Does controlled ovarian hyperstimulation in women with a history of endometriosis influence recurrence rate?

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Does Controlled Ovarian Hyperstimulation in Women with a History of Endometriosis Influence Recurrence Rate?

Maria Elisabetta Coccia, M.D., Ph.D.,[1] Francesca Rizzello, M.D.,[2] and Scarselli Gianfranco, M.D.[1]

Abstract

Background: Endometriosis is a common estrogen-dependent disease. The aim of this study was to assess whether controlled ovarian hyperstimulation (COH) for assisted reproductive technology (ART) was associated with an increased incidence in endometriosis recurrence as documented by transvaginal ultrasound (TV-US).
Methods: In a retrospective cohort study of 592 patients submitted to laparoscopy for endometriosis, 177 with infertility-related endometriosis who underwent a periodic ultrasound follow-up after laparoscopy were selected. Women who started ART after laparoscopy ($n = 90$) were compared with the control group, who did not undergo ART ($n = 87$). Recurrence of endometriosis was defined as the presence of endometriotic lesions observed through TV-US.
Results: During a long-term TV-US follow-up (1–15 years), 40 (22.6%) recurrences were observed. Patients submitted to ART showed a cumulative recurrence rate similar to that of the control group (28.6% and 37.9% respectively, $p = 0.471$). Recurrent lesions were ovarian cysts (47.5%), ovarian nodules (37.5%), and rectovaginal disease (15%). The stratified analysis based on stages of endometriosis and pelvic pain did not show differences.
Conclusions: Gonadotropin treatments do not seem to affect the natural history of endometriotic lesions. The most important prognostic factors in recurrent disease observed by TV-US seem to be the stage of endometriosis and the presence of pelvic pain at the time of the first laparoscopic treatment.

Introduction

Endometriosis is a benign gynecological disease defined as the presence of endometrial glands and stroma outside of the uterine cavity. It affects 5%–10% of women of reproductive age and produces symptoms including dysmenorrhea, deep dyspareunia, and chronic pelvic pain.[1] The demographics of this disorder support a close relationship between endometriosis and ovarian hormone levels. Signs and symptoms are rarely observed before menarche and usually regress after menopause. Because conditions of estrogen excess have been reported to exacerbate endometriosis, traditional medical treatments aim to decrease ovarian production of estradiol (E_2).[2] The recurrence rate in women who undergo conservative surgery for endometriosis ranges from 2% to 51%.[3,4] Some authors suggest that the risk of recurrence tends to rise with further age and advanced stages of the disease, whereas it lessens in women with infertility.[3] These data are still controversial, however.

Early studies showed that 30%–50% of women with endometriosis are infertile.[1] Frequently, infertile women with a history of endometriosis are encouraged to undergo treatment with assisted reproductive technology (ART) in order to conceive. Some authors recommend that if the objective is basically treating infertility, *in vitro* fertilization (IVF) without first performing surgery is probably a good option.[5] On the other hand, controlled ovarian hyperstimulation (COH) for ART produces a high level of E_2 for short periods of time that could induce the growth of endometriotic implants.

Although endometriosis is a recurrent disease and is estrogen dependent, there are surprisingly few data about recurrence risks in patients with infertility-associated endometriosis after COH. As a consequence of the wide diffusion of ART in these women, there is a need to evaluate the risk of causing the recurrence or worsening of endometriosis because of human chorionic gonadotropin (HCG) treatment. Only a few case reports have been published on this topic. These data imply that COH may lead to a higher recurrence rate of

[1]Department of Gynaecology, Perinatology and Human Reproduction, University of Florence, Florence, Italy.
[2]Department of Medical Pathophysiology, Sapienza University of Rome, Rome, Italy.

endometriosis. One case report describes a patient experiencing acute renal colic after ovarian stimulation.[6] In a second case series, 4 patients showed rapid growth of sigmoid endometriosis under COH for IVF.[7]

In a retrospective cohort study (including patients with moderate-severe endometriosis and a history of multiple endometriosis surgeries), the cumulative endometriosis recurrence rate in 36 months of follow-up was similar in the pre-ART group without COH and the post-ART group with COH. Moreover, cumulative recurrence rates were lower after ovarian hyperstimulation for IVF than after lower-dose ovarian stimulation for intrauterine insemination (IUI).[8]

The current study attempts to answer the question of whether patients with a previous history of endometriosis, when submitted to COH for ART, are exposed to a higher recurrence risk compared with a control group of women never submitted to COH.

