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Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis

Ludovico Muzii, M.D., Chiara Di Tucci, M.D., Mara Di Feliciantonio, M.D., Giulia Galati, M.D., Violante Di Donato, M.D., Angela Musella, M.D., Innocenza Palaia, M.D., and Pierluigi Benedetti Panici, M.D.

Department of Obstetrics and Gynecology, "Sapienza" University of Rome, Rome, Italy

Objective: To evaluate if the presence of endometriomas impacts on the ovarian reserve as evaluated with antimüllerian hormone (AMH).

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Patients with unoperated endometriomas versus controls without endometriomas.

Intervention(s): Electronic databases searched up to June 2017 to identify articles evaluating AMH levels in patients with unoperated endometriomas versus controls without endometriomas.

Main Outcome Measure(s): The primary analysis was aimed at evaluation of AMH levels (mean and SD) in patients with and without endometriomas. Secondary analyses were aimed at evaluating AMH levels in patients with ovarian endometriomas compared to patients with either non-endometriosis benign ovarian cysts or healthy ovaries.

Result(s): Of the 39 studies evaluated in detail, 17 were included, for a total of 968 patients with endometriomas and 1874 without endometriomas. AMH was significantly lower in patients with unoperated endometriomas compared to patients with no endometriomas (mean difference −0.84, with 95% confidence interval [CI] −1.16 to −0.52). At secondary analyses, AMH in patients with endometriomas was significantly lower both versus non-endometriosis benign ovarian cysts (mean difference −0.85, 95% CI −1.37 to −0.32, and versus women with healthy ovaries (mean difference −0.61, 95% CI −0.99 to −0.24).

Conclusion(s): Ovarian reserve evaluated with AMH is reduced in patients with ovarian endometriomas compared both to patients with other benign ovarian cysts, and to patients with healthy ovaries. (Fertil Steril® 2018;110:932–40. ©2018 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Antimüllerian hormone, endometrioma, endometriosis, ovarian reserve

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Ovarian endometriomas are present in 17% to 44% of women with endometriosis, and are often associated with infertility and pelvic pain (1–3). Treatment options in case of an endometrioma include expectant management, medical treatment, surgical treatment, or in-vitro fertilization (IVF) in case of associated infertility (2–5).

Surgery is generally indicated in case of associated pain when medical treatment fails, or when the cyst shows non-reassuring features or fast growth at sonography (3–7). Surgery may also be considered in case of infertility if the patient complains also of associated pain symptoms, on which IVF is not effective (2, 4, 5, 7). When surgery is indicated, the preferred approach should be complete cyst excision by laparoscopy, since cyst excision is associated with better results in terms of postoperative pain relief, pregnancy rates, and cyst recurrence rates compared to non-excisional techniques (8).

A recent meta-analysis, however, has questioned the safety of the excisional technique, since it may be associated with a significant postoperative reduction of ovarian reserve as measured by antimüllerian hormone

(AMH) (9). There are evidences, therefore, that surgery for the excision of the ovarian endometrioma may damage the ovarian reserve. What is much less investigated in the literature, however, is the possibility that the presence of the endometrioma per se, and not only its excision, may damage the ovarian reserve. Benaglia et al. (10) demonstrated that the ovary with an unoperated endometrioma ovulates significantly less often than the contralateral healthy ovary. Kitajima et al. (11) demonstrated that follicular density is significantly reduced in cortex from ovaries with untreated endometriomas compared to contralateral ovaries without cysts. These findings may entail a damage to the ovarian reserve determined by the mere presence of an ovarian endometrioma, that may negatively affect the surrounding ovarian tissue in the absence of surgery. On the other hand, Leone Roberti Maggiore et al. (12) recently reported similar ovulation rates for ovaries affected by endometriomas compared to healthy ovaries, data therefore conflicting with those previously reported by Benaglia et al. (10). The aim of the present systematic review and meta-analysis is to answer the question if the presence of an ovarian endometrioma impacts on the ovarian reserve as measured by AMH, comparing AMH levels in patients with unoperated endometriomas versus controls without endometriomas.

MATERIALS AND METHODS

The present systematic review included all published research articles that evaluated AMH as a marker of ovarian reserve in patients with ovarian endometriomas, reporting comparisons of AMH levels in patients with untreated endometriomas versus a control group of patients without endometriomas. The control patients could be patients with non-endometriosis benign ovarian cysts, patients with other non-ovarian benign gynecological conditions, or healthy subjects.

Studies considered were randomized clinical trials (RCT), prospective controlled, prospective cohort, or retrospective studies. Only articles written in English were included. Proceedings of scientific meetings were not included. Institutional Review Board approval was not requested since the present study is a review of published studies.

An electronic database search was performed using PubMed, MEDLINE, and Embase for the identification of articles published until June 30, 2017, using a combination of the following search terms: antimüllerian hormone, AMH, ovarian reserve, endometriosis, endometrioma, endometriotic cyst. The search was conducted independently by three investigators (L.M., C.D.T., M.D.F.). Following the search, all articles considered pertinent on the basis of the title and abstract were retrieved, and their reference lists were searched for additional potential studies.

