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Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: a systematic review and meta-analysis

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BACKGROUND: Ovarian endometrioma is a frequent manifestation of endometriosis in women of reproductive age. Several issues related to its space occupying effects, local reactions and surgical removal continue to be actively debated today. The impact of ovarian endometrioma per se on ovarian reserve is still controversial and the effect of ovarian surgery is still actively discussed. Furthermore, the

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optimal biomarker of ovarian reserve estimation in women with ovarian endometrioma is still under examination. Additionally, there is no consistent agreement on the effect of endometrioma bilaterality on ovarian reserve.

OBJECTIVE AND RATIONALE: The objective of this systematic review and meta-analysis was to study the impact of unilateral versus bilateral ovarian endometrioma on ovarian reserve biomarkers before and after endometrioma cystectomy.

SEARCH METHODS: We performed an extensive electronic database search employing PubMed, EBSCO, Web of Science, ClinicalTrials.gov and the Cochrane Library, to identify published research articles published between January 2000 and October 2018. Search terms included endometriotic cyst OR endometrioma OR endometriomata, cystectomy OR resection OR stripping OR removal OR excision and infertility OR subfertility. Only prospective controlled studies that compared the impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve tests in the same setting were included. Studies which included cases with PCOS, ovarian failure, early menopause, oral contraception treatment, or prior chemotherapy and/or radiotherapy or ovarian surgery, were excluded from evaluation. We used the Newcastle–Ottawa Scale for assessing the quality of studies found eligible for meta-analysis. We registered the systematic review on PROSPERO and its number is CRD42018117170.

OUTCOMES: Twelve studies were eligible for meta-analysis including collectively 783 women: 489 and 294 in the unilateral and bilateral groups, respectively. The included studies had a low risk of bias. The pre-operative weighted mean difference (WMD) showed that serum AMH levels did not differ significantly between the groups. Conversely, AMH levels were significantly ($P < 0.05$) lower in bilateral groups than in unilateral groups at the early, intermediate and late post-operative periods, corresponding WMDs of 0.78 ng/ml (95% CI: 0.41–1.15), 0.59 ng/ml (95% CI: 0.14–1.04) and 1.08 ng/ml (95% CI: 0.63 to 1.52), respectively. Heterogeneity among eligible studies reporting on before the operation and at the early and intermediate post-operative periods was high. Pre-operative and post-operative AFC values were not significantly different between the groups. The heterogeneity among the studies reporting on AFC was high. Analysis of each of the unilateral and bilateral groups separately showed a significant and sustained serum AMH drop by 39.5% and 57.0%, respectively from baseline to after the operation.

WIDER IMPLICATIONS: Our results challenge the concept that endometrioma per se adversely affects ovarian reserve, whereas endometrioma cystectomy, especially as bilateral operation, has a deleterious and sustained effect on ovarian reserve. AMH seems to be a more appropriate biomarker of ovarian reserve than AFC in cases with endometrioma. Since low AMH implies a shorter reproductive lifespan, excision of endometrioma should be cautiously considered, especially in bilateral cases.

Key words: endometrioma / cystectomy / bilateral / ovarian reserve / anti-Müllerian hormone / antral follicle count

Introduction

Endometriotic ovarian cyst or endometrioma is the most pathognomonic feature of endometriosis. It is considered the most commonly diagnosed form of endometriosis, most likely related to the improvement and accuracy of contemporary ultrasound technology. The presence of endometrioma has been reported to affect 17–44% of women with endometriosis (Busacca and Vignali, 2003) and bilateral ovarian endometriomata have been shown to complicate about 19–28% of cases (Vercellini *et al.*, 1998; Busacca *et al.*, 2006).

While the topic of ovarian endometrioma is widely discussed in the literature, several issues related to its space occupying effects, local reactions and surgical removal remain actively debated today. The impact of ovarian endometrioma per se on ovarian reserve is still controversial (Streuli *et al.*, 2012; Uncu *et al.*, 2013; Santulli *et al.*, 2016). In addition, the impact of ovarian surgery on ovarian reserve is actively discussed (Dunselman *et al.*, 2014; RCOG, 2018). The mechanism of ovarian reserve damage before or following surgery is still being investigated and whether this damage is reversible after surgery is still controversial (de Ziegler *et al.*, 2010). Furthermore, the optimal ovarian reserve test (ORT) to apply to quantify damage to ovarian reserve in women with ovarian endometrioma is still under examination (Raffi *et al.*, 2012; Muzii *et al.*, 2014).

Additionally, there is no consistent agreement on the effect of ovarian endometriotic cyst bilaterality on ovarian reserve integrity. While some investigations have indicated that bilateral ovarian endometrioma removal is implicated in more ovarian reserve damage and postsurgical ovarian failure development as compared to a unilateral procedure (Busacca *et al.*, 2006; Coccia *et al.*, 2011), others have not found a difference (Ercan *et al.*, 2010; Celik *et al.*, 2012). Studying the impact of unilateral versus bilateral ovarian endometrioma on ovarian reserve before and after their surgical removal has the potential to shed more light on all of these open questions and may contribute to the resolution of the ongoing debate. It may also help practitioners understand the pathophysiology of the disease and may contribute to the management of women of reproductive age.

Furthermore, since endometriosis is a chronic and progressive disease, it is likely to encounter cases with endometriomata, as the disease advances with reproductive age (Haas *et al.*, 2012). With the continuing postponement of reproduction in modern societies and the progressively increasing demand for ART (Schmidt *et al.*, 2012; Kocourkova *et al.*, 2014), it is to be expected that more cases with advanced endometriosis and endometriomatic cysts will be diagnosed, which may constitute a clinical dilemma when such patients present for care.

The aim of the present systematic review and meta-analysis was to examine the impact of unilateral versus bilateral ovarian endometrioma on ovarian reserve biomarkers before and after ovarian endometriotic cystectomy. Specifically, only prospective studies which compared cases with unilateral and bilateral endometriomata in the same setting and examined serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) values were included.

Methods

Search strategy

We performed an extensive electronic database search employing PubMed, EBSCO, Web of Science, ClinicalTrials.gov and the Cochrane Library to identify research articles, published between January 2000 and October 2018, which examined the effect of unilateral versus bilateral ovarian endometriotic cystectomy on ORTs in reproductive age women. The results were restricted to the English language. Three groups of search terms were used as free text and MeSH expressions: endometriotic cyst OR endometrioma OR endometriomata; cystectomy OR resection OR stripping OR removal OR excision; and infertility OR subfertility. We also combined these terms with AND to complete the search.

We employed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in our analysis (Moher *et al.*, 2009). All reports relevant to the research question were retrieved and their reference lists were manually reviewed to identify further studies. Two authors (N.S. and J.S.Y.) independently performed the search (twice) and reviewed all publications found relevant to this study, and both selected the studies to be included in the systematic review and meta-analysis. We resolved any disagreements about inclusions or analyses by consensus or mediation by a third reviewer (I.B.).

Study selection and quality assessment

We selected only prospective controlled studies that compared the impact of unilateral versus bilateral ovarian endometriotic cystectomy on ORTs in the same setting. Studies that employed either serum AMH level or AFC values were eligible. Only studies that presented their serum AMH in ng/mL or AFC data as mean $\pm$ SD, before and after surgery in the unilateral and bilateral groups separately were included. Retrospective studies were excluded from analysis. Furthermore, studies that examined the impact of unilateral versus bilateral endometriotic cystectomy following chemotherapy and/or radiotherapy were omitted to eliminate a gonado-toxic effect on the ovarian reserve. Similarly, reports that included women who had a history of previous ovarian surgery, such as ovarian cystectomy or unilateral oophorectomy, were excluded. Studies that included only women with polycystic ovary syndrome were omitted, as ORT results may differ in these women. Papers that included cases with a history of ovarian failure or postmenopausal FSH level were also excluded. Studies that included women taking oral contraception at least three months before recruitment were omitted to eliminate a possible effect on ORTs. Studies presented exclusively as abstracts in scientific meetings were also excluded.

We used the Newcastle–Ottawa Scale for assessing the quality of the prospective controlled studies eligible for quantitative analysis based on the recommendation of the Cochrane Collaboration (Wells *et al.*, 2010; Higgins and Green, 2011). We have entered our study to the international prospective register of systematic reviews, PROSPERO and its number is CRD42018117170.