Materials and Methods

Patient recruitment

A retrospective cohort study was conducted on 592 patients submitted to laparoscopy for endometriosis between March 1993 and November 2007 in the Department of Gynaecology, Perinatology and Human Reproduction at the University of Florence, Italy. Our eligibility criteria for this study were the following: patients undergoing their first laparoscopy for endometriosis, histologically confirmed diagnosis of endometriosis, infertility diagnosed either before or after laparoscopy, and at least once a year periodic clinical and transvaginal ultrasound (TV-US) follow-up after surgery.

During follow-up evaluation, we studied the patient's clinical history, symptoms at the time of her first surgery, TV-US findings, and reproductive outcome. Data were analyzed and compared on the basis of ART treatments: patients deciding to undergo ART after laparoscopy were considered the study group, and the control group consisted of women not submitting to ART. Women who chose to attempt ART after surgery but were diagnosed with recurrent endometriosis before ART cycles were included in the control group. Possible effects of ART treatment type (IUI or IVF) and number of cycles attempted were also analyzed. We did not include in the analysis the values of E_2 on the day of hCG because patients included in the study had differing numbers and types of cycles (IUI/IVF).

In a further analysis, we stratified the results considering the stage of endometriosis and the presence of pain before undergoing the first surgery. Endometriosis was staged according to the revised American Society for Reproductive Medicine criteria (r-ASRM).[9] Presence of pain (dysmenorrhea, dyspareunia, or chronic pelvic pain) before surgery was defined on the basis of a visual analogue scale (VAS) measurement superior to 5 cm. The institution does not claim board approval for this retrospective study.

Laparoscopy

All our laparoscopies were performed by the same three skilled surgeons under general anesthesia. A 10-mm laparoscope was inserted in the standard umbilical position, and three 5-mm trocars were inserted suprapubically under direct vision. During surgery, all visible endometriotic lesions were excised. The stripping technique was used to remove ovarian endometriomas. Tubo-ovarian adhesions were lysed using sharp dissection to restore normal anatomy. The complete excision of pelvic endometriotic lesions was carried out using scissors and bipolar coagulation. Chromoperturbation with methylene blue dye was performed in all patients.

Controlled ovarian stimulation

In patients choosing ART after the first surgery, a long-acting downregulation drug regimen was used. Daily subcutaneous administration of triptorelin (Decapeptyl® 0.1 mg, IPSEN Italy) was started on day 21 of the previous cycle. After downregulation (verified after adequate ovarian suppression at pelvic US and circulating E_2 values <35 pg/mL), we initiated a daily subcutaneous administration of 150 IU (for IUI) and 225–300 IU of follicle-stimulating hormone (FSH) (purified urinary FSH, Metrodin HP® 75 IU, or recombinant FSH, Gonal-F® 600 IU, Serono, Italy). Serial US scans and E_2 dosage determinations were performed during ovarian stimulations. When at least two follicles reached a maximum diameter of 17–18 mm, 10,000 IU of hCG (Gonasi® 5000 IU, two ampoules, Amsa, Italy) was administered subcutaneously.

In women submitted to IUI, an intrauterine insemination was done after 36 hours. In IVF patients, echo-guided transvaginal oocyte retrieval was performed 35–36 hours later. All oocytes retrieved were scored and inseminated for IVF (only three oocytes after the assisted reproduction Law 40/2004), and fertilization was assessed the following day. Two days after oocyte pickup, a maximum of two to three embryos were transferred. The luteal phase was supported with a daily administration of 50 mg intramuscularly of natural progesterone in oil (Prontogest®, Amsa, Italy) starting the day after the oocyte retrieval. Pregnancy was assessed through plasma β-hCG values 14 days after oocyte retrieval. At 6 weeks, clinical pregnancies were confirmed through the presence of an intrauterine gestational sac with a fetal pole and heart activity observed by a TV-US examination.

