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Ablation and risk of recurrence in endometrioma: a systematic review and meta-analysis

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ABSTRACT

Objective. Ovarian endometriosis, or endometriomas, is a common manifestation and is typically treated via laparoscopic cystectomy. However, this method may compromise ovarian function. Ablation, involving thermal destruction of endometriosis cells, is emerging as an alternative. Despite some evidence suggesting less impact on ovarian function, there is a lack of robust data on the efficacy of ablation in preventing recurrence. This systematic review and meta-analysis aim to evaluate the recurrence rates of ablation compared to standard cystectomy for ovarian endometriomas.

Materials and Methods. This study followed PRISMA guidelines and was registered with PROSPERO (protocol number CRD549177). Comprehensive searches were conducted in PubMed, EMBASE, Scopus, Google Scholar, ClinicalTrials.gov, and the Cochrane Central Register up to May 2024. Inclusion criteria focused on studies involving patients with at least one ovarian endometrioma treated with ablation or cystectomy, reporting recurrence rates, and having a minimum follow-up of 12 months. The studies were assessed for quality using the Newcastle-Ottawa Scale. Data were analysed using fixed-effect or random-effect models based on heterogeneity, with statistical significance set at $p < 0.05$.

Results. The search identified 58 articles, with 16 meeting the criteria for review. 5 studies, encompassing 395 patients, were included in the final analysis. 4 studies compared ablation and cystectomy. Recurrence rates varied, with ablation ranging from 0% to 37.7% and cystectomy from 0% to 22%. Meta-analysis revealed a non-significant trend toward higher recurrence rates with cystectomy (OR 1.99, 95%CI 0.95-4.16, $p = 0.07$). The heterogeneity was low ($I2 = 0\%$, $p = 0.45$).

Conclusions. This systematic review and meta-analysis did not find a statistically significant difference in recurrence rates between ablation and cystectomy for treating ovarian endometriomas. However, there was a non-significant trend favouring ablation. Further randomized controlled trials are necessary to confirm these findings and to better understand the long-term efficacy and safety of ablation compared to cystectomy.

INTRODUCTION

Endometriosis, a condition affecting about 10% of women of childbearing age, involves the displacement of endometrial tissue outside the uterus [1, 2]. Ovarian endometriosis, also known as endometriomas, is its most frequent presentation and involves several therapeutic approaches. While

laparoscopic cystectomy, also called stripping, is the current standard, surgery can cause damage to ovarian tissue, diminishing its endocrinological and reproductive potential [3]. Various approaches have been studied to minimize this risk [4]. Among these, ablation, which involves destroying the endometriosis cells by applying energy from different sources, but which has in common the thermal damage done to the endometrioma, has found increasing use in recent years [5]. Although it is now considered an alternative method to laparoscopic stripping, the scarcity of prospective studies raises questions about its efficacy in terms of risk of disease recurrence. Recently, a meta-analysis has shown its minor impact on ovarian function [6].
In contrast, solid data on its efficacy over time in controlling the development of new endometriomas are lacking in the literature. Moreover, the lack of standardization of the technique may make it even more challenging to understand its efficacy fully. This is why we wanted to collect all the data to date in the literature on this topic. This systematic review and meta-analysis aim to assess ablation's recurrence outcomes compared to standard cystectomy for ovarian endometriomas.

MATERIALS AND METHODS

The methods for this study were specified a priori based on the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. We registered the Review for meta-analysis on the PROSPERO site with protocol number CRD549177.

Search Method

We performed systematic research for records about the use of sclerotherapy in man-aging ovarian endometriomas in PubMed, EMBASE, Scopus, Google Scholar, Clinical-trials.gov, and the Cochrane Central Register of Controlled Trials in May 2024. We did not restrict country or year of publication and considered only entirely English-published studies. We adopted the following string of idioms in each database to identify studies fitting to our review's topic: "Endometriosis and Ablation".

