The Effects of Laparoscopic Surgery on Anti-Müllerian Hormone (AMH) Levels for Ovarian Endometriomas: A Systematic Review and Meta-Analysis

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ABSTRACT
Background: The anti-Müllerian Hormone (AMH) is an important sign that gives clues about the ovarian reserve; it is mostly made by the granulosa cells of ovarian follicles. AMH plays a crucial role in the complicated process of folliculogenesis, controlling the "recruitment" of primordial follicles, regulating growth and atresia in primary and secondary follicles, and suppressing the excessive growth of ovarian follicles.
Purpose: To ascertain the effect of laparoscopic surgery on AMH levels in patients with ovarian endometrioma.
Materials and methods: A systematic review and meta-analysis were performed. Searches of the PubMed, Medline, Scopus, and Embase databases were conducted by two independent reviewers. The search strategy identified relevant randomized controlled trials (RCTs) and quasi-experimental studies from 2000 to 2023. The quality of the studies was assessed using the Cochrane Risk of Bias tool. The study's primary outcome was the change in AMH levels from baseline to 12 months after laparoscopic surgery for endometrioma. We used a random effects model to estimate pooled means. **Findings:** The results from the six included RCTs studies involving a total of 681 patients were pooled. The meta-analysis revealed that patients who underwent laparoscopic surgery experienced an overall decline in AMH levels in the 12-month time frame post-surgery, with a mean difference of - 1.41ng/mL (95% CI = - 2.04 to - 0.78, $P < 0.0001$, $I^2 = 93\%$). **Conclusion**: Laparoscopic surgery on ovarian endometriomas may adversely affect ovarian reserve. Notably, a decline in AMH levels has been observed 12 months post-surgery, indicating potential long-term effects on ovarian function. Therefore, a cautious approach is recommended when considering laparoscopic surgery, emphasizing the importance of monitoring ovarian reserve in the postoperative period to mitigate any adverse outcomes.
Keywords: Anti-Müllerian hormone, Endometrioma, Endometriosis, Laparoscopy.

INTRODUCTION
Ovarian endometrioma is a specific kind of endometriosis that affects the ovary. Ovarian endometrioma is a complex condition that affects women in their reproductive years, and it may have serious consequences for their fertility [1-3].

The ovarian endometrioma, a condition with unclear etiology, is by far the most common type of endometriosis-related ovarian mass, and it carries with it significant risks for cancer and substantial morbidity associated with its diagnosis and treatment [4]. Though it is primarily a benign entity, the ovarian endometrioma poses serious challenges to the reproductive health of women. The microscopic structure of ovarian endometriomas usually looks like the microscopic structure of normal endometrial glands and stroma. The cystic spaces that are characteristic of endometriomas sometimes contain normal endometrial tissue [5].

Ovarian endometriomas are considered to be highly detrimental to fertility because they impair normal ovarian function and are managed surgically when they become large or symptomatic. Laparoscopic surgery has mostly replaced traditional open surgery for endometrioma management because it is less invasive, reduces the chances of major complications, and shortens the recovery time [6].

Even with its benefits related to surgical results and recovery comfort, the concern that surgery might affect ovarian reserve is still present. Ovarian reserve is a critical factor when it comes to considering any kind of future pregnancy; hence, the effect of surgery on it has to be looked at closely [7].

The AMH is an important sign that gives clues about the ovarian reserve; it is mostly made by the granulosa cells of ovarian follicles. AMH plays a crucial role in the complicated process of folliculogenesis, controlling the "recruitment" of primordial follicles, regulating growth and atresia in primary and secondary follicles, and suppressing the excessive growth of ovarian follicles. The ovarian reserve is the number and quality of oocytes in the ovaries at a given time [8,9].