Subsequently, three investigators (L.M., C.D.T., M.D.F.) independently read the full text of the pre-selected articles, to verify the pertinence of the articles to the systematic review on AMH as a marker of ovarian reserve in patients with ovarian endometriomas compared to patients without endometriomas. After confirmation of pertinence, studies were excluded if reporting partial or complete duplicate data sets.

In case of data judged as pertinent but reported in forms not appropriate for meta-analysis, in case of incomplete data, or in case of uncertainty on any of the issues addressed in the systematic review as detailed here, the authors of the original articles were contacted to obtain the information needed.

In the event of disagreement on the inclusion or exclusion of the pre-selected studies for the meta-analysis, or for any other disagreement through the review process as outlined above, consensus was reached after discussion, or after involvement of further investigators (V.D.). Data from included studies were independently collected by three investigators on standardized forms, including items regarding study design, patient characteristics and AMH levels.

The primary analysis was aimed at evaluation of AMH levels in patients with and without endometriomas, and the outcome output was expressed as the mean weighted difference in AMH levels (expressed in ng/mL) in patients with endometriomas compared with AMH levels in control patients, considering all categories of control patients as a single group (patients with non-endometriosis benign ovarian cysts, patients with non-ovarian pathology, and healthy subjects).

Secondary analyses compared AMH levels in patients with endometrioma either versus patients with non-endometriosis benign ovarian cysts, or versus patients with healthy ovaries (benign uterine pathologies, tubal pathologies, other non-ovarian pathologies, healthy women). In case of articles reporting data of patients in the control group without the details necessary to include them in the secondary analyses, the authors were contacted to obtain separate data for the group of patients with non-endometriosis ovarian pathology versus patients with healthy ovaries. In case of non-response, the data were utilized only for the primary analysis.

If articles evaluated different subgroups of patients with endometriomas, some without previous adnexal surgery and others with previous adnexal surgery, only the first ones were included in the meta-analysis. When reporting on patients with moderate and severe endometriosis, or stage III and IV according to the revised American Society for Reproductive Medicine (rASRM) classification of endometriosis (13), without a clearly defined subgroup of patients with endometriomas, the authors were contacted to know the number of patients with endometriomas, and the corresponding AMH levels. When reporting patients affected by endometriosis at all rARSM stages, only the subgroup with endometriomas was included in the analysis. In articles evaluating both pre and post-operative AMH levels, only preoperative data were included. When reporting AMH levels separately for patients with monolateral and bilateral endometriomas, the authors were contacted to obtain data from the whole population, and, in the absence of a response, only the monolateral group was arbitrarily included in the analysis, to follow a more conservative approach towards the comparison with controls.

Articles including any patient with previous adnexal surgery (unless data for previously operated patients were reported separately and excluded), articles in which there was a statistically different mean patient age between the endometrioma and control groups, articles evaluating only patients with minimal/mild endometriosis, and articles

TABLE 1

Characteristics of the studies included in the systematic review.

| Author, year | Study design | Patients with endometrioma, n | Control patients | | | Age (y), mean ± SD | Endometrioma diameter (cm), mean ± SD | Unilateral/bilateral endometrioma | Serum AMH levels (ng/mL) | |
			Control patient, n	Other benign ovarian cysts	Healthy ovaries				Endometrioma, mean ± SD	Control, mean ± SD
Chen, 2014	Prospective	40	58	22	36	30.34 ± 4.63	7.70 ± 3.66	24/16	1.53 ± 1.37	2.58 ± 1.58 (C) 2.20 ± 1.23 (OC) 2.82 ± 1.74 (HO)
Chiang, 2015	Retrospective	23	496			35.0 ± 5.83	NR	23/0	2.6 ± 2.0	4.2 ± 2.0
Ercan, 2010	Prospective	47	12		12	28.2 ± 4.36	6.7 ± 0.91	33/14	1.62 ± 1.09	2.06 ± 0.51
Ergun, 2015	Prospective	26	24	24		28.39 ± 6.76	5.9 ± 1.98	16/10	1.92 ± 2.31	3.10 ± 2.64
Jeon, 2015	Retrospective	65	32	32		29.41 ± 4.50	6.73 ± 5.64	34/31	4.12 ± 2.42	6.02 ± 2.29
Kim JY, 2013	Retrospective	102	198	48	150	36.92 ± 6.69	5.5 ± 0.2	67/35	2.84 ± 2.98	3.61 ± 3.30 (C) 3.99 ± 3.23 (OC) 3.49 ± 3.32 (HO)
Kim YJ, 2017	Prospective	59	16	16		30.07 ± 4.87	4.9 ± 0.2	28/31	4.3 ± 3.07	5.6 ± 4.0
Kwon, 2014	Prospective	68	32	32		31.1 ± 5.9	5.99 ± 2.26	42/26	5.03 ± 3.07	4.84 ± 2.26
Lind, 2015	Prospective	18	36	36		32.1 ± 6.2	5.7 ± 2.2	18/18	2.25 ± 2.14	3.3 ± 3.25
Pacchiarotti, 2013	Prospective	65	130		130	32.93 ± 2.02	NR	NR	0.97 ± 0.59	1.72 ± 0.63
Salihoglu, 2016	Prospective	34	33	33		Range, 18–40 y	>4	NR	3.1 ± 1.9	5.7 ± 3.7
Somigliana, 2014	Prospective	122	163	50	113	32.33 ± 4.88	4.0 (1–120) median and range	39/83	2.27 ± 2.01	2.67 ± 2.68 (C) 3.00 ± 3.20 (OC) 2.53 ± 2.42 (HO)
Streuli, 2012	Prospective	77	413	99	306	32.07 ± 5.76	NR	46/31	4.0 ± 3.0	4.1 ± 3.4 (C) 4.1 ± 3.5 (OC) 4.07 ± 3.35 (HO)
Tanprasertkul, 2014	Prospective	39	38		38	33.73 ± 6.21	5.46 ± 1.70	33/6	2.84 ± 2.47	2.33 ± 1.91
Uncu, 2013	Prospective	30	30		30	29.55 ± 4.91	42.5 (38.6–51.7) median and range	15/15	2.81 ± 2.15	4.20 ± 2.26
Wdowiak, 2016	Retrospective	144	115		115	Range, 30–34 y	NR	NR	3.64 ± 1.94	3.71 ± 2.09
Yoo, 2011	Retrospective	9	48		48	35.18 ± 4.46	NR	NR	1.5 ± 0.9	4.1 ± 2.9

