Comparison of two fertility-sparing approaches for bilateral borderline ovarian tumours: a randomized controlled study

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BACKGROUND: During the childbearing years, the standard fertility-sparing treatment for bilateral borderline ovarian tumours (BOTs) is the unilateral oophorectomy plus controlateral cystectomy. The aim of the present study was to compare the effects of two laparoscopic fertility-sparing surgical procedures for the treatment of bilateral BOTs on recurrence and fertility in young women who desire to conceive as soon as possible. METHODS: Thirty-two women affected by bilateral early-stage BOTs who desired to conceive were randomized to receive bilateral cystectomy (experimental group, n = 15) or oophorectomy plus controlateral cystectomy (control group, n = 17). At the first recurrence after childbearing completion, each patient was treated with non-conservative standard treatment. Recurrences and reproductive events were recorded. RESULTS: After a follow-up period of 81 months (19 inter-quartile; 60–96 range), the cumulative pregnancy rate (CPR) (14/15 versus 9/17; P = 0.003) and the cumulative probability of first pregnancy (P = 0.011) were significantly higher in the experimental than in control group. No significant (P = 0.358) difference between groups was detected in cumulative probability of first recurrence. CONCLUSIONS: The laparoscopic bilateral cystectomy followed by non-conservative treatment performed at the first recurrence after the childbearing completion is an effective surgical strategy for patients with bilateral early-stage BOTs who desire to conceive as soon as possible.

Key words: borderline ovarian tumour/cystectomy/fertility/recurrence/surgery

Introduction

The borderline ovarian tumours (BOTs), also referred to as low malignant potential tumours, are a subgroup of epithelial ovarian tumours accounting for ∼10–15% of all ovarian tumours, which are characterized by histologic features of malignant tumours without identifiable destructive stromal invasion (Acs, 2005).

Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the gold standard treatment for BOTs in peri- or post-menopausal women, patients who have completed childbearing or those who have no desire to preserve their fertility (Tinelli et al., 2006). Because BOTs are characterized by common presentation during the childbearing years at an early stage and by an excellent long-term survival, fertility preservation becomes an important issue in their management (Morice et al., 2003). In this regard, a fertility-sparing surgical treatment, consisting of uterine preservation and at least a part of one ovary, has been proposed to patients with early-stage BOTs who want to preserve their childbearing potential, and, over the years, this treatment has become a pivotal and well-consolidated approach for patients with BOTs who want to preserve their fertility (Morice et al., 2003; Tinelli et al., 2006).

Even if obtained in a retrospective fashion, in a non-selected population after laparotomy, the available data suggest that in patients with BOTs, cystectomy is related to a higher recurrence rate compared with oophorectomy (Morice et al., 2003; Tinelli et al., 2006). For these reasons, salpingo-oophorectomy has been widely used to reduce recurrence and to preserve good reproductive capabilities in patients with unilateral BOTs (Morice et al., 2003).

BOTs are bilateral in ∼25–50% and in ∼5–10% of the serous and mucinous histotypes, respectively (Acs, 2005; Tinelli et al., 2006). In these cases, the standard fertility-sparing surgery consists of salpingo-oophorectomy plus controlateral cystectomy (Morice et al., 2003). At present, it is not known whether patients with bilateral BOTs of reproductive age could benefit by a more minimally invasive approach, such as a bilateral cystectomy.

During the last few years, laparoscopic treatment of adnexal masses has proved to be a useful diagnostic and therapeutic tool (Pejovic and Nezhat, 2001). In terms of reproductive outcomes, the laparoscopic approach also seems to be safer than laparotomy in reproductive age patients (Pejovic and Nezhat, 2001).
The purpose of the present study was to compare the effects of two laparoscopic fertility-sparing surgical procedures, that is, oophorectomy plus contralateral cystectomy versus bilateral cystectomy, on the safety and fertility in young women who desire to conceive as soon as possible and are affected by bilateral BOTs.

Materials and methods

The procedures used in the present study were in accordance with the Helsinki Declaration on human experimentation guidelines. The study was approved by the Institutional Review Board. The purpose of the protocol was explained to patients before entering the study, and their written consent was obtained.

Study population

Between February 1997 and March 2000, 173 patients in reproductive age with bilateral adnexal masses desiring to preserve their childbearing potential were screened for suspected BOTs in the Department of Obstetrics and Gynecology of the University ‘Magna Graecia’ of Catanzaro, Italy.