Study Selection

Study selection was made independently by G.A. and M.G.V. In case of discrepancy, C.R. decided on inclusion or exclusion. Inclusion criteria were: 1) studies that included patients with at least one ovarian endometrioma, treated with ablation and/or cystectomy; 2) studies reporting the outcome of interest: Recurrence Rate (RR); 3) Studies with at least 12 months of follow-up; 4) peer-reviewed articles, published originally. We excluded non-original studies, pre-clinical trials, animal trials, abstract-only publications, and articles in languages other than English. If possible, the authors of studies that were published as conference abstracts were tried to be contacted via e-mail and asked to provide their data. We mentioned the studies selected and all reasons for exclusion in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (**Figure 1**). We assessed all included studies regarding potential conflicts of interest.

Statistical analysis

Heterogeneity among the studies was tested using the Chi-square test and I-square tests [7]. The Odds Ratio (OR) and 95% confidence intervals (CI) were used for dichotomous variables. Fixed-effect models conducted statistical analysis without significant heterogeneity ($I^2 < 50\%$), or random-effect models if $I^2 > 50\%$. Recurrence rate (RR) was used as clinical outcomes. In each study, RR was defined as the percentage of recurrence till the last follow-up. Chi-square tests were used to compare continuous variables. Review Manager version 5.4.1 (REVman 5.4.1) and IBM Statistical Package for Social Science (IBM SPSS version 25.0) for MAC were used for statistic calculation. For all performed analyses, a P-value < 0.05 was considered significant.

Quality assessment

We assessed the quality of the included studies using the Newcastle-Ottawa scale (NOS) [8]. This assessment scale uses three broad factors (selection, comparability, and exposure), with the scores ranging from 0 (lowest quality) to 8 (best quality). Two authors (CR and II) independently rated the study's quality. Any disagreement was subsequently resolved by discussion or consultation with PDF. We reported NOS Scale in **Appendix 1**.
We used a funnel plot analysis to assess publication bias. We used Egger's regression test to determine the asymmetry of funnel plots (**Appendix 2**).

Risk of Bias

The RCTs and prospective cohort studies were separately assessed, and the risk of bias in these studies was low or moderate. Saito *et al*. [11] only in-

