Oocytes cryopreservation in two women with borderline ovarian tumor recurrence.

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ABSTRACT

Borderline ovarian tumors (BOTs) commonly occur during reproductive years. Given the good prognosis, fertility-sparing surgery can be considered in young women wishing to preserve their fertility. However, conservative management exposes patients to the risk of recurrence. In these cases, the new surgery may be radical (completing the removal of both adnexa) or, when conservative, it may be associated to a relevant damage to the ovarian reserve. In this study, we report on two women who decided to perform ovarian hyper-stimulation and oocytes cryostorage at the time of the diagnosis of recurrence, but before undergoing the new surgery. They both obtained a satisfactory number of oocytes, the retrieval was unremarkable and no main detrimental effects on the ovarian lesions were noticed. These two cases suggest that ovarian hyper-stimulation and oocytes retrieval before planned surgery for BOT recurrence is a feasible option.

KEY WORDS: Borderline ovarian tumor; oocytes; fertility preservation

Introduction

Borderline ovarian tumors (BOTs) are peculiar epithelial ovarian neoplasms that commonly occur in young women [1,2]. Given their good prognosis, fertility-sparing surgery can be considered in young women wishing to preserve their fertility [3]. However, this approach exposes patients to the risk of recurrence [4,5]. According to a recent systematic review, this risk is about 13% (95%CI: 10-16%) [5].

In this scenario, we previously advocated fertility preservation after first surgery in order to store oocytes that could be used in case of recurrence requiring castrating surgery [3]. However, only a minority of affected women may benefit from this approach. Most women with a history of surgery for BOT conceives naturally [5]. In fact, a policy of systematic fertility preservation following first surgery would uselessly expose a consistent proportion of women to the risks of fertility preservation procedures and could cause a significant wastage of financial resources.

In this study, we propose a new strategy that was not previously foreseen. Specifically, given the impressive progresses of transvaginal ultrasound in properly detecting and diagnosing BOT recurrences [6], we suggest to cryopreserve oocytes only in case of recurrence and prior to undergo the new surgery. This innovative approach is herein illustrated with two successful cases.

Cases

Case 1 was a 24 years old nulliparous woman who had right cystectomy for serous BOT and a right adnexiectomy two years later for an ipsilateral recurrence. In November 2018, she was diagnosed with a left ovarian unilocular-solid cyst of 11 x 12 x 13 mm with two non vascularized papillae, the biggest of 4 x 7 x 4 mm, suggestive for BOT recurrence [6] (Figure 1). Fertility issues were

discussed and the patient requested for oocytes cryopreservation prior to undergo surgery. AMH was 1.0 ng/mL, Antral Follicle Count (AFC) was 12. She immediately started ovarian hyper-stimulation according to a random start protocol [7]. She concomitantly received Letrozole 5 mg daily. Fifteen mature oocytes were cryo-preserved, corresponding to a theoretical chance of live birth of 80-85% [8]. The retrieval was complete (all follicles could be aspirated) and uneventful. Transfixion or accidental aspiration of the cyst was avoided and the lesion appeared unchanged at the end of the procedure. In February 2019, preoperative ultrasound highlighted a unilocular-solid cyst of 19 x 16 x 20 mm with 3 papillae, the biggest of 10 x 11 x 11 mm. The woman underwent left ovarian cystectomy and peritoneal biopsies. Histology revealed a serous BOT relapse with no superficial infiltration. Peritoneal biopsies and cytology were both negative for malignancy.