Inclusion criteria for each patient were bilateral BOTs diagnosed in clinical early stage, that is, stage I according to International Federation of Gynecology and Obstetrics (FIGO) classification (International Federation of Gynecology and Obstetrics, 1987), and desire to conceive as soon as possible.

Exclusion criteria were age over 35 years, FSH > 15 UI/l, obesity [body mass index (BMI, kg/m²) > 30], unilateral adnexal tumour, absence of remnant ovarian parenchyma [as detected by transvaginal ultrasonography (USG)], other premalignancies or malignancies, major medical conditions, psychiatric disorders, organic pelvic diseases, previous pelvic surgery, clinical tumour stage > I, tumour size over 8 cm, history of infertility, oligo-anovulatory cycles, tubal and male factor infertility (as determined by hysterosalpingogram and semen analysis). Patients were also excluded when not compliant to our close post-surgical follow-up.

Study protocol

At entry, age, parity, BMI, socio/economic and work status, previous major surgical laparotomies and associated medical conditions were carefully assessed in each patient. A gynaecological and rectal examination, Papanicolaou smear test, venous blood draw, transabdominal and transvaginal USG, hysteroscopic assessment with endometrial biopsy when required, liver USG, chest X-ray and computerized tomography were also performed in all subjects.

Blood samples were obtained in the morning after overnight fasting, and resting in bed during early follicular phase (2nd-3rd day of the cycle) was requested to evaluate a complete hormonal assay (including basal FSH) and serum CA 125 and CA 19.9 levels.

Each subject underwent a transabdominal and transvaginal USG by the same experienced operator (T.R.) who assessed dimensions, morphology and vascularity of the bilateral adnexal masses and the residual tumour-free ovarian tissue.

Randomization

Only 80 of 173 patients (46.3%) were eligible for our study protocol. Ninety-three patients were not enrolled for reasons detailed in Figure 1.

All eligible patients were randomized into a prospective controlled study design and allocated in two treatment groups (experimental and control). The randomization was carried out using computer software (University of Catanzaro) to generate a random allocation to two independent groups. The random allocation sequence was concealed in closed and dark envelope until the interventions were assigned.

Surgical procedures

Immediately before surgery and one hour after surgery, each patient received an antibiotic prophylaxis, whereas no treatment for thrombosis prophylaxis was administered. All surgical procedures were performed by the same experienced laparoscopist (F.Z.) following the same standardized procedure for each intervention.

During each surgical intervention, a careful and systematic inspection of the ovarian masses and the pelvis was performed to search macroscopic areas suggestive of malignancy, and each suspected lesion was excised. Peritoneal fluid was collected and processed for cytological examination in all cases. The same procedure was performed after washing with saline solution the paracolic gutters, diaphragms and pelvis. Bilateral cystectomy was performed in 40 patients (experimental group), whereas other 40 patients were treated with oophorectomy plus contralateral cystectomy (control group). The side to perform the oophorectomy was decided by the surgeon after laparoscopic access according to the ovary mostly involved. No biopsy was performed on the remnant ovarian tissue without macroscopic involvement, whereas excisional biopsies were performed only in the presence of exophytic lesions on ovarian surface. Salpingectomy was performed in the presence of macroscopic involvement of the tube.

In all cases, the removed ovary and/or mass were sent for intraoperative histological examination (frozen section). When frozen-section analysis detected benign ovarian tumour, the intervention was stopped. On the contrary, when the histological examinations demonstrated invasive ovarian cancer, the laparoscopic procedure was converted to midline laparotomy and a standard cytoreductive surgery was carried out. In all cases of intra-operative BOTs diagnosis, surgical intervention was continued according to the following steps: all macroscopic peritoneal implants were excised, whereas multiple peritoneal biopsies were obtained in all patients without macroscopic peritoneal involvement. Systematic infracolic omentectomy was also performed in each case. Appendectomy was carried out in all cases of mucinous or mixed tumour. Systematic pelvic and para-aortic lymphadenectomy were performed only in selected cases, that is, spread macroscopic pelvic and peritoneal involvement (advanced stages).

All tissue samples were removed from the abdominal cavity using laparoscopic plastic baskets to reduce the possibility of peritoneal implantation of neoplastic cells. In case of cyst rupture and

Figure 1. Study profile according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.
The final diagnosis of BOTs was confirmed after post-operative histological examination of all tissue samples. Histopathologic analysis of the ovarian tissue and peritoneal implants was performed by the same pathologist using the 1987 FIGO staging classification (International Federation of Gynecology and Obstetrics, 1987). Peritoneal implants were classified as either non-invasive or invasive, according to the absence or presence of stromal invasion of the peritoneum, respectively.

