The Impact of excision of Benign Non-Endometriotic Ovarian Cysts on Ovarian Reserve: A systematic review

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PII: S0002-9378(16)30004-7

DOI: 10.1016/j.ajog.2016.03.045

Reference: YMOB 11024

To appear in: *American Journal of Obstetrics and Gynecology*

Title: The Impact of excision of Benign Non-Endometriotic Ovarian Cysts on Ovarian Reserve: A systematic review

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Funding

Funding was obtained from Egyptian Cultural Centre and Education bureau in London and British Council in Cairo

Disclosure statement: the authors have nothing to disclose

Word count: 3582 words

Condensation: This meta-analysis included ten studies investigating the impact of benign non-endometriotic ovarian cystectomy on ovarian reserve as determined by circulating AMH. The analysis revealed a marked postoperative reduction of circulating AMH.

Short title: Impact of ovarian cystectomy on ovarian reserve

Abstract

Background: Benign non-endometriotic ovarian cysts are very common and often require surgical excision. However, there has been a growing concern over the possible damaging effect of this surgery on ovarian reserve.

Objective: The aim of this meta-analysis was to investigate the impact of excision of benign non-endometriotic ovarian cysts on ovarian reserve as determined by serum anti-Müllerian hormone (AMH) level.

Data Sources: MEDLINE, Scopus, ScienceDirect and Embase were searched electronically.

Study design: All prospective and retrospective cohort studies as well as randomised trials that analyzed changes of serum AMH concentrations after excision of benign non-endometriotic cysts were eligible. Twenty-five studies were identified, of which ten were included in this analysis.

Data Extraction: Two reviewers performed the data extraction independently.

Results: Pooled analysis of 367 patients showed a statistically significant decline in serum AMH concentration after ovarian cystectomy (weighted mean difference (WMD) -1.14 ng/ml; 95% confidence interval (CI) -1.36 to -0.92; I^2=43 %). Subgroup analysis including studies with a three-month follow-up, studies using Gen II AMH assay and studies using IOT AMH assay improved heterogeneity and still showed significant postoperative decline of circulating AMH (WMD -1.44 [95% CI -1.71 to -1.1; I^2= 0%], -0.88 [95% CI -1.71 to -0.04; I^2=0%], and -1.56 [95% CI -2.44 to -0.69; I^2= 22%] respectively). Sensitivity analysis including studies with low risk of bias and excluding studies with possible confounding factors still showed a significant decline in circulating AMH.

Conclusion: Excision of benign non-endometriotic ovarian cyst(s) seems to result in marked reduction of circulating AMH. It remains to be established whether this reflects a real compromise to ovarian reserve.

Keywords: anti-Müllerian hormone; benign ovarian cysts; ovarian cystectomy; ovarian reserve

Introduction:

Benign ovarian cysts are very commonly seen in Gynecological practice with the majority requiring (excluding functional cysts) surgical excision preferably through the laparoscope. However, there has been growing evidence suggesting a decline in ovarian reserve as a result of ovarian cystectomy with possible compromise to fertility potential (1, 2, 3). It remains to be determined whether this damage to the ovarian reserve is related to the procedure itself or to the nature, size and laterality of the cyst.

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein, which is a member of the transforming growth factor family. In the female, it is exclusively secreted by granulosa cells of primary, preantral and small antral follicles (4-6 mm) (4). It is now well established that circulating AMH gradually declines with advancing age reflecting the decline in the number of the small antral follicles, rendering it an ideal marker for the early detection of reduced ovarian reserve. Furthermore, serum AMH concentration is generally stable with minimal inter- and intra-cycle fluctuations (5). This makes it an ideal candidate for measuring changes in ovarian reserve following cyst excision.

To date, several studies have investigated the impact of ovarian cystectomy on ovarian reserve showing a postoperative decline in circulating AMH (2, 6–19). However, given the relatively small size of these studies, further evidence is required to allow a firm conclusion. We have previously conducted a meta-analysis of studies investigating the effect of excision of endometriomas on ovarian reserve (1).