Recurrence definition

Recurrence was defined as the presence of endometriotic cysts or nodules observed during a TV-US. In particular, an ovarian endometrioma was characterized by a persistent circular homogeneous, hypoechoic tissue without papillary proliferations and with a clear demarcation from the ovarian parenchyma.[10–15] Ovarian nodules were defined as lesions <20 mm in mean diameter. Deep endometriosis implants, in particular rectosigmoid and rectovaginal septum involvement, were suspected from the presence of hypoechoic linear thickening or nodules/masses with or without regular contours that had thin bandlike echoes departing from the center of the mass that were defined as Indian headdress.[16,17]

Recurrent endometriosis may develop from residual microscopic lesions left after the first surgery. On this basis, we decided to consider as the time of entry into the study the date of primary surgery for both control and study groups. If the patient had received an additional treatment with gonadotropin-releasing hormone (GnRH) analogues immediately after the surgery, the time of entry into the study was delayed 1 month after the last injection of GnRH analogues. The time

in which patients left the study was considered either the time at which recurrence was diagnosed or the conclusive follow-up visit date.

Statistical analysis

Statistical analyses were performed using a *t* test for parametric data or a chi-square test for categorical data. Because life table analysis is a method that allows the time of follow-up to be taken into account, we estimated the differences in cumulative recurrence rates of endometriosis between groups according to the Kaplan-Meier method. Statistical differences between the curves were calculated using the log-rank test. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software, version 13 (SPSS, Chicago, IL).

Results

Overall, 177 patients satisfied the criteria and were included in the study. One hundred sixteen (65.5%) women were submitted to ovarian cystectomy for ovarian endometriomas, 80 monolateral and 36 bilateral (mean diameter 35.3 ± 16.3 mm). In 9 cases (5.1%), ovarian endometriosis was associated with rectovaginal nodules. The remaining 61 patients showed peritoneal lesions or adhesions or both In the long-term follow-up examinations (mean time 6.9 ± 4.1 years, range 1–15 years), 134 (75.7%) women were followed for more than 2 years (Fig. 1). Ninety of these women decided to undergo ART treatment after surgery (study group), and 87 never underwent ART during the follow-up period (control group). In the study group, 20 patients were submitted to both IUI (1–6 cycles) and IVF (1–6 cycles). Thirty-six were treated with IVF only and 34 with IUI only.

Patients' characteristics in the study and control groups are shown in Table 1. When comparing patients' characteristics in the ART and control (no ART) groups, the mean age, follow-up period, and number of pregnancies were similar. In the ART group, the duration of infertility was significantly longer (4.7 ± 3 years vs 2.8 ± 1.9 years, respectively), and endometriosis was diagnosed at a more severe stage than in the no ART group (control group). The proportion of infertile women with endometriosis who undergo ART was surprisingly higher in stages I–II. These differences can be explained partly by longer duration of infertility in this group. One hundred seven (60.4%) patients were treated with 3–6 months of GnRH-a immediately after the first laparoscopy, 61 (67.8%) in the ART group and 46 (52.9%) controls ($p = 0.043$). No further medical treatments were proposed immediately after laparoscopy, giving the couple an opportunity to seek spontaneous conception for a period of time. In the long-term follow-up examinations, we observed a total of 40 (22.6%) recurrences through TV-US. Eighteen (20%) were observed in patients submitted to ART, and 22 (25.3%) were observed in the control group. No differences were observed on the basis of postoperative medical treatment, with 27 (25.2%) recurrences in 107 women treated with GnRH-a after surgery and 13 (18.6%) in 70 not receiving any medical treatment ($p = 0.3$).

A second surgery was performed in 15 women (37.5%) with TV-US recurrence. Two of these women were in the ART group (2.2%), and 13 were in the control group (14.9%, $p = 0.002$). In all our cases, surgery confirmed previous US findings. Six patients experiencing recurrence (15%) followed

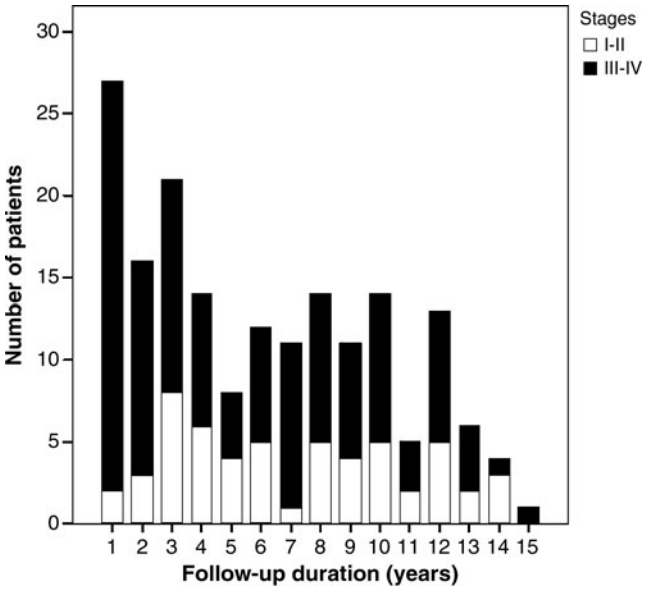

FIG. 1. Number of patients involved in follow-up for every year. Each bar represents the total number of women. The black portions indicate the number of women with stages III–IV, and the open portion shows the number of women with stages I–II.