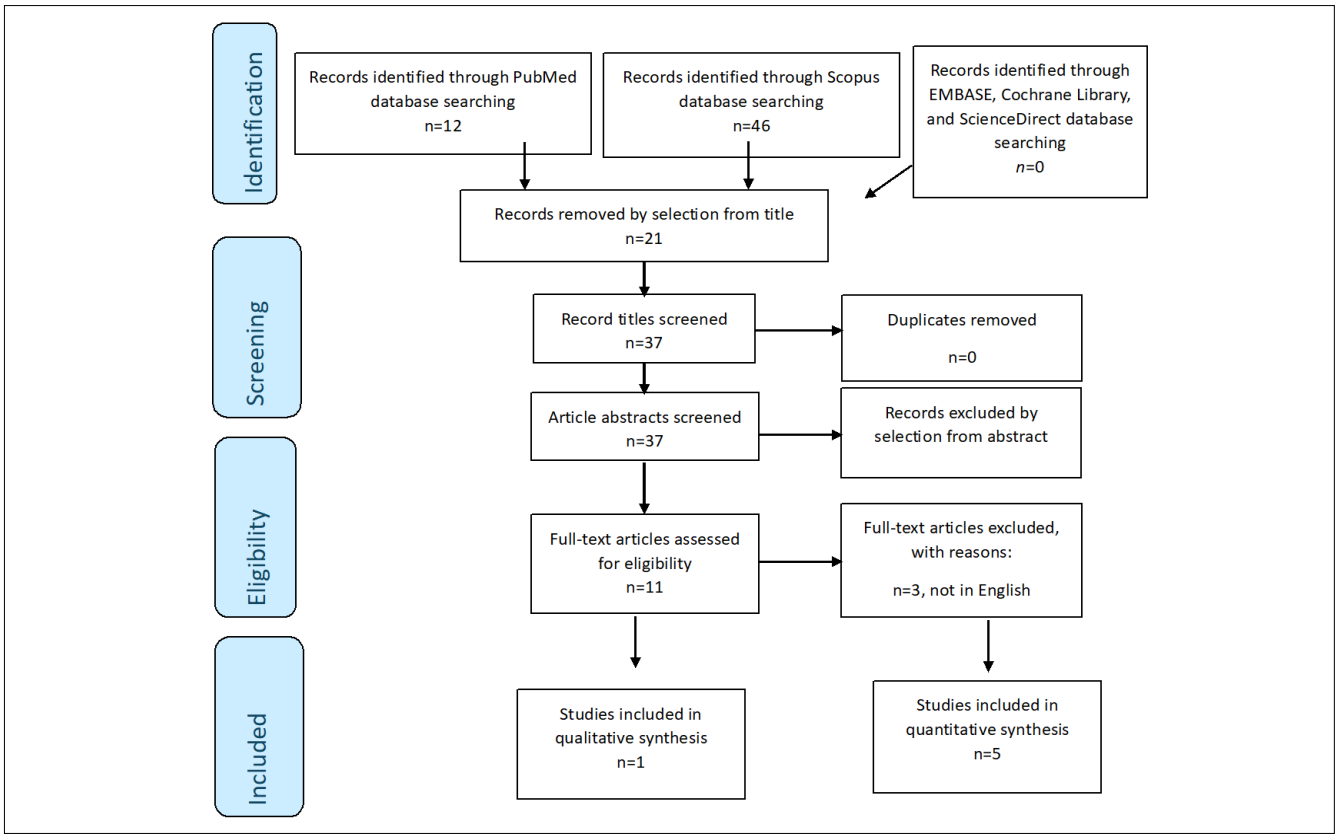

Figure 1. *Flowchart.*

cluded nulliparae in the ablation group and reported bigger dimensions of endometrioma in the ablation group. In addition, he has the shortest follow-up and has not reported any recurrence events in either group during these twelve months. Haghgoo *et al*. included 30 patients with unilateral endometrioma and 30 with bilateral endometrioma [9]. Candiani *et al*. used a CO_2 fibre laser for cyst vaporization [12], whereas argon is employed commonly.

RESULTS

Studies' Characteristics

After the database search, 58 articles matched the search criteria. After removing records with no full text, duplicates, and wrong study designs (*e.g.*, reviews), 16 were eligible. 5 matched the inclusion criteria and were included in the systematic review. 4 were comparative studies between the Ablation technique and laparoscopic stripping and were included in quantitative analysis (**Figure 1**). The countries where the studies were conducted, the publication year range, the studies' design, follow-up months, and the number of participants are summarized in **Table 1**.

NOS [8] (**Appendix 1**) assessed the quality of all studies. Overall, the publication years ranged from 2011 to 2021. In total, 395 patients with endometrioma were enrolled: 215 were treated with ablation and 180 with laparoscopic stripping.

Table 1. *Characteristics of included studies.*

Author, year of publication	Country	Period of enrollment	Study design	No. of participants	Ablation	Cystectomy
Haghgoo *et al.* 2021 [9]	Iran	2017-2019	Prospective Monocenter Cohort	58	0	58
Carmona *et al.* 2011 [10]	Spain	N/A	Prospective Monocenter Randomized	74	38	36
Saito *et al.* 2017 [11]	Japan	2011-2013	Prospective Monocenter Cohort	62	28	34
Candiani *et al.* 2019 [12]	Italy	2015-2018	Prospective Monocenter Cohort	125	61	64
Chen *et al.* 2021 [13]	China	2016	Retrospective Monocenter Cohort	76	30	46

Table 2. *Outcomes.*

Author, year of publication	Cystectomy RR (%)	Ablation RR (%)	P-value	Median FU period (months)
Single-arm studies				
Haghgoo *et al.* 2021 [9]	-	0.0	N/A	15.0
Carmona *et al.* 2011 [10]	22.0	37.0	0.4	64.0
Saito *et al.* 2017 [11]	0.0	0.0	N/A	12.0
Candiani *et al.* 2019 [12]	6.3	4.9	0.74	29.0
Chen *et al.* 2021 [13]	4.4	16.7	0.11	31.38

RR: recurrence rate; FU: follow-up.

