Human Reproduction, Vol.31, No.2 pp. 339–344, 2016
Advanced Access publication on December 18, 2015 doi:10.1093/humrep/dev313

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Comparison between the stripping technique and the combined excisional/ablative technique for the treatment of bilateral ovarian endometriomas: a multicentre RCT

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Submitted on January 12, 2015; resubmitted on November 12, 2015; accepted on November 24, 2015

STUDY QUESTION: Is the combined excisional/ablative technique for the treatment of ovarian endometriomas better than the traditional stripping technique in terms of recurrence rate?

SUMMARY ANSWER: There is no evidence that the combined excisional/ablative technique is better than the traditional stripping technique, as similar recurrence rates were observed for the two techniques.

WHAT IS KNOWN ALREADY: The stripping technique is associated with better results compared with ablative, non-excisional techniques for the treatment of ovarian endometriomas. Excisional techniques, such as stripping, have, however, been associated with reduced ovarian reserve as evaluated with anti-Mullerian hormone, and surgical techniques that better preserve the ovarian reserve are needed.

STUDY DESIGN, SIZE, DURATION: A prospective, multicentre, randomized blinded clinical trial was carried out on 51 patients with bilateral endometriomas larger than 3 cm. For each patient, serving as her own control, one ovary was randomized to the stripping technique and the contralateral to the combined excisional/ablative technique. Patients were enrolled between January 2013 and April 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients of reproductive age with pelvic pain and/or infertility affected by bilateral endometriomas larger than 3 cm were included ($n = 51$). The patients underwent laparoscopic removal of endometriomas with two different surgical techniques performed at either side after random assignment: complete removal by stripping on one side versus the combined technique, consisting of partial excisional cystectomy followed by completion with ablative surgery using bipolar coagulation, on the other side. Post-operative follow-up was performed at 1, 3 and 6 months after surgery for the evaluation of endometrioma recurrence (primary outcome) and of antral follicle count (AFC) and ovarian volumes (OVs) to assess ovarian reserve (secondary outcome).

MAIN RESULTS AND THE ROLE OF CHANCE: Recurrence rates were 5.9% for the stripping technique versus 2.0% for the combined technique (odds ratio 3.00; 95% confidence interval: 0.24–157.5; $P = 0.62$). AFC in the ovaries treated with the stripping technique did not differ

significantly from AFC in ovaries treated with the combined technique at all follow-up visits, whereas OV was significantly lower after the combined technique at the 6-month follow-up visit ($P = 0.04$).

LIMITATIONS, REASONS FOR CAUTION: A major limitation of this study is the small sample size and particularly for ovarian reserve, the secondary outcome, for which no formal sample size calculation was performed. The lower-than-expected recurrence rates in the present series may be related to the shorter follow-up in our study compared with most studies in the literature. Further studies with larger sample sizes and longer follow-up are needed to confirm the findings of this study. The combined technique using CO_2 laser energy instead of bipolar coagulation should also be evaluated.

WIDER IMPLICATIONS OF THE FINDINGS: The traditional excisional technique, i.e. the stripping technique, should still be considered the gold standard approach for the surgical treatment of endometriomas.

STUDY FUNDING/COMPETING INTEREST(S): No commercial funding was received. The authors report no relevant conflict of interest.

TRIAL REGISTRATION NUMBER: ANZCTR number ACTRN12614000653662.

TRIAL REGISTRATION DATE: 23 June 2014.

DATE OF FIRST PATIENT'S ENROLMENT: 1 January 2013.

Key words: antral follicle count / endometrioma / endometriosis / ovarian reserve / ovarian surgery

Introduction

Ovarian endometriomas are present in 17–44% of patients with endometriosis (Chapron *et al.*, 2002) and may be associated with infertility and pelvic pain. In approximately one-third of the cases, the endometrioma is bilateral (Guo *et al*, 2008). When therapy is indicated, surgical excision of the endometrioma is the recommended treatment (Leyland *et al.*, 2010; Dunselman *et al.*, 2014). Endometriomas, in fact, do not respond to medical treatment whereas non-excisional surgical techniques are associated with lower cure rates and higher recurrence rates compared with excisional techniques (Hart *et al.*, 2008).