a medical treatment, whereas 19 (47.5%) did not receive any treatment. The recurrent lesions observed were 19 ovarian cysts (47.5%), 15 ovarian nodules (37.5%), and 6 deep rectovaginal endometriosis (15%). Small hypoechoic nodules were observed mainly in women who underwent ART after laparoscopy, whereas ovarian endometriomas were observed in women in the control group. To specify, the recurrent lesions were 10 small hypoechoic nodules in the ART group and 5 in the control group, 5 ovarian endometriomas in the ART group

Table 1. Patient Characteristics of Women in Study Group (Those Submitted to Assisted Reproductive Technology After Surgery) and in Control Group (Those Never Submitted)

Characteristic	*ART postsurgery* (n = *90*)	*No ART* (n = *87*)	p
Mean age at surgery, mean ± SD	33.7 ± 4.3	33.2 ± 5	0.502
Mean follow-up duration, months, mean ± SD	68.9 ± 41.8	73.2 ± 53.3	0.549
Duration of infertility, years (mean ± SD)	4.7 ± 3	2.8 ± 1.9	0.001
Stages I–II, *n* (%)	35 (38.9)	20 (23)	0.022
Stages III–IV, *n* (%)	55 (61.1)	67 (77)	
Patients with pain, *n* (%)	50 (55.6)	60 (69)	0.066
Postlaparoscopy GnRH-a, *n* (%)	61 (67.8)	46 (52.9)	0.043
Total pregnancies, *n* (%)	49 (55.1)	47 (54)	1
Spontaneous pregnancies, *n* (%)	16 (17.8)	47 (54)	0.0001
ART pregnancies, *n* (%)	33 (36.7)	-	

ART, assisted reproductive technology; GnRH-a, gonadotropin-releasing hormone; SD, standard deviation.

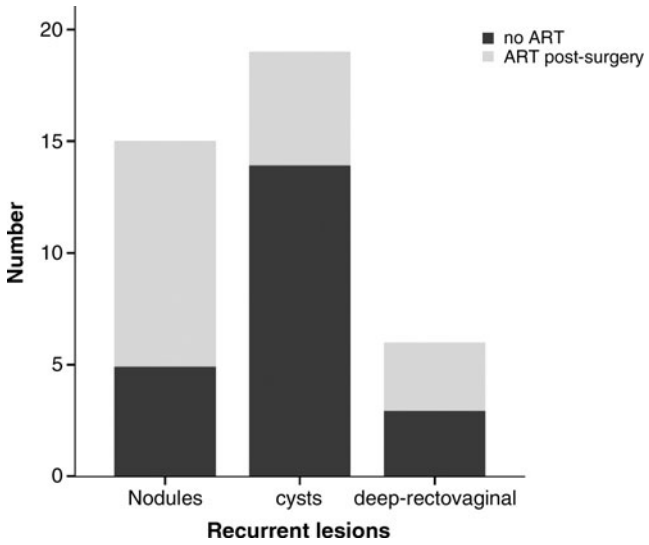

FIG. 2. Recurrent lesions observed during follow-up examinations. Each bar represents the total number of recurrent lesions (cyst, nodule, or deep endometriosis). Bars are stacked on the basis of study/control group. ART, assisted reproductive technology.

and 14 in the control group, and 3 cases of deep rectovaginal endometriosis in each group (Fig. 2).

Most recurrences were observed in the first 2 years after surgery (22 recurrences, representing a rate of 55%). Figure 3 shows the distribution of recurrent lesions in relation to the time after the first laparoscopy in the ART and control groups. The overall cumulative recurrence rate was 35.2%; the cumulative recurrence rates in the study and control groups were 28.6% and 37.9%, respectively ($p = 0.471$) (Fig. 4). The mean time for recurrence was similar in both groups (39.3 ± 31.6 in the ART group and 38.8 ± 43 in the control group, $p = 0.964$). In addition, the type and number of cycles performed did not show any significant association with the risk of recurrences. The recurrence rate was 19.4% (7 of 36 recurrences) in the IVF-only group, 17.6% (6 of 34 recurrences) in the IUI-only group, and 25% (5 of 20 recurrences) in the IVF-IUI group. Women with recurrence underwent a number of IUI and IVF cycles (2.5 ± 0.7 IUI cycles and 1.8 ± 1.3 IVF cycles, respectively), comparable to that of women who did not show recurrences (3.04 ± 1.4 IUI cycles and 2.3 ± 1.5 IVF cycles, respectively) ($p = 0.25$ and $p = 0.21$).

