The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis

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Objective: To investigate the effect of surgical treatment of endometrioma on pregnancy rate and ovarian response to gonadotrophin stimulation in women undergoing IVF.
Design: A systematic review and meta-analysis.
Setting: Tertiary referral center for reproductive medicine.
Patient(s): Subfertile women with endometrioma undergoing IVF.
Intervention(s): Surgical removal of endometrioma or expectant management.
Main Outcome Measure(s): Clinical pregnancy rate and ovarian response to gonadotrophins (number of gonadotrophin ampoules, peak E_2 levels, number of oocytes retrieved, and number of embryos available for transfer).
Result(s): A search of three electronic databases for articles published between January 1985 and November 2007 yielded 20 eligible studies. Meta-analysis was conducted for five studies that compared surgery vs. no treatment of endometrioma. There was no significant difference in clinical pregnancy rate between the treated and the untreated groups. Similarly, no significant difference was found between the two groups with regard to the outcome measures used to assess the response to controlled ovarian hyperstimulation with gonadotrophins.
Conclusion(s): Collectively the available data in the literature show that surgical management of endometriomas has no significant effect on IVF pregnancy rates and ovarian response to stimulation compared with no treatment. Randomized controlled trials are needed before producing best-practice recommendations on this topic. (Fertil Steril® 2009;92:75–87. ©2009 by American Society for Reproductive Medicine.)

Key Words: Endometrioma, surgery, IVF, ovarian response, pregnancy outcome

Endometriosis is defined as the presence of endometrial glandular and stromal tissue outside the uterus that induces a chronic inflammatory reaction. It may be present in up to 22% of asymptomatic women and 30% of women with unexplained subfertility (1).

Endometrioma is an ovarian mass arising from growth of ectopic endometrial tissue within the ovary. Most investigators believe that endometriomas result from a deposit of endometrium passed through the fallopian tubes—the transplantation theory (2)—causing adherence of the ovary to the pelvic peritoneum and its progressive invagination (3–5). According to this theory, an endometrioma would be a pseudocyst the wall of which is the inverted ovarian cortex, and hence its removal might involve removal of normal ovarian tissue with possible adverse implications for future fertility (6).

At present it is estimated that 10%–25% of all patients undergoing IVF are diagnosed with endometriosis, and 17%–44% of those also have ovarian endometriomas (7, 8). In vitro fertilization has become the mainstay of treatment for endometriosis-related subfertility (9, 10). Although there is some evidence to suggest that medical treatment with GnRH agonist can lead to a reduction in the size of the endometrioma by up to 51% (11), surgical removal of endometriomas remains the most effective approach for patients presenting with subfertility (12, 13).

As yet, there are no robust data on the effectiveness of surgery for endometriomas on the IVF success rate. Furthermore there is an increasing concern regarding the amount of ovarian tissue that may be inadvertently removed or damaged during surgery.

The objective of the present study was to evaluate the effect of surgical treatment of endometrioma on IVF outcomes, including clinical pregnancy rate and ovarian stimulation response.

MATERIALS AND METHODS

Search Strategy and Data Extraction

We searched the MEDLINE (1966–November 2007), EMBASE (1974–November 2007) and SCISEARCH (1974–November 2007) databases for relevant studies. The search

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strategy used terms such as "endometrioma," "cystectomy," "ovarian response," "pregnancy," "IVF," and "ICSI." We also searched the Cochrane Library, the Intercollegiate Study Institute Proceedings for conference abstracts, and the International Standard Randomized Controlled Trial Number Register and the Meta-register for Randomized Controlled Trials for ongoing and archived trials using the same key words. The references of retrieved articles together with the proceedings of relevant conferences were hand-searched to identify other potentially eligible studies for inclusion in the analysis missed by the initial search or any unpublished data. Articles frequently cited were used in the Science Citation Index to identify additional citations.

The literature search, inclusion and exclusion criteria, quality of studies, and extraction of data were independently undertaken and verified by two investigators (I.T., M.K.). The results were then compared and, in case of discordance, a consensus was reached with the involvement of a third investigator (T.G.). Descriptive tables for population and study characteristics for all eligible studies were generated. For each eligible study we recorded the first author, publication year, journal title, sample size, the characteristics of the study and control groups, the type of interventions, the characteristics of endometriomas (laterality and size), the ovarian stimulation protocol, and all the relevant outcomes reported. The authors were contacted in an attempt to obtain missing and/or additional data. There was no language restriction.

Types of Studies, Interventions, and Inclusion and Exclusion Criteria

All controlled retrospective or prospective studies that evaluated the effect of surgery (ovarian stripping or cystectomy) for endometrioma, compared with a defined control group, on IVF outcome and on the ovarian response to gonadotrophin stimulation were included in this review.

We excluded studies in which women received any medical therapy for endometriosis before or after surgery and whenever the study group was treated by either aspiration of the endometriotic cyst or by oophorectomy. In the case of duplicate studies we included only the most comprehensive one.

The Meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed for the systematic review and meta-analysis of observational studies (14). The quality of studies was assessed with respect to their design, the inclusion and exclusion criteria, the type of interventions, the characteristics of the study and control groups, and the presentation of outcomes.

Types of Outcome Measures

The primary outcome was the clinical pregnancy rate per cycle. Other related outcomes (fertilization rate, number of embryos available for transfer, implantation rate, pregnancy rate, and live birth rate per cycle) were also explored if reported by individual studies. Pregnancy was defined as a positive urinary or serum β-hCG result. Clinical pregnancy was defined as visualization of fetal heart activity on transvaginal ultrasound scan at $\geq$6 weeks' gestation.

