

ORIGINAL ARTICLE

Anti-Mullerian hormone trend evaluation after laparoscopic surgery of monolateral endometrioma using a new dual wavelengths laser system (DWLS) for hemostasis

Luigi Nappi¹, Stefano Angioni², Felice Sorrentino¹, Gilda Cinnella³, Michela Lombardi¹, and Pantaleo Greco⁴

¹Department of Medical and Surgical Sciences, Institute of Obstetrics and Gynecology, University of Foggia, Foggia, Italy, ²Department of Surgical Sciences, Institute of Obstetrics and Gynecology, University of Cagliari, Cagliari, Italy, ³Department of Anesthesia and Intensive Care, University of Foggia, Foggia, Italy, and ⁴Section of Obstetrics and Gynecology, Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy

Abstract

Operative laparoscopy is the gold standard in the treatment of endometriotic ovarian cysts. Excisional surgery is the best technique to prevent recurrences and improve symptoms but it may result in ovarian reserve damage due to the removal of healthy ovarian cortex. The aim of this study was to assess the impact on ovarian reserve of the use of dual wavelengths laser system (DWLS) hemostasis after stripping technique of monolateral endometrioma, by dosing the anti-Mullerian hormone (AMH). This prospective study was conducted at the Institute of Obstetrics and Gynecology, University of Foggia, from December 2013 to January 2015. Forty-five women underwent excision of monolateral endometriotic ovarian cyst by stripping without using a bipolar coagulation and performing hemostasis with a DWLS. The AMH serum levels were estimated before the surgery (T0), 4–6 weeks (T1) and 6–9 months (T2) after surgery. Our results suggest that an appropriate surgical technique with the use of laser hemostasis does not determine a significant reduction of ovarian reserve. Laser hemostasis could prevent follicular reserve loss after ovarian endometrioma surgery.

Keywords

AMH, endometriosis, laser hemostasis, ovarian reserve

History

Received 5 June 2015

Accepted 30 June 2015

Published online 28 August 2015

Introduction

Endometriosis is a common gynecological disorder of still unknown pathogenesis [1]. It is a chronic disease associated with chronic pain, severe impairment of quality of life and it is a recognized cause for infertility [2,3]. Surgery has a fundamental role to play in the treatment of endometriomas. The management of ovarian endometriomas in women wishing to become pregnant remains challenging [4,5]. Although several investigators have questioned whether endometriomas should be removed or left *in situ*, in case of an endometrioma greater than 4 cm, surgical removal may be offered as a treatment option. However, endometrioma and its laparoscopic excision may reduce ovarian reserve [6]. Endometrioma results from the invagination of the ovarian cortex, often endowed with primordial follicles that are lost during stripping. Consequently, the size of the endometrioma also contributes to the amount of ovarian parenchyma that is removed during surgery. Moreover, there is a direct function between the severity of disease and ovarian reserve [7,8]. Nevertheless, laparoscopic endometrioma excision still is the gold standard treatment as it increases the chance of spontaneous pregnancy and reduces the risk of recurrence of endometriosis [9].

The aim of our study was to evaluate the loss of ovarian parenchyma and decrease in antral follicle count (AFC) after ovarian endometrioma ablation using a new approach on hemostasis control: the use of a diode laser (dual wavelengths laser system [DWLS]).

Methods

After ethical approval of the local research ethics committee, women presenting to the general gynecology unit of our tertiary referral teaching hospital were recruited between December 2013 and January 2015. Inclusion criteria were: age 18–45 years, unilateral endometrioma greater than 35 mm, and no previous gynecological surgery or hormonal therapy 3 months before surgery. Women with previous surgery for endometriosis, hormone therapy 3–6 months before the current surgery, coagulation disorders, current pregnancy, pelvic inflammatory disease, malignant disorders, non-endometriotic ovarian cysts, GnRH analogues or contraceptive therapy during the follow-up, BMI ≥ 30 kg/m² or endocrine disorders were excluded. A written consent form was obtained from all participants. We collected personal data and patients symptoms such as dysmenorrhea, dyschezia, chronic pelvic pain, dyspareunia, and presence of infertility. AMH was assayed with a commercial enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX). The AMH assay had a sensitivity of 0.006 ng/mL; the intra-assay and inter-assay coefficients of variation were 9.4% and 7.2%, respectively. We performed the hormone assay before surgery,

