Human Reproduction Update, Vol.21, No.6 pp. 809–825, 2015
Advanced Access publication on July 12, 2015 doi:10.1093/humupd/dmv035

human reproduction update

The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis

M. Hamdan[1,2,3], G. Dunselman[4], T.C. Li[5], and Y. Cheong[1,3,*]

[1]Human Development and Health Unit, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, UK [2]Faculty of Medicine, Department of Obstetrics and Gynaecology, University of Malaya, Kuala Lumpur 50603, Malaysia [3]Complete Fertility Centre Southampton, Princess Anne Hospital, Coxford Road, Southampton SO16 5YD, UK [4]Department of Obstetrics and Gynaecology, Research Institute GROW, Maastricht University Medical Centre, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands [5]Faculty of Medicine, Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Hong Kong, Hong Kong

*Correspondence address. Complete Fertility Centre Southampton, Level F, Princess Anne Hospital, Coxford Road, Southampton SO16 5YA, UK; E-mail: y.cheong@soton.ac.uk, yingcheong@hotmail.com

Submitted on January 30, 2015; resubmitted on June 18, 2015; accepted on June 26, 2015

TABLE OF CONTENTS

BACKGROUND: Endometriosis is a disease known to be detrimental to fertility. Women with endometriosis, and the presence of endometrioma, may require artificial reproductive techniques (ART) to achieve a pregnancy. The specific impact of endometrioma alone and the impact of surgical intervention for endometrioma on the reproductive outcome of women undergoing IVF/ICSI are areas that require further clarification. The objectives of this review were as follows: (i) to determine the impact of endometrioma on IVF/ICSI outcomes, (ii) to determine the impact of surgery for endometrioma on IVF/ICSI outcome and (iii) to determine the effect of different surgical techniques on IVF/ICSI outcomes.

METHODS: We performed a systematic review and meta-analysis examining subfertile women who have endometrioma and are undergoing IVF/ICSI, and who have or have not had any surgical management for endometrioma before IVF/ICSI. The primary outcome was live birth rate (LBR). Our secondary outcomes were clinical pregnancy rate (CPR), mean number of oocyte retrieved (MNOR), miscarriage rate (MR), fertilization rate, implantation rate, antral follicle count (AFC), total stimulating hormone dose, and any rates of adverse effects such as cancellation and associated complications during the IVF/ICSI treatment.

RESULTS: We included 33 studies for the meta-analysis. The majority of the studies were retrospective (30/33), and three were RCTs. Compared with women with no endometrioma undergoing IVF/ICSI, women with endometrioma had a similar LBR (odds ratio [OR] 0.98; 95% CI [0.71, 1.36], 5 studies, 928 women, $I^2 = 0\%$) and a similar CPR (OR 1.17; 95% CI [0.87, 1.58], 5 studies, 928 women, $I^2 = 0\%$), a lower mean

number of oocytes retrieved (SMD −0.23; 95% CI [−0.37, −0.10], 5 studies, 941 cycles, $I^2 = 37\%$) and a higher cycle cancellation rate compared with those without the disease (OR 2.83; 95% CI [1.32, 6.06], 3 studies, 491 women, $I^2 = 0\%$). Compared with women with no surgical treatment, women who had their endometrioma surgically treated before IVF/ICSI had a similar LBR (OR 0.90; 95% CI [0.63, 1.28], 5 studies, 655 women, $I^2 = 32\%$), a similar CPR (OR 0.97; 95% CI [0.78, 1.20], 11 studies, 1512 women, $I^2 = 0\%$) and a similar mean number of oocytes retrieved (SMD −0.17; 95% CI [−0.38, 0.05], 9 studies, 810 cycles, $I^2 = 63\%$).

CONCLUSIONS: Women with endometrioma undergoing IVF/ICSI had similar reproductive outcomes compared with those without the disease, although their cycle cancellation rate was significantly higher. Surgical treatment of endometrioma did not alter the outcome of IVF/ICSI treatment compared with those who did not receive surgical intervention. Considering that the reduced ovarian reserve may be attributed to the presence of endometrioma *per se*, and the potential detrimental impact from surgical intervention, individualization of care for women with endometrioma prior to IVF/ICSI may help optimize their IVF/ICSI results.

Key words: endometriosis / IVF/ICSI / surgery / pregnancy / endometrioma

Introduction

Endometriosis is a disease known to be detrimental to fertility (Giudice and Kao, 2004; Farquhar, 2007; Holoch and Lessey, 2010). A significant number of women with endometriosis will eventually seek ART, namely *in vitro* fertilization (IVF) with or without intra-cytoplasmic sperm injection (ICSI) for conception. Between 17 and 44% of women with endometriosis will have endometrioma (Jenkins *et al.*, 1986; Redwine, 1999). The exact pathophysiology of endometrioma related to infertility is still unknown. It can be detrimental to fertility directly by distorting tubo-ovarian anatomy (Young *et al.*, 2013), or indirectly by invoking inflammatory (Gazvani and Templeton, 2002; Iwabe *et al.*, 2002) and oxidative damage (Matsuzaki and Schubert, 2010; Agarwal *et al.*, 2012) on the oocytes resulting in poorer quality oocytes (Gupta *et al.*, 2006).

Our group and others have shown that the presence of endometriosis does not adversely affect IVF outcomes in terms of live birth, even though women with endometriosis have lower oocytes yield per cycle compared with those without endometriosis (Barnhart *et al.*, 2002; Harb *et al.*, 2013; Hamdan *et al.*, 2015). The latter finding is somewhat counter-intuitive given that pregnancy rate increases proportionately with the number of oocytes collected until a threshold (Sunkara *et al.*, 2011; Ji *et al.*, 2013). The impact of endometriosis is likely to be more profound in those with reduced ovarian reserve although this has not been specifically investigated. Furthermore, the differential impact of the presence or absence of endometrioma was not specifically examined in the above-mentioned studies.

There is now molecular, histological and morphological evidence to suggest that endometriosis is detrimental to the ovaries (Sanchez *et al.*, 2014). Toxic content from an endometrioma may lead to unfavourable events such as increased oxidative stress, increase fibrosis, loss of cortex specific stroma, smooth muscle cell metaplasia, vascularization defect and, later, reduced follicular maturation. Whether this vicious cycle of damage can be ameliorated by surgical treatment or IVF/ICSI is still controversial.

Surgical treatment of endometriosis and endometrioma prior to IVF/ICSI is widely practiced (Vercellini *et al.*, 2009) even though very little evidence exists to provide robust guidance to clinicians (Dunselman *et al.*, 2014). More recent studies have generated some concern that the surgical treatment on endometrioma could be detrimental to ovarian reserve (Raffi *et al.*, 2012; Somigliana *et al.*, 2012; Muzii *et al.*, 2014) and subsequently adversely affect IVF/ICSI reproductive outcomes (Tsoumpou *et al.*, 2009; Benschop *et al.*, 2010). The possible adverse outcomes associated with the presence of endometrioma during IVF/ICSI have also not been studied. The risks of surgery and its potential damage to ovarian reserve have to be balanced with the complications associated with the persistence of the endometrioma during IVF/ICSI (Fig. 1). As such, this area of management often poses a clinical conundrum for health care practitioners.

The specific impact of endometrioma alone, the differential influences of the disease entity (that of endometrioma rather than endometriosis *per se*) and the impact of surgical intervention of endometriosis on the reproductive outcome of women undergoing IVF/ICSI are areas that require further clarification. To this end, we performed a systematic review and meta-analysis with the following objectives: (i) to determine the impact of endometrioma on IVF/ICSI outcomes, (ii) to determine the impact of surgery for endometrioma on IVF/ICSI outcomes and (iii) to determine the effect of different surgical techniques on IVF/ICSI outcomes. The primary outcome was live birth rate (LBR); the secondary outcomes were clinical pregnancy rate (CPR), miscarriage rate (MR), mean number of oocyte retrieved (MNOR) and rates of any adverse effects such as cancellation and associated complications during the IVF/ICSI treatment.

Methods

Criteria for considering studies for this review

Type of studies

Published cohort or case–control studies (retrospective or prospective) and randomized controlled trials were eligible for inclusion. Where studies reported similar or overlapping data, only the latest or those with the largest dataset were considered for this review.

Type of participants

The included studies had: (i) women who underwent IVF/ICSI, (ii) a study group of women with the presence of identified endometrioma and (iii) a control group. Studies that satisfied the above criteria were included whether or not the participants had prior surgical treatment for their endometrioma. The diagnosis of endometrioma could be by laparoscopy or imaging modalities. Studies were excluded if: (i) the participants had ovarian cysts other than endometrioma, (ii) the participants had received any known non-surgical treatment (medical management, alternative treatment) prior to IVF/ICSI, (iii) the participants were involved with donor/recipient oocytes treatment or (iv) an appropriate control group was not included. We considered appropriate control groups to be: (i) women