Since the AMH concentration reflects the number of follicles in the ovaries and their kind (healthy ones in a large number), it serves as a good measure for the ovarian reserve. Clinicians can glean essential details about a woman's remaining ovarian reserve and reproductive lifespan just by watching the levels of AMH. It says when a woman has a number of follicles in a normal, healthy condition. And it says when she is approaching the time in her life that she will not have those follicles, or eggs, in reserve [10]. Understanding AMH signals really has only become possible in the past 15 to 20 years. Yet, among reproductive endocrinologists, the hormone now has a stellar reputation as a reliable and cutting-edge marker for assessing a woman's fertility potential [11].

Research on the effects of laparoscopic surgery for ovarian endometrioma on AMH levels post-surgery is clearly inconsistent. Some studies show substantial drops in AMH levels after the operation, some find no

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significant effects, and most fall somewhere in between. The reasons for this lack of consensus are not fully understood, but they may include the size of endometriomas, the amount of tissue excised, and the caliber of a woman's ovaries before surgery [12,13].

To date, no study has been designed to provide a clear picture of what happens to AMH after laparoscopic surgery anywhere from 3 to 12 months post-operation. This systematic review and meta-analysis aimed to furnish thorough understanding of the laparoscopic surgery's impact on anti-Müllerian hormone levels 12 months post-operation. When clinicians understand the long-term effects of ovarian endometriomas, they can make better-informed decisions about how to manage this condition. They also can offer women better counseling about their individual situations and the fertility-preserving decisions they might consider.

MATERIALS AND METHODS

Ethical considerations:

This review and meta-analysis of the randomized controlled trials indicated that because of the design of the study, institutional review board approval was not necessary. The study's authors reported the work in adherence to the established standards for transparency and rigor of the systematic review and meta-analysis work. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Selection criteria:

The criteria for selecting studies for the meta-analysis specified that the studies included must have reported AMH levels measured both preoperatively and at 12 months postoperative. The evidence base we've established is composed entirely of randomized controlled trials conducted in English. Each of these trials provided detailed, standardized information about inclusion and exclusion criteria, preoperative and postoperative AMH results, and underwent a rigorous review process to ensure that the findings were reliable. The way these studies were reported made it easy to understand the impact of laparoscopic surgery on AMH levels in the context of endometriosis.

Search strategy and study selection:

A systematic search was carried out to find pertinent studies in the databases of PubMed, Embase, Medline, and Scopus. For this, we used specific Medical Subject Heading terms. The terms we searched for included endometriotic cyst, endometrioma, anti-Müllerian hormone, AMH, and laparoscopy. We looked for relevant studies from the years 2000 to 2023. The titles and abstracts of the records retrieved had two colleagues working for them. Titles and abstracts were screened, by the two to find additional studies not otherwise discovered. They also found them by checking reference lists of what they considered relevant articles. They reviewed the full texts of the partially selected articles for duplicates, to ensure that was maintained in the meta-analysis. At the end of this rigorous process, they could guarantee only appropriate data were used for the review.

Data extraction:

Data from the studies included in this review were extracted independently by two reviewers. They used standardized forms to cover the key details of each study, including its design, the characteristics of the patients, any surgical procedures that were performed, the timing of the measurements, and the outcomes related to AMH. If the two reviewers disagreed about any aspect of a study, they resolved the disagreement by reaching a consensus or, if necessary, calling in a third reviewer.

Assessment of risk of bias in eligible studies:

To determine the risk of bias in the studies we included, we used the Cochrane Collaboration tool for RCTs. Two reviewers working independently used this method to examine seven domains of potential bias. For each domain, we rendered a judgment of "low risk," "high risk," or "unclear risk" regarding how well the trial was protected against that bias. These judgments were based on evidence in the reports of the trials, using the evidence to work backward through the trial procedures to determine how closely the trials adhered to the ideal RCT design.

