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Article type : Systematic review

Surgery versus conservative management of endometriomas in subfertile women. A systematic review

Running headline: Surgery for endometriomas before ART?

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Conflict of interest:

The authors declare no conflicts of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/aogs.13154

Abstract

Introduction: Endometriomas are present in up to 44% of all women with endometriosis and have a detrimental effect on fertility. However, it is controversial whether endometriomas should be surgically removed before assisted reproduction technology (ART). Our purpose was to evaluate whether surgical stripping of endometriomas in subfertile women improves the chance of a live birth. Secondary outcomes were impact on ovarian reserve and pain. *Material and methods*: We conducted a systematic review and metaanalysis with results reported in accordance to the PRISMA guidelines. Summary of findings table was developed using GRADE. We searched Medline and Embase. Two reviewers performed the screening. *Results*: Out of 686 manuscripts we included one randomized controlled trial and nine retrospective cohort studies most of low quality. Odds ratio for live birth after surgery (compared with conservative management before in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI)) was 0.87 (95% CI; 0.64-1.18, six studies, I^2 = 3%; ⊕◯◯◯, VERY LOW quality). The mean difference of antral follicle count was -2.09 (95% CI; -4.84 - +0.67, four studies). No difference was observed regarding antral follicle count between the two groups (MD -2.09, 95% CI -4.84 to +0.67, four studies, ⊕◯◯◯, VERY LOW quality). Pain outcome was not reported in the included studies. *Conclusion*: Very low quality evidence suggests no difference in odds ratio of live birth between women who underwent surgery for endometriomas before IVF/ICSI compared to conservative management. Further high quality studies are needed, but due to lack of convincing evidence favoring surgery we recommend considering conservative treatment if the only indication is subfertility.

Keywords

Endometriomas, Assisted Reproduction Technology, Surgery, Laparoscopy, Subfertility, Ovarian reserve

Abbreviations

AFC: antral follicle count

AMH: anti Müllerian hormone

ART: assisted reproduction technology

IVF: in vitro fertilization

ICSI: intracytoplasmic sperm injection

LBR: live birth rate

OR: Odds Ratio

PICO: Population, Intervention, Comparator, Outcome

RCT randomized controlled trial

Key Message

Surgical removal of endometriomas before in vitro fertilization or intracytoplasmic sperm injection does not improve the chance of a live birth.

Introduction

Endometriosis is a common condition estimated to affect around 10% of women of fertile age (1). It is a disease characterized by the presence of endometrial tissue located in sites outside the uterine cavity. Frequent symptoms are pain during menstruation, lower abdominal pain, dyspareunia and in severe cases affection of micturition, pain or difficulties emptying the bowel. Another substantial complication to endometriosis is subfertility. The prevalence of endometriosis among subfertile women has been reported to be 20-40 % (2,3). The cause for subfertility associated with endometriosis is assumedly multifactorial, possibly involving components such as inflammatory factors, adhesions involving the internal genitalia but also the presence of endometriomas.

Endometriomas are ovarian cysts containing ectopic endometrial tissue. Endometriomas have been observed in 17-44% of patients with endometriosis (4). The influence of endometriomas on fertility and in vitro fertilization (IVF) is not clear. Two studies reported that endometriomas are detrimental to the ovary causing lower oocyte quality and negatively affecting the number of oocytes retrieved during fertility treatment(5,6).

Current clinical practice is laparoscopic removal (7,8). Endometriomas can be removed by several methods, such as stripping, excision, ablation or drainage. However, laparoscopy carries a risk of complications. Beyond the inherent complications to surgery and regardless of the operating technique damage to the ovary is inevitable. The use of bipolar cauterization for hemostasis appears to induce most damage, but a recent review suggests, that all procedures used for treatment of endometriomas cause adverse ovarian damage (9).

Using various surrogate measures of ovarian function or reserve, several studies have looked into this topic. Most frequently, ovarian reserve markers such as anti Müllerian hormone (AMH) and antral follicle count (AFC) have been used (10). Several studies have reported a reduced AMH after excisional surgery for endometriomas (9,11–13), whereas AFC does not seem to be affected to the same extent (14).