Outcome measures

We explored the impact of unilateral versus bilateral endometriotic cystectomy on ORTs, specifically AMH and AFC. Since endometrioma per se is suspected to adversely affect ovarian reserve before surgery, basal ORT results were compared between unilateral and bilateral cases. In addition, the timing of ORT evaluation following unilateral versus bilateral endometriotic cystectomy was evaluated. Early, intermediate and late postsurgical periods were allocated in accordance with the available data. In studies where more than one ORT evaluation was performed in the same post-surgical period, a mean of these values was calculated.

Moreover, factors that could have an impact on ORTs, such as the size and number of endometrioma, the revised American Society for Reproductive Medicine (rASRM) classification, surgical technique and haemostasis method were examined.

Data extraction

We generated descriptive tables for population and study characteristics for all eligible studies, to prepare for quantitative analysis. For each eligible study, we recorded the first author, publication year, country, study design, sample size, mean age of women in each of the unilateral and bilateral ovarian endometriotic cystectomy groups (Table I). The indication for cystectomy, size of endometrioma, number of endometriomata (whether mono- or multi-cystic), revised ASRM stage of disease, type of surgery (laparoscopy or laparotomy), technique of surgery (endometrioma stripping or other) and method of haemostasis (bipolar coagulation or suture) were also recorded (Table II). We also recorded the ovarian reserve tests employed (AMH testing method and AFC), the timing of their performance, and their results (Tables III and IV).

Since several AMH assay kits were available during the period reviewed in this study, the method of evaluation was recorded. When data were missing in the studies included for analysis, we attempted to contact the authors.

Data analysis and statistical methods

Continuous measures were extracted as mean and standard deviation (SD) and meta-analysed to produce a weighted mean difference (WMD). Analysis was performed with the open source software 'OpenMeta [Analyst]' (www.cebm.brown.edu/openmeta).

We assessed statistical heterogeneity by Cochran's *Q*, and inconsistency was estimated by the I^2 statistic (Higgins *et al.*, 2003). An X^2 statistic that was larger than its degree of freedom or an I^2 with a value greater than 50% provided evidence for substantial heterogeneity between studies. Anticipating substantial heterogeneity, we used random-effects models.

Results

Search results and excluded studies

The search flow results of our systematic review are described in Fig. 1. Of the 28 full-text articles assessed for eligibility, 16 were excluded from the quantitative analysis: four employed AMH medians and quartiles to present their data (Iwase *et al.*, 2010; Sugita *et al.*, 2013; Nieweglowska *et al.*, 2015; Vignali *et al.*, 2015) and two presented their data as rate of decline without AMH mean levels before and after surgery (Chen *et al.*, 2014; Goodman *et al.*, 2016). In all six of these studies, data on the absolute post-operative AMH level were missing, making a numerical comparison impossible. In addition, four studies did not present data on AMH level in the unilateral and the bilateral groups separately (Biacchiardi *et al.*, 2011; Song *et al.*, 2015; Candiani *et al.*, 2018; Choi *et al.*, 2018). Two studies did not provide data concerning the number of patients in each group of laterality (Salihoğlu *et al.*, 2016; Henes *et al.*, 2018). One report included only data regarding unilateral endometrioma resection (Hwu

Table I Studies eligible for meta-analysis focusing on the impact of unilateral vs. bilateral endometrioma removal on ovarian reserve tests.

Author	Publication site	Country	Design	Number of patients			Age ± SD (years)			Ovarian reserve tests	AMH assay
				Study group	Unilateral	Bilateral	Study group	Unilateral	Bilateral		
Ercan et al. (2010)	Gynecol Endocrinol	Turkey	Prospective	47	33	14	28.0 ± 4.47	ND	ND	AMH	DSL
Hirokawa et al. (2011)	Hum Reprod	Japan	Prospective	38	20	18	33.8 ± 4.7	34.0 ± 3.9	33.6 ± 5.4	AMH	IOT
Celik et al. (2012)	Fertil Steril	Turkey	Prospective	65	46	19	28.4 ± 5.7	ND	ND	AMH, AFC	DSL
Uncu et al. (2013)	Hum Reprod	Turkey	Prospective	30	15	15	29.0 ± 5.4	ND	ND	AMH, AFC	DSL
Alborzi et al. (2014)	Fertil Steril	Iran	Prospective	193	121	72	28.4 ± 5.3	ND	ND	AMH, AFC	DSL
Saito et al. (2014)	JMIG	Japan	Prospective	68	40	28	34.6 ± 8.6	33.7 ± 6.0	35.9 ± 6.2	AMH	IOT
Tanprasertkul et al. (2014)	Minim *Invasive* Surg	Thailand	Prospective	39	33	6	32.7 ± 7.0	ND	ND	AMH	DSL
Ding et al. (2015)	JMIG	China	Prospective	50	29	21	32.3 ± 4.7	32.0 ± 4.6	32.7 ± 4.9	AMH, AFC	DSL
Shao et al. (2016)	Arch Gynecol Obstet	China	Prospective	68	36	32	29.1 (21–35)	ND	ND	AMH	DSL
Kashi et al. (2017)	Int J Gynecol Obstet	Iran	Prospective	70	45	25	29.7 ± 5.6	ND	ND	AMH	DSL
Sweed et al. (2018)	J Minim Invasive Gynecol	Egypt	Prospective	61	34	27	27.1 ± 4.6	ND	ND	AMH, AFC	Glory Science
Kovačević et al. (2018)	Fertil Steril	Serbia	Prospective	54	37	17	30.3 ± 4.5	ND	ND	AMH	DSL

ND, not disclosed; AMH, anti-Müllerian hormone; DSL, Diagnostic Systems Laboratories; IOT, Immunotech.

et al., 2011). One publication included AMH data concerning endometriotic and non-endometriotic ovarian cystectomy combined (Chang et al., 2010); one did not report on AMH values after endometrioma resection (Streuli et al., 2012); and one included patients already involved in a previous publication (Saito et al., 2018).

The authors of nine studies were contacted to complete missing data. The authors of one study replied (Celik et al., 2012), providing further information concerning unpublished data and this information was used in the analysis.

Included studies

Twelve studies were found to be eligible for quantitative synthesis (Ercan et al., 2010; Hirokawa et al., 2011; Celik et al., 2012; Uncu et al., 2013; Alborzi et al., 2014; Saito et al., 2014; Tanprasertkul et al., 2014; Ding et al., 2015; Shao et al., 2016; Kashi et al., 2017; Kovačević et al., 2018; Sweed et al., 2018). All eligible studies focused on the impact of unilateral versus bilateral removal of ovarian endometrioma on biomarkers of ovarian reserve before and after surgery. All studies followed a prospective design.

Collectively, the 12 eligible studies included 783 women: 489 and 294 women in the unilateral and bilateral groups, respectively. The weighted mean age (± weighted SD) of all women in both groups of the meta-analysis was 29.9 ± 5.5 years.

Surgical indications, endometriotic cyst features, surgical technique and method of haemostatsis of these studies are summarised in Tables I and II. Selected information regarding the size of treated endometrioma was available in all qualified studies, however the presentation of these data varied (Table II).

Serum AMH and AFC data, in eligible studies, before and after surgery and their length of follow-up are shown in Tables III and IV. Post-operative serum AMH levels were merged in accordance with the available data to comprise three time strata: 1 week to 1 month, 6 weeks to 6 months and 9 to 12 months following surgery, respectively.

