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Original Article

Fertility Outcome after CO_2 Laser Vaporization versus Cystectomy in Women with Ovarian Endometrioma: A Comparative Study

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ABSTRACT **Study Objective:** To assess the postoperative likelihood of conception in patients with endometriomas managed by either CO_2 laser vaporization or cystectomy.

Design: A retrospective study with prospective recording of data.

Setting: University hospital.

Patients: One hundred and forty-two patients with symptomatic endometriomas.

Interventions: Patients underwent a standardized laparoscopic stripping technique (Group 1) or cyst vaporization with CO_2 fiber laser (Group 2). Patients wishing to become pregnant were allowed to attempt a spontaneous conception after surgery. If spontaneous conception failed, patients were referred for in vitro fertilization (IVF).

Measurements and Main Results: The primary objective was to compare pregnancy rates between the 2 groups. The secondary objective was the identification of independent predictors of pregnancy. Thirty-nine women in Group 1 (53.4%) and 39 women in Group 2 (56.5%) desired to conceive after surgery. Three patients (7.7%) in Group 1 became pregnant following donor-IVF and were excluded. Pregnancies were recorded in 72.2% of patients treated with cystectomy and in 74.3% of those managed with CO_2 fiber laser ($p = .83$). Twenty patients (55.6%) in Group 1 and 14 patients (35.9%) in Group 2 conceived spontaneously ($p = .08$). Among patients who failed spontaneous conception, 21 patients (28%) achieved pregnancy through IVF (Group 1: $n = 6$, 16.7%; Group 2: $n = 15$, 38.5%; $p = .08$). Twenty patients (26.7%) never became pregnant. Age at the time of surgery (odds ratio (OR) = 0.86; 95% Confidence intervals (CI): 0.78−0.96, $p = .002$) and duration of infertility (OR=0.80; 95% CI: 0.69−0.92, $p = .006$) were identified as independent indicators for pregnancy.

Conclusion: CO_2 laser-treated endometrioma is associated with pregnancy rates equal to those observed after cystectomy and favorable IVF outcomes. The one step CO_2 fiber laser technique may represent a viable alternative to cystectomy. Journal of Minimally Invasive Gynecology (2020) 00, 1−8. © 2020 AAGL. All rights reserved.

Keywords: Carbon dioxide fiber laser; Ovarian endometriosis; Reproductive surgery; Pregnancy rate

The management of ovarian endometrioma in women wishing to conceive still remains a matter of debate. Ovarian cystectomy appears to be superior to fenestration and ablation (i.e., electrocoagulation), in terms of endometrioma recurrence, pain symptoms, and spontaneous conception rate among subfertile patients [1,2]. There is a general agreement that pregnancy rates observed after laparoscopic excision of ovarian endometriomas are increased, varying from 30% to 67%, with an average value of about 50% [3]. However, researchers have expressed concern regarding the negative effect of cystectomy on ovarian reserve by way of removing healthy ovarian tissue and vascular injury [4,5]. When performing a cystectomy, the experience of the surgeon could be very important in relation to ovarian damage. Cystectomy is not an easy procedure and when performed by an inexperienced surgeon, increased damage to healthy ovarian tissue may occur. On the other hand, as a clear histologic cleavage plan between the fibrotic layer of endometrioma pseudocapsule and ovarian parenchyma misses, the risk of inadvertent removal of ovarian tissue also exists in experienced hands [6,7]. For these reasons, some authors suggested that ablative techniques may represent a less aggressive approach toward the healthy ovarian cortex, as long as the energy employed

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avoids thermal diffusion to the surrounding ovarian tissue. In this surgical approach, the "pseudo-capsule" is not removed, but it is ablated with CO_2 laser or plasma energy [8−10]. In our daily practice, we have introduced ablation using CO_2 fiber laser technology, and we have already been able to report encouraging results in terms of ovarian reserve preservation [9,11]. CO_2 fiber laser vaporization is simple, easy to use, and has the advantage of eliminating the 'surgeon's experience' factor as recently demonstrated in a study conducted by Vanni and coworkers. Residents without surgical experience showed better skills with the flexible CO_2 laser fiber delivery system compared with the standard line-of-sight CO_2 laser system after a 2-month training period with a gynecologic laparoscopic box. According to these results, flexible CO_2 laser fiber delivery system is technically accessible and holds a potential in gynecologic surgery [12].

Moreover, good results in terms of postoperative pregnancy rates [10,13] and recurrence risk [14,15] after ablation using energies with little thermal spread, such as in line-of-sight CO_2 laser and plasma energy, have been published.

To the best of our knowledge, no previous study has compared the impact of cystectomy and "one-step" (without preoperative GnRHa treatment) CO_2 fiber -laser vaporization for endometrioma treatment on reproductive performance.

Therefore, the present study aimed to investigate the postoperative likelihood of conception in women undergoing surgery (cystectomy vs "one step" CO_2 fiber laser vaporization) for symptomatic endometriomas.