Live birth rate (LBR) is only sparsely reported as the outcome following surgical removal although this outcome is the most clinically relevant. Accordingly, controversies exist regarding whether surgical resection of endometriomas should precede assisted reproduction technology (ART) (IVF/ intracytoplasmic sperm injection (ICSI)) or if conservative management or direct referral to ART is preferable in women with endometriosis. The aim of this review was therefore to evaluate efficacy and safety of surgical removal of endometriomas prior to IVF/ICSI.

Material and methods

In April 2016 we searched Medline and Embase using the following keywords and medical subject heading (MeSH) search-terms: In vitro fertilization (IVF), intracystoplasmic sperm injection (ICSI), assisted reproductive techniques, endometriosis, endometriomas, chocolate cyst, cystectomy, general surgery, enucleation, stripping, ablation, excision, laparoscopy. Furthermore, we manually searched bibliographies of relevant articles. The search was conducted with the assistance of a search specialist at University Hospital of Southern Denmark (SDU).

Only randomized controlled trials (RCTs) and observational studies were considered for inclusion. We excluded reviews, conference abstracts and case reports. Only studies with an intervention group and a control group where both groups had endometriomas were included. Our search was limited to studies published within the last 15 years. We had no language restrictions.

The participants of the studies included in the review were women of fertile age with a fertility wish, who were eligible for ART and who had one or more ultrasonically identified endometriomas.

The intervention group was women who had undergone surgical excision/stripping of endometriomas before ART (IVF or ICSI) and the control group women with endometriomas followed with conservative management or direct referral to ART (IVF or ICSI). The stripping technique has proven to be the most efficient when it comes to recurrence of endometriomas, recurrence of pain and subsequent pregnancy in women with previous infertility (15,16) and since it is also the most common approach for surgical removal, we therefore decided to exclude studies with alternative interventions (Laser ablation, drainage etc.)

Our primary outcome was live birth, defined as total number of live births among the total number of women in the respective studies included. Our secondary outcomes were clinical pregnancy (defined as all pregnancies among all women in the respective studies diagnosed by ultrasound in week 7 with the presence of a beating heart), ovarian reserve as measured by AFC or AMH and pain as reported by visual analog scale (VAS) or similar or as part of a quality of life evaluation.

Two reviewers (MR and JBL) independently screened titles and abstracts of all the selected studies identifying the studies for inclusion in full text screening. Data extraction was done using the Covidence online tool, developed for systematic reviews by the Cochrane Collaboration (17). Data extraction was done individually and independently and then compared between two reviewers (JBS and JBL). If there were discrepancies between the data extracted the study was further discussed until consensus was reached.

Risk of bias in the included RCTs was assessed using the risk of bias tool from Cochrane(18) and for the observational studies the quality of the studies - including assessment of bias - was performed using GRADE (19).

RevMan was used to create the meta-analyses which were performed by using fixed effects model. Statistical heterogeneity was evaluated by measure of I^2. In case of high heterogeneity (I^2>50%) the random effects model was applied. We used odds ratio (OR) as our effect measure for dichotomous data and Mean Difference for continuous outcomes. All results are presented with 95% confidence interval.

The systematic review was registered in Prospero on 15th of April, 2016 (CRD42016037851). This review adheres to the PRISMA guidelines (19)(see appendix).

Results

Our initial search yielded 685 studies. Manual search of references of previous studies yielded one additional study(21) providing a total of 686 studies(fig. 1). 568 of these were found to be irrelevant after title and abstract screening. After full text review further 108 were excluded leaving 10 studies for inclusion (Table 1). Exclusion criteria were labelled according to the categories of Covidence.

We excluded 108 studies because they deviated from our research question on the following domains: Study design (n=49), patient population (n=10), intervention (n=8), comparator (n=32) and outcomes (n=2). Six studies were excluded because the control group did not have endometriomas and one study because the indication differed from our research question.

Only one study was an RCT (22). Athough the study by Pabuccu et al (23) was published as an RCT, the intervention was response to controlled ovarian hyperstimulation with GnRH agonists and antagonists. Since the study contains two subgroups; one consisting of women with previous laparoscopic surgery for endometriomas and a control group consisting of women with current endometriomas the study was included in the meta-analysis as a prospective cohort study.