Case 2 was a 30 years old nulliparous woman treated for a sero-mucinous BOT with a 6 mm area of invasive adenocarcinoma. She also had non-invasive peritoneal implants of seromucinous BOT and cytology was positive for malignancy. She had right oophorectomy and a definitive diagnosis of ovarian neoplasia stage IC G1 associated to BOT in May 2018. In November 2018, a left ovarian unilocular-solid cyst of 21 x 15 x 18 mm with ground glass content and a papilla of 9 x 5 x 11 mm with uncertain vascularization was detected, suggestive for BOT recurrence [5] (Figure 2). AMH was 0.4 ng/mL, AFC was 5. Fertility issues were discussed and the patient decided to cryopreserve oocytes. She was treated with three sequential random start hyper-stimulation cycles and concomitant Letrozole, consenting to overall freeze 14 mature oocytes (4 + 5 + 5), corresponding to a theoretical chance of live birth of 80% [8]. The retrievals were complete and uneventful in all cases. In all three attempts the general aspect of the lesion appeared unchanged at the end of the procedure. On March 2019, the cyst measured 28 x 30 x 31 mm with 3 papillae, the biggest of 4 x 9 x 6 mm. A laparoscopic cystectomy was performed. Histology confirmed a seromucinous BOT. Peritoneal biopsies and cytology were both negative for malignancy.

For both cases, the modifications in size of the lesions, i.e. the comparison between the dimension before and after the hyper-stimulation cycles, were within the 95%CI of the expected growths [9] (Figure 3).

Discussion

In both patients, ovarian hyper-stimulation was not associated with a clinically relevant acceleration of the growth of the ovarian lesions (Figure 2). In addition, no change could be detected in the general ultrasound appearance of these lesions. For case 2, the oocytes collection could have postponed surgery of some weeks because of the need to perform three cycles but the clinical relevance of this delay is doubtful. To note, in both cases, the lesion did not reach the threshold of 4 cm in diameter, a size above which expectant management is generally no more recommended [9]. Overall, the observed growth of the lesions is unlikely to be secondary to the hyper-stimulation and cannot be claimed to have modified prognosis and surgical management.

The presented approach exposed women to the risk of accidental puncture of the ovarian lesions or the need to transfix them to reach follicles that developed behind. This might cause the spread of pathologic cells, even inadvertently. However, our cases did not support these concerns. In both cases, transfixion of the lesions was not necessary and the subsequent surgical interventions that did not reveal peritoneal implants or presence of pathologic cells in the peritoneal fluids. Nonetheless, our findings have to be viewed as preliminary. Larger series with long term follow-up are needed for a definitive answer on the safety. In the meantime, we suggest that the oocytes retrieval is performed only by experienced physicians and recommend to avoid aspiration of follicles that require BOT transfixion to be reached.

The approach proposed in this study is rooted in a confident sonographic diagnosis of BOT recurrence. To note, all sonographic scans were done by two of the authors (F.F. and V.C.) with long-standing expertise and using a high quality instrument (GE Voluson E8 ultrasound system with a 5–9 MHz transvaginal transducer). In fact, transvaginal ultrasound is considered accurate for the diagnosis of BOT if performed in experienced hands [6]. Of relevance here is that the diagnosis of recurrences may be simpler compared to first diagnosis. Indeed, a recent study suggested that recurrent lesions typically mimic the morphological features of the primary tumor [9]. If confirmed in future and larger studies, this peculiar feature of BOT would clearly significantly simplify the diagnosis. In this regard, it has to be underlined that, in the reported cases, diagnosis could be particularly challenging for case 2 because this woman had an area of invasive adenocarcinoma at first surgery. In fact, sonographic features of the lesion were reassuring in this woman. There was no sonographic sign suggestive for invasive carcinoma and definitive histology confirmed the diagnosis of BOT without invasive areas. However, we have to acknowledge that utmost expertise and confidence in oncologic sonography was required in this case. In this regard, one has also to consider that change in ultrasound appearance and growth acceleration are not prognostic factors for subsequent (invasive) recurrences. More in general, we advocate referral to oncological centers with extensive experience and expertise in ultrasound if oocytes cryopreservation in cases of suspected BOT is foreseen.

The concomitant use of letrozole during ovarian hyper-stimulation lacks a robust scientific rational. The decision to prescribe this treatment was based on the principle of caution given that both estrogen and progesterone receptors are constitutively expressed in BOT lesions, in particular in serous histotypes [3]. However, whether these molecular findings justify *per se* the use of letrozole remains debatable, given in particular the absence of functional and epidemiological evidence.

