



Controversy

Fertility preservation in women with borderline ovarian tumours



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ABSTRACT

Borderline ovarian tumours (BOT) may occur in young women and have an excellent survival rate. Therefore, there is the obligation to put emphasis on fertility preservation in affected women. On the other hand, it has also been underlined that the disease should be managed with caution because these tumours can relapse and, albeit rare, malignant transformation can also occur. Unfortunately, evidence on fertility preservation in women with BOT is scanty. In this opinion paper, we tried to draw some clinical indications based on the few available studies on the clinical management of BOT and their possible relation with controlled ovarian hyper-stimulation (COH). We ultimately came to the following conclusions: (1) Fertility counselling should become an integral part of the clinical management of women with BOT. Conservative management without pre-surgical counselling may expose women without reasonable chances of future conceptions to undue risks. (2) Despite some epidemiological concerns on the possible relation between COH and BOT, the conservative surgical treatment should be associated to oocyte cryopreservation considering the high risk of recurrence of the disease. (3) Letrozole during COH should be considered to temper the theoretical risk of increased recurrences. (4) Pregnancy should not be delayed in women at low-moderate risk of recurrences. Fertility preservation may be avoided in these women provided that they start active pregnancy seeking early. (5) Albeit experimental, oocytes retrieval from affected ovaries removed at the time of surgery can be considered. Conversely, ovarian cortex cryopreservation is not justified given the possible risks of malignant reseeded.

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Introduction

Borderline ovarian tumours (BOT) have been recognized as a separate diagnostic category of epithelial ovarian tumours [1,2]. They are characterized by features of malignant tumours, including cellular proliferation, stratification of the epithelial lining of the papillae, nuclear atypia, and mitotic activity, but without destructive stromal invasion [3]. They represent about 10–20% of all ovarian epithelial tumours with an estimated incidence ranging from 1.8 to 5.5 per 100,000 women per year [4]. One-third of BOT are observed in patients younger than 40 years of age [5].

BOT are diagnosed at stage I in 82% of cases and have a 5-year survival rate of more than 90% across all tumour stages, with a considerable number of patients cured [6]. However, BOT may relapse and, albeit rare, malignant transformation can occur. FIGO stage, younger age, the presence of peritoneal implants, especially invasive implants, and the type of surgery are the most significant predictive factors of relapse [5,7].

Overall, given the peculiar epidemiological profile of BOT, there is the indisputable obligation to put emphasis on ovarian function and fertility preservation in affected women.

Fertility-sparing surgery, conservative treatment of BOT

The basic treatment of BOT is surgery. In most cases, this is the exclusive treatment.

The intervention aims at complete resection of the tumour, besides full surgical staging. In postmenopausal or in women who do not wish to preserve fertility the complete staging procedure includes: peritoneal washing, bilateral salpingo-oophorectomy,

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multiple peritoneal biopsies, omentectomy, resection of grossly visible metastases and inspection and palpation of the abdominal cavity. Conversely, there is no rationale for systematic lymphadenectomy and hysterectomy [5,8].

Considering the good prognosis of BOT, fertility-sparing surgery can be considered for young women who desire to preserve fertility. Fertility-sparing surgery is defined as preservation of the uterus and at least part of one ovary. Thus, in patients desiring fertility preservation and with tumour confined to one ovary, surgical management may be limited to unilateral salpingo-oophorectomy or ovarian cystectomy with complete surgical staging [9]. In this case, the contralateral normal-appearing ovary should be carefully inspected but biopsy is not required since it may cause unnecessary damage to the ovarian reserve and/or peritoneal adhesions [10,11]. If there is bilateral ovarian involvement and complete resection can be achieved, unilateral or bilateral ovarian cystectomy may be considered, even if patients should be informed about the higher recurrence rate [12]. In all stages and disease extension, the uterus should be preserved because of the increasingly used egg donation option [13].

The most common histotypes are serous (65%) and mucinous (35%). Serous borderline tumours are unilateral in 50% of cases and bilateral in 30%; extraovarian diffusion may occur in 35% of cases in the form of peritoneal implants which may be non invasive (75%) or invasive (25%) [14,15]. Mucinous BOT represent a peculiar situation. In these tumours, benign, borderline and invasive lesions can coexist [16] and there is thus the necessity for an in-depth histological evaluation of the lesions. Moreover, mucinous BOT tend to recur as invasive ovarian carcinoma more frequently than serous BOT after conservative treatment [17,18]. Appendectomy for mucinous type BOT is also strongly recommended. Therefore, the mere excision of the tumour is not feasible in women with mucinous BOT and at least unilateral salpingo-oophorectomy is required regardless of the dimension of the lesion [19].

