioma(s) persisting for three or more cycles between 20 and 70 mm and indicated for IVF or ICSI • Age: 20–39 years • Regular: 21–35-day menstrual cycle • BMI: 18–30 kg/m^2 • Negative urinary pregnancy test on treatment day 1 Exclusion criteria O GnRH-agonist treatment withinthe last 3 months History of osteopenia, hepatic, renal,cardiovascular, or thromboembolic disorder	1 arm received goserelin 3.6 mg s on treatment days 1, 28, and 56 and 1 mg of anastrozole from day 1 to day 69. COH initiated from day 70ncompared to a standard IVF/ICSI treatment in 15 women who underwent a previous or subsequent standard cycle, with present endometrioma(s)	Endometrioma volume changes Serum CA125 changes Stimulation duration Total Gn dose No. of oocytes retrieved No. of embryos Total Gn dose FR IR CPR LBR Miscarriage rate
Maged (2018) [23]	Single center, Egypt	RCT	90	Inclusion criteria O Subfertile women indicated for ICSI and having a single endometrioma of 2–5 cm • Normal uterine cavity Exclusion criteria • Bilateral or multiple endometriomas, • FSH > 10 • BMI > 30 kg/m^2 • Age > 40 years • Cases who received GnRH within 12 months of the study • Patients who received OCPs or other hormones within 3 months • Previous surgical resection of endometrioma Severe male factor	2 arms • Group A (n = 45): Received standard long protocol Group B (n = 45): Received Intramuscular injections of 3.75-mg triptorelin every 28 days for 3 doses followed by thestandard long protocol 28 days after the last injection	Ch PR CPR Ongoing PR Miscarriage rate ectopic pregnancy MPR

Table 1 (continued)

Study	Settings	Design	Size	Participants	Intervention	Outcome
Muller (2017) [24]	Single center, Russia	Prospective cohort	144	Inclusion criteria: • Age 23–42 years • Infertility • Surgical treatment of endometrioma • ≤ 4 months before enrollment • No endometriomas or other ovarian cysts at thestart of stimulation • FSH < 12.0 IU/L and AMH ≥ 0.5 ng/mL Exclusion criteria • BMI ≥ 30 kg/m^2 • Uterine fibroids ≥ 2 cm in diameter and/or deforming the uterine cavity • III/IV stage ofadenomyosis Contraindications to COS or gestation	3 arms O Group 1 (n = 38): Received 2-mg dienogest daily for 6 months before IVF • Group 2 (n = 70): Received 3.75-mg triptorelin every 28 days for six doses before IVF • Group 3 (n = 38): Without any hormone therapy before IVF	CPR LBR Total Gn dose Stimulation duration No oocyte retrieved Cancellation rate
Pabuccu (2004) [25]	Single center, Turkey	Prospective cohort	171	Inclusion criteria • Women candidate for ICSI • Normal uterine cavity Exclusion criteria • Thaw cycles	4 arms • Group 1 (n = 41): Aspiration of endometriomas and no history of previous surgery • Group 2 (n = 40): Nonaspirated endometriomas • Group 3 (n = 44): History of ovarian surgery for endometriomas in patients without ovarian endometriomas at the beginning of COH Group 4 (n = 46): Tubal factor infertility	Total Gn dose Stimulation duration No MII oocytes FR IR CPR Miscarriage rate
Pabuccu (2007) [26]	Single center, Turkey	RCT	246	Inclusion criteria • Women candidate for ICSI • Normal uterine cavity Exclusion criteria • Patients with recurrent endometrioma or with advanced endometriosis (stages III–IV) without endometrioma were excluded from group 1 • Hydrosalpinx • Tuberculosis • Male factor infertility • Thaw cycles	3 arms O Group 1 (n = 98): Mild-to-moderate endometriosis • Group 2 (n = 81): Ovarian surgery for endometrioma • Group 3 (n = 67): Non-operated endometrioma	Total Gn dose Stimulation duration E2 levels on the day of hCG trigger No oocytes retrieved No MII oocytes FR ChPR CPR