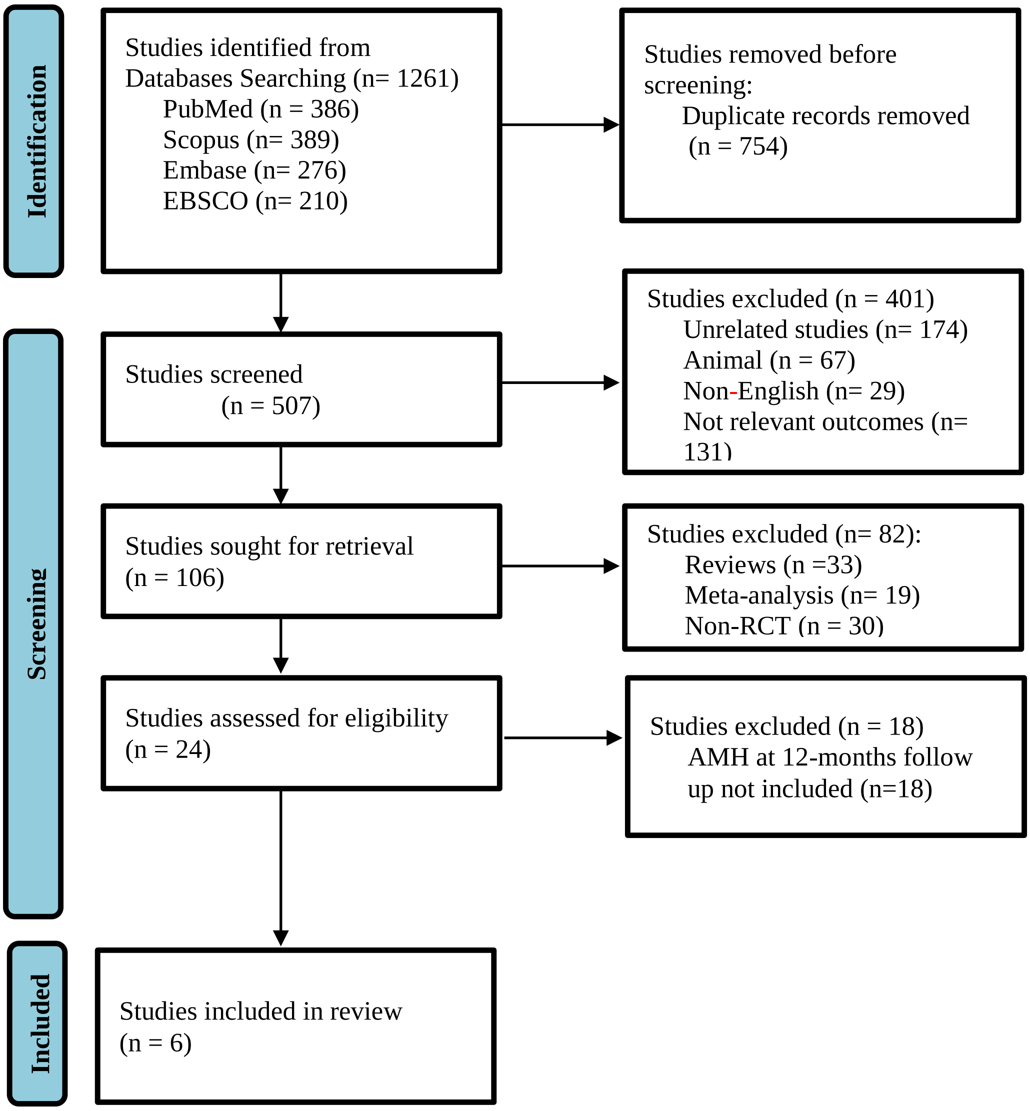
Outcomes: This meta-analysis assessed the changes in AMH serum levels following laparoscopic surgery for ovarian endometriomas. It specifically evaluated the mean AMH level and its standard deviation at 12 months post-op, as an important reflection of the impact lap surgery had on ovarian reserve.

Statistical analysis: The Review Manager Software version 5.3 was used to carry out the data extraction from original articles. This software extracted mean values and standard deviations from the articles. To assess the effectiveness of continuous outcomes, mean differences (MD) with 95% credible intervals were calculated. The MDs were combined to yield an overall effect. To evaluate the statistical heterogeneity of the combined studies, we used the X^2 and I^2 tests. The data were analyzed using a random-effects model. P value < 0.05 was considered significant.