The studies were conducted in Turkey (22,23). Italy (24,25), China (26), Finland (21), South Korea (27), Japan (28), Spain (29) and United States (30). Six studies reported live birth and six reported CP. All studies included a description of the surgical procedure by laparoscopy, one study performed both laparoscopies and laparotomies (21).

Kuroda et al (28) used suturing of the ovary for hemostasis whereas four other studies used bipolar coagulation (22,24,29,30). Five studies did not specify the method of hemostasis (21,23,25–27). In general, the studies were of low quality with a high risk of bias. Only three studies were adjusted for confounders (25,26)

Three studies (24,26,29) did not report LBR although it appeared form the results that LBR might have been registered in these studies. We contacted the authors of these studies, but only one responded and was not able to provide information on LBR.

Details of the individual studies can be found in Table 1. Meta-analyses including live birth, CP and AFC appear from Figure 2 - 5.

Calculation of OR for live birth was initially based on eight studies (21,23,24,26–30)(Fig 3). Our calculation included two studies that did not report live birth and we attempted to calculate this by subtracting miscarriage/spontaneous abortion rate from clinical pregnancy rate (29,30). Sensitivity analysis showed, however, that these two studies had impact on the final result. Considering our indirect calculation was based on an uncertain presumption we excluded these two studies from the final meta-analysis, which therefore includes 6 studies (21,23,24,26–28)(Fig. 2).

The pooled OR for live birth (after sensitivity analysis) was 0.87 (95% CI; 0.64-1.18, p=0.36, six observational studies) when surgery was compared to conservative treatment. Heterogeneity in the analysis was 3% (I^2=3%). (Fig. 2)

Analysis of clinical pregnancy failed to demonstrate any difference between surgery and conservative management (Fig. 4). The OR for clinical pregnancy in the RCT was 0.87 (95% CI; 0.38-1.97, p=0.73, 1 RCT) and for the observational studies 1.10 (95% CI; 0.79-1.52, p=0.58, three studies). Since only one RCT was included, test for heterogeneity was not applicable. The observational studies showed no heterogeneity (I^2=15%).). Regarding AFC, four studies were included in total (24,25,27,31)(Fig. 5). We observed a mean difference in AFC of -2.09 in the control group (95% CI; -4.84 - 0.67, four studies).

We found no studies that reported pain or quality of life for the two different interventions.

Most of the studies included a high risk of bias. Following the GRADE approach the highest risk of bias was observed in development and application of eligibility criteria, where four studies were biased (21,24,29,30).

Discussion

Our study shows that surgical removal of endometriomas does not improve chance of a live birth. We used a narrow approach compared to other reviews in order to more precisely answer the specific questions posed. Recently, Hamdan et al (32) did a substantial review on the impact of endometriomas on IVF/ICSI outcomes, including surgical impact but included a broad spectrum of endometriosis-related outcomes affecting fertility, compared to our more specific PICO question. Furthermore, Hamdan et al (31) included different types of surgical interventions, which may interfere with the results since different surgical methods have different effects on the ovarian tissue. Their results, however, are in agreement with ours, showing no benefit of surgery compared to conservative management. This is underlined by our observation of an OR of live birth 13 % lower in women who had laparoscopic removal of endometriomas before ART, although this did not reach statistical significance.

Clinical pregnancy rate has been more frequently reported in the literature most likely because of its immediacy compared to LBR, but it should be noted that clinical pregnancy rate does not reflect LBR. Our observed trend towards lower number of live births in women with surgical removal of endometriomas was not supported by the clinical pregnancy metananalysis, which showed a 6% higher OR in the surgery group compared to conservative management in the pooled result. Thus, one might speculate that uterine factors may also interfere thereby explaining the difference between the parameters. It is well-known that the presence of endometriomas is associated with endometriosis elsewhere including in the uterus (33).

We were not able to draw any safe conclusion regarding the impact of surgical excision of endometriomas on AFC due to the low number of studies reporting AFC and the heterogeneity of the studies, especially in relation to age. Although our results point towards a lower AFC in women undergoing conservative treatment, our results were not statistically significant (p=0.14) (Fig. 5), and consequently, further studies are warranted before the impact of surgery on AFC can be determined.