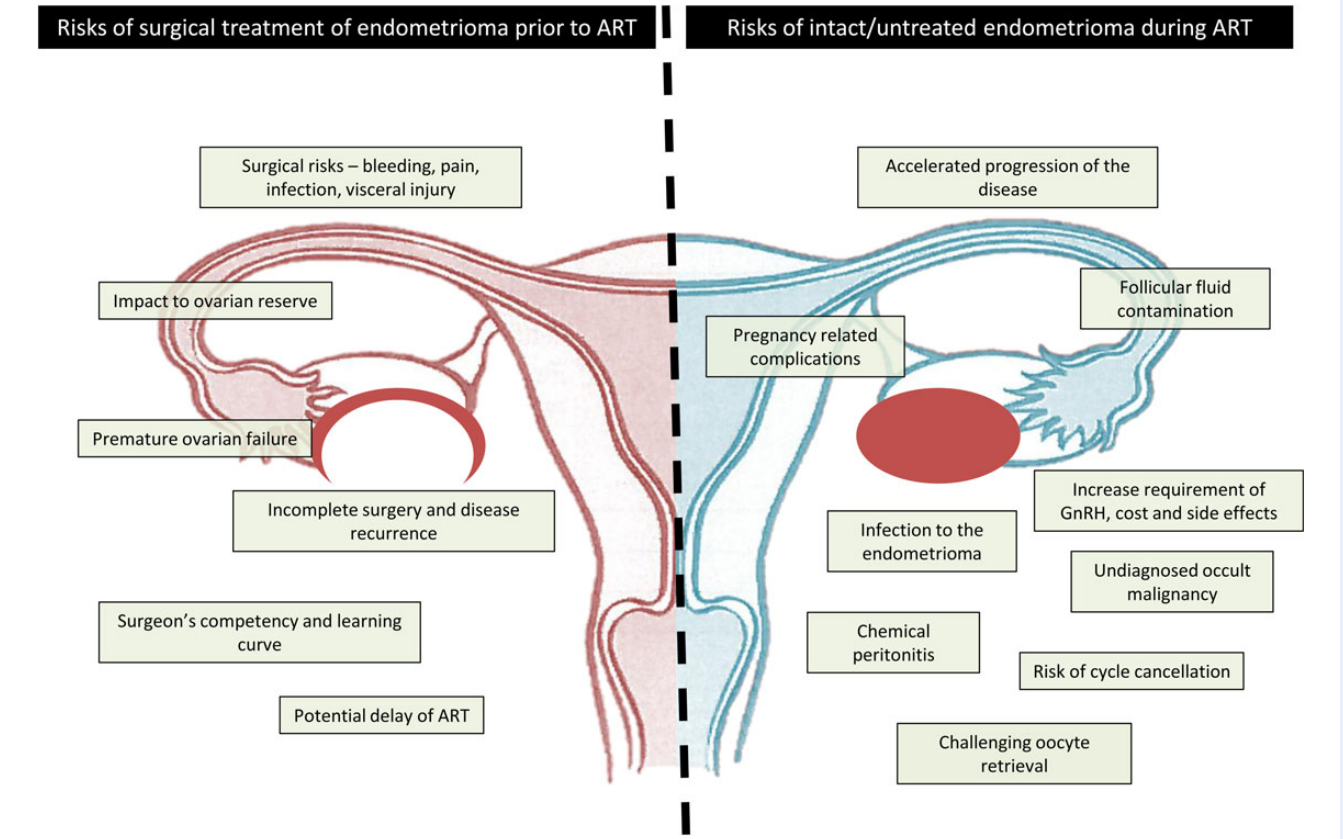

Figure 1 Risks of surgical treatment of endometrioma before ART and risks of intact endometrioma during ART.

who underwent IVF/ICSI for indications not related to endometriosis, (ii) women with endometriosis in the absence of endometrioma or (iii) women with endometrioma that was left untreated, (iv) women who had endometrioma treated by different surgical techniques.

Type of interventions

Surgical treatment for endometriomas includes drainage of the endometrioma without removal of the cyst wall, with or without coagulation of the cyst wall (laparoscopic or transvaginal ultrasound guided), or cystectomy with drainage and/or excision/stripping of the cyst wall (by laparoscopy/laparotomy or both). Aspiration of endometrioma during oocyte retrieval was not considered an operative surgical treatment prior to IVF/ICSI.

We included participants who either underwent IVF or ICSI or both. We excluded participants who underwent gamete intra-fallopian transfer or *in vitro* maturation.

Type of outcome measures

The primary outcome measure was LBR per woman, defined as the number of deliveries that resulted in at least 1 live born baby expressed per 100 patients.

Secondary outcome measures were as follows: (i) CPR per woman, defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy and was expressed per 100 patients (Zegers-Hochschild *et al.*, 2009), (ii) mean number of oocytes retrieved per cycle, (iii) MR, (iv) fertilization rate, (v) implantation rate, (vi) rates of adverse outcomes including cycle cancellation and surgical complications such as infection, bleeding or pain during IVF/ICSI. Where available, comparison was also made between participants' characteristics of ovarian reserve: antral follicle count (AFC), follicle stimulating hormone (FSH) and anti-mullerian hormones (AMH).

Search methods for identification of studies

We searched all published and unpublished studies from January 1980 to December 2014 on surgical treatment of endometrioma and IVF/ICSI outcomes, without language restriction and in consultation with a search methodologist.

Electronic searches

The following electronic databases, trial registers and websites were searched: MEDLINE, EMBASE, Cochrane Central register of Controlled Trials, and Web of Science. A search strategy was carried out based on the following keywords and/or medical subject heading (MeSH) terminology: IVF/ICSI, endometriosis, endometrioma, IVF, ICSI, *in vitro* fertilization, ICSI, outcome, pregnancy and live birth.

Searching other resources

Reference lists of all primary and review articles were hand searched, and experts in the field were contacted to obtain additional articles not captured in the electronic searches. Relevant journals and conference abstracts that were not covered in the databases were also hand searched.

Data collection and analysis

Selection of studies

After a primary screen of all titles and abstracts retrieved (by M.H.), the full texts of all potentially eligible studies were retrieved. Two review authors

(M.H., Y.C.) independently examined these articles for compliance with the inclusion criteria and selected the studies that were eligible for inclusion in the review. Study investigators were contacted if clarification was needed for study eligibility. Disagreement as to study eligibility was resolved after discussion by both reviewers. The process is documented in the PRISMA chart (Fig. 2).

Data extraction and management

Two review authors independently extracted the data using a data extraction form designed and pilot-tested by the authors on two independent occasions. Any disagreements were resolved by discussion between both review authors. Data retrieved included study characteristics and their various outcomes data. Both reviewers counterchecked these extracted data repeatedly. Where studies had multiple publications or were using the same database, the latest and main trial report was used as the reference and the additional details were scanned from the secondary or earlier papers. Authors were contacted for further data and/or results, as required. All the available data were extracted into Review Manager 5 for further analysis.

Comparative analysis

Analyses were performed in studies where IVF/ICSI outcomes in women with intact endometrioma during IVF/ICSI were compared with those with no endometriosis or those with peritoneal endometriosis.

IVF/ICSI outcomes after surgical treatment for endometrioma were compared with those where the women had untreated endometrioma, peritoneal endometriosis or a normal unaffected contralateral ovary.

We also performed a head-to-head comparison of different ovarian cystectomy surgical techniques including laparoscopic or transvaginal aspiration and different laparoscopic cystectomy techniques.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Statistical heterogeneity was evaluated by the measure of the I^2. We used a fixed-effect model and examined heterogeneity between the results of different studies by inspecting the scatter in the data points, the overlap in their CIs and by checking the results of the chi^2 test and the I^2 statistic. The threshold for the interpretation of I^2 varies and

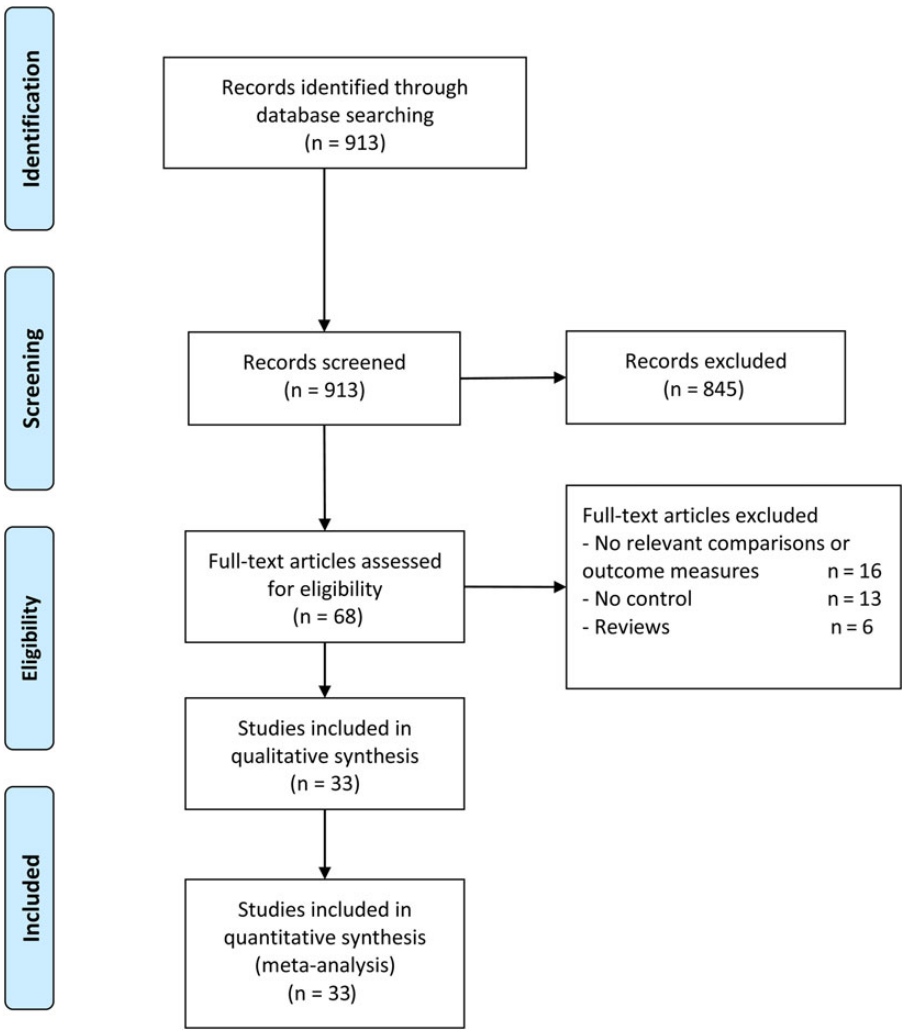

Figure 2 Flow diagram.

inconsistencies depend on several factors. Scores below 50% were considered to represent low or moderate heterogeneity whereas, I^2 equal to or greater than 50% was taken to indicate substantial heterogeneity and, in that case, a random-effects analysis was used. Incorporation of a random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical but follow some distribution. Sensitivity analyses were not performed. Where there were at least 10 studies in our comparative analysis, we also generated funnel plots for comparison to inspect for small study effects.

Data synthesis

Quality assessment of the data

Two authors (M.H., Y.C.) assessed the methodological quality of the studies and extracted relevant data such as diagnosis of endometriosis, surgical treatment, staging of the disease, selection of controls and definition of primary and secondary outcomes. Where available, we extracted statistical data from the original papers or calculated missing parameters by using data provided. The quality of individual studies was assessed in accordance with the MOOSE criteria and the Newcastle–Ottawa Scale (Wells *et al.*, 2010). By using the Newcastle–Ottawa scale, non-randomized studies were rated according to eight items categorized in three domains: study group selection, comparability of the groups and ascertainment of outcome (maximum scores of 4, 2 and 3, respectively). Scores were represented with stars for each quality item to provide a visual assessment. Studies were awarded up to nine stars if they fulfilled all the quality items. Randomized controlled trials were assessed on the risk of methodological bias (Higgins JPT, 2011).

Measures of treatment effects

For dichotomous data (e.g. CPR), the numbers of events in the control and intervention groups of each study were keyed into Review Manager 5 and analysed using Mantel-Hansel odds ratio (OR). For continuous data, standardized mean differences (SMD) between treatments groups were calculated.