Risk of bias assessment

Quality assessment of the studies that qualified for meta-analysis, employing the Newcastle–Ottawa scale, is provided in Table V. Overall, quality assessment of these studies showed a low risk of

Table II Indication for surgery, endometrioma characteristics, surgery techniques and rASRM score in studies eligible for meta-analysis

Author	Indication for surgery	Endometrioma size (mm)		Number of endometrioma monocystic/multi-cystic (%)			LPS/LPT		rASRM score		Technique of cyst removal	Haemostasis
		Unilateral	Bilateral	Total number	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral		
Ercan *et al.* (2010)	• Pelvic pain • Infertility • Exclusion of malignancy	59.0 ± 8.2	86.0 ± 11.1	ND	ND	ND	all LPS	all LPS	ND	ND	Stripping[‡]	Bipolar
Hirokawa *et al.* (2011)	ND	61.0 ± 25.0	106.0 ± 25.0	6/32	5/15	1/17	18/2	15/3	36.7 ± 23.5	63.7 ± 26.3	Stripping	Bipolar + suture
Celik *et al.* (2012)	ND	At least 30 ≥50 (61.5%) <50 (38.5%)		ND	ND	ND	all LPS	all LPS	Stage III or IV		Stripping	Bipolar
Uncu *et al.* (2013)	• Pelvic pain • Infertility	Median 42.5 (38.6–51.7)		12/18	ND	ND	all LPS	all LPS	ND	ND	Stripping	Bipolar
Alborzi *et al.* (2014)	• Pelvic pain • Infertility	30 (91%) <30 (9%)		156/37	107/14	49/23	all LPS	all LPS	Stage III – 36% Stage IV – 62%		Cystectomy[#]	Bipolar ± suture
Saito *et al.* (2014)	ND	51.5 ± 13.6	46.5 ± 21.3	ND	ND	ND	all LPS	all LPS	40.8 ± 21.8	69.6 ± 24.2	Stripping	Bipolar
Tanprasertkul *et al.* (2014)	ND	Mean 54.6 (3–-100)		ND	ND	ND	all LPS	all LPS	Stage III – 61.5% Stage IV – 38.5%		Cystectomy	ND
Ding *et al.* (2015)	ND	61.9 ± 22.1 (maximal)	55.7 ± 20.9 (maximal)	ND	ND	ND	all LPS	all LPS	ND	ND	Stripping	Suture
Shao *et al.* (2016)	ND	At least 40		ND	ND	ND	all LPS	all LPS	ND	ND	Stripping	Suture
Kashi *et al.* (2017)	• Endometrioma >30 or • Infertility • Dysmenorrhoea • Dyspareunia • Dyschyzia	<50 13/45 ≥50 32/45	both <50 2/25 both ≥50 19/25 one <50 4/25	ND	ND	ND	all LPS	all LPS	ND	ND	Cystectomy	ND
Sweed *et al.* (2018)	• Pain • Infertility	52.0 ± 6.0		ND	ND	ND	all LPS	all LPS	ND	ND	Stripping	Bipolar
Kovačević *et al.* (2018)	• Pain • Infertility	At least 40		ND	ND	ND	all LPS	all LPS	49.7 ± 24.1		Stripping	Bipolar

ND, not disclosed; LPS, laparoscopy; LPT, laparotomy; rASRM, revised American Society of Reproductive Medicine.
[‡]Stripping—the technique of endometrioma removal in which two atraumatic grasping forceps are used to pull the cyst wall and the normal ovarian parenchyma in opposite directions, thus developing the cleavage plane. [#]Cystectomy—the technique is not defined in the article.

Table III Timing and values of AMH tests before and after surgery in studies eligible for meta-analysis.

Author	AMH assay	Timing of AMH testing and values unilateral group				Timing of AMH testing and values bilateral group			
		Baseline	After surgery			Baseline	After surgery		
			1 wk-1 mo.	6 wk-6 mo.	9–12 mo.		1 wk-1 mo.	6 wk-6 mo.	9–12 mo.
Ercan et al. (2010)	DSL	2.24 ± 1.95	1.62 ± 1.02			1.45 ± 1.05	1.35 ± 0.98		
Hirokawa et al. (2011)	IOT	4.10 ± 2.30	2.90 ± 1.60			3.60 ± 2.70	1.20 ± 1.00		
Celik et al. (2012)	DSL	1.58 ± 1.34		1.48 ± 1.25		2.18 ± 2.05		1.19 ± 1.44	
Uncu et al. (2013)	DSL	2.04 ± 1.38	2.03 ± 1.18	1.76 ± 1.18		3.58 ± 2.53	2.11 ± 1.76	1.88 ± 1.45	
Alborzi et al. (2014)	DSL	4.19 ± 3.71	1.99 ± 2.08	2.53 ± 2.82	2.18 ± 1.87	3.29 ± 3.28	1.03 ± 1.40	1.24 ± 1.48	1.19 ± 1.43
Saito et al. (2014)	IOT	3.90 ± 2.50	1.70 ± 1.70			2.50 ± 1.70	0.50 ± 0.40		
Tanprasertkul et al. (2014)	DSL	2.94 ± 2.47	1.75 ± 1.57	1.94 ± 1.66		2.01 ± 1.02	1.44 ± 0.89	0.96 ± 0.42	
Shao et al. (2016)	DSL	5.02 ± 3.05		4.43 ± 2.13	4.07 ± 2.06	4.68 ± 2.87		3.05 ± 1.99	2.26 ± 1.88
Kashi et al. (2017)	DSL	3.01 ± 2.58		2.10 ± 1.28		3.41 ± 2.83		2.27 ± 1.33	
Sweed et al. (2018)	Glory Science	4.23 ± 0.97	1.97 ± 0.93			4.32 ± 0.43	1.24 ± 1.00		
Kovačević et al. (2018)	DSL	3.31 ± 1.74		1.43 ± 1.01	1.72 ± 1.23	2.55 ± 1.87		0.98 ± 0.91	0.89 ± 0.82

DSL, Diagnostic Systems Laboratories; IOT, Immunotech.

Table IV Timing and values of AFC tests before and after surgery in studies eligible for meta-analysis.

Author	Timing of AFC testing and values unilateral group				Timing of AFC testing and values bilateral group			
	Baseline	After surgery			Baseline	After surgery		
		1 wk- 1 mo.	2–6 mo.	9–12 mo.		1 wk- 1 mo.	2–6 mo.	9–12 mo.
Uncu et al. (2013)	11.73 ± 4.56	12.00 ± 4.16	10.57 ± 2.56		7.73 ± 4.22	10.0 ± 6.35	10.20 ± 5.67	
Ding et al. (2015)	5.80 ± 1.76	5.20 ± 1.62	5.40 ± 1.36	5.60 ± 1.31	5.20 ± 2.13	4.30 ± 1.52	4.60 ± 1.32	4.80 ± 1.32

bias. Among the nine applicable stars to assess the three main categories: selection, comparability and outcomes, the eligible studies received seven to nine stars.

AMH assay kits

The AMH assays employed in the eligible studies varied. There was a single version of the Immunotec (IOT) ELISA kit (Immunotec, Marseille, France) used in two of the studies (Hirokawa et al., 2011; Saito et al., 2014), while it is likely that there were two or even three versions of the Diagnostic Systems Lab (DSL) assays employed in the remaining nine studies. All versions of the DSL assay used the same pair of antibodies, but different calibration was used in the assays applied after 2013 (so called 'Generation II'; Gen II; Nelson et al., 2014). The second version of the GEN II assay was adapted to obviate an effect of complement yielding falsely low absolute values in fresh serum. The lower baseline values seen in the studies by Ercan et al. (2010), Celik et al. (2012) and Uncu et al. (2013) suggest that they used the original DSL assay, whilst the later studies (Alborzi et al.,. 2014; Tanprasertkul et al., 2014; Shao et al., 2016; Kashi et al., 2017; Kovačević et al., 2018) showed higher baseline concentrations, probably reflecting the revised calibration of the Gen II assay. The AMH assay employed in the paper of Sweed et al. (2018) may differ from those of the other papers, where there is extensive evidence of validation. There is no reason to consider that this assay is inappropriate, but evidence of comparability with established assays would have been beneficial. The intra- and inter-assay coefficients of variation as well as the minimal detection limits of the assays are presented in Table VI.

Some studies used best-practice analyses for longitudinal assessment of analytes, with simultaneous assessment of all samples of AMH within the same assay, while others recorded the factor as the sample became available. There appeared to be no difference in the nature of the observations between these studies.

Table VII demonstrates AMH percentage reduction from baseline in each of the eligible studies, irrespective of the AMH assay employed, following unilateral and bilateral endometrioma cystectomy in the early, intermediate and late post-operative periods.

