Management, prognosis and reproductive outcomes of borderline ovarian tumor relapse during pregnancy: from diagnosis to potential treatment options

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Abstract

Background: fertility sparing surgery is the first option for treatment of childbearing age women affected by borderline ovarian tumor (BOT). This review put in evidence the benefits and the risks of conservative surgery procedure. Moreover, the literature review is aimed to analyze the possibility of fertility sparing surgery in BOTs and to define a standard treatment in the management of this pathology during pregnancy.

Methods: systematic analysis of the relevant literature for fertility sparing during pregnancy for BOT, accessed through MEDLINE (1982-2015), bibliographies, and interactions with investigators. The data were assimilated into a rigorous and objective contemporary description, enriched by prospective, controlled, and evidence-based studies.

Results: there are not many studies about BOT during pregnancy. It can reasonably assumed that after the diagnosis of a suspected BOT during the third trimester of pregnancy, an attitude of close surveillance could be adopted. To the best of our knowledge, we report the only case in literature focused about the treatment and management of borderline ovarian tumor relapse detected during pregnancy.

Conclusion: basing on our experience and on literature reported, the conservative management of BOT during gestation up to delivery could be considered feasible. The conservative debulking surgery should be performed at the time of cesarean section in a third referral center for gynecologic oncology.

Key words: borderline ovarian tumor, diagnostic ultrasound, prenatal diagnosis, fertility sparing surgery.

Introduction

The borderline ovarian tumor (BOT) is an epithelial tumor with low rate of growth and low potential to invade or metastasize (1, 2). The incidence is the 10-15% of all ovarian tumors (3, 4). In particular, BOTs are characterized by a specific proliferation pattern consisting of stratification of the epithelial lining of the papillae, nuclear atypia and mitotic activity, without stromal invasion (5). The 1987 International Federation of Gynecology and Obstetrics classification is commonly used for staging (6), basing on macro-
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...scopic description during the surgical procedure and revised by pathologist on the surgical specimens.

Stage I is defined as a tumor limited to one or both ovaries; stages II and III are defined by the presence of implants to pelvic (stage II) or abdominopelvic (stage III) peritoneal peritoneum. The presence of stromal invasion of the peritoneum classified the peritoneal implants as non invasive or invasive (7, 8).

BOTs are generally diagnosed at an earlier stage than malignant ovarian tumors. Because BOTs affect young women, the necessity of a conservative and minimally invasive surgery management is mandatory with the intent to preserve reproductive function (9).

Patients affected by early BOTs could be treated by laparoscopic approach, since all the surgical procedures (adnexectomy and hysterectomy) and staging (peritoneal biopsies, omentectomy, appendectomy in patients with mucinous tumors histotype, and eventual removal of pelvic and paraaortic lymph nodes) could be performed. Laparoscopic management seems feasible in early BOT (10-12). In any case, laparoscopic approach for treatment of adnexal masses has proved to be feasible and safe in diagnostic and therapeutic intent if performed by high experience laparoscopic surgeons (13). Guidelines for surgical treatment of BOT, in women not in childbearing age or who do not wish pregnancy, suggest to perform peritoneal cytology, hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and multiple peritoneal biopsies (14-17). Because BOTs affect more often younger women, fertility sparing surgery is an important issue for many of these patients. Previous studies have shown the feasibility and safety of fertility sparing surgery with unilateral salpingo-oophorectomy or cystectomy for patients with stage I BOT: in particular, this kind of approach is characterized by an excellent long-term survival (14, 18-20).

Laparoscopic cystectomy is considered favorable in preserving woman’s fertility compared with monolateral adnexectomy because more ovarian parenchyma is saved. However this procedure could increase the risk of inadvertently leaving malignant cells in the preserved ovarian tissue. Considering the risks, this procedure should be reserved only for patients already submitted to unilateral salpingo-oophorectomy or when bilateral lesions are detected in order to preserve as much as possible ovarian parenchyma (13). Conversely, when bilateral ovarian lesions are detected during chilbearing-age in motivated to preserve fertility function, the intraoperative surgical strategy is more complex. Before any surgical procedure, the ovarian masses should be carefully assessed. On one hand, it is advisable that the more suspicious mass, if present, should be removed; however at the same time assumes great importance to proceed with more conservative surgical procedure on the contralateral adnexal mass (ovarian cystectomy, if possible) after that the more suspicious ovary has been sent for frozen section analysis. If a borderline tumor diagnosis is confirmed, then either ovarian cystectomy or salpingo-oophorectomy should be performed on the contralateral side (7, 8, 21-23).