Materials and Methods

This study was based on a retrospective analysis of a surgical database prospectively collected from January 2015 and January 2019 at San Raffaele Scientific Institute in Milan.

All of the women signed written informed consents to record their data for scientific purposes and the Institutional Review Board of our Institution approved the study (01End).

Patients who underwent surgical management for unilateral or bilateral endometriomas, larger than 3 cm were included. Patients were excluded in case their age was 40 years or more at the time of surgery; had surgical antecedents on both ovaries; had had previous salpingectomy or hysterectomy; had a follow-up of less than 12 months. The concomitant presence of deep endometriosis was not an exclusion criterion.

All laparoscopies were performed by 2 experienced surgeons (M.C., S.F.) with the intention to remove all endometriotic lesions. Endometriomas were treated either by cystectomy (Controls) or vaporization with CO_2 fiber laser (Cases).

The procedure for CO_2 fiber laser vaporization has already been described clearly and in detail in our previous papers [9,11]. Once the cyst has been emptied and washed, the surgeon attempted to turn it completely inside out. Vaporization of the inner surface of the cyst was then performed using CO_2 fiber laser (UltraPulse Duo system, Lumenis Ltd) in a radial way moving from the center outward at a power density of 13 W/cm^2.

This is a retrospective study with prospective recording of data. However, patients included in the present study are mostly patients who were initially part of a pilot study [11] and other patients who were part of a randomized clinical trial (RCT) started in 2017 [9], both assessing the postoperative changes of ovarian reserve after treatment (cystectomy vs CO_2 fiber laser vaporization). After showing the benefits of CO_2 on ovarian reserve, we decided to focus our attention on the pregnancy rate after the 2 surgical procedures.

After surgery, patients were referred to the endometriosis outpatient clinic for clinical follow-up.

Patients wishing to become pregnant, following the surgeon's advice, were allowed to attempt a spontaneous conception after surgery for a different time depending on the patient's age and the type of surgery. After cystectomy, women younger than 35 years were allowed to seek pregnancy for 12 months, whereas patients older than 35 years attempted a spontaneous conception for 6 to 9 months. Because we had no data about recurrence rate after "one step" CO_2 fiber laser vaporization (without GnRHa) at the beginning of the study, patients undergoing laser treatment were allowed to attempt a spontaneous conception for a shorter time regardless of age (6−9 months). If spontaneous conception failed, patients were immediately referred for assisted reproductive techniques (ART).

Data regarding age at surgery, clinical history, surgical technique, intraoperative findings, Revised American Fertility Society (r-AFS) score [16], endometrioma recurrence, pregnancy (spontaneous or by ART), and "time taken to spontaneous conception" were collected. Cyst recurrence was considered as the presence of a cyst with a typical sonographic aspect and a diameter of more than 10-mm arising on the operated ovary identified by transvaginal ultrasound. All scans were performed by experienced operators (J.O., I.T.). Pregnancy was defined as the evidence of a vital embryo in utero by transvaginal ultrasound at 6 weeks of pregnancy. "Time taken to spontaneous conception" was defined as the interval between surgery and spontaneous conception (or the first in vitro fertilization (IVF) when natural conception failed). Patients who became pregnant following donor-IVF were excluded from the analysis.

The primary objective of this study was to assess the postoperative pregnancy rate (either spontaneous or as part of fertility treatment) in the 2 treatment groups (cystectomy and CO_2 laser vaporization). The secondary objective was the identification of independent predictors of pregnancy.

Statistical Analysis

Analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS 21.0, Chicago, IL). Continuous variables were presented as mean and standard

deviation, categorical variables were expressed as absolute values and percentages (%). A binomial distribution model was used to calculate the 95% Confidence intervals (CI) of proportions. Chi-square test was used to compare categorical variables and the Student *t*-test was used to compare continuous variables between the 2 study groups (Cases and Controls).

Kaplan-Meier curves were built to estimate the probability of pregnancy depending on postoperative time and the log-rank test was used to test the statistical significance. A Cox's regression analysis was performed to evaluate independent predictor factors for pregnancy. Univariate and multivariate regression analyses were performed to evaluate the influence of different clinical characteristics and treatment strategies on pregnancy outcomes. Variables with $p < .05$ on univariate analysis were selected for multivariate analysis.

Adjusted hazard ratios (HRs) with 95% CI were evaluated when a statistically significant correlation was found. p values $< .05$ were considered statistically significant.