More in general, there is the pressing need for more data on the safety of ovarian hyper-stimulation in women carrying BOTs. Our two reassuring cases are not sufficient for firm conclusions.

Performing oocytes cryopreservation only in case of recurrence has the considerable advantage of limiting the number of women to be treated. To note, even if performing controlled ovarian hyper-stimulation after surgery for BOT was not shown to increase the risk of relapse [3,5], the procedure of oocytes retrieval is associated to the rare but clinically relevant risks of hemorrhage, infection, adnexal torsion and ovarian hyper-stimulation syndrome (OHSS) [10,11]. In addition, the costs of the gonadotropins for ovarian hyper-stimulation, of the procedure of oocytes retrieval and of the cryostorage are not negligible [12]. These risks and costs have to be balanced with the observation that only a minority of women operated for BOT subsequently face a recurrence and that more than half of them achieves a natural pregnancy after treatment [5]. Overall, performing oocytes retrieval for fertility preservation only in women with a recurrence may be clinically wiser and more cost-beneficial. In this regard, one should acknowledge that a new fertility sparing surgery was still possible in both described cases, thus preserving the chance of natural conception and potentially hinder the interest of egg storage. Both cases were treated very recently and none is currently attempting to become pregnant. Therefore, we cannot provide useful information on this point. On the other hand, one should also consider the additional damage to the ovarian reserve caused by the new surgery and the possible detrimental effects on natural fertility of the pelvic adhesions that typically develop after repeated surgeries [13].

In conclusion, oocytes cryopreservation at the time of recurrence of BOT is feasible and may be considered in the decision-making process with the patients. Further evidence is however needed to draw conclusions on the safety and the cost-beneficial profile of this approach.