In the first 24 h following surgery, all patients received i.v. analgesics [tramadol 100 mg immediately after surgery followed by patient-controlled analgesia consisting of tramadol 200 mg in 500 cc of saline solution]. A blood sample was taken from each patient for calculating haemoglobin variation (Δ Hb), 3 and 24 h after surgery.

Surgical assessments
For each surgical intervention, global operative time of surgical procedures, intra-operative blood loss, amount of blood transfusion and intra-operative complications were recorded. Intra-operative complications were defined as bowel, bladder, urethral or vascular injuries and estimated blood loss exceeding 500 ml. Criteria for transfusion were an intra-operative blood loss equal or higher than 1500 cc and/or a Δ Hb equal or higher than 4 mmol/l in a double assay.

Post-operative complications, hospital stay and time needed to return to full activity and/or work were also recorded in both groups. Post-operative complications were defined as adverse events occurring within 30 days from intervention because of surgery and were considered major if they resulted in unplanned readmission, blood transfusion, or secondary surgical procedure.

Reproductive function evaluations
After surgery, all patients were instructed to have free intercourses from the first month after surgery and to record on a personal diary the length and the quantity of menstrual bleedings and number of sexual intercourses. Management in our Centre for Reproduction, with ovulation monitoring followed by timed intercourse, was proposed to each patient.

For each patient the number of pregnancies, abortions and live births was recorded. Cumulative pregnancy rate (CPR), our primary end-point, was defined as ratio between number of pregnant patients and total patients. Abortion and live birth rates were defined as ratio between abortions and live births and total number of pregnancies, respectively. The cumulative pregnancy and live birth rate was also calculated according to time to the first event as detailed in the statistical analysis section.

Follow-up and safety assessment
At study design, a follow-up period of at least 5 years for each patient was established.

Follow-up visits after 3, 6 and 12 months from surgery in the first year and thereafter every 6 months were performed. The follow-up visits included physical and gynaecologic examinations, transabdominal and transvaginal USG and blood sample assay. All blood samples were obtained in the morning during early follicular phase (3rd day) of the menstrual cycle, and serum tumoural markers and FSH levels were measured. Patients who conceived were examined every 3 months during pregnancy and every 6 months after delivery. No second-look laparoscopy was done in any case.

Throughout the follow-up study, all patients were treated conservatively with laparoscopic approach. The conservative treatment of recurrences consisted of cystectomy and excision of each peritoneal/pelvic implant. On the contrary, patients who completed childbearing were treated with a non-conservative standard treatment for BOTs at the first recurrence. This treatment consisted of midline abdominal total hysterectomy plus bilateral or unilateral salpingo-oophorectomy, according to previous surgery. No adjuvant treatment (chemotherapy and/or radiotherapy) followed the radical treatment.

Statistical analysis
The live birth rate was the primary end-point of our study. Moreover, data available in literature mostly concern the pregnancy rate as surrogate end-point of fertility. According to English literature, we can estimate CPR after surgery using control procedure (control group), which ranges between 31.8 and 66.3%. Assuming we observe, in the patients enrolled by our centre, a CPR equal to 47% for control surgery (control group), we define it clinically remarkable to observe a pregnancy rate equal or superior to 93% for experimental surgery (experimental group). With a two-tailed test, a sample of 16 patients for each group was needed to define as statistically significant the estimated difference of 46% between groups, with α = 0.05 and 1–β = 0.85.

Continuous variables were expressed as median and inter-quartile range (IQR) and analysed using Mann–Whitney U-test or Wilcoxon signed ranks test for two independent or related samples, respectively. For categorical variables, the Pearson chi-square test, the exact method and the Fisher’s exact test were applied as required.

Cumulative event rates (pregnancy and recurrences) were calculated by the Kaplan–Meier method, using the time to a first event as the outcome variable. The statistical significance of differences in outcome between the two groups was assessed with the log-rank test. In addition, Cox proportional hazards model was used to calculate the hazard risk (HR) for recurrence and pregnancy in patients with bilateral cystectomy (experimental group) or oophorectomy plus contralateral cystectomy (control group). The HR represents also the relative risk (RR) because it is calculated for a dichotomous variable in which there are two levels (experimental and control groups) (Steinberg, 1999).