Methods

Systematic analysis of the most relevant literature for fertility sparing management during pregnancy for BOT, accessed through MEDLINE (1982-2015), bibliographies, and interactions with investigators.

Results

Darai et al. (26) published a series of 25 patients with BOTs treated by laparoscopy. Of them, 15 were managed with a fertility sparing treatment and 10 underwent radical treatment. Recurrences after cystectomy reported where three (30%). Twenty-three patients were alive and disease-free, one died for intercurrent and not related disease. These results suggested that laparoscopic surgery in BOTs is feasible in early stage disease, but it is associated with a higher risk of recurrence if only cystectomy then adnexectomy is performed (21).

Maneo et al. (27), compared laparoscopy and laparotomy approaches; they observed the risk related to the different surgical techniques in treatment of BOT-affected patients. Sixty-two patients had fertility-sparing surgery: 30 operated by laparoscopy and 32 by laparotomy. Intraoperative cyst spillage and ruptures were more frequent in the laparoscopic group. After a follow-up of 61 months for the laparoscopic group, they recorded that 11 patients (37%) had persistent disease after primary laparoscopy. After primary laparotomy procedures instead, no patients showed early persistence of tumor. Ovarian relapses were observed in seven women (22%) treated. Authors concluded that laparoscopic approach should be used for the treatment of BOTs with ovarian neoformations not larger than 5 cm (21). When fertility sparing surgery is requested, the entire affected ovary should be removed in presence of monolateral disease, while if the neoplasia is bilateral, monolateral or bilateral cystectomy should be performed. In any case, the patient should be informed that the cystectomy could expose her to an higher risk of relapse (21).
Morice et al. (28) reported in their study the higher proportion of patients (42.5%) with peritoneal implants (stage II or III disease). Among patients who had a fertility sparing surgery, 27% was at stage II or III disease. In patients with peritoneal spread, the abdominal location of implants (stage II or III) was less significant compared with their histological characteristics (invasive as non-invasive) in terms of prognosis (7, 8, 21).

In a study by Gershenson et al. (7), 39 patients had invasive BOTs peritoneal implants, of which 30% developed into progressive or recurrent disease. Considering this potential rate of progression, the conservative procedures in patients with invasive implants seem to be more dangerous (21).

In a series reported by Morice et al. (28) and Tazelaar et al. (19), they demonstrated that all patients that experienced BOTs recurrence, who initially received a fertility sparing surgery, had a very good prognosis. The relapses recorded in patients conservatively treated were never in form of invasive ovarian cancer. None of 10 patients with non-invasive peritoneal implants who were treated conservatively experienced invasive recurrence. All recurrences were diagnosed during routine follow-up procedures (clinical examination or pelvic ultrasound) and were treated by surgery (21). The only three patients who had poor outcome had initial radical surgery, and therefore cannot be considered a failure of conservative treatment (21, 28). Actually we can assume that even if fertility sparing surgery exposes the patient to higher risk of BOT recurrence, this occurrence could be treated by second surgery procedure and the overall survival is not deflected. Conservative treatment should therefore be considered safe only for treatment of young patients with BOTs who will comply with routine follow-up (21, 28).

Boran et al. (29) reported that recurrence after cystectomy and adnexectomy was 15 and 2.4%, respectively. They recommended unilateral oophorectomy in conservative treatment, because of the higher rate of recurrence after cystectomy.