The ovarian response to gonadotrophin stimulation was considered as a secondary outcome. Ovarian response was assessed by parameters such as the total number of gonadotrophin ampoules (recombinant FSH or hMG) required for ovarian stimulation, the number of follicles (>14 mm in diameter) on day 10 of ovarian stimulation, the peak E_2 levels on the day of hCG administration, and the total number of oocytes retrieved.

Statistical Analysis

The outcomes of interest included dichotomous variables (pregnancy, clinical pregnancy, and live birth rates), for which the odds ratio (OR) and 95% confidence interval (CI) were calculated, and continuous variables, such as the number of gonadotrophin ampoules required for ovarian stimulation, the number of mature follicles recruited, the peak E_2 levels, and the number of oocytes retrieved, for which a weighted mean difference (WMD) and 95% CI were calculated. All variables were assessed as per cycle.

Interstudy heterogeneity was assessed with Cochran's Q test. The random-effects model was used for pooling when the P value corresponding with the Cochran's Q test was $<.05$; otherwise fixed-effect models were used, whereby each individual study was weighed with the reciprocal of its variance (15). The OR, WMD, and 95% CI were calculated using Revman 4.2 software (The Cochrane Collaboration, Copenhagen, Denmark). Continuous data were presented in the majority of analyses as mean $\pm$ SD. In two studies (16, 17) in which the data were presented as mean $\pm$ SEM, the SEM was converted to SD.

RESULTS

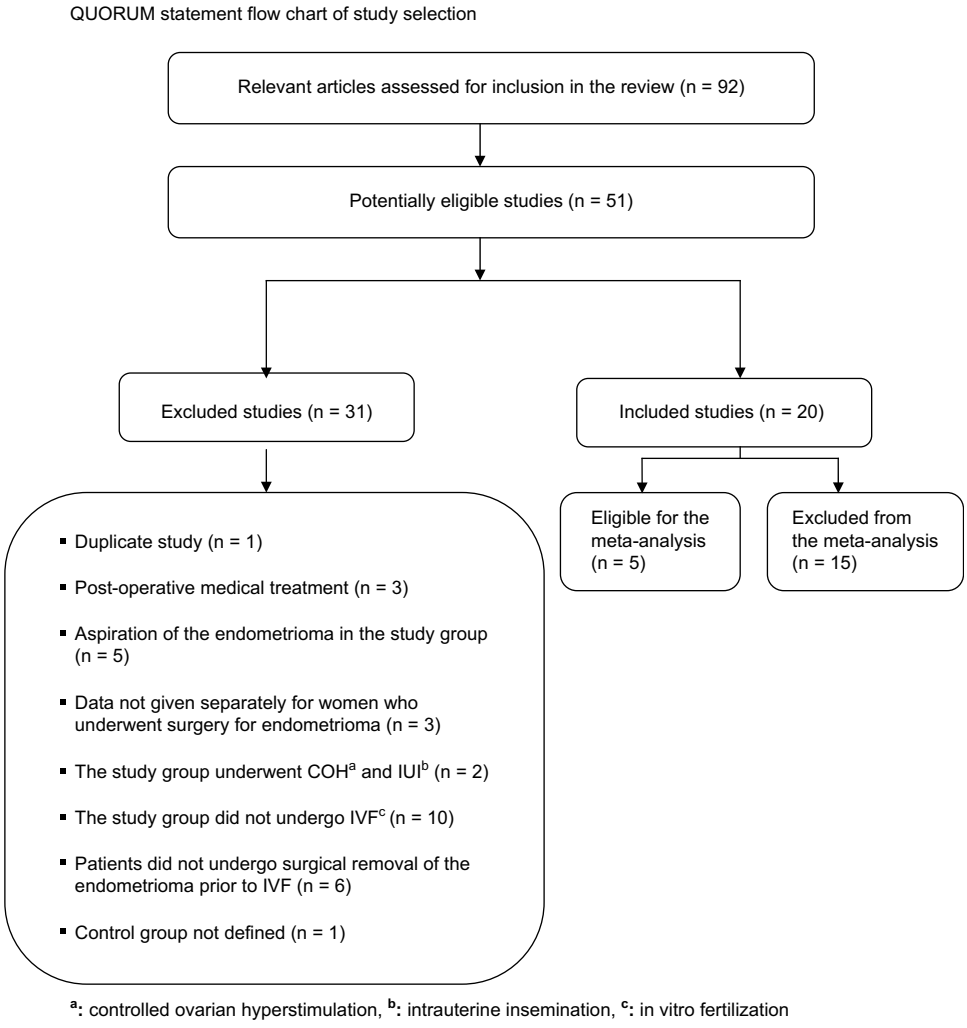
A search of the electronic databases yielded 92 relevant studies that were assessed for inclusion in this review. Fifty-one of these studies were found to be potentially eligible and were subsequently scrutinized in full text (Fig. 1).

Excluded Studies

Among the relevant studies, 31 were excluded because they did not meet the inclusion criteria. A GnRH analogue was used postoperatively in three studies (18–20), whereas in five series (21–25) the study population underwent aspiration of the endometrioma instead of surgery. Another study (26) was excluded because it was reporting duplicate results and we retained the data from the most recent and comprehensive version (27). The population studied was either not referred for IVF in 10 series (28–37) or did not undergo surgical treatment in six (38–43). Two reports did not meet the inclusion criteria because the study group underwent controlled ovarian hyperstimulation and IUI but not IVF (44, 45). The IVF success rates and ovarian response were not demonstrated separately for the group that underwent surgical treatment

FIGURE 1

QUORUM statement flow chart of study selection. COH = controlled ovarian stimulation.



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for endometrioma in three studies (46–48), and in one study the control group was not defined (49).