Table 1 (continued)

Study	Settings	Design	Size	Participants	Intervention	Outcome
Suganuma (2002) [27]	Single center, Japan	Retrospective cohort	79 P 127 C	*Inclusion*: Infertile women with endometrioma who underwent IVF-ET	3 arms • Surgery group ($n=36$ women, 62 cycles) underwent laparotomy or laparoscopy • Cyst-aspirated group ($n=23$ women, 35 cycles): Endometrioma content aspirated under transvaginal ultrasonic imaging andtreated with or without alcohol fixation No treatment group ($n=20$ women, 30 cycles): Nontreated endometrioma	Retrieved oocytes, no. of mature oocytes, fertilization, and pregnancy
Takashima (2013)[28]	Single center, Japan	Retrospective cohort	44	Inclusion criteria ○ Patients who had undergone laparoscopic excision of ovarian endometrioma followed by IVF treatment • Age 32–40 years • BMI 18–25 kg/m^2 • Both ovaries present • Menstrual cycle length between 25 and 35 days Exclusion criteria • Hormonal treatment within 1 year prior to the laparoscopy • Previous adnexal surgery Clinical hyperandrogenism	2 arms Women who had laparoscopic excision for unilateral endometrioma among infertile women • Group 1 ($n=21$): Hemostasis during the surgery achieved by coagulation • Group 2 ($n=23$): Hemostasis during the surgery achieved by suture	No. of mature oocytes retrieved No. of embryos Total Gn dose Stimulation duration CPR
Wong (2004) [29]	Single center, USA	Retrospective cohort	204	Inclusion criteria • Women candidate for ICSI • Couples with male factor infertility treated by ICSI Exclusion criteria • Tubal factor infertility • Ovulatory dysfunction	3 arms • Group 1A ($n=36$ cycles): Previous laparoscopic ovarian cystectomy for endometrioma • Group 1B ($n=38$ cycles): Nontreated endometrioma • Group 2 ($n=183$ cycles): Endometriosis without endometrioma	CPR Cancellation rate No mature oocytes FR IR Miscarriage rate MPR

C cycles, *ChPR* chemical pregnancy rate, *CPR* clinical pregnancy rate, *FR* fertilization rate, *IR* Implantation rate, *LBR* Live birth rate, *P* Participants

Table 2 Risk of bias

	Random sequence generation	Allocation concealment	Participants blinding	Outcome assessor blinding	Incomplete data	Selective reporting	Other bias
Demirol (2006) [16]	U	U	H	H	L	L	L
Maged (2018) [23]	L	L	H	H	L	L	L
Pabuccu (2007) [26]	L	U	H	H	L	L	L

H High riskm *L* Low risk, *U* Unclear risk

Table 3 Risk-of-bias assessment of non-RCTs

Study	Selection		Comparability		Outcome/exposure				Total score
	Case cohort	Control	Design	Analysis	Ascertainment of exposure	Outcome negative at start	Outcome assessment	Follow-up duration	
Candiani (2020)	*	*	**	*	*	*	*	*	9
Canton (2018)	*	*	**	*	*	*	*	*	9
Demirdag (2021) [15]	*	*	*	*	*	*	*	*	8
DeZiegler (2010)	*	*	*	*	*	*	*	X	7
Garcia-Velasco (2004) [17]	*	*	*	*	*	*	*	*	8
Guler (2017) [18]	*	*	*	*	*	*	*	X	7
Kuroda (2009) [19]	*	*	**	*	*	*	*	*	9
Lee (2014) [20]	*	*	*	*	*	*	*	*	8
Liang (2019) [21]	*	*	*	*	*	*	*	X	7
Lossl (2009) [22]	*	*	*	*	*	*	*	*	8
Muller (2017) [24]	*	*	*	*	*	*	*	X	7
Pabuccu (2004)[25]	*	*	**	*	*	*	*	*	9
Suganuma (2002) [27]	*	*	*	*	*	*	*	*	8
Takashima (2013) [28]	*	*	*	*	*	*	*	*	8
Wong (2004) [29]	*	*	*	*	*	*	*	*	8

Medical intervention versus no treatment

Ongoing rate was evaluated in 2 studies (270 participants). The OR effect estimate was 3.39 with [1.83, 6.26] 95% CI and < 0.001 *P*-value (Figure S7).