In a French multicenter study of 358 women with BOT, 149 women underwent laparoscopy (30). Conservative treatment and cyst rupture were more frequent in the laparoscopic group than in the laparoscopy and laparotomy group. No difference in the recurrence rate was recorded between the groups, but a higher recurrence rate was observed after conservative treatment (21, 30). Considering these data, laparoscopic approach in BOTs surgery is clearly associated with a higher rate of intraoperative spillage and incomplete staging if not performed by experienced surgeons.

Seracchioli et al. (13) reported a series of 19 reproductive-age women; they suggested that a limited laparoscopic approach to the surgical management of BOT may be safe. In this series only one patient developed a recurrence. She had the recurrence in the same ovary after the previous enucleation of ovarian cyst for her initial tumor and subsequently treated with second cystectomy at recurrence. Six spontaneous physiological pregnancies were recorded (13). Lymph nodes dissection for staging is nowadays misused. In fact according to a recent study in 317 women with diagnosis of BOT (31), the evidence of incidence of retroperitoneal metastasis is very low (3.7%) as well as lymph node recurrence (0.4%) after a median follow-up exceeding 6 years. Therefore lymph node removal does not influence survival outcomes, in fact less than 1% of patients experienced lymphnode recurrences (32). At present, complete staging has not been shown to improve survival rate. In a study by Winter et al. (33), the overall 5-year survival and recurrence rates were similar with or without lymphadenectomy. The histology, than massive surgery, seems to influence more the disease free survival and the overall survival in those cases in which the tumor seems to be in early-stage. Serous micro-papillary tumors and micro-invasive tumors have been associated with poorer outcomes (34). The presence of peritoneal implants may be the most significant prognostic factor (35). To reduce the risk of recurrent contralateral lesions, the complete removal of the remaining ovary could be proposed to patients that are not confident with fertility sparing surgery (28, 36). The contralateral health ovarian tissue may be cryopreserved although is advisable to perform radical surgery. In this case after that women had completed their childbearing desire, in order to prevent the risk of contralateral ovarian relapse (28, 37). In fact, there are fewer recurrences if bilateral oophorectomy is performed (21, 37). Zanetta et al. (37), in their large series noted that the recurrence rate was 15.2% in contralateral sparing surgery and 2.5% in radical surgery for stage I disease, and 40% and 12.9% for stage II respectively. For these Authors is reasonable to propose to child-bearing-age women a fertility sparing surgery followed by radical surgery if a successful pregnancies happen.

The most recent review of Vasconcelos et al. (38) examines the optimal oncological approach of conservative surgery in unilateral BOT cystectomy versus unilateral salpingo-oophorectomy and in bilateral BOT (bilateral cystectomy versus unilateral salpingo-oophorectomy and contralateral cystectomy), as well as fertility outcomes. The Authors analysed 39 studies that included 5105 women (2624 serous BOT, 2120 mucinous BOT and the remaining with other types of BOT). 2752 of which underwent conservative surgery: in particular 817 underwent cystectomy, 89 bilateral cystectomy, 1686 unilateral salpingo-oophorectomy and 118 unilateral salpingo-oophorectomy and contralateral cystectomy. For patients undergoing cystectomy, bilateral cystectomy, unilateral salpingo-oophorectomy and unilateral salpingo-oophorectomy with contralateral cystectomy, recurrence rate was respectively 25.3, 25.6, 12.5 and 26.1%. In this meta-analysis, unilateral salpingo-oophorectomy was significantly favored compared with cystectomy with an OR for recurrence reduction=2200, 95% CI=0.793-2.841 and p<0.0001. The
pooled recurrence estimate as invasive ovarian cancer was 15.4% (38). They concluded that cystectomy in unilateral serous BOT is significantly associated with a higher recurrence rate but no impact on survival was demonstrated. These Authors advises surgeons to perform unilateral salpingo-oophorectomy in mucinous BOT. A conservative approach should be definitively favored in bilateral BOT, which is almost always serous, because no significant difference was seen in terms of recurrence rate when compared to unilateral salpingo-oophorectomy with contralateral cystectomy (38).