Results

A total of 142 consecutive patients with a history of endometrioma surgical treatment were included in the study. Cystectomy was performed in 73 patients (Group 1) and endometrioma ablation using CO_2 fiber laser in 69 patients (Group 2). Clinical features and treatment details of our patients are summarized in Table 1. The 2 groups were homogeneous with regard to age, indications for surgery, bilateral involvement, ovarian reserve before surgery, concomitant deep endometriosis, and r-AFS score. The mean endometrioma diameter was significantly larger in Group 1 than in Group 2 (Group 1: 5.4 ± 1.6-cm; Group 2: 4.3 ± 1.4; p = .041). The antral follicle count (AFC) of the operated ovary and serum antimüllerian hormone (AMH) levels were significantly higher after laser vaporization when compared with cystectomy (AFC Group 1 = 5.6 ± 3.1; AFC Group 2 = 9 ± 4.3 p = .023; AMH Group 1 = 1.5 ± 1 ng/mL; AMH Group 2 = 2.3 ± 1.8; p = .039). Thirty-nine patients in Group 1 (53.4%) and 38 patients in Group 2 (55.1%) were preoperatively recorded as infertile (p = .13). Thirty-nine women in Group 1 (53.4%) and 39 women in Group 2 (56.5%) desired to conceive after surgery (p = .79). Three patients in the cystectomy group (3/39, 7.7%), who had a severely impaired ovarian function before surgery, became pregnant following donor-IVF and were excluded from the analysis.

Table 1

Baseline clinical characteristics, intraoperative findings and follow-up of the 2 groups of patients (Group 1= cystectomy; Group 2 = CO_2 laser vaporization)

Characteristics	Group 1 (n = 73)	Group 2 (n = 69)	p value
Age (yrs)	31.8 ± 5.2	32.7 ± 3.9	.06
Indications for surgery			
Dysmenorrhea	40 (54.8%)	43 (62.3%)	.33
Chronic pelvic pain	31 (42.5%)	28 (40.6%)	.20
Dyspareunia	12 (16.4%)	11 (15.9%)	.22
Infertility	39 (53.4%)	38 (55.1%)	.13
BMI (kg/mq)	21.5 ± 3.0	20.1 ± 2.1	.023
Diameter of the cyst (cm)	5.4 ± 1.6	4.3 ± 1.4	.041
Bilateral endometrioma	16 (21.9%)	20 (28.9%)	.33
r-AFS score	41.9 ± 21.4	41.5 ± 17.7	.12
Associated deep endometriosis	24 (32.9%)	21 (30.4%)	.38
Uterosacral ligaments	9 (12.3%)	8 (11.6%)	.76
Rectovaginal septum	13 (17.8%)	13 (18.8%)	.98
Ureter	3 (4.1%)	3 (4.3%)	.96
Bladder	4 (5.5%)	8 (11.6%)	.08
AMH (ng/mL) before surgery	2.4 ± 1.7	2.7 ± 1.9	.21
AFC operated ovary before surgery	3 ± 2.6	3.7 ± 2.7	.47
Follow-up (months)	38.6 ± 11.5	31.7 ± 12.8	.20
Postoperative pregnancy intent	39 (53.4%)	39 (56.5%)	.79
AMH (ng/mL) 3 months after surgery	1.5 ± 1	2.3 ± 1.8	.039
AFC operated ovary 3 months after surgery	5.6 ± 3.1	9 ± 4.3	.023
Recurrence of symptoms	5 (6.8%)	9 (13%)	.78
Recurrence of disease	6 (8.2%)	7 (10.1%)	.67
Diameter of recurrent endometrioma (cm)	1.7 ± 0.8	3.3 ± 1.5	.28
Recurrence on the contralateral ovary	1 (1.4%)	3 (4.3%)	.17

AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; r-AFS = Revised American Fertility Society.
Data are expressed in values as mean [± standard deviation] or number (%).

The mean follow-up was 35.2 ± 12.6 months (range 13−59 months). The length of follow-up periods was comparable in the 2 different groups.

During pregnancy research, endometrioma recurrence was observed in 4/36 patients (11.1%, 95% CI: 2.8−22.5) in Group 1 and in 5/39 patients (12.8%, 95% CI: 4.5−22.8) in Group 2 (p = .82). Total recurrences (patients with pregnancy intention and patients under hormonal treatment) are reported in Table 1.

During the follow-up period, pregnancies were recorded in 72.2% (26/36, 95% CI: 58−88) of patients treated with cystectomy and in 74.3% (29/39, 95% CI: 61−88) of those managed with CO_2 fiber laser (p = .83). Thirty-four women (34/75; 45.3%) conceived spontaneously: 20/36 (55.6%, 95% CI: 41−70) patients in the cystectomy group and 14/39 (35.9%, 95% CI: 23−50) in the laser group (p = .08).

Cumulative spontaneous pregnancy rate for all infertile patients who wished to conceive after surgery is shown in Fig. 1. Of note, 61% (95% CI: 44−79) and 85.3% (95% CI: 68−94) of patients spontaneously conceived within postoperative 6 months and 9 months, respectively.