Clinical pregnancy rate was evaluated in 3 studies (330 participants). The OR effect estimate was 3.36 with [2.01, 5.63] 95% CI and < 0.001 *P*-value (Figure S8).

Miscarriage rate was evaluated in 2 studies (270 participants). The OR effect estimate was 1.31 with [0.46, 3.72] 95% CI and 0.61 *P*-value (Figure S9).

Cancellation rate was evaluated in 2 studies (270 participants). The OR effect estimate was 0.48 with [0.21, 1.10] 95% CI and 0.08 *P*-value (Figure S10).

Number of MII oocytes was evaluated in 3 studies (330 participants). The mean difference (MD) effect estimate was 2.04 with [0.72, 3.36] 95% CI and 0.003 *P*-value (Figure S11).

Subgroup analysis of all outcomes based on the type of surgical and medical intervention is shown in supplementary Table S1.

Candiani and colleagues (2020) [30] conducted a retrospective study on 142 women diagnosed with symptomatic endometrioma who were subjected to laparoscopic cyst stripping or CO2 cyst vaporization and then tried to conceive spontaneously and if failed through IVF. They reported pregnancy rates of 72.2% vs 74.3% (55.6% vs. 35.9% spontaneously;16.7% vs.38.5% through IVF) in stripping vs. laser respectively ($P=0.83$), and 26.7% do not achieve pregnancy. They identified age and duration of infertility as independent indicators for pregnancy. They concluded that the pregnancy rate was not different between the two groups and suggest that CO2 laser one-step technique could be a good alternative to conventional cystectomy.

Cantor et al. in 2019 [31] conducted a retrospective study on 126 women with endometrioma and had a history of previous IVF cycle. Participants were subjected to either two doses of intramuscular 3.75-mg intramuscular depo-leuprolide with 1-month interval or daily 5-mg oral letrozole for 60 days along with the same leuprolide