RESULTS

Study selection:

We began with a total of 1,261 citations. After a title and abstract screening, we removed 754 duplicates found through this screening. After evaluating the remaining 507, we found that a substantial number were unrelated to the interventions we were interested in (n = 174); these were in publications not in English (n = 29); they reported on outcomes that did not pertain to our objectives (n = 131); or they examined problems that were so basic or used such animal models that they were not relevant (n = 67) to our study. Another 82 studies that were reviews or meta-analyses or that did not use randomization were also eliminated from consideration (Figure 1). Thus, after this standard method of critical appraisal for randomized controlled trials, only 6 out of 24 RCTs met our criteria for inclusion in a meta-analysis [15-20].



RCT, randomized controlled trial; **AMH**, anti-mullerian hormone.

Figure (1): Flow diagram of study selection

Characteristics of the trials:

Table 1 summarizes the key aspects of the eligible studies. In total, these studies included 681 patients. All procedures were laparoscopic. Five of the randomized controlled trials (RCTs) involved endometriomas on either one or both sides [15-19], and one trial involved only a unilateral endometrioma [20].

The surgeries all laparoscopic were of a variant type of cystectomy [16, 18-20], a "cyst stripping" surgery [15], and a study that performed cystectomy vs. "cyst de-roofing" [17]. The studies' postoperative follow-up times included 1, 3, and 12 months in three studies [15,18,20], 1, 2, 6, and 12 months in two studies [16,19], and 1 and 12 months in one study [17].

Table (1): Characteristics of the studies included in the meta-analysis

Authors	Location	Study time	Participants	Patients' age (years)[a]	Laterality of endometrioma	Diameter of endometrioma (cm)[a]	Type of Laparoscopic surgery	outcome
Alborzi *et al.* 2022[20]	Iran	2016-2020	120	30.5[b]	Unilateral	Data can't be identified	Ovarian cystectomy	AMH before surgery and at 3, 6, and 12 months after surgery.
Chung *et al.* 2021[18]	Hong Kong	2014-2019	75	32.0 ± 5.0	Unilateral and Bilateral	4.2 ± 1.4	Ovarian cystectomy	AMH before surgery and at 3, 6, and 12 months after surgery.
Ferrero *et al.* 2012[15]	Italy	2007-2010	100	32 ± 3.8	Unilateral and Bilateral	7.5 ± 2.6	Stripping of endometriomas	AMH before surgery and at 3, 6, and 12 months after surgery.
Muraoka *et al.* 2021[19]	Japan	2016-2020	57	33.0 ± 5.6	Unilateral and Bilateral	6.7 ± 2.3	Ovarian cystectomy	AMH before surgery and at 1, 2, 6, and 12 months after surgery.
Sweed *et al.* 2019[17]	Egypt	2013-2017	122	26.3 ± 4.2	Unilateral and Bilateral	5.4 ± 0.8	Ovarian cystectomy vs. Cyst de-roofing	AMH before surgery and at 1 and 12 months after surgery.
Zhang *et al.* 2016[16]	China	2013	207	31.8 ± 8.0	Unilateral and Bilateral	5.1 ± 2.7	Ovarian cystectomy	AMH before surgery and at 1, 2, 6, and 12 months after surgery.

[a] Data presented as mean ± standard deviation
[b] standard deviation can't be identified

Risk of Bias

The six randomized controlled trials (RCTs) we assessed had a low risk of bias (Figure 2 and 3). The only RCT for which we could not find a clear description of blinding of outcome assessors was that of **Alborzi *et al.*** [20].

Two of the studies [16,20] did not clearly describe their sample sizes. **Alborzi *et al.*** [20] reported that they had determined their sample size using a power analysis with power set to 95% (α error = 0.05). **Zhang *et al.*** [16] indicated that their sample size was determined using a non-inferiority test. Instead, **Sweed and colleagues**[17] did not present a sample size calculation, but they included 122 patients in their trial. **Ferrero *et al.*** [15] **and Muraoka *et al.*** [19]**,** on the other hand, relied on a priori pilot studies for their sample size calculations in their trials.