When stratifying results considering the stage of endometriosis, recurrences were significantly higher in patients with moderate to severe stages of the disease in both groups: 27.3% (15 of 55 patients) in the ART group and 31.3% (21 of 67 patients) in the control group. The estimated mean delay for recurrence was 37.9 ± 39.4 months in stages III–IV and 51.5 ± 15.3 in stages I–II ($p = 0.494$).

One hundred ten women suffered from pelvic pain (chronic pelvic pain, dysmenorrhea, or dyspareunia) at the time of the first laparoscopy. Mean VAS as scored by patients before the first surgery was chronic pelvic pain 7.7 ± 1.2 (29 patients), dysmenorrhea 8.4 ± 1.3 (92 patients), and dyspareunia 7.6 ± 1.2 (20 patients). The stratified analysis for pelvic pain at the time of surgery did not show any differences. Furthermore, in both the ART and control groups, the mean time surgery recurrence was shorter in women with pelvic pain in comparison to asymptomatic patients (32.2 ± 35.5 months vs. 56.9 ± 39.5 months, respectively, $p = 0.065$). Table 2 shows the results of this analysis.

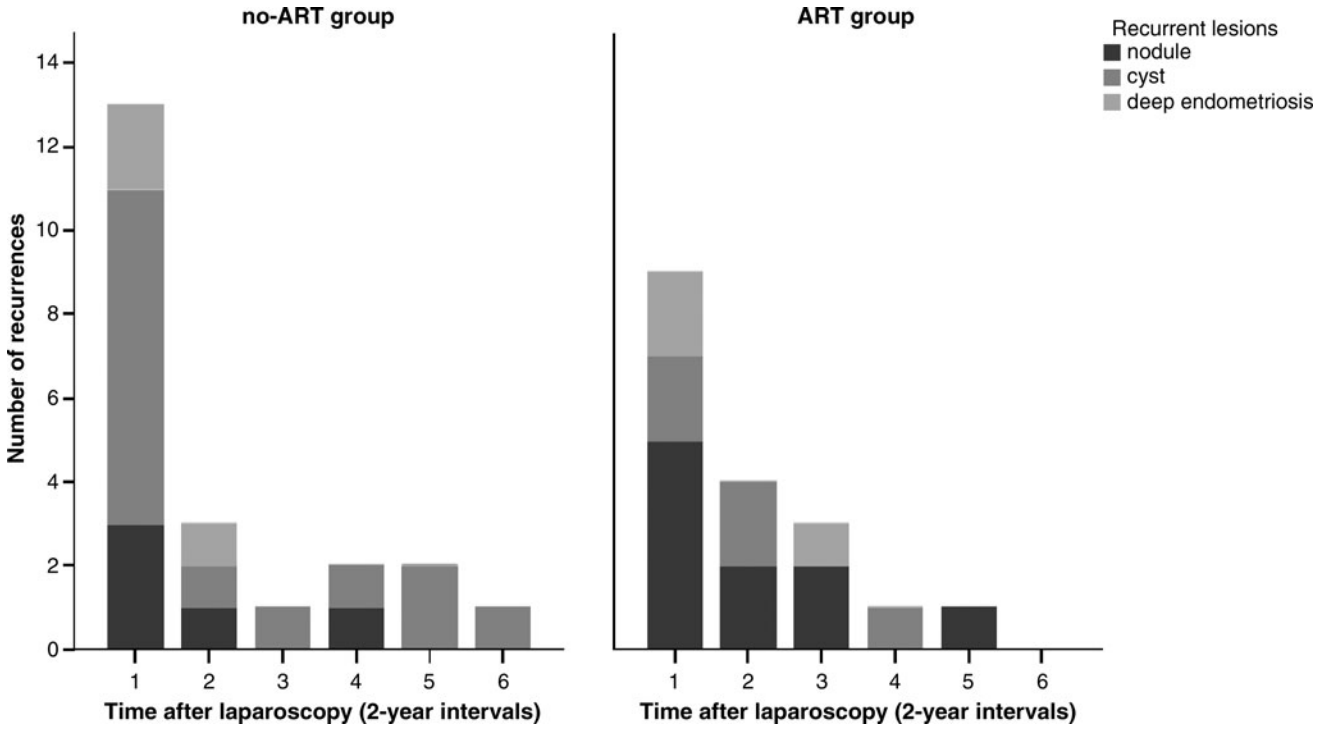

FIG. 3. Recurrent lesions observed in the study and control groups. The stacked bars show the number of patients having recurrences during follow-up examinations (2-year interval). In each column, recurrent lesions (cyst, nodule, deep endometriosis) are shown.

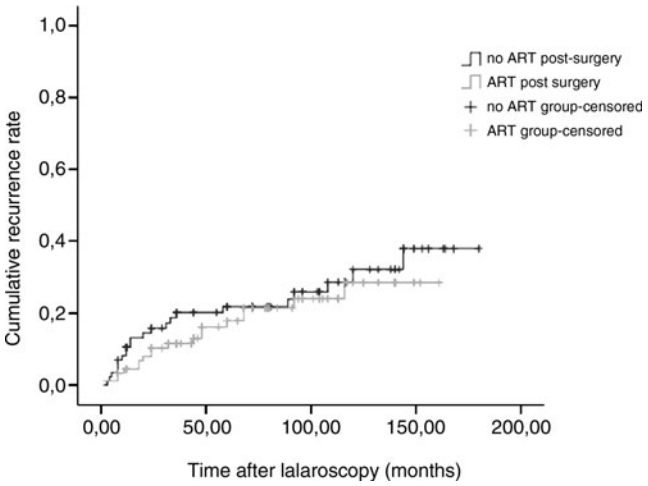

FIG. 4. Kaplan-Meier analysis of the effect of ovarian hyperstimulation on recurrence of endometriosis. Cumulative recurrence rates in the study and control groups were not statistically significant ($p = 0.471$, two-sided log-rank test). Vertical tick marks represent censored patients.

Discussion

Endometriosis is a chronic disease, and recurrence rates after the first surgery are estimated to range from approximately 2% to 51%.[3,4] This wide range may, in part, be ascribed to different criteria for the definition of recurrence, a lack of long-term follow-up studies, and a lack of homogeneous groups. Most of the published studies to date have focused on recurrence rates after short or intermediate periods. Only a few studies have provided long-term follow-up data. In a prospective cohort multicenter study, the 2-year recurrence rate was 5.7% among stage I–II patients and 14.4% among stage III–IV patients ($p < 0.05$).[3]