Notes: AMH = antimüllerian hormone; C = control; E = endometrioma; HO = healthy ovaries; NR = not reported; OC = other benign ovarian cysts.

Muzii. AMH is reduced with endometriomas. Fertil Steril 2018.

reporting only patients with deep infiltrating endometriosis, were excluded. In case of subgroups of patients with polycystic ovary syndrome, these were excluded from the meta-analysis.

Quality assessment of observational studies was carried out using the Newcastle-Ottawa Scale (14). Two investigators (V.D.D., A.M.) independently assessed the quality of the selected studies. A third investigator (I.P.) was involved in case of disagreement. The data were pooled using RevMan software (Review Manager version 5.1, the Cochrane Collaboration, 2011). Mean AMH values, expressed in ng/mL, and SD were extracted from the original articles, or after contacting the authors of the article in case of incomplete, missing, or implausible data, or data presented in a non-usable format. Weighted mean differences were calculated for the AMH values. Heterogeneity between studies was based on the results of the X^2 and I^2 statistics. At meta-analysis, a fixed-effect model was used in case of low heterogeneity, whereas a random-effect model was used in case of high heterogeneity between studies. $P < .05$ was considered statistically significant.

RESULTS

Thirty-nine studies were pre-selected after the electronic search based on article title and abstract, and after manual search of the reference list of the full articles (Supplemental Fig. 1). After reading the full text, a total of 22 studies were excluded. Nine studies did not express AMH results with media and standard deviation, but they used median and range, interquartile range, or confidence intervals (15–23). The authors were contacted to obtain data expressed with mean and standard deviation; the requested data were provided by two authors (18, 19), with subsequent inclusion of their studies, whereas the remaining seven studies were excluded (15–17, 20–23). Five studies included patients with endometriosis at various rASRM stages without a subgroup analysis for endometriomas (24–28). The authors were contacted to obtain the number of patients and the AMH levels in the subgroup with endometriomas. Two authors provided the missing information, and these studies were included (26, 28). The other three studies were excluded (24, 25, 27). After contacting the authors, four studies were excluded for missing data about the endometrioma group (29–32). Three studies were excluded because the authors considered only patients with stage I-II endometriosis, without a subgroup with endometriomas (33–35). Three studies were excluded because patient age was significantly different between endometrioma group compared to controls (36–38). One study expressed AMH values using pg/mL and, when converting the values to ng/mL, the data were too divergent, and therefore implausible, compared to all other studies (39); the authors were contacted but no reply was received, so the study was excluded. One study was excluded because all included patients had a history of adnexal surgery (40).

Two studies expressed results with media and standard error of the mean; in these cases, the standard error of the mean was converted to standard deviation (41, 42). A total of 17 studies were therefore included at final analysis, for a total of 968 patients with endometrioma and 1874 patients in the control group (Table 1) (18, 19, 26, 28, 41–53). Twelve studies were prospective studies (18, 19, 28, 42–47, 49, 51, 53) and five were retrospective studies (26, 41, 48, 50, 52). Six studies included in the control group only patients with non-endometriosis benign ovarian cysts (19, 42, 46, 49–51). Six studies included in the control group only women with healthy ovaries (26, 28, 43, 47, 52, 53). One study divided the control group in patients with or without previous adnexal surgery, but it was not specified if the group without previous surgery had ovarian or non-ovarian pathology, or if the patients were healthy women (48). The authors of this study were contacted to receive additional information about the control groups, but no answer was received. The study was therefore included in the systematic review and in the primary analysis, considering only patients without previous surgery, but excluded from the secondary analysis. Four studies (18, 41, 44, 45) included in the control group both patients with non-endometriosis benign ovarian cysts and patients with healthy ovaries (non-ovarian pathology and/or healthy patients), and reported the results for AMH levels separately for the two subgroups; for this reason, they were included both in the primary and secondary meta-analyses.

