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The impact on ovarian reserve of CO_2 laser fiber vaporization in the treatment of ovarian endometrioma: a prospective clinical trial

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ABSTRACT

Background: In recent years, excisional surgery has been questioned as an ideal surgical approach for endometriomas because it is associated with potential removal of healthy ovarian tissue and loss of ovarian follicles with subsequent reduction of ovarian reserve. The aim of our study was to evaluate the benefits of CO_2 laser vaporization through a clinical trial assessing the postoperative changes in ovarian reserve as indicated by antral follicle count (AFC) and anti-Müllerian hormone (AMH).

Materials and methods: Fifteen patients undergoing surgery for primary unilateral or bilateral symptomatic endometriomas were enrolled in the study. During surgery, the cystic lining was completely vaporized with CO_2 laser fiber (AcuPulse Duo system, Lumenis); before surgery and at 1 and 3 months after surgery, ovarian reserve was evaluated by pelvic ultrasound to determine the AFC, and blood sample to determine AMH levels.

Results: The AFC of the operated ovary was significantly increased after treatment at 1 and 3 months' follow-up ($p = 0.0021$; $p = 0.005$, respectively); the increase is particularly significant in women younger than 35 years ($p = 0.012$). No statistically significant changes were reported in serum AMH concentrations at 1 or 3 months' follow-up. No recurrences of symptoms and no recurrences of endometrioma were reported.

Conclusions: These data support the hypothesis that endometrioma vaporization with CO_2 laser fiber may be a valid method to preserve ovarian function; however, further studies are required before advocating the routine use of CO_2 laser vaporization for the management of ovarian endometriosis.

Keywords: CO_2 laser, Endometrioma, Fiber, Ovarian reserve, Surgery

Introduction

Laparoscopic stripping, also called cystectomy, is the recommended treatment for ovarian endometrioma because of higher pregnancy rate and lower recurrence rate compared with drainage and ablation (1). In recent years, excisional surgery has been questioned as an ideal surgical approach for endometriomas because it is associated with excessive removal of ovarian tissue and loss of ovarian follicles, with subsequent reduction of ovarian reserve (2, 3). According to a recent report, absence of follicular growth was observed in 13% of operated ovaries, although this event never occurred in the contralateral gonad (4).

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In our practice, fear of ovarian failure after cystectomy resulted in the introduction of an ablative technique involving CO_2 laser technology, which possesses the ability to deliver energy with little thermal spread. More than 40 patients were treated with CO_2 laser at our institution over a 2-year period. Our surgical procedure was inspired by that employed by Jacques Donnez for more than 20 years, in which CO_2 laser is used to ablate endometriomas' inner wall, after 3-months gonadotropin-releasing hormone agonist (GnRHa) therapy (5). Laser vaporization, according to the ''three-step procedure", has also been proposed as the best method to preserve ovarian function (6). However, no data are available about the single use of CO_2 laser fiber vaporization (without GnRHa therapy) with respect to the ovarian reserve.

Since 2015, we have continuously evaluated the benefits of CO_2 laser vaporization through a clinical trial assessing the postoperative changes in ovarian reserve as indicated by antral follicle count (AFC) and anti-Mullerian hormone (AMH).

Sonographic assessment of the AFC has been strongly associated with the primordial follicle pool and is currently used as a reliable sonographic indicator of ovarian reserve (7, 8). Furthermore, AMH may represent a reliable serum marker

able to indicate the number of growing follicles and may reflect ovarian follicular reserve.

Compared with AMH, AFC has the advantage of correlating directly with the ovarian reserve of a single ovary. The validity of AMH is also debatable because the relative contribution of the affected and intact ovaries cannot be definitely discriminated.

The aim of the study was to determine whether, and to what extent, CO_2 laser fiber vaporization for ovarian endometriotic cyst affects ovarian reserve by measuring changes in sonographic AFC and serum AMH concentrations before and after treatment.

Materials and methods

This prospective cohort study included patients who underwent surgery for primary unilateral or bilateral symptomatic endometriomas at San Raffaele Scientific Institute between November 2015 and August 2016.

The ultrasonographic criteria for the diagnosis of endometrioma were as follows: round cystic mass with thick walls; regular margins; homogeneous hypoechoic fluid content with scattered internal echoes and without papillary projections; no or poor vascularization of capsule. For the diagnosis of endometrioma, the cyst had to be present on at least two consecutive ultrasounds performed with an interval of at least one month (9).