Included Studies

The characteristics of the 20 studies included in the systematic review are presented in Table 1. The majority of them were retrospective case–control studies, except for two retrospective (17, 50) and two prospective cohort studies (51, 52). Only one randomized control trial (RCT) was retrieved from the literature (53). We found no unpublished studies or any conference abstracts that met our inclusion criteria.

The surgical approach for endometriomas >3 cm was reported as ovarian cystectomy (16, 17, 54–62) or drainage and stripping of the cyst wall (50–53, 63–66). A laparoscopic approach was adopted in the majority of cases, with the exception of four studies (51, 64–66) in which either laparoscopy or laparotomy was performed. Ovarian stimulation was induced with either recombinant FSH or hMG using various protocols (long, short, or ultra-short). The diagnosis of endometrioma was confirmed histologically in the surgery group and was based on ultrasound evaluation and/or measurement of CA-125 levels in the control group.

The size, the laterality of the cyst removed, and the time interval between surgical approach and IVF treatment are documented in Table 1. The control group varied substantially among the studies that were found eligible for the review (Table 1). Four studies (17, 27, 51, 65) used heterogeneous control groups.

In all the included reports, there were no differences between the study and the control groups with regard to patient characteristics, IVF protocol, or other confounding factors. The various clinical outcomes and the parameters of ovarian response to gonadotrophin stimulation are presented in Table 2. The outcomes are stratified according to the control group adopted by each study.

TABLE 1

Characteristics of all studies included in the systematic review.

Study (reference)	Design	Intervention	Study group	Control group	Type of surgery	Cyst size (cm)	Laterality	Dt	Outcomes
Nargund et al. 1995 (54)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Ovarian cystectomy for simple (52) and dermoid cyst (2)	Cystectomy	ND	Unilateral	ND	Mature follicles, NOR
Loh et al. 1999 (55)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Contralateral normal ovary	Laparoscopic cystectomy	4.23 ± 2	Either	ND	Mature follicles
Tinkanen et al. 2000 (63)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Non-treated endometrioma	Endometrioma stripping	1.5–7	Either	1–7 y	NOR, no. of embryos, FR, IR, PR, LBR
Ho et al. 2002 (64)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Contralateral normal ovary	Endometrioma stripping (laparoscopy or laparotomy)	ND	Unilateral	31± 27 mo	Mature follicles, ampoules[a], E_2 peak
Marconi et al. 2002 (50)	Retrospective cohort	IVF-ET long protocol	Surgical treatment of endometrioma	Tubal factor infertility	Endometrioma stripping (laparoscopy)	4.8 ± 2.3	Either	12 ± 7 mo	Mature follicles, NOR, CPR, ampoules[a], E_2 peak
Suganuma et al. 2002 (65)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Aspirated endometrioma Non-treated endometrioma	Endometrioma stripping (laparoscopy or laparotomy)	ND	ND	31 ± 27 mo	NOR, FR, PR
Takuma et al. 2002 (56)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Laparoscopic aspiration of endometrioma	Laparoscopic cystectomy	ND	ND	12 mo	NOR, PR
Somigliana et al. 2003 (57)	Retrospective case–control	IVF/ICSI long protocol	Surgical treatment of endometrioma	Contralateral normal ovary	Laparoscopic cystectomy	3.9 ± 1.5	Unilateral	2.4 ± 1.7 mo	Mature follicles, NOR, no. of embryos, IR, CPR, ampoules[a], E_2 peak
Wu et al. 2003 (58)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Tubal factor infertility Contralateral normal ovary	Laparoscopic cystectomy	>6	ND	ND	NOR, FR, PR, LBR, CPR, E_2 peak
Wyns and Donnez 2003 (27)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Tubal factor infertility Laparoscopically treated peritoneal endometriosis Idiopathic infertility Contralateral normal ovary	Laparoscopic cyst wall laser vaporization	ND	ND	ND	Mature follicles, number of embryos, FR, IR, CPR, ampoules[a], E_2 peak

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TABLE 1

Continued.

Study (reference)	Design	Intervention	Study group	Control group	Type of surgery	Cyst size (cm)	Laterality	Dt	Outcomes
Garcia-Velasco et al. 2004 (16)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Non-treated endometrioma	Laparoscopic cystectomy	>3	Unilateral	12 mo	NOR, no. of embryos, FR, IR, CPR, MR, units[a], E_2 peak
Pabuccu et al. 2004 (51)	Prospective cohort	IVF/ICSI long protocol	Surgical treatment of endometrioma	Non-treated endometrioma Aspirated endometrioma Tubal factor infertility	Endometrioma stripping (laparoscopy or laparotomy)	ND	Either	≤4 y	Mature follicles, FR, IR, CPR, MR, ampoules[a], E_2 peak
Wong et al. 2004 (17)	Retrospective cohort	IVF/ICSI long protocol	Surgical treatment of endometrioma	Non-treated endometrioma Non-treated peritoneal endometriosis	Laparoscopic cystectomy	ND	ND	3–48 mo	Mature follicles, FR, IR, PR, CPR, MR, ampoules[a], E_2 peak
Loo et al. 2005 (59)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Tubal factor infertility	Laparoscopic cystectomy	>3	ND	6 mo	NOR, no. of embryos, FR, IR, CPR, units[a], E_2 peak
Ragni et al. 2005 (52)	Prospective cohort	IVF/ICSI long protocol	Surgical treatment of endometrioma	Contralateral normal ovary	Endometrioma stripping (laparoscopy)	4.0 ± 2.4	Unilateral	2.4 ± 2 y	Mature follicles, NOR, FR, IR, CPR, ampoules[a], E_2 peak
Demirol et al. 2005 (53)	RCT	ICSI long protocol	Surgical removal of endometrioma	Aspirated endometrioma	Endometrioma stripping (laparoscopy)	3–6	Unilateral	3 mo	NOR, FR, IR, CPR, E_2 peak
Esinler et al. 2006 (60)	Retrospective case–control	ICSI long protocol	Surgical treatment of endometrioma	Tubal factor infertility	Laparoscopic cystectomy	>3	Either	ND	Mature follicles, IR, CPR, MR, LBR, units[a], E_2 peak
Yazbeck et al. 2006 (61)	Retrospective case–control	IVF-ET long protocol	Surgical treatment of endometrioma	Non-treated endometriosis stage I–II	Laparoscopic cystectomy	≥4	Unilateral	ND	Mature follicles, FR, PR, CPR, ampoules[a], E_2 peak
Duru et al. 2007 (66)	Retrospective case–control	IVF/ICSI	Surgical treatment of endometrioma	Laparoscopically treated peritoneal endometriosis Contralateral normal ovary	Endometrioma stripping Laparoscopy (28) Laparotomy (10)	ND	Unilateral	≥1 y	Mature follicles, CPR
Matalliotakis et al. 2007 (62)	Retrospective case–control	IVF/ICSI long protocol	Surgical treatment of endometrioma	Tubal factor infertility	Laparoscopic cystectomy	ND	ND	ND	Mature follicles, NOR, no. of embryos, IR, FR, PR, CPR, MR, LBR, ampoules[a], E_2 peak

