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Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas

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Objective: This study was undertaken to determine the frequency of postsurgical ovarian failure in patients undergoing laparoscopic excision of bilateral endometriomas.
Study design: Patients who had been operated on for bilateral ovarian endometriosis between January 1995 and December 2003 and who were younger than 40 years at the time of surgery were contacted by telephone and interviewed.
Results: A total of 126 patients were recruited. Mean ± SD age of patients at the time of surgery was 30.4 ± 4.3 years. Postsurgical ovarian failure was documented in 3 cases, corresponding to a rate of 2.4% (95% CI 0.5%-6.8%). In all cases, this complication occurred immediately after surgery.
Conclusion: Patients who had been operated on for bilateral endometriomas have a low but definite risk of premature ovarian failure occurring immediately after surgery.
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There is a general consensus that operative laparoscopy represents the first-line treatment in women with endometriotic ovarian cysts.[1-3] In recent years, however, the safety of the laparoscopic excision of endometriomas in terms of damage to ovarian reserve has been questioned. First, 2 independent authors observed the presence of healthy ovarian tissue adjacent to the cyst wall in the majority of excised endometriomas, while this is an accidental finding in nonendometriotic benign ovarian cysts.[4,5] Other findings supporting a surgery-mediated injury are the documentation of adverse changes in the ovarian artery blood flow after excision of

endometriomas and the observation that spontaneous ovulation occurs less frequently in the operated gonads.[6-8] The most convincing evidence supporting the presence of a surgery-mediated damage derives from results of ovarian hyperstimulation cycles performed in women who had been previously operated on for monolateral endometriomas. Four independent groups have reported that responsiveness to hyperstimulation is consistently reduced in the operated gonads when compared for the contralateral intact ovaries.[7,9-11]

The observation that ovarian reserve may be severely damaged in cystectomized ovaries is of particular relevance for women who have endometriomas diagnosed in both gonads. Bilateral ovarian endometriosis is a less

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frequent but not a rare condition, occurring in 19% to 28% of patients with this form of the disease.[12-14] Whereas the contralateral intact gonad may adequately compensate for the reduced function of the affected ovary in patients with monolateral disease, women with bilateral endometriotic ovarian cysts may be at elevated risk of postsurgical ovarian function impairment. To address this issue, women who were operated on for bilateral endometriomas in our units were contacted and interviewed. The primary aim of the study was to determine the frequency of ovarian failure. The secondary aim was to evaluate long-term benefits of surgery in terms of fertility and pelvic pain.

Material and methods

Patients referring to the surgical units of the II Department of Obstetrics and Gynecology of the "Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena" and of the Department of Obstetrics and Gynecology of the "Macedonio Melloni" Hospital between January 1995 and December 2003 were reviewed. Inclusion criteria were as follows: (1) laparoscopic enucleation of bilateral ovarian endometriotic cysts (patients who simply underwent bipolar coagulation of the cyst wall on at least 1 side were not included), and (2) age younger than 40 years at the time of surgery. Exclusion criteria were as follows: (1) previous laparoscopy for endometriotic or nonendometriotic ovarian cysts, (2) presurgical evidence of early menopause, (3) necessity to perform mono/bilateral adnexectomy, (4) histologic diagnosis of ovarian malignancy, (5) uninterrupted postsurgical assumption of hormonal therapy after surgery, (6) impossibility to contact patients at follow-up (patients lost to follow-up), and (7) patients' refusal to participate. Hormonal therapy was defined as assumption of oral contraceptives and/or progestins and/or gonadotrophin releasing hormone antagonists with or without add-back therapy. Postsurgical ovarian failure was defined as the absence of menses for more than 12 months and elevated serum levels of follicle-stimulating hormone and luteinizing hormone. Premature ovarian failure (POF) was defined as the cessation of menstruation before the age of 40 years.[15] The incidence of POF was thus calculated on the subgroup of patients who were older than 40 years at the time of follow-up. Patients who have tried to become pregnant for more than 12 months were defined infertile. Information regarding baseline clinical characteristics, surgical technique, dimension, and histology of the cyst were obtained from surgical, sonographic, and pathologic evidence. If more than 1 cyst was excised from each ovary, the diameter of the largest one was recorded. Endometriosis was staged according to the revised American Society for Reproductive Medicine (ASRM) Classification.[16]