The primary analysis aimed at the evaluation of the difference in AMH levels between a group of patients with endometrioma versus a control group including both non-endometriosis benign ovarian cysts and healthy ovaries (Fig. 1). It was observed that AMH levels were significantly lower in the endometrioma group compared to patients with no endometrioma (mean difference −0.84, 95% confidence interal [CI] −1.16 to −0.52; $P < .00001$). Heterogeneity for this comparison was high ($I^2 = 71\%$).
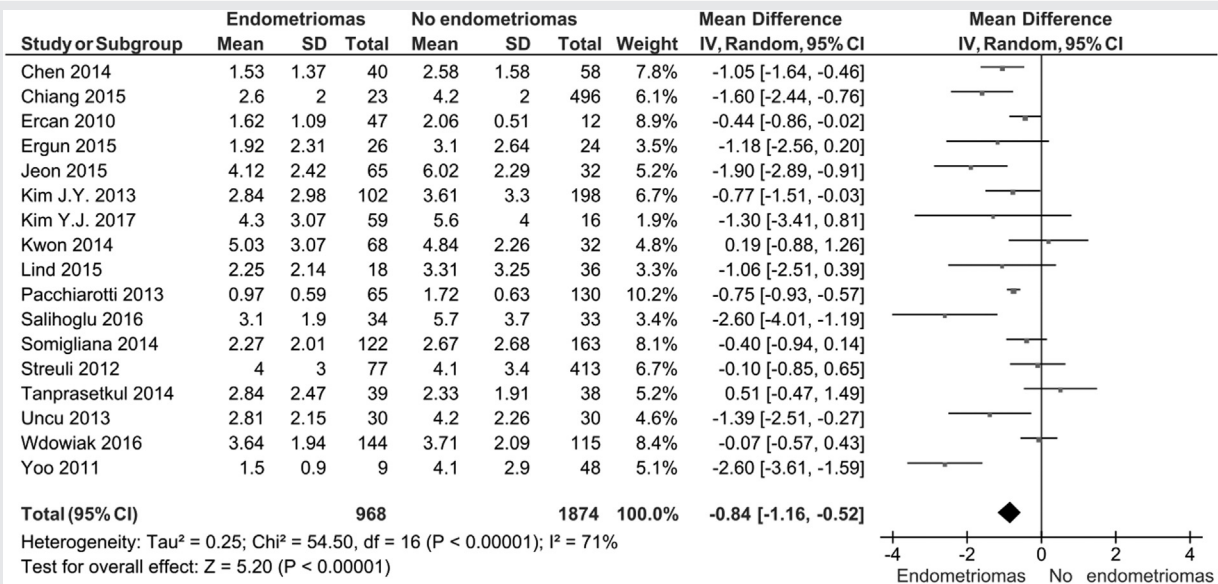
The secondary analyses aimed at the evaluation of the difference in AMH levels between a group of patients with endometrioma versus a control group of either patients with non-endometriosis benign ovarian cysts (Fig. 2) or patients with healthy ovaries (Fig. 3). As to the former comparison (Fig. 2), a significantly lower AMH level was observed in the endometrioma group compared to non-endometriosis ovarian cysts (mean difference −0.85, 95% CI −1.37 to −0.32; $P = .002$). Heterogeneity for this comparison was high ($I^2 = 58\%$). As to the latter comparison (Fig. 3), AMH levels were significantly lower in endometrioma group compared to healthy ovaries (mean difference −0.61, 95% CI −0.99 to −0.24; $P = .001$). Heterogeneity for this comparison was high ($I^2 = 76\%$).

All the included studies were at low risk of bias according to the Newcastle-Ottawa Scale (Supplemental Table 1). A sensitivity analysis was therefore performed according to study design, including only the prospective studies, and confirmed a significant difference in AMH levels for patients with endometriomas compared to patients without endometriomas (mean difference −0.64, with 95% CI −0.95 to −0.33; $P < .0001$). Heterogeneity for this comparison was high ($I^2 = 55\%$).