Data were analysed using the intention-to-treat (ITT) method. The Statistics Package for Social Science (SPSS 14.0, 5 September 2005; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The number needed to treat (NNT) was calculated with StatsDirect, release 2.4.3.

Results
In Figure 1, the flow diagram of the present study according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines is shown. Eighty patients were eligible for the study protocol and randomized in the two treatment groups, but only 15 and 17 patients for experimental and control groups, respectively, were included in the final analysis.

Demographic data
In Table I, the demographic characteristics of the experimental and control groups are shown.

After randomization and exclusion of several patients from the final analysis, the two groups still showed no differences in any characteristic assessed. All patients were present during the followed-up period after surgery until June 2005 [81 months (19 IQR; 60–96 range)].

At the end of the study, the follow-up period was 81 (IQR: 62–96 range) and 86 (IQR: 60–96 range) months for experimental and control groups, respectively.
Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n = 15)</th>
<th>Control group (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (9.0 IQR; 21–34 range)</td>
<td>28 (9.0, IQR; 20–35, range)</td>
<td>0.507</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22 (4.0 IQR; 19–26 range)</td>
<td>23 (4.0 IQR; 19–28 range)</td>
<td>0.148</td>
</tr>
<tr>
<td>Gravida (n)</td>
<td>0 (1.0 IQR; 0–2 range)</td>
<td>0 (1.0 IQR; 0–1 range)</td>
<td>0.595</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>0 (1.0 IQR; 0–1 range)</td>
<td>0 (1.0 IQR; 0–1 range)</td>
<td>0.605</td>
</tr>
<tr>
<td>Pre-operative CA 125 serum levels (IU/ml)</td>
<td>112.0 (67.0 Q; 64.0–218.0 range)</td>
<td>97.0 (77.9 Q; 42.0–243.0 range)</td>
<td>0.571</td>
</tr>
<tr>
<td>Basal FSH (IU/l)</td>
<td>5.1 (2.1 IQR; 2.8–8.2 range)</td>
<td>5.3 (1.8 IQR; 3.1–7.9 range)</td>
<td>0.610</td>
</tr>
<tr>
<td>Main dimension of tumour (cm)</td>
<td>Left ovary 3.6 (3.3 IQR; 1.8–6.9 range)</td>
<td>4.7 (3.2 IQR; 1.2–7.9 range)</td>
<td>0.461</td>
</tr>
<tr>
<td></td>
<td>Right ovary 5.0 (4.4 IQR; 1.2–8.0 range)</td>
<td>3.6 (4.2 IQR; 1.4–8.0 range)</td>
<td>0.584</td>
</tr>
<tr>
<td>Residual ovarian tissue (cm²)</td>
<td>Left ovary 0.9 (1.4 IQR; 0.3–4.0 range)</td>
<td>0.6 (0.8 IQR; 0.3–4.0 range)</td>
<td>0.402</td>
</tr>
<tr>
<td></td>
<td>Right ovary 0.8 (3.3 IQR; 0.3–4.0 range)</td>
<td>0.8 (2.7 IQR; 0.3–4.0 range)</td>
<td>0.909</td>
</tr>
</tbody>
</table>

All data are reported as median and inter-quartile range (IQR) and analysed by Mann–Whitney U-test.

**Surgical data**

In all the cases included in the final analysis, the laparoscopic procedure was successfully completed.

No patient allocated in the standard surgical treatment group was treated with bilateral cystectomy, whereas in only one case the bilateral cystectomy was not technically feasible because no plane of cleavage and no visible healthy tissue on an ovary (remnant ovarian surface covered with vegetations) were found. This patient had an oophorectomy plus contralateral cystectomy. According to ITT analysis, she was included in the experimental group.

For both treatment groups, FIGO stage, grading and histological type of the BOTs were similar (Table II). The micropapillary pattern was observed in 23/64 (36%) BOTs with no difference between groups (10/30, 33.3%, versus 13/34, 38.2%, respectively for experimental and control groups; P = 0.683).