The aim of this meta-analysis was to investigate the impact of excision of benign non-endometriotic cysts on ovarian reserve as determined by serum AMH levels.

Materials and Methods:

Criteria for study selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (20). All published cohort studies and randomized trials (including at least five patients) that investigated the impact of excision of benign non-endometriotic ovarian cysts on ovarian reserve as determined by changes in postoperative serum AMH concentration were included in this meta-analysis.

Outcome measures

Primary measure:

This included postoperative changes in serum AMH concentration.

Secondary measures:

These included postoperative changes in serum FSH concentration and antral follicle count (AFC).

Search strategy

An extensive electronic database search was performed using MEDLINE, Scopus, Embase and ScienceDirect to identify published research articles between January 2000 and January 31, 2016, on the impact of excision of benign ovarian cysts (excluding endometriomas) on ovarian reserve as determined by serum AMH concentration. No restrictions were placed on language. A combination of following search terms was used: laparoscopy, laparotomy, ovarian cystectomy, excision, anti-Müllerian hormone, benign ovarian cysts, and ovarian reserve. All searches were carried out by the first author and then independently repeated using the same criteria by an accredited clinical librarian. All relevant reports were retrieved, and their reference lists were reviewed manually to identify further studies. A manual search of related articles on

PubMed was also performed. We also considered published abstracts from conferences.

Data extraction

All the identified papers were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two investigators scored the studies and collected the information independently. In the case of discrepancies in scoring between the two investigators, a consensus was reached after discussion or after involvement of the senior investigator. In five studies the mean±SD was not presented (2, 11, 14, 16, 17). The authors of these studies were contacted, but only two replied providing the missing data, which were used in our analysis (11, 14). In another study, which was a conference abstract, the authors did not describe methods of recruitment (inclusion and exclusion criteria) nor they specified the type of AMH assay kit (13). This study was included in the initial analysis, but was excluded from the sensitivity analysis. The authors were contacted to provide the missing information, but no response was received.

Quality of included studies and risk of bias assessment

The quality and risk of bias of the included studies were assessed using modified Newcastle-Ottawa scale, as previously described (1). The original Newcastle-Ottawa scale assesses three main categories including selection, comparability, and outcomes giving a maximum of four, two, and three stars for each category respectively (21, 22). This scale was modified to suite the nature of this study giving a maximum of three stars for selection, four for comparability, and two for outcome criteria. Selection was rated according to recruitment bias, selection of consecutive patients and power calculation. Comparability was assessed based on studies adjusting their analysis for four confounders including patients' age (<40), cyst diameter (>5cm), baseline serum AMH (≥ 3.1ng/ml) and cyst laterality. Outcome was scored according to completeness of at least three-month follow-up after surgery. It is generally agreed that a limit of five stars could identify studies at low risk of bias (23, 24). However, in this study, we have given more weight to comparability factors and used the cutoff level of six stars with a minimum of three stars in the comparability category (1). Table 1 shows the results of quality scores of the studies included in this analysis.

Data analysis

Pre- and post-operative data including mean ± SD serum concentrations AMH (ng/mL) and FSH (mIU/mL) and AFC were extracted from the individual studies and pooled using RevMan software (Review Manager, version 5.1, The Cochrane Collaboration, 2011; The Nordic Cochrane Centre, Copenhagen, Denmark). The weighted mean difference (WMD) between pre- and post-operative values was calculated. Statistical heterogeneity was assessed by chi-squared (χ^2, or Chi^2) test and I^2 statistics. A Chi^2 statistic larger than its degree of freedom or an I^2 higher than 50% was indicative of significant heterogeneity between studies. When heterogeneity was significant, a random-effect model was used for meta-analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity.