Pooled AMH results

Eleven eligible studies included data concerning serum AMH level at baseline in the unilateral and bilateral groups. These studies included 460 and 273 women in the unilateral and bilateral groups,

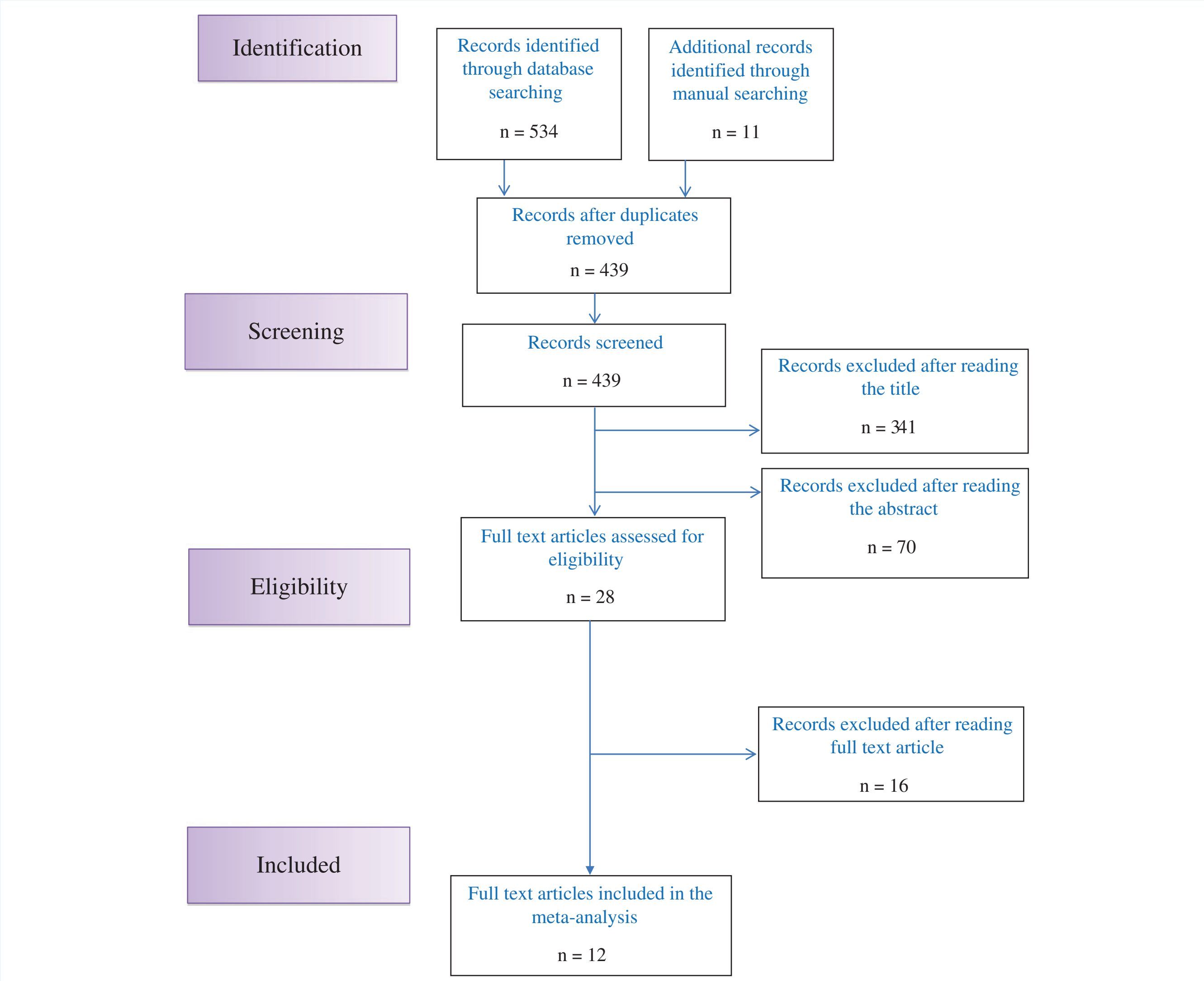

Figure 1 **Flow diagram of identified studies.**

respectively. The WMD before surgery between the two groups was not significant with an estimate of 0.31 ng/ml (95% CI: −0.15 to 0.77, P = 0.19). Heterogeneity between the studies was high (I^2 = 57%, P = 0.01) (Fig. 2).

Seven among the eligible studies evaluating serum AMH levels in unilateral versus bilateral endometrioma removal included data collected 1 week to 1 month following the procedure. These studies included 296 and 180 women in the unilateral and bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 0.78 ng/mL (95% CI: 0.41–1.15, P = 0.001). Heterogeneity between the studies was high (I^2 = 56%, P = 0.04) (Fig. 3A).

Seven studies evaluating serum AMH levels in unilateral versus bilateral endometrioma removal included data from 6 weeks to 6 months following operation. These studies included 332 and 183 women in the unilateral and bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 0.59 ng/mL (95% CI: 0.14–1.04, P = 0.01). Heterogeneity between the studies was high (I^2 = 65%, P = 0.009) (Fig. 3B).

Three among the eligible studies evaluating serum AMH levels in unilateral versus bilateral endometrioma removal included data collected 9–12 months following the procedure. These studies included 194 and 121 women in the unilateral and bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 1.08 ng/ml (95% CI: 0.63–1.52, P = 0.001). Heterogeneity between the studies was low (I^2 = 37%, P = 0.20) (Fig. 3C).

To evaluate the serum AMH level trend following surgery, we performed a meta-analysis of serum AMH concentrations in eligible studies following surgery as related to baseline, for unilateral and bilateral endometrioma cystectomy, separately. Meta-analysis results are summarised in Table VIII, showing a significant serum AMH drop in all three periods following surgery in both the unilateral and bilateral groups. The post-operative AMH drop rate was more pronounced in bilateral as compared to unilateral endometrioma cystectomy groups, corresponding to 43.4%–57.0% and 26.9–39.5%, respectively. Notably, in both the unilateral and bilateral groups, the serum AMH drop rate was partially reversed in the intermediate as compared to

Table V **Newcastle–Ottawa quality assessment scale of *cohort studies* for the comparison between unilateral and bilateral resection of endometriomas.**

Author, year	Selection				Comparability	Outcome			Total stars
	Representativeness of cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate duration of cohort	
Ercan *et al.* (2010)	*	*	*	*	**	*	*	*	9
Hirokawa *et al.* (2011)	*		*	*	**	*	*	*	8
Alborzi *et al.* (2014)	*		*	*	**	*	*	*	8
Celik *et al.* (2012)	*		*	*	**	*	*	*	8
Saito *et al.* (2014)	*		*	*	**	*	*	*	8
Tanprasertkul *et al.* (2014)	*	*	*	*	*	*	*	*	8
Uncu *et al.* (2013)	*	*	*	*	**	*	*	*	9
Ding *et al.* (2015)	*	*	*	*	**	*	*	*	9
Shao *et al.* (2016)	*		*	*	**	*	*	*	8
Kashi *et al.* (2017)	*		*	*	*	*	*	*	7
Sweed *et al.* (2018)	*		*	*	**	*	*	*	8
Kovačević *et al.* (2018)	*		*	*	*	*	*	*	7

Table VI AMH assay kits employed by the eligible studies.

Author and year	Name of AMH assay	Company	Country	Intra-coefficients of variation	Inter-coefficients of variation	Lowest detection limit ng/ml	Fresh or frozen sample
Ercan *et al.* (2010)	ELISA	DSL	USA	Intra-assay precision at 0.843 ng/ml is 2.4%	Inter-assay precision at 0.850 ng/ml is 4.8%	ND	Frozen
Hirokawa *et al.* (2011)	EIA AMH/MIS	IOT	Marseille, France	Below 12.3%	Below 14.2%	ND	Frozen
Celik *et al.* (2012)	ELISA	DSL	ND	4.57%	ND	0.006	Frozen
Uncu *et al.* (2013)	*Active*® MIS/ AMH ELISA	DSL	Webster, USA	ND	ND	0.006	Frozen
Alborzi *et al.* (2014)	*Active*® MIS/ AMH ELISA	DSL	ND	4.02%	4.62%	0.006	Fresh
Saito *et al.* (2014)	EIA AMH/MIS	IOT	Brea, USA	Below 12.3%	Below 14.2%	ND	Fresh
Tanprasertkul *et al.* (2014)	ELISA	DSL	Webster, USA	ND	ND	ND	Frozen
Shao *et al.* (2016)	ELISA	DSL	USA	9.4%	7.2%	0.006	ND
Kashi *et al.* (2017)	ELISA	DSL	Webster, USA	ND	ND	0.006	ND
Sweed *et al.* (2018)	ELISA	Glory Science	Del Rio, TX USA	$<10\%$	$<10\%$	0.5	Frozen
Kovačević *et al.* (2018)	ELISA	DSL	ND	5.3%	7.7%	0.08	ND

ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; ND, not disclosed; DSL, Diagnostic Systems Laboratories; IOT, Immunotech.
NB. DSL and IOT assays share the same ownership in the form of Beckman Coulter®.