However, concerns have been recently raised as to the possible damage caused by excisional surgery to the ovarian reserve (Raffi *et al.*, 2012; Somigliana *et al.*, 2012; Shah *et al.*, 2014). A recent meta-analysis demonstrated a 38% reduction in anti-Mullerian hormone (AMH) values after excision of the endometrioma with the stripping technique (Raffi *et al.*, 2012). A second systematic review confirmed consistent results among various studies, reporting a reduction of the ovarian reserve evaluated by AMH, although a formal meta-analysis was deemed inappropriate due to high heterogeneity between the included studies (Somigliana *et al.*, 2012).

With the intent of combining the advantages of excisional techniques in terms of lower recurrence rates (Hart *et al.*, 2008), with the advantages of non-excisional techniques in terms of better preservation of the normal ovarian tissue (Flyckt and Falcone, 2013; Shah *et al.*, 2014), a new surgical technique has been recently proposed (Donnez *et al.*, 2010; Muzii and Benedetti Panici, 2010). Both groups reported the feasibility and safety of the combined technique with regard to post-operative ovarian reserve evaluated by antral follicle count (AFC) in two small cohort studies (Donnez *et al.*, 2010; Muzii and Benedetti Panici, 2010). No study has ever evaluated the combined technique in comparison with standard excisional (i.e. the stripping technique) or non-excisional techniques.

The aim of this study was to compare the standard excisional technique versus the combined excision/ablation technique for the treatment of bilateral endometriomas in a multicentre, randomized study, with cyst recurrence rates as the primary outcome, and ovarian reserve as the secondary outcome.

Methods

Between 1 January 2013 and 30 April 2014, all patients presenting at the participating centres with the diagnosis of bilateral endometriomas were considered for inclusion in this multicentre study.

Inclusion criteria were age between 18 and 40 years, regularly menstruating, ultrasonographic diagnosis of a single endometrioma larger than 3 cm on both ovaries, pain and/or infertility as indication to surgical treatment and no major present or past chronic illness. A second sonogram was performed, at least 8 weeks apart from the first one, in order to confirm the presence of the suspect endometriomas, and therefore exclude the possibility of functional cysts (Marana *et al.*, 2004).

Exclusion criteria at study enrolment were any previous surgical treatment for endometriosis or medical treatment for endometriosis administered in the previous 3 months. Patients were excluded after initial evaluation if a second sonogram performed 8 weeks later did not confirm the presence of a bilateral endometrioma. Patients were excluded, after randomization, if surgical procedures performed were different from the planned procedures, or if histology did not confirm the endometriotic nature of bilateral cysts. Patients were also excluded if, at surgery, more than one cyst of any type was present on either ovary.

After enrolment, patients were submitted to operative laparoscopy for the treatment of both ovaries. A computer-generated sequence was produced and concealed in an opaque, sealed envelope for each enrolled patient, which was opened when the laparoscopic findings confirmed the eligibility of the patient. The endometrioma on one side was randomly assigned to treatment with the conventional stripping technique, as previously reported (Muzii *et al.*, 2007), whereas the contralateral endometrioma was treated with the combined excision/ablation technique (Muzii and Benedetti Panici, 2010; Unlü and Yıldırım, 2014). In brief, the combined procedure was carried out with a first step, consisting of the stripping technique, from the site of ovarian adhesion to the posterior leaf of the broad ligament up to approximately 80–90% of the surface of the cyst. This was followed by a second step consisting of bipolar coagulation with 30–40 W power to treat the last 10–20% of the cyst surface attached to the ovarian hilus and

left on site (Muzii and Benedetti Panici, 2010; Unlü and Yıldırım, 2014). The patients and the personnel involved in the follow-up evaluations were blinded as to the treatment allocation regarding the laterality of the procedure. No post-operative medical treatment was prescribed routinely. When indication to surgery was pelvic pain, oral contraceptives were allowed if pain recurred at least 1 month after surgery and was not responsive to non-steroidal anti-inflammatory drugs (NSAIDs).

Follow-up visits were planned on Day 2 to 4 of the cycle at 1, 3 and 6 months after surgery. Each visit consisted of a detailed history regarding the possible recurrence of pain symptoms or occurrence of pregnancy, a bimanual examination and a transvaginal ultrasound (TVUS) scan to detect any endometrioma recurrence. Recurrence of pain was defined as any pain symptom (dysmenorrhoea, dyspareunia and acyclic pelvic pain) graded as 4 or more on a visual analogue scale, graded from 0 (no pain) to 10 (worst possible pain). Recurrence of an endometrioma was defined as any persisting cyst with a classic 'ground-glass' aspect, larger than 2 cm (Seracchioli *et al.*, 2009). At TVUS, the blinded operator evaluated AFC separately for each ovary between Day 2 and Day 4 of the menstrual cycle. AFC was defined as the number of follicles between 2 and 10 mm in diameter, observed on each side. As an additional parameter of ovarian reserve, the operator evaluated the ovarian volume (OV), calculated using the prolate ellipsoid formula (length × width × height × 0.523). AFC, ovarian measurements on three planes and calculated OV were recorded separately for each ovary on apposite forms.