The inclusion criteria were: symptomatic (pain and/or infertility) patients of reproductive age; primary unilateral or bilateral endometriomas; largest diameter of the endometrioma ≥3 cm and ≤8 cm. The diameter cut-off was chosen according to previous data present in the literature and guidelines for the management of endometriomas (1).

The exclusion criteria were: patients aged ≥40 years; presence of deep infiltrating endometriosis and adenomyosis; previous surgical procedures on the ovaries; unilateral oophorectomy; previous salpingectomy or hysterectomy; other endocrine diseases such as thyroid disease, hyperprolactinemia, diabetes mellitus, or adrenal disorders; suspected or proven ovarian malignancy; evidence of premature ovarian failure (POF) or premature menopause; hormonal treatment within 3 months fromovarian reserve assessment and 3 months after surgery.

All cases fitting the above-mentioned criteria were included in a prospectively collected database.

Operative laparoscopy was performed by a team of surgeons with extensive experience in the treatment of endometriosis (MC, SF).

During laparoscopy, the ovary was freed from adhesions. The ovarian surface was incised, the endometriotic cyst was drained and opened to expose the inner surface. A biopsy of the cystic wall was sent for routine histologic examination to confirm the diagnosis of endometriosis. When possible, the cyst was everted to expose the inner cystic wall completely. After that, the cystic lining was completely vaporized with CO_2 laser fiber (AcuPulse Duo system, Lumenis Ltd) in a radial way starting from the center to the periphery, at a power density of 13 W/cm^2 in the continuous mode. No suture was placed after vaporization and all patients were discharged the following day (see Supplementary Video, available online as supplementary material at www.j-endometriosis.com).

In all patients, the diagnosis of endometrioma was confirmed by surgical exploration and histopathologic examination.

Patients underwent gynecologic examination with pelvic ultrasound to determine the antral follicle count, and blood sample to determine AMH levels at baseline (prior to surgery) and at 1 and 3 months after surgery. Patients were then referred to our endometriosis outpatient clinic for further follow-up.

The AFC was assessed on the second and the fifth day of the menstrual cycle by counting the number of follicles with average diameter of 2-10 mm in both ovaries; the AFC of both ovaries was recorded. During ultrasound examination, the volume of each ovary and endometrioma expressed in cm^3 was also assessed using the Prolate ellipsoid formula: volume = 0.5233 × D1 (longitudinal) × D2 (transverse) × D3 (anterior-posterior). In addition, the largest diameter of the endometrioma was recorded. Pelvic ultrasound was performed by an experienced ultrasonographer (JO).

AMH levels were assessed on venous blood samples (Beckman-Coulter 2nd-generation; Gen II) obtained on days 2-5 of the menstrual cycle.

Our Institutional Review Board approved the study protocol and its consent form, and written informed consent was obtained from all participants.

Statistical analysis

Comparisons of continuous variables in the study group between each sampling point, pre- and postoperatively, were analyzed by using the paired Student t-test and the signed rank test accordingly to data distribution.

Statistical calculations were performed using the Statistical Package for the Social Sciences version 20.0 (SPSS, Chicago, USA). A $p<0.05$ was considered statistically significant.

Results

This prospective study included 15 patients who agreed to participate in this study and gave written informed consent.

The baseline clinical characteristics and ultrasonographic findings are shown in Table I. Overall, 93.3% of patients were nulliparous and 40% of patients were symptomatic for dysmenorrhea or chronic pelvic pain. Infertility was documented preoperatively in 66.7% of patients. Mean age at diagnosis was 32.9 years (range: 21-39 years).

The mean diameter of endometriomas was 4.6 cm (range: 3-8.6 cm). Bilateral endometriomas were present in five cases, and both ovaries were operated with the same surgical technique.

AFC at 1 and 3 months' follow-up was significantly higher compared to baseline (from 9.1 at baseline to 12.2 at the 1-month follow-up, $p = 0.034$; from 9.1 at baseline to 14.7 at the 3-month follow-up, $p = 0.021$).

The AFC of the operated ovary was also significantly increased after treatment at 1 and 3months' follow-up (from 3.8 at baseline to 6.1 at 1-month follow-up, $p = 0.031$; from 3.8 at baseline to 8.1 at 3-month follow-up, $p = 0.005$) (Fig. 1). No differences emerged from analysis of the AFC of the non-operated ovary, at baseline and 3 months after surgery ($p = 0.49$).