The initial analysis included data from all studies, irrespective of length of follow-up and cyst characteristics (diameter, laterality and pathological type). In studies with multiple post-operative measurements at different follow up points, we used the latest AMH level. Further subgroup analyses of AMH levels were then performed based on the laterality of the excised cysts, AMH kits used, and duration of follow-up. To examine and account for heterogeneity, a sensitivity analysis was carried out based on modified Newcastle Ottawa scale for risk of bias as described above. Studies with the lowest risk of bias were defined as those with a score of ≥6 with at least three stars on comparability score and using the same surgical approach (laparoscopy).

Results

A total of 25 articles were identified (Fig. 1). Initially all articles were screened on the basis of the title and abstract to exclude studies which were not relevant to our objectives. As a result, ten articles were viewed in full.

Excluded studies

After the initial screening on the basis of the title and abstract, ten studies did not use AMH to investigate ovarian reserve after surgery for benign non-endometriotic cyst and were therefore excluded (25–34). Five further studies were excluded, one due to the small number of patients (n=3) (19), another study due to extremely low AMH levels (below the sensitivity of AMH assays) (16) and three studies due to missing the mean±SD of serum AMH concentrations (data were either presented as median{IQR}) (2, 18) or mean±SE% (17). The authors of the latter three studies were contacted to provide the AMH data, but no response was received.

Included studies

Details of the included ten studies are shown in table 2.

Study design

The included studies were all cohort studies except one, which was a randomized controlled trial (RCT) (7). However, both arms of the RCT (laparoscopy and laparotomy) were combined and included in the initial meta-analysis as a cohort study. One arm (laparoscopy) was then included in the sensitivity analysis (7).

Participants

Selection criteria were appropriate for all studies. All participants underwent the same type of surgery (cystectomy) through laparoscopy except one study, where patients were randomly allocated to either laparoscopy or laparotomy (7). Patients of this RCT were consecutive and were followed up within their particular group and the results were given separately for each arm of the RCT. All studies reported inclusion and exclusion criteria that were appropriate except one (13).

The author of that study was contacted but did not reply. All patients were accounted for in all studies.

Ovarian cyst diagnosis

Most of the studies reported that the initial diagnosis of the cysts was achieved through transvaginal ultrasound. The ultrasound scans were performed by Gynecologists with sufficient experience. Postoperatively, the nature of the cyst was confirmed with histopathological examination. Six studies reported the mean ± SD cyst diameter (6–9, 12, 15) and six studies determined the side and laterality of the cysts (6–8, 11, 12,15).

Surgery and length of follow up

All studies included patients undergoing ovarian cystectomy carried out laparoscopically except one study, which was an RCT comparing laparoscopic versus open cystectomy (7). The length of follow up was one month in four studies (11, 12, 14, 15), three months in six studies (6, 8, 9, 10, 12, 14), six months in one study (7).

AMH kits

AMH concentration was measured using one of the four available kits. The first one was IOT AMH / MIS enzyme immunoassay (EIA) kit (Immunotech, Beckman Coulter, Marseille, France). The intra- and inter-assay coefficients of variation for the AMH assay were below 12.3% and 14.2%, respectively, with a detection limit of 0.14 ng/mL (9, 11). Second AMH kit was DSL active Müllerian- inhibiting substance / AMH ELISA kit (Diagnostic Systems Laboratories, Webster TX). The intra- and inter-assay coefficients of variation for AMH were 4.6% and 8.0%, respectively, with a detection limit of 0.017 ng/mL (7, 10, 12, 14). The third kit was the AMH Gen II enzyme linked immunosorbent assay (ELISA) (Beckman Coulter, Chaska, MN, USA). The intra and enter-assay coefficients of variation for the AMH assay were both below 10%, with a detection limit of 0.08 ng/mL (6, 8). Two studies used this kit including Ergun and co-workers (6) who used the modified AMH Gen II kit and Kwon and co-workers who used the original Gen II assay (8). The fourth kit was the Ultra-Sensitive AMH ELISA Ansh Labs assay (Ansh Labs, UK). The intra and Inter-assay coefficients of variation for the AMH were 0.02 (2.22/95) and 7.81 (15.62/2), respectively, with a detection limit of 0.06 ng/ml (15).