Results

Result of search

The search strategy yielded 913 studies; however, 845 studies were excluded because it was clear from the title or abstract that they did not fulfil the selection criteria. Out of 68 potential studies for the analysis, we further excluded 16 studies that had no relevant comparisons (non-endometrioma), 13 studies that had no available control groups and 6 publications that were reviews (Gupta *et al.*, 2006; Somigliana *et al.*, 2006; Vercellini *et al.*, 2009; Tsoumpou *et al.*, 2009; Benschop *et al.*, 2010; Gelbaya and Nardo, 2011). A final number of 33 studies were included for the meta-analysis.

Description of studies and participants

The majority of the included studies (Table I) were non-RCT (Nargund *et al.*, 1996; Yanushpolsky *et al.*, 1998; Diaz *et al.*, 2000; Tinkanen and Kujansuu, 2000; Canis *et al.*, 2001; Ho *et al.*, 2002; Marconi *et al.*, 2002; Suganuma *et al.*, 2002; Takuma *et al.*, 2002; Wu *et al.*, 2003; Wyns and Donnez, 2003; Garcia-Velasco *et al.*, 2004; Wong *et al.*, 2004; Loo *et al.*, 2005; Ragni *et al.*, 2005; Suzuki *et al.*, 2005; Esinler *et al.*, 2006; Yazbeck *et al.*, 2006; Duru *et al.*, 2007; Matalliotakis *et al.*, 2007; Nakagawa *et al.*, 2007; Somigliana *et al.*, 2008; Kuroda *et al.*, 2009; Yamamoto *et al.*, 2009; Barri *et al.*, 2010; Almog *et al.*, 2011; Bongioanni *et al.*, 2011; Takashima *et al.*, 2013; Takebayashi *et al.*, 2013; Lee *et al.*, 2014) ($n = 30$) and the remaining studies ($n = 3$) were RCTs (Pabuccu *et al.*, 2004; Demirol *et al.*, 2006; Pabuccu *et al.*, 2007). There were 30 studies that included women with endometriosis who had surgical treatment to their endometrioma prior to IVF/ICSI; 12 studies included more than one comparative group and 13 studies included women with intact endometrioma (either as a study or control group). From the included studies, 18 indicated the laterality of the disease (bilateral disease $n = 2/18$, unilateral disease $n = 6/18$, and unilateral and/or bilateral $n = 10/18$). Less than half ($n = 14$) of the included studies specified the size of endometrioma as their inclusion criteria, and the sizes ranged from 1 cm or more to size of >6 cm. There were 19 other studies that did not specify the size of the endometrioma (Table I).

All studies except one (Barri *et al.*, 2010) stated the stimulation protocol: long protocol ($n = 28/33$), mixed protocols ($n = 3/33$) or short agonist protocol (1/33). Women in the majority of the studies underwent ovarian cystectomy ($n = 27$), either by laparoscopy (25/27) or by laparoscopy and/or laparotomy (2/27), whereas in three studies some women had transvaginal cyst aspiration.

In five studies where women with endometrioma had no surgical treatment, the comparative controls included women with no endometriosis. Studies examining the outcome of surgical treatment in women with endometriomas included various comparative control groups: (i) untreated endometrioma ($n = 11$), (ii) endometriosis with no previous endometrioma ($n = 7$), (iii) tubal factor ($n = 10$) and (iv) normal contralateral ovary ($n = 4$). Three studies compared ovarian cystectomy with transvaginal aspiration prior to IVF/ICSI whereas three other studies made head-to-head comparisons of different ovarian cystectomy surgical techniques.

Amongst all the included studies, reported outcomes were as follows: LBR (11/33), CPR (29/33), MNOR (33/33), MR (9/33), implantation rate (14/33), fertilization rate (19/33), FSH dose requirement (17/33), cycle cancellation rate (7/33), baseline characteristics of baseline FSH level (14/33) and AFC (7/33). None of the included studies reported baseline characteristics of AMH levels or any clinical adverse outcomes related to infection, bleeding or pain. Papers that reported IR and FR have presented the data in percentages and none provide the raw data. None of the studies exclusively examined women with recurrent endometrioma although some (Tinkanen and Kujansuu, 2000; Wong *et al.*, 2004; Barri *et al.*, 2010) included women with endometrioma who had prior surgical treatment.

Quality assessment of studies

Systematic risk assessment of methodological bias (Higgins JPT, 2011) of the three included RCTs revealed all studies to have a high risk of reporting bias (Pabuccu *et al.*, 2004; Demirol *et al.*, 2006; Pabuccu *et al.*, 2007) and two studies (Pabuccu *et al.*, 2004; Demirol *et al.*, 2006) to have a risk of blinding bias (Table II). By assessment using the NOS (Wells *et al.*, 2010), the majority of the non-randomized studies were awarded with eight stars whereas two studies were awarded nine stars, the highest possible score (Table III).

Impact of endometrioma without intervention on IVF/ICSI outcomes

Endometrioma (intact) compared with no endometriosis

When compared with women with no endometriosis, women with intact endometrioma had a similar LBR (OR 0.98; 95% CI [0.71, 1.36],

Table I Characteristics of all studies included in the systematic review.

No	Study (year)	Location	Duration	Design	Intervention/ protocol	Study Group	Type of surgery	*N*	Control group	*N*	Cyst size (cm)	Side	Outcomes
1	Lee *et al.* (2014)	Korea	2008–2012	Retrospective cohort	IVF/ICSI long protocol antagonist	Surgically treated endometrioma	Laparoscopic cystectomy Transvaginal Aspiration (+Ethanol)	36 29	Non-treated endometrioma	36	>3	ND	LBR, CPR, NOR, MR, FR, DFSH, CR, AFC
2	Benaglia *et al.* (2008)	Italy and Spain	2006–2010	Retrospective cohort	IVF/ICSI long protocol	Non-treated endometrioma	Intact endometrioma	39	No endometriosis	78	>1	BL	LBR, CPR, NOR, FR, DFSH, CR, AMH, AFC
3	Takebayashi *et al.* (2013)	Japan	1997–2011	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	12	Laparoscopic laser ablation	15	2–7	Either	LBR, CPR, NOR, IR, FR, DFSH
4	Takashima *et al.* (2013)	Japan	2008–2010	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy (+Coagulation)	21	Laparoscopic cystectomy (+suture)	23	ND	UL	CPR, NOR, DFSH, AMH, BFSH, AFC
5	Bongioanni *et al.* (2011)	Italy	ND	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	112	Non-treated endometrioma tubal factor	142 174	<6	Either	LBR, CPR, NOR, IR, FR, DFSH, CRBFSH, AFC
6	Barri *et al.* (2010)	Spain	2001–2005	Retrospective case–control	IVF ND	Surgically treated endometrioma	Laparoscopic cystectomy	483	Non-treated endometrioma male factor	173 334	ND	ND	CPR, NOR
7	Almog *et al.* (2011)	Canada	1998–2008	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	80	Normal contralateral ovary	80	ND	UL	NOR
8	Kuroda *et al.* (2009)	Japan	2006–2008	Retrospective case–control	IVF/ICSI mix protocol	Surgically treated endometrioma	Laparoscopic cystectomy	18	Non-treated endometrioma peritoneal endometriosis tubal factor	36 15 21	ND	ND	LBR, CPR, NOR, MR, IR, CR, BFSH
9	Yamamoto *et al.* (2009)	Japan	2000–2008	Retrospective case–control	IVF/ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy Transvaginal aspiration	41 11	Peritoneal endometriosis	50	>2	Either	CPR, NOR, FR, DFSH
10	Somigliana *et al.* (2008)	Italy	2002–2007	Retrospective cohort	IVF/ICSI long protocol	Surgically treated endometrioma	Laparoscopic/ laparotomy cystectomy	68	Male, tubal, unexplained, combination	136	ND	BL	LBR, CPR, NOR, IR, CR, BFSH
11	Nakagawa *et al.* (2007)	Japan	2002–2006	Retrospective cohort study	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	10	No endometriosis	70	>4	ND	CPR, NOR, FR, DFSH
12	Pabuccu *et al.* (2007)	Turkey	2002–2006	Randomized control trial	IVF/ICSI long protocol antagonist	Surgically treated endometrioma	Laparoscopic cystectomy	81	Non-treated endometrioma peritoneal endometriosis	67 98	ND	Either	CPR, LBR, NOR, MR, IR, FR, DFSH, BFSH, AFC

13	Duru *et al.* (2007)	Turkey	ND	Retrospective case–control	ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy Laparotomy cystectomy+ Reconstruction	28 10	Peritoneal endometriosis	10	ND	UL	CPR, NOR, FR, DFSH, BFSH
14	Demirol *et al.* (2006)	Turkey	2001–2005	Randomized control trial	ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	49	Non-treated endometrioma	50	3–6	UL	CPR, NOR, IR, FR, DFSH, BFSH
15	Esinler *et al.* (2006)	Turkey	NA	Retrospective case–control	ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	23	Tubal factor	99	>3	Either	CPR, NOR, MR, IR, DFSH, BFSH, AFC
16	Matalliotakis *et al.* (2007)	USA	1996–2002	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	68	Tubal factor	106	ND	ND	LBR, CPR, MR, NOR, FR, BFSH
17	Yazbeck *et al.* (2006)	France	1998–2001	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	63	Peritoneal endometriosis	50	ND	Either	CPR, NOR, DFSH
18	Loo *et al.* (2005)	Taiwan	2000–2002	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	127	Tubal factor	95	>3	ND	CPR, NOR, IR, FR, DFSH, BFSH
19	Ragni *et al.* (2005)	Italy	2002–2004	Retrospective case–control	IVF/ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	17	Normal contralateral ovary	17	<3, >3	UL	NOR
20	Suzuki *et al.* (2005)	Japan	1996–2002	Retrospective cohort	IVF short protocol	Non-treated endometrioma	Intact endometrioma	80	Peritoneal endometriosis tubal factor	248 283	ND	Either	LBR, CPR, NOR, IR, FR
21	Pabuccu *et al.* (2004)	Turkey	1999–2002	Randomized control trial	ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy Transvaginal aspiration	44 41	Non -treated endometrioma tubal factor	40 46	ND	Either	CPR, NOR, MR, IR, FR, DFSH, BFSH, AFC
22	Wong *et al.* (2004)	USA	1995–2002	Retrospective cohort	IVF/ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	45	Non-treated endometrioma	29	ND	ND	CPR, NOR, MR, IR, FR, DFSH, BFSH
23	Garcia-Velasco *et al.* (2004)	Spain	1997–2001	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	133	Non-treated endometrioma	56	ND	ND	CPR, NOR, MR, IR, FR, DFSH, BFSH, CR
24	Wyns and Donez (2003)	Belgium	1997–2002	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	85	Tubal factor unexplained	193 135	<3, >3	ND	CPR, NOR, IR, FR
25	Wu *et al.* (2003)	Taiwan	NA	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	22	Tubal factor normal contralateral ovary	20 10	>6	ND	LBR, CPR, NOR, FR, BFSH
26	Suganuma *et al.* (2002)	Japan	NA	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy Transvaginal aspiration	36 23	Non-treated endometrioma	30	ND	ND	CPR, NOR, FR
27	Marconi *et al.* (2002)	Argentina	1999–2000	Retrospective cohort	IVF long protocol	Surgically treated endometrioma	Laparoscopic Cystectomy	39	Tubal factor	39	ND	Either	CPR, NOR, DFSH
28	Takuma *et al.* (2002)	Japan	NA	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic Cystectomy	36	Laparoscopic aspiration only (+electro therapy) (+alcohol therapy)	41	ND	ND	CPR, NOR