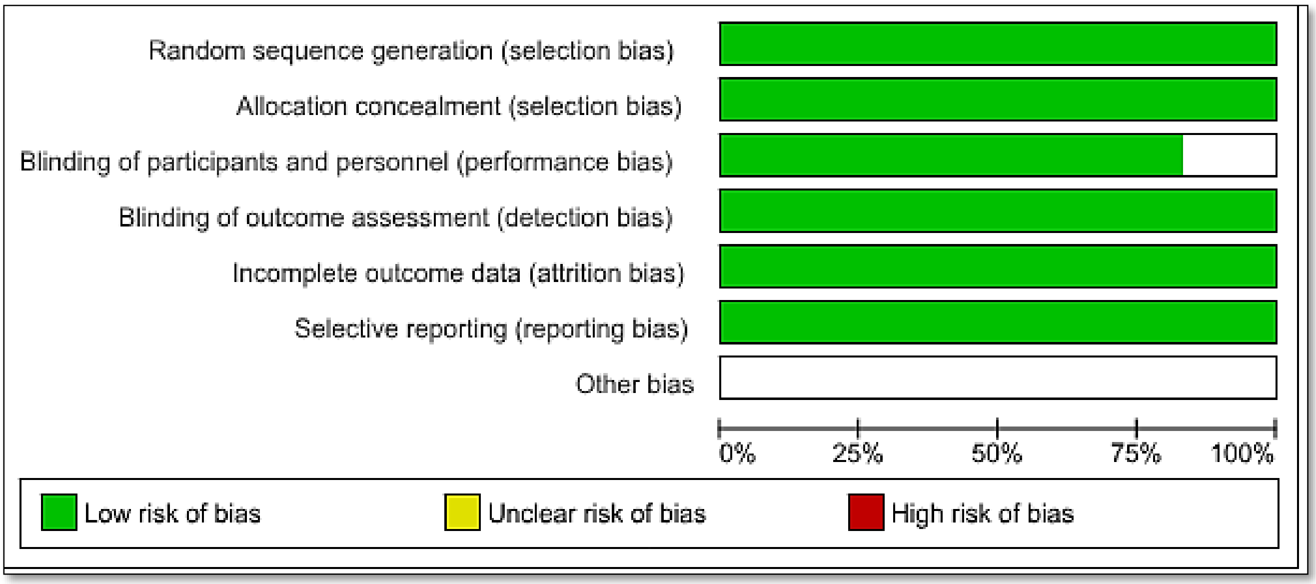


Figure (2): Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

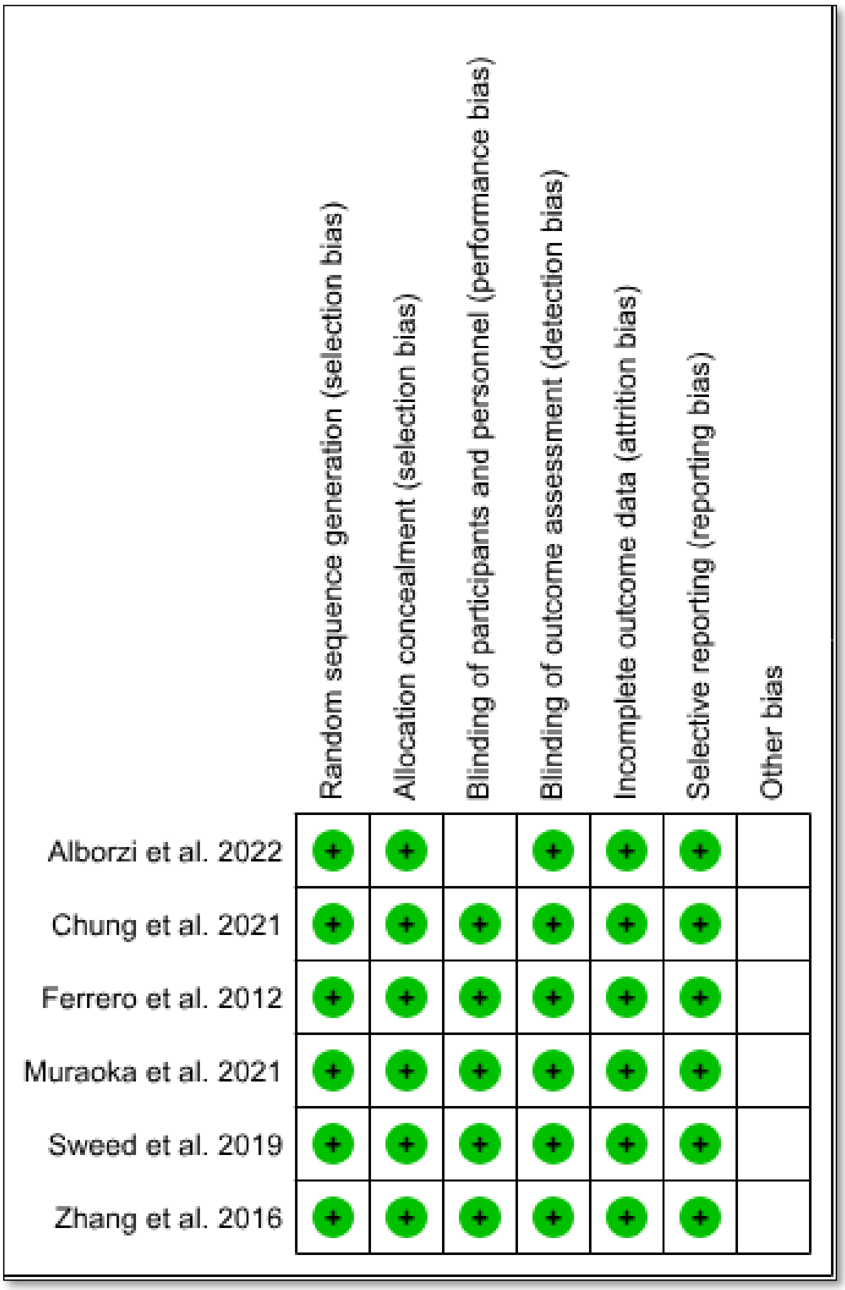


Figure (3): Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Outcome:

The levels of serum AMH were significantly lower after laparoscopic surgery for endometriomas than they were before the operation. The mean difference was -1.41 ng/mL (CI, -2.04 to -0.78; $P < 0.0001$; $I^2 = 93\%$). Analysis of AMH levels at 12 months after surgery found that the ovarian reserve was reduced post-operatively, regardless of the use of cystectomy or ablation. The hemostatic methods or agents used during surgery did not affect the outcome either. Thus, the surgery itself appeared to have an adverse effect on the ovarian reserve.