Potential source of bias

In all studies, patients were selected in a consecutive fashion (6–15). The selection method was clearly described making it easy to assess selection bias.

Overall pooled results for all studies

The initial analysis of the ten studies included all 367 patients who underwent cystectomy for unilateral or bilateral benign non-endometriotic ovarian cysts. The analysis revealed a statistically significant postoperative fall in serum AMH concentrations (WMD -1.14 ng/ml; 95% confidence interval (CI) -1.36 to -0.92). Heterogeneity between studies was low (I^2 = 43 %) (6–15) (Fig. 2).

Subgroup analysis

Laterality of benign non-endometriotic ovarian cysts

Six studies included 206 patients undergoing unilateral ovarian cystectomy (6–8, 11, 12, 15). Results showed a statistically significant decline in serum AMH level after surgery (WMD -0.97 ng/ml; 95% CI -1.58 to -0.37; I^2= 73%). Bilateral ovarian cystectomy was reported in five studies including 23 patients (6, 8, 11, 12, 15). Pooled analysis of the data revealed no statistical significant change in postoperative serum AMH level (WMD -0.80; 95% CI -1.76 to 0.16; I^2= 0%).

Studies with different length of follow up

Six studies (n=270) with one-month follow up revealed a statistically significant decline in serum AMH level (WMD -1.16; 95% CI -1.69 to -0.63; I^2= 76%) (7, 9, 11, 12, 14, 15). Similarly, seven studies (n=253) with a three-month follow up showed a statistically significant fall of serum AMH concentration after surgery (WMD -1.44; 95% CI -1.71 to -1.16; I^2= 0%) (6, 7, 8, 9, 10, 13, 14).

Studies using different AMH assays

Analysis of four studies (n=197) using DSL AMH kit revealed a statistically significant decline in postoperative AMH level (WMD -1.18; 95% CI -1.85 to -0.52; I^2=81%) (7, 10, 12, 14). Pooled analysis of two studies (n=56) using Gen II AMH assay showed a statistically significant fall in postoperative serum AMH level (WMD -0.88; 95% CI -1.71 to -0.04; I^2=0%) (6, 8). Two other studies (n=58) using IOT AMH assay revealed a statistically significant decline in postoperative AMH level (WMD -1.56; 95% CI -2.44 to -0.69; I^2= 22%) (9, 11). Heterogeneity between studies was low for studies using Gen II and IOT AMH kits. One study used the new Ultrasensitive AMH ELISA assay an showed significant decline I circulating AMH (15).

Sensitivity analysis

Pooled analysis of eight studies with low risk of bias (as defined above) including 297 patients showed a statistically significant fall in postoperative serum AMH concentration (WMD -1.05; 95% CL -1.29 to -0.81; I^2= 43%). Heterogeneity between studies was low (6, 7, 8, 9, 11, 12, 14, 15).

Studies with ovarian cyst >5 cm:

Seven studies including 276 patients were identified (6, 7, 8, 9, 12, 14, 15). Pooled analysis revealed a statistically significant fall in postoperative serum AMH concentration (WMD -1.13; 95% CI -1.56 to -0.70; I^2=62%). Heterogeneity between studies was high.

Studies with different histological types

Analysis of six studies including 158 patients with dermoid cysts revealed a statistically significant fall in serum AMH concentration (WMD -1.27; 95% CI -1.93 to -0.62; I^2= 55%) (6, 7, 9, 11, 12, 14). Similarly, analysis of four studies including 84 patients with cystadenomas showed a statistically significant decline in serum AMH concentration (WMD -1.59; 95% CI -2.00 to -1.17; I^2= 0%) (6, 7, 11, 14).