Outcomes

The review included 395 patients. All 5 selected studies presented RR data. Overall, the RR ranged from 0 to 37.7% in the ablation group and from 0 to 22.0% in the stripping group. The follow-up period ranged from 12 to 64 months on average. Those results are summarized in **Table 2**.

By alphabetic, Candiani *et al*. [12] reported a RR of 6.3 *vs* 4.9 for ablation compared to stripping in 29 months of follow-up (p = 0.74). Carmona *et al*. [10] reported the oldest series with the highest RR in both arms (22% *vs* 37%, p = 0.4) and longest follow-up (64 months). On the contrary, Chen *et al*. [13] is the newest one, with RR 4.4% *vs* 16.7% (p = 0.11) and 31 months of observation. Haghgoo *et al*. [9] reported the only single-arm trial with no recurrence reported after 15 months. Finally, Saito *et al*. [11] did not observed recurrence in both arms.

Ablation Procedure

Haghgoo *et al.* avoided hot energy devices, as cautery, on ovaries for ablation [9]. In Carmona *et al*.'s study, the vaporization of the cyst's internal wall was performed through CO_2 laser at 30 W/cm² power density [10]. Saito *et al.* performed vaporization using bipolar current forceps (35 W) on the internal wall [11]. Candiani *et al.* used a CO_2 fibre laser in a "one-step" procedure [12]. In Chen *et al.* study, bipolar forceps were applied on the internal wall at 30W until the colour of the cyst turned white [13]. The average duration of contact between the forceps and the lesion was approximately 1 second [13]. In all cases, a biopsy was performed before proceeding with vaporization [9-13].

Meta-analysis

The 4 studies comparing ablation and stripping were enrolled in the meta-analysis. A total of 337 patients were analysed. 157 patients in the ablation arm were compared with 180 patients who underwent cystectomy, exploring RR outcome. 23 recurrences occurred in the ablation group and 14 in the stripping. Because of low heterogeneity ($I^2 = 0\%$; p = 0.45), the fixed-effects model was applied. The Cystectomy group showed a slightly non-significant higher risk for recurrence than the ablation arm (RR 1.99 [95%CI 0.95-4.16] p = 0.07) (**Figure 2**).

DISCUSSION

Main Findings

This systematic review and meta-analysis included five studies, four cohort studies, and one randomized trial. The qualitative data analysis could not show a statistically significant difference between the ablation technique and laparoscopic stripping based on recurrence (p = 0.07). However, stripping

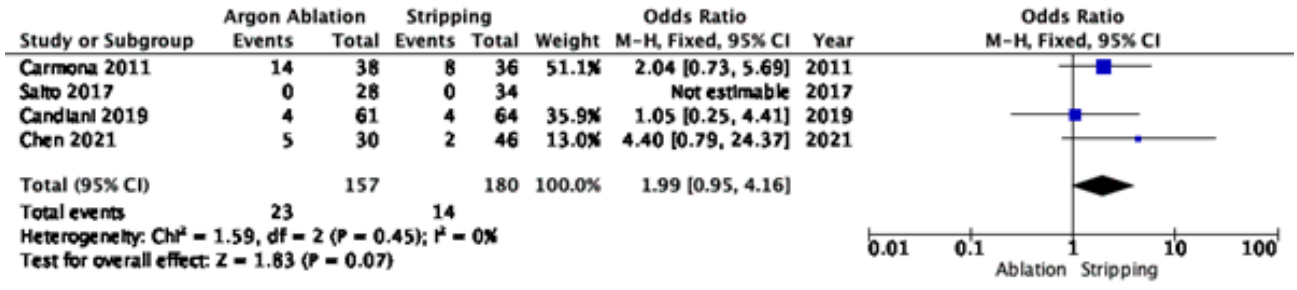

Figure 2. *Forest Plot.*

seems to show a worsening trend with an OR per recurrence of 1.99 and a 95%CI slightly including neutrality (0.95-4.16). This could be confirmed as the sample size increases. Moreover, the largest weighting (51.1%) is represented by Carmona *et al*. [10] which has the advantage of being the only randomised clinical trial and the disadvantage of being the oldest included study, risking being flawed by a technological backwardness, which may undermine the efficacy of the ablative technique.

