Ultra-conservative fertility-sparing strategy for bilateral borderline ovarian tumours: an 11-year follow-up

Stefano Palomba1,*, Angela Falbo1, Serena Del Negro1, Morena Rocca1, Tiziana Russo2, Francesco Cariati1, Gianluca Annunziata1, Achille Tolino3, Pierosandro Tagliaferri4, and Fulvio Zullo2

1Department of Obstetrics and Gynaecology, University ‘Magna Graecia’ of Catanzaro, Via T. Campanella 182/1- 88100, Viale Europa, 88100 Catanzaro, Italy 2Department of Gynecology Oncology Cancer Center of Excellence ‘Tommaso Campanella’ of Germaneto, Viale Europa, 88100 Catanzaro, Italy 3Department of Obstetrics and Gynaecology, University ‘Federico II’ of Naples, Via Pansini, 80131 Naples, Italy 4Department of Oncology, Cancer Center of Excellence ‘Tommaso Campanella’ of Germaneto, Viale Europa, 88100 Catanzaro, Italy

*Corresponding address. Tel: +39-3475880503; Fax: +39-961-883234; E-mail: stefanopalomba@tin.it

Submitted on March 21, 2010; resubmitted on April 28, 2010; accepted on May 25, 2010

BACKGROUND: This is a prospective long-term extension study of a randomized controlled trial aimed to assess the risk–benefit ratio of an ultra-conservative fertility-sparing approach in patients with bilateral borderline ovarian tumours (BOTs).

METHODS: The experimental group (n = 15) was treated with an ultra-conservative surgical approach consisting of bilateral cystectomy, whereas the control group (n = 17) received a less conservative surgery consisting of oophorectomy plus controlateral cystectomy alone. All patients received a complete laparoscopic staging followed by a fertility enhancement programme. Patients who completed childbearing were treated with a non-conservative standard treatment at the first recurrence.

RESULTS: After a follow-up period of 128 (9 interquartile range (IQR); 115–150 range) and 132 (7 IQR; 117–152 range) months for the experimental and control groups, respectively (P = 0.25), the time to first baby-in-arm (P, 0.02) and the relative rate (RR) of baby-in-arm (8.05 [95% confidence interval (CI), 1.20–9.66; P, 0.01]) were significantly lower and higher, respectively, for the experimental compared with the control group. Although the time to first recurrence was significantly shorter for the experimental group, in the regression analysis the difference did not reach the statistic significance (P = 0.41; RR = 1.23 [95% CI, 0.62–3.17; P = 0.41]) was not significant. Finally the number needed to treat for pregnancy was three, the number needed to harm for radical surgery was only two.

CONCLUSIONS: The ultra-conservative fertility-sparing approach is more effective than the standard approach in terms of reproductive outcomes, but presents a higher oncological risk.

Key words: BOTs / fertility-sparing strategy / pregnancy / recurrence / ultra-conservative surgery

Introduction

In recent years, fertility-sparing surgery has been arousing growing interest, with particular regard for young patients with gynaecological cancers, such as those affected by borderline ovarian tumours (BOTs) (Liu et al., 2005; Farthing, 2006; Maltaris et al., 2006; Tinelli et al., 2009).

BOTs are, in fact, characterized by common presentation during the childbearing years at an early stage and by an excellent long-term survival (Morice et al., 2003). In addition, BOTs are bilateral in a percentage of cases (Acs, 2005; Tinelli et al., 2006) influencing the choice of the surgery to perform, especially for those of young age.

On the other hand, progress in improving reproductive function in patients with gynaecological malignancies has been made owing to advances not only in surgical techniques, but also in combined fertility treatment (Liu et al., 2005).

In a randomized controlled trial (RCT) (Palomba et al., 2007), we compared oophorectomy plus controlateral cystectomy with bilateral cystectomy in patients with bilateral early-stage BOTs who desired to conceive. The latter ultra-conservative fertility-sparing option was superior to the traditional approach in terms of cumulative pregnancy rate and time to first pregnancy, even if a higher recurrence rate and a lower time to first recurrence was recorded for this experimental procedure than for the standard one. However, it
was not defined whether these benefits were maintained at longer follow-up.

Based on these considerations, the present study is an extension follow-up of the previous RCT (Palomba et al., 2007) aimed to evaluate the long-term oncological safety and the reproductive outcomes of patients treated with an ultra-conservative fertility-sparing strategy for clinical stage I bilateral BOTs in order to define the risk–benefit ratio.

