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Review Article

Live Birth Rate after Surgical and Expectant Management of Endometriomas after In Vitro Fertilization: A Systematic Review, Meta-Analysis, and Critical Appraisal of Current Guidelines and Previous Meta-Analyses

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ABSTRACT Controversy exists regarding surgical management of endometriomas in infertile women before in vitro fertilization (IVF) because growing evidence indicates that surgery may impair the ovarian response. The objective of the present systematic review and meta-analysis was to compare surgical and expectant management of endometriomas regarding IVF outcomes. Prospective and retrospective controlled studies were found via the Cochrane Library, Embase, and MEDLINE databases. Thirteen studies (1 randomized controlled trial and 12 observational studies, N = 2878) were pooled, and similar live birth rates were observed in the surgically and expectantly managed groups (odds ratio = 0.83; 95% confidence interval [CI], 0.56−1.22; p = .98). The clinical pregnancy rates (odds ratio = 0.83; 95% CI, 0.66−1.05; p = .86), the number of mature oocytes retrieved, and the miscarriage rates were not statistically different between study groups. However, the total number of oocytes retrieved was lower in the surgery group (mean difference = −1.51; 95% CI, −2.60 to −0.43; p = .02). Findings suggest that surgical management of endometriomas before IVF therapy yields similar live birth rates as expectant management. However, future properly designed randomized controlled trials are warranted. Journal of Minimally Invasive Gynecology (2019) 26, 299−311. © 2018 AAGL. All rights reserved.

Keywords: Assisted reproductive technologies; Cystectomy; Ovarian endometriosis; Intracytoplasmic sperm injection

Endometriomas are ovarian masses that arise from the growth of ectopic endometrial glandular and stromal tissue. Previous studies have suggested that 10% to 15% of infertile women have endometriosis and that 30% to 50% of women with endometriosis are infertile [1]. Mechanisms linking endometriosis/endometriomas and infertility include distorted pelvic anatomy, altered peritoneal function, changed hormonal and cell-mediated function, endocrine and ovulatory abnormalities, impaired implantation, altered oocyte and embryo quality, and abnormal uterotubal transport [2]. Surgical resection by laparoscopy or laparotomy may increase fecundity in infertile patients with early-stage endometriosis [3,4]. However, current guidelines are unclear regarding the benefit to endometrioma resection before in vitro fertilization (IVF) [5]. Recent evidence indicates that surgical manipulation may compromise ovarian reserve, impede the ovarian response, and possibly decrease IVF success [5,6]. Large discrepancies exist in the literature regarding the best management of endometriomas in patients undergoing IVF. Despite more than 2 decades of research, substantial evidence involving surgical versus expectant management of endometriomas is lacking.

The objective of the present systematic review and meta-analysis was to compare the effect of surgical versus expectant management of endometriomas on IVF outcomes. The primary end point involves live birth rates per cycle after IVF; the

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secondary end points include the number of total and mature oocytes retrieved, the antral follicle count (AFC), clinical pregnancy, fertilization, miscarriage, and cycle cancellation rates.

Methods

Data Sources

The Cochrane Library (1989−January 2018), Embase (1947−January 2018), and MEDLINE (1946−January 2018) databases were systematically searched. Clinical trial databases such as www.clinicaltrialresults.org, the International Standard Randomized Controlled Trial Number Register, and Meta-register for Randomized Controlled Trials were also searched for relevant randomized controlled trials (RCTs). In addition, the reference lists of the included studies were reviewed. The search words included cystectomy, endometrioma, endometriosis, intracytoplasmic sperm injection, IVF, ovarian stripping, ovarian response, and pregnancy. The search strategy is included in Appendix 1.

Inclusion Criteria

We included retrospective or prospective studies investigating surgical management of endometriomas or IVF outcomes, studies including a comparator group with no surgical treatment, and studies published in English. Studies were excluded if they examined endometriomas treated with any other procedures, such as cyst aspiration or oophorectomy.

Data Extraction

Data involving study and population characteristics, type of surgical procedures, and IVF outcomes (live birth, pregnancy, fertilization, miscarriage, and cycle cancellation rates) were retrieved independently by 2 reviewers (C.Q.W. and S.A.). Incongruities were resolved by consensus or a third reviewer (O.T.). This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (Fig. 1) [7].

Statistical Analyses

We analyzed all data using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) [8] and random effects meta-analysis as implemented in the R package 'metafor' [9] to calculate the estimated average odds ratios and the mean difference. The odds ratio and mean difference with 95% confidence intervals were weighted by the inverse variance to give greater weight to larger studies. The meta-analysis of reproductive outcomes after IVF for both groups was performed for the primary outcome (live birth rate) as well as the secondary outcomes (number of total and mature oocytes retrieved, AFC, clinical pregnancy, and miscarriage rate). A descriptive analysis of fertilization and cycle cancellation rates was performed.

Subgroup analysis with the 2 most common study designs (retrospective cohort and retrospective case control) was performed when sufficient data were available. However, subgroup analyses were not possible for the miscarriage and live birth rates because there were too few studies. The I^2 metric was calculated to assess study heterogeneity, with I^2 >50% indicating substantial heterogeneity. Publication bias was assessed via funnel plots and the Egger test [10], and study quality was assessed using the Newcastle-Ottawa Quality Assessment scale (Appendix 2) [11−24].

Results

Literature Search

Six hundred fifty-nine potentially relevant studies were identified (Fig. 1); 546 titles and abstracts were screened for inclusion after the removal of duplicates. Of these, 437 were excluded for irrelevance. Two case reports, 10 editorials/commentaries, 4 practice guidelines, and 18 review articles were also excluded. Fifty-nine additional studies were excluded because of study design. After the retrieval of full texts, 16 articles were further scrutinized in their entirety, leading to the exclusion of 3 additional studies (1 was an abstract, 1 was a duplicate of an included study, and the other study had an inappropriate comparator group).