Note: Dt = interval between surgery and IVF; ND = not documented; NOR = number of oocytes retrieved; FR = fertilization rate; IR = implantation rate; PR = pregnancy rate; LBR = live birth rate; CPR = clinical pregnancy rate; MR = miscarriage rate; ICSI: intracytoplasmic sperm injection; RCT = randomized control trial.

[a] Ampoules/units of gonadotrophin used for ovarian stimulation.

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TABLE 2

Clinical outcomes and parameters of ovarian response assessed in the studies included in the systematic review.

Study (reference)	Cycles (n)		Oocytes retrieved (n)		Mature follicles (n)	
	S	C	S	C	S	C
Control group: non-treated endometrioma						
Tinkanen et al. 2000 (63)	55	45	6.50	6.10		ND
Suganuma et al. 2002 (65)	62	30	7.2 ± 6.2	9.7 ± 6.7		ND
Garcia-Velasco et al. 2004 (16)	147	63	10.8 ± 7	11.8 ± 7		ND
Pabuccu et al. 2004 (51)	44	40		ND	5.3 ± 1.3	5.2 ± 1.1
Wong et al. 2004 (17)	36	38		ND		ND
Control group: tubal factor infertility						
Marconi et al. 2002 (50)	39	39	7.5 ± 3.9	8.7 ± 5.1	10.3 ± 5	10.8 ± 5
Wu et al. 2003 (58)	30	30	6.0 ± 0.8	11.3 ± 1[a]		ND
Wyns and Donnez 2003 (27)	187	422		ND	15.3 ± 5	12.9 ± 6[a]
Pabuccu et al. 2004 (51)	44	46		ND	5.3 ± 1.2	6.8 ± 2[a]
Loo et al. 2005 (59)	85	71	5.0 ± 3.7	7.0 ± 4.4[a]		ND
Esinler et al. 2006 (60) (UE)	34	99	10.8 ± 6.2	11.1 ± 6.2	10 ± 4	11.3 ± 3
Esinler et al. 2006 (60) (BE)	23	99	7.1 ± 4.4	11.1 ± 6[a]	7.1 ± 2.6	11.3 ± 3[a]
Matalliotakis et al. 2007 (62)	133	208	9.4 ± 6.7	12.3 ± 7[a]	9.1 ± 5.5	10.4 ± 4[a]
Control group: aspirated endometrioma						
Suganuma et al. 2002 (65)	62	35	7.2 ± 6.3	6.6 ± 5.5		ND
Takuma et al. 2002 (56)	69	43		ND		ND
Pabuccu et al. 2004 (51)	44	41		ND	5.3 ± 1.4	5.9 ± 1.1
Demirol et al. 2006 (53)	49	50		ND		ND
Control group: laparoscopically treated peritoneal endometriosis						
Wyns and Donnez 2003 (27)	187	71		ND		ND
Duru et al. 2007 (66) (L/S)	28	10		ND	7.1 ± 3	12 ± 4.2[a]
Duru et al. 2007 (66) (L/T)	10	10		ND	6 ± 1.6	12 ± 4.2[a]
Control group: non-treated peritoneal endometriosis						
Wong et al. 2004 (17)	36	183		ND		ND
Yazbeck et al. 2006 (61)	119	95	5.8 ± 3.8	7.4 ± 4.6[a]	4.2 ± 1.7	4.8 ± 2[a]
Control group: idiopathic infertility						
Wyns and Donnez 2003 (27)	187	275		ND	15.3 ± 5	15.57 ± 9
Control group: non-endometriotic benign ovarian cyst						
Nargund et al. 1995 (54)	36	54	3.71 ± 2.9	5.5 ± 4.3[a]	5.5 ± 3	7.8 ± 5[a]
Control group: normal non-operated contralateral ovary						
Loh et al. 1999 (55)	12			ND	4.6	3.6
Ho et al. 2000 (64)	38		2.9 ± 2.6	6.1 ± 4.1[a]	1.9 ± 1.5	3.3 ± 2[a]
Somigliana et al. 2003 (57) (cyst >3 cm)	20			ND	1.9 ± 1.4	4.4 ± 3[a]
Somigliana et al. 2003 (57) (cyst ≤3 cm)	18			ND	2.1 ± 1.7	4.2 ± 2[a]
Wyns and Donnez 2003 (27)	87		4.5 ± 2.6	5.3 ± 2.8[a]	5.2 ± 3.0	6.6 ± 4[a]
Ragni et al. 2005 (52) (cyst >3 cm)	17		1.9 ± 1.9	5.5 ± 2.6[a]	1.4 ± 1.7	5.1 ± 2[a]
Ragni et al. 2005 (52) (cyst ≤3 cm)	15		2.5 ± 2.2	5.2 ± 3.6[a]	1.9 ± 2.0	3.9 ± 2[a]
Duru et al. 2007 (66) (L/S)	28			ND	3.1 ± 1.8	4.4 ± 1[a]
Duru et al. 2007 (66) (L/T)	10			ND	2.1 ± 1.4	5.0 ± 2[a]