Ovarian responsiveness to hyperstimulation is also considered a reliable measure of ovarian reserve along with AFC (34). However, most likely AFC is a more appropriate indicator of ovarian function, as this is unaffected by the condition of the contralateral ovary, which may compensate for damage induced by surgery as suggested by Muzii et al. (14)

Regarding AMH, this parameter was only expressed as a baseline measure in one of the included studies, making further analysis obsolete (25). It should be noted, though, that other studies have shown that AMH is reduced by 37% in unilateral ovarian surgery and by up to 50% in bilateral ovarian surgery (11,35). A factor that could limit the validity of our observations regarding ovarian reserve is the fact that only one study used suturing for hemostasis. Although most surgeons use electrocoagulation for hemostasis, suturing might be preferable as suggested by Asgari et al. (36). However, judged by the absence of studies specifying suturing as the method for hemostasis, it appears that this method has not yet been widely implemented.

The correlation between level of pain and the stage of the disease has been widely discussed, and it appears that pain does not correlate to the stage of endometriosis (37). None of the studies included in our study reported pain as an outcome. We find this problematic, since it is likely to assume, that women undergoing surgery would be the ones suffering the most from pain. If this is the case and if the indication for surgery is primarily pain rather than infertility, then this would lead to selection bias.

The limitations of this review are mainly due to the low to very low quality of the studies included and the fact that studies brought together in systematic reviews differ thereby causing high clinical heterogeneity. Thus, only one RCT was included. Furthermore, we included only studies using a single operating technique since this method seems to be the most effective way of removal of endometriomas (15,16). However, this may change as other surgical procedures may prove to induce less harm to the ovaries.

In conclusion, we find no evidence in favor of surgical removal of endometriomas in women prior to ART if the indication is solely optimizing fertility. On the contrary, surgery poses a risk of complications including adverse effects on ovarian reserve. Physicians should take this into account when counselling their patients, and we recommend considering conservative management if the only indication is subfertility. However, quality of evidence is very low and high quality studies are needed.

Funding

We received no funding for this project

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Legends

Table 1 – characteristics of studies.

Table 2. Summary of findings.

Figure 1. PRISMA flowdiagram.