The surgical technique used first implied the complete lysis of the adhesions surrounding the affected ovary. During that phase, the endometrioma was generally ruptured. The site of rupture was enlarged by gently stripping the edges so that the cleavage plan became easily identifiable. Then, the stripping of the cyst wall from the remaining ovarian parenchyma was performed through traction exerted in opposite directions by using 2 grasping forceps. When necessary, hemostasis was achieved with bipolar forceps applied on the ovarian parenchyma. Monopolar electrosurgery was never used. No sutures were performed for reapproximation of the ovarian edges.[4] Peritoneal endometriosis was coagulated if lesions were superficial and excised if lesions were deep. All adhesions were lysed, included cul-de-sac obliteration. In all cases, diagnosis was histologically confirmed. The local Institution Review Board approved the study. All patients operated on in our unit routinely gave informed consent for successive phone contacts for follow-up.

Between January and May 2005, patients were contacted by phone. An ad-hoc questionnaire aimed to investigate menstrual characteristics, pain symptoms, and fertility status was used. The following items were specifically investigated: hormonal therapies, surgical treatments for endometriosis, menstrual characteristics, pelvic pain symptoms (dysmenorrhea and dyspareunia), and fertility status. Patients who had sought for a way to become pregnant and have a child were asked about duration of their search, infertility tests results, use of assisted reproduction techniques, and pregnancy outcome. The length of follow-up was defined as the period between surgery and the date of telephone contact if patients were not receiving hormonal treatment at the time of contact. If medically treated, women were censored at the time of last spontaneous menstrual cycle. If patients successively underwent a second surgery for endometriosis, length of follow-up was defined as time between the 2 interventions.

Data analysis was performed with the Statistics Package for Social Sciences (SPSS 12.0, Chicago, IL). The pregnancy rate survival curve was drawn by using the Kaplan-Meier method. A binomial distribution model was used to calculate the 95% CI of the percentage of patients who had postsurgical ovarian failure develop.

Results

A total of 126 patients met eligibility criteria. Baseline clinical features of these patients are reported in Table I. A brief description of endometriosis characteristics at the time of surgery is summarized in Table II. The mean ± SD duration of follow-up was 4.6 ± 2.7 years. Mean ± SD age of patients at the time of follow-up was

Table I Baseline clinical characteristics at the time of surgery

Characteristics	Mean ± SD or number (%)
Age (y)	30.4 ± 4.3
Menstrual cycle characteristics	
Regularity	
Regular	102 (81.0%)
Irregular	21 (16.7%)
Oligo-amenorrhea	3 (2.4%)
Length (d)*	
<24	6 (5.9%)
24-27	12 (11.8%)
28-31	75 (73.5%)
32-35	9 (8.8%)
Previous pregnancies	23 (18.3%)
Symptoms at the time of surgery	
Dysmenorrhea	113 (89.7%)
Dyspareunia	62 (49.2%)
Infertility	30 (23.8%)

* Only the 102 women with regular menstrual cycles were considered.

Table II Endometriosis characteristics at the time of surgery

Characteristics	Mean ± SD or number (%)
ASRM Classification*	
Stage III	14 (11.1%)
Stage IV	112 (88.9%)
Ovarian endometriomas	
Right ovary	
Number	
1	110 (87.3%)
≥2	16 (12.7%)
Diameter (mm)	36 ± 18
Left ovary	
Number	
1	112 (88.9%)
≥2	14 (11.1%)
Diameter (mm)	39 ± 18
Deep peritoneal endometriosis	22 (17.5%)
Superficial peritoneal endometriosis	85 (67.5%)
Douglas obliteration	
Partial	29 (23.0%)
Complete	25 (19.8%)
Adnexal adhesions*	
<8	39 (31.0%)
8-15	46 (36.5%)
>15	41 (32.5%)

* Adhesion and stage were calculated according to the revised ASRM Classification.