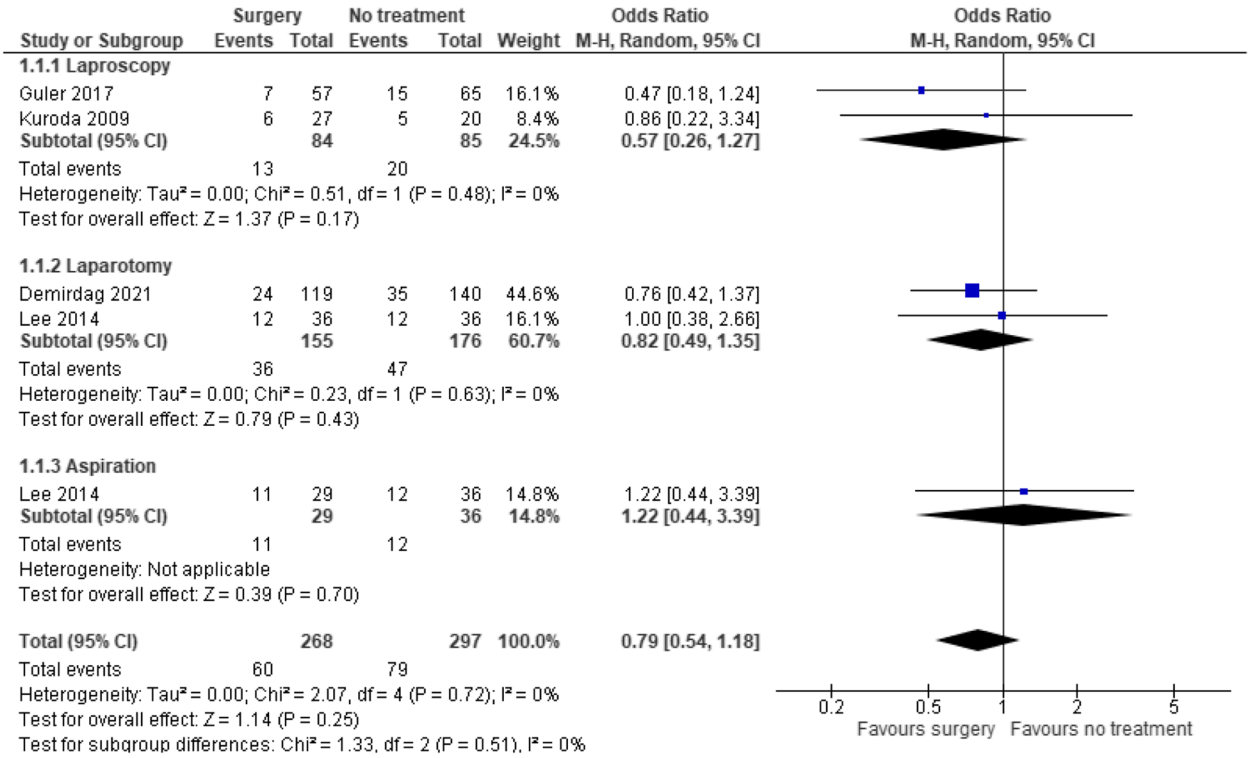

Fig. 2 Live birth rate (surgical intervention vs. no treatment)

treatment before fresh IVF cycle. They reported a significantly higher AFC (10.3 ± 2.0 vs. 6.4 ± 2.5; $P=0.0001$), lower required total doses of Gn (2079 ± 1119 versus 3716 ± 1314; $P=0.0001$), higher number of mature oocytes (9.1 ± 2.4 versus 4.0 ± 1.7; $P=0.0001$), clinical pregnancy rate (50% versus 22%, $P=0.003$), and live birth rate (40% versus 17%, $P=0.008$) in letrozole GnRH group compared to GnRH only group, respectively.

Lossl et al. in 2009 [22] conducted a prospective single arm study on 20 women candidate for IVF and diagnosed with endometrioma. They were subjected to three subcutaneous injections of 3.6 goserelin every 28 days in addition to daily oral tablet of 1-mg anastrozole for 70 days. They reported a significant decrease in endometriomal volume by 29% ($P=0.007$) and serum CA125 by 61% ($P=0.001$).

Discussion

In this review, women with untreated endometrioma had significantly higher numbers of MII oocytes ($P=0.04$), higher number of obtained embryos ($P<0.001$), and required lower doses of gonadotropins for induction ($P<0.001$) compared to those who had undergone surgical management of endometrioma. However live birth ($P=0.25$), clinical pregnancy ($P=0.73$), miscarriage ($P=0.45$), cancellation rates ($P=0.37$), and the duration of stimulation ($P=0.54$) did not show any significant difference between the two groups of women.

Our systematic review also confirmed that hormonal treatment of endometrioma was associated with higher ongoing pregnancy rate ($P<0.001$), higher clinical pregnancy rate ($P<0.001$), and higher numbers of MII oocytes ($P=0.003$) when compared to women who did not receive such therapy. These effects were evident in treatment with GnRH agonists, OCPs, and dienogest, while the miscarriage ($P=0.61$) and cycle cancellation rates ($P=0.08$) did not show these differences.

Given the thorough search strategy and clear inclusion and exclusion criteria, this review provides a comprehensive overview of the current scientific evidence regarding surgical and medical treatment of endometriomas prior to IVF/ICSI. All 18 included studies included various comparisons, different study designs, and heterogenous reporting of data. This marked heterogeneity in study design, sample size, included population characteristics, intervention differences in type and timing, and different treatment modalities after intervention completion prevents the proper meta-analysis reporting of different outcome parameters. The review presented two different comparisons either surgical or medical treatment options.