Among patients who failed spontaneous conception after surgery (41/75, 54.7%), 21 patients (28%) achieved pregnancy through IVF, 11 patients (14.7%) had 1 or more failed ART attempts, 4 patients (5.3%) are on an ART waiting list, 4 patients (5.3%) are still actively trying to conceive (because of ART refusal), and 7 patients (9.3%) have abandoned the pregnancy desire (after multiple IVF failures).

Among patients who underwent IVF (33/75, 44%), 6/12 patients (50%, 95% CI: 18−80) in the cystectomy group and 15/21 patients (71.4%, 95% CI: 52−90) in the laser group became pregnant (p = .22). The mean number of IVF treatments until conception was 1.6 ± 0.8 in Group 1 and 1.7 ± 0.9 in Group 2, respectively (p = .74).

Twenty patients (20/75, 26.7%) never became pregnant either spontaneously or with ART: 10/36 patients (27.8%, 95% CI: 15−42) in Group 1 and 10/39 (25.6%, 95% CI: 13−40) in Group 2 (p = .08).

Fertility outcome in patients wishing to conceive according to the type of surgery is shown in Table 2.

Clinical characteristics of pregnant (spontaneous or through IVF) patients and nonpregnant patients are reported in Table 3. Specifically, women who achieved spontaneous pregnancy were younger, had lower body mass index (BMI), and had been infertile for less time when compared with patients who never became pregnant (age: 33.1 ± 3.1 years vs 35.3 ± 3.6 years, p = .043; BMI: 19.2 ± 1.7 Kg/mq vs 21.8 ± 2.4 Kg/mq, p = .005; duration of infertility: 19.2±6.4 months vs 34.1 ± 20.4 months, p = .006; ANOVA, post hoc test).

Cox proportional hazard analysis was performed to investigate independent predictors for pregnancy (Table 4). Age at the time of surgery (Hazard ratio(HR) = 0.86; 95% CI: 0.78−0.96, p = .002) and duration of infertility (HR=0.80; 95% CI: 0.69−0.92, p = .006) were identified as independent indicators for pregnancy. Endometrioma size at surgery, unilateral versus bilateral involvement, r-AFS score, concomitant deep endometriosis, type of surgery (cystectomy vs ablation with CO_2 fiber laser), recurrence of disease did not retain significant predictive value for pregnancy.

Kaplan-Meyer survival analysis failed to demonstrate a significant difference in postoperative spontaneous pregnancy

Fig. 1

Kaplan-Meier curves showing the cumulative spontaneous pregnancy rate after surgery in infertile patients with endometriosis.

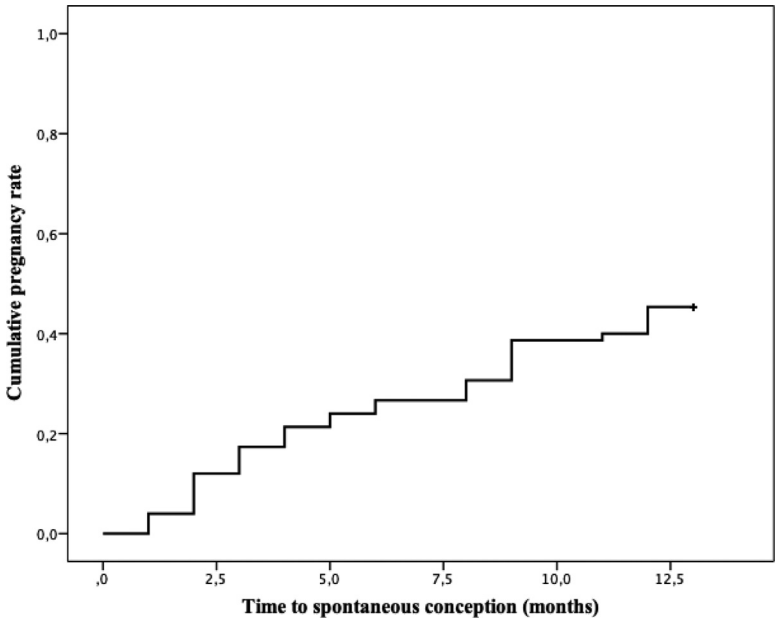


Table 2

Fertility outcome in patients wishing to conceive according to the type of surgery (Group 1= cystectomy; Group 2 = CO_2 laser vaporization). No significant differences were observed between the 2 groups (p = .08)

Study population	Total pregnancies (%)	Spontaneous pregnancies (%)	ART pregnancies (%)	No pregnancy (%)
Group 1 (n = 36)*	26 (72.2)	20 (55.5)	6 (16.7)	10 (27.8)
Group 2 (n = 39)	29 (74.3)	14 (35.9)	15 (38.5)	10 (25.6)
Total women wishing to conceive (n = 75)*	55 (73.3)	34 (45.3)	21 (28)	20 (26.7)

ART = assisted reproductive technique.
* Patients (n = 3) who became pregnant following donor- in vitro fertilization were excluded from the analysis.