The benefits of surgical therapy for endometriosis-related infertility have been well documented.[1,18,19] With the large diffusion of ART, however a growing number of infertile women with a history of endometriosis attempt this treatment. In a previous study, after an integrated laparoscopy-IVF approach, we obtained a pregnancy rate of 56.1%, which is significantly higher than the 37.4% observed after surgery only.[20] During COH for ART, the risks of recurrence or worsening of endometriosis could be higher because of the elevated E_2 levels induced. On the other hand, this assumption could be simplistic, as we have acknowledged that estrogen and progesterone receptors have different expressions in eutopic and ectopic endometrium.[21]

Although several articles about endometriosis have been published in recent years, long-term data about recurrence risk rates in infertile women subsequent to ART are scarce. To determine if COH for ART might be associated with an increased incidence of endometriosis recurrence, we compared two homogeneous groups of women with infertility-related endometriosis: 90 women submitted to COH for ART after surgery (study group) and 87 women never undergoing COH (control group). In the literature, there is still no standardized definition of endometriosis recurrence. Some authors have considered recurrence of pain (dysmenorrhea, dyspareunia, chronic pelvic pain), US findings, or increased CA125 levels. This fact makes it difficult to compare results among previous studies about endometriosis recurrence. We decided to examine our findings through TV-US, which is generally considered the most objective, noninvasive, reproducible, and cost-effective method. Many studies have validated the nonsurgical diagnosis of endometriomas and deep endometriosis through TV-US.[10–17] Some authors observed a sensitivity of 81%–89% and a specificity of 91%–97% in predicting the endometriotic nature of ovarian cysts.[22] Regarding deep endometriosis, Guerriero et al.[17] observed a high specificity and sensitivity in the detection of vaginal wall lesions (sensitivity of 91%, specificity of 89%) and rectovaginal endometriosis (sensitivity of 74%, specificity of 88%). For other locations, the sensitivity was lower (ranging from 67% to 33%) with a comparable specificity. We observed a total of 40 (22.6%) recurrences by TV-US, 18 (20%) in patients submitted to ART and 22 (25.3%) in the control group. Survival curves showed a cumulative recurrence rate of 28.6% in patients submitted to ART, which was similar to the 37.9% observed in the control group ($p = 0.471$).