After a complete surgical staging, one (1/15, 6.7%) and two (2/17, 11.8%) patients for experimental and control groups, respectively, were upstaged. In fact, tubal and peritoneal implants were discovered in one and in two cases, respectively. Specifically, in the control group, one patient (1/17, 5.9%) had spread tubal involvement (stage IIA), and another one patient (1/17, 5.9%) had macroscopic peritoneal disease less than 2 cm (stage IIIB), whereas in the experimental group one patient (1/15, 6.7%) had microscopic peritoneal disease (stage IIIA). No difference in patients with tubal [0/15 (0%) versus 1/17 (5.9%), P = 0.340] and peritoneal involvement [1/15 (6.7%) versus 1/17 (5.9%); P = 0.927] was detected between experimental and control groups. In the two cases of advanced stage (stage IIIA, one for each group, a mucinous histotype was observed, with no difference between groups [1/15 (6.7%) versus 1/17 (5.9%); P = 0.927]. In these same cases, a systematic lymphadenectomy was performed. The number of pelvic (10 versus 8) and para-aortic (6 versus 4) lymph nodes removed were similar between the two patients. In no cases were peritoneal invasive lesions or metastasis at lymph nodes discovered.

In Table III, all surgical data are summarized. No difference in any surgical parameter evaluated was observed between groups.

No significant difference in intra-operative [3/15 (20.0%) versus 4/17 (23.5%) for experimental and control groups, respectively; P = 0.810] and post-operative [1/15 (6.7%) versus 1/17 (5.9%); P = 0.927] complications was observed between experimental and control groups. The intra-operative complications consisted of five cases of spillage for incidental cyst rupture [3/15 (20.0%) versus 2/17 (11.8%) for experimental and control group, respectively; P = 0.522], one case of bowel [0/15 (0%) versus 1/17 (5.9%) for experimental and control groups, respectively; P = 0.340] and vascular injury [0/15 (0%) versus 1/17 (5.9%) for experimental and control group, respectively; P = 0.340]. Fever >38°C was the only post-operative complication, and it was observed in one patient for each group [1/15 (6.7%) versus 1/17 (5.9%) for the experimental and the control groups, respectively; P = 0.927]. There was no major adverse event.

The rate of patients with recurrence and multiple recurrences was not different between groups (Table IV). The Kaplan–Meier procedure showed that the cumulative probability of first recurrence for experimental and control patients did not

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**Table I.** Baseline patient characteristics

**Table II.** Surgical stage, grade and histology of the bilateral borderline ovarian tumours (BOTs) in patients treated with bilateral cystectomy (experimental group) or with unilateral oophorectomy plus contralateral cystectomy (control group)

<table>
<thead>
<tr>
<th>FIGO stage [n (%)]</th>
<th>Experimental group (n = 15)</th>
<th>Control group (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>9 (60.0)</td>
<td>12 (70.6)</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>5 (33.3)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>1 (6.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>IIIIB</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Grade [n (%)]</td>
<td></td>
<td></td>
<td>0.472*</td>
</tr>
<tr>
<td>1</td>
<td>13 (86.7)</td>
<td>14 (82.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (6.7)</td>
<td>2 (11.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (6.7)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Histology [n (%)]</td>
<td></td>
<td></td>
<td>0.5487</td>
</tr>
<tr>
<td>Serous</td>
<td>14 (93.3)</td>
<td>15 (88.2)</td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (6.7)</td>
<td>2 (11.8)</td>
<td></td>
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</table>

FIGO, International Federation of Gynecology and Obstetrics.
All data are reported as frequency and analysed by *chi-square test with exact method or †Fisher’s exact test.
Surgical data in patients with bilateral borderline ovarian tumours (BOTs) treated with bilateral cystectomy (experimental group) or with unilateral oophorectomy plus contralateral cystectomy (control group)

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n = 15)</th>
<th>Control group (n = 17)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Global operative time (min)</td>
<td>80.6 (6.6 IQR; 75.3–100.3 range)</td>
<td>80.3 (17.8 IQR; 76.9–101.9 range)</td>
<td>0.762</td>
</tr>
<tr>
<td>Intra-operative blood loss (ml)</td>
<td>72.8 (11.4 IQR; 64.2–92.7 range)</td>
<td>81.1 (15.9 IQR; 64.4–102.3 range)</td>
<td>0.176</td>
</tr>
<tr>
<td>Δ Hb</td>
<td>0.7 (0.4 IQR; 0.3–1.5 range)</td>
<td>0.8 (0.5 IQR; 0.5–1.3 range)</td>
<td>0.143</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>3.0 (0.0 IQR; 3.0–6.0 range)</td>
<td>3.0 (2.0 IQR; 3.0–6.0 range)</td>
<td>0.672</td>
</tr>
<tr>
<td>Time to return activity and/or work (days)</td>
<td>15.0 (5.0 IQR; 10.0–21.0 range)</td>
<td>15.0 (IQR 2.0; 10.0–21.0 range)</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Δ Hb, haemoglobin variation.
All data are reported as median and inter-quartile range (IQR) and analysed by Mann–Whitney U-test.