Table 3

Clinical characteristics of pregnant (spontaneous or through in vitro fertilization) patients and nonpregnant patients (ANOVA analysis)

Characteristic	No pregnancy (n = 20)	Spontaneous pregnancies (n = 34)	ART pregnancies (n = 21)	p value
Age (yrs)	35.3 ± 3.6	33.1 ± 3.1	34.2 ± 2.4	.047
BMI (kg/mq)	21.8 ± 2.4	19.2 ± 1.7	21 ± 1.7	.006
Duration of infertility (mon)	34.1 ± 20.4	19.2 ± 6.4	22.3 ± 10.1	.007
Serum AMH levels (ng/mL)	1.8 ± 1.4	2.8 ± 1.9	2.5 ± 1.8	.50
Endometrioma size (cm)	4.5 ± 1.2	4.7 ± 1.6	4.1 ± 0.9	.27
Type of surgery	cy= 10 (50%) lv= 10 (50%)	cy= 20(58.8%) lv= 14 (41.2%)	cy= 6 (28.6%) lv= 15 (71.4%)	.91
r-AFS score	42.8 ± 14.5	40.8 ± 15.3	43.1 ± 18.5	.83
Associated DE	6 (30%)	9 (26.5%)	9 (42.9%)	.44
Recurrence of disease	4 (20%)	3 (8.8%)	2 (9.5%)	.42

ANOVA = Analysis of Variance; AMH = antimüllerian hormone; ART = assisted reproductive technique; BMI = body mass index; cy = cystectomy; DE = deep infiltrating endometriosis; lv = laser vaporization; r-AFS = Revised American Fertility Society.
Values are expressed as mean [± standard deviation] or number (%).

rates between the 2 treatment groups (cystectomy vs CO_2 laser vaporization) (log-rank p = .16) (Fig. 2). The probability of pregnancy at 6 and 9 months after surgery in in patients submitted to cystectomy and CO_2 laser vaporization was 60% (95% CI: 39−81) versus 64% (95% CI: 36−87) and 75% (95% CI: 55−91) versus 93% (95% CI: 39−81), respectively (p = .16).

Kaplan-Meier survival analysis showed a significant difference in postoperative spontaneous pregnancy rate according to age groups (Fig. 3).

Table 4

Independent predictors for pregnancy (Cox's regression multivariate analysis)

Factor	p value	HR (95% CI)
Age at the time of surgery	.002	0.86 (0.78-0.96)
Duration of infertility	.006	0.80 (0.69-0.92)
Endometrioma size at surgery	NS	
Unilateral versus bilateral endometriomas	NS	
r-AFS score	NS	
Concomitant deep endometriosis	NS	
Type of surgery (cystectomy vs CO_2 fiber laser)	NS	
Recurrence of disease	NS	

CI = confidence intervals; HR = hazard ratio; NS = not significant; r-AFS = revised American Fertility Society.

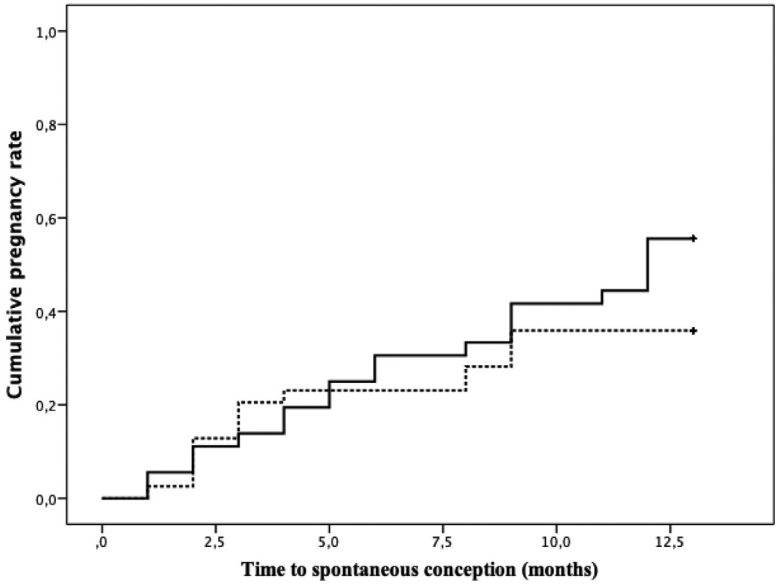
Discussion

The present study was designed to estimate the reproductive outcome in infertile women with endometriomas managed by either cystectomy or CO_2 laser vaporization. It revealed comparable probabilities of postoperative pregnancy in the 2 study groups. Of note, women treated with CO_2 laser vaporization were nearly one and a half times as likely to get pregnant with ART compared with those patients who underwent cystectomy. Conversely, they were 30% less likely to be pregnant spontaneously. More specifically, these women had higher AFC and AMH levels following surgery compared with those who had surgical excision of the cyst.