Address for correspondence: Felice Sorrentino, MD, Department of Medical and Surgical Sciences, Institute of Obstetrics and Gynecology, University of Foggia, Viale L. Pinto, 71100 Foggia, Italy. Tel: +390881732350. Fax: +39 0881732281. E-mail: felice.sorrentino@alice.it

4–6 weeks and 6–9 months from surgery, in the early proliferative phase (second to third of the menstrual cycle), to record changes in ovarian reserve before and after surgery observed and to evaluate suspicious changes due to hormonal disorders. Patients received anti-microbial prophylaxis before surgery [10]. The operative laparoscopy was performed during the proliferative phase of the menstrual cycle by the same surgical team [11], which boasted extensive experience in the treatment of endometriosis. During the diagnostic laparoscopic phase, the surgeons followed the same protocol: inspection of the pelvic organs, peritoneal washing, peritoneal staging of endometriosis, and adhesiolysis to release the ovary from the surrounding structures if needed. In order to possibly prevent or decrease the occurrence of post-surgical adhesions, 500cl of warm lactated Ringer's solution was instilled in the pelvis [12]. In all cases, a histological intraoperative examination confirmed the diagnosis of endometrioma. The severity of endometriosis was staged according to the classification of the American Society for Reproductive Medicine (ASRM) [13]. In detail, the most part of endometrioma was excised following the conventional stripping technique. The hemostasis of residual ovarian tissue was performed using the DWLS, with a conic fiber of 1000 micron (Biolitec Ceralas HPD, wavelength of 980 nm and 1470 nm, model 120 W). Statistical analyses were performed with SPSS version 21.0 (IBM Corp., Armonk, NY). Concentrations of AMH were compared between each sampling point (pre-operatively, post-operatively at week 4–6 and month 6–9) using paired samples *t*-test and Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant.

Results

Fifty-eight patients were recruited. Thirteen of them were excluded from the study (three patients for previous surgery for endometriosis, two for hormone therapy in the 3 months prior to the current surgery, one patient for BMI ≥ 30 kg/m², two patients because of unilateral endometrioma smaller than 35 mm, one patient with bilateral endometrioma, and four patients who were older than 45 years). Table 1 shows the characteristics of the study population, the mean age of the patients and the mean diameter of the larger endometriotic cyst. No major complications occurred during surgery. Women were discharged 2 d after the surgery. Ovarian reserve, as evaluated through assay, showed a reduction in serum AMH levels after surgery (Table 2). At both T1 and T2,

Table 1. Demographic characteristics of women enrolled.

Number of patients (n)	45
Age (years)	31 (± 4.3)
Parity	0.6 (± 0.9)
BMI (kg/m ²)	22.1 (± 2.65)
Diameter of the larger endometriotic cyst (cm, mean $\pm$ SD [95% CI])	7.3 $\pm$ 2.4 (6.3–7.8)
Duration of surgery (min)	50 $\pm$ 16.3

Values are given as mean ($\pm$ SD).

Table 2. AMH levels at baseline, 4–6 weeks (T1) and 6–9 months (T2).

Overall cohort	Mean plasma level (ng/ml) $\pm$ SD	Mean $\pm$ SD difference from baseline	<i>p</i> (from baseline) [CI 95%]	Mean $\pm$ SD difference (T1–T2)	<i>p</i> (T1–T2) [CI 95%]
<i>n</i> = 45					
Baseline	3.01 $\pm$ 0.78				
T1	2.41 $\pm$ 0.76	–0.60 $\pm$ 0.26	<0.0001 [0.53–0.68]		
T2	2.76 $\pm$ 0.80	–0.25 $\pm$ 0.11	<0.0001 [0.22–0.28]	0.35 $\pm$ 0.24	<0.0001 [–0.43–(–0.28)]

CI, confidence interval; SD, standard deviation.