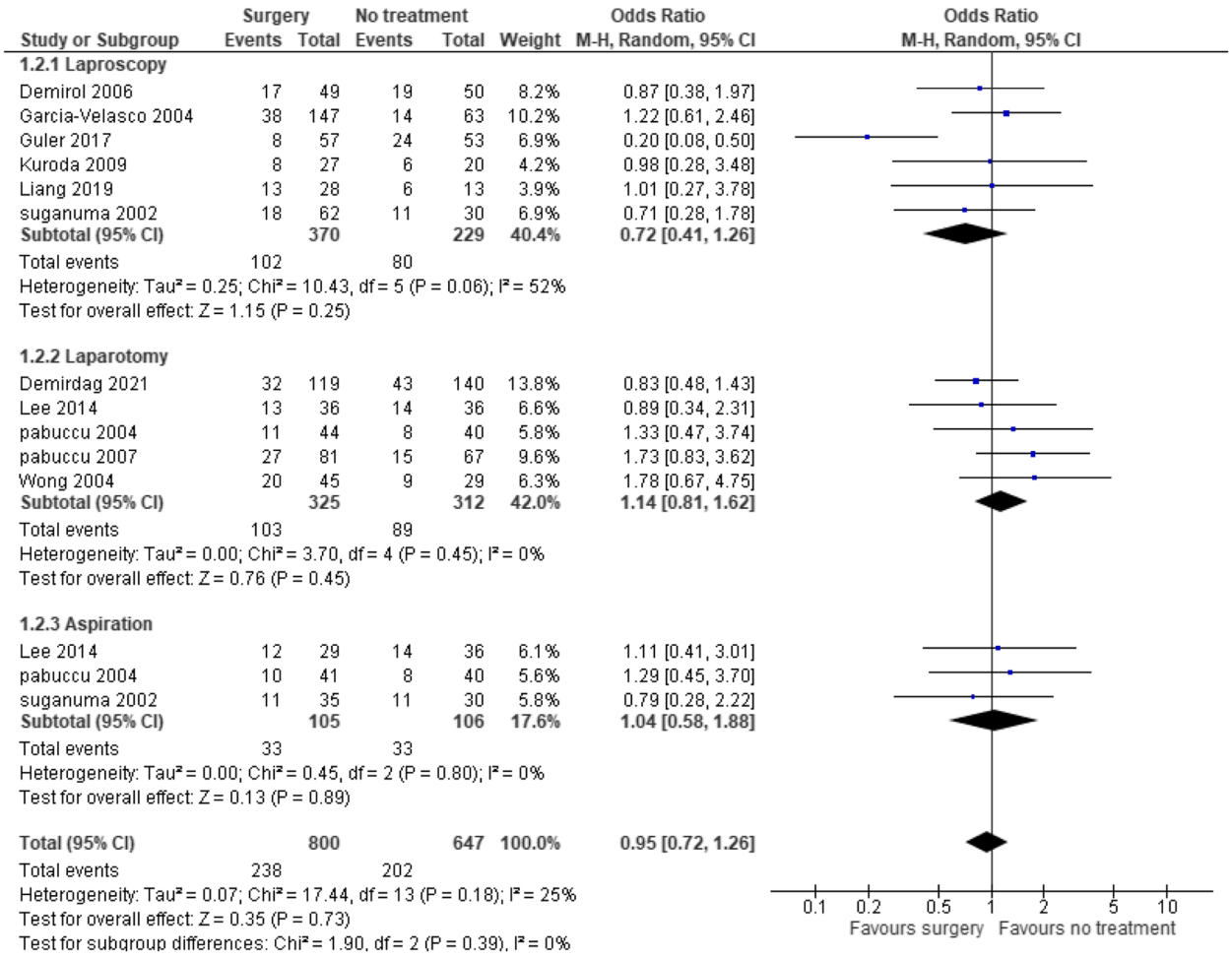

Fig. 3 Clinical pregnancy rate (surgical intervention vs. no treatment)