Secondary outcomes

Three studies measured changes in serum FSH concentrations (6, 11, 12), but only two (including 95 patients) of them provided full pre- and post-operative data (6, 12). Pooled analysis of these two studies revealed no significant change in circulating FSH following ovarian cystectomy (WMD -0.50; 95% CI -1.28 to 0.28; I^2= 0%). Authors of the other study (11) reported that FSH levels did not change after surgery, but failed to present the actual data.

With regards to AFC, although one study included this ovarian reserve marker as an outcome measure, the authors provided the postoperative AFC data only and failed to present the preoperative values (7).

Comment

This is the first meta-analysis to investigate the impact of ovarian cystectomy for benign non-endometriotic cysts on ovarian reserve as determined by changes in postoperative serum AMH concentration. The initial analysis revealed a marked decline of 1.14 ng/ml, which represents about 38% of the cut-off level of normal AMH (3.1 ng/ml). This decline in AMH seems to be sustained for up to six months. Further subgroup and sensitivity analysis were performed to minimise the risk of bias and to take into account all possible confounding factors. Heterogeneity was lowest between studies using Gen II and IOT AMH kits, studies with three-month follow-up after surgery and studies including excision of cystadenomas. This further analysis still showed a statistically significant decline in postoperative serum AMH.

Interestingly, this magnitude of AMH decline is similar to that observed after excision of ovarian endometriomas as reported in our previous meta-analysis (1). This is surprising as excision of endometriomas is generally perceived to be more destructive to the ovary than excision of non-endometriotic cysts. This may therefore suggest that the decline in circulating AMH after ovarian cystectomy is not related to the nature of the cyst excised.

The mechanism of the observed fall in circulating AMH following ovarian cystectomy remains largely unknown. Possible explanation could be the concomitant removal of normal ovarian tissue with significant follicular loss (35). Another possible mechanism is the thermal damage to ovarian tissue due to excessive use of diathermy for hemostasis (2, 3).

It is interesting to see this marked drop of circulating AMH (about 38%) following unilateral ovarian cystectomy. It is well established that circulating AMH is generally stable throughout the reproductive years with minimal inter-cycle variation and with very small and gradual decline with advancing age until 40. Bentzen and co-workers reported an AMH level decline of 5.6% per year (36). We therefore believe that a 38% decline in AMH level after cystectomy represents a relatively marked drop, which appears to be clinically significant. However, unlike the age related decline, it is unlikely that the observed post cystectomy AMH fall reflects an equivalent decline in ovarian reserve and fertility potential. It is well established that circulating AMH corresponds to the number of small antral follicles, but does not directly correspond to the total follicular pool of the ovary. It is possible that postoperative fall in AMH reflects loss/damage of small antral follicles, which are the only source of AMH, but may have no significant impact on the total number of primordial follicles. In order to investigate this hypothesis, further studies are required to assess the long term changes in circulating AMH as well as the reproductive performance following ovarian cystectomy. Until such evidence becomes available, it may be prudent for clinicians to counsel their patients with regards to the potential damaging effect of cystectomy on ovarian reserve. A more conservative approach (if malignancy can be confidently ruled out) could be considered whenever clinically possible and appropriate such as deferring surgery until completion of family.

Timing of postoperative serum AMH measurements

The timing of postoperative measurement of circulating AMH varied in the ten studies included in this meta-analysis. The majority of studies (Seven studies, n=253) performed the measurement at three-month follow-up after surgery (6, 7, 8, 9, 10, 13, 14) and one study (7) performed multiple measurements (n=59). In this study, we used the latest samples, which are likely to reflect the most sustained change of circulating AMH after surgery. Analysis of studies with repeated AMH measurements at one and three-month follow-up showed a sustained decline in AMH, indicating that ovarian reserve does not seem to recover within three months.

Surgery for bilateral ovarian cysts

Although, excision of bilateral ovarian cysts is expected to cause more damage to ovarian reserve, it was surprising to see that analysis of studies with bilateral cystectomy did not reveal a significant drop in AMH. However, the numbers included in this analysis was too small (n=23) to allow any firm conclusion.