Table VII AMH percentage reduction from baseline following unilateral and bilateral endometrioma cystectomy at early, intermediate and late post-operative periods in each of the eligible studies.

		Post-operative AMH percentage reduction					
		One week to one month		Six weeks to six months		Nine to twelve months	
Study	Year	Unilateral cystectomy	Bilateral cystectomy	Unilateral cystectomy	Bilateral cystectomy	Unilateral cystectomy	Bilateral cystectomy
Ercan	2010	27.7%	6.9%				
Hirokawa	2011	29.3%	66.7%				
Celik	2012			6.3%	45.4%		
Uncu	2013	0.5%	41.1%	13.7%	47.5%		
Alborzi	2014	52.5%	68.7%	39.6%	62.3%	48.0%	63.8%
Saito	2014	56.4%	80.0%				
Tanprasertkul	2014	40.5%	28.4%	34.0%	52.2%		
Shao	2016			11.8%	34.8%	18.9%	51.7%
Kashi	2017			30.2%	33.4%		
Sweed	2018	53.4%	71.5%				
Kovačević	2018			56.7%	61.6%	48.0%	65.1%

the early post-operative period. Nevertheless, the WMD of serum AMH reached its maximum at 9–12 months following surgery in both the unilateral and bilateral groups, corresponding to 1.65 ng/ml (95% CI: 1.15–2.15, $P < 0.001$) and 2.03 ng/ml (95% CI: 1.47–2.58, $P < 0.001$) below baseline, respectively.

Pooled AFC results

Only two eligible studies included data on AFC results that could be incorporated into meta-analysis (Uncu *et al.*, 2013; Ding *et al.*, 2015) (Table IV). Data available allowed analysis of basal AFC values and post-operative values at 1 week to 1 month and 2–6 months

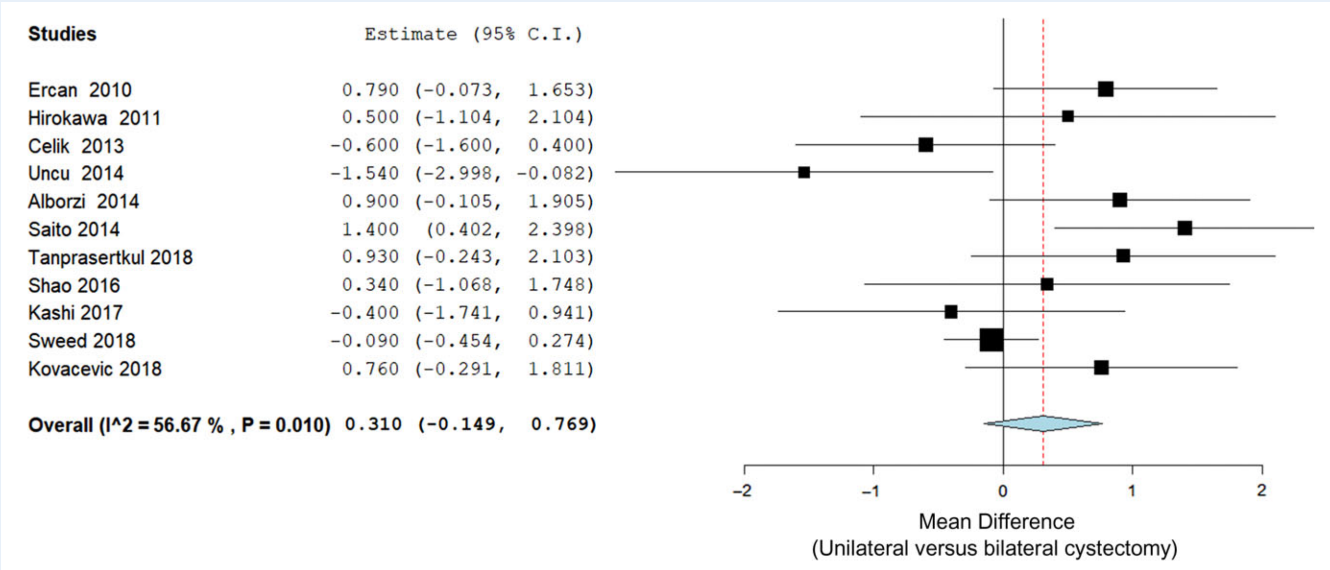

Figure 2 **Forest plot for pre-operative AMH levels in women with unilateral versus bilateral endometrioma.**

following surgery in the unilateral and bilateral groups. These two studies included 44 and 36 women in the unilateral and bilateral groups, respectively. The WMD between the two groups at baseline was not significant with an estimate of 2.04 (95% CI: –0.95 to 5.04, $P = 0.18$). Heterogeneity between the studies was high ($I^2 = 72\%$, $P = 0.06$). In addition, post-operative AFC values at 1 week to 1 month and 2–6 months after surgery did not significantly differ between the unilateral and bilateral groups. Furthermore, separate analysis of AFC values in each of the unilateral and bilateral endometrioma removal groups at 1 week to 1 month and 2–6 months as compared to baseline levels did not show any significant difference.

Sub-group analyses

The diversity of data available for meta-analysis precluded sub-group analysis in relation to endometrioma size and number of endometrioma (mono- or multi-cystic) in the unilateral and bilateral groups, although in the majority of studies, the endometrioma mean diameter was more than 40 mm (Table II). Likewise, the diversity of available data precluded sub-group analysis in relation to age, rASRM classification, surgical technique and haemostasis method.

Two nominal AMH assays were employed in eligible studies; pooled data allowed sub-group analysis for each of the assays separately. Available data permitted separate analysis for the DSL assay (eight studies using two versions) and IOT assay (two studies), but only before surgery and in the early post-operative period (1 week to 1 month following operation).

Eight studies employing the DSL assay included data on serum AMH level at baseline in the unilateral versus bilateral groups. These studies included 366 and 200 women in the unilateral and bilateral groups, respectively. The WMD between the two groups was not significant with an estimate of 0.23 ng/mL (95% CI: –0.35 to 0.81, $P = 0.44$). Heterogeneity between the studies was high ($I^2 = 53\%$, $P = 0.04$) (Fig. 4A), some of which is likely to be due to the use of two versions of the assay with different calibration values.

Two studies employing the IOT assay included data on serum AMH level at baseline in the unilateral versus bilateral groups. These studies included 60 and 46 women in the unilateral and bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 1.15 ng/ml (95% CI: 0.30–2.00, $P < 0.008$). Heterogeneity between the studies was low ($I^2 = 0\%$, $P = 0.35$) (Fig. 4B).

Four studies employing the DSL assay included data on AMH level 1 week to 1 month following surgery. These studies included 202 and 107 women in the unilateral versus bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 0.48 ng/mL (95% CI: 0.015–0.95, $P < 0.04$). Heterogeneity between the studies was low ($I^2 = 41\%$, $P = 0.17$).

Two studies employing the IOT assay included data on AMH level 1 week to 1 month following surgery. These studies included 60 and 46 women in the unilateral versus bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 1.35 ng/ml (95% CI: 0.89–1.81, $P < 0.001$). Heterogeneity between the studies was low ($I^2 = 0\%$, $P = 0.33$).

As the DSL assay introduced in 2010 had technical issues related to complement in fresh serum samples, we performed a sub-group analysis of absolute values in the studies reporting use of frozen samples with the DSL assay (Table VI) and the studies using the IOT assay, both of which were calibrated to the same standard. The aim of this examination was to explore whether this resulted in low heterogeneity. The studies involved were Hirokawa *et al.*, (2011), Celik *et al.*, (2012), Saito *et al.*, (2014), Tanprasertkul *et al.*, (2014) as frozen serum was used. Available data permitted analysis before surgery and in the early post-operative period (1 week to 1 month following operation).