Primary outcome for the study was the endometrioma recurrence rate on one ovary versus the contralateral, with a comparison of the results obtained with the stripping technique on one side versus the combined technique performed on the contralateral side. Secondary outcome was the ovarian reserve after surgery evaluated with the AFC and the OV for each side. Pain recurrence rates and pregnancy rates obtained in the follow-up period were also recorded, although obviously not directly attributable to either surgical technique.

Institute Review Board approval was obtained for this study. All patients signed an informed consent form and agreed to treatment and follow-up. The trial was registered on the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), with the identification number ACTRN12614000653662. The sample size needed for the study (50 ovaries for each treatment arm) was calculated based on the assumption that the recurrence rate after endometrioma excision is 34% (Vercellini *et al.*, 2013), and a change of one-third in the recurrence rate (Beretta *et al.*, 1998) was considered clinically significant, with an α-value of 0.05 and a β-value of 0.80. Paired Student's *t*-test and Wilcoxon paired test for continuous variables, and McNemar's test and chi-square for categorical variables, were used. Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 19 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Sixty-two patients with presumed bilateral endometriomas were initially evaluated for inclusion in this study. Eleven patients were excluded because a second sonogram performed 8 weeks after the first did not confirm the presence of a bilateral endometrioma. A total of 51 patients therefore met the inclusion criteria and were enrolled in this study. All patients meeting the inclusion criteria agreed to participate and signed the informed consent. The mean (±SD) age of the patients was 32.9 ± 5.7 years. The main indication for surgery was pain in 31 patients, and infertility in 20 patients. Both pain and infertility were present in 10 patients (Table I). No patient was excluded after study enrolment. All 51 patients were treated by laparoscopy following the random assignment to the stripping or combined technique for either ovary. Figure 1 shows the flow of participants through each stage of the study.

The mean cyst size for all treated cyst was 4.1 ± 1.7 cm, and there was no difference in cyst size in the stripping arm versus the combined technique arm ($P = 0.58$). The stripping technique was utilized for 26 patients on the left size, and for 25 patients on the right side, whereas the combined technique was used in 25 cases on the left, and 26 on the right side ($P = 0.84$) (Table I).

No major intra- or post-operative complication occurred. All patients were discharged within 48 h from surgery. Histology analysis confirmed the endometriotic nature of the treated cyst on both sides in all cases.

No patient was lost to follow-up. All 51 patients attended the scheduled follow-up visits. Cyst recurrence rates were evaluated for all patients at the three follow-up visits. However, AFC and OVs were not considered at data analysis for four patients at the scheduled 3-month visit, and for seven additional patients at the 6-month visit because of pregnancy or starting medical treatment for pain recurrence not responsive to NSAIDs. In detail, two and two pregnancies occurred before the 3 and 6-month visit, respectively, whereas two and five patients were started on medical treatment for pain recurrence before the 3 and 6-month visit, respectively. Pregnancy rate at 6-month follow-up was 20% (4 out of the 20 infertile patients). Pain recurrence rate was 17% (7 patients out of the 41 with pain symptoms at the time of study entry).

A total of four recurrences out of 51 patients (7.8%) occurred in the 6-month follow-up period. All recurrences were monolateral and were diagnosed at the 6-month visit, thus representing true recurrences and not persistence of the disease. The recurrence rate did not differ significantly between the two techniques (3 recurrences out of 51 treated ovaries, 5.9%, for the stripping technique, versus 1 recurrence out of 51 treated ovaries, 2.0%, for the combined technique; odds ratio: 3.00; 95% confidence interval: 0.24–157.5; $P = 0.62$).

Table I Characteristics of patients ($n = 51$) in a comparison between the stripping and combined excisional/ablative techniques for treatment of bilateral ovarian endometriomas.