Cyst diameter (*>5 cm*)

The purpose of this analysis was to adjust for the variation in cyst size as a possible confounding factor. Cyst size did not seem to affect the magnitude of postoperative fall in circulating AMH as indicated by the WMD, which is similar to that of the overall analysis of all included patients regardless of the cyst size.

AMH kits

It is well recognized that different AMH kits give different results and have different sensitivities and inter- and interassay CV. IOT assay (Immunotech, Beckman Coulter, Marseille, France) has been found to produce AMH concentrations 40% higher compared with DSL AMH assay (DSL, Webster, TX, USA), making it difficult to combine/compare results from different studies (37). In 2010 both companies merged under Beckman Coulter and a single new two-step, sandwich-type enzymatic, microplate assay (the AMH Gen II assay) was introduced. The Gen II assay is calibrated to the old IOT standards and AMH levels are thus comparable to the IOT assay and

40% higher than the previous DSL version (38, 39, 40, 41).

Interestingly, studies using AMH Gen II assay showed a significantly smaller postoperative decline in AMH (WMD -0.88 ng/ml) compared with that observed with IOT kit (WMD -1.56 ng/ml), and with DSL assay (WMD -1.18 ng/ml). It is difficult to explain this unexpected difference in the magnitude of AMH decline between Gen II and IOT kits, which have been calibrated to produce comparable results.

Conclusion

In conclusion, excision of benign non-endometriotic ovarian cyst seems to cause marked decline (38%) in circulating AMH. Whether this reflects a long term damage to ovarian reserve with subsequent decline in fertility potential remains to be determined. Given the high heterogeneity between studies, this meta-analysis should be interpreted with caution.

Acknowledgment

The authors are grateful to the Egyptian Cultural Centre and Education bureau in London and the British Council in Cairo for funding the work presented in this manuscript.

The authors are also grateful to Cathryn James, Clinical Librarian at Derby Teaching Hospitals, for her effort and expertise in carrying out a comprehensive electronic search of all available databases.

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Figure legends

Figure 1. PRISMA Flow Chart of the study selection process

FIG 2. WMD in serum AMH concentrations after excision of benign non-endometriotic ovarian cysts: pooled results for all ten studies.