Previous studies have shown that recurrence rates of endometriosis tend to be lower in women with infertility and higher in women with advanced stages of the disease or pelvic pain.[3,23] Our study confirmed these conclusions. Patients with severe stages of the disease were more likely to have a recurrence in both the ART and control groups. Furthermore, patients with pelvic pain at the time of their first surgery for endometriosis seemed more likely to develop recurrence in a shorter time span. However, no differences were found between the two groups based on the stage of endometriosis and the presence of pelvic pain before surgery.

Of the 177 patients included in the study, 15 (19.5%) were submitted to a second surgery during the follow-up period. Two of these patients were from the ART group and 13 were

Table 2. Recurrences Stratified on Basis of Pelvic Pain and Stages

ART postsurgery	*Patients*	*Recurrences*			*Control group*	*Patients*	*Recurrences*		
	n	n	%	p		n	n	%	p
	90	18	20	-		87	22	25.3	-
Stages I–II	35	3	8.6	0.031	Stages I–II	20	1	5	0.017
Stages III–IV	55	15	27.3		Stages III–IV	67	21	31.3	
Pelvic pain	50	13	26	0.185	Pelvic pain	60	16	26.7	0.861
No pelvic pain	40	5	12.5		No pelvic pain	27	6	22.2	

from the control group. In a recent study evaluating reoperation rates over a 10-year period, 51% of patients underwent an additional operation after the initial surgery.[4] In the present study, there was a noticeable reduction of reoperation rates. This could be explained by the fact that our study selected women with subfertility problems who subsequently achieved pregnancy. As we acknowledge, pregnancy could have a protective effect on endometriosis recurrence. In addition, women with infertility are less likely to be reoperated on compared with women whose principal symptom is pelvic pain. The rationale is partly because there are still doubts about the effect of repeated surgery on the outcome of subsequent IVF treatments.

Our study is partially limited by the self-selected group choosing to have ART treatment after laparoscopy because the decision is related to personal and ethical issues where physicians cannot interfere. Furthermore, we acknowledge that we might have missed the presence of minimal recurrent lesions not diagnosed by TV, and because of the long term follow-up period, our patients were observed using US machines of progressively improved resolution and for different durations of observation. To minimize the potential diagnostic mistakes, we included patients in the study who underwent TV-US at least once a year after the first laparoscopy. Indeed, minimal recurrent lesions not visualized at the beginning could be diagnosed in the later scans. In addition, Kaplan-Meyer analysis allowed us an estimation of recurrence risk over time even when patients dropped out or were studied for different lengths of time. Consequently, each patient contributed to the survival curve for the entire length of time she was followed but was statistically removed from the curve after that time.

Considering these points, we finally conclude that GnRH treatments causing high E_2 blood levels for brief periods do not appear to affect the natural history of endometriosis. Although endometriosis is typically an estrogen-dependent disease and can frequently recur, we obtained similar recurrence rates in patients submitted to ART and those in the control group. Therefore, the results of our study may be encouraging for patients with infertility-related endometriosis who decide to attempt ART after surgery. The most important prognostic factors for this recurrent disease seem to be the stage of endometriosis and the degree of pain at the time of first laparoscopic treatment.

To the best of our knowledge, this study represents one of the first large-scale studies that provides long-term results of cumulative recurrence rates using TV-US in women with infertility-related endometriosis. Further trials, with larger samples and long-term follow-up, might possibly give additional strength to our findings. In the literature, there is almost no information on clinical trials estimating recurrence risks in infertile women with endometriosis treated with ART, probably because of the difficulty of designing such a study. However, the information provided by this research field is essential in order to offer the best counseling to infertile patients with endometriosis.

Acknowledgments

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Disclosure Statement

The authors have no conflicts of interest to report.