There are contradictory observations regarding the impact of endometriosis on ovarian responsiveness to gonadotropins during controlled ovarian stimulation and IVF. Some studies reported diminished ovarian response to COH in women with unilateral endometriomas [33, 34]. On the other hand, a systematic review and meta-analysis of nine RCTs reported difference between the ovary with endometrioma compared to the contralateral nonaffected ovary regarding the numbers of retrieved oocytes, MII oocytes, and obtained embryos. All were reported to be lower from the affected ovaries. They suggested different mechanism for these findings including changes in immune markers as IL-6, VEGF, and oxidative stress markers with resultant decrease in density and diameters of primordial follicles. However, there was no differences regarding clinical pregnancy and live birth rates [35].

The impact of surgical treatment for endometrioma before IVF remains a controversy. In a retrospective trial that involved 292 women with existing endometrioma, no history of surgery who were candidate for IVF, they reported lower numbers of antral follicles and required higher doses of Gn in women with existing endometriomas compared to those with previous surgery for endometriomas and absent endometrioma at time of IVF without any significant difference in live birth rate between them [36].

In a recent meta-analysis, there was a significantly lower number of retrieved oocytes and higher rate of cycle cancellation in women with existing endometrioma during IVF cycle with similar clinical pregnancy and live birth rates when compared to women without endometriomas [37, 38]. Hamadan and colleagues suggested that the presence of ovarian endometrioma exerts a negative effect on the ovarian tissue with resultant decrease in number and quality of retrieved oocytes and increase in baseline FSH level [37].

On the other hand, a retrospective study reported a significantly higher clinical pregnancy and live birth rates trial in women who underwent laparoscopic cystectomy for endometrioma when compared to those underwent diagnostic laparoscopy without resection before IVF [39]. In a large

observational study that involved 825 women diagnosed with endometriosis-related infertility, there was a significantly higher overall pregnancy rates in women who underwent endometrioma surgical resection followed by IVF compared to those who underwent surgical resection without IVF, IVF without prior resection, or no treatment [40].

Furthermore, several studies have reported the adverse effects of surgical treatment of endometrioma on ovarian reserve markers as the reduction of serum AMH levels after surgery [41]. After surgery, the level of AMH is reduced by 34% 1 week after surgery and gradually improves to reach 65% of its preoperative level 3 months after the operation. Measurement of AMH after 1 year of surgery revealed similar level to that reported after 1 month of surgery. Bilateral ovarian cystectomy is associated with more damage to ovarian reserve [42].

Regarding the medical treatment before IVF, a systematic review included 19 studies with 1709 participants compared with dydrogesterone to other hormonal therapies. It concluded that dydrogesterone caused better relieve of dysmenorrhea and improved the pregnancy rate compared to gestrinone with less side effects. They also concluded that dydrogesterone decreased the recurrence rate compared to with GnRH-a treatment. There are insufficient data to compare the efficacy of dydrogesterone, letrozole and leuprolide acetate, and the traditional Chinese medicine remains [43]. A Cochrane overview concluded that a 3-month regimen with GnRH agonist before IVF improves the pregnancy rates [44].

Strengths and limitations

This review is the first systematic review to study the clinical parameters of the effects of both surgical and medical treatment of endometrioma before IVF cycles. We included all the available studies that included all types of interventions. Adequate data extractions and proper meta-analysis when possible was done. The main limitation of this review is the low quality of evidence because of the absence of adequate numbers of RCTs and the marked heterogeneity among the included studies.

Conclusion

In conclusion, the optimal approach for treating endometrioma prior to IVF is not clear yet due to lack of well-designed randomized controlled trials.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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All data used are available within the manuscript itself.
Data used and/or analyzed during the study are available from the corresponding author upon request.

Declarations

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Not applicable.

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All authors give their consent for publication.

Competing interests
The authors declare that they have no competing interests.

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