At baseline, these four studies included 139 and 71 women in the unilateral and bilateral groups, respectively. The WMD between the

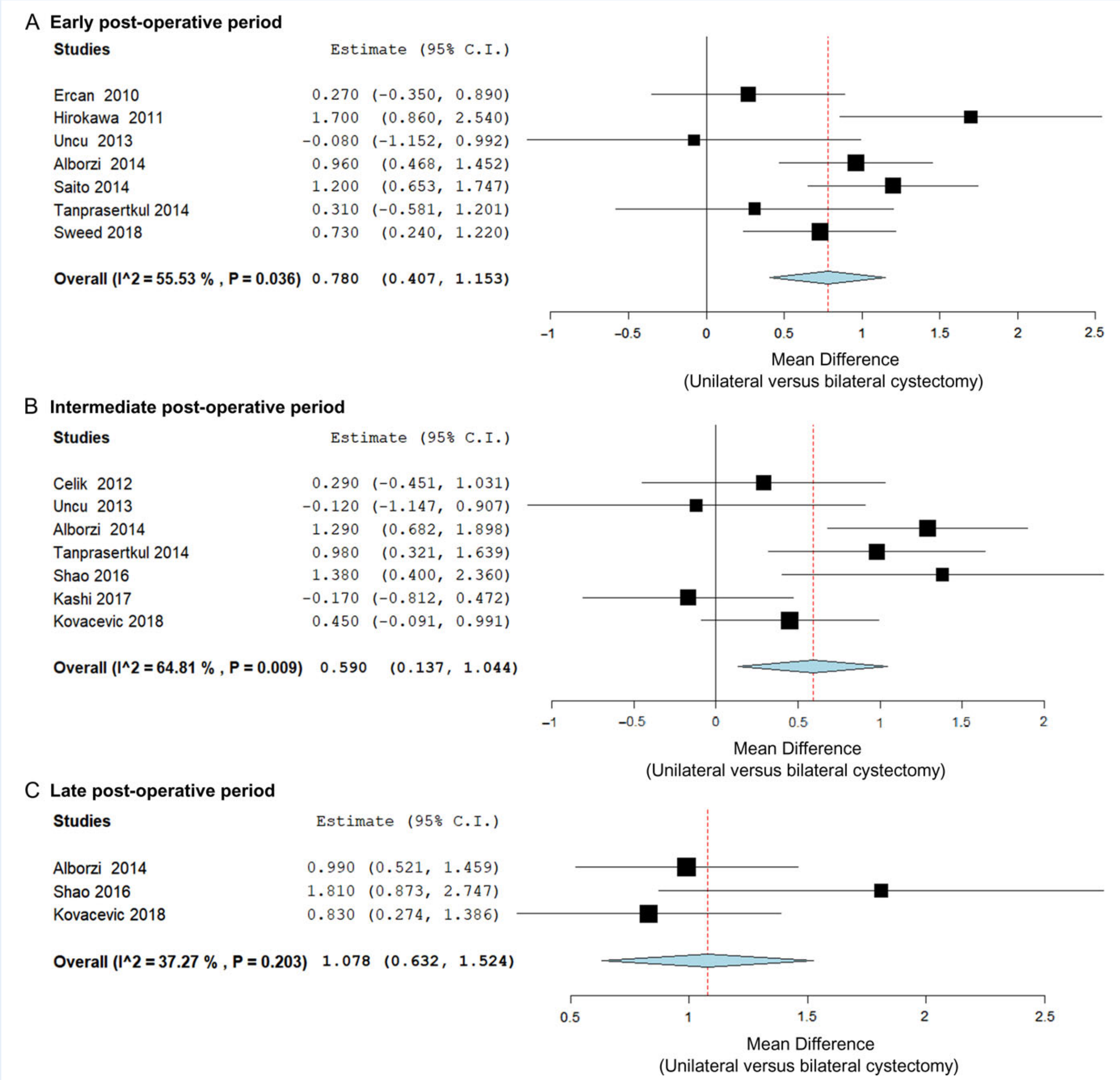

Figure 3 **Forest plot for post-operative AMH levels in women with unilateral versus bilateral endometrioma.** AMH levels were assessed at (**A**) 1 week to 1 month, (**B**) 6 weeks to 6 months and (**C**) 9–12 months, following surgery.

Table VIII **Separate unilateral and bilateral meta-analysis results of eligible studies showing WMD of AMH level at different periods following surgery as compared to baseline levels and their rate of decrease.**

AMH timing	Unilateral cystectomy						Bilateral cystectomy					
	WMD	*N*	95% CI	Post-operative AMH decrease	*P*	I^2	WMD	*N*	95% CI	Post-operative AMH decrease	*P*	I^2
1w – 1 m	1.42	296	0.72 to 2.11	38.4%	<0.001	81%	1.72	180	0.78 to 2.66	53.9%	<0.001	90%
6w – 6 m	0.93	333	0.33 to 1.53	26.9%	<0.002	74%	1.47	186	1.07 to 1.87	43.4%	<0.001	0%
9 m – 12 m	1.65	194	1.15 to 2.15	39.5%	<0.001	11%	2.03	121	1.47 to 2.58	57.0%	<0.001	0%

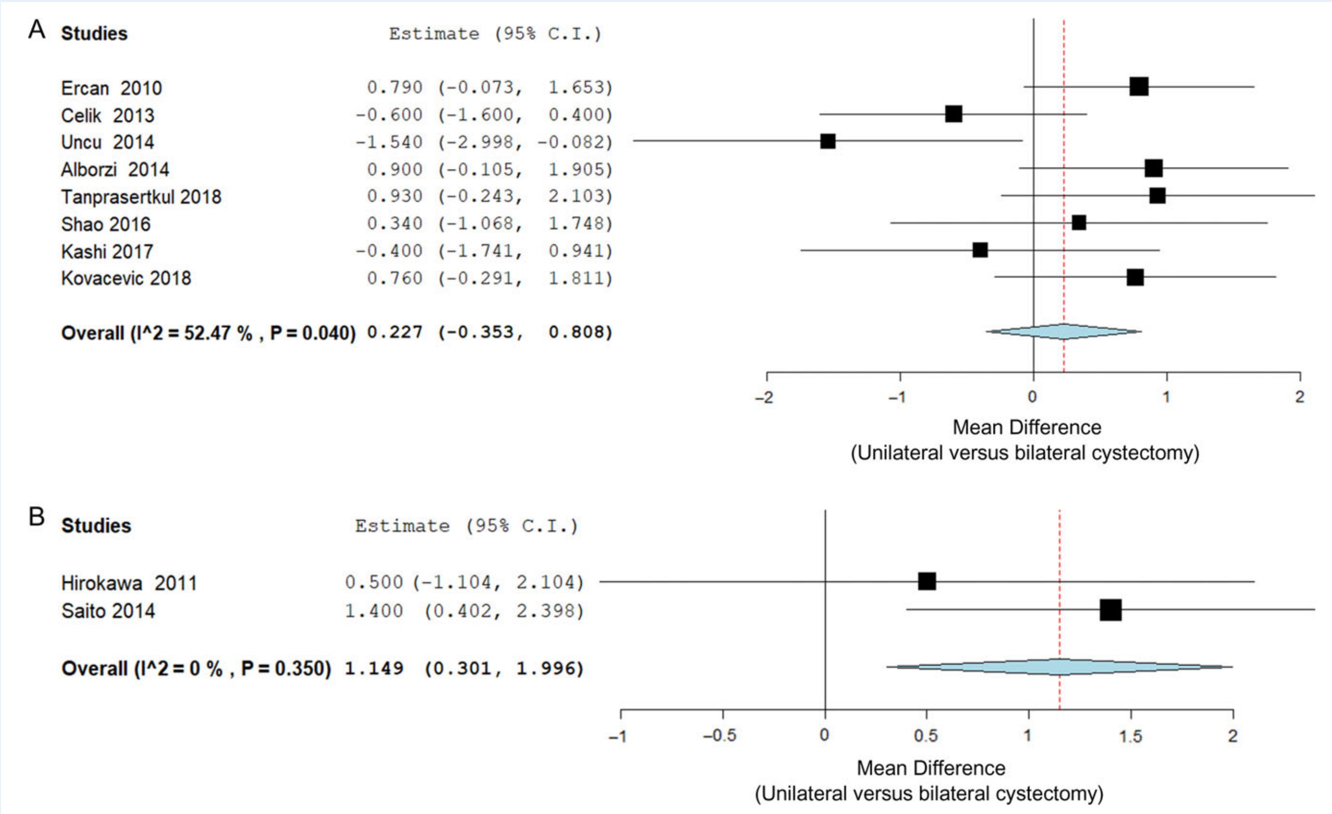

Figure 4 Forest plot of sub-group analysis for pre-operative AMH level in women with unilateral versus bilateral endometrioma. AMH levels were assessed by employing the (**A**) Diagnostic System Laboratories (DSL) assay and the (**B**) Immunotech (IOT) assay ELISA kits.

two groups was not significant with an estimate of 0.55 ng/ml (95% CI: −0.41 to 1.52, $P = 0.26$). Heterogeneity between the studies was high ($I^2 = 64\%$, $P = 0.04$).