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n = 15)</th>
<th>Control group (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with recurrence [n (%)]</td>
<td>9 (60.0)</td>
<td>10 (58.8)</td>
<td>0.964*</td>
</tr>
<tr>
<td>Multiple recurrence rate [n (%)]</td>
<td>3 (23.1)</td>
<td>0 (0.0)</td>
<td>0.092 †</td>
</tr>
<tr>
<td>Time to first recurrence (months)</td>
<td>16.0 (12.0, IQR; 4–24, range)</td>
<td>48.0 (7.0 IQR; 17–75 range)</td>
<td>&lt;0.001 ‡</td>
</tr>
<tr>
<td>Age at first recurrence (years)</td>
<td>27.0 (9.0, IQR; 23.0–34.0, range)</td>
<td>32.0 (6.0 IQR; 23.0–34.0 range)</td>
<td>0.622 ‡</td>
</tr>
<tr>
<td>Age of patients who received radical surgery (years)</td>
<td>28.0 (4.5 IQR; 25.0–37.0 range)</td>
<td>37.0 (—; 28.0–38.0 range)</td>
<td>0.112 ‡</td>
</tr>
<tr>
<td>Radical treatment of recurrences [n (%)]</td>
<td>9 (60.0)</td>
<td>3 (17.6)</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

Data reported as frequency and analysed by *chi-square test and †Fisher’s exact test or as median and inter-quartile range (IQR) and analysed by ‡Mann–Whitney U-test.

attain statistical significance (P = 0.358) by log-rank testing (Figure 2A). Using a Cox regression analysis, the women treated with the experimental procedure had a RR of recurrence of 1.521 [95% confidence interval (95% CI), 0.614–3.771; P = 0.365].

All recurrences were detected at follow-up visits and treated conservatively with laparoscopic approach. In no case was observed a progression to invasive ovarian carcinoma. In all cases the ovaries were the site of recurrence, and in no case was observed port-site metastasis. Specifically, the contralateral and both ovaries (without differences between the two sides) were involved in the experimental and control group, respectively.

No difference between groups was observed in number of patients with recurrence, in multiple recurrence rates, in age at first recurrence and in age of patients who received demolitive surgery (Table IV). On the contrary, the time for first recurrence (P = 0.001) and the rate of patients who underwent radical surgery (P = 0.014) were significantly lower and higher, respectively, in the experimental than in the control group (Table IV).

There were no deceases during our procedure and follow-up period.

Reproductive data

At each follow-up visit, no difference in frequency of menstrual cycles and sexual intercourse was detected between groups (data not shown). The length and the quantity of menstrual bleedings were similar between the two treatment groups and unchanged from baseline (data not shown).

At 3-month visit, basal FSH levels were unchanged in the experimental group [5.1 (2.1 IQR; 2.8–8.2 range) versus 5.2 (2.4 IQR; 3.4–8.7 range) at basal versus at 3-month visit, respectively; P = 0.656], whereas in the control group they were significantly increased [5.3 (1.8 IQR; 3.1–7.9 range) versus 7.0 (3.5 IQR; 4.3–10 range) at basal versus at 3-month visit, respectively; P = 0.003] and significantly higher than in experimental group [5.2 (2.4 IQR; 3.4–8.7 range) versus 7.0 (3.5 IQR; 4.3–10 range) for the experimental and the control groups, respectively; P = 0.007]. No other variation was observed during the study in basal FSH levels in the experimental group in comparison with control surgery (data not shown).

In 33.3% (5/15 patients) and 35.3% (6/17 patients) of cases for experimental and control groups, respectively, the ovulation monitoring followed by timed intercourses was accepted, whereas the remaining patients had free intercourses. This distribution was not statistically different between treatment groups.

At the end of the study, no significant (P = 0.849) difference in live birth rate was observed between experimental (25/26, 96.2%) and control (19/20, 95.0%) groups.