Previous studies suggested that ablation using energies with minor in depth thermal spread (CO_2 laser or plasma

Fig. 2

Kaplan-Meier curves presenting the probability of postoperative pregnancy in patients submitted to cystectomy (continuous line) and CO_2 laser vaporization (dashed line) (Log-rank p = .16).

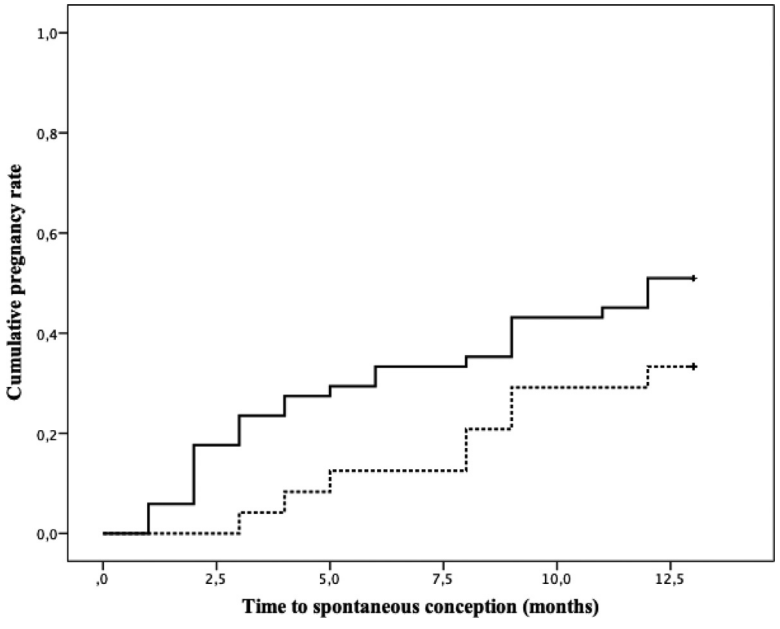


energy) may potentiates endometrioma treatment while eliciting the minimal damage to the ovarian reserve [9,11,13,17–19]. We have previously reported the positive effects of CO_2 technology on ovarian reserve through a RCT comparing the postoperative changes in ovarian reserve in terms of AFC and AMH levels in patients who had their endometrioma excised or vaporized with CO_2 laser [9]. Thus, planning a study comparing fertility outcomes between patients managed by ablation and those treated by cystectomy was the next logical step.

Very different outcomes have been reported in uncontrolled studies evaluating the impact of endometrioma

Fig. 3

Kaplan-Meier curves presenting the probability of postoperative pregnancy in patients younger (continuous line) and older (dashed line) than 35 years (Log-rank p = .050).



treatment on postoperative fertility outcomes. Pregnancy rates vary from 30% to 67%, with an overall weighted mean of about 50% [3], which is most likely an overestimate because of selection bias and publication bias. Excluding from the analysis women whose fertility status before surgery was unknown and those who conceived postoperatively by means of ART, this would most probably result in lower spontaneous pregnancy rates [3,20]. Moreover, whether the surgical modality adopted to treat endometriomas may influence the outcome is still debated. Many authors assume that, as endometriomas are the result of the invagination of ovarian cortex ("pseudo-cysts") [21], excising the capsule means removal of a large part of ovarian cortex with the reduction in follicular reserve [4,6,22]. Pooling data from only 2 RCTs available that specifically addressed this issue [23,24] confirms a substantial benefit in favor of the excision technique (pregnancy rate: 60.9% vs 23.4%) versus fenestration and coagulation, with a pregnancy HR of 5.11 (95% CI: 2.03−12.85) [2]. However, the validity of these results has been questioned, especially as the coagulation group consisted of bipolar energy only, which is most likely responsible for a deeper thermal effect compared to CO_2 laser or other energies [9,13,18,25,26].

Our results showed slightly higher rates of pregnancy (spontaneous and assisted) in both groups (Group 1: 72.2%, Group 2: 74.3%, p = NS) compared with those reported in the literature after endometrioma surgery [3]. Noteworthy, our rates are also higher compared with those reported for patients with untreated endometrioma undergoing ART as a first approach (pregnancy rate: 35.1%) [27]. These results support other published data [28,29] and suggest that surgery is a good option in infertile women with endometrioma to improve their chances to get pregnant. These findings are likely related to the operator expertise in endometriosis surgery in our study that performed the procedures and to the improvement of techniques and instrumentation over time. Significant surgical experience means greater competence in removing all visible peritoneal and ovarian implants, removing the cyst wall or completely vaporizing the capsule, removing the adhesions to restore the normal pelvic anatomy and being attentive to the fallopian tubes, which are essential in spontaneous conception. This can greatly benefit postoperative pregnancy.