DISCUSSION

Recently, concerns have been raised as to the possibility that surgical excision of the endometrioma may damage the

FIGURE 1

Study or Subgroup	Endometriomas Mean	SD	Total	No endometriomas Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2014	1.53	1.37	40	2.58	1.58	58	7.8%	-1.05 [-1.64, -0.46]
Chiang 2015	2.6	2	23	4.2	2	496	6.1%	-1.60 [-2.44, -0.76]
Ercan 2010	1.62	1.09	47	2.06	0.51	12	8.9%	-0.44 [-0.86, -0.02]
Ergun 2015	1.92	2.31	26	3.1	2.64	24	3.5%	-1.18 [-2.56, 0.20]
Jeon 2015	4.12	2.42	65	6.02	2.29	32	5.2%	-1.90 [-2.89, -0.91]
Kim J.Y. 2013	2.84	2.98	102	3.61	3.3	198	6.7%	-0.77 [-1.51, -0.03]
Kim Y.J. 2017	4.3	3.07	59	5.6	4	16	1.9%	-1.30 [-3.41, 0.81]
Kwon 2014	5.03	3.07	68	4.84	2.26	32	4.8%	0.19 [-0.88, 1.26]
Lind 2015	2.25	2.14	18	3.31	3.25	36	3.3%	-1.06 [-2.51, 0.39]
Pacchiarotti 2013	0.97	0.59	65	1.72	0.63	130	10.2%	-0.75 [-0.93, -0.57]
Salihoglu 2016	3.1	1.9	34	5.7	3.7	33	3.4%	-2.60 [-4.01, -1.19]
Somigliana 2014	2.27	2.01	122	2.67	2.68	163	8.1%	-0.40 [-0.94, 0.14]
Streuli 2012	4	3	77	4.1	3.4	413	6.7%	-0.10 [-0.85, 0.65]
Tanprasetkul 2014	2.84	2.47	39	2.33	1.91	38	5.2%	0.51 [-0.47, 1.49]
Uncu 2013	2.81	2.15	30	4.2	2.26	30	4.6%	-1.39 [-2.51, -0.27]
Wdowiak 2016	3.64	1.94	144	3.71	2.09	115	8.4%	-0.07 [-0.57, 0.43]
Yoo 2011	1.5	0.9	9	4.1	2.9	48	5.1%	-2.60 [-3.61, -1.59]
Total (95% CI)			**968**			**1874**	**100.0%**	**-0.84 [-1.16, -0.52]**

Heterogeneity: Tau² = 0.25; Chi² = 54.50, df = 16 (P < 0.00001); I² = 71%
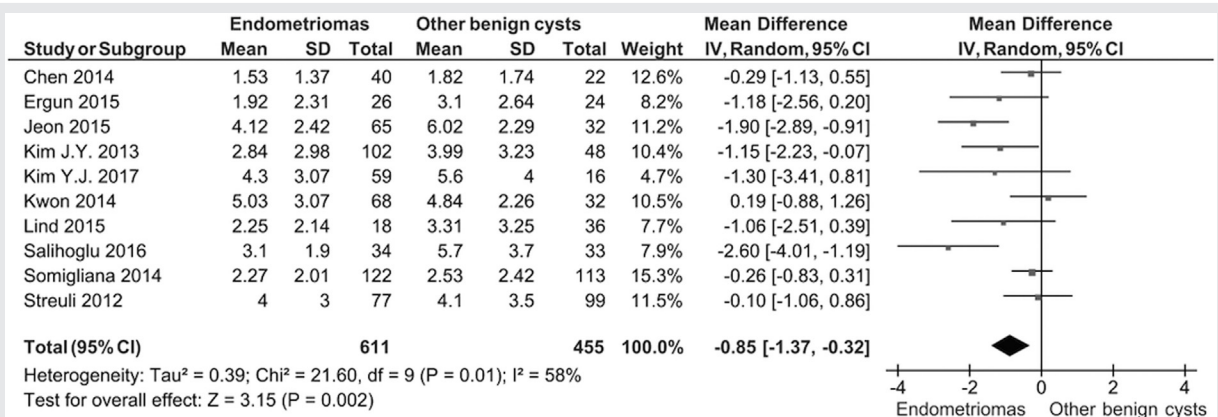Test for overall effect: Z = 5.20 (P < 0.00001)

Meta-analysis. Weighted mean difference in AMH in patients with ovarian endometriomas compared to patients without ovarian endometriomas.

Muzii. AMH is reduced with endometriomas. Fertil Steril 2018.

ovarian reserve. Two recent systematic reviews report in fact a decrease in levels of AMH compared to preoperative levels after endometrioma excision (9, 54). If, on one hand, the damage to the ovarian reserve due to surgical excision of the endometrioma has gained much attention in the last few years, on the other hand the possibility that the presence of the endometrioma per se may damage the ovarian reserve has received much less attention. Scanty evidence is in fact available from the literature to support the hypothesis of a diminished ovarian reserve in the presence of an endometrioma. A recent meta-analysis evaluating antral follicle count as a marker of ovarian reserve both before and after surgical excision of endometriomas demonstrated that, in patients with monolateral endometriomas, antral follicle count is lower on the site with the unoperated cyst compared to the contralateral, healthy ovary, although nonsignificantly (55). Some evidences that part of the damage to the ovarian reserve may be due to the mere presence of the endometrioma, regardless of surgery, is available from pathology studies. Kitajima et al. (11) reported that the follicular density in the ovary where the endometrioma is located is significantly lower than in the contralateral, unaffected ovary