In Table V, the reproductive outcomes in the experimental and control groups are shown. Our primary outcome, that is, the CPR, was significantly higher (P = 0.011) in the experimental than in the control group. This difference in our primary end-point resulted at post-study power calculation to be >75%. Considering the absence of pregnancy as treatment-related event, the NNT was of 3 benefits (2–11 benefits; 95% CI). The probability of first pregnancy by the Kaplan–Meier survival analysis was also higher for experimental than for control group (P = 0.003) with an estimated median of 5 and 14 months, respectively (Figure 2B). The benefit associated with bilateral cystectomy was also calculated with a Cox
Discussion

To our knowledge, this is the first study on the laparoscopic fertility-sparing treatment of BOTs performed in a prospective randomized controlled fashion with a follow-up of at least 5 years. Data on the efficacy of this approach are produced essentially by retrospective analysis of patients with suspected malignant ovarian tumours having or not having received a complete laparotomic staging (Morice et al., 2003).

The available data regarding the use of laparoscopy for the surgical management of BOTs are also retrospective and obtained by analysis of cases not deliberately approached by laparoscopy but treated conservatively using a laparoscopic access for clinically benign ovarian cysts or tumours (Nezhat et al., 1992; Barnhill et al., 1995; Blanc et al., 1995; Zanetta et al., 1997; Darai et al., 1998; Gotlieb et al., 1998; Seracchioli et al., 2001; Camatte et al., 2002, 2004; Chan et al., 2003; Donnez et al., 2003; Querleu et al., 2003; Maneo et al., 2004; Boran et al., 2005; Deffieux et al., 2005; Desfeux et al., 2005; Fauvet et al., 2005; Rao et al., 2005; Romagnolo et al., 2006). From these findings, it seems that the laparoscopic approach did not change the safety of the fertility-sparing surgery. Accordingly, even if it is the gold standard surgical approach in women wanting to conceive, presently, it is not known whether the laparoscopic approach improves fertility in these patients.

Our series was composed of a large percentage of patients with surgical stage I serous BOTs, whereas in a small percentage the pathologic examinations showed mucinous BOTs only in those cases which were upstaged for peritoneal implants (stage III). Moreover, the peritoneal implants were not invasive in all our cases of advanced stage BOTs. In this regard, we confirm that the recurrence is higher in patients with advanced stage BOTs, that is, with peritoneal implants, particularly when the cystectomy is performed (Camatte et al., 2002). Furthermore, the fertility-sparing surgery has shown to be still a valid approach in those patients in which peritoneal implants are not invasive (Camatte et al., 2002).

Throughout the follow-up study, all recurrences were treated conservatively with laparoscopic approach and in no case was there a port-site metastasis or a progression to invasive ovarian carcinoma. Our results on the recurrence rate in the control group are consistent with those observed in the previous studies on the laparoscopic approach to BOTs (Tinelli et al., 2006).

On the contrary, no difference in cumulative recurrence rate between experimental and control groups was observed during the long-term follow-up, showing that in our study the bilateral cystectomy did not increase significantly the cumulative

Table V. Reproductive outcomes in patients with bilateral borderline ovarian tumours (BOTs) treated with bilateral cystectomy (experimental group) or with unilateral oophorectomy plus contralateral cystectomy (control group)

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n = 15)</th>
<th>Control group (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pregnancy [n (%)]</td>
<td>14 (93.3)</td>
<td>9 (52.9)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Age at first conception (years)</td>
<td>25.0 (6.0 IQR; 21–34 range)</td>
<td>27.0 (7.0 IQR; 22–31 range)</td>
<td>0.613†</td>
</tr>
<tr>
<td>Time to conceive (months)</td>
<td>5.0 (3.0 IQR; 3–9 range)</td>
<td>8.0 (5.0 IQR; 3–14 range)</td>
<td>0.025†</td>
</tr>
<tr>
<td>First-trimester abortion [n (%)]</td>
<td>1 (3.9)</td>
<td>1 (5.0)</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