Age (years; mean ± SD)	32.9 ± 5.7
Cyst diameter (cm; mean ± SD)	
Stripping technique	4.0 ± 1.7
Combined technique	4.2 ± 1.7
Main indication for surgery	
Pain	31 (61%)
Infertility	20 (39%)
Parity	
0	39 (76%)
1 or more	12 (24%)
Procedure performed on left versus right ovary	
Stripping (*n*/*n*)	26/25
Combined (*n*/*n*)	25/26

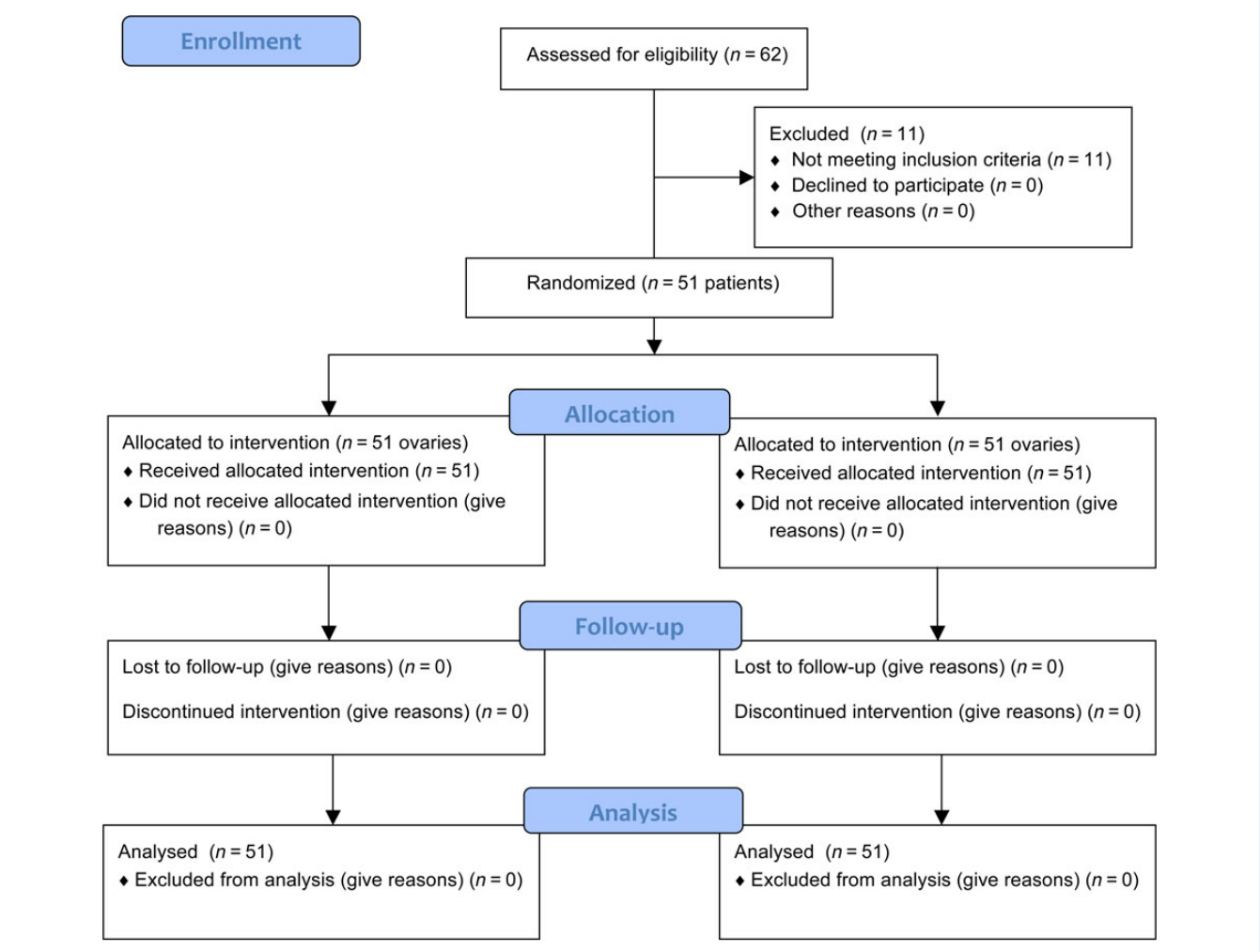

Figure 1 CONSORT diagram showing flow of participants through each stage of the RCT on the stripping technique versus the combined excisional/ablative technique for treatment of bilateral ovarian endometriomas.

Table II AFC, and OV, for the stripping technique and the combined technique at 1, 3 and 6-month follow-up.