Three studies included data collected 1–4 weeks following surgery. These studies included 93 and 52 women in the unilateral and bilateral groups, respectively. Serum AMH was significantly lower in the bilateral group with an estimated WMD of 1.10 ng/ml (95% CI: 0.41–1.79, $P = 0.002$). Heterogeneity between the studies was high ($I^2 = 61\%$, $P = 0.08$).

Discussion

Main findings

Endometriotic ovarian cystectomy, in women of reproductive age, results in significant suppression of circulating AMH in both the short and long term. The effect is more profound following bilateral as compared to unilateral endometrioma excision, in the early (1 week to 1 month), intermediate (6 weeks to 6 months) and late (9–12 months) terms following surgery.

Analysing AMH data in the unilateral and bilateral endometrioma separately shows that both groups had significant decreases in serum AMH levels that continued until the end of the first year following surgery. Maximum post-operative AMH drop, during the analysis, was 39.5% and 57.0% in the unilateral and bilateral endometrioma cystectomy groups, respectively, far exceeding any natural decline in AMH. For women in their third decade of life, the natural decline in AMH is approximately 5% per year (Nelson *et al.*, 2014), so the magnitude of the impact of surgery exceeds the natural decline by a considerable margin: the equivalent of 5–10 years. None of the changes during the evolution of the AMH assay would have led to a decrease in absolute AMH concentration values. Therefore, this observation is unlikely to be related to an assay artefact.

Furthermore, primary analysis of the basal serum AMH level prior to surgery does not differ significantly between women with unilateral and bilateral endometrioma. The baseline results challenge the notion that the diagnosis of endometrioma is associated with a reduction in ovarian reserve.

Although AFC results before surgery corroborated AMH data, no significant difference was found between the unilateral and bilateral groups following surgery. Similarly, when both groups were analysed separately, no significant decrease was found between post-operative and basal AFC values. These findings may call into question the reliability of AFC as an ovarian reserve biomarker in cases with endometrioma, especially when managing bilateral cases.

Strengths and limitations

Our systematic review and meta-analysis is the first to focus on the impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve during the reproductive years. Former systematic reviews evaluated ovarian reserve tests focusing on unilateral endometrioma removal (Raffi et al., 2012; Somigliana et al., 2012; Muzii et al., 2014). In one systematic review, five studies investigating bilaterality were narratively summarised without conducting meta-analysis (Somigliana et al., 2012). In a second systematic review, sub-group meta-analysis for bilateral endometrioma cystectomy was conducted, evaluating only two studies including 32 women; the post-operative AMH estimate did not differ significantly from the pre-operative value (Raffi et al., 2012).

Our meta-analysis included 12 prospective, strictly selected studies, evaluating AMH and/or AFC before and following surgery in unilateral versus bilateral endometrioma. Collectively, eligible studies included 783 women, 489 and 294 in the unilateral and bilateral groups, respectively, reaching significant estimates. Quality assessment of eligible studies included in our meta-analysis was thoroughly evaluated and was found to have a low risk of bias.

Our study may have several limitations. The heterogeneity among eligible studies evaluating serum AMH level before surgery and at the early and intermediate post-operative periods was high. This may drive from the use of different AMH assays in the respective studies. Indeed, the early DSL ELISA kit and IOT, considered first generation commercially available immunoassays, employed different antibodies and calibration (Nelson and La Marca, 2011). However, later DSL assays (after 2010) used calibration similar to IOT. Examination of the baseline values recorded in the studies using the DSL assay suggests that earlier studies used the original DSL assay, while later studies deployed the DSL assay with revised calibration. Overall, an assessment of correlation of the DSL and IOT showed a linear relationship ($r = 0.88$). However, since the precise assay versions are not clear and published conversion factors or regression equations between the two AMH assays seem to be inappropriate for routine clinical practice or research studies, we have abandoned this assessment approach and chosen to perform sub-group analysis (Li et al., 2012; Rustamov et al., 2012; Su et al., 2014).

Sub-group analysis for DSL and IOT assays evaluation corroborated the results of the primary meta-analysis in the early post-operative period. Both assays showed a significant AMH decrease following bilateral as compared to unilateral endometrioma cystectomy. Conversely, basal pre-operative AMH evaluation employing each of the two assays separately were different, possibly due to a significant number of cases evaluated with the early DSL assay. Although DSL assay analysis did not show a significant difference between the bilateral and unilateral groups and corroborated the results of the primary analysis, IOT assays showed a significant estimate. However, only two studies employed the IOT assay, including 60 and 46 women, as compared to eight studies that employed the DSL assay, including 366 and 200 women in the unilateral and bilateral groups, respectively. This may limit the strength of the IOT estimate. Furthermore, the United Kingdom National External Quality Assessment Service (NEQAS) data of the DSL assay over the last four years has shown the DSL assay to be of the highest calibre (Fleming et al., 2018). Its results are very similar to the new automated assays, of which the DSL assay uses recombinant human AMH as the calibrator. This calibration is likely to be close to an international standard for AMH, which may evolve for all such assays in the future (Fleming et al., 2018).

The high heterogeneity among studies employing the DSL assay in the sub-group analysis pre- and post-operatively may suggest different kit calibrations before and after 2010. Indeed, different inter- and intra-coefficients of variation, presented in Table VI, may well support this.

Among the 12 eligible studies, only three included AMH data at 9–12 months following surgery (Alborzi et al., 2014; Shao et al., 2016; Kovačević et al., 2018) and this may limit the strength of the long-term estimate. Furthermore, only two studies included AFC data that could be pooled into meta-analysis (Uncu et al., 2013; Ding et al., 2015) and this may limit the conclusions of the AFC findings. The high heterogeneity among all AFC analyses supports cautious interpretation of these findings.

Additionally, the diversity of available AMH data precluded sub-group analysis for age and endometrioma size as well as for surgery and haemostasis techniques.

Comparison with existing literature

The main finding of the present meta-analysis, that greater ovarian reserve loss follows bilateral as compared to unilateral endometrioma resection, is supported by previous publications (Busacca et al., 2006; Di Prospero and Micucci, 2009; Benaglia et al., 2010; Coccia et al., 2011; Takae et al., 2014) while it contradicts others (Ercan et al., 2010; Ding et al., 2015; Vignali et al., 2015). Retrospective cohort studies have shown early severe ovarian damage or late onset ovarian failure following bilateral endometrioma resection (Busacca et al., 2006; Di Prospero and Micucci, 2009; Benaglia et al., 2010; Takae et al., 2014). It is emphasised that even experienced surgeons and accurate technique cannot avoid operative ovarian reserve damage (Roman et al., 2010; Biacchiardi et al., 2011; Muzii et al., 2011). One prospective longitudinal study found that women are at increased risk of premature ovarian failure and early menopause following bilateral ovarian endometrioma cystectomy (Coccia et al., 2011).

Our systematic review and meta-analysis targeted only prospective studies that compared unilateral to bilateral endometrioma excision, showing a significant and sustained decrease of serum AMH level in the bilateral as compared to the unilateral groups. A low AMH level is predictive of the reproductive lifespan, occult premature ovarian insufficiency, early menopause and, possibly, age at menopause (Tehrani et al., 2013; Broer et al., 2011, 2014; Depmann et al., 2018) many years earlier, and may therefore reduce the chance of achieving a live birth.