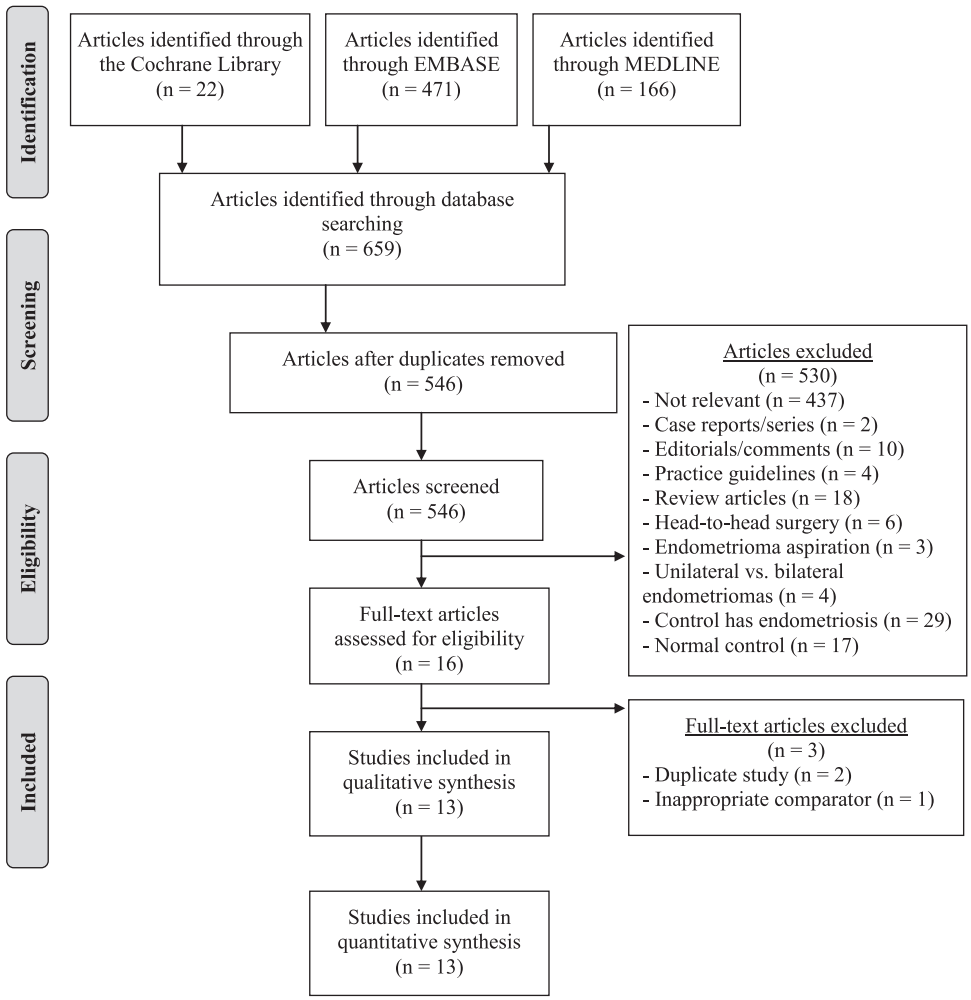
Included Studies

A total of 13 studies investigating fertility outcomes in women with endometriomas were included in the systematic review and subsequent quantitative analysis, including 12 observational studies (7 retrospective and prospective cohorts and 5 retrospective case-control studies) and 1 RCT (Table 1) [12−24]. The total patient population was 1588. The studies took place from 1994 to 2015 around the world in Brazil, China, Finland, Italy, Japan, Korea, Spain, Turkey, and the United States. The study duration ranged from 2 to 13 years. The surgery group had a total of 852 patients, whereas the expectant management group had 736 patients. Both laparoscopic and open techniques were used for endometrioma resection.

Patient characteristics were comparable between the surgery and expectant management groups (Table 2) [12−24]. Patients were between 29.6 and 35.5 years old in the surgical group and between 30.1 and 38.4 years old in the expectantly managed group. The mean duration of infertility was between 3.0 and 8.5 years in the surgery group and 2.9 and 5.6 years in the expectantly managed group. Enrolled patients were typically diagnosed with either unilateral and/or bilateral endometriomas, with 2 studies limiting their patient population to patients with unilateral

Fig. 1

A flow diagram.



endometriomas only [14,17]. The mean endometrioma size and interval between surgery and the commencement of IVF cycles were heterogeneous across studies; the mean interval before IVF was between 3 months and 7 years after surgery for endometriomas [12−24].

Reproductive Outcomes

The primary end point of this study was live birth rates per cycle after IVF; the secondary end points included the number of total and mature oocytes retrieved, clinical pregnancy, fertilization, miscarriage rates, and cycle cancellation rates (Table 3) [12−24]. Live birth rates per cycle ranged between 11.8% and 37.9% in the surgically managed group compared with 16.1% to 42.6% in the group that proceeded directly to IVF without surgery. Comparable numbers of mature oocytes were retrieved in the surgery and expectantly managed groups. Fertilization rates in the surgery patients ranged from 48% to 86.2%, whereas fertilization rates in the expectant management group ranged from 56.5% to 88.3%. The implantation rate ranged from 12.8% to 32.1% in the surgery group compared with 12% to 24.2% in the expectant group. Pregnancy rates per cycle were similar in both groups (15.7%−43.1% in the surgery group and 19.4%−51.5% in the expectant management group). The miscarriage rates were 7.6% to 25.0% in the surgery group and 10% to 28.6% in the expectantly managed group. Likewise, the overall cycle cancellation rates were higher in the surgery group compared with the control group; 6.3% to 47.1% of cycles were canceled in the surgery group, and 1.5% to 35.5% of cycles were canceled in the control group.

The random effects model was used for all analyses. Pooled results showed no significant difference in live birth rates per cycle between the surgically and expectantly managed groups (Fig. 2) [12,19,22−24]. However, there was a significant

Table 1

Study Characteristics of Comparative Studies Examining In Vitro Fertilization (IVF) Outcomes after Surgical Management of Endometriomas

Study*	Study Design	n	Country	Study Period	Study Population
Tinkanen et al, 2000 [12]	Retrospective case control	100	Finland	1994−1998	Patients with endometriosis admitted for IVF
Suganuma et al, 2002 [13]	Retrospective case control	79	Japan	NR	Infertile women with endometrioma
Garcia-Velasco et al, 2004 [14]	Retrospective case control	189	Spain	1997−2001	Women with endometriomas who underwent IVF
Pabuccu et al, 2004 [15]	Prospective cohort	171	Turkey	1995−2002	Patient with ovarian endometriosis
Wong et al, 2004 [16]	Retrospective cohort	204	US	1995−2002	Infertile patients with endometriosis who underwent IVF-ET
Demirol et al, 2006 [17]	Randomized controlled trial	99	Turkey	2001−2005	Patients with endometriomas who were referred for ICSI
Bianchi et al, 2009 [18]	Prospective cohort	179	Brazil	2005−2008	Infertile patients aged <38 with symptoms/signs of endometriosis and sonographic images suggestive of DIE
Kuroda et al, 2009 [19]	Retrospective case control	61	Japan	2006−2008	Patients with major indications for IVF/ICSI with endometriosis
Barri et al, 2010 [20]	Retrospective cohort	825	Spain	2001−2008	Patients aged 20−40 with endometriosis-associated infertility
Bongioanni et al, 2011 [21]	Retrospective case control	428	Italy	2004−2009	Patients with previous or present diagnosis of ovarian endometriosis undergoing IVF
Lee et al, 2014 [22]	Retrospective cohort	101	Korea	2008−2012	Infertile women with endometrioma undergoing IVF/ICSI
Dong et al, 2014 [23]	Retrospective cohort	292	China	2011−2013	Patients with endometriomas who were undergoing IVF/ICSI
Guler et al, 2017 [24]	Retrospective cohort	150	Turkey	2002−2015	Infertile patients with endometriosis undergoing ICSI
		N = 2878			

DIE = deep infiltrating endometriosis; ET = embryo transfer; ICSI = intracytoplasmic sperm injection; NR = not reported.
* Studies are listed according to year of publication, from earliest to most recent.

association between fewer total number of oocytes and endometrioma surgery (Fig. 3) [13,14,18,19,21−24], reflecting a trend toward lower AFC in the surgically managed group (Fig. 4) [15,21−24]. However, when it came to mature oocytes, no significant association between the number of mature oocytes and surgery was noted (Fig. 5) [13−17,19,20,22,24].