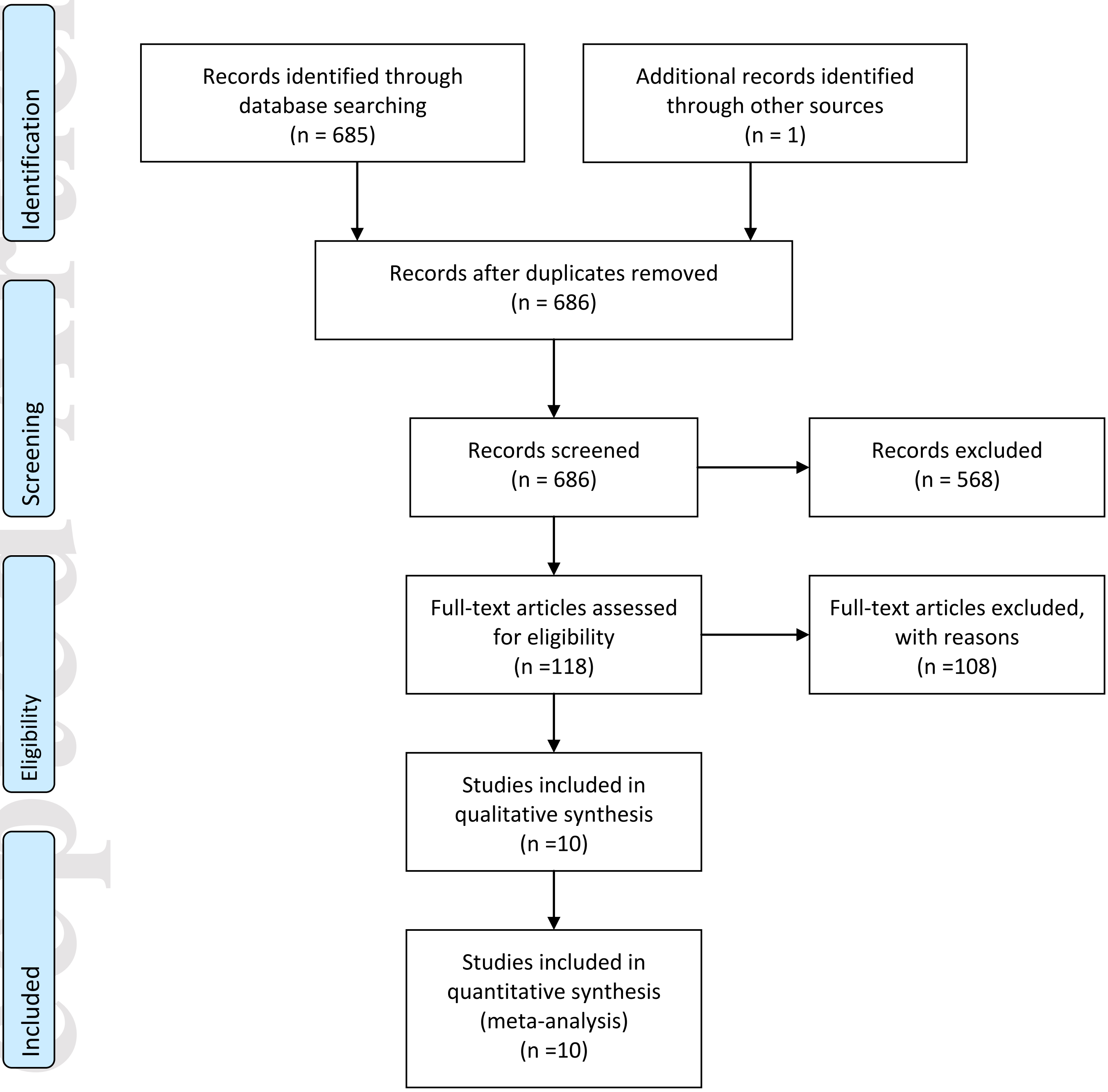


Fig. 2 Forrest plot for live birth – after sensitivity analysis.

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.2 Observational						
Bongioanni 2011	29	112	49	142	35.3%	0.66 [0.38, 1.15]
Dong 2014	58	153	29	68	27.4%	0.82 [0.46, 1.47]
Kuroda 2009	6	51	5	31	6.0%	0.69 [0.19, 2.50]
Lee 2014	12	36	12	36	8.8%	1.00 [0.38, 2.66]
Pabuccu 2007	25	81	13	67	10.8%	1.85 [0.86, 3.99]
Tinkanen 2000	11	55	12	45	11.6%	0.69 [0.27, 1.75]
Subtotal (95% CI)		**488**		**389**	**100.0%**	**0.87 [0.64, 1.18]**
Total events	141		120			
Heterogeneity: Chi² = 5.17, df = 5 (P = 0.40); I² = 3%						
Test for overall effect: Z = 0.91 (P = 0.36)						

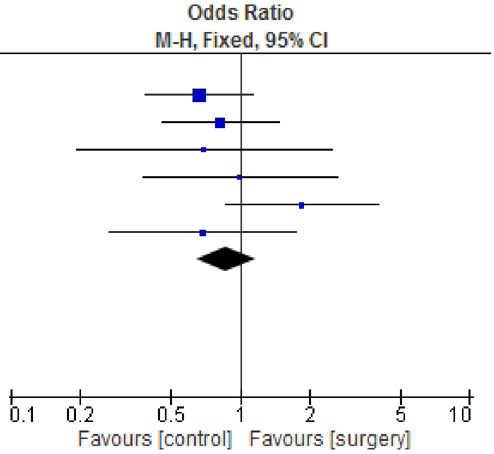


Fig. 3 Forrest plot for live birth.

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.2 Observational						
Bongioanni 2011	29	112	49	142	28.5%	0.66 [0.38, 1.15]
Dong 2014	58	153	29	68	22.2%	0.82 [0.46, 1.47]
Garcia-Velasco 2004	36	147	14	63	13.2%	1.14 [0.56, 2.29]
Kuroda 2009	6	51	5	31	4.9%	0.69 [0.19, 2.50]
Lee 2014	12	36	12	36	7.1%	1.00 [0.38, 2.66]
Pabuccu 2007	25	81	13	67	8.7%	1.85 [0.86, 3.99]
Tinkanen 2000	11	55	12	45	9.4%	0.69 [0.27, 1.75]
Wong 2004	13	36	11	38	6.1%	1.39 [0.52, 3.68]
Subtotal (95% CI)		**671**		**490**	**100.0%**	**0.94 [0.72, 1.22]**
Total events	190		145			
Heterogeneity: Chi² = 6.33, df = 7 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						