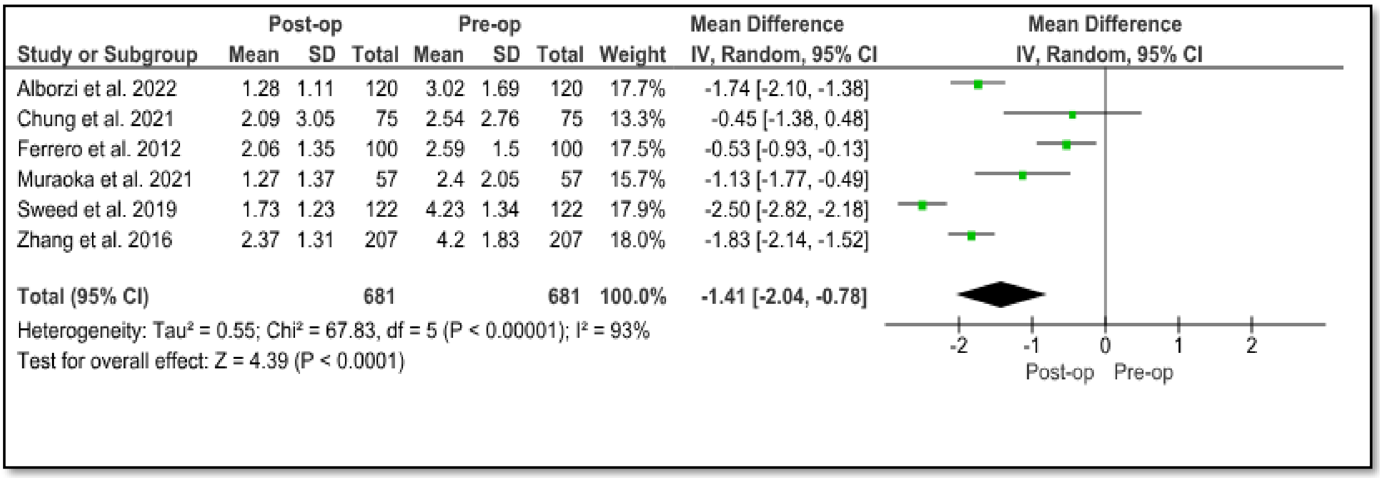


Figure (4): Forest plot comparing pre-operative and post-operative AMH levels in the study groups.

DISCUSSION

The meta-analysis included studies of various patient populations and laparoscopic surgical techniques. This variety allowed for a comprehensive yet clear look at the data. Despite this diversity and the many methodological differences among the studies, they all reported the same main finding; a significant decrease in post-operative AMH levels at 12 months after the surgery. One suggested reason for the reduction in serum AMH levels is unintentional harm done to non-endometrioma ovarian tissue during surgical endometrioma removal (excision). Because endometriomas can be fused to normal ovarian tissue, it is not always straightforward to remove them without affecting the adjacent healthy tissue [21-23]. Furthermore, heat from electro-cautery and laser surgery can damage ovarian tissue and, presumably, reduce subsequent AMH production [24].

The meta-analysis pooled a number of studies and presented the outcome in a clear and simple way. From these pooled data, we could see how much our surgical technique might be compromising the ovarian reserve. Not all studies agreed on the degree of AMH decline, however, which makes sense when considering the variety of surgical approaches and conditions of the patients among the studies. Some showed a slight decrease in AMH [15,18]. While, others found more substantial reductions [16,17,20].

In line with our findings, a 2022 meta-analysis by **Moreno-Sepulveda *et al.*** [25] that included nine studies found that AMH levels experienced a significant long-term decline post-laparoscopy. The decline was modest but consistent, with a reduction of 1.54 ng/ml. The authors of the analysis did not report the decrease at any particular time point; rather, they collapsed across the "short," "medium," and "long" postoperative time intervals, with the latter being at least 1 year post laparoscopy. They compared AMH levels at the intervals to baseline levels from before surgery and found substantial decreases in all time intervals. In the same way, a 2020 meta-analysis by **Nankali and others**[26] evaluated the effect of laparoscopic surgery, both unilateral and bilateral, on levels of AMH at three and six months postoperatively. They used eleven studies for the unilateral group and eight for the bilateral group. They found that both types of surgeries led to decreased AMH levels over time.

A different research team, led by **Deckers *et al.*** [27], conducted a study that pulled together data from three randomized controlled trials. This team of researchers focused on using bipolar electrocoagulation during laparoscopic stripping procedures. Their patient population, which totaled 210, allowed them to calculate the average change in the AMH level for this particular large group. The average change, when the procedure was done, was in the direction of the hormone level going down—so this was not supposed to happen if the procedures were really preserving the ovarian reserve. They found a decrease of 0.79 ng/mL (95% CI, - 1.19 to - 0.39).