Note: Data are presented as mean ± SD or as noted. S = group that underwent surgical removal of endometrioma; C = control group; ND = not documented; UE = unilateral endometrioma; BE = bilateral endometrioma; L/S = laparoscopy group; L/T = laparotomy group; NA = non-applicable.

[a] Significantly increased ($P<.05$).

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Meta-analysis

To reduce the heterogeneity of subjects and interventions we have included in our meta-analysis only five studies that compared women who had surgical treatment for endometrioma with women with untreated endometrioma (16, 17, 51, 63, 65). Among the included studies there were three retrospective case–control studies (16, 63, 65), one retrospective study (17), and one prospective cohort study (51).

TABLE 2

Continued

E_2 peak (pg/mL)		Implantation rate (%)		Fertilization rate (%)		Pregnancy rate (%)		Clinical pregnancy rate (%)	
S	C	S	C	S	C	S	C	S	C
	ND	13	20[a]	48	58	22	38	ND	
	ND		ND	56.8	56.5	29	37	ND	
1,910 ± 1,285	2,472 ± 2,062[a]	12.8	14.1[a]	76.5[a]	69.9	30	29	25	22
1,196 ± 445[a]	946.7 ± 264	18[a]	12	72 ± 13	68 ± 16		ND	25	20
1,956 ± 1,290	1,928 ± 1,227.6	20[a]	18	85	88	50	34	47	34
2,410 ± 1,611	2,705 ± 2,113		ND		ND		ND	38	33
1,459 ± 251.9	1,674 ± 196.9		ND	76 ± 5	72 ± 3.9	15	40[a]		ND
2,258 ± 1,663	2,095 ± 1159	15	13.9	60.9	62.5		ND	37[a]	27
1,196 ± 444	1,859.6 ± 853	18	14	72 ± 13	74 ± 12		ND	25	30
1,285 ± 1,089	1,914 ± 1,271[a]	18.7[a]	11	77.8	84.7[a]		ND	32	30
2,536.4 ± 1,514	1,949.4 ± 1,323	23.2[a]	19,1		ND		ND	41	43
1,730.6 ± 1,060	1,949 ± 1,323[a]	27[a]	19,1		ND		ND	35	43
1,522 ± 897.9	1,959 ± 1,110[a]	11.4	11.8	60.2	60.1	35	39	28	30
	ND		ND	56.8	67.4	29	31	ND	
	ND		ND		ND	26	9	ND	
1,196 ± 446	1,632 ± 670[a]	18	13	72 ± 13	72 ± 10		ND	25	24
1,170 ± 417.1	1,680 ± 428.69[a]	16.5	18.5	86.2	88.3		ND	35	38
2,258 ± 1,663.7	2,333.7 ± 1,148	15	17.7	60.9	61.8		ND	37	32
1,779 ± 826	3,742 ± 1,161[a]		ND	62 ± 25	70 ± 21		ND	21	40
1,513 ± 906	3,742 ± 1,161[a]		ND	60 ± 39	70 ± 21		ND	20	40
1,956 ± 1,290	2,027 ± 1,431	20	17	85	81	50	55	47	47
1,741.3 ± 825	1,898.7 ± 921		ND	49 ± 35	62 ± 32[a]		ND		ND
2,258 ± 1,663.7	2,282 ± 1,252	15	18		ND		ND	37	30
	ND		ND		ND		ND		ND
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA
	NA		NA		NA		NA		NA