If considering only spontaneous conception, in our study the postoperative pregnancy rate for all infertile patients was 45.3%, which is consistent with data reported in the recent meta-analysis by Alborzi et al [28]. Moreover, our results showed slightly lower rates of spontaneous pregnancy after CO_2 laser vaporization compared to cystectomy (35.9% vs 55.5%, respectively); however, this finding did not reach statistical significance. It is tempting to hypothesize that the lower spontaneous pregnancy rate in the laser group may be more closely linked with the shorter time given to these patients to attempt a spontaneous conception compared to cystectomy. At the beginning of the study, concerns about recurrences after CO_2 fiber laser vaporization resulted in the decision to decrease the time given to the patients to conceive spontaneously and, if that fails, proceed immediately with ART. This "time restriction" could have affected the spontaneous pregnancy rates in the laser group. We can speculate that giving these patients more time, would allow us to assess these pregnancies long-term.

On the other hand, compared with women treated with cystectomy, women managed by CO_2 laser achieved higher pregnancy rates, though not statistically significant, by means of ART (50% vs 71.4%, p = NS). This positive finding could be related to the benefits of CO_2 laser technology on ovarian reserve: patients treated with CO_2 fiber laser had higher AFC and AMH levels after surgery compared to cystectomy. A better ovarian reserve and an early referral for IVF procedures after surgery could explain successful results following ART [30,31].

Moreover, our study evaluated predictive factors for pregnancy. Age at the time of surgery and duration of infertility were identified as the only independent indicators for pregnancy. These results are in line with previously published data [10,32,33], which identify age as one of the major reproductive prognostic factors.

As regards recurrences, the present study showed that ablation with CO_2 laser is associated with recurrence rates similar to those observed after cystectomy. These results reinforce those previously reported [13−15].

This study has some weaknesses. The major limitation is represented by the retrospective design of the study. Moreover, the sample size is small, thus estimation of results may be less precise. Another limitation of the study is related to the strategies that each group followed trying to conceive. The different time restrictions could account for the lower spontaneous pregnancy rates in the CO_2 laser treatment group.

The strengths of this study are related to the prospective recording of data and the subsequent accurate estimation of all pregnancies. Moreover, all procedures were performed by a team of 2 surgeons, thus eliminating many inherent confounding factors like introducing selection bias.

Surprisingly, despite different populations and different ablative techniques, our fertility outcomes are very similar to those reported by Mircea and coworkers, with a comparable mean follow-up (35.36 ± 17.5 months vs 35.2 ± 12.6 months) [10]. This similarity highly strengthens reproducibility of ablative techniques and the external validity of the study.

In addition, CO_2 fiber laser is easy to use and highly reproducible. Unlike cystectomy, the use of CO_2 fiber laser does not necessitate trained niche surgeons and allows gynecologists with general training in reproductive and endometriosis surgery to approach endometrioma. This straightforward system is envisaged to offer effective treatment to women with endometrioma outside the premises of specialized referral centers for endometriosis. On the other hand, it is extremely important to ensure an accurate

preoperative assessment of the patients in daily clinical practice, to select cases according to surgeon's experience.

In conclusion, CO_2 fiber laser vaporization may represent a viable alternative to traditional cystectomy. In light of our results showing that CO_2 laser-treated endometrioma is associated with pregnancy rates equal to those observed after cystectomy and favorable reproductive ART outcomes, we are confident in the positive effects of this technology on the ovarian reserve. Additional well-designed trials investigating fertility outcomes in this context are needed to further consolidate this notion.