Continued

Table I *Continued*

No	Study (year)	Location	Duration	Design	Intervention/ protocol	Study Group	Type of surgery	N	Control group	N	Cyst size (cm)	Side	Outcomes
29	Canis *et al.* (2001)	France	NA	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	41	Tubal factor peritoneal endometriosis	59 139	>3	Either	CPR, NOR
30	Tinkanen and Kujansuu (2000)	Finland	1994–1998	Retrospective cohort	IVF/ICSI long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	55	Non-treated endometrioma	45	ND	Either	CPR, NOR
31	Ho *et al.* (2002)	Taiwan	1996–2001	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	38	Normal contralateral ovary	38	ND	UL	NOR
32	Yanushpolsky *et al.* (1998)	USA	1994–1995	Retrospective cohort	IVF long protocol	Non-treated endometrioma	Intact endometrioma	37	No endometriosis	56	>1	Either	LBR, CPR, NOR, MR, IR, FR
33	Nargund *et al.* (1996)	United Kingdom	1988–1994	Retrospective case–control	IVF long protocol	Surgically treated endometrioma	Laparoscopic cystectomy	36	Surgically treated benign cyst	54	ND	UL	NOR

LBR, Live birth rate; CPR, Clinical pregnancy rate; NOR, Number of oocytes retrieved; MR, Miscarriage rate; IR, Implantation rate; FR, Fertilization rate; CR, cancellation rate; DFSH, Total FSH dose; BFSH, Baseline FSH; AMH, Anti-Mullerian Hormone; AFC, Antral follicle count; ND, Not documented; IVF, *In Vitro* Fertilization; RCT, Randomized control trial; BL, Bilateral; UL, Unilateral; NA, Not applicable; ND, not defined.

5 studies, 928 women, $I^2 = 0\%$), CPR (OR 1.17; 95% CI [0.87, 1.58], 5 studies, 928 women, $I^2 = 0\%$) and a similar MR (OR 1.70; 95% CI [0.86, 3.35], 3 studies, 171 pregnancies, $I^2 = 37\%$), but a lower MNOR (SMD −0.23; 95% CI [−0.37, −0.10], 5 studies, 941 cycles, $I^2 = 37\%$). There was a higher cancellation rate (OR 2.83; 95% CI [1.32, 6.06], 3 studies, 491 women, $I^2 = 0\%$) in women with intact endometrioma. None of the studies reported other adverse events such as bleeding, infection or pain (Fig. 3a and b).

Baseline FSH levels in women with endometrioma were higher when compared with women with no endometriosis (SMD 0.20; 95% CI [0.02, 0.38], 3 studies, 491 cycles, $I^2 = 57\%$). Other parameters such as AFC (SMD −0.02; 95% CI [−0.21, 0.18], 2 studies, 433 cycles, $I^2 = 0\%$) and total stimulation dose (SMD −0.07; 95% CI [−0.27, 0.12], 2 studies, 433 cycles, $I^2 = 65\%$) were comparable between both groups.

Endometrioma (intact) compared with peritoneal endometriosis

When compared with women with peritoneal endometriosis, women with intact endometrioma had a similar LBR (OR 0.92; 95% CI [0.92, 1.79], 2 studies, 353 women, $I^2 = 0\%$), a similar CPR (OR 0.87; 95% CI [0.56, 1.35], 3 studies, 518 women, $I^2 = 18\%$), a similar MR (OR 0.86; 95% CI [0.18, 4.17], 2 studies, 175 pregnancies, $I^2 = 0\%$) and a similar MNOR (SMD −0.31; 95% CI [−1.03, 0.42], 3 studies, 539 cycles, $I^2 = 91\%$). Other parameters such as cancellation rate (OR 0.82; 95% CI [0.23, 2.93], 1 study, 46 cycles) were similar in women with intact endometrioma (Fig. 4a and b).

Baseline FSH levels (SMD 0.41; 95% CI [−0.29, 1.10], 2 studies, 190 patients, $I^2 = 60\%$) and AFC (SMD −0.81; 95% CI [−1.13, −0.49], 1 study, 165 cycles) in women with endometrioma were comparable with that in women with peritoneal endometriosis. None of the studies reported total stimulation dose or adverse events such as bleeding, infection or pain.

Impact of surgical intervention of endometrioma on IVF/ICSI outcomes

Endometrioma (surgically treated) versus intact endometrioma

In women with endometrioma, those who had surgical treatment before IVF/ICSI had a similar LBR (OR 0.90; 95% CI [0.63, 1.28], 5 studies, 655 women, $I^2 = 32\%$), a similar CPR (OR 0.97; 95% CI [0.78, 1.20], 11 studies, 1512 women, $I^2 = 0\%$), a similar MR (OR 1.32; 95% CI [0.66, 2.65], 4 studies, 195 pregnancies, $I^2 = 0\%$), a similar MNOR (SMD −0.17; 95% CI [−0.38, 0.05], 9 studies, 810 cycles, $I^2 = 63\%$) and a similar cancellation rate per cycle (OR 1.17; 95% CI [0.69, 2.00], 4 studies, 647 cycles, $I^2 = 0\%$) compared with those with untreated endometrioma (Fig. 5a and b).

Women with endometrioma who had surgical treatment had a lower AFC (SMD −0.53 [−0.88, −0.18], 4 studies, 558 cycles, $I^2 = 73\%$) and required a higher dose of FSH (SMD 1.45 [0.23, 2.68], 4 studies, 635 cycles, $I^2 = 98\%$). Both comparison groups had similar baseline FSH levels (SMD 0.11 [−0.36, 0.57], 7 studies, 951 cycles, $I^2 = 73\%$). None of the studies reported adverse outcomes such as pain, infection and bleeding during the course of treatment.

Endometrioma (surgically treated) versus women with peritoneal endometriosis alone

Compared with women with only peritoneal endometriosis, those with surgically treated endometrioma had a similar LBR (OR 0.72; 95% CI

Table II 0 Risk of bias using Cochrane risk assessment tool for RCT.

Bias	Selection		Performance	Attrition	Reporting
Studies (Year)	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Pabuccu *et al.* (2007)	Low risk	Low risk	Low risk	Low risk	High risk
Demirol *et al.* (2006)	Low risk	Low risk	High risk	Low risk	High risk
Pabuccu *et al.* (2004)	Low risk	Low risk	High risk	Low risk	High risk

[0.37, 1.37], 2 studies, 371 women, $I^2 = 28\%$), CPR (OR 0.99; 95% CI [0.71, 1.38], 6 studies, 893 women, $I^2 = 74\%$) and a similar MR (OR 0.80; 95% CI [0.17, 3.72], 2 studies, 69 pregnancies, $I^2 = 0\%$), but a lower MNOR (SMD −0.33; 95% CI [−0.53, −0.13], 7 studies, 1101 cycles, $I^2 = 51\%$). There was no difference in baseline FSH (SMD 1.25 [−0.43, 2.93], 2 studies, 283 cycles, $I^2 = 96\%$) and total dose of FSH requirement for stimulation (SMD 0.18 [−0.25, 0.61], 2 studies, 167 cycles, $I^2 = 23\%$). Only one study reported AFC and cancellation rate, respectively; however, no difference was found between the groups compared.

Endometrioma (surgically treated) versus normal contralateral ovary

In women who had surgical treatment in one ovary, a lower number of oocytes were retrieved (MD −2.59 [−4.13, −1.05], 4 studies, 222 cycles, $I^2 = 83\%$) compared with the contralateral normal ovary without endometrioma of the same patient.

Impact of different surgical techniques to IVF/ICSI outcomes

Laparoscopic cystectomy versus transvaginal aspiration prior to IVF/ICSI

Women with endometrioma who had surgical treatment, compared with those who underwent laparoscopic/laparotomy cystectomy, had a similar CPR (OR 0.98; 95% CI [0.57, 1.69], 3 studies, 232 women, $I^2 = 37\%$), a similar MR (OR 1.00; 95% CI [0.19, 5.31], 2 studies, 74 pregnancies, $I^2 = 0\%$) and a similar MNOR (SMD −0.17 [−0.56, 0.22], 4 studies, 289 cycles, $I^2 = 55\%$). Total FSH dose (SMD −0.02 [−0.42, 0.38], 2 studies, 100 cycles, $I^2 = 0\%$) and AFC (SMD −0.13 [−1.31, 1.05], 2 studies, 150 cycles, $I^2 = 92\%$) were similar compared with those who had transvaginal aspiration. Only one study reported LBR, cancellation rate and baseline FSH level, all of which showed no difference between the groups.

Different laparoscopic cystectomy surgical techniques

We found three studies comparing the effect of different laparoscopic surgical techniques to IVF outcomes. One study (Takebayashi *et al.*, 2013) compared the conventional laparoscopic cystectomy technique to the laser ablation technique; the authors reported no difference in pregnancy rates and MNOR. Another study (Takashima *et al.*, 2013) examined different haemostatic techniques following laparoscopic cystectomy between coagulation and suture and reported no difference in pregnancy rate; however, the authors only reported the number of oocytes retrieved from the treated ovary compared with the contralateral ovary without disease. An earlier study (Takuma *et al.*, 2002) examined four different techniques namely laparoscopic cystectomy, laparoscopic aspiration and sclerotherapy, and laparoscopic aspiration with and without coagulation. They found no differences in the MNOR but a higher pregnancy rate in the group that had laparoscopic aspiration with coagulation of the cyst wall. None of the studies reported adverse outcomes during IVF/ICSI. Meta-analysis of these available data was not possible as the comparison groups were not similar.