35.0 ± 4.7 years. Six women (4.8%) successively underwent a second surgery for endometriosis recurrence. The mean ± SD time between the 2 interventions was 4.0 ± 1.1 years.

Postsurgical ovarian failure occurred in 3 cases, corresponding to a rate of 2.4% (95% CI, 0.5%-6.8%). Characteristics of these patients are shown in Table III. All women reported regular menstrual cycle before the intervention and none was receiving hormonal treatment before surgery. Ages of these cases at the time of surgery were 31, 33, and 39 years. They were all operated on by skilled surgeons. Ovarian failure occurred immediately after surgery in all cases.

Twenty women (15.9%) were older than 40 years at the time of follow-up, of whom 1 had POF diagnosed. The incidence of POF in this subcohort was thus 5.0% (95% CI, 0.3%-24.4%).

Postsurgical pain symptom relief was observed in the vast majority of patients: improvement of dismenorrhea and dispareunia was reported in 95 of 113 (84.1%) and 55 of 62 (88.7%) symptomatic patients, respectively. Sixty-five women have tried to become pregnant after surgery, 43 of them had at least 1 pregnancy (66.2%). In 1 case, pregnancy was achieved through an in vitro fertilization procedure. Cumulative pregnancy rate according to the duration of infertility is shown in the Figure. Of the 18 women who were infertile at the time of surgery, 9 subsequently conceived (50.0%).

Comment

Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas is a rare but possible complication. In the current series, this event occurred in 3 cases, corresponding to a rate of 2.4%. More precisely, our study suggests that the risk of ovarian failure would range between 0.6% and 6.8%. Larger series are required to more precisely define the entity of this risk. Of relevance here is that the percentage of postsurgical ovarian failure does not represent the incidence of POF. POF is indeed defined as the cessation of menstruation before the age of 40 years, its frequency should thus be investigated in a population of patients who are at least older than 40 at the time of contact.[15] In our series, only 20 patients fulfilled this criterion. As a consequence, the 95% CI of the rate of POF that resulted was excessively wide (0.3%-24.4%) to draw reliable inferences. Overall, it is inappropriate to relate the 2.4% rate of postsurgical ovarian failure observed in this study to the 1.1% incidence of POF observed in the general population.[15]
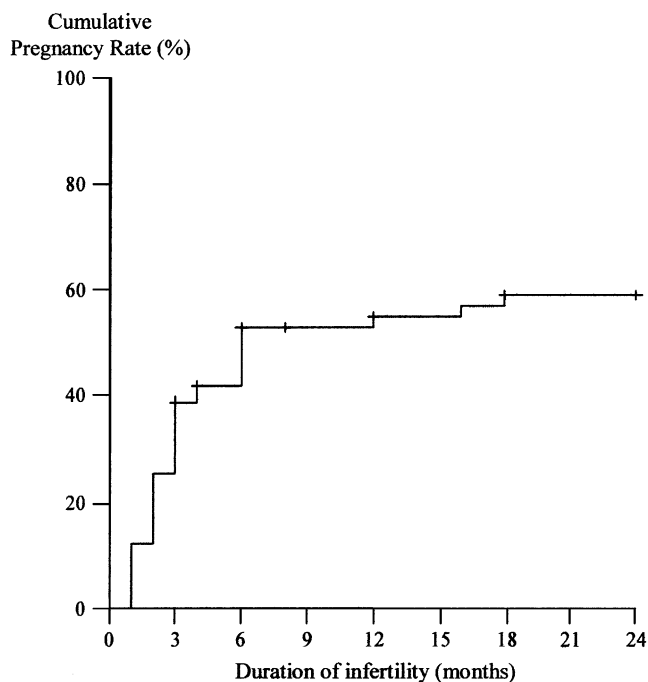
To our knowledge, this is the first report suggesting that ovarian failure may occur after laparoscopic removal of bilateral endometriotic ovarian cysts. Twenty years have passed since the first description of this surgical technique.[17] Given the low but not extremely rare frequency of this complication, the lack of previous studies on this topic is surprising. Fear about possible criticisms toward surgical skillfulness of specific research groups might explain the absence of previous reports in the literature. A publication