Data reported as frequency and analysed by *chi-square test and †Fisher’s exact test or as median and inter-quartile range (IQR) and analysed by ‡Mann–Whitney U-test.
recurrence rate. These findings seem apparently inconsistent with those reported in literature demonstrating that the cystectomy is related to a significantly higher recurrence rate than salpingo-oophorectomy (Moric et al., 2003; Salomon et al., 2006). Three reasons could explain these findings. Firstly, each surgical procedure was performed by laparoscopy. We feel that the magnification of laparoscopy can ameliorate the precision of surgical approach in the excision of the ovarian mass and all suspected lesions, with particular reference to peritoneal implants. Secondly, since our patients were initially screened for bilateral BOTs, our series had a high percentage of serous BOTs. In fact, serous BOTs are frequently bilateral and are probably the histotype with the lowest rate of recurrence (Moric et al., 2003; Acs, 2005; Salomon et al., 2006; Tinelli et al., 2006) and progression to invasive ovarian cancer (Salomon et al., 2006) and lower upstage rate from the frozen section (Salomon et al., 2006). Thirdly, our patients underwent non-conservative surgery at the first relapse after childbirth completion. In this view, the strategy proposed to patients at enrolment, consisting of minimally invasive approach, that is, bilateral cystectomy, followed by non-conservative surgery at termination of reproductive cycle, has shown to be effective in terms of reproductive outcome without a significant increase in cumulative recurrence rate. In other words, the higher risk of recurrence due to bilateral cystectomy is reduced or mitigated by a higher rate of non-conservative procedures performed after childbirth completion. This strategy was feasible because of the higher rate of recurrence after cystectomy versus oophorectomy observed after long-term follow-up alone (Barnhill et al., 1995; Gottlieb et al., 1998).

Finally, we suggest that the cumulative recurrence rate was similar between the two laparoscopic approaches because the time to obtain a pregnancy was significantly shorter in the experimental group than in the control group. In fact, the number of patients who received a standard radical treatment for BOTs was significantly higher in the experimental group than in the control group, the delay between first surgery and non-conservative surgery being significantly shorter for patients who underwent extremely conservative surgery. Although no difference between groups was detected in cumulative recurrence rate, the ultra-conservative surgery resulted in a statistically significant earlier time to relapse. This issue should be addressed during counselling, and the patient should be informed of the risk of developing a recurrence ~2.5 years earlier after bilateral cystectomies than after standard fertility-sparing surgical treatment.

To date, the few data on the efficacy and safety of bilateral cystectomy can be extracted only from retrospective series of patients who received conservative laparoscopic surgery for BOTs. Seracchili et al. (2001) reported two cases treated with bilateral cystectomy for serous BOTs tumors. No recurrence was observed after a mean follow-up of 42 months, and only one patient achieved pregnancy. Maneo et al. (2004) described six cases of bilateral cystectomy concluding that in patients with bilateral neoplasia, although with a high risk of relapse, the cystectomy could be performed in women willing to preserve fertility. Also other more recent studies (Borain et al., 2005; Fauvet et al., 2005; Romagnolo et al., 2006) described some cases treated with bilateral cystectomy as a fertility-sparing procedure to preserve fertility in patients of reproductive age. Furthermore, the analysis of recurrences seems to demonstrate a non-significant increase in patients treated with bilateral cystectomy (Borain et al., 2005; Fauvet et al., 2005; Romagnolo et al., 2006).

The cumulative probability of pregnancy and live births in our series was very high. In fact, a higher CPR was also observed after traditional surgery in comparison with those expected at the start of the current clinical study. Moreover, in study protocol were enrolled all patients younger than 35 years of age, with good ovarian function (as assessed by serum FSH level), non-obese and without suspected or diagnosed infertility factors. In addition, a proposed post-surgical follow-up in our Centre for Human Reproduction for ovulation monitoring followed by timed intercourse was accepted by at least one-third of patients per group.

After bilateral cystectomy, cumulative pregnancy, our primary end-point, was significantly higher in the experimental group in comparison with traditional surgery. Apparently, conservative treatment can preserve a minimal ovarian tissue to assure the best reproductive function.

An important finding of the present study was the significant increase in basal FSH value detected after oophorectomy plus contralateral cystectomy. Although no difference in menstrual cyclicity was observed between groups, it could be suggested that the loss of a considerable part of ovarian tissue after oophorectomy plus contralateral cystectomy with subsequent reduction of ovarian reserve could be the explanation. On the contrary, bilateral cystectomy seems to preserve a more intact pituitary–ovary axis, with beneficial effects on the reproductive function. On the basis of these considerations, patients with BOTs who should be undergoing ovarian hyperstimulation and IVF for tubal and/or male factor infertility could benefit from an extremely conservative surgical approach.

In conclusion, our findings, although obtained on a small population, demonstrate that laparoscopic bilateral cystectomy followed by non-conservative treatment performed at the first recurrence after childbirth completion is an effective surgical strategy in terms of reproductive outcomes for patients with bilateral early stage BOTs who desire to conceive as soon as possible and accept to undergo a radical treatment. Powered studies on a wider sample are needed to draw definitive conclusions on the safety of this ultra-conservative treatment.

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References


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