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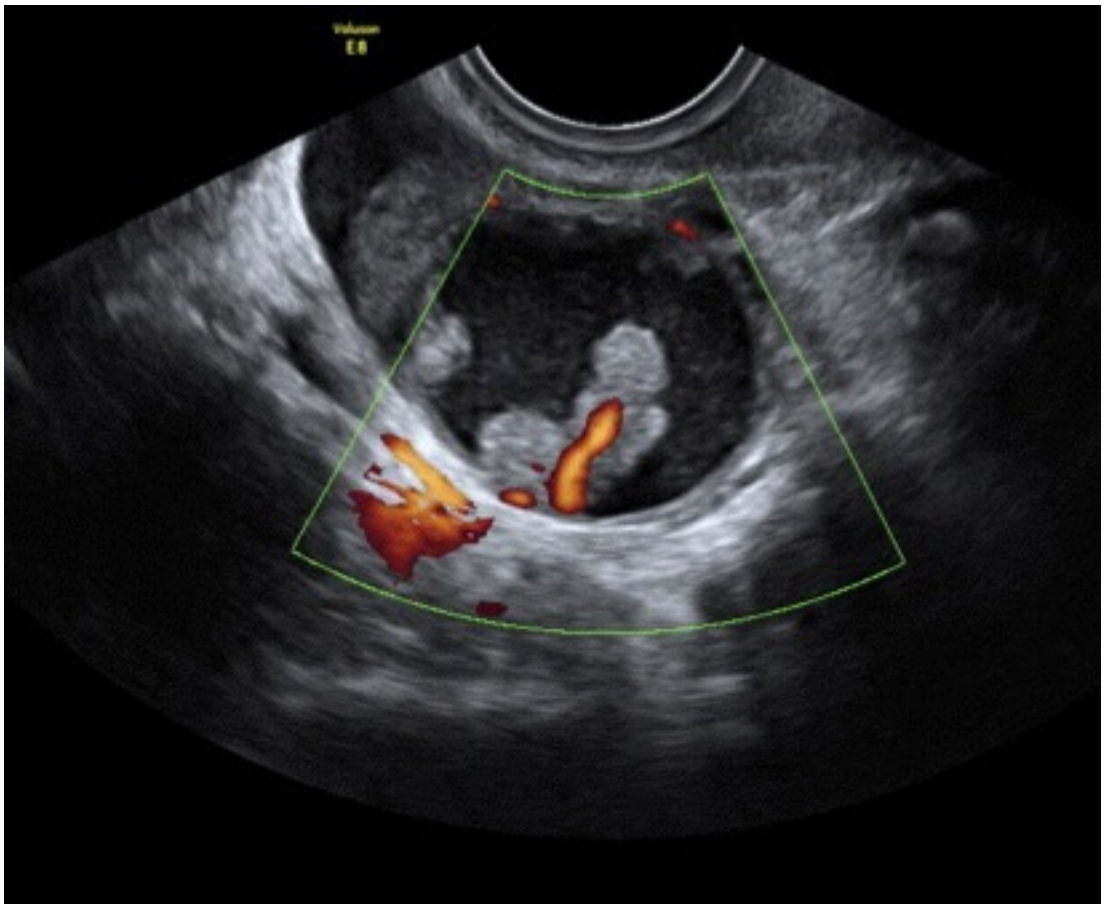
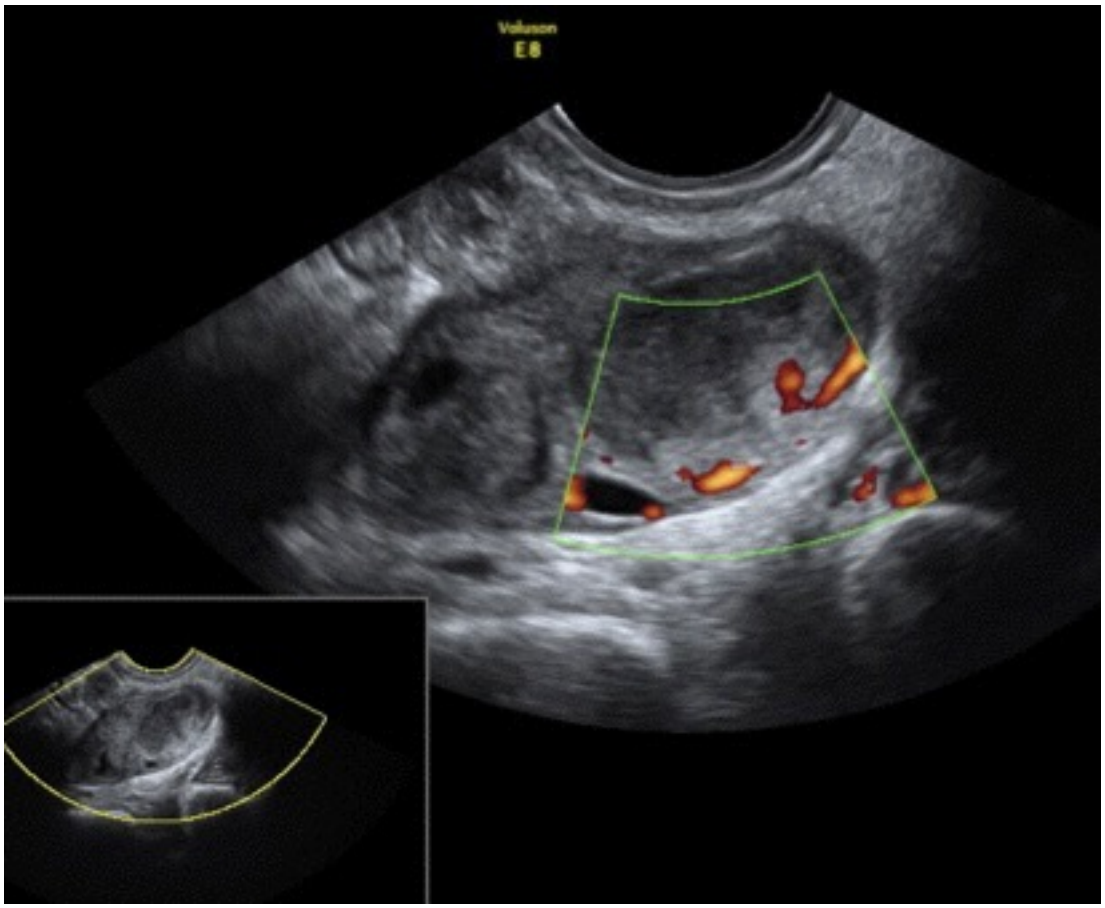
Figure legends