Discussion

We found a similar LBR, CPR and MR, but a lower mean number of oocytes retrieved in women with intact endometrioma when compared with women without endometrioma. Women with endometrioma, however, were nearly three times as likely to have a cancelled cycle compared with those without the disease. Amongst those with endometrioma, women who had surgical treatment prior to IVF/ICSI had similar LBR, CPR, MNOR and MR compared with those women with intact endometrioma. However, these women had a lower AFC and required a higher total gonadotrophin stimulation dose compared with those who had no surgery (Fig. 6).

Our previous publication (Hamdan *et al.*, 2015) concluded that women with more severe endometriosis (Stage III and Stage IV) had a poorer reproductive outcomes. Severe endometriosis exists in varied forms and is a rather heterogeneous group (Burney and Giudice, 2012). In this review, we have exclusively examined a defined group of women with endometrioma that would inevitably overlap with those categorized at stage III/IV endometriosis. The observation of poorer reproductive outcomes of stage III and IV endometriosis overall but not of endometrioma on its own suggests that endometrioma alone is unlikely to be the major contributory cause, at least in the context of IVF/ICSI. The poorer reproductive outcomes with severe disease may be more closely linked with factors such as the non-ovarian aspects of the disease entity, the presence or absence of surgical interventions and the baseline ovarian reserve.

The diminished number of oocytes retrieved and the higher baseline levels of FSH in women with endometrioma compared with women with no endometriosis allows speculation that the ovarian endometriotic disease *per se* exerts some detrimental impact on the ovary. The impact of the disease may not be solely on diminished oocyte numbers but more importantly on oocyte quality, with supportive evidence drawn from oocyte donor recipient studies where recipients of oocyte donors with endometriosis achieved lower pregnancy rates than those who received oocytes from non-endometriosis donors (Diaz *et al.*, 2000). In addition,

Table III Newcastle–Ottawa quality assessment scale of the included studies.

No	Reference	Case-cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow-up	Score
1	Lee *et al.* (2014)	*	*	*	*	*	*	*	*	8
2	Benaglia *et al.* (2008)	*	*	*	*	*	*	*	*	8
3	Takebayashi *et al.* (2013)	*	*	*	*	*	*	*	*	8
4	Takashima *et al.* (2013)	*	*	*	*	*	*	*	*	8
5	Bongioanni *et al.* (2011)	*	*	*	*	*	*	*	*	8
6	Barri *et al.* (2010)	*	*	*	*	*	*	*	*	8
7	Almog *et al.* (2011)	*	*	*	*	*	*	*	*	8
8	Kuroda *et al.* (2009)	*	*	*	*	**	*	*	*	9
9	Yamamoto *et al.* (2009)	*	*	*	*	**	*	*	*	9
10	Somigliana *et al.* (2008)	*	*	*	*	*	*	*	*	8
11	Nakagawa *et al.* (2007)	*	*	*	*	*	*	*	*	8
12	Duru *et al.* (2007)	*	*	*	*	*	*	*	*	8
13	Esinler *et al.* (2006)	*	*	*	*	*	*	*	*	8
14	Matalliotakis *et al.* (2007)	*	*	*	*	*	*	*	*	8
15	Yazbeck *et al.* (2006)	*	*	*	*	*	*	*	*	8
16	Loo *et al.* (2005)	*	*	*	*	*	*	*	*	8
17	Ragni *et al.* (2005)	*	*	*	*	*	*	*	*	8
18	Suzuki *et al.* (2005)	*	*	*	*	*	*	*	*	8
19	Wong *et al.* (2004)	*	*	*	*	*	*	*	*	8
20	Garcia-Velasco *et al.* (2004)	*	*	*	*	*	*	*	*	8
21	Wyns and Donez (2003)	*	*	*	*	*	*	*	*	8
22	Wu *et al.* (2003)	*	*	*	*	*	*	*	*	8
23	Suganuma *et al.* (2002)	*	*	*	*	*	*	*	*	8
24	Marconi *et al.* (2002)	*	*	*	*	*	*	*	*	8
25	Takuma *et al.* (2002)	*	*	*	*	*	*	*	*	8
26	Canis *et al.* (2001)	*	*	*	*	*	*	*	*	8
27	Tinkanen and Kujansuu (2000)	*	*	*	*	*	*	*	*	8
28	Ho *et al.* (2002)	*	*	*	*	*	*	*	*	8
29	Yanushpolsky *et al.* (1998)	*	*	*	*	*	*	*	*	8
30	Nargund *et al.* (1996)	*	*	*	*	*	*	*	*	8

*Indicates that the feature is present; x, that the feature is absent. But for comparability by design this checklist awards maximum of two stars (**), one (*) or none if the feature is completely absent.

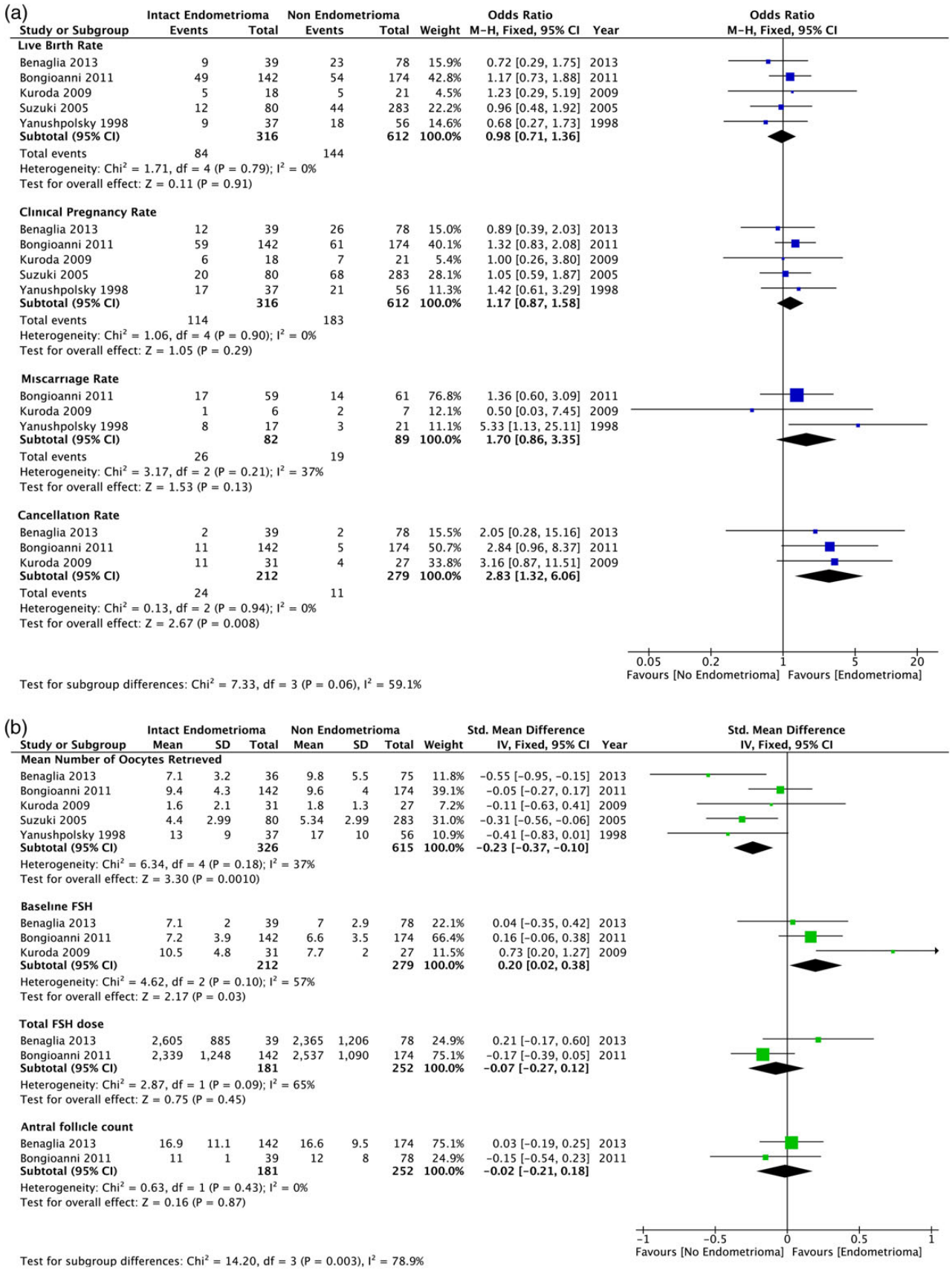

Figure 3 (**a**) Forest plot of LBR, CPR, MR and CR for endometrioma versus no endometrioma. (**b**) Forest plot of MNOR, Baseline FSH, Total FSH, AFC for endometrioma versus no endometrioma.