Comparison with existing literature

Since its first publication, ablation has been an attractive alternative for treating endometriomas. This is because the relationship between endometriosis and infertility is an intrinsic one, worsened by all treatment episodes of a surgical nature. Cyst removal inevitably results in a reduction in the patient's reproductive and endocrinological potential. Much scientific society has struggled to minimize this impact, on the one hand, by attempting to optimize post-stripping coagulation techniques [3] and, on the other hand, in seeking alternative approaches for treating endometrioma, such as sclerotherapy [4]. In the same vein, all alternatives provided to stripping, including ablation, have always been weighed first in assessing their impact on fertility. Recently, Zhang *et al*. [5] published a meta-analysis on pre- and post-operative differences in AMH and Antral Follicle Count (AFC) determined by ablation and stripping. The 294 patients enrolled in this meta-analysis showed a lower AFC in the stripping arm, both in the immediate postoperative period (mean differences [MD], 1.33; 95% credible interval, 2.15 to 0.51; I^2 1/4 57%), and at 6-month follow-up (MD, 1.93; 95% credible interval, 2.40 to 1.45; I^2 1/4 0%). The intragroup comparisons of AMH levels supported negative effects on ovarian reserve of both cystectomy (MD, 1.26; 95% credible interval, 1.64 to 0.88; I^2 1/4 45%) and ablation (MD 0.70; 95% credible interval, 1.07 to 0.32; I^2 1/4 0%). These data support the evidence from another systematic review on the use of cystectomy [14] and a meta-analysis [15] conducted by two independent groups. A group in our analysis also published data from the same series on this subject, with a more significant impact of cystectomy on AMH and AFC [16]. On the other hand, much rarer are the papers that focus on ablation's efficacy regarding recurrence risk. In this scenario, to our knowledge, our meta-analysis stands as the only meta-analysis focusing on this topic.

Clinical Implication

Once the lower impact on patients' fertility has been established, it is also essential to weigh up the effectiveness of the ablative technique over time. This is why, in our opinion, the evidence derived from our work supports the therapeutic choices for treating patients with endometriosis. Endometriosis is a chronic condition where gaining time between treatment episodes is crucial to optimizing treatment. To date, surgery remains the diagnostic gold standard, but this contrasts with the need to be minimally invasive. This discrepancy often creates diagnostic delays that condition the severity of the clinical presentation [17]. On the one hand, we need to optimize diagnosis by identifying biomarkers, such as liquid biopsy [18], that can intercept our patients before organic progression, and on the other hand, we need to improve our therapeutic options to chronicle the disease with as little morbidity as possible. Fortunately, the pharmacological landscape has recently expanded with new drugs such as Relugolix, which have shown promising results in controlling symptoms [19]. Surgery should go hand in hand with adapting to the growing number of therapeutic options. In this scenario, we believe standardization of the ablative technique would also be fundamental to improve its reproducibility.

Strengths and Limitations

Our study is the first meta-analysis to evaluate whether cystectomy or ablation results in higher endometrioma RR. Unfortunately, very few studies on this subject limit our case series to 395. Our results were not statistically significant, even though they showed a clear trend against cystectomy. Another limitation is the lack of standardization in ablative techniques and haemostatic approaches in the case of stripping. This attempt to compare the two methods is more ambitious.

Furthermore, studies that have used bipolar coagulation have not reported any data on its intensity. A further limitation is the possibility of bilateral neoformations, which were included in the studies as a single patient, even though it is assumed that the double procedure exposes one to a double risk of recurrence. Finally, no data have been reported regarding spillage during treatment, which may promote intraabdominal spillage of endometriosis tissue and increase the chances of recurrence [20, 21].

Finally, a final point should be made that our review does not take into account additional outcomes that may differentiate the two techniques, such

as the risk of postoperative pain [22] or the risk of malignant transformation [23].