FIGURE 2

Study or Subgroup	Endometriomas Mean	SD	Total	Other benign cysts Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2014	1.53	1.37	40	1.82	1.74	22	12.6%	-0.29 [-1.13, 0.55]
Ergun 2015	1.92	2.31	26	3.1	2.64	24	8.2%	-1.18 [-2.56, 0.20]
Jeon 2015	4.12	2.42	65	6.02	2.29	32	11.2%	-1.90 [-2.89, -0.91]
Kim J.Y. 2013	2.84	2.98	102	3.99	3.23	48	10.4%	-1.15 [-2.23, -0.07]
Kim Y.J. 2017	4.3	3.07	59	5.6	4	16	4.7%	-1.30 [-3.41, 0.81]
Kwon 2014	5.03	3.07	68	4.84	2.26	32	10.5%	0.19 [-0.88, 1.26]
Lind 2015	2.25	2.14	18	3.31	3.25	36	7.7%	-1.06 [-2.51, 0.39]
Salihoglu 2016	3.1	1.9	34	5.7	3.7	33	7.9%	-2.60 [-4.01, -1.19]
Somigliana 2014	2.27	2.01	122	2.53	2.42	113	15.3%	-0.26 [-0.83, 0.31]
Streuli 2012	4	3	77	4.1	3.5	99	11.5%	-0.10 [-1.06, 0.86]
Total (95% CI)			**611**			**455**	**100.0%**	**-0.85 [-1.37, -0.32]**

Heterogeneity: Tau² = 0.39; Chi² = 21.60, df = 9 (P = 0.01); I² = 58%
Test for overall effect: Z = 3.15 (P = 0.002)

Meta-analysis. Weighted mean difference in AMH in patients with ovarian endometriomas compared to patients with other non-endometriosis benign ovarian cysts.

Muzii. AMH is reduced with endometriomas. Fertil Steril 2018.

FIGURE 3
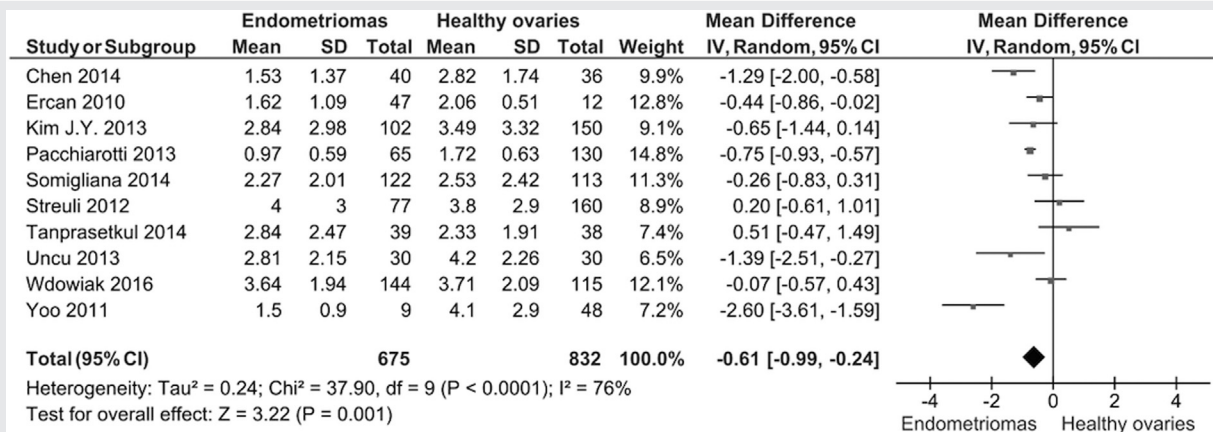
Meta-analysis. Weighted mean difference in AMH in patients with ovarian endometriomas compared to control women with healthy ovaries.

Muzii. AMH is reduced with endometriomas. Fertil Steril 2018.

(6.3 ± 4.1 vs. 25.1 ± 15.0 follicles/mm³, respectively; $P = .0002$). In a second study, Kitajima et al. reported a percentage of atretic follicles of 20.3% in ovaries with endometriomas, compared to 6.3% in the contralateral ovaries without endometriomas ($P < .001$) (56). In both studies by Kitajima et al. (11, 56), the biopsies for the evaluation of the follicular density and atresia were collected in an area of the ovary more than 1 cm away from the endometrioma, on macroscopically normal-looking ovarian cortex. The deleterious effect of the presence of the endometrioma is therefore evident at a significant distance from the endometrioma cyst wall. A plethora of factors potentially toxic to the ovarian tissue and to growing follicles, such as reactive oxygen species, free iron, proteolytic enzymes, are present in high concentrations in the endometrioma fluid (57). These factors may penetrate the tissue surrounding the cyst, therefore causing fibrosis, smooth muscle metaplasia, and consequent reduction of cortex-specific stroma and follicular loss (58).

If the presence of the endometrioma per se, regardless to its surgical excision, is associated to some damage to the ovarian tissue pre-existent to surgery, one may hypothesize that markers of ovarian reserve, such as AMH, may be lower in patients with endometriomas compared to control patients with non-endometriotic ovarian cysts, or with healthy ovaries.