DWLS was associated to lower AMH levels than baseline, with mean AMH levels at T1 2.41 ng/ml. AMH levels in the DWLS group seemed to increase towards baseline levels (mean 2.76 ng/ml, $p < 0.0001$), and this difference was statistically significant between T1 and T2 (mean difference +0.35 ng/ml, $p < 0.0001$). In patients with a low AMH levels at baseline (< 2 ng/ml) the AMH levels slightly recovered from T1 to T2 to 87.0% of the mean baseline value (1.64 ng/ml; Table 3). In patients with higher AMH serum level at baseline (≥ 3 ng/ml), the mean serum AMH corresponded to 93.6% of baseline levels (Supplementary Table S1).

Discussion

AMH has been recommended as a superior marker for predicting ovarian response over age, FSH, inhibin B and E₂ levels, as the last three biomarkers are all involved in the pituitary-ovary axis negative feedback, resulting in great variations during menstrual cycle [14,15]. Therefore, AMH may also be a very informative marker regarding the degree of ovarian reserve damage, due to endometrioma or ovarian cystectomy, because of its independence from menstrual period and its ability for early detection of ovarian damage as compared to other hormones [6–8,16,17]. A few studies in the literature report the assessment of pre- and post-operative AMH levels in patients undergoing laparoscopic excision of unilateral/bilateral endometriomas. Moreover, there is still not a standard timepoint to assess post-operative AMH changes. Early measurements within the first post-operative month generally demonstrated a significant decrease in AMH levels. This decrease did not seem to change through the 3rd, 6th, and even 12th month in some studies [18–22]. In others papers, AMH levels were observed to increase after 3 months, although values were still lower than pre-operative levels [17]. In other studies, no significant decrease in AMH levels after surgery was evidenced [6,23]. These contradictory results may be explained by the different techniques used, as well as by the characteristics of endometriotic cysts (size, number) reported in the studies [24]. However, even if the surgery could damage ovarian reserve, there is evidence that an intervention is better than no treatment, even if surgery could not be the best treatment to improve fertility [25]. The two most common techniques used for endometriomas treatment are the stripping technique and pseudo-capsule vaporization. The first technique may cause accidental removal of a large amount of ovarian tissue, while the second one is often associated with an increased endometrioma recurrence after surgery [9]. A recent study asserts that the negative results obtained with the ablation technique may be related to the use of bipolar current, which is most likely responsible for a deeper thermal effect compared to plasma energy or CO₂ laser use [4]. In addition, hemostatic techniques may be involved in the loss of ovarian reserve. The common use of bipolar coagulation may cause thermal damage to the ovarian follicles [21,22], while ovarian suture could induce a tissue ischemic injury [26]. Roman et al. showed that plasma energy ablation of the cyst wall may be

Table 3. AMH levels at baseline, 4–6 weeks (T1) and 6–9 months (T2): sub-analysis in patients with lower AMH levels at baseline (<2 ng/ml).

Low AMH levels at baseline	Mean plasma level (ng/ml) $\pm$ SD	Mean $\pm$ SD difference from baseline	<i>p</i> (from baseline) [CI 95%]	Mean $\pm$ SD difference (T1–T2)	<i>p</i> (T1–T2) [CI 95%]
<i>n</i> = 7					
Baseline	1.88 $\pm$ 0.10				
T1	1.42 $\pm$ 0.31	–0.46 $\pm$ 0.21	0.001 [0.26–0.66]		
T2	1.64 $\pm$ 0.21	–0.24 $\pm$ 0.12	0.002 [0.13–0.35]	+0.22 $\pm$ 0.12	0.003 [–0.33–(–0.11)]

CI, confidence interval; SD, standard deviation.