Figure 1 Transvaginal ultrasound findings prior to initiate ovarian hyper-stimulation. Case 1 is illustrated. The mean diameter of the unilocular lesion was 12 mm. Color score was 1. Two non vascularized papillae, the biggest of 4 x 7 x 4 mm, were visualized.

Figure 2 Transvaginal ultrasound findings prior to initiate ovarian hyper-stimulation. Case 2 is illustrated. A unilocular solid cyst with a mean diameter of 18 mm with ground glass content and a color score of 1 was documented. The lesion was also characterized by an internal non vascularized papilla of 9 x 5 x 11 mm.

Figure 3 Lesion growth during ovarian hyper-stimulation. Cases 1 and 2 are represented in red (*upper panel*) and blue (*lower panel*), respectively. The arrows represent the time points of ovarian hyper-stimulation (one for case 1 and three for case 2). The straight lines represent the observed growth. The dotted lines and the included colored areas represent the 95%CI of the predicted growth of the lesions in the corresponding period of time (3.7 months for case 1, 3.9 months for case 2). These estimates of growth were obtained applying the predictive model of Franchi *et al*. [8]. The observed growth was well within the range of the predictive growth for case 1, whereas, for case 2, the growth was at the superior limit of the 95%CI.

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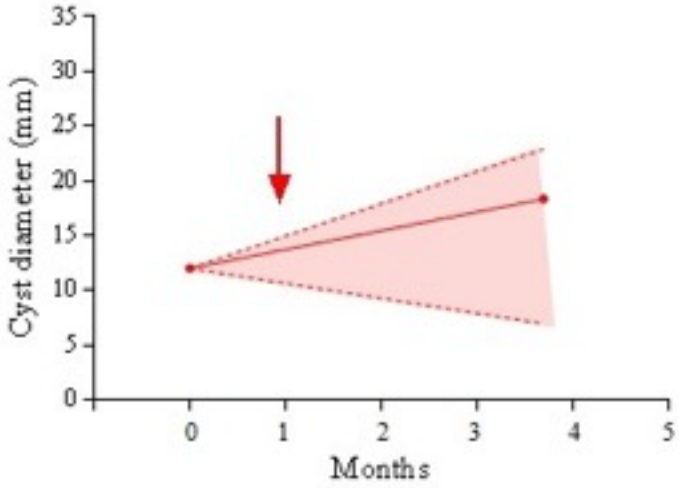
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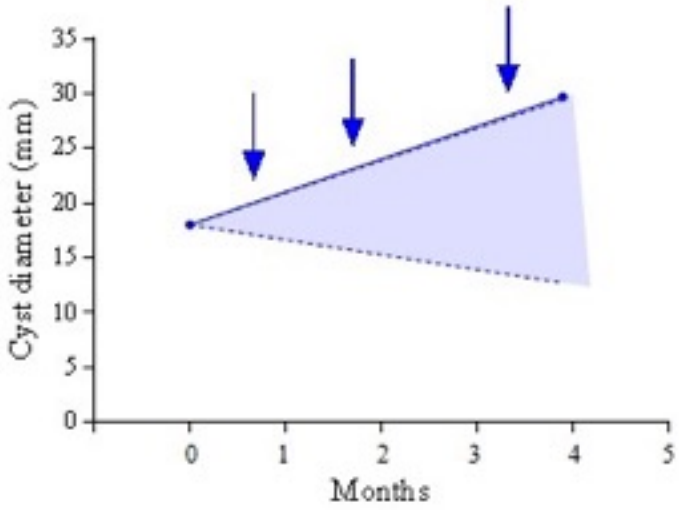
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