The concept that endometrioma per se could affect ovarian reserve was implied when histological studies reported a significant reduction in the primordial follicle cohort in affected ovaries (Maneschi et al., 1993; Kitajima et al., 2011). Some clinical studies have indicated that endometrioma by itself could decrease AMH level and adversely affect ovarian reserve (Hwu et al., 2011; Uncu et al., 2013; Chen et al., 2014). The first study was retrospective in design (Hwu et al., 2011) while the other two prospective studies included only 30 and 40 cases, respectively (Uncu et al., 2013; Chen et al., 2014). The adverse effect was explained via direct mass effect, local inflammatory reactions and by increased tissue oxidative stress leading to fibrosis (Sanchez et al., 2014). A recent meta-analysis showed reduced serum AMH level in patients with ovarian endometriomas compared both to patients with other benign ovarian cysts, and to patients with healthy ovaries (Muzii et al., 2018). This paper included several retrospective reports and it did not address the issue of AMH assay methodology evolvement over the years of the study.

Conversely, other clinical studies have questioned these results. Nieweglowska *et al.* (2015) reported that low serum AMH level is encountered only in women with bilateral endometrioma but not in cases with unilateral endometrioma (Nieweglowska *et al.*, 2015). Ferrero *et al.* (2015) showed that endometrioma recurrence has no detrimental effect of AMH level (Ferrero *et al.*, 2015). Others have shown that in women with endometriosis, AMH levels are decreased only in those with previous endometrioma surgery (Streuli *et al.*, 2012). Our systematic review and meta-analysis challenge studies implying that endometrioma per se may adversely affect ovarian reserve and supports the findings of Streuli *et al.* (2012) and Ferrero *et al.* (2015).

A subtle finding in our meta-analysis is the partially reversed decline in serum AMH level in the intermediate term as compared to the early post-operative period, consistent with 26.9% versus 38.4% from baseline in the unilateral endometrioma group, and 43.4% versus 53.9% from baseline in the bilateral endometrioma group, respectively. Certain prospective studies evaluating small cohorts of women with endometrioma have suggested that some degree of ovarian reserve damage is reversed. This was explained by other surgery-related reversible mechanisms related to ovarian vasculature and inflammation-mediated injuries (Chang *et al.*, 2010; Sugita *et al.*, 2013; Goodman *et al.*, 2016). Our results may support such a mechanism, however, the late post-operative AMH level at 9–12 months suggests that this effect does not persist. Since only three studies were included in the meta-analysis of the late post-operative period, although with low heterogeneity, this conclusion should be interpreted with caution.

The literature does not yet provide clear evidence which of the contemporary, reliable ovarian reserve biomarkers is more suitable to evaluate women with endometrioma: AMH or AFC. Previous systematic reviews and meta-analyses reached contradictory conclusions. While Raffi *et al.* (2012), employing AMH, posited that surgery impacts negatively on ovarian reserve, Muzii *et al.* (2014), using AFC, concluded that it does not. Our meta-analysis may shed some light on these differing conclusions, perhaps inclining towards AMH as a more reliable ovarian reserve biomarker in women with endometrioma. However, since only two studies using AFC were eligible for meta-analysis in the present review and due to the high heterogeneity among the studies included, a targeted study ought to be conducted to resolve this question.

It may be argued that the AMH sustained decrease, as a surrogate end-point to draw inferences regarding the potential damage of ovarian cystectomy on natural fertility, is not conclusive (Esinler *et al.*, 2006; Broer *et al.*, 2013; Somigliana *et al.*, 2015b). The reliability of AMH to predict fecundability in the fertile population is still under investigation in prospective studies (Steiner *et al.*, 2011; Somigliana *et al.*, 2015b; Zarek *et al.*, 2015). The most important end-point is the live-birth rate following endometriotic cystectomy and future studies should be conducted to establish a possible adverse effect. Nevertheless, there is evidence to show that bilateral endometriotic cystectomy is coupled with a high rate of IVF failure (not reaching embryo transfer) and reduced live birth (Ragni *et al.*, 2005; Somigliana *et al.*, 2008). Furthermore, recently IVF outcome and live birth rate were shown to be significantly more impaired in women with low ovarian reserve caused by a previous endometriotic cystectomy as compared to women with idiopathic low ovarian reserve (Roustan *et al.*, 2015).

The topic of endometriotic cystectomy is further complicated in women undergoing treatment for infertility. While some reports have found that surgery was associated with a higher ongoing pregnancy and live birth rate than diagnostic laparoscopy (Duffy *et al.*, 2014), there is an abundance of evidence, as found in our meta-analysis, to show damage to ovarian reserve (Raffi *et al.*, 2012; Somigliana *et al.*, 2012). This inconsistency may complicate therapeutic management even further and medical judgement ought to be based on individual characteristics such as age, ovarian reserve and associated clinical manifestations, as well as informed consent.

It should also be noted that surgical abstention in young women not yet seeking conception is feasible in cases where endometrioma features are typical on ultrasound exam. Since the appearance of endometrioma differs among women of different ages, physician awareness may facilitate a correct diagnosis of endometrioma (Van Holsbeke *et al.*, 2010; Guerriero *et al.*, 2016). The poorer diagnostic performance of ultrasound with regard to diagnosing endometriomas in premenopausal women 40 years or older as compared with younger women (Guerriero *et al.*, 2016) is perhaps providential. When endometriosis associated-pain appears in these women, hormonal therapy or surgery should be examined taking into account patient preferences, side effects, efficacy, costs and availability into consideration (Dunselman *et al.*, 2014). In cases where the endometrioma is increasing in size under hormonal treatment, a re-valuation is advised and the question of surgery should be cautiously considered.

Conclusions and wider implications

Our systematic review and meta-analysis clearly show that bilateral endometrioma resection engenders significantly more damage to ovarian reserve as compared to unilateral resection. The maximum post-operative AMH decrease was found to be 39.5% and 57.0% in the unilateral and bilateral groups, respectively, reducing considerably the potential reproductive lifespan of women following bilateral endometrioma cystectomy. Furthermore, our meta-analysis calls into question the claim of a deleterious effect of endometrioma per se on ovarian reserve. These two main findings may have wider implications, joining other recent publications dealing with endometrioma in the reproductive years.

Endometriotic cysts, irrespective of the volume, have been shown not to influence the rate of spontaneous ovulation in the affected ovary. It does not preclude a good spontaneous pregnancy rate if the couple has no other risk factors for infertility (Leone Roberti Maggiore *et al.*, 2015). Additionally, the available evidence on the risks of conservative management of existing endometrioma, such as infection during oocyte retrieval, follicular fluid contamination with endometriotic cyst content during *in vitro* fertilisation and increased complications during pregnancy, has been shown to be modest. The possibility of developing ovarian cancer is troublesome but seems to be a rare event and may perhaps be prevented by postponing surgery until the fulfilment of reproductive wishes (Somigliana *et al.*, 2015a; Kvaskoff *et al.*, 2017). The present evidence does not support systematic surgery before IVF, as the hazard of surgery-related ovarian reserve damage surpasses the risks of conservative management

(Somigliana *et al.*, 2015a). Furthermore, ovarian endometriotic cystectomy does not improve IVF-ET outcome, since clinical pregnancy rates and live birth rates were shown to be comparable to women with normal ovaries (Hamdan *et al.*, 2015; Nickkho-Amiry *et al.*, 2018) or to women who did not undergo surgery (Hamdan *et al.*, 2015; Tao *et al.*, 2017).

Taken together, endometrioma cystectomy, especially bilateral surgery, is implicated in a considerable decrease in ovarian reserve and may have no obvious reproductive advantage. Therefore, until proven otherwise, conservative treatment should be counselled as the first line of treatment, until the patient's reproductive aspirations are realised. Women should be encouraged to prefer early parenthood in these cases. Surgery might be postponed until family planning is complete.

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Authors' roles

J.S.Y. conceived the idea of this systematic review and meta-analysis, contributed to study design and construction of the protocol, contributed to data extraction and executed the study, performed the analyses and data interpretation, and drafted the manuscript; N.S. reviewed the protocol, contributed to data extraction, analyses and interpretation, and contributed to statistical analysis and drafting of the manuscript; R.F. examined the study design and execution, contributed to data extraction, analyses and the interpretation of data, and revised the manuscript for important intellectual content; I.B. reviewed the protocol, contributed to data extraction and interpretation, and revised the manuscript for important intellectual content; I. I. contributed to study design and execution, contributed to the analyses and the interpretation of data, performed the statistical analysis, and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

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