Compared to the findings of **Deckers *et al.*** [27], our results showed a significantly greater decrease in AMH levels. The disagreement may arise from that the present meta-analysis looked at a broad array of techniques; however, **Deckers *et al.*** [27], in their study, concentrated their efforts on a single method: laparoscopic stripping with bipolar electro-cautery, which could have a more harmful impact on ovarian reserve. This increased risk is likely due to the nature of the procedure and how it affects ovarian tissue. The use of hemostatic techniques, coupled with endometrioma stripping, may reduce ovarian reserve after surgery because they may remove tissue accidentally and kill follicles.

Yet endometrioma stripping is still often called safe and effective, as in a study by **Muzii and colleagues** [28]. They examined the tissues involved in endometriosis and found distinct appearances when comparing the cyst wall of an endometrioma to normal ovarian tissue. They commented on the lack of any follicle structures—primordial, primary, or secondary—in the endometriomas that underwent excision. This unhealthiness mirrors what was previously written about how tissue adjacent to endometriomas did not behave in a healthily follicular way, either. The study's results indicate that the presence of endometriomas may cause changes in the structure of nearby ovarian tissue. Such structural modifications could conceivably impact the kind of hormones that the ovaries produce, the overall function of the ovaries, and the ovaries' reserve status—that is, their ability to give rise to oocytes—and could do all of this even in the absence of directly damaging the neighboring tissue. In contrast, many studies have found that endometrioma stripping can negatively affect post-operative AMH levels and ovarian reserve [29-32].

However, despite these findings, no widespread agreement exists about how directly the procedure impacts those two important aspects of reproductive health. The ongoing debate highlights the complicated appraisal of the effect of this surgical procedure on ovarian function. This stems from the many types of conflicting research findings and the not-so straightforward and obvious evidence in the scientific literature [27].

Many factors probably influence the reserve of the ovaries, including the size of the endometriotic cyst [8], laterality of the cyst [33], and how proficiently the surgeon strips the cyst [34]. Indeed, we have no definite idea how much any of these factors probably affect the outcome. Nevertheless, many endo experts believe a poorly performed surgery stripping successively or too cautiously, for instance, could dwarf the benefits of anything done along the lines of laparoscopic salpingectomy [35].

Strengths and Limitations

The present study is the first to conduct a meta-analysis of the 12-month postoperative anti-Müllerian hormone levels after laparoscopic surgery. It should be noted that we had a considerably larger number of patients in our cohort than in prior meta-analyses and systematic reviews. Our follow-up period and method of AMH level assessment 12 months post-operatively is more consistent with the study designs of these previous review articles, and we now have the advantage of incorporating recent findings from a handful of other studies [25-27].

In addition, the analysis comprised randomized controlled trials nearly balanced in study weight, which allows for a more even accounting of the outcome of interest—the change in AMH levels after surgery (Figure 4). Even more important, the studies included have high methodological quality and have controlled for several important variables—surgical indication, fertility status, operating room time, and number of hospitalization days—that could have affected the outcome.

There are several limitations associated with this meta-analysis. The first is that the clinical trials underpinning the RCTs included in this analysis did not all provide sufficient registration information. The overall quality of evidence and the potential introduction of publication bias can be compromised. Secondly, in the eligible studies, we observed variability in the AMH assay kits used. They included enzyme immunoassays (e.g., Elecsys AMH Plus; Roche) and ELISA kits (e.g., Glory Science Co., Ltd.; Diagnostic Systems Laboratories; and, Diagnostic Systems Laboratories; Webster, TX). With only a few studies included, it was not feasible to categorize them by specific AMH assays utilized and then pool them in a meta-analysis. Lastly, the meta-analysis displayed substantial heterogeneity, as shown by I^2 values for the main outcome measures, which suggested a moderate level of precision in these results and lessened our ability to generalize them to different contexts or populations.

CONCLUSION

In conclusion, even if laparoscopic surgery is a cornerstone in the treatment of endometriomas, its effect—potentially detrimental—on ovarian reserve as measured by AMH levels obtained 12 months postoperatively demands that we take a more careful approach in the counsel we provide to our patients. We must individualize our treatment recommendations based not only on the patient's current symptoms but also on their reproductive plans and the clear status of their ovarian reserve.

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