References

1. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29:400–412.
2. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev*. 2008;2:CD004992.
3. Berlanda N, Vercellini P, Somigliana E, Frattaruolo MP, Buggio L, Gattei U. Role of surgery in endometriosis-associated subfertility. *Semin Reprod Med*. 2013;31:133–143.
4. Busacca M, Riparini J, Somigliana E, et al. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. *Am J Obstet Gynecol*. 2006;195:421–425.
5. Muzii L, Bellati F, Bianchi A, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part II: pathological results. *Hum Reprod*. 2005;20:1987–1992.
6. Benaglia L, Somigliana E, Vighi V, Ragni G, Vercellini P, Fedele L. Rate of severe ovarian damage following surgery for endometriomas. *Hum Reprod*. 2010;25:678–682.
7. Muzii L, Marana R, Angioli R, et al. Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter? *Fertil Steril*. 2011;95:2116–2119.
8. Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-Roux F. Large ovarian endometriomas. *Hum Reprod*. 1996;11:641–646.
9. Candiani M, Ottolina J, Posadzka E, et al. Assessment of ovarian reserve after cystectomy versus 'one-step' laser vaporization in the treatment of ovarian endometrioma: a small randomized clinical trial. *Hum Reprod*. 2018;33:2205–2211.
10. Mircea O, Puscasiu L, Resch B, et al. Fertility outcomes after ablation using plasma energy versus cystectomy in infertile women with ovarian endometrioma: a multicentric comparative study. *J Minim Invasive Gynecol*. 2016;23:1138–1145.
11. Ottolina J, Castellano LM, Ferrari S, et al. The impact on ovarian reserve of CO_2 laser fiber vaporization in the treatment of ovarian endometrioma: a prospective clinical trial. *J Endometr Pelvic Pain Disord*. 2017;9:206–210.
12. Vanni VS, Ottolina J, Candotti G, et al. Flexible CO_2 laser fiber: first look at the learning curve required in gynecological laparoscopy training. *Minerva Ginecol*. 2018;70:53–57.
13. Roman H, Auber M, Bourdel N, Martin C, Marpeau L, Puscasiu L. Postoperative recurrence and fertility after endometrioma ablation using plasma energy: retrospective assessment of a 3-year experience. *J Minim Invasive Gynecol*. 2013;20:573–582.
14. Carmona F, Martínez-Zamora MA, Rabanal A, Martínez-Román S, Balasch J. Ovarian cystectomy versus laser vaporization in the treatment of ovarian endometriomas: a randomized clinical trial with a five-year follow-up. *Fertil Steril*. 2011;96:251–254.
15. Candiani M, Ottolina J, Schimberni M, Tandoi I, Bartiromo L, Ferrari S. Recurrence rate after ''one-Step'' CO_2 fiber laser vaporization versus cystectomy for ovarian endometrioma: a 3-year follow-up study. *J Minim Invasive Gynecol*. 2020;27:901–908.
16. American Society for Reproductive Medicine. Revised American Fertility Society classification of endometriosis: 1996. *Fertil Steril*. 1997;67:815–816.
17. Canis M, Pouly JL, Tamburro S, Mage G, Wattiez A, Bruhat MA. Ovarian response during IVF-embryo transfer cycles after laparoscopic ovarian cystectomy for endometriotic cysts of >3 cm in diameter. *Hum Reprod*. 2001;16:2583–2586.
18. Tsolakidis D, Pados G, Vavilis D, et al. The impact on ovarian reserve after laparoscopic ovarian cystectomy versus three-stage management in patients with endometriomas: a prospective randomized study. *Fertil Steril*. 2010;94:71–77.
19. Var T, Batioglu S, Tonguc E, Kahyaoglu I. The effect of laparoscopic ovarian cystectomy versus coagulation in bilateral endometriomas on ovarian reserve as determined by antral follicle count and ovarian volume: a prospective randomized study. *Fertil Steril*. 2011;95:2247–2250.
20. Vercellini P, Somigliana E, Viganò P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod*. 2009;24:254–269.
21. Brosens IA. Endometriosis—a disease because it is characterized by bleeding. *Am J Obstet Gynecol*. 1997;176:263–267.
22. Muzii L, Bianchi A, Crocè C, Manci N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure. *Fertil Steril*. 2002;77:609–614.
23. Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril*. 1998;70:1176–1180.
24. Alborzi S, Momtahan M, Parsanezhad ME, Dehbashi S, Zolghadri J, Alborzi S. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril*. 2004;82:1633–1637.
25. Roman H, Pura I, Tarta O, et al. Vaporization of ovarian endometrioma using plasma energy: histologic findings of a pilot study. *Fertil Steril*. 2011;95:1853–1856. .e1—e4.
26. Pados G, Tsolakidis D, Assimakopoulos E, Athanatos D, Tarlatzis B. Sonographic changes after laparoscopic cystectomy compared with three-stage management in patients with ovarian endometriomas: a prospective randomized study. *Hum Reprod*. 2010;25:672–677.
27. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. *Hum Reprod Update*. 2015;21:809–825.
28. Alborzi S, Zahiri Sorouri Z, Askari E, Poordast T, Chamanara K. The success of various endometrioma treatments in infertility: a systematic review and meta-analysis of prospective studies. *Reprod Med Biol*. 2019;18:312–322.
29. Motte I, Roman H, Clavier B, et al. In vitro fertilization outcomes after ablation of endometriomas using plasma energy: a retrospective case-control study. *Gynecol Obstet Fertil*. 2016;44:541–547.
30. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. *Fertil Steril*. 2012;98:591–598.
31. AlKudmani B, Gat I, Buell D, et al. In vitro fertilization success rates after surgically treated endometriosis and effect of time interval between surgery and in vitro fertilization. *J Minim Invasive Gynecol*. 2018;25:99–104.
32. González-Foruria I, Peñarrubia J, Borràs A, et al. Age, independent from ovarian reserve status, is the main prognostic factor in natural cycle in vitro fertilization. *Fertil Steril*. 2016;106:342–347e2.
33. Benoit L, Boujenah J, Poncelet C, et al. Predicting the likelihood of a live birth for women with endometriosis-related infertility. *Eur J Obstet Gynecol Reprod Biol*. 2019;242:56–62.