Across studies, no significant association was found between the clinical pregnancy rates and the type of endometrioma treatment (Fig. 6) [12−15,17,19,20,22−24], suggesting that there was no overall difference in the odds of clinical pregnancy per cycle between groups. Comparable miscarriage rates were also observed between the endometrioma resection and control groups (Fig. 7) [12,14,15,19,22].

Discussion

Society Guidelines

The current practice guidelines regarding surgical management of endometriomas before IVF therapy are inconsistent (Table 4) [2,25−31]. The European Society of Human Reproduction and Embryology guidelines published in 2013 suggest that there is no evidence for cystectomy before assisted reproductive technologies in infertile patients with endometriomas [27]. Similarly, the French National College of Obstetrician and Gynecologists recommends against surgical treatment of endometriomas when the sole purpose is to improve IVF outcomes [28]. However, the American Society of Reproductive Medicine guidelines (2012) recommend surgery to improve access to follicles and ovarian response in patients with ovarian endometriomas >4 cm [2,30]. However, this cutoff is not evidence based. Subanalysis of fertility outcomes in relation to endometrioma size is grossly lacking. Recent evidence also suggests that deep infiltrating endometriosis, which is commonly associated with endometriomas, may play a larger role in fertility than endometriomas only [31]. The National Institute for Clinical Excellence (2018) recommends offering laparoscopic ovarian cystectomy to women with endometriomas, without specification on size or laterality [29]. The American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada guidelines published in 2010 indicate that surgical management of endometriosis-related infertility improves pregnancy rates, but they do not provide specific criteria for surgery [25,26].

Current Analysis

The present meta-analysis was designed to review the literature on the management of endometriomas in

Table 2

Patient Characteristics of Comparative Studies Examining In Vitro Fertilization (IVF) Outcomes after Surgical Management of Endometriomas

Study*	Surgery, n†	Expectant, n‡	Type of Surgery	Mean Age, years ± SD		Mean Duration of Infertility, Years ± SD		Cyst, cm	Laterality	Interval between Surgery and IVF
				Surgery	Expectant	Surgery	Expectant			
Tinkanen et al, 2000 [12]	55	45	Cystectomy	30.9	30.4	4.4	4.3	1.5−7	Either	1−7 years
Suganuma et al, 2002 [13]	36	20	Cystectomy	32.2 ± 3.5	32.4 ± 2.8	NR	NR	NR	Either	31.2 ± 27.4 months
Garcia-Velasco et al, 2004 [14]	133	56	Laparoscopic cystectomy	34.7 ± 0.3	33.9 ± 0.5	NR	NR	>3	Unilateral	12 months
Pabuccu et al, 2004 [15]	44	40	Cystectomy	29.6 ± 3.3	30.1 ± 4.5	5.5 ± 3.1	5.6 ± 3	2.6 ± 1.09	Either	≤4 years
Wong et al, 2004 [16]	NR	NR	Laparoscopic cystectomy	35.5 ± 0.8	32.3 ± 0.7	NR	NR	2−5.0	Either	3−24 months
Demirol et al, 2006 [17]	49	50	Laparoscopic cystectomy	35.2 ± 0.3	34.9 ± 0.2	NR	NR	3−6.0	Unilateral	>3 months
Bianchi et al, 2009 [18]	29	35	Laparoscopic cystectomy	32.8 ± 3	32.6 ± 3	3 ± 1.7	2.9 ± 1.3	NR	NR	>3 months
Kuroda et al 2009 [19]	36	18	Laparoscopic cystectomy	35.5 ± 3.4	38.4 ± 3.0	NR	NR	NR	Either	NR
Barri et al, 2010 [20]	144	173	Laparoscopic cystectomy	35.3 ± 3.1	35.3 ± 3.1	3.2 ± 2.3	3.2 ± 2.3	5.4 ± 3.2	Either	NR
Bongioanni et al, 2011 [21]	112	142	Laparoscopic cystectomy	33.6 ± 4.4	33.8 ± 2.9	3.9 ± 2.9	4.0 ± 2.5	≤6	Either	NR
Lee et al, 2014 [22]	36	36	Cystectomy	33.6 ± 2.9	34.3 ± 4.3	3.4 ± 2.9	2.9 ± 2.4	>3	Either	20.3 ± 19.5 months
Dong et al, 2014 [23]	153	68	Laparoscopic cystectomy	30.4 ± 4.4	31.1 ± 4.2	4.3 ± 3.1	4.7 ± 4	NR	Either	NR
Guler et al, 2017 [24]	25	53	Laparoscopic cystectomy	32.5 ± 4.5	32.2 ± 4.7	8.5 ± 6	5.2 ± 3.6	>3	Either	NR
	n = 852	n = 736								

NR = not reported.

* Studies are listed according to year of publication, from earliest to most recent.

† Patients underwent surgical removal of endometriomas before IVF treatment.

‡ Patients underwent IVF treatment without surgical removal of endometriomas.

Table 3

In Vitro Fertilization (IVF) Outcomes of Comparative Studies Involving Surgical Management of Endometriomas per Cycle