Table III   Characteristics of patients with postsurgical ovarian failure

Characteristics	Patient 1	Patient 2	Patient 3
Clinical characteristics			
Age (y)	31	33	39
Menstrual cycle characteristics			
Regularity	Regular	Regular	Regular
Length (d)	28-31	28-31	28-31
Previous pregnancies	No	No	Yes
Symptoms at the time of surgery			
Dysmenorrhea	Yes	Yes	Yes
Dyspareunia	No	Yes	No
Infertility	No	No	Yes
Surgical characteristics			
Stage (ASRM Classification*)	IV	IV	IV
Ovarian endometriomas			
Right ovary			
Number	1	2	3
Diameter (mm)	50	55	20
Left ovary			
Number	1	1	3
Diameter (mm)	30	20	20
Deep peritoneal endometriosis	No	No	No
Superficial peritoneal endometriosis	Yes	No	Yes
Douglas obliteration	No	Partial	No
Adnexal adhesions score*	16	4	8

  * Adhesion and stage were calculated according to the revised ASRM Classification.

Figure   Cumulative pregnancy rate according to the duration of infertility. Sixty-five women have tried to become pregnant and have a child after surgery, 43 of them had at least 1 pregnancy (66.2%).

bias cannot also be excluded because a complication that may be consequent to inadequate surgical expertise may deserve scanty consideration. Our study indicates that the complication is strictly consequent to surgery. All affected women reported regular menstrual cycle before the intervention, and ovarian failure occurred immediately after surgery in all the women. Reasons explaining this complication can herein only be speculated. Surgical expertise and/or severely distorted anatomic condition first have to be considered. Technical difficulties may have played a role in at least 1 case (a 39-year-old woman who had 3 cysts per each ovary removed). Conversely, expertise does not seem to be a relevant factor because surgeons with noteworthy laparoscopic surgical expertise operated on these patients. From a pathogenetic point of view, the observation that ovarian failure occurred immediately after surgery suggests that injury to ovarian vascularization may have played an important role. Even if debated, adverse changes in ovarian artery blood flow have been reported after laparoscopic stripping.[6,8] This effect may be consequent to the electrosurgical coagulation that is routinely performed in our units to achieve hemostasis after cyst excision. Other potentially involved pathogenetic insults include the accidental removal of a consistent amount of ovarian tissue during cystectomy and a condition of

autoimmune reaction from severe local inflammation causing autoimmune damage to residual ovarian stroma.[4,5,17] In this context, one may wonder whether alternative surgical techniques such as fenestration and coagulation of the internal layer of the cyst would be more appropriate. Unfortunately, although potentially more tissue sparing, this technique has been shown to be associated with a lower pregnancy rate and a higher percentage of recurrences.[18,19]