CONCLUSIONS

Our study failed to show a statistically significant ($p = 0.07$) increased safety profile of ablation compared to cystectomy in terms of RR. However, the data show a clear trend with almost doubled risk of recurrence in patients undergoing laparoscopic cystectomy (OR 1.99, 95%CI 0.95-4.16). Further randomised trials may support or refute this trend.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions
C.R.: Conceptualization, formal analysis, methodology, project administration, software, supervision, validation, writing - original draft, writing - review & editing. I.I.: Data curation, writing - review & editing. M.G.V: Data curation, investigation, project administration, software, supervision. C.V.: Data curation, investigation. G.A.: Data curation, formal analysis. M.T.: Supervision, validation, visualization. P.dF.: Supervision, validation, visualization.

Funding
None.

Study registration
We registered the Review for meta-analysis on the PROSPERO site with protocol number CRD549177.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
N/A.

Informed consent
N/A.

Data sharing
Data are available along with the article.

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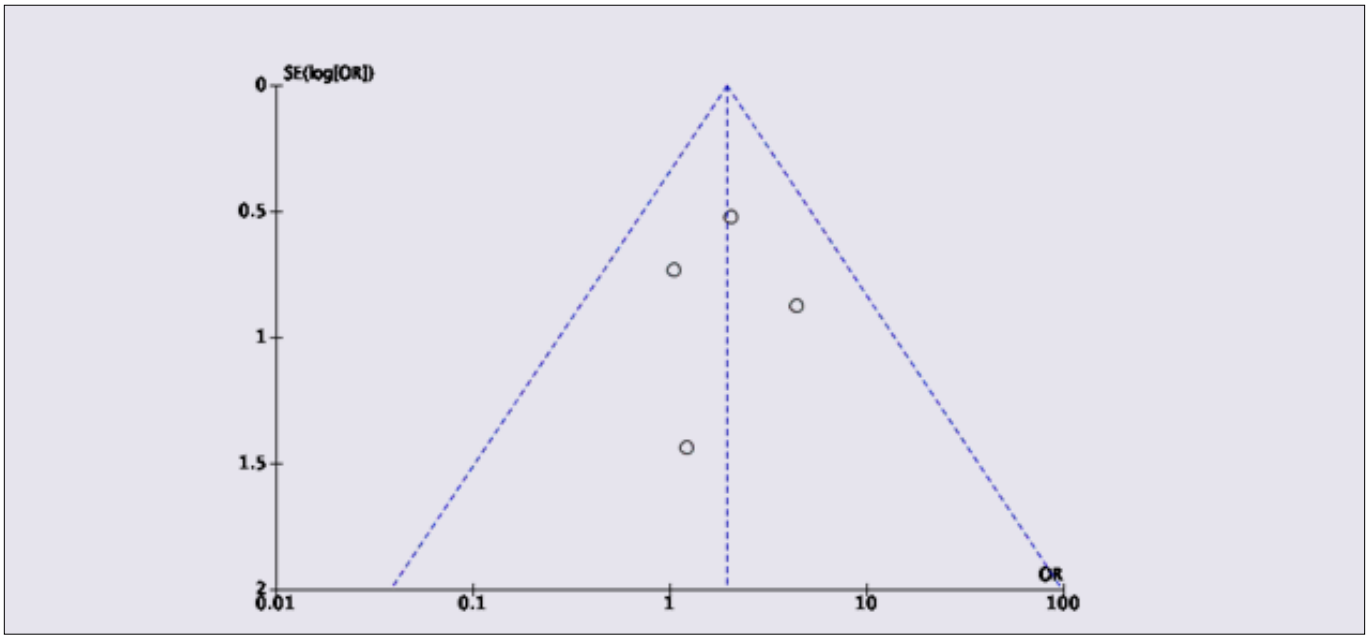
SUPPLEMENTS

Appendix 1. *Newcastle-Ottawa Scale.*

Author, year of publication	Country	Selection	Comparability	Exposure	Total
Single-arm studies					
Haghgoo *et al.* 2021	Iran	3	1	1	5
Carmona *et al.* 2011	Italy	3	2	2	7
Saito *et al.* 2017	Japan	2	1	2	5
Candiani *et al.* 2019	Italy	2	1	3	6
Chen *et al.* 2021	China	2	2	3	7



Appendix 2. *Funnel Plot.*