**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, and written consent was obtained by each patient before entering the study.

**Protocol**

Between February 1997 and March 2000, 80 patients of reproductive age with clinical stage I bilateral BOTs (International Federation of Gynecology and Obstetrics, 1987) and a desire to conceive as soon as possible were enrolled in the original study protocol (Palomba et al., 2007). Subjects were followed until October 2009.

After considering the exclusion criteria elsewhere reported (Palomba et al., 2007), patients were randomized in two arms of 40 subjects each: one consisting of an ultra-conservative surgical approach with bilateral cystectomy (experimental group) and the other consisting of oophorectomy plus contralateral cystectomy alone (control group).

All surgical procedures were performed by the same experienced team (S.P., F.Z.), as previously described (Palomba et al., 2007).

Briefly, in case of BOT diagnosis at the intra-operative histological examination, the surgical intervention consisted of collection and cytological examination of the peritoneal fluid, infracolic omentectomy, excision of the macroscopic peritoneal implants otherwise collection of multiple peritoneal biopsies in the absence of macroscopic peritoneal involvement, salpingectomy only in the presence of macroscopic involvement of the tube, appendectomy in case of mucinous or mixed tumour, and pelvic and para-aortic lymphadenectomy only in selected cases (Palomba et al., 2007).

BOTs were definitively diagnosed after post-operative histological examination of all tissue samples.

After surgery, all patients were followed up in order to improve their reproductive chances and to assess the safety of the fertility-sparing interventions.

**Fertility outcomes**

Figure 1 summarizes the fertility programme scheduled for enrolled subjects. Ovation monitoring followed by timed intercourse was proposed during the first 12 months after surgery for each patient. All patients who did not achieve a pregnancy spontaneously were managed with a fertility enhancement programme. In particular, subjects with a negative hysterosalpingogram underwent three trials of controlled ovarian stimulation (COS) followed by intrauterine insemination (IUI), and successively three cycles of in vitro fertilization (IVF), whereas those with a tubal factor of infertility directly underwent three trials of IVF.

COS plus IUI and IVF were performed according to standard procedures, as previously described (Palomba et al., 2005, 2006, 2008). In both cases, a gonadotrophin [highly purified FSH (hpFSH)] step-down protocol was used. Specifically, hpFSH was initially administered at starting dose of 150 and 225 IU/day intramuscularly injected for 5 days for non-IVF and IVF, respectively. Then, the regimen was personalized according to ovarian response. In all cases, 10,000 IU of human chorionic gonadotrophin (hCG) was administered for triggering ovulation.

For each patient, the cancelled cycles, the stimulation length, the units of gonadotrophins administered, the number of dominant follicles on the day of hCG administration were recorded. For IVF cycles, the number of retrieved oocytes, the number of metaphase II (MII) oocytes, the fertilization rate and the number of arrested embryos were also noted.

The absence of ovarian response after 35 days of treatment or a serum estradiol (E2) value >2500 pg/ml was considered as indication for abandoning the cycle (cancelled cycle).

The cumulative rate of patients with pregnancy and with baby-in-arm was recorded. The cumulative pregnancy and baby-in-arm rates were also calculated according to the time to the first event as detailed in the statistical analysis section. A regular rising HCG level and the sonographic evidence of intrauterine gestational sac were considered criteria to define a pregnancy.

**Oncological outcomes**

According to our internal and multidisciplinary protocols, patients were followed every 3 months during the first year after surgery, then every 6 months for 3 years and, successively, once a year. Patients who conceived were examined every 3 months during pregnancy and every 6 months after delivery (Palomba et al., 2007).

Patients were treated conservatively with a laparoscopic approach in case of recurrence, whereas women who completed childbearing were treated with a non-conservative standard treatment for BOTs at the first recurrence (Palomba et al., 2007).

Recurrence-free survival and overall survival were evaluated, considering relapse or death as censoring events, respectively. The cumulative recurrence rate was also calculated according to the time to the first event as detailed in the statistical analysis section.

**Statistical analysis**

The population sample was previously determined defining as primary end point the cumulative pregnancy rate and assuming a cumulative pregnancy rate equal to 47% for control surgery (control group) and a pregnancy rate equal or superior to 93% for experimental surgery (experimental group), with an estimated difference of 46% between groups (Palomba et al., 2007).