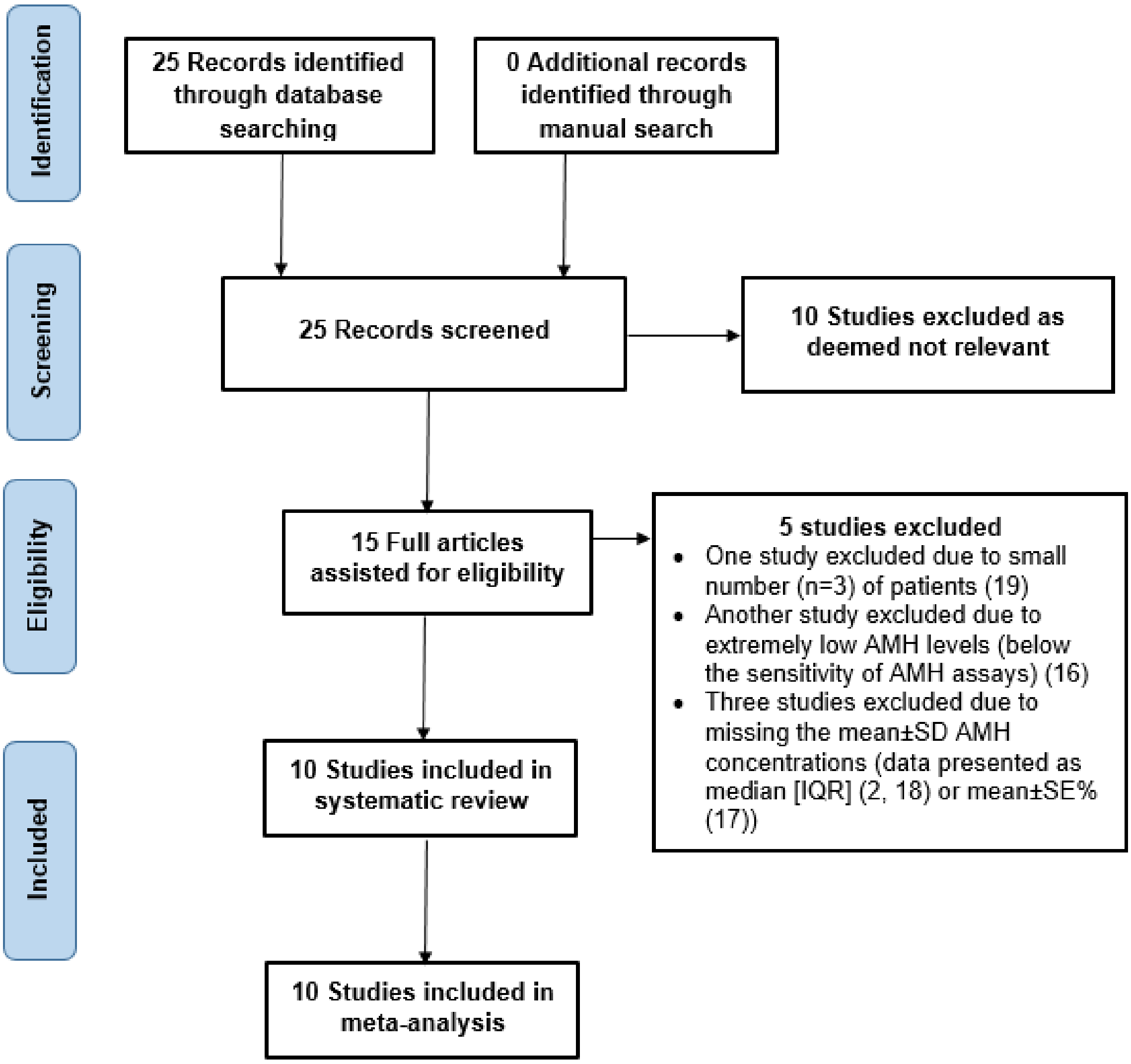
Table 1 Modified Newcastle Ottawa scale for risk of bias and quality assessment of the included studies

Author	**Year**	**selection**	**Comparability**	**Outcome**	**Total score**
Chang *et al.* (10)	2010	*	*	**	4
Iwase *et al.* (11)	2010	**	***	*	6
Mohamed *et al.* (7)	2011	**	****	**	8
Kim *et al.* (13)	2013	*	*	**	4
Chen *et al.* (15)	2014	**	***	*	6
Huang *et al.* (12)	2014	**	****	*	7
Kwon *et al.* (8)	2014	**	****	**	8
Yoon *et al.* (9)	2014	**	***	**	7
Amooee *et al.* (14)	2015	**	***	**	7
Ergun *et al.* (6)	2015	*	****	**	7