The laparoscopic approach in stage I BOT seems to be safe and it is now commonly accepted. The development of laparoscopic techniques with the use of Endo-Bag, which allows the confinement of the tumour within a plastic bag during laparoscopy, gives less risk of spillage and less port-site metastases [20,21].

Indications of adjuvant platinum-based chemotherapy remain rare in this disease and are limited to patients with invasive peritoneal implants or with nodal spread located near the nodal sinus. Of note, no randomized studies have demonstrated any survival advantage of adjuvant chemotherapy [5,22].

The risk of relapse after conservative treatment of BOT

The overall risk of recurrence after fertility-sparing surgery is higher (0–25%) than after bilateral salpingo-oophorectomy (0–5%) [23]. For women with stage I BOT treated with either unilateral salpingo-oophorectomy or ovarian cystectomy, after an average follow-up of three to six years, the borderline recurrence rate was 13%, recurrence with malignant disease was 1.6% and the death rate was 0.5% [23]. Comparing unilateral salpingo-oophorectomy or ovarian cystectomy, the recurrence rate was higher and recurrence occurred sooner with the latter [23,24]. A recent meta-analysis based on clinical case series compared the oncological outcome between different surgical approaches in BOT. The authors defined fertility sparing surgery as uni- or bilateral cystectomy or unilateral salpingo-oophorectomy with or without contralateral cystectomy while radical surgery was defined as bilateral salpingo-oophorectomy. Interestingly, based on their analyses, in patients with unilateral BOT, unilateral salpingo-oophorectomy was significantly favoured over cystectomy in terms of reduction of recurrences (OR = 2.20, 95%CI:

0.79–2.84; $p < 0.0001$), namely the recurrence rates were 12% and 25% respectively. No other significant results emerged. Noteworthy, the survival rates did not differ. Pooled mortality estimates for fertility sparing surgery and radical treatment were 1.6% (95% CI: 1.1–2.3%) and 2.0% (95%CI: 1.4–2.9%), respectively [25].

Unfortunately, only one small RCT on conservative management of BOT is available [26]. Thirty-two women with bilateral BOTs were randomized to unilateral salpingo-oophorectomy with contralateral cystectomy versus bilateral cystectomy. After a follow-up period of 81 months, there were no differences in terms of cumulative rate of recurrences between the two groups but the pregnancy rate was higher in women allocated to bilateral cystectomy. However, in this latter group, the time to first recurrence was shorter and the rate of radical treatment of the recurrence was higher [26]. The above-mentioned recent meta-analyses also showed a similar rate of recurrence between the two approaches (28% versus 26%) [25]. Hence, if indicated, a more conservative approach could be chosen also in bilateral BOT.

Stage is an important factor to be considered when conservative surgery is planned because this variable is significantly associated with the risk of progression to invasive disease. In a recent study investigating clinical outcome after conservative surgery for stage II–IV serous BOT, the recurrence rate was 38% and, among recurrences, eight (6%) were invasive [23]. In another study on 59 women with advanced disease ($\geq$ IC FIGO stage), 33 (75%) patients were treated conservatively and the rate of recurrence was similar to those receiving radical treatment [27].

Conservative management may be an option also for patients with peritoneal implants if the implants can be entirely removed [28,29], while it should be used with more caution in the presence of invasive implants considering the aggressiveness of these lesions and the association with a poorer prognosis [29,30].

About 70% of recurrent lesions shows borderline histology and can be effectively cured by surgery without any impact on the long-term survival [6,28,31]. If technically feasible, conservative management thus represents a valuable alternative also in patients with recurrent BOT [32]. In all kind of BOT, malignant transformation to invasive ovarian cancer occurs in about 30% (29/74) of relapses (74/950), i.e. in 2.3% of cases [6]. However, in patients younger than 40 years who underwent conservative management that risk seems to be lower [7,25]. Tables 1a and 1b report patients' outcome in early and advanced stages BOT after fertility-sparing surgery [33–65].

Tailoring fertility-sparing surgical treatment

Overall, fertility-sparing management exposes women to a higher risk of recurrences. Clinical monitoring should be more intensive and a considerable proportion of women require additional surgeries. This situation may cause supplementary risks, more patients' stress and increased costs. Therefore, conservative management should always be carefully balanced and should not be thoroughly advocated exclusively based on women age. A comprehensive evaluation of the clinical situation and an in-depth counselling are mandatory. A shared decision should be reached.

Surprisingly, scanty attention to the evaluation of the fertility potential prior to an intervention for BOT is given in the literature. Fertility-sparing surgery in young women is commonly presented as a dogma rather than a therapeutic option to be tailored to the woman. In our opinion, conservative surgery should be mainly aimed at future pregnancies and should not be considered if the woman has already fulfilled her reproductive wishes or if future pregnancies are implausible (such as in women older than 40 and in those with infertility and concomitant compromised ovarian reserve prior to surgery). Prevention of early menopause and

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