TABLE I - Baseline characteristics and intraoperative findings

Characteristics	
Age (y)	
Mean ± SD	32.9 ± 5.7
Indications to surgery	
Dysmenorrhea	6 (40%)
Chronic pelvic pain	3 (20%)
Dyspareunia	1 (6.7%)
Infertility	10 (66.7%)
Preoperative AFC	
Mean ± SD	8 ± 5.6
Preoperative AMH level (ng/mL)	
Mean ± SD	2.1 ± 1.5
Diameter of the cyst (mm)	
Mean ± SD	48.4 ± 17.6
Endometrioma in right ovary	
No.	10
Endometrioma in left ovary	
No.	17
Operative time (min)	
Mean ± SD	70.4 ± 25.5
Follow-up (mo.)	
Mean ± SD	6.4 ± 2.9

AFC = antral follicle count; AMH = anti-Müllerian hormone; SD = standard deviation.

In case of bilateral endometriomas, AFC 1 and 3 months after surgery appeared to increase when each ovary was considered individually. However, no statistical significance was found in these results, probably due to the small sample size (n = 5). If adjusted for patient's age, AFC was still significantly higher at the 3-month follow-up when compared with that measured before surgery. The AFC increase was particularly significant in women aged <35 years (p = 0.012).

AMH at the 3-month follow-up did not differ from baseline (p = 0.08).

No intraoperative or postoperative complications were reported.

No recurrences of symptoms and of endometrioma were reported at a mean follow-up of 7.9 months (range: 3-12 months).

According to surgeon's advice, six patients with immediate pregnancy desire, were allowed to attempt a spontaneous conception at the end of the 3-month follow-up. At present, one of the six patients had spontaneously conceived at the 3-month follow-up. The remaining five patients have been attempting a pregnancy for a period ranging from 2 to 6 months (mean: 4.2 months).

Four patients who had undergone surgery because symptomatic, were referred to IVF at the end of the 3-month follow-up, considering the age >37 years and the baseline levels of AMH.

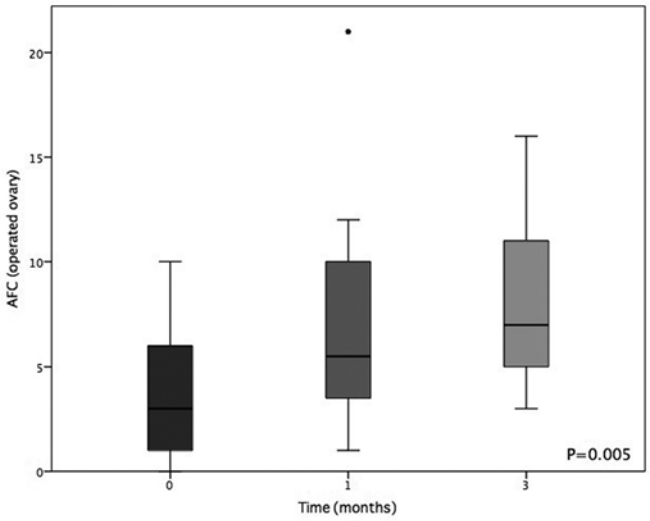

Fig. 1 - Changes in the antral follicle count AFC (operated ovary) before surgery (0) and at 1- and 3-month follow-up.

Five patients had no immediate pregnancy intentions and received medical therapy (estro-progestins) at the end of the study.

Discussion

The optimal surgical approach for the management of endometriomas remains a controversial issue in the literature; an unsolved debate continues on the most effective surgical technique between excision and ablation of the cyst (10-14). Few articles in the literature compare these different surgical approaches. When surgically treating endometriomas, it is necessary to strike a balance between the almost unavoidable destruction of healthy ovarian tissue and the prevention of recurrence of the cyst. This represents a major challenge for the surgeon when choosing the most suitable technique. Excisional surgery involves careful removal of the cyst capsule from the ovarian cortex by traction with grasping forceps. Concerns have been raised about the possible damage caused by cystic wall excision on the ovarian reserve. Muzii et al (15) showed that inadvertent removal of healthy ovarian tissue, together with the capsule of the cyst, occurs in most cases, especially near the hilus where 70% of endometrioma specimens contained follicles (15). An additional mechanism for functional loss in the ovarian reserve after cystectomy may be devascularization of the ovary due to excessive use of bipolar coagulation for hemostatic purposes (16, 17).