	1 month (*n* = 51)		3 months (*n* = 47)		6 months (*n* = 40)	
	AFC	**OV (mL)**	**AFC**	**OV (mL)**	**AFC**	**OV (mL)**
Stripping side	4.5 ± 2.1	8.4 ± 5.1	5.0 ± 2.9	7.7 ± 4.6	4.8 ± 2.9	8.4 ± 5.0
Combined side	4.8 ± 2.4	7.3 ± 4.0	4.6 ± 2.3	7.0 ± 3.7	4.4 ± 2.3	6.5 ± 3.3
P value[a]	0.42	0.24	0.43	0.42	0.57	0.04

Data are presented as mean ± SD.
[a]Paired Student's *t*-test.

The AFC for the ovary operated with the stripping technique was not significantly different from the contralateral ovary operated with the combined technique at all three follow-up visits (Table II). The OV also was not significantly different for the two techniques at the first two follow-up visits, whereas it was significantly lower for the combined technique versus the stripping technique at the third follow-up visit, 6 months after surgery ($P = 0.04$; Table II).

Discussion

Excisional surgery is considered the gold standard for the surgical treatment of ovarian endometriomas (Leyland *et al.*, 2010; Dunselman *et al.*, 2014) since it is associated with lower recurrence rates and higher pregnancy rates compared with ablative techniques (Hart *et al.*, 2008).

Concerns have, however, been recently raised as to the possibility that removal of healthy ovarian tissue together with the endometrioma wall (Muzii *et al.*, 2002), associated with the use of coagulation on the residual ovary, may damage the ovarian reserve (Busacca and Vignali, 2009; Shah *et al.*, 2014). Two systematic reviews reported consistent evidence of a reduction of ovarian reserve evaluated with AMH after excisional surgery for endometriomas (Raffi *et al.*, 2012; Somigliana *et al.*, 2012).

Within this context, non-excisional techniques, where the endometrioma wall is left in place and either ablated with bipolar coagulation or vaporized with CO_2 laser, may theoretically represent a less aggressive approach with respect to the healthy ovarian tissue, and therefore to the post-operative ovarian reserve (Donnez *et al.*, 1996; Pados *et al.*, 2010; Tsolakidis *et al.*, 2010; Flyckt and Falcone, 2013), since no ovarian tissue is removed. Non-excisional techniques are, however, associated with higher recurrence rates (Hart *et al.*, 2008; Pados *et al.*, 2010), possibly as a consequence of the less aggressive nature of the surgery.

The two systematic reviews reporting a decrease of AMH after surgery (Raffi *et al.*, 2012; Somigliana *et al.*, 2012) did not include studies on non-excisional techniques. A recent meta-analysis reporting no significant change of AFC after surgery for ovarian endometriomas (Muzii *et al.*, 2014) evaluated separately studies utilizing non-excisional techniques only. In this additional meta-analysis, no change in AFC was reported after non-excisional surgery (Muzii *et al.*, 2014).

One RCT compared the conventional excisional technique versus a three-stage technique, where a first laparoscopy for cyst fenestration was followed by a second laparoscopy with CO_2 laser vaporization, with a 3-month course of GnRH analogue therapy in between the two laparoscopies (Pados *et al.*, 2010; Tsolakidis *et al.*, 2010). The authors reported separately the outcome in terms of ovarian reserve measured with AFC (Pados *et al.*, 2010) and AMH (Tsolakidis *et al.*, 2010). The non-excisional, three-stage technique was associated with better post-operative ovarian reserve, expressed by both AFC and AMH, than the conventional stripping technique. However, recurrences at 12 months were higher for the three-stage technique (20%) versus the stripping technique (0%). Also, the issues of higher costs and possible risks of a repeat surgical procedure in the three-stage technique should be considered. For these reasons, the three-stage technique cannot yet be recommended as a valid alternative to the standard stripping technique (Muzii *et al.*, 2013; Endometriosis Treatment Italian Club, 2014).