Data were analysed using the intention-to-treat method. Continuous variables were expressed as median and interquartile 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 fisher’s exact test were applied as required.

Cumulative event rates (pregnancies and recurrences) were calculated by the Kaplan–Meier method, with 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 relative rate (RR) with 95% confidence interval (95% CI) for pregnancy and recurrence. The number needed to treat (NNT) and the number needed to harm (NNH) for pregnancy and radical treatment for recurrence, respectively, were also calculated.

Statistical analysis was performed using the SPSS 11.0 (SPSS Inc., Chicago, IL, USA) package. A P < 0.05 value was considered as statistically significant, whereas a P ranging between 0.05 and 0.08 was considered as a trend towards significance. The power analysis and the sample size calculation were performed using SamplePower release 2.0.

**Results**

There were 80 patients initially enrolled and randomized in the two groups (Palomba et al., 2007). Of these 80 patients, 48 were excluded because their surgery was converted to laparotomy for a malignant tumour (one and three subjects for the experimental and control groups, respectively), or because they were affected by benign cysts (24 and 20 subjects for the experimental and control groups, respectively). Thus, only 15 and 17 patients for the experimental and control groups, respectively, were included in the final analysis (Palomba et al., 2007).

No differences in age, body mass index, gravidity, parity, preoperative serum CA 125 and basal FSH levels, or main dimensions of tumour and residual ovarian tissue were observed between two groups (Palomba et al., 2007). Patients were followed for a follow-up period of 128 (9 IQR; 115–150 range) and 132 (7 IQR; 117–152 range) months for the experimental and control groups, respectively (P = 0.25).

Surgical data were elsewhere reported, and no differences in surgical results were observed between the experimental and control groups (Palomba et al., 2007).

**Fertility data**

In Fig. 2, the mean percent change from baseline in serum FSH levels within and between groups was shown. At each follow-up visit, no significant change from baseline was observed in the mean percent change of basal FSH levels in the experimental group during the first 2 years after surgery, whereas in the control group, the mean FSH levels were significantly (P < 0.01) increased from the third month of follow-up and were significantly (P < 0.01) higher in the experimental group than in the control group.

After the first 12 months of follow-up, all patients from both groups were followed according to a fertility enhancement programme. In the experimental and control groups, respectively, one [1/15 (6.7%)] and two patients [2/17 (11.8%)] underwent IVF because of a newly diagnosed tubal factor of infertility, whereas 14/15 (93.3%) and 15/17 (88.2%) subjects received COS followed by IUI. Of them, 10/15 (66.7%) and 13/17 (76.5%) from the experimental and control groups, respectively, successively underwent IVF because they did not achieve a pregnancy after the first three trials of COS followed by IUI.

In Table I, the main characteristics of the fertility enhancement programme are shown.

With regard to the COS cycles, a significant (P = 0.03) difference between groups was detected in cycle cancellation rate and in all cases the cycle was cancelled because of the absence of a follicular response after 35 days of treatment (Table I). The stimulation length and the units of gonadotrophins used were also significantly (P < 0.01) lower in the experimental group than in the control group (Table I). A trend towards a significantly (P = 0.07) higher number of dominant follicles on day of hCG administration was detected in the experimental group in comparison with the control group (Table I).

Similarly, in IVF cycles, the cancellation rate was significantly (P = 0.04) lower in the experimental than in the control group, and in all cases, the cycles were cancelled for lack of a follicular response after 35 days of stimulation (Table I). Significant (P < 0.05) differences between groups were detected in stimulation length and the units of gonadotrophins used (Table I). No significant differences between the experimental and control groups were observed in dominant follicles on day of hCG administration, number of retrieved oocytes, number of MII oocytes, fertilization rate or number of embryos arrested (Table I).

Table II summarizes the main reproductive outcomes. The cumulative pregnancy rate was significantly higher (P = 0.04) in the experimental than in the control group (Table II). No significant difference between the two groups was observed in the distribution of patients who had one, two or three pregnancies throughout the study (P = 0.13) and in the number of multiple births (P = 0.77) (Table II).