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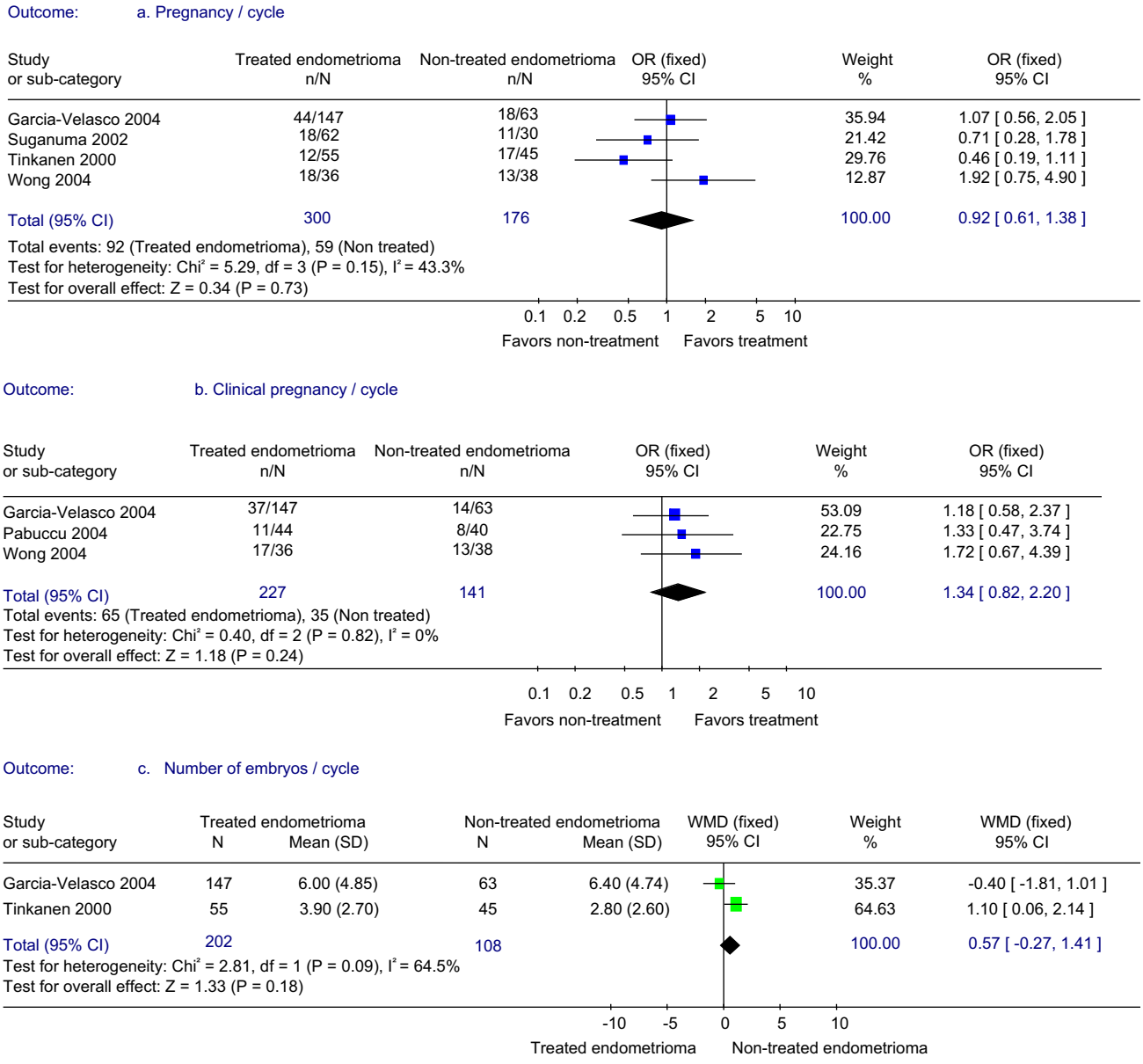
The forest plots of the meta-analysis stratified by the type of outcomes are presented in Figure 2. There were no significant differences in pregnancy and clinical pregnancy rate per cycle between women who underwent surgery and those who received no treatment for endometrioma (OR for pregnancy rate per cycle 0.92 [95% CI 0.61, 1.38]; OR for clinical pregnancy rate per cycle 1.34 [95% CI 0.82, 2.20]) (Fig. 2A and B). No significant difference was shown in the number of

FIGURE 2

(**A–F**) Forest plots of the meta-analysis on clinical outcomes and on the parameters of ovarian response to gonadotrophin stimulation in women who underwent surgical treatment for endometrioma versus women with non-treated endometrioma.



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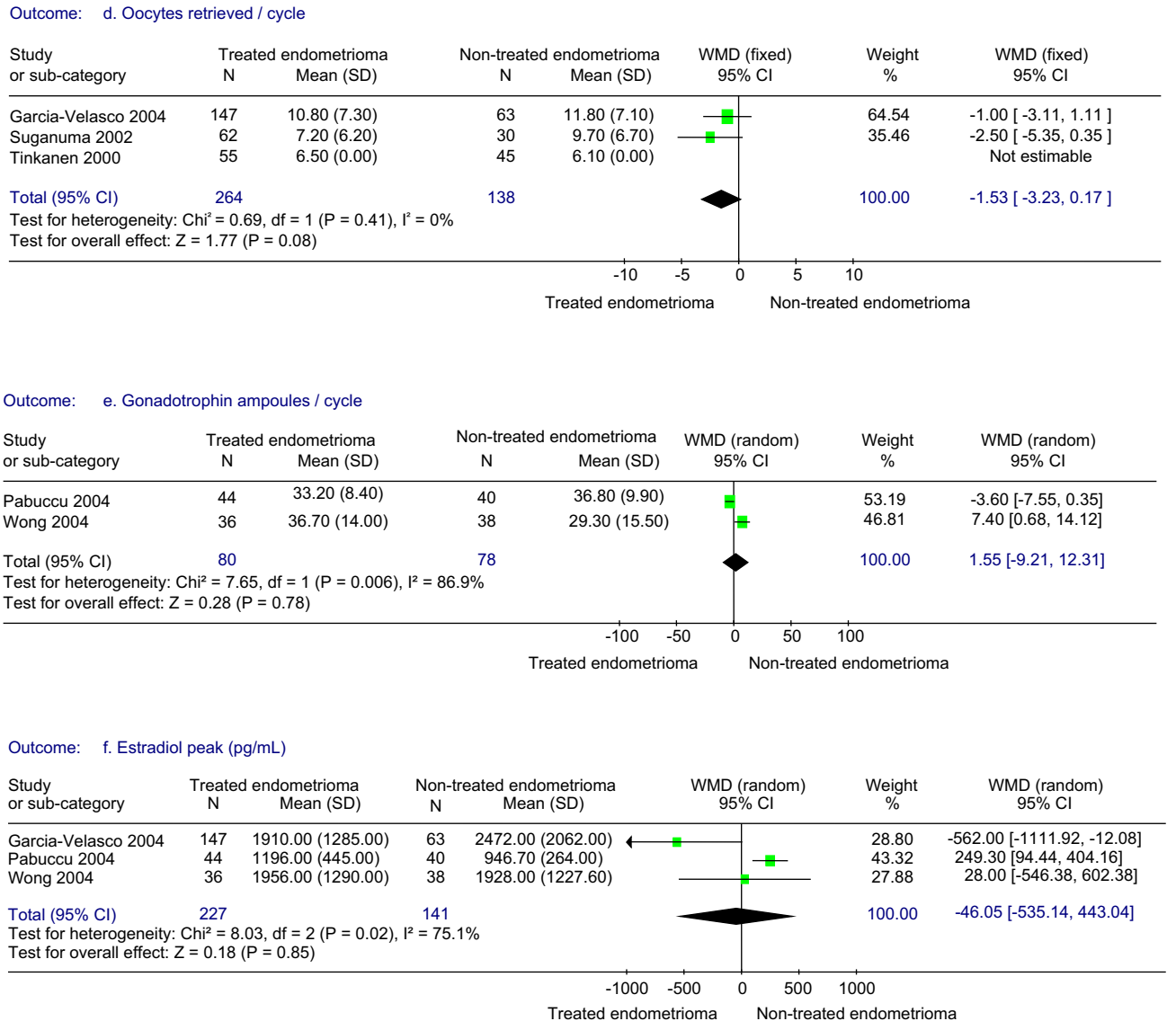
embryos available for transfer between the surgery group and the control group (WMD 0.57 [95% CI −0.27, 1.41]) (Fig. 2C).