In the present systematic review, we report a significant reduction in AMH levels, in the absence of surgery, in patients with ovarian endometriomas, compared to control patients with no endometrioma, either patients with non-endometriotic ovarian cysts, or women with no ovarian pathology. Patients with endometriomas have a weighted mean difference in AMH levels of −0.84 ng/mL (95% CI −1.16 to −0.52) compared to patients without endometriomas. This holds true, with statistical significance, both in comparison with non-endometriotic cysts (weighted mean difference of −0.85 ng/mL), or with healthy ovaries (non-ovarian pathology or healthy subjects) (weighted mean difference of −0.61 ng/mL). The data from the present

meta-analysis therefore support the hypothesis that the presence of the endometrioma per se, and not only the surgical procedure of cyst excision, may be responsible for a decrease in AMH levels in patients with ovarian endometriomas. Since the reduction in AMH levels in patients with endometriomas is significant compared to patients with other ovarian cysts, this reduction does not seem to be caused by the simple stretching of the surrounding ovarian tissue due to the mere presence of the cyst.

In the present study we did not address the issue of AMH levels in relation with cyst size, which may be crucial in endometrioma-related damage to the ovarian reserve. It is reasonable that larger cysts may be associated with lower levels of AMH. However, we did not attempt a secondary analysis based on endometrioma size, since most of the included studies reported on patients with a relatively narrow distribution of cyst dimension, whereas a minority of studies did not report on cyst size (Table 1). As to the possible influence of cyst size on ovarian function, recently Ferrero et al. (59) reported a reduced response to superovulation for *in vitro* fertilization in ovaries with endometriomas larger than 5 cm compared to contralateral healthy ovaries, therefore confirming the hypothesis that larger cysts may be associated with more severe damage to the ovarian reserve. Also, the issue of bilaterality versus monolaterality of the cyst was not addressed in the present systematic review. Most studies did not report separate values of AMH for bilateral versus monolateral cysts, and a secondary analysis on bilaterality was not attempted. It is reasonable to speculate that AMH levels may be lower in case of bilateral cysts compared to monolateral ones. On the same line, although related to postsurgical ovarian function, damage to the ovarian reserve has been reported to be more severe in bilateral cases, expressed as a higher risk of premature ovarian insufficiency after surgery for bilateral endometriomas (60).

Current guidelines recommend that clinicians counsel women with an ovarian endometrioma regarding the risks

of reduced ovarian function after surgery (2, 5), due to the evidence of a postoperative decrease in AMH values (9, 54). The evidence from the present systematic review supports the possibility that a reduction of AMH as a marker of ovarian reserve may be due also to the presence of the endometrioma per se, in addition to its surgical excision. The patient with an ovarian endometrioma should therefore be made aware of the possibility that the presence of the unoperated cyst may lower the levels of AMH in patients with endometriomas compared to control patients. There are no data available in the literature to evaluate the relative contribution of the mere presence of the endometrioma versus its surgical excision to the decrease in AMH levels. Additional studies are therefore needed, to evaluate markers of ovarian reserve in patients with ovarian endometriomas that are managed expectantly. If such studies demonstrate a progressive reduction of markers of ovarian reserve with time when the cyst is managed expectantly, one may hypothesize that abstention from treatment may not be as safe as previously believed with respect to the ovarian reserve, as measured by AMH. On the other hand, a retrospective study on 29 patients undergoing two in vitro fertilization cycles at least 6 months apart failed to observe a progressive endometrioma-related reduction of ovarian responsiveness with time (61) and represents the only available evidence on the longitudinal evaluation of ovarian function in the presence of an endometrioma. However, mean cyst size in this study (2.6 cm) was relatively small compared to the studies included in the present review (Table 1). Therefore, these reassuring data (61) may not be extrapolated to the general population with endometriomas.

In conclusion, the present systematic review and meta-analysis demonstrates that the presence of an ovarian endometrioma, and not only its surgical excision, is associated with reduced levels of serum AMH, both when compared to non-endometriosis ovarian cysts and to healthy ovaries.

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Los niveles de hormona antimülleriana se reducen en presencia de endometriomas ováricos: revisión sistemática y meta-análisis

Objetivo: Evaluar si la presencia de endometriomas afecta la reserva ovárica medida a través de los valores de la hormona antimülleriana (HAM).

Diseño: Revisión sistemática y meta-análisis.

Setting: No aplica.

**Pacientes:** Pacientes con endometriomas no intervenidas quirúrgicamente versus controles sin endometriomas.

Intervenciones: Búsqueda sistemática en bases de datos electrónica hasta junio de 2017 para identificar artículos en los que se comparaba los niveles de HAM en pacientes no intervenidas quirúrgicamente de endometriomas con respecto a los controles sin endometriomas.