less harmful to the follicular reserve than endometrioma excision [27]. Donnez et al. proposed a combined technique (stripping and ablation) using CO₂ laser to vaporize the remaining 10–20% of endometrioma wall, close to the hilum. The pregnancy rate was 41% at 8.3 months and the recurrence rate was only 2% [28]. Inspired by these promising results, we decided to apply this combined technique (stripping and ablation of the hilum) to our patients. In order to improve the results obtained in terms of ovarian reserve sparing, we decided to use a new diode laser for ablation: the DWLS. The combination of two wavelengths, 980 nm and 1470 nm gives a contemporary absorption in H₂O and in Hb with excellent ability of hemostasis, cutting and vaporization, as was previously shown in laparoscopic surgery [29,30]. Moreover, the thermal penetration of DWLS is low and the surgery is safe and accurate, especially for delicate anatomical structures such as the ovarian hilum. In our study, the intraoperative blood loss was significantly low (129.2 $\pm$ 26.8 ml) as well as the total drainage fluid volume (200.4 $\pm$ 12.4 ml). Ovarian reserve, as evaluated through hormonal assay, showed a reduction of serum AMH levels after surgery. Measurements within the first postoperative month showed a significant decrease in ovarian reserve. AMH levels increased at 6–9 months, although values were lower than preoperative levels. DWLS seemed to allow for partial AMH recovery towards baseline. In conclusion, the combined technique (stripping, ablation using DWLS) could be an interesting alternative to cystectomy in ovarian endometrioma management. Type and size of the tissue damage may be a function of power density and duration of the source emission: use of pulsed mode minimizes damages. In conclusion, the results of our study validate laser application in terms of ovarian reserve's recovery after surgery for ovarian endometrioma.

Declaration of interest

The authors have no conflicts of interest to declare.