Recently, a new surgical technique has been proposed (Donnez *et al.*, 2010; Muzii and Benedetti Panici, 2010; Unlü and Yıldırım, 2014), with the aim of combining the completeness of disease removal achieved with excisional techniques (Muzii *et al.*, 2007; Hart *et al.*, 2008) with the minor aggressiveness towards the normal ovarian tissue of the ablation technique (Donnez *et al.*, 1996; Flyckt and Falcone, 2013). This combined technique consists of a first excisional step, where the cyst capsule is stripped from the ovary for most of its surface, followed by a second step consisting of ablation with bipolar coagulation (Muzii and Benedetti Panici, 2010) or vaporization with CO_2 laser (Donnez *et al.*, 2010) of the remaining cyst capsule in the vicinity of the hilus. Two small series reported on 12 (Muzii and Benedetti Panici, 2010) and 20 cases (Donnez *et al.*, 2010) with monolateral endometriomas operated with the combined technique. Both studies reported AFC and OVs not significantly different between the operated and the contralateral unaffected ovary at short-term follow-up. Based on these promising cohort studies and on the theoretical advantages of the new technique (i.e. radical for the disease while more protective of the normal ovarian tissue), claims have been made as to the possibility that the combined technique may represent the procedure of choice for the surgical treatment of ovarian endometriomas (Donnez *et al.*, 2010; Muzii and Benedetti Panici, 2010; Flyckt and Falcone, 2013; Unlü and Yıldırım, 2014).

This study is the first study comparing the combined technique to the standard excisional technique, i.e. the so-called 'stripping' technique, for the surgical treatment of ovarian endometriomas. In this RCT, we demonstrate that endometrioma recurrence rates and ovarian reserve are similar for the ovary operated with the stripping technique and for the contralateral ovary operated with the combined technique. As regard recurrence rates, after 6 months the recurrence rate is 5.9% for the stripping technique and 2.0% for the combined technique, a difference that is not statistically significant. At 1 and 3 months after surgery, both ovaries show comparable AFC and OVs. At 6 months, AFC remains comparable between the two techniques, whereas OV is significantly lower for the ovary operated with the combined technique, possibly as a consequence of a type I statistical error, or because of excessive bipolar coagulation at the ovarian hilus when performing the ablative part of the combined technique. However, even in the latter case, the clinical importance of a reduced OV with comparable AFC is questionable. AFC is in fact considered a more reliable marker of ovarian reserve compared with OV (Broekmans *et al.*, 2006).

Although not attributable to either technique, the post-operative pain recurrence rate of 17% and the pregnancy rate of 20% in the present series with a short-term follow-up (6 months) appear to be in line with the literature (Vercellini *et al.*, 2009, 2013), even if the population included in this study, i.e. patients with bilateral endometriomas larger than 3 cm, may represent a subgroup of patients with worse prognosis compared with the general population of patients affected by endometriosis. The lower-than-expected recurrence rates in the present series may instead be due to the shorter follow-up in our study compared with most of the studies reported in the literature (Vercellini *et al.*, 2009, 2013).

In conclusion, this study suggests that the traditional technique and the combined technique may yield similar results in terms of post-operative ovarian reserve and recurrence rates, since no evidence of a difference between the two techniques could be demonstrated. According to the results of this study, the combined technique seems not to be associated with better preservation of the ovarian reserve, as previously hypothesized (Donnez *et al.*, 2010; Muzii and Benedetti Panici, 2010; Flyckt and Falcone, 2013; Unlü and Yıldırım, 2014). A major limitation of this study is the small sample size, with the consequence of a wide 95% confidence interval for the outcome of endometrioma recurrence. Also, given the lower-than-expected recurrence rate, and the non-significant difference in recurrence rates, the sample size utilized in this study may be not large enough to detect smaller, yet clinically significant differences. Furthermore, for the outcome of ovarian reserve, a formal sample size calculation was not performed. Additional studies with a larger sample size and longer follow-up are therefore needed to confirm the findings of this study. The centres participating in this study were using bipolar coagulation for the treatment of the remaining part of the cyst wall in the combined technique arm, and this may account for some uncontrolled damage due to excessive coagulation on the ovarian hilus vessels. There is the possibility that other energy sources may be more respectful of the ovarian vascularization. The conclusions of this study may not be extrapolated to the combined technique using CO_2 laser energy, or

other energy sources, instead of bipolar electrocautery, as was done in this study. Further studies are needed for the validation of the combined technique with the use of CO_2 laser or other energy sources. Also, studies should be conducted with evaluation of the ovarian reserve as the primary outcome.

In the absence of additional evidence from the literature, traditional excisional techniques may still be considered the gold standard approach for the surgical treatment of endometriomas (Hart *et al.*, 2008; Leyland *et al.*, 2010; Dunselman *et al.*, 2014).

Authors' roles

All authors made substantial contributions to conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the manuscript.

Funding

No external funding was sought or obtained for this study.

Conflict of interest

None declared.

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