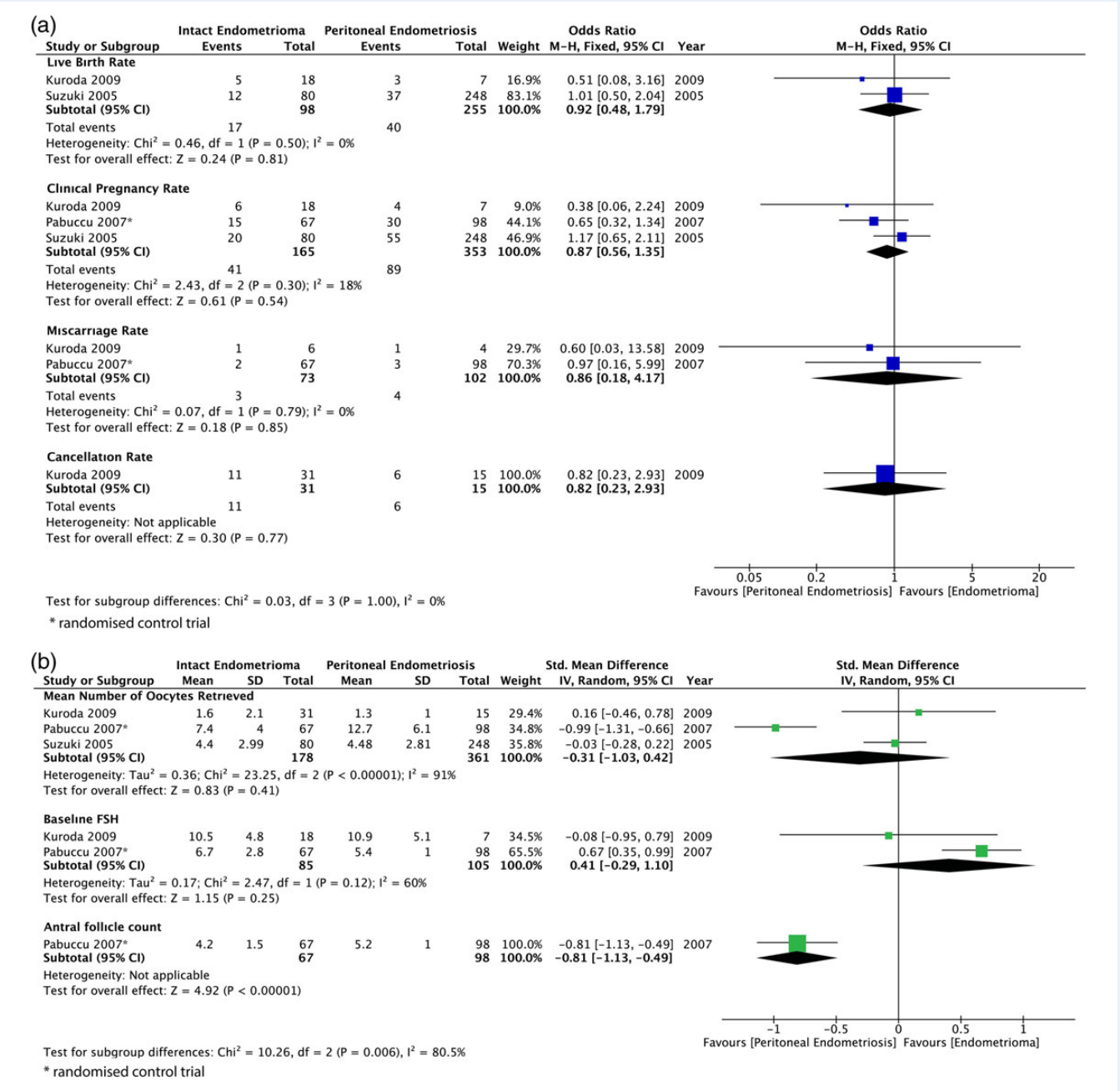

Figure 4 (**a**) Forest plot of LBR, CPR, MR and CR for women with endometrioma compared with those with peritoneal endometriosis. (**b**) Forest plot of MNOR, Baseline FSH and AFC for women with endometrioma compared with those with peritoneal endometriosis.

studies have found the peritoneal (Young *et al.*, 2013) and follicular environment (Oral *et al.*, 1996) of women with endometriosis to be hostile to the integrity and intrinsic functions of the oocyte (Da Broi *et al.*, 2014) and subsequent embryo development (Sanchez *et al.*, 2014). However, other studies examining the basic morphology of oocytes and embryo development in women with and without endometriosis have not found any differences in the two groups (Suzuki *et al.*, 2005; Reinblatt *et al.*, 2011; Ashrafi *et al.*, 2014; Filippi *et al.*, 2014). There were no embryo development data that we could utilize in this review for comparison. The question that has arisen but is yet unanswered is whether treatment, be it medical or surgical, should be established at the earliest opportunity to reduce the adverse impact of the disease on the ovary. Given that the diagnosis of endometriosis is often delayed (Ballard *et al.*, 2010; Hudelist *et al.*, 2012; Nnoaham *et al.*, 2012), there is a clear need for more effective non-invasive diagnostic clinical tools, and innovative fertility preserving treatments for this condition.

There is no doubt, as revealed by this study and studies on ovarian reserve markers by others, that surgery on endometrioma has a detrimental impact on ovarian reserve (Raffi *et al.*, 2012; Somigliana *et al.*, 2012; Muzii *et al.*, 2014). Arguably, the most reliable data where

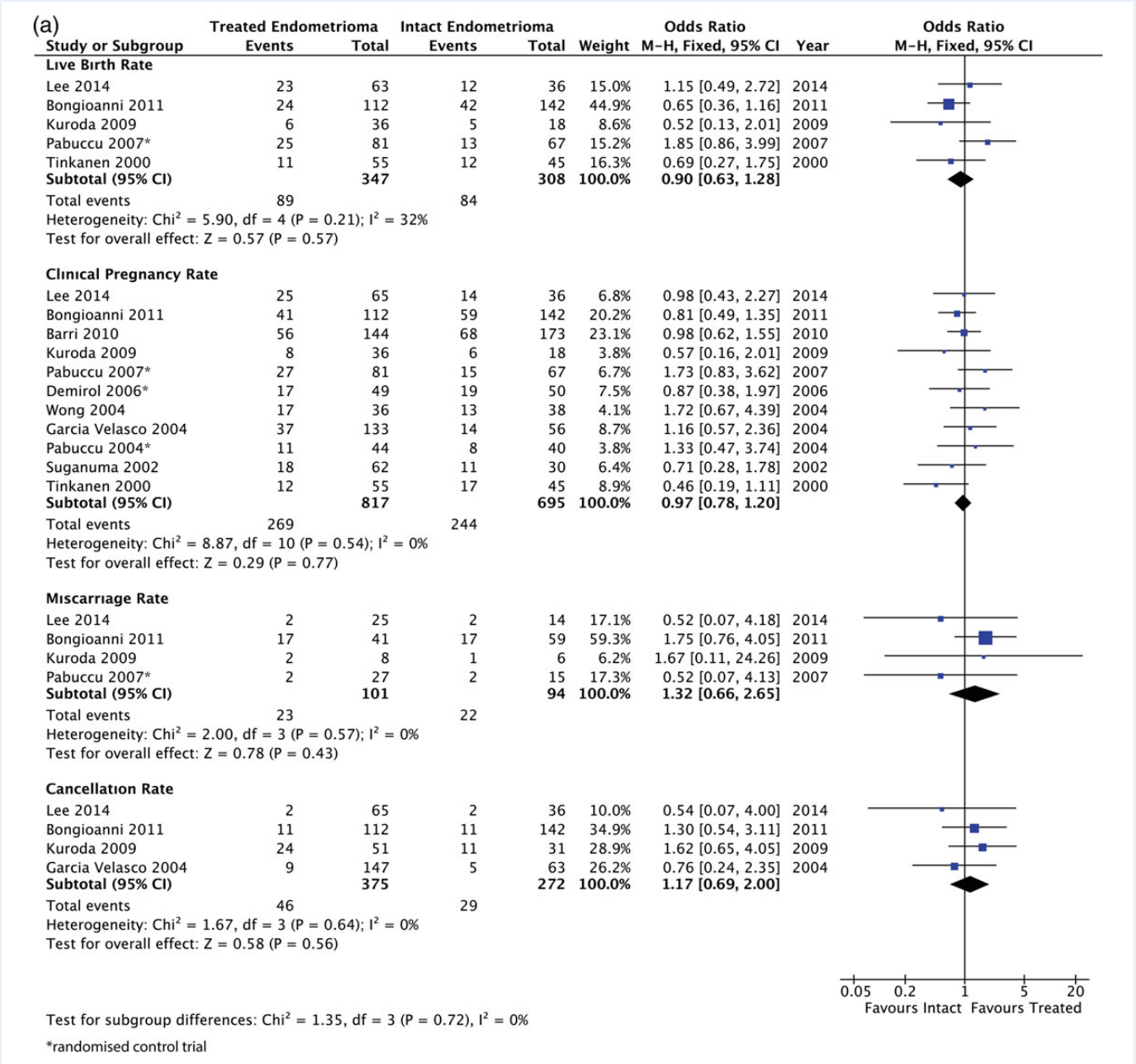

Figure 5 (**a**) Forest plot of LBR, CPR, MR and CR for women with treated endometrioma versus intact endometrioma. (**b**) Forest plot of MNOR, Baseline FSH, Total FSH and AFC for women with treated endometrioma versus intact endometrioma.

conclusions can be drawn would be those relating specifically to women with bilateral endometriomas; however, it is not possible to extrapolate such data from the current available published studies. The physiological functional compensation of one ovary in the presence of a compromised contralateral ovary, coupled with the use of stronger gonadotrophin ovarian stimulation, as shown by the higher dose of FSH required for ovarian stimulation in women who had surgery prior to their IVF/ICSI, may well account for the observation that surgery did not have any apparent impact on the LBR. However, such compensatory mechanisms may not be present in those already with a lower ovarian reserve, where an even lower than usual cumulative LBR may be pre-empted given the additive impact of lower oocyte yield in these patients and the presumptive effect on reducing the number of embryos potentially available for frozen embryo transfers. Hence, the presence of endometrioma would be a justifiable indication for the assessment of ovarian reserve prior to surgery even in the younger patients. It is hence important to consider individualizing the care of women with endometrioma prior to IVF/ICSI, adopting a more conservative approach in those who are asymptomatic, are older or have established low ovarian reserve. The advantages of pituitary down-regulation prior to IVF/ICSI may in this case be helpful (Sallam *et al.*, 2006).

Our study has highlighted the lack of clinical studies examining the complications associated with the surgical treatment of endometrioma (Dunselman *et al.*, 2014) and the complication rate during the course