No significant (P = 0.48) difference between the groups was detected for age at first conception, whereas the time to conceive was significantly (P = 0.01) shorter in the experimental than in the control group (Table II).
The time to first pregnancy was significantly \((P < 0.01)\) lower for the experimental than the control group with estimated medians of 5 and 8.5 months, respectively, whereas the RR of pregnancy was significantly \((P < 0.01)\) higher in the experimental than in the control group (Fig. 3a).

At the end of the study, a trend towards a significantly \((P = 0.06)\) higher number of women with a baby-in-arm was observed in the experimental \((13/15)\) than in the control group \((9/17)\) (Table II). The time to have a first baby-in-arm was significantly \((P = 0.02)\) shorter in the experimental group than in the control group (Table II) with estimated medians of 14 and 18 months, respectively, and the RR of a baby-in-arm was significantly \((P < 0.01)\) higher in the experimental group in comparison with the control one (Fig. 3b).

### Table I Characteristics of the fertility enhancement programme.

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Control group</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COS followed by IUI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects studied ((n))</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cycles studied ((n))</td>
<td>37</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Cancellation rate ((n\text{ cancelled cycle}/total cycles, %))</td>
<td>4/37 (10.8)</td>
<td>14/42 (33.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stimulation length ((\text{days}))</td>
<td>11 (IQR: 9–14, range)</td>
<td>13 (IQR: 11–19, range)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gonadotrophins dose ((\text{units}))</td>
<td>950 (IQR: 700–1400, range)</td>
<td>1300 (IQR: 900–1900, range)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dominant follicles on day of hCG administration ((n))</td>
<td>2 (IQR: 1–3, range)</td>
<td>1 (IQR: 1–3, range)</td>
<td>0.07</td>
</tr>
<tr>
<td>IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects studied ((n))</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cycles studied ((n))</td>
<td>27</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Cancellation rate ((n\text{ cancelled cycle}/total cycles, %))</td>
<td>1/27 (3.7)</td>
<td>7/41 (17.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stimulation length ((\text{days}))</td>
<td>11 (IQR: 9–16, range)</td>
<td>13 (IQR: 10–18, range)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gonadotrophins dose ((\text{units}))</td>
<td>2100 (IQR: 1400–2000, range)</td>
<td>2400 (IQR: 1500–2900, range)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dominant follicles on day of hCG administration ((n))</td>
<td>7 (IQR: 3–12, range)</td>
<td>5 (IQR: 3–10, range)</td>
<td>0.18</td>
</tr>
<tr>
<td>Retrieved oocytes ((n))</td>
<td>5 (IQR: 2–9, range)</td>
<td>4 (IQR: 2–8, range)</td>
<td>0.11</td>
</tr>
<tr>
<td>MII oocytes ((n))</td>
<td>3 (IQR: 1–6, range)</td>
<td>3 (IQR: 0–7, range)</td>
<td>0.29</td>
</tr>
<tr>
<td>Fertilization rate ((n\text{ fertilized oocytes}/\text{maximum three oocytes}, %)^a)</td>
<td>58/73 (79.5)</td>
<td>63/81 (77.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Embryos arrested ((n))</td>
<td>8/58 (13.8)</td>
<td>7/63 (11.1)</td>
<td>0.78</td>
</tr>
</tbody>
</table>


### Table II Reproductive outcomes in patients with bilateral BOTs treated with bilateral cystectomy (experimental group) or with unilateral oophorectomy plus controlateral 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>Total number of pregnancies ((n)) (^a)</td>
<td>27</td>
<td>21</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with pregnancy ((n, %)) (^a)</td>
<td>14 (93.3)</td>
<td>10 (58.8)</td>
<td></td>
</tr>
<tr>
<td>Distribution of pregnancy ((n, %)) (^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One pregnancy</td>
<td>5 (33.3)</td>
<td>2 (11.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Two pregnancies</td>
<td>5 (33.3)</td>
<td>5 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Three pregnancies</td>
<td>4 (26.7)</td>
<td>3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Multiple births ((n, %)) (^a)</td>
<td>2 (13.3)</td>
<td>3 (17.6)</td>
<td>0.77</td>
</tr>
<tr>
<td>Age at first conception ((\text{years})) (^b)</td>
<td>25 (IQR: 21–34 range)</td>
<td>27.5 (IQR: 22–31 range)</td>
<td>0.48</td>
</tr>
<tr>
<td>Time to conceive ((\text{months})) (^c)</td>
<td>5 (IQR: 3–21 range)</td>
<td>8.5 (IQR: 3–43 range)</td>
<td>0.01</td>
</tr>
<tr>
<td>Patients with a baby-in-arm ((n, %)) (^d)</td>
<td>13 (86.7)</td>
<td>9 (52.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Time to have a baby-in-arm ((\text{months})) (^d)</td>
<td>14 (IQR: 12–18 range)</td>
<td>18 (IQR: 12–52 range)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(^a\)Data reported as frequency and analysed by chi-square test.