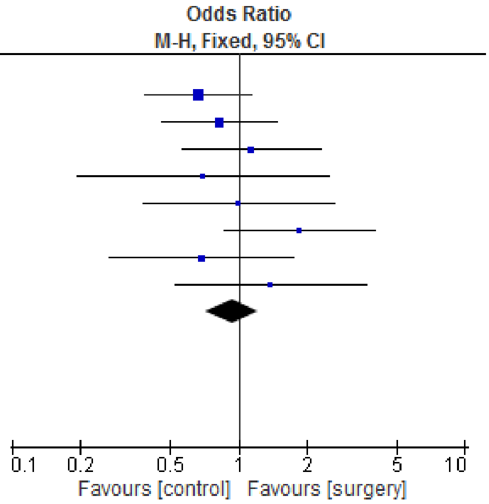


Fig. 4 Forrest plot for clinical pregnancy.

Study or Subgroup	Surgery Events	Surgery Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 RCT						
Demirol 2006	17	49	19	50	15.2%	0.87 [0.38, 1.97]
Subtotal (95% CI)		**49**		**50**	**15.2%**	**0.87 [0.38, 1.97]**
Total events	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.2.2 Observational						
Dong 2014	66	153	35	68	34.0%	0.72 [0.40, 1.27]
Garcia-Velasco 2004	37	147	14	63	18.1%	1.18 [0.58, 2.37]
Lee 2014	13	36	14	36	11.0%	0.89 [0.34, 2.31]
Pabuccu 2007	27	81	15	67	13.5%	1.73 [0.83, 3.62]
Wong 2004	17	36	13	38	8.2%	1.72 [0.67, 4.39]
Subtotal (95% CI)		**453**		**272**	**84.8%**	**1.10 [0.79, 1.52]**
Total events	160		91			
Heterogeneity: Chi² = 4.73, df = 4 (P = 0.32); I² = 15%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**502**		**322**	**100.0%**	**1.06 [0.78, 1.44]**
Total events	177		110			
Heterogeneity: Chi² = 5.00, df = 5 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						

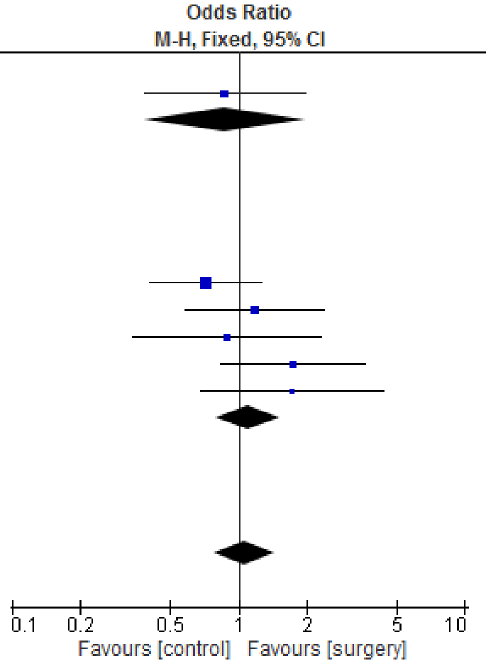
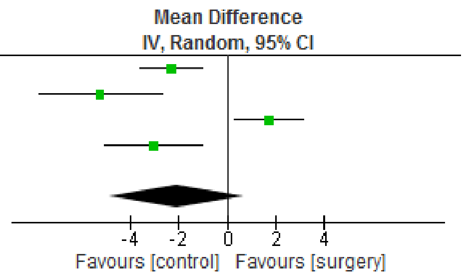


Fig. 5 Forrest plot for antral follicle count.