Study*	IVF Cycles		Number of Oocytes		Number of Mature Oocytes		E2 Peak, pg/mL		Implantation Rate, %		Fertilization Rate per Cycle, %		Pregnancy Rate per Cycle, %		Live Birth Rate per Cycle, %		Miscarriage Rate per Cycle, %	
	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant
Tinkanen et al, 2000 [12]	55	45	6.1	6.5	NR	NR	NR	NR	13	20	48	58	21.8	37.7	20.0	26.7	8.3	23.5
Suganuma et al, 2002 [13]	62	30	7.2 ± 6.2	9.7 ± 6.7	5.7 ± 4.8	8.0 ± 5.4	NR	NR	NR	NR	56.8	56.5	29.0	36.6	NR	NR	NR	NR
Garcia-Velasco et al, 2004 [14]	147	63	10.8 ± 7	11.8 ± 7	8.7 ± 0.6	8.4 ± 0.8	1910 ± 106	2472 ± 261	12.8	14.1	76.5	69.9	25.4	22.7	NR	NR	16.2	28.6
Pabuccu et al, 2004 [15]	44	40	NR	NR	5.7 ± 1.3	5.6 ± 1.2	1196 ± 444	946.7 ± 264	18	12	72	68	25	20	NR	NR	8.3	10
Wong et al, 2004 [16]	36	38	NR	NR	10.3 ± 1.2	9.4 ± 0.9	1956 ± 215	1928 ± 198	20	18	85	88	NR	NR	NR	NR	21	18
Demirol et al, 2006 [17]	49	50	NR	NR	7.8 ± 3.07	8.6 ± 2.82	1170 ± 417.14	1680 ± 428.69	16.5	18.5	86.2	88.3	34.4	38.2	NR	NR	NR	NR
Bianchi et al, 2009 [18]	86	153	10 ± 4	7 ±4	NR	NR	NR	NR	32.1	19	83.9	86.5	NR	NR	NR§	NR§	NR	NR
Kuroda et al, 2009 [19]	51	31	1.2 ± 1.1	1.6 ± 2.1	NR	NR	661 ± 631	864 ± 624	15.7	19.4	NR	NR	15.7	19.4	11.8	16.1	25.0	16.7
Barri et al, 2010 [20]	184	211	NR	NR	7.3 ± 5	10.1 ± 2.2	NR	NR	NR	NR	NR	NR	30.4	32.2	NR	NR	NR	NR
Bongioanni et al, 2011 [21]	72†	77	8.2 ± 5.3	9.4 ± 4.3	NR‡	NR	NR	NR	24.6	24.2	73.4	67.7	36.6	41.5	NR	NR	NR	NR
Lee et al, 2014 [22]	36	36	8.2 ± 4.7	12.4 ± 7.5	6.9 ± 3.7	10.7 ± 6.7	NR	NR	NR	NR	NR	NR	36.1	38.8	33.3	33.3	7.6	14.2

Table 3

Continued

Study*	IVF Cycles		Number of Oocytes		Number of Mature Oocytes		E2 Peak, pg/mL		Implantation Rate, %		Fertilization Rate per Cycle, %		Pregnancy Rate per Cycle, %		Live Birth Rate per Cycle, %		Miscarriage Rate per Cycle, %	
	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant	Surgery	Expectant
Dong et al, 2014 [23]	153	68	9.5 ± 5	9 ± 5.5	NR	NR	3623.5 ± 2175.3	3711.7 ± 2284.3	NR	NR	NR	NR	43.1	51.5	37.9	42.6	NR	NR
Guler et al, 2017 [24]	25	53	7.1 ± 4.7	10.3 ± 8.1	5.8 ± 3.9	7.1 ± 5.4	1258.8 ± 1012.2	2391 ± 1994.5	NR	NR	66.8	73.6	32	45.2	28	28.3	NR	NR

E2 peak = estradiol peak; NR = not reported.

* Studies are listed according to their year of publication, from the earliest to the most recent.

† Twenty-three patients underwent intracytoplasmic sperm injection in the surgery group, and 19 patients underwent intracytoplasmic sperm injection in the comparator group.

‡ Metaphase II oocytes were 68.8% in the surgery group and 71.2% in the comparator group.

§ The percentage of pregnancies resulting in live births was 94.4% in the surgery group and 87.5% in the comparator group.

patients undergoing IVF. Our findings suggest that surgical and expectant management of endometriomas before IVF yield comparable live birth, clinical pregnancy, AFC, mature oocytes, and miscarriage rates. Our results also suggest that surgically managed patients seem to have a lower number of total oocytes retrieved and greater IVF cycle cancellations.

All of the included studies used ovarian cystectomy for endometrioma removal, either by laparoscopy or laparotomy. Emerging evidence shows that surgery may not overcome the peritoneal, hormonal, immunologic, and anatomic alterations associated with inflammation in endometriosis-associated infertility. Prospective and retrospective studies alike have reported that an ovary after surgery produces fewer follicles, oocytes, and high-quality embryos than their untouched counterpart after ovarian hyperstimulation [32−35]. It is thought that ovarian surgery further decreases the amount of viable ovarian tissue [36,37] and, consequently, the available ovarian reserve [38,39]. Individual cases have also provided evidence of patients who developed ovarian failure after excision of bilateral ovarian endometriomas [6]. In addition, the risk of endometrioma recurrence after resection remains high, around 30% at 2 to 5 years after surgery [40].

On the other hand, some studies have suggested that conservative management of endometriomas in IVF patients is associated with poorer response to gonadotropin stimulation [41,42], lower spontaneous ovulation rates [43], lower oocyte quality [44], and higher miscarriage rates [45]. Furthermore, unoperated endometriomas are at risk of spontaneous rupture, leakage, or torsion [46]. Larger endometriomas can increase the difficulty of oocyte retrieval as well as the risk of infection [47,48]. In addition, excessive growth and/or size of endometriotic cysts can be a sign of malignancy [49]. Recent studies also reported adverse pregnancy outcomes in patients with known endometriomas [49] and associated pelvic disease [50,51].

Surgery may be indicated for patients with severe pain, rapid endometrioma growth, suspicious features for malignancy, or inability to access follicles at oocyte retrieval [52−54]. The European Society of Human Reproduction and Embryology recommends that ovarian reserve testing be completed before surgery and consideration be given to preoperative freezing of oocytes, especially in cases of bilateral disease [55]. Bipolar electrocoagulation appears to impact ovarian reserve more negatively than nonthermal hemostatic methods such as suture or hemostatic polymer [56]. Irrespective of the surgical technique, it is crucial to minimize any compromise of ovarian blood supply and to preserve normal ovarian tissue [57]. Complex surgical planning may be necessary, especially in cases with extensive pelvic disease.

Previous Meta-analyses

Few previous meta-analyses examined live birth rates as their primary end point. A systematic review

Fig. 2

A forest plot of random effects meta-analysis comparing live birth rates per cycle in surgically and expectantly managed infertile patients with endometriomas [12,19,22–24].

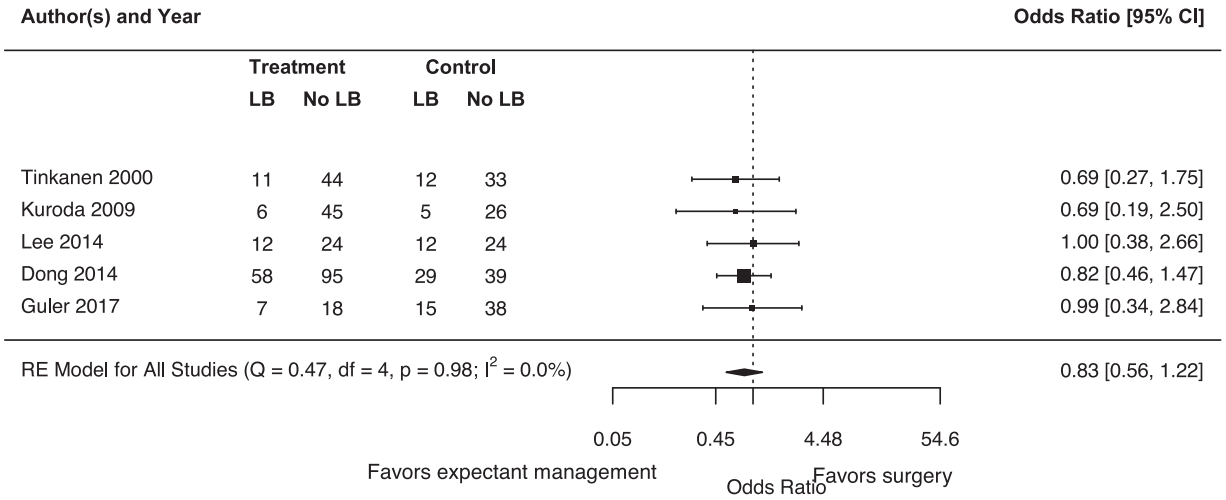


Fig. 3

A forest plot of random effects meta-analysis comparing the total number of oocytes retrieved in surgically and expectantly managed infertile patients with endometriomas [13,14,18,19,21–24].