\(^b\)Data reported as frequency and analysed by Fisher’s exact test.

\(^c\)Data reported as median and interquartile range (IQR) and analysed by Mann–Whitney U test.

\(^d\)All multiple births were twins.
At the end of the study, no [0/15 (0.0%)] and two [2/17 (11.7%)] subjects from the experimental and control groups, respectively, went through menopause ($P = 0.49$).

The NNT was three experimental procedures to obtain one additional pregnancy.

**Oncological data**

The main oncological data are shown in Table III.

No significant differences between the experimental and control groups were observed in the number of patients with recurrence ($P = 0.73$), the multiple recurrence rate ($P = 0.09$), the age at first recurrence ($P = 0.62$) and the age of patients who received radical surgery ($P = 0.11$).

On the other hand, subjects from the experimental group, when compared with controls, had significantly shorter times to first recurrence ($P < 0.01$) and a higher rate of patients who underwent radical surgery ($P = 0.01$).

The regression analysis showed that the time to first recurrence and the RR of recurrence were not significantly ($P = 0.14$ and $P = 0.41$) different between the experimental and control groups (Fig. 3c).

All recurrences were detected at follow-up visits and treated with conservative laparoscopic surgery. In all cases, local (ovarian) recurrences were detected at controlateral and both ovaries (without differences between the two sides) in the experimental and control groups, respectively. In no case, was either progression to an invasive ovarian carcinoma or death observed.

The NNH was two experimental procedures for one additional radical intervention.

**Discussion**

Several reports have been published regarding fertility-sparing surgery for early-stage BOTs (Morice, 2003; 2006; Desfeux et al., 2005; Romagnolo et al., 2006; Salomon et al., 2006; Laurent et al., 2008, 2009; Wong et al., 2007) and the long-term safety of this conservative treatment (Kumpulainen et al., 2007; Laurent et al., 2008; Tinelli et al., 2009). However, to date, only one RCT is available in the literature (Palomba et al., 2007).

In a previous report of this RCT (Palomba et al., 2007), we showed the feasibility and the reproductive effectiveness of a complex strategy consisting of ultra-conservative surgery followed by 12 months of ovulation monitoring and timed intercourse before starting a fertility enhancement programme, i.e. three trials of COS/IUI followed by three cycles of IVF or, in case of tubal factor infertility detection, directly three trials of IVF. Moreover, to define the definitive risk–benefit ratio of this approach, we designed a 4-year extension study. In particular, the current study was aimed to evaluate the balance for the patients between better fertility and worse chance of recurrence at long-term follow-up, providing a real picture of the fertility history of a well-selected young population of patients with clinical stage I bilateral BOTs who desire to conceive as soon as possible.

Here, we confirmed that the ultra-conservative fertility-sparing strategy has significant reproductive time-saving advantages, in terms of cumulative pregnancy rate and time to conceive, over the standard procedure. A trend towards a significantly higher cumulative baby-in-arm rate, but a significantly shorter time to have a first baby-in-arm was detected after ultra-conservative fertility-sparing surgery. These beneficial effects were also confirmed by the Kaplan–Meier survival analysis in terms of the time to first pregnancy.
Table III  Oncological outcomes in patients with bilateral 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 recurrence (n, %)</td>
<td>10 (66.7)</td>
<td>10 (58.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Multiple recurrence rate (n, %)³</td>
<td>3 (23.1)</td>
<td>0 (0.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Time to first recurrence (months)³</td>
<td>16.2 (12, IQR: 3–36, range)</td>
<td>48 (7, IQR: 18–72, range)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at first recurrence (years)³</td>
<td>27 (9, IQR: 23–34, range)</td>
<td>32 (6, IQR: 23–34, range)</td>
<td>0.62</td>
</tr>
<tr>
<td>Age of patients who received radical surgery (years)³</td>
<td>28.1 (4.5 IQR: 25–37 range)</td>
<td>37 (3 IQR: 28–38 range)</td>
<td>0.11</td>
</tr>
<tr>
<td>Radical treatment of recurrences (n, %)³</td>
<td>9 (60.0)</td>
<td>3 (17.6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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

and/or to baby-in-arm and of the RR for pregnancy and/or for baby-in-arm. In this regard, the proportional hazards RR for a baby-in-arm was 8.05, that was much higher than the crude RR, probably due to the early intervals of follow-up performed in a small population.