In literature there are few data regarding the incidence and the treatment of BOTs during pregnancy. The only paper about this topic is a French multicenter retrospective study of Fauvet et al. (39) on 40 patients that try to evaluate the characteristics of BOTs diagnosed during pregnancy and try to determine a therapeutic strategy. The incidence of BOTs in pregnancy ranging from 0 to 8%. BOTs detected during pregnancy have specific characteristics with a high frequency of advanced stage and patterns of aggressiveness. In fact, 20% of patients in this study was at FIGO stage II to III instead of not pregnant population in which 90% of BOTs is diagnosed at FIGO stage I (39). Histologic typing of BOTs in pregnant patients also revealed a high incidence of mucinous BOTs instead of serous BOTs, more common in non-pregnant population (48 vs 30%, respectively). 21% of mucinous BOTs had features of aggressiveness including intraepithelial carcinoma and microinvasion (39). Also serous BOTs had aggressive patterns with micropapillary features in 41.2%, frequently bilateral with invasive implants. This aggressiveness could be justified by the presence of estrogen and progesterone receptors on BOTs that are more triggered during pregnancy because of higher circulating hormones concentration (39). The importance of fertility sparing surgery in child bearing age women clashes with the possibility of recurrence and the surgical management in this particular time of a woman’s life like pregnancy.

**Borderline ovarian tumor recurrence during pregnancy: our experience**

We report the case of a 29-year-old woman affected by a BOT diagnosed accidentally during a caesarean section (CS) performed for term pregnancy in 2010. As standard protocol of the university hospital in which the case was reported, the patient was informed and signed a consent allowing data collection for research purposes. This case report is in accordance with the Helsinki Declaration, conforms to the Consensus-based Clinical Case Reporting Guideline Development (http://www.equator-network.org/), the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/) and was approved by the Institutional Review Board (IRB) of the university hospital in which it was reported.

During CS, bilateral ovarian cysts were accidentally discovered and the surgeons proceeded to remove them without the standard procedures for the staging of a gynecologic tumor (7, 8). Histological examination of the cysts deposited for a bilateral serous papillary BOT, with aspects of exophytic growth in the left cyst and endophytic growth in the right mass (FIGO staging IC). Fetal outcomes were within normal limits. Basing on the relevance of the tumor diagnosis, the patient was addressed at our Gynecologic Oncologic Division for the management of the case. Considering the young age of the patient and her desire to maintain fertility, a close follow-up was prescribed. The patient declined further surgical oncologic staging, as prescribed after CS. During the gynecological and ultrasound screening for oncologic follow-up, a suspected BOT recurrence of 5 cm in the left ovary was detected one year later the first surgery. After an accurate counseling with the patient, that at the time of diagnosis of the first recurrence was 30 years old, she decided to underwent laparoscopic conservative fertility sparing surgery. Thus, she underwent laparoscopic removal of left ovarian cysts, peritoneal washing and multiple staging biopsies of the peritoneum of paracolic gutters and omentum. During the procedure, the presence of 1 cm exofitic lesion in the Douglas peritoneum was found and removed. During cyst enucleation a minimum intraperitoneal spillage occurred. After procedure, about 80% of the left ovarian parenchyma was preserved. The histological examination confirmed the diagnosis of recurrent serous BOT in the left ovarian cyst. The peritoneal lesion of the Douglas was positive for non invasive implant of BOT.

The patient proceeded to strict oncologic follow-up. During this period, she had a spontaneous pregnancy. The pregnancy was managed by her private obstetrician with no evidence of disease relapse reported up to 30 weeks of gestation. During this period, it was found a rise in blood pressure measurements (mean values 150/100 mmHg) and a suspected fetal growth defect (estimated weight at the lower limits of the standard 10° percentile) and the presence of pathological proteinuria. The antihypertensive therapy was administered using alpha-methyl-dopa (250 mg/3 times daily). Home monitoring of blood pressure and periodically evaluation of the proteinuria was recommended. Subsequent weekly blood pressure check resulted under good control. During a routine obstetric ultrasound to monitor fetal wellness, a lesion suspected for recurrence of BOT in the right ovary was detected. The patient was sent to our Division and submitted to a third level pelvic ultrasound and Doppler scan that confirmed the suspicion of right ovarian recurrence. In particular, the scan finding was a multilocular lesion (>6 niches) of about 8 cm in the right ovary.