Similarly there was no statistical significant difference between the two groups with regard to the number of oocytes retrieved (WMD −1.53 [95% CI −3.23, 0.17]) (Fig. 2D) and the number of gonadotrophin ampoules required for ovarian stimulation (WMD 1.55 [95% CI −9.21, 12.31]) (Fig. 2E). The E_2 peak was also similar in the two groups of women (WMD −46.05 [95% CI −535.14, 443.04]) (Fig. 2F).

The meta-analysis for other outcomes, such as fertilization and implantation rates, was not possible because the contacted authors did not provide the original data on the number of fertilized oocytes and the total number of gestational sacs and transferred embryos. Similarly a meta-analysis was not feasible for the live birth rate after surgical treatment of

FIGURE 2 Continued.



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endometrioma compared with nontreatment because only one study reported on this outcome (63).

We intended to perform subgroup analyses of relevant studies with regard to the size and laterality of the endometrioma and the time interval between surgery and IVF to assess whether the observed differences in outcomes were confounded by discrepancies in the compared study populations. Nevertheless, further meta-analytical pooling was unfeasible. The size of the cyst was documented to be >3 cm in only one study (16), whereas in the rest the size was either not documented (17, 51, 65) or a cut-off was not clearly indicated (63) (Table 1). The endometrioma was unilateral in one study (16); however, the laterality was not documented in the remaining four (17, 51, 63, 65). Although women who underwent surgical treatment were referred for IVF after a period of at least 3 months, the exact time interval was not documented in any of the included reports.

DISCUSSION

Subfertile women with endometrioma comprise a small group among a heterogeneous population of women who undergo IVF treatment. To date, there is no consensus on the standard management of these cases.

There are significant concerns regarding the potential deleterious impact of surgical treatment of endometrioma on ovarian reserve. It has been reported that removing ovarian cysts that have well-defined ovarian capsules (dermoids, serous, and mucinous cysts) resulted in some ovarian tissue being removed in 6% of cases (37). Conversely, a small rim

of tissue containing primordial follicles is removed in more than 50% of endometriomas (6, 37). This is probably related to the technical difficulties encountered in removing the endometrioma adherent to the normal ovarian tissue. A small, retrospective, case–control study (54) reported significantly fewer mature follicles recruited and fewer oocytes collected in women who underwent surgical removal of endometrioma compared with those who had surgical removal of a non-endometriotic benign cyst (Table 2).

One needs to be cautious when attributing the diminished response of the postcystectomy ovaries solely to the surgical injury to the ovary. It has been shown that ovaries with endometriotic cysts already exhibited reduced number of follicles and vascular activity compared with other types of benign cysts (43, 67). Furthermore, it is difficult to identify the impact of an isolated endometrioma per se on the cycle outcome because the majority of cases are associated with concomitant peritoneal disease, which is another confounding variable.

Several studies that were eligible for inclusion in the systematic review could not be included in the meta-analysis because the control group did not consist of women with non-treated endometrioma. The only retrieved RCT (53) showed some evidence of reduced ovarian response after surgical treatment of endometrioma as shown by longer duration of stimulation, higher dose of gonadotrophins used, lower peak E_2 levels, and lower number of oocytes retrieved. The study, however, was not included in the meta-analysis because the control group consisted of women who underwent drainage of endometrioma at the time of oocytes retrieval. Some fertility physicians, including us, believe that drainage of endometrioma should be avoided at the time of oocytes retrieval because this may increase the risk of ovarian or pelvic infection (68–71) and may also lead to contamination of oocytes with the fluid drained from the endometrioma, affecting their quality. Although the authors of the RCT did not find a difference in pregnancy rate between the two groups, they did not comment on the quality of the embryos and provided no data on the incidence of ovarian or pelvic infection. The number of women was small (49 in the study group and 50 in the control group) to provide reliable statistically significant data on ovarian infection after aspiration of endometrioma.

A possible explanation for the lack of evidence might stem from the fact that subfertile women with endometrioma comprise only a small proportion of the total population of women referred for IVF. This hampers attempts to recruit large numbers for subjects for the control and the study groups and to reach adequate statistical power, especially to calculate the pregnancy and live birth rates.

The meta-analysis of the studies that compared surgical treatment with non-treatment of endometrioma before IVF showed no statistically significant difference in any of the outcomes for which meta-analytic pooling was feasible (i.e., clinical pregnancy rate, peak serum E_2 levels, number of oocytes retrieved, number of gonadotrophin ampoules required, and number of embryos available for transfer).