Table 2 Characteristics of the ten studies included in the meta-analysis

Author	country	Design	n	Age mean±SD	Laterality	Cyst diameter mean±sd	FU Months	Primary outcome	Secondary Outcome
Chang *et al.* 2010 (10)	Korea	Prospective cohort	7	33.75±7.20	Not specified	Not specified	3	AMH (DSL kit),	–
Iwase *et al. 2011 (11)*	Japan	Prospective cohort	21	29.40±7.3	Uni=16 Bil=5	Not specified	1	AMH (IOT kit),	FSH
Mohamed *et al. 2011 (7)*	Egypt	RCT*	Arm 1=30 Arm 2=29	23.00±4.1	All unilateral	Arm 1, 5.1±2.2 Arm 2, 5.6±2.0	6	AMH (DSL kit),	AFC
Kim *et al. 2013 (13)*	Korea	Prospective cohort	34	Not specified	Not specified	Not specified	3	AMH (kit not specified)	–
Chen *et al.* 2014 (15)	China	Prospective cohort	22	29.95 ± 3.92	Uni=18 Bil=4	6.35 ± 2.88	1	AMH (Ansh Labs)	–
Huang *et al. 2014 (12)*	Taiwan	Retrospective case control	71	34.59±10.18	Uni=67 Bil=4	7.05±2.37	1	AMH (DSL kit),	FSH
Kwon *et al. 2014 (8)*	Korea	Prospective cohort	32	30.00±6.23	Uni=24 Bil=8	7.28±2.80	3	AMH (original Gen II)	–
Yoon *et al. 2014 (9)*	Korea	Prospective cohort	37	30.30±5.0	Not specified	7.28±2.80	3	AMH (IOT kit)	–
Amooee *et al. 2015 (14)*	Iran	Prospective cohort	60	25.80 Average	Not specified	7.6 Average	3	AMH (DSL kit)	–
Ergun *et al. 2015 (6)*	Turkey	Prospective cohort	24	28.39±6.76	Uni=22 Bil=2	5.9±1.98	3	AMH (modified Gen II),	FSH

* RCT Arm 1, laparoscopy; Arm 2, laparotomy
** SD not available
Abbreviation: FU, follow up; OV, ovarian volume; Uni, unilateral; Bil, bilateral


Identification
Screening
Eligibility
Included
25 Records identified through database searching
0 Additional records identified through manual search
25 Records screened
10 Studies excluded as deemed not relevant
15 Full articles assisted for eligibility
5 studies excluded
One study excluded due to small number (n=3) of patients (19)
Another study excluded due to extremely low AMH levels (below the sensitivity of AMH assays) (16)
Three studies excluded due to missing the mean±SD AMH concentrations (data presented as median [IQR] (2, 18) or mean±SE% (17))
10 Studies included in systematic review
10 Studies included in meta-analysis

Study or Subgroup	postoperative Mean [ng/ml]	postoperative SD [ng/ml]	postoperative Total	preoperative Mean [ng/ml]	preoperative SD [ng/ml]	preoperative Total	Weight	Mean Difference IV, Fixed, 95% CI [ng/ml]
Amooee S 2015	2.48	1.4	60	3.77	1.4	60	19.2%	-1.29 [-1.79, -0.79]
Chang HJ 2010	1.93	0.51	7	2.75	2.28	7	1.6%	-0.82 [-2.55, 0.91]
Chen 2014	1.48	0.86	22	2.2	1.23	22	12.3%	-0.72 [-1.35, -0.09]
Ergun B 2015	1.84	1.72	24	2.67	2.67	24	3.0%	-0.83 [-2.10, 0.44]
Huang B-S 2014	3.37	1.24	71	3.94	1.53	71	23.0%	-0.57 [-1.03, -0.11]
Iwase A 2010	3.6	2.51	21	4.4	2.74	21	1.9%	-0.80 [-2.39, 0.79]
Kim SH 2013	3.4	2.1	34	5.1	3	34	3.2%	-1.70 [-2.93, -0.47]
Kwon SK 2014	3.75	2.05	32	4.84	2.26	32	4.3%	-1.09 [-2.15, -0.03]
Mohamed ML. 2011	2.6	0.7	59	4.2	1.5	59	27.1%	-1.60 [-2.02, -1.18]
Yoon BS 2014	2.5	1.5	37	4.4	2.9	37	4.4%	-1.90 [-2.95, -0.85]
Total (95% CI)			**367**			**367**	**100.0%**	**-1.14 [-1.36, -0.92]**

Heterogeneity: $Chi^2 = 15.92$, $df = 9$ ($P = 0.07$); $I^2 = 43\%$
Test for overall effect: $Z = 10.15$ ($P < 0.00001$)