Because an optimal blood pressure control was not reached despite antihypertensive therapy and the reappearance of proteinuria at 38 weeks of gestation, the accomplishment of delivery was recom-
mended throw CS after induction of pulmonary maturity with corticosteroids (betamethasone 12 mg in two administration at 24 hours) according with international guidelines (40). Even if CS was performed for obstetric indication, during the same procedure, the oncologic surgical treatment was performed by gynecologic oncology team with the therapeutic intent of debulking. During the procedure the uterus appeared adherent to the anterior abdominal wall since the previous cesarean section. The surgeons proceeded to hysterotomy and extraction of fetus in cephalic presentation that was entrusted to the neonatology for specialized medical treatment. The placenta was sent for histological examination to evaluate the eventual presence of neoplastic embolism. After obstetric surgical procedure, the surgeon proceeded to externalization of uterus to better explore the abdominal cavity and pelvis. The pelvis was occupied by the right ovarian mass of about 8 cm with cystic polylobed consistency as a characteristics bunch of grapes. Because of the complete macroscopic transformation of the right ovary in neoplastic mass, the surgeon proceeded to right adnexectomy. During surgery a left paratubaric neofor- mation about 3 cm was discovered, suspected for secondary BOT localization, not reported by preoperative imaging investigations. The left ovary was reduced in size but macroscopically normal. Douglas and abdominal peritoneum explored were normal. The surgeons proceeded to removal of left paratubaric cluster formation and performed new peritoneal and omental biopsies. Fetal outcome was good even if the baby was a low birth weight (LBW) of 2400 g. Histological examination of the right ovarian mass of 8 cm and the paratubaric left neoformation of 3 cm confirmed the diagnose of serous BOT recurrence. The placenta was negative for neoplastic embolism at pathologic analysis. Peritoneal and omental biopsies were negative. Because of the histology of a second BOT recurrence and because the goal of procreation have been achieved, the patient, informed about the risks and benefits of the procedure, decided to underwent radical surgery, consisting of total hysterectomy, left adnexectomy and radicalization of omentectomy. The surgical procedure was performed laparoscopically using Robot Xi Da Vinci Intuitive® in our Division after about 6 months after the CS. During histologic examination of the specimens, a micro focus of serous BOT of about 2 mm in the residual right ovary was found. Currently the patient is in good health condition, she is under transdermal hormone replacement therapy (HRT) and undergoes regular clinical follow-up.

Conclusion

Our case is the only example reported in literature of treatment of BOT recurrence during pregnancy. Although there are no many studies about BOT during pregnancy, it can reasonably be assumed that after the diagnosis of a suspected BOT during the third trimester of pregnancy, an attitude of close surveillance could be adopted as could be supported by the study of Fauvet et al. (39). This pregnancy surveillance should be performed in a tertiary referral center, waiting for the end of pregnancy. The time and the procedure for completion of delivery are not established by the diagnosis of BOT in pregnancy unless there are no signs suspected for cancer transformation during examinations such us progressive enlargement of the tumor, the appearance of solid tissue and abnormal vascularization and the danger of ovarian torsion favored by mass dimension. According to the most updated literature, accumulating evidence suggests that the high rate of recurrence is thought to be due to remaining drug-resistant cells, biologically distinct, identified as cancer stem cells (CSC) (41).

In our experience, in fact the CS was performed for obstetric indication for preeclampsia that is present in 5% of pregnancy affected by BOTs (39). If delivery is spontaneously occurred or after an induced labor, cytoreduction with conservative or radical intent can be performed during the postnatal period. If a CS is indicated, it is advisable and feasible a concomitant debulking surgery and a conservative staging surgery awaiting the definitive histological diagnosis; in this way it could be avoided the risks of an hysterectomy during CS and gynecologist oncologists can perform a thorough counseling with the patient after the definitive histologic diagnosis. In all cases it is advisable that pregnancy and delivery with the next consensual or surgical treatment are carried out in a tertiary center specializing in gynecology oncology.

Declaration of interest

All Authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company. The Authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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