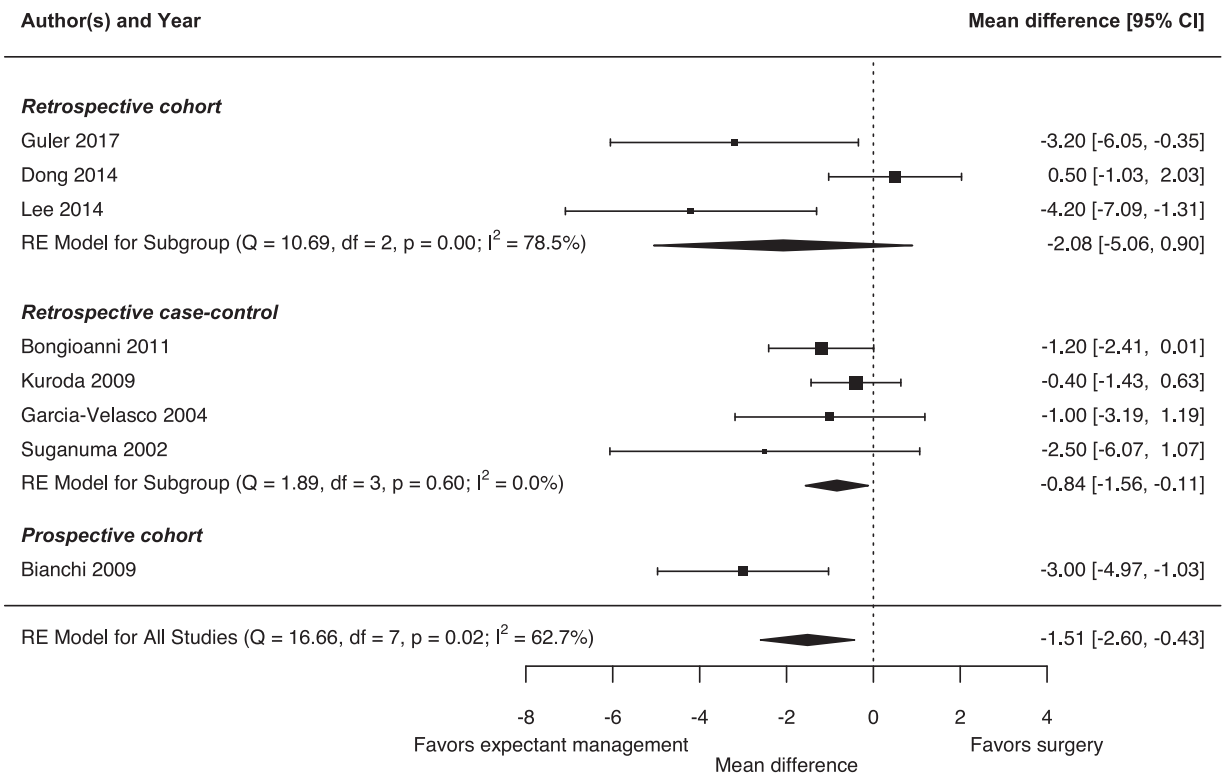


Fig. 4

A forest plot of random effects meta-analysis comparing baseline AFCs in surgically and expectantly managed infertile patients with endometriomas [15,21–24].

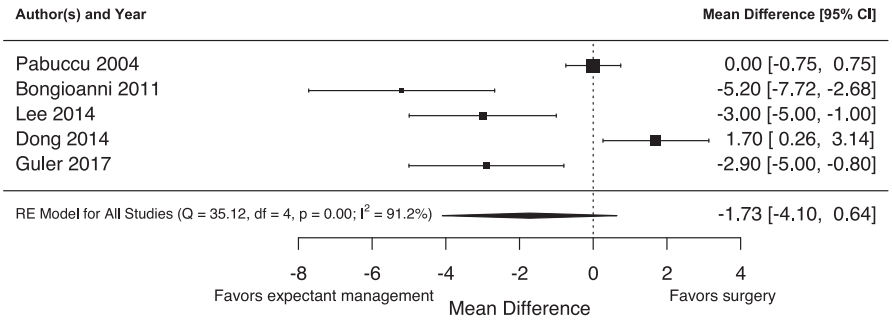
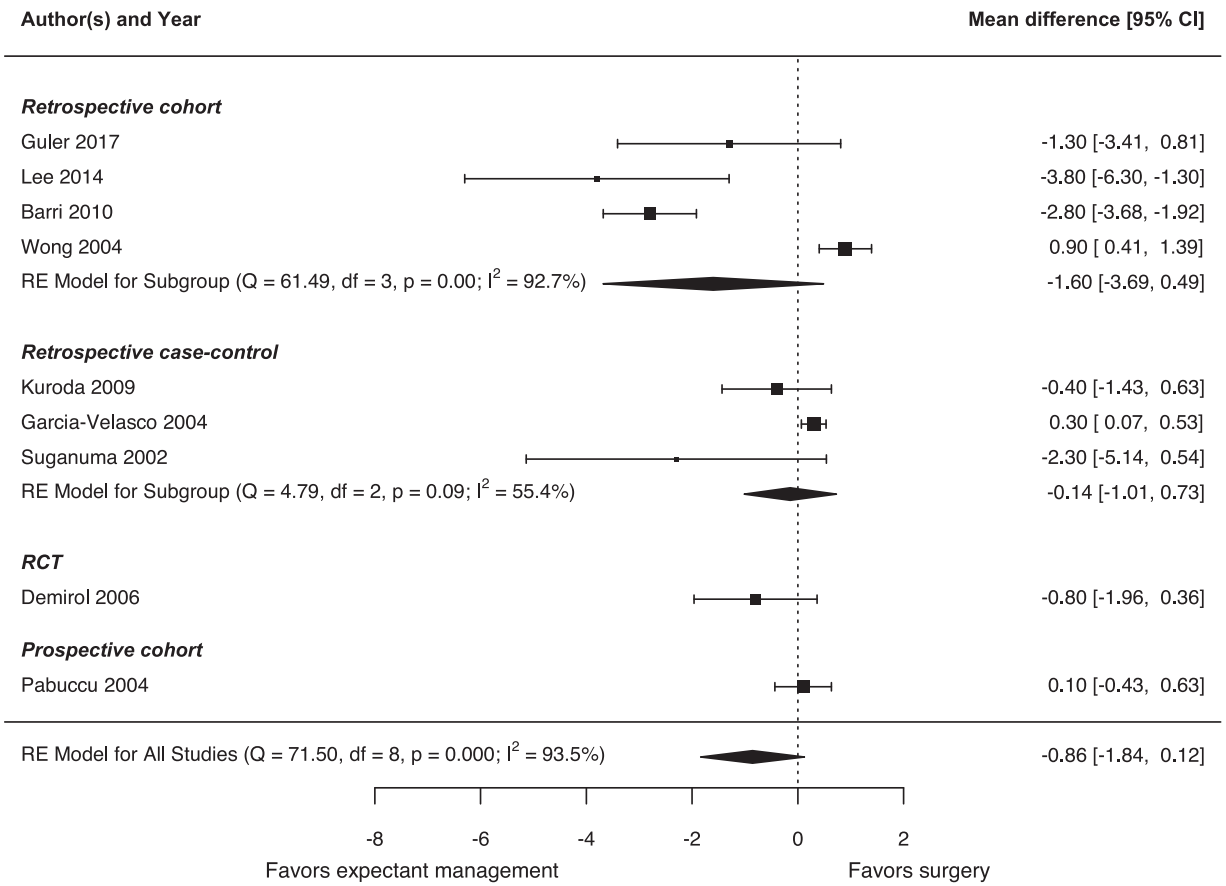


Fig. 5

A forest plot of random effects meta-analysis comparing the number of mature oocytes retrieved in surgically and expectantly managed infertile patients with endometriomas [13–17,19,20,22,24].



and meta-analysis published in 2009 reported that surgical management of endometriomas has no significant effect on IVF pregnancy rates compared with no treatment [46]. Similarly, a Cochrane systematic review published the following year also reported that cystectomy or aspiration did not improve reproductive outcomes compared with expectant management [58]. Concordant findings were reported by Brink Laursen and colleagues in 2017 [59] and most recently by Nickkho-Amiry et al [60].

Fig. 6

A forest plot of random effects meta-analysis comparing clinical pregnancy rates per cycle in surgically and expectantly managed infertile patients with endometriomas [12−15,17,19,20,22−24].

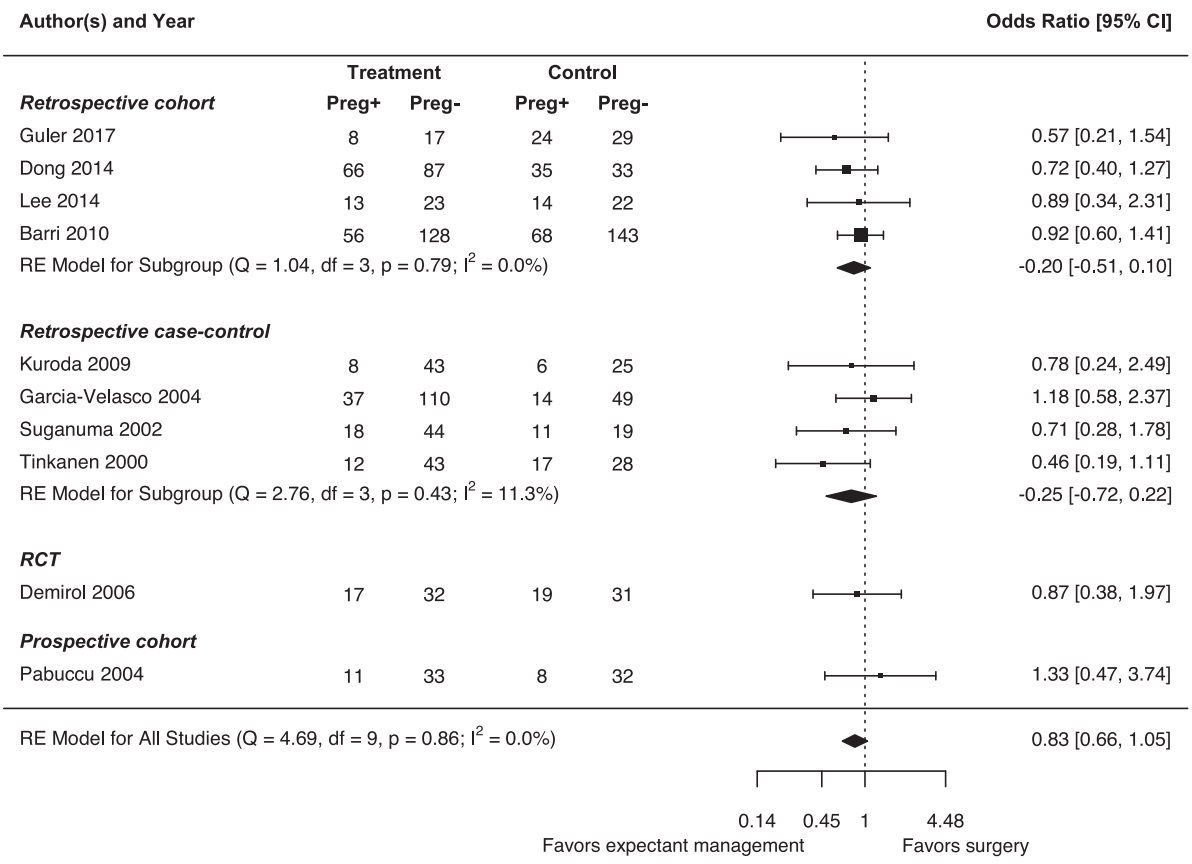


Fig. 7

A forest plot of random effects meta-analysis comparing miscarriage rates per patient in surgically and expectantly managed infertile patients with endometriomas [12,14,15,19,22].

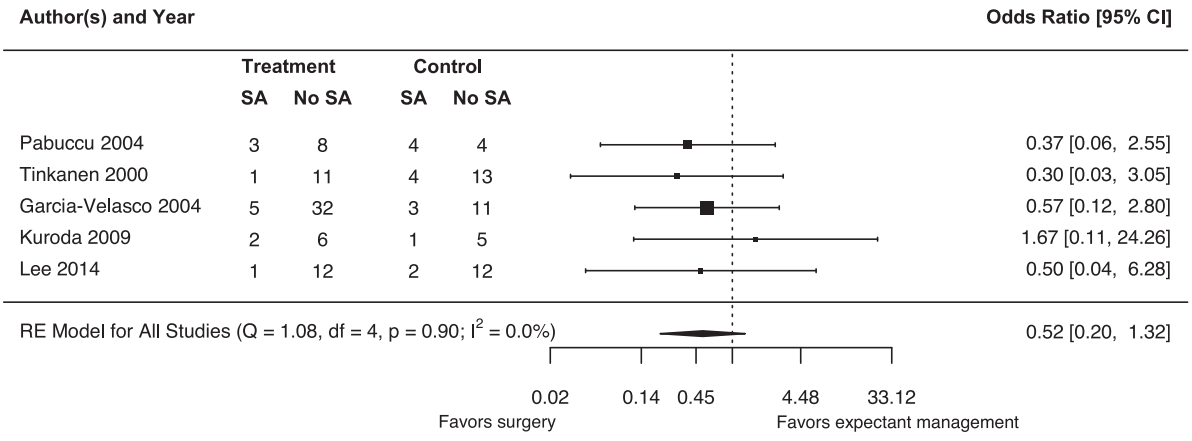


Table 4

Current Society Guidelines on the Management of Endometriomas in Assisted Reproductive Technologies (ARTs)

Society	Guideline Recommendations
ACOG [25] July 2010	• Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude is unclear.
SOGC [26] July 2010	• Laparoscopic treatment of minimal or mild endometriosis improves pregnancy rates regardless of treatment modality. • The effect on fertility of surgical treatment of deeply infiltrating endometriosis is controversial. • Laparoscopic excision of ovarian endometriomas >3 cm in diameter may improve fertility.
ASRM [2] September 2012	• For infertile patients with ASRM stage III/IV endometriosis and no other identifiable infertility factor, conservative surgery with laparoscopy and/or possible laparotomy or IVF are recommended. • For patients with asymptomatic endometrioma planning to undergo IVF/ICSI, there is insufficient evidence to suggest that removal of endometrioma will improve IVF success rates; however, if the endometrioma is large (>4 cm), surgery should be considered to confirm diagnosis histologically, improve access to follicles during oocyte retrieval, and possibly improve ovarian response.
ESHRE [27] September 2013	• In infertile patients with endometrioma >3 cm, there is no evidence that cystectomy before treatment with ART improves pregnancy rates. • In patients with endometriomas >3 cm, consider cystectomy before ART to improve endometriosis-associated pain or accessibility of follicles. • Counsel patients with endometrioma regarding the risks of reduced ovarian function after surgery and possible loss of the ovary; the decision to proceed with surgery should be considered carefully if the patient has had previous ovarian surgery.
CNGOF-HAS [28] March 2018	• Surgical treatment of endometriomas with the sole purpose of improving IVF outcomes is not recommended. • It is not recommended to perform systematic aspiration under ultrasound guidance for endometriomas before IVF to increase pregnancy rates. • Endometrioma drainage may be considered if location impedes oocyte retrieval.
NICE [29] August 2018	• Laparoscopic ovarian cystectomy with excision of the cyst wall for women with ovarian endometriomas improves the chance of spontaneous pregnancy and reduces recurrence, taking into account ovarian reserve.

ACOG = American College of Obstetricians and Gynecologists; ART = assisted reproductive technologies; ASRM = American Society of Reproductive Medicine; CNGOF-HAS = French National College of Gynecologists and Obstetricians-Haute Autorité de Santé; ESHRE = European Society of Human Reproduction and Embryology; SOGC = Society of Obstetricians dand Gynaecologists of Canada.

Limitations

This study is limited by confounders inherent to each individual included study, such as variations in surgical technique, postoperative duration, and degree of peritoneal disease. The majority of the included studies failed to stratify patients based on endometrioma laterality (unilateral vs bilateral disease), the extent of endometriosis disease (isolated endometrioma vs concurrent peritoneal disease and/or deep infiltrating endometriosis), endometrioma size, and endometrioma recurrence. The live birth rate was chosen as the primary end point because it is the ultimate end point of IVF treatment. However, many other confounders such as maternal age, cause of infertility, maternal medical conditions, and pregnancy complications can impact this outcome. Additionally, 12 of the 13 included studies were observational in nature and are thus subject to confounding by indication [12−16,18−24]. Publication bias may also have influenced the current results because studies with inconclusive or suboptimal results may have been selectively unpublished. There was no evidence of systematic bias in the funnel plot, and the Egger test was mostly nonsignificant for the primary outcome, but the same could not be said for secondary outcomes (Appendices 3−8). There was no significant heterogeneity among studies assessed for live birth, clinical pregnancy, or miscarriage rates based on the I^2 measurement.

Conclusion

Evidence suggests that surgical and expectant management of endometriomas yields similar fertility outcomes in terms of live birth and pregnancy rates. Surgical alternatives with a focus on preservation of the ovarian reserve should be explored, and further prospective studies specifically designed for the evaluation of IVF outcomes after surgery in infertile women with endometriomas should be conducted. Subgroup analyses of fertility outcomes in relation to endometrioma size, laterality, extent, associated pelvic pathologies, and method of resection are warranted.

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Appendix 1. Bibliographic Search Strategy

Database	Search Strategy
Cochrane Library Online	1. endometrioma 2. endometriosis 3. ivf 4. icsi 5. surgery 6. cystectomy 7. ovarian stripping 8. pregnancy 9. ovarian response.mp. 10. #1 or #2 11. #3 or #4 12 #5 or #6 or #7 13. #8 or #9 14. #10 and #11 and #12 and #13 15. limit #14 to Cochrane Reviews, Other Reviews, and Trials
EMBASE	1. endometrioma.mp or endometrium tumor/ 2. endometriosis.mp. or endometriosis/ 3. fertilization in vitro/ or ivf.mp. 4. icsi.mp. or intracytoplasmic sperm injection/ 5. gynecologic surgery/ or surgery.mp. 6. cystectomy.mp. or cystectomy/ 7. ovarian stripping.mp. 8. pregnancy.mp. or pregnancy/ 9. ovarian response.mp. 10. 1 or 2 11. 3 or 4 12. 5 or 6 or 7 13. 8 or 9 14. 10 and 11 and 12 and 13 15. limit 14 to (human and female)
MEDLINE	1. endometrioma.mp or Endometriosis/ 2. endometriosis.mp. 3. Fertilization in Vitro/ or ivf.mp. 4. icsi.mp or Sperm Injections, Intracytoplasmic/ 5. surgery.mp. or General Surgery/ 6. cystectomy.mp. or Cystectomy/ 7. ovarian stripping.mp. 8. Pregnancy/ or pregnancy.mp. 9. ovarian response.mp. 10. 1 or 2 11. 3 or 4 12. 5 or 6 or 7 13. 8 or 9 14. 10 and 11 and 12 and 13 15. limit 14 to (female and humans)

Appendix 2. Newcastle-Ottawa Quality Assessment of Observational Studies Included in the Systematic Review