References

1. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. Fertil Steril 2006;86(Suppl 5):S156–160.
2. Brandenberger AW, Lebovic DI, Tee MK, et al. Oestrogen receptor (ER)-alpha and ER-beta isoforms in normal endometrial and endometriosis-derived stromal cells. Mol Hum Reprod 1999;5:651–655.
3. Parazzini F, Bertulessi C, Pasini A, et al. Gruppo Italiano di Studio Endometriosi Determinants of short term recurrence rate of endometriosis. Eur J Obstet Gynecol Reprod Biol 2005;121:216–219.
4. Cheong Y, Tay P, Luk F, Gan HC, Li TC, Cooke I. Laparoscopic surgery for endometriosis: How often do we need to re-operate? J Obstet Gynecol 2008;28:82–85.
5. Aboulghar MA, Mansour RT, Serour GI, Al-Inany HG, Aboulghar MM. The outcome of *in vitro* fertilization in advanced endometriosis with previous surgery: A case-controlled study. Am J Obstet Gynecol 2003;188:371–375.
6. Renier M, Verheyden B, Termote L. An unusual coincidence of endometriosis and ovarian stimulation. Eur J Obstet Gynecol Reprod Biol 1995;63:187–189.
7. Anaf V, El Nakadi I, Simon P, et al. Sigmoid endometriosis and ovarian stimulation. Hum Reprod 2000;15:790–794.
8. D'Hooghe TM, Denys B, Spiessens C, Meuleman C, Debrock S. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? Fertil Steril 2006;86:283–290.
9. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817–821.
10. Mais V, Guerriero S, Ajossa S, Angiolucci M, Paoletti AM, Melis GB. The efficiency of transvaginal ultrasonography in the diagnosis of endometrioma. Fertil Steril 1993;60:776–780.
11. Guerriero S, Mais V, Ajossa S, et al. The role of endovaginal ultrasound in differentiating endometriomas from other ovarian cysts. Clin Exp Obstet Gynecol 1995;22:20–22.
12. Volpi E, De Grandis T, Zuccaro G, La Vista A, Sismondi P. Role of transvaginal sonography in the detection of endometriomata. J Clin Ultrasound 1995;23:163–167.
13. Alcazar JL, Laparte C, Jurado M, Lopez-Garcia G. The role of transvaginal ultrasonography combined with color velocity imaging and pulsed Doppler in the diagnosis of endometrioma. Fertil Steril 1997;67:487–491.
14. Ubaldi F, Wisanto A, Camus M, Tournaye H, Clasen K, Devroey P. The role of transvaginal ultrasonography in the detection of pelvic pathologies in the infertility workup. Hum Reprod 1998;13:330–333.
15. Patel MD, Feldstein VA, Chen DC, Lipson SD, Filly RA. Endometriomas: Diagnostic performance of U.S. Radiology 1999;210:739–745.
16. Bazot M, Detchev R, Cortez A, Amouyal P, Uzan S, Daraï E. Transvaginal sonography and rectal endoscopic sonography for the assessment of pelvic endometriosis: A preliminary comparison. Hum Reprod 2003;18:1686–1692.
17. Guerriero S, Ajossa S, Gerada M, Virgilio B, Angioni S, Melis GB. Diagnostic value of transvaginal "tenderness-guided" ultrasonography for the prediction of location of deep endometriosis. Hum Reprod 2008;23:2452–2457.

18. Bulletti C, Panzini I, Borini A, Coccia E, Setti PL, Palagiano A. Pelvic factor infertility: Diagnosis and prognosis of various procedures. Ann NY Acad Sci 2008;1127:73–82.
19. Garrido N, Pellicer A, Remohí J, Simón C. Uterine and ovarian function in endometriosis. Semin Reprod Med 2003;21:183–192.
20. Coccia ME, Rizzello F, Cammilli F, Bracco GL, Scarselli G. Endometriosis and infertility surgery and ART: An integrated approach for successful management. Eur J Obstet Gynecol Reprod Biol 2008;138:54–59.
21. Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. Climacteric 2006; 9:325–335.
22. Moore J, Copley S, Morris J, Lindsell D, Golding S, Kennedy S. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. Ultrasound Obstet Gynecol 2002;20:630–634.
23. Busacca M, Chiaffarino F, Candiani M, et al. Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. Am J Obstet Gynecol 2006;195:426–432.

Address correspondence to:
Maria Elisabetta Coccia, M.D., Ph.D.
via Ippolito Nievo, 2
50100, Florence
Italy

E-mail: cocciame@tin.it