References

- Locci R, Nisolle M, Angioni S, et al. Expression of the gamma 2 chain of laminin-332 in eutopic and ectopic endometrium of patients with endometriosis. *Reprod Biol Endocrinol* 2013;11:94.
- Melis I, Agus M, Pluchino N, et al. Alexithymia in women with deep endometriosis? A pilot study. *J Endometr* 2014;6:26–33.
- Melis I, Litta P, Nappi L, et al. Sexual function in women with deep endometriosis: correlation with quality of life, intensity of pain, depression, anxiety and body image. *Int J Sex Health* 2015;27:175–85.
- Roman H, Auber M, Mokdad C, et al. Ovarian endometrioma ablation using plasma energy versus cystectomy: a step toward better preservation of the ovarian parenchyma in women wishing to conceive. *Fertil Steril* 2011;96:1396–400.
- Angioni S, Mereu L, Maricosu G, et al. Single port access laparoscopy (SPAL) for endometrioma excision. *J Endometr* 2010;2:95–8.
- Litta P, D'Agostino G, Conte L, et al. Anti-Mullerian hormone trend after laparoscopic surgery in women with ovarian endometrioma. *Gynecol Endocrinol* 2013;29:452–4.
- Streuli I, de Ziegler D, Gayet V, et al. In women with endometriosis anti-Mullerian hormone levels are decreased only in those with previous endometrioma surgery. *Hum Reprod* 2012;27:3294–303.
- Chang HJ, Han SH, Lee JR, et al. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Mullerian hormone levels. *Fertil Steril* 2010;94:343–9.
- Hart RJ, Hickey M, Maouris P, et al. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008;2:CD004992.
- Cormio G, Bettocchi S, Ceci O, et al. Antimicrobial prophylaxis in laparoscopic gynecologic surgery: a prospective randomized study comparing amoxicillin-clavulanic acid with cefazolin. *J Chemother* 2003;15:574–8.
- Cinnella G, Grasso S, Spadaro S, et al. Effects of recruitment maneuver and positive end-expiratory pressure on respiratory mechanics and transpulmonary pressure during laparoscopic surgery. *Anesthesiology* 2013;118:114–22.
- Rizzo A, Spedicato M, Mutinati M, et al. Peritoneal adhesions in human and veterinary medicine: from pathogenesis to therapy. A review. *Immunopharmacol Immunotoxicol* 2010;32:481–94.
- American Fertility Society. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817–21.
- Yoo JH, Cha SH, Park CW, et al. Serum anti-Mullerian hormone is a better predictor of ovarian response than FSH and age in IVF patients with endometriosis. *Clin Exp Reprod Med* 2011;38:222–7.
- Sowers M, McConnell D, Gast K, et al. Anti-Mullerian hormone and inhibin B variability during normal menstrual cycles. *Fertil Steril* 2010;94:1482–6.
- Kitajima M, Khan KN, Hiraki K, et al. Changes in serum anti-Mullerian hormone levels may predict damage to residual normal ovarian tissue after laparoscopic surgery for women with ovarian endometrioma. *Fertil Steril* 2011;95:2589–91.
- Iwase A, Hirokawa W, Goto M, et al. Serum anti-Mullerian hormone level is a useful marker for evaluating the impact of laparoscopic cystectomy on ovarian reserve. *Fertil Steril* 2010;94:2846–9.
- Celik HG, Dogan E, Okay E, et al. Effect of laparoscopic excision of endometriomas on ovarian reserve: serial changes in the serum antimullerian hormone levels. *Fertil Steril* 2012;97:1472–8.
- Biacchiardi CP, Piane LD, Camanni M, et al. Laparoscopic stripping of endometriomas negatively affects ovarian follicular reserve even if performed by experienced surgeons. *Reprod Biomed Online* 2011;23:740–6.
- Uncu G, Kasapoglu I, Ozerkan K, et al. Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve. *Hum Reprod* 2013;28:2140–5.
- Zaitoun MM, Zaitoun MM, El Behery MM. Comparing long term impact on ovarian reserve between laparoscopic ovarian cystectomy and open laprotomy for ovarian endometrioma. *J Ovarian Res* 2013;6:76.
- Li CZ, Liu B, Wen ZQ, et al. The impact of electrocoagulation on ovarian reserve after laparoscopic excision of ovarian cysts: a prospective clinical study of 191 patients. *Fertil Steril* 2009;92:1428–35.
- Suksompong S, Dejarkom S, Petyim S, et al. Ovarian reserve evaluation by anti-mullerian hormone in women undergoing laparoscopic cystectomy of endometrioma. *J Med Assoc Thai* 2012;95:1389–95.
- Hwu YM, Wu FS, Li SH, et al. The impact of endometrioma and laparoscopic cystectomy on serum anti-Mullerian hormone levels. *Reprod Biol Endocrinol* 2011;9:80.

25. Angioni S, Pontis A, Cela V, et al. Surgical technique of endometrioma excision impacts on the ovarian reserve. Single-port access laparoscopy versus multiport access laparoscopy: a case control study. *Gynecol Endocrinol* 2015;31:454–7.
26. Ferrero S, Venturini PL, Gillott DJ, et al. Hemostasis by bipolar coagulation versus suture after surgical stripping of bilateral ovarian endometriomas: a randomized controlled trial. *J Minim Invasive Gynecol* 2012;19:722–30.
27. Roman H, Auber M, Bourdel N, et al. Postoperative recurrence and fertility after endometrioma ablation using plasma energy: retrospective assessment of a 3-year experience. *J Minim Invasive Gynecol* 2013;20:573–82.
28. Donnez J, Lousse JC, Jadoul P, et al. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. *Fertil Steril* 2010;94:28–32.
29. Angioni S, Mais V, Pontis A, et al. First case of prophylactic salpingectomy with single port access laparoscopy and a new diode laser in a woman with BRCA mutation. *Gynecol Oncol Case Rep* 2014;9:21–3.
30. Angioni S, Pontis A, Sorrentino F, et al. Bilateral salpingo-oophorectomy and adhesiolysis with single port access laparoscopy (SPAL) and use of diode laser in a BRCA carrier. *Eur J Gyn Oncol* 2015;36(4).

Supplementary material available online

Supplementary Table S1