The occurrence of this rare but clinically relevant complication may lead to question the indication to surgery in patients with bilateral endometriomas. There is a consistent body of evidence in the literature supporting the concept that patients benefit considerably from laparoscopic excision of endometriomas. Two specific points have to be considered. First, pain symptoms are reduced after surgery. In a recent prospective study, Abbott et al[3] clearly documented a relevant and long-term relief of pain symptoms in patients operated for endometriosis irrespective of stage. Our results are in line with this finding. Although our study was not adequately designed to address this point (a prospective study using standardized tools to quantify pain would have been more appropriate), the vast majority of patients reported improvement of symptoms after surgery. Second, there is a general consensus indicating operative laparoscopy as the first-line treatment in subfertile women with endometriotic ovarian cysts. Postsurgical pregnancy rate has been shown to vary between 23% and 67%.[2] Our findings are in line with this evidence since 43 of 65 women (66%) conceived after surgery. The relatively

high pregnancy rate observed in this study when compared with others may be consequent to the long follow-up (periods of follow-up longer than 24 months have been rarely reported) and the inclusion of patients whose fertility status was unknown at the time of surgery. In line with this latest hypothesis, the pregnancy rate in women who were infertile before surgery was lower in our series (50.0%). Overall, we believe that in symptomatic patients the benefits of surgery overcome the risks and particularly the risk of ovarian failure. Drawing a definite balance of pros and cons is, however, beyond the scope of this study.

In conclusion, patients who are operated on for bilateral endometriomas should be informed that they have a low but definite risk of POF occurring immediately after surgery. Taking into consideration the significant benefits in terms of both pain relief and improvement of fertility associated with laparoscopic treatment, this risk should not currently lead to banning surgery in these patients.

References

1. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. Hum Reprod Update 2002;8:591-7.
2. Jones KD, Sutton CJ. Pregnancy rates following ablative laparoscopic surgery for endometriomas. Hum Reprod 2002;17:782-5.
3. Abbott JA, Hawe J, Clayton RD, Garry R. The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. Hum Reprod 2003;18:1922-7.
4. Muzii L, Bianchi A, Croce C, Manci N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? Fertil Steril 2002;77:609-14.
5. Hachisuga T, Kawarabayashi T. Histopathological analysis of laparoscopically treated ovarian endometriotic cysts with special reference to loss of follicles. Hum Reprod 2002;17:432-5.
6. La Torre R, Montanino-Oliva M, Marchiani E, Boninfante M, Montanino G, Cosmi EV. Ovarian blood flow before and after conservative laparoscopic treatment for endometrioma. Clin Exp Obstet Gynecol 1998;25:12-4.
7. Loh FH, Tan AT, Kumar J, Ng SC. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. Fertil Steril 1999;72:316-21.
8. Candiani M, Barbieri M, Bottani B, Bertulessi C, Vignali M, Agnoli B, et al. Ovarian recovery after laparoscopic enucleation of ovarian cysts: insights from echographic short-term postsurgical follow-up. J Minim Invasive Gynecol 2005;12:409-14.
9. Nargund G, Cheng WC, Parsons J. The impact of ovarian cystectomy on ovarian response to stimulation during in-vitro fertilization cycles. Hum Reprod 1996;11:81-3.
10. Ho HY, Lee RK, Hwu YM, Lin MH, Su JT, Tsai YC. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. J Assist Reprod Genet 2002;19:507-11.
11. Somigliana E, Ragni G, Benedetti F, Borroni R, Vegetti W, Crosignani P. Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles. Hum Reprod 2003;18:2450-3.
12. Vercellini P, Aimi G, De Giorgi O, Maddalena S, Carinelli S, Crosignani PG. Is cystic ovarian endometriosis an asymmetric disease? BJOG 1998;105:1018-21.
13. Prefumo F, Todeschini F, Fulcheri E, Venturini PL. Epithelial abnormalities in cystic ovarian endometriosis. Gynecol Oncol 2002;84:280-4.
14. Al-Fozan H, Tulandi T. Left lateral predisposition of endometriosis and endometrioma. Obstet Gynecol 2003;101:164-6.
15. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod 2003;18:199-206.
16. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817-21.
17. Reich H, McGlynn F. Treatment of ovarian endometriomas using laparoscopic surgical techniques. J Reprod Med 1986;31:577-84.
18. 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;70:1176-80.
19. 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;82:1633-7.