This complication could possibly be explained by inadequate stripping performed by inexperienced surgeons, as well as by difficulties in dissection (due to endometriosis-induced fibrosis and consequent absence of cleavage plane) even in cases of experienced laparoscopists (18).

For these reasons, some practitioners suggest that ablative techniques represent a less aggressive approach towards the healthy ovarian cortex. In this surgical approach, the capsule of the endometrioma is not excised, but it is either completely ablated with electrocoagulation, or it is vaporized with CO_2 laser or plasma energy (5, 6, 19, 20).

Indeed, some authors have compared ablation with excision, and results after ovarian cystectomy (i.e., excision technique) showed lower values of AFC, ovarian volume, AMH levels, and ovarian responsiveness to hyperstimulation for in vitro fertilization (21, 22).

Nevertheless, a large number of surgeons abandoned ablative techniques after a 2008 Cochrane review (23). This review reported better outcomes with stripping technique with respect to cyst ablation, in terms of recurrence of endometrioma or symptoms and subsequent spontaneous pregnancy rates. However, including only three older randomized trials, the validity of this Cochrane review has been questioned, especially as the ablation group consisted of only bipolar energy, which is most likely responsible for a deeper thermal effect, not taking into account results from CO_2 laser or plasma energy studies.

There is consistent literature about the safety and efficacy of CO_2 laser technology: it provides a precise tissue dissection, ablation, controlled depth of tissue penetration and thermal damage without sacrificing the adjacent healthy ovarian cortex (5, 24-27). According to Donnez and his colleagues, ablation cannot penetrate into the tissue by more than 1.0-1.5 mm. Therefore, this technique appears to vaporize the internal lining of the cyst selectively, without reaching the fibrotic capsule surrounding the endometrioma or the ovarian parenchyma (28).

Laser vaporization, according to the ''three-step procedure", has been proposed as the best method to preserve ovarian function (6).

However, no data are available about the single use of CO_2 laser fiber vaporization (without the use of GnRHa therapy before surgery) with respect to the ovarian reserve.

In our daily practice, we have adopted CO_2 laser technology in the surgical treatment of ovarian endometriosis and we do not use GnRHa therapy before surgery. To evaluate the impact of CO_2 laser fiber vaporization on ovarian function, we prospectively analyzed changes in sonographic AFC and serum AMH concentrations before and after surgery. AFC and AMH have been shown to best correlate with the primordial follicle pool (29), and are therefore considered the most reliable methods of ovarian reserve evaluation (30, 31). In the present study, we set the change in AFC at the 3-month follow-up as the primary outcome of the study, since it has the advantage of correlating directly with the ovarian reserve of a single ovary (32). Our study demonstrated that ovarian reserve based on AFC measurements improved after surgical treatment with CO_2 laser technology, even if adjusted for patient's age. The increase in AFC values was particularly significant in women aged <35 years ($p = 0.012$), suggesting that the younger the patient, the higher the chances of recovering follicular activity after surgery.

These results reinforce those of Pados et al (19) who found an increase in AFC in the treated ovary 6 months after the "three-stage procedure" and of Donnez et al (33) who reported AFC values similar to those of the contralateral ovary after using a combined excisional and ablative technique.

In this study, progressively higher serum AMH levels after ablation were described; however, no statistically significant decrease in serum AMH concentrations was reported at 1 or 3 months after surgery. These data are consistent with those reported by Roman et al (34).

Cyst ablation with CO_2 laser technology could result not only in healthy ovarian tissue sparing and decrease in inflammatory phenomena, but could also promote the development of primordial, primary and secondary follicles. This hypothesis could explain the progressive increase in AFC of the treated ovary as well as the absence of decrease of AMH serum levels after surgery.

Moreover, no recurrences of symptoms or of endometrioma were reported in our cohort, even if no definitive conclusion can be drawn due to the short-term follow-up. However, Carmona and his colleagues reported data about a 5-year follow-up after surgery and no significant differences in recurrence rates were found (22).

Despite these encouraging preliminary data, we are aware that further studies are required before advocating the routine use of CO_2 laser vaporization for the management of ovarian endometriosis. Our group has already planned a randomized controlled trial to provide more conclusive data about the potential advantage of CO_2 laser ablation with respect to ovarian cystectomy in terms of fertility outcomes. Results will be available in the future.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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