The conservative treatment of bilateral BOTs seemed likely to have advantages through the preservation on a greater amount of ovarian tissue. Even if the most accurate marker of ovarian reserve is still debated (Lutchman Singh et al., 2005), our findings showed no significant change in the mean variation of serum FSH levels during the 11-year observation after bilateral cystectomy, whereas FSH was significantly increased within the first months from surgery in patients who received the standard surgical procedure. In this regard, patients receiving ultra-conservative surgery were more responsive to ovarian stimulation in both COS/IUI and IVF cycles, showing less cancelled cycles, shorter stimulation lengths and use of fewer units of gonadotrophins. However, they did not show any further clinically relevant reproductive advantage probably due to the small sample size.

The current study showed encouraging findings for novel fertility preservation possibilities in women with bilateral BOTs. In fact, to date only few cases of oocytes retrieval followed by in vitro maturation and subsequent cryopreservation have been reported (Huang et al., 2007), but in the near future new proposals for fertility preservation could be extended to a larger population with malignancies. Notwithstanding data are still lacking, and the cornerstone of the clinical management of patients with BOTs is certainly an early diagnosis and an aggressive treatment in order to ensure such patients have the most effective treatment in the shortest time, avoiding the overlap of other factors affecting the reproductive function.

From an oncological point of view, the ultra-conservative strategy resulted in a statistically significant earlier time to relapse. These data are in agreement with other authors (Taylor, 1929; Morice, 2006; Tinelli et al., 2006; Borgfeldt et al., 2007; Uzan et al., 2010), who demonstrated that the rate of recurrences in patients who underwent conservative surgery was significantly higher than among those underwent radical surgery. Moreover, our findings from a very long-term follow-up seemed to be more reassuring since ultra-conservative surgery showed acceptable rates of single and multiple recurrences.

In addition, the age at first recurrence and the age of patients who received radical surgery were similar between subjects treated with the ultra-conservative approach and those treated with the less conservative fertility-sparing surgery.

A possible explanation for this finding is the choice of the follow-up schedule and of the surgical strategy. In particular, all patients were followed at 3, 6 and 12 months from surgery in the first year and thereafter every 6 months. This follow-up schedule seemed to be effective for precocious diagnosis of recurrence. In fact, in our report, all recurrences were asymptomatic and detected at a follow-up visit. On the other hand, according to our protocol, all patients who completed childbearing were treated with a non-conservative standard treatment for BOTs at the first recurrence. Indeed, we reported a significant difference between groups in the rate of radical treatment for recurrences, 60 and 18% for patients treated with the ultra-conservative surgery and those treated with the less conservative surgery, respectively.

As already reported (Taylor, 1929; Morice, 2006; Tinelli et al., 2006; Borgfeldt et al., 2007; Uzan et al., 2010), the conservative management did not affect patients’ survival because we studied only patients with histologically confirmed stage I BOT, carrying an excellent prognosis. In fact, no case of death was reported in the current analysis.

Although we proposed the ultra-conservative fertility-sparing strategy to well-selected patients (i.e. aged <35 years, with basal FSH not higher than 15 IU/l, without history of infertility or oligoamenorrhoea, or tubal and/or male infertility factors by appropriate tests), our results showed an unfavourable risk–benefit ratio in the experimental population. In fact, the NNT was three ultra-conservative fertility-sparing procedures to obtain one additional pregnancy, but the NNH was just two experimental procedures for one additional radical intervention.

In conclusion, our study demonstrates that in well-selected young patients with bilateral stage I BOTs who desire to preserve their childbearing potential, an ultra-conservative fertility-sparing approach followed by an enhancement fertility programme gives real reproductive advantages, despite a higher risk of recurrence which could be managed through a close monitoring and a demolitive surgery after childbearing completion.
References