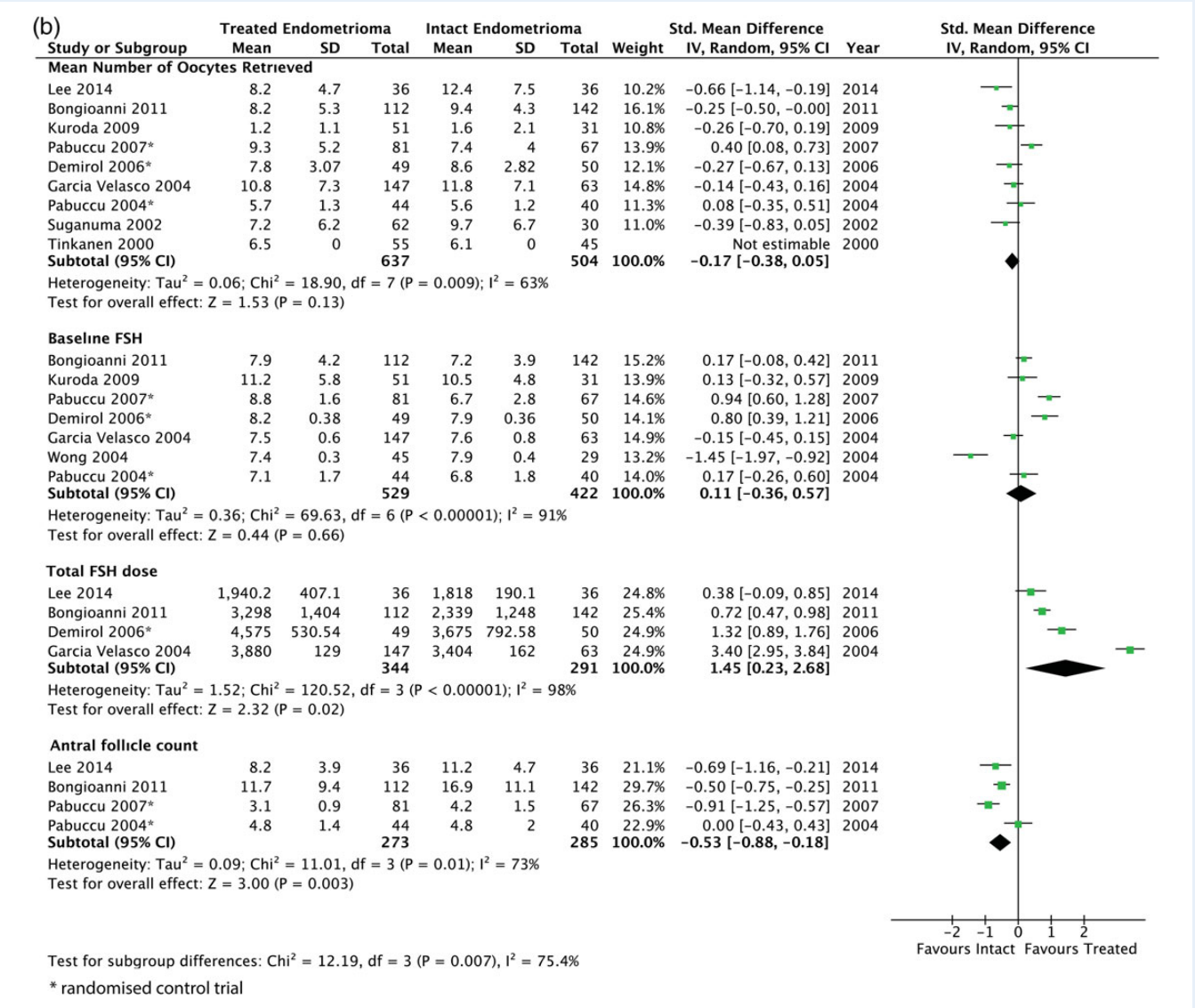

Figure 5 Continued

of the IVF treatment and ovum pickup such as pain, infection or fever. The exact reasons for the high IVF cancellation rate in women with endometrioma compared with those without the disease as found in this study are yet to be determined and could be attributed by chance. However, we wish to highlight the paucity of the data available for analysis and recommended that future studies include outcome measures, which examine adverse events including cancellation rates as such events forms crucial aspects of our patients' IVF/ICSI journey, and such information will help in the counselling process.

Due to the heterogeneity of data, we are unable to evaluate the reproductive outcomes pertaining to the size of the endometrioma. The endometrioma size and the patients' symptoms in addition to the accessibility of the ovaries for oocyte retrieval are also logical reasons to justify the consideration for their removal prior to IVF/ICSI. The latter recommendation is in line with the recent ESHRE guidance on the management of the condition (Dunselman *et al.*, 2014).

As with many other meta-analyses, our study may be confounded by the high clinical heterogeneity of the included studies, as inevitably, studies brought together in a systematic review will differ. The majority, with the exception of three studies, were all not randomized controlled trials. Some of the comparisons were only based on non-randomized studies and therefore will limit the robustness of the findings. Of relevance however, whilst the Newcastle–Ottawa Scoring assessment provided a means to assess non-randomized studies, the scoring system itself is not without its drawbacks and criticisms (Stang, 2010). Additionally, the primary outcome of the comparison between women with treated versus intact endometriomas before IVF/ICSI was based on only 5 of the 33 considered studies, and only one was an RCT. We note that differences identified from analysis of too few studies can be due to chance and also are subjected to confounders such as age and body mass index. Overall, the conclusions drawn from this review represents a current collation of best evidence.

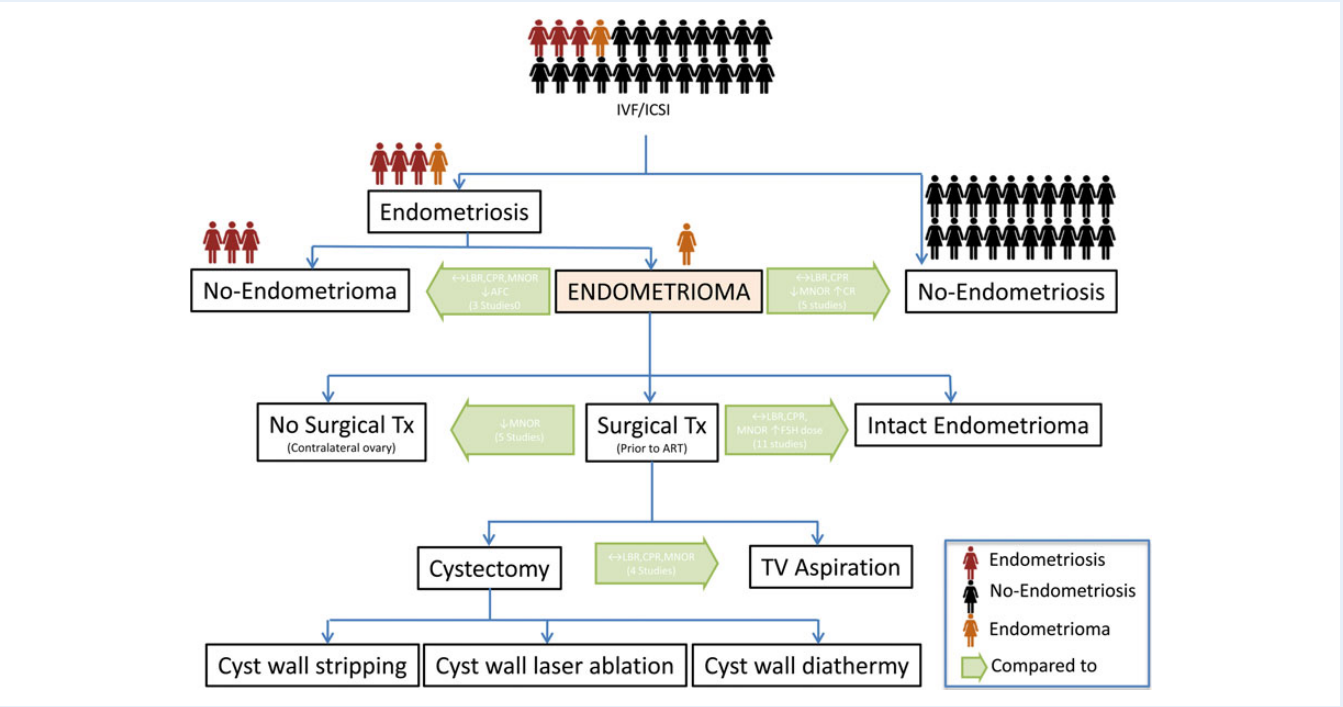

Figure 6 Flow chart on the summary of results for each comparison.

Conclusion

Compared with women without the disease, women with endometrioma have a similar LBR, CPR and MR although they have a lower mean number of oocyte retrieved, require higher FSH dosage for ovarian stimulation and have a lower AFC, suggesting that their ovarian reserve is diminished prior to IVF/ICSI. Women with endometrioma should be counselled regarding their increased risk of cycle cancellation. Whilst surgery did not seem to influence the LBR, surgical treatment of endometrioma prior to IVF/ICSI could exert a further detrimental impact on ovarian reserve. There is therefore not one dogmatic recommendation as to whether women with endometrioma should or should not have surgical intervention prior to IVF/ICSI, but based on current evidence, consideration should be given to individualize the care of these patients.

Authors' roles

Y.C. conceived and designed the study, performed the analysis, and drafted and revised the manuscript. M.H. developed the search strategy for the identification of articles, identified the articles, acquired and analysed the data, and drafted the manuscript. G.D. and T.C.L. revised the manuscript. All authors approved the final version of the manuscript.

Funding

This review was funded by the Ministry of Education Malaysia and Complete Fertility Centre, Southampton.

Conflict of interest

None declared.

References

Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reprod Biol Endocrinol* 2012;**10**:49.

Almog B, Shehata F, Sheizaf B, Tan SL, Tulandi T. Effects of ovarian endometrioma on the number of oocytes retrieved for in vitro fertilization. *Fertil Steril* 2011;**95**:525–527.

Ashrafi M, Fakheri T, Kiani K, Sadeghi M, Akhoond MR. Impact of the endometrioma on ovarian response and pregnancy rate in in vitro fertilization cycles. *Int J Fertil Steril* 2014;**8**:29–34.

Ballard K, Lane H, Hudelist G, Banerjee S, Wright J. Can specific pain symptoms help in the diagnosis of endometriosis? A cohort study of women with chronic pelvic pain. *Fertil Steril* 2010;**94**:20–27.

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;**77**:1148–1155.

Barri PN, Coroleu B, Tur R, Barri-Soldevila PN, Rodriguez I. Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach. *Reprod Biomed Online* 2010;**21**:179–185.

Benaglia L, Somigliana E, Iemmello R, Colpi E, Nicolosi AE, Ragni G. Endometrioma and oocyte retrieval-induced pelvic abscess: a clinical concern or an exceptional complication? *Fertil Steril* 2008;**89**:1263–1266.

Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010;CD008571.

Bongioanni F, Revelli A, Gennarelli G, Guidetti D, Delle Piane LD, Holte J. Ovarian endometriomas and IVF: a retrospective case-control study. *Reprod Biol Endocrinol* 2011;**9**:81.

Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril* 2012;**98**:511–519.

Canis M, Pouly JL, Tamburro S, Mage G, Wattiez A, Bruhat MA. Ovarian response during IVF-embryo transfer cycles after laparoscopic ovarian cystectomy for endometriotic cysts of >3 cm in diameter. *Human Reprod* 2001;**16**:2583–2586.

Da Broi MG, Malvezzi H, Paz CC, Ferriani RA, Navarro PA. Follicular fluid from infertile women with mild endometriosis may compromise the meiotic spindles of bovine metaphase II oocytes. *Human Reprod* 2014;**29**:315–323.

Demirol A, Guven S, Baykal C, Gurgan T. Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study. *Reprod Biomed Online* 2006; **12**:639–643.

Diaz I, Navarro J, Blasco L, Simon C, Pellicer A, Remohi J. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. *Fertil Steril* 2000;**74**:31–34.

Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A *et al.* ESHRE guideline: management of women with endometriosis. *Human Reprod* 2014;**29**:400–412.

Duru NK, Dede M, Acikel CH, Keskin U, Fidan U, Baser I. Outcome of in vitro fertilization and ovarian response after endometrioma stripping at laparoscopy and laparotomy. *J Reprod Med* 2007;**52**:805–809.

Esinler I, Bozdag G, Aybar F, Bayar U, Yarali H. Outcome of in vitro fertilization/ intracytoplasmic sperm injection after laparoscopic cystectomy for endometriomas. *Fertil Steril* 2006;**85**:1730–1735.

Farquhar C. Endometriosis. *BMJ* 2007;**334**:249–253.

Filippi F, Benaglia L, Paffoni A, Restelli L, Vercellini P, Somigliana E, Fedele L. Ovarian endometriomas and oocyte quality: insights from in vitro fertilization cycles. *Fertil Steril* 2014;**101**:988–993 e981.

Garcia-Velasco JA, Mahutte NG, Corona J, Zuniga V, Giles J, Arici A, Pellicer A. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 2004;**81**:1194–1197.

Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. *Reproduction* 2002;**123**:217–226.

Gelbaya TA, Nardo LG. Evidence-based management of endometrioma. *Reprod Biomed Online* 2011;**23**:15–24.

Giudice LC, Kao LC. Endometriosis. *Lancet* 2004;**364**:1789–1799.

Gupta S, Agarwal A, Agarwal R, Loret de Mola JR. Impact of ovarian endometrioma on assisted reproduction outcomes. *Reprod Biomed Online* 2006;**13**:349–360.

Hamdan M, Omar SZ, Dunselman G, Cheong Y. Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis. *Obstet Gynecol* 2015;**125**:79–88.

Harb HM, Gallos ID, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. *BJOG* 2013; **120**:1308–1320.

Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: http://handbook.cochrane.org.

Ho HY, Lee RK, Hwu YM, Lin MH, Su JT, Tsai YC. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. *J Assist Reprod Genet* 2002;**19**:507–511.

Holoch KJ, Lessey BA. Endometriosis and infertility. *Clin Obstet Gynecol* 2010; **53**:429–438.

Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, Tammaa A, Salzer H. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Human Reprod* 2012;**27**:3412–3416.

Iwabe T, Harada T, Terakawa N. Role of cytokines in endometriosis-associated infertility. *Gynecol Obstet Invest* 2002;**53**(Suppl 1):19–25.

Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol* 1986;**67**:335–338.

Ji J, Liu Y, Tong XH, Luo L, Ma J, Chen Z. The optimum number of oocytes in IVF treatment: an analysis of 2455 cycles in China. *Hum Reprod* 2013;**28**:2728–2734.

Kuroda K, Kitade M, Kikuchi I, Kumakiri J, Matsuoka S, Kuroda M, Takeda S. The impact of endometriosis, endometrioma and ovarian cystectomy on assisted reproductive technology. *Reprod Med Biol* 2009;**8**:113–118.

Lee KH, Kim CH, Lee YJ, Kim SH, Chae HD, Kang BM. Surgical resection or aspiration with ethanol sclerotherapy of endometrioma before in vitro fertilization in infertile women with endometrioma. *Obstet Gynecol Sci* 2014;**57**:297–303.

Loo TC, Lin MY, Chen SH, Chung MT, Tang HH, Lin LY, Tsai YC. Endometrioma undergoing laparoscopic ovarian cystectomy: its influence on the outcome of in vitro fertilization and embryo transfer (IVF-ET). *J Assist Reprod Genet* 2005;**22**:329–333.

Marconi G, Vilela M, Quintana R, Sueldo C. Laparoscopic ovarian cystectomy of endometriomas does not affect the ovarian response to gonadotropin stimulation. *Fertil Steril* 2002;**78**:876–878.

Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril* 2007;**88**:1568–1572.

Matsuzaki S, Schubert B. Oxidative stress status in normal ovarian cortex surrounding ovarian endometriosis. *Fertil Steril* 2010;**93**:2431–2432.

Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. *Human Reprod* 2014; **29**:2190–2198.

Nakagawa K, Ohgi S, Kojima R, Sugawara K, Ito M, Horikawa T, Irahara M, Saito H. Impact of laparoscopic cystectomy on fecundity of infertility patients with ovarian endometrioma. *J Obstet Gynaecol Res* 2007;**33**:671–676.

Nargund G, Cheng WC, Parsons J. The impact of ovarian cystectomy on ovarian response to stimulation during in-vitro fertilization cycles. *Human Reprod* 1996; **11**:81–83.

Nnoaham KE, Hummelshoj L, Kennedy SH, Jenkinson C, Zondervan KT, World Endometriosis Research Foundation Women's Health Symptom Survey C. Developing symptom-based predictive models of endometriosis as a clinical screening tool: results from a multicenter study. *Fertil Steril* 2012;**98**:692–701 e695.

Oral E, Arici A, Olive DL, Huszar G. Peritoneal fluid from women with moderate or severe endometriosis inhibits sperm motility: the role of seminal fluid components. *Fertil Steril* 1996;**66**:787–792.

Pabuccu R, Onalan G, Goktolga U, Kucuk T, Orhon E, Ceyhan T. Aspiration of ovarian endometriomas before intracytoplasmic sperm injection. *Fertil Steril* 2004; **82**:705–711.

Pabuccu R, Onalan G, Kaya C. GnRH agonist and antagonist protocols for stage I-II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. *Fertil Steril* 2007;**88**:832–839.

Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. *J Clin Endocrinol Metabol* 2012;**97**:3146–3154.

Ragni G, Somigliana E, Benedetti F, Paffoni A, Vegetti W, Restelli L, Crosignani PG. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: a quantitative rather than a qualitative injury. *Am J Obstet Gynecol* 2005;**193**:1908–1914.

Redwine DB. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999;**72**:310–315.

Reinblatt SL, Ishai L, Shehata F, Son WY, Tulandi T, Almog B. Effects of ovarian endometrioma on embryo quality. *Fertil Steril* 2011;**95**:2700–2702.

Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006;CD004635.

Sanchez AM, Vigano P, Somigliana E, Panina-Bordignon P, Vercellini P, Candiani M. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage to the ovary. *Hum Reprod Update* 2014;**20**:217–230.

Somigliana E, Vercellini P, Vigano P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? *Hum Reprod Update* 2006;**12**:57–64.

Somigliana E, Arnoldi M, Benaglia L, Iemmello R, Nicolosi AE, Ragni G. IVF-ICSI outcome in women operated on for bilateral endometriomas. *Human Reprod* 2008;**23**:1526–1530.

Somigliana E, Berlanda N, Benaglia L, Vigano P, Vercellini P, Fedele L. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimullerian hormone level modifications. *Fertil Steril* 2012;**98**:1531–1538.

Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**:603–605.

Suganuma N, Wakahara Y, Ishida D, Asano M, Kitagawa T, Katsumata Y, Moriwaki T, Furuhashi M. Pretreatment for ovarian endometrial cyst before in vitro fertilization. *Gynecol Obstet Invest* 2002;**54**(Suppl 1):36–40. discussion 41–32.

Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Human Reprod* 2011;**26**:1768–1774.

Suzuki T, Izumi S, Matsubayashi H, Awaji H, Yoshikata K, Makino T. Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization. *Fertil Steril* 2005;**83**:908–913.

Takashima A, Takeshita N, Otaka K, Kinoshita T. Effects of bipolar electrocoagulation versus suture after laparoscopic excision of ovarian endometrioma on the ovarian reserve and outcome of in vitro fertilization. *J Obstet Gynaecol Res* 2013; **39**:1246–1252.

Takebayashi A, Shimizu Y, Takahashi A, Yamanaka A, Takashima A, Kimura F, Kita N, Takahashi K, Murakami T. Comparison of the outcome of in vitro fertilization after laparoscopic laser ablation surgery versus laparoscopic cystectomy for endometrioma. *Gynecol Minim Invasive Ther* 2013;**2**:27–29.

Takuma N, Sengoku K, Pan B, Wada K, Yamauchi T, Miyamoto T, Ohsumi D, Ishikawa M. Laparoscopic treatment of endometrioma-associated infertility and pregnancy outcome. *Gynecol Obstet Invest* 2002;**54**(Suppl 1):30–34. discussion 34–35.

Tinkanen H, Kujansuu E. In vitro fertilization in patients with ovarian endometriomas. *Acta Obstet Gynecol Scand* 2000;**79**:119–122.

Tsoumpou I, Kyrgiou M, Gelbaya TA, Nardo LG. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. *Fertil Steril* 2009;**92**:75–87.

Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod* 2009; **24**:254–269.

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2010. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wong BC, Gillman NC, Oehninger S, Gibbons WE, Stadtmauer LA. Results of in vitro fertilization in patients with endometriomas: is surgical removal beneficial? *Am J Obstet Gynecol* 2004;**191**:597–606; discussion 606–597.

Wu MH, Tsai SJ, Pan HA, Hsiao KY, Chang FM. Three-dimensional power Doppler imaging of ovarian stromal blood flow in women with endometriosis undergoing in vitro fertilization. *Ultrasound Obstet Gynecol* 2003;**21**:480–485.

Wyns C, Donnez J. Vaporisation laser des endométriomes ovariens : impact sur la réponse aux gonadotrophines. *Gynécologie Obstétrique Fertilité* 2003;**31**:337–342.

Yamamoto S, Umeki M, Maeda T, Yamaguchi M, Hamano T. Poor pregnancy outcome following assisted reproductive technology among women operated on for bilateral endometriomas. *Reproduct Med Biol* 2009;**9**:43–49.

Yanushpolsky EH, Best CL, Jackson KV, Clarke RN, Barbieri RL, Hornstein MD. Effects of endometriomas on ooccyte quality, embryo quality, and pregnancy rates in in vitro fertilization cycles: a prospective, case-controlled study. *J Assist Reprod Genet* 1998; **15**:193–197.

Yazbeck C, Madelenat P, Sifer C, Hazout A, Poncelet C. Ovarian endometriomas: effect of laparoscopic cystectomy on ovarian response in IVF-ET cycles. *Gynécologie, Obstétrique Fertilité* 2006;**34**:808–812.

Young VJ, Brown JK, Saunders PT, Horne AW. The role of the peritoneum in the pathogenesis of endometriosis. *Hum Reprod Update* 2013;**19**:558–569.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S, International Committee for Monitoring Assisted Reproductive T, World Health O. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod* 2009;**24**:2683–2687.