Case-control Studies

	Selection					Exposure			
Study	Adequate case definition	Representative of the cases	Selection of Controls	Definition of Controls	Comparability	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Nonresponse Rate	Total Score
Tinkanen, 2000 [12]	*	*	*	*	**	*	*	*	9
Suganuma, 2002 [13]	*	*	*	*	**	*	*	*	9
Garcia-Velasco, 2004 [14]	*	*	*	*	**	*	*	*	9
Kuroda, 2009 [19]	*	*	*	*	**	*	*	*	9
Bongioanni, 2011 [21]	*	*	*	*	**	*	*	*	9

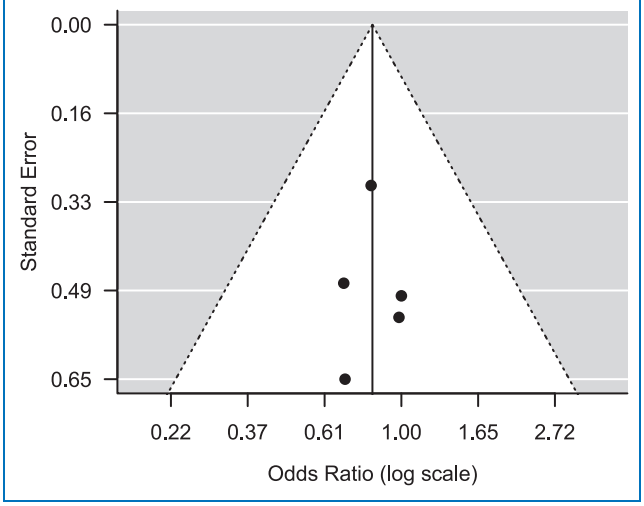
Cohurt Studies

	Selection					Exposure			
Study	Representative of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability	Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts	Total Score
Pabuccu, 2004 [15]	*	*	*	*	*	*	*	*	8
Wong, 2004 [16]	*	*	*	*	**	*	*	*	9
Bianchi, 2009 [18]	*	*	*	*	**	*	*	*	9
Barri, 2010 [20]	*	*	-	*	**	*	*	-	7
Lee, 2014 [22]	*	*	*	*	**	*	*	*	9
Dong, 2014 [23]	*	*	*	*	**	*	*	*	9
Guler, 2017 [24]	*	*	*	*	**	*	*	*	9

A study was awarded a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars were given for comparability.

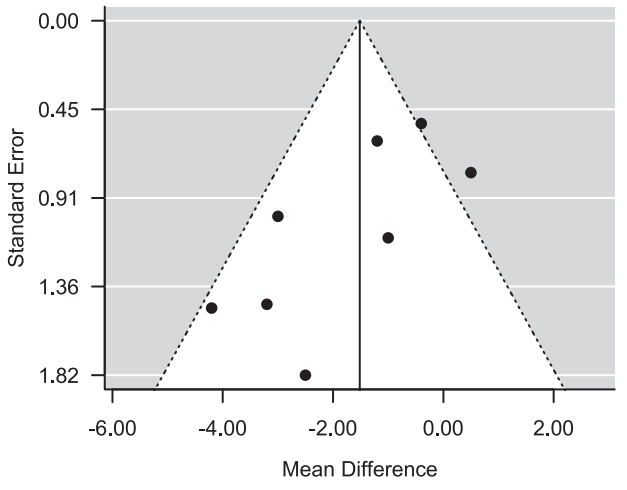
Appendix 3

A Funnel Plot of the Studies Included in the Live Birth Rates per Cycle Analysis



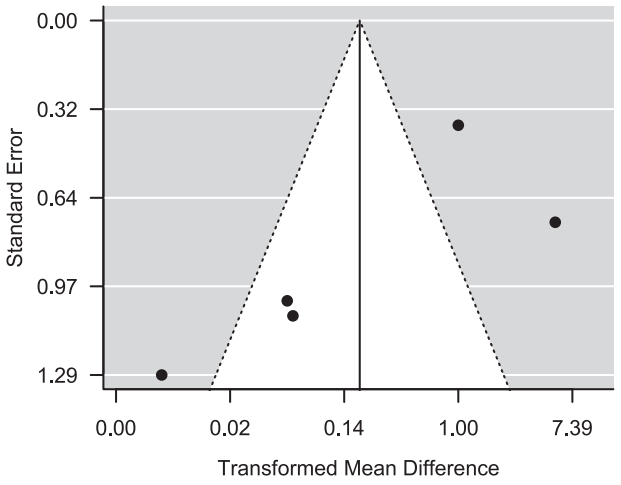
Appendix 4

A Funnel Plot of the Studies Included in the Total of Oocytes Retrieved Analysis



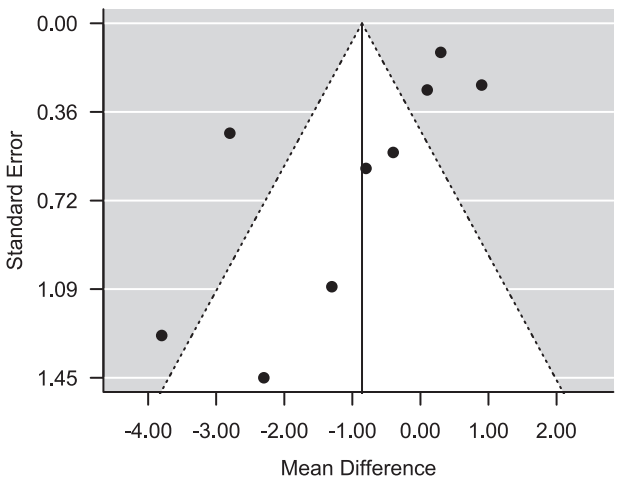
Appendix 5

A Funnel Plot of the Studies Included in the Antral Follicle Count Comparison Analysis



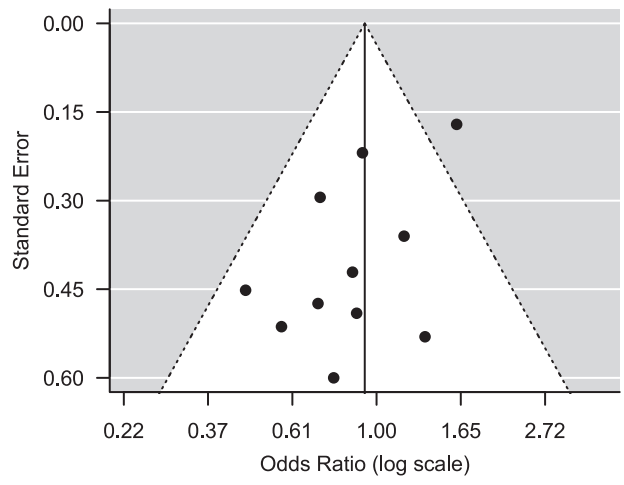
Appendix 6

A Funnel Plot of the Studies Included in the Number of Mature Oocytes Retrieved Analysis



Appendix 7

A Funnel Plot of the Studies Included in the Clinical Pregnancy Rates per Cycle Analysis



Appendix 8

A Funnel Plot of the Studies Included in the Miscarriage Rates per Patient Analysis