Medidas principales: El análisis principal fue la evaluación de los niveles de HAM (media y desviación estándar) entre pacientes con y sin endometriomas. Análisis secundarios evaluaron los niveles de HAM en pacientes con endometriomas ováricos comparados con pacientes con quistes ováricos benignos no endometriosicos y pacientes con ovarios sanos.

Resultados: De los 39 estudios evaluados en detalle, se incluyeron 17, con un total de 968 pacientes con endometriomas y 1874 sin endometriomas. Los niveles de HAM fueron significativamente menores en pacientes no intervenidas por endometriomas comparadas con pacientes sin endometriomas (la diferencia de las medias, fue - 0.84, con un intervalo de confianza (IC) del 95% con rango de -1.16 a - 0.52). Los análisis secundarios mostraron que los niveles de HAM en pacientes con endometriomas eran significativamente menores comparados con pacientes con quistes ováricos benignos (mostrando una diferencia de las medias de -0.85, y un IC del 95% entre -1.37 y -0.32), así como con las pacientes con ovarios sanos (con una diferencia de las medias de - 0.61, y un IC del 95% comprendido entre -0.99 y - 0.24).

Conclusiones: La reserva ovárica evaluada mediante los niveles de HAM se reduce en pacientes con endometriomas ováricos en comparación tanto con pacientes con quistes ováricos benignos como con pacientes con ovarios sanos.

SUPPLEMENTAL FIGURE 1
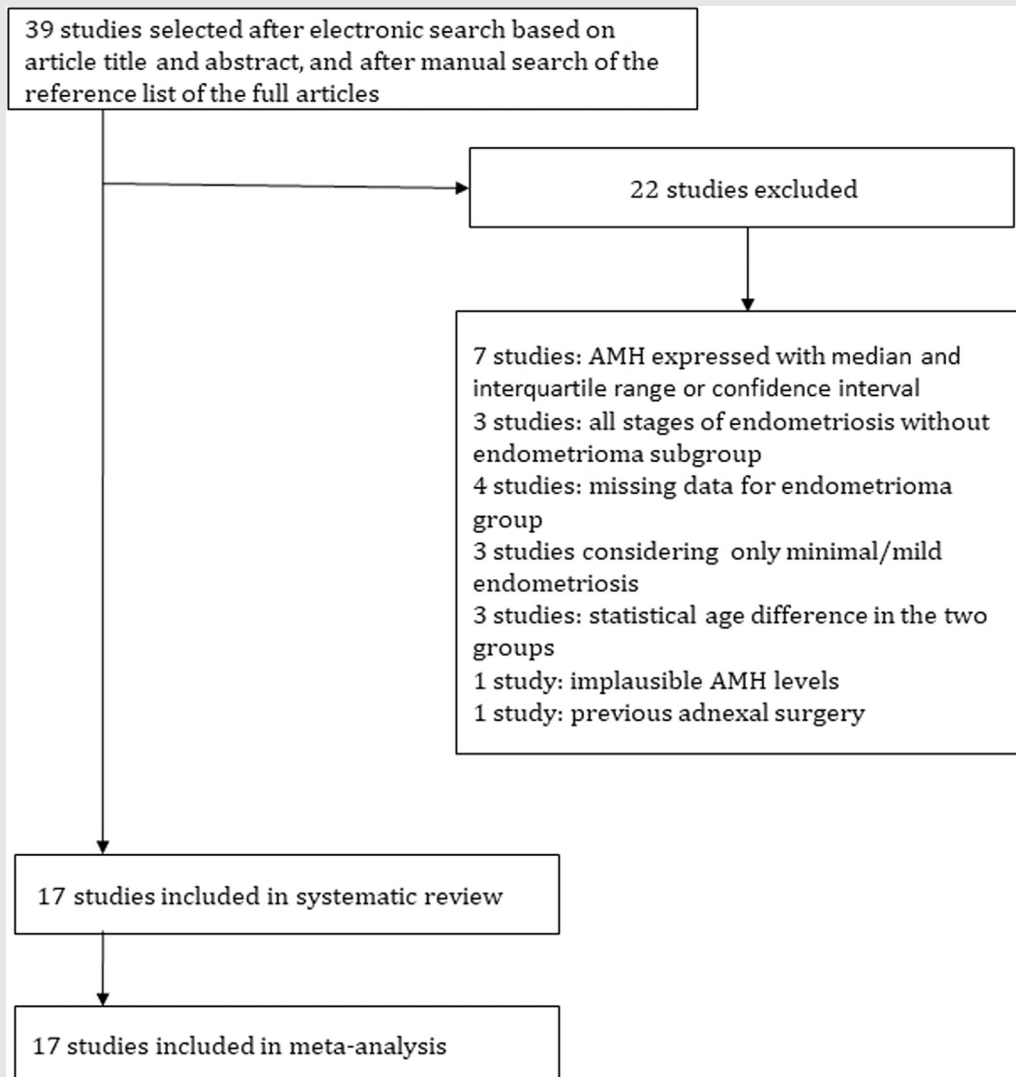
Flow-chart of the study selection process.

Muzii. AMH is reduced with endometriomas. Fertil Steril 2018.