The significance of the size of the endometrioma on treatment outcome was not addressed in the majority of studies. The decision for surgical interference for endometrioma encountered in asymptomatic women before IVF should take into account the anticipated difficulty in accessing the follicles and the risk of pelvic infection after inadvertent drainage of endometrioma at the time of oocytes retrieval. It is perhaps sensible not to operate on a very small endometrioma because this might be technically more difficult and might increase the proportion of normal ovarian tissue inadvertently removed. Small cysts will probably interfere less with oocyte retrieval and will present a lower risk of infection.

With regard to the surgical approach for endometriotic cysts, this is still a matter of debate. It has been shown that surgery for endometrioma is not free of complications because there is a risk of postsurgical ovarian failure of 2.4% (72) and a 30.4% risk of disease recurrence (73). Of note, two randomized trials have reported a higher pregnancy rate and a lower recurrence rate after laparoscopic ovarian cystectomy than after fenestration and bipolar coagulation (30, 33). It has also been suggested that the use of laser vaporization of the internal cyst wall (26) may lead to higher recurrence rate (74).

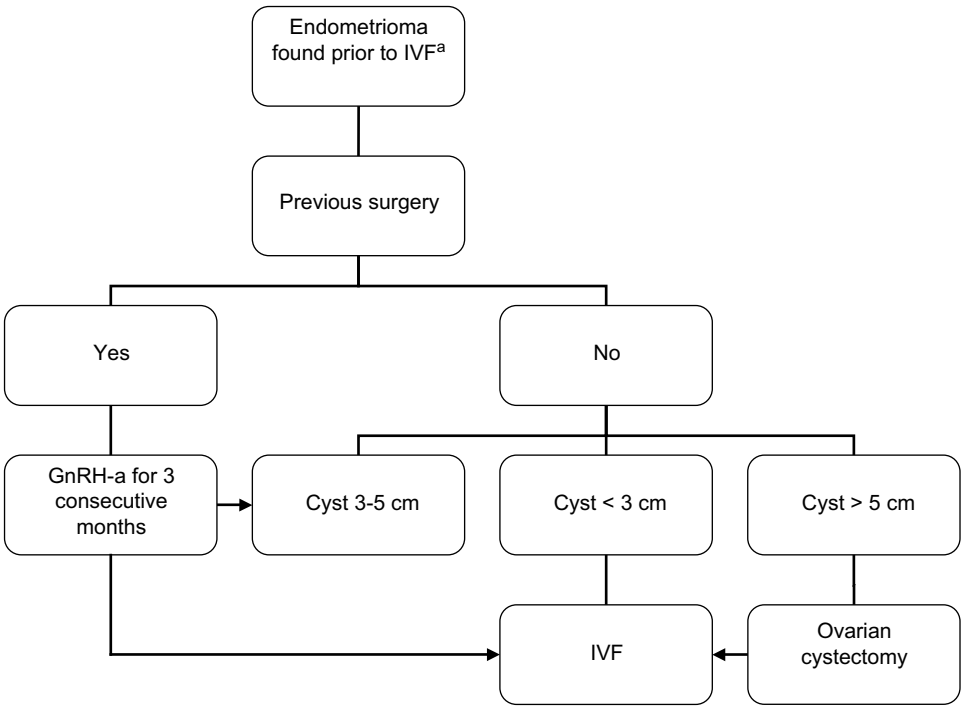
No studies have attempted to investigate the risks of expectant management of endometrioma before IVF. In theory the risks include difficulty in monitoring follicular growth by ultrasound scan during controlled ovarian hyperstimulation, spontaneous rupture or leakage of the endometrioma that could cause peritoneal irritation and pelvic symptoms, difficult access to some ovarian follicles at the time of oocytes retrieval, and the inadvertent drainage of the endometrioma at the time of oocytes retrieval. The latter may increase the risk of ovarian or pelvic infection, but also contamination of the needle used for oocytes retrieval may adversely affect oocytes and embryos potentials, thus reducing the chance of implantation. Another possible disadvantage of expectant management could be the absence of tissue for histologic examination to confirm the diagnosis and exclude malignancy.

The evidence supporting medical treatment of endometrioma before IVF is not solid either. Some investigators have suggested that GnRH agonist might help in reducing the size of endometrioma (11), but the effect of this on the success rates of patients undergoing IVF is not known and has not been tested in an RCT. A Cochrane review (75) of three RCTs involving 165 participants concluded that women with endometriosis treated with IVF should receive GnRH agonist therapy for a minimum of 3 consecutive months before assisted conception treatment because this will induce a fourfold increase in the odds of clinical pregnancy.

When trying to pull together all the available data included in this systematic review and meta-analysis, we were far from reaching any robust recommendations for best clinical practice. Nevertheless, we thought to propose what could be seen

FIGURE 3

Flow chart for management of endometrioma.



[a]: in vitro fertilization

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as at-a-glance guidance for the management of subfertile women with endometriomas needing IVF treatment (Fig. 3).

In conclusion, the standard management of endometrioma in subfertile women before IVF remains controversial owing to the insufficient evidence to suggest superiority of one treatment strategy over another. A large, well-designed, adequately powered multicenter RCT that would compare the effects of surgical removal with expectant management of endometrioma on ovarian performance and pregnancy outcomes in women undergoing IVF is clearly overdue. Until such a trial is conducted and definite conclusions can be drawn, the management of women with endometrioma before IVF should be individualized. All the therapeutic options, including conservative, medical, or surgical treatment, as well as the advantages and disadvantages should be fully discussed with the patient. Any decision for surgery should be carefully considered and balanced against the risks, especially in women with previous adnexal surgery or women with suboptimal ovarian reserve. If the woman opts for surgical treatment, she should be appropriately counseled about the potential risks of reduced ovarian function after surgery, including the remote possibility of oophorectomy.

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