Study or Subgroup	Surgery Mean	Surgery SD	Surgery Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Benaglia 2015	2.4	2.4	55	4.7	3.9	46	26.5%	-2.30 [-3.59, -1.01]
Bongioanni 2011	11.7	9.4	112	16.9	11.1	142	22.8%	-5.20 [-7.72, -2.68]
Dong 2014	11	5.3	153	9.3	4.9	68	26.2%	1.70 [0.26, 3.14]
Lee 2014	8.2	3.9	36	11.2	4.7	36	24.5%	-3.00 [-5.00, -1.00]
Total (95% CI)			**356**			**292**	**100.0%**	**-2.09 [-4.84, 0.67]**
Heterogeneity: Tau² = 7.03; Chi² = 30.95, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 1.48 (P = 0.14)								



No	Study	Country	Year	Design	N	Age of participants		BMI		Type of Intervention	Method for hemostasis	Outcomes
						intervention	control	intervention	control			
1	Benaglia(22)	Italy	2015	Retrospective cohort	83	35.4 (3.5)*	35.4 (3.5)*	21.2 (3.1)*	21.2 (3.1)*	surgery (not specified further)	not specified	AFC
2	Bongioanni(23)	Italy	2011	Restrospective cohort	254	33.6 (4.4)	33.8 (3.1)	22.4 (3.2)	22.7 (3.2)	laparoscopic stripping	bipolar cautery	LBR, AFC
3	Demirol(21)	Turkey	2006	RCT	99	35.2 (0.3)	34.9 (0.2)	not specified	not specified	drainage and	bipolar cautery	CPR
4	Dong(30)	China	2014	Retrospective cohort	292	31.1 (4.2)	30.0 (3.1)	19.1 (5.9)	19.6 (5.9)	laparocopic cystectomy	not specified	LBR, CPR, AFC
5	Garcia-Velasco(28)	Spain	2004	Retrospective cohort	189	34.7 (0.3)	33.9 (0.5)	not specified	not specified	drainage and excision/coagulation	bipolar coagulation	CPR
6	Kuroda(27)	Japan	2009	Retrospective cohort	82	35.5 (4.0)	38.1 (2.6)	not specified	not specified	laparoscopic stripping	purse-string suture	LBR
7	Lee(26)	South Korea	2014	Retrospective cohort	101	33.6 (2.9)	34.3 (4.3)	21.9 (2.1)	21.6 (1.7)	surgical resection	not specified	LBR, CPR, AFC
8	Pabuccu(22)	Turkey	2007	Prospective cohort**	246	30.9 (4.5)	32.0 (4.4)	25.0 (3.7)	24.4 (4.6)	resection by laparoscopy or laparotomy	not specified	CPR
9	Tinkanen(20)	Finland	2000	Retrospective cohort	100	30.9 (SD not specified)	30.4 (SD not specified)	not specified	not specified	cystectomy by laparoscopy or laparotomy	not specified	LBR
10	Wong(29)	USA	2004	Retrospective cohort	204	35.5 (0.8)	32.3 (0.7)	not specified	not specified	drainage and excision	cauterisation	CPR

LBR: live birth rate, CPR: Clinical pregnancy rate, AFC: Antral follicle count
***: Age and BMI are not specifically stated for intervention and controlgroup but only for the entire population**

****: The study is designed as a RCT, but it is included as a retrospective cohort study as only two subgroups are included in the metaanalysis**

Table 2. Summary of Findings - Surgery compared to nothing for women with endometriomas and subfertility.

Patient or population: Women with endometriomas and subfertility
Intervention: Surgery versus conservative treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants (N)	Quality of the evidence (GRADE)
	Risk conservative treatment	**Risk with Surgery**			
Live birth after fertility treatment	31 per 100	**28 per 100** (22 to 34)	**OR 0.87** (0.64 to 1.18)	877 (6 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Clinical pregnancy	38 per 100	**35 per 100** (19 to 55)	**OR 0.87** (0.38 to 1.97)	99 (1 RCT)	⊕⊕◯◯ LOW [b]
Clinical pregnancy	33 per 100	**36 per 100** (28 to 43)	**OR 1.10** (0.79 to 1.52)	725 (5 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Antral follicle count	AFC ranged from **4.7-11.2**	The mean AFC in the intervention group was 0,98 lower (0,98 lower to 0,11 lower)		(3 observational studies)	⊕◯◯◯ VERY LOW [a,b,d]
Pain - not reported	-	see_comment	-	-	-

*__The risk in the intervention group__ (CI 95%) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (CI 95%).
Abbreviations: CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect