Fertility preservation in patients with borderline ovarian tumors

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Borderline ovarian tumors (BOTs) account for 10–20% of all ovarian epithelial tumors. They are characterized by low-grade malignancy and rarely metastasize, but occur bilaterally in 15–40% of patients (1, 2). BOTs are usually diagnosed at an early stage and have an excellent prognosis. However, in some individuals (2–4% of cases), they can become more aggressive, considerably worsening the prognosis. Patients are typically 45 years of age at diagnosis, but in one-third of cases, they are under 40 years and therefore potential candidates for fertility-sparing surgery (2, 3).

The gold standard treatment for BOT patients is radical surgery with bilateral salpingo-oophorectomy, but conservative surgery, either unilateral salpingo-oophorectomy or cystectomy, can be performed to preserve fertility in the youngest patients (3, 4). Although the risk of recurrence after unilateral salpingo-oophorectomy is higher than after radical surgery (0–25% versus 0–5%) (2, 3), and even more so in case of cystectomy (5, 6), relapses are almost always of BOT histology and can be safely managed with repeat surgery (7). Indeed, the disease may recur contralaterally on the spared ovary, or involve both ovaries, requiring radical surgery as a second intervention (2), but recurrence appears to have no demonstrable impact on survival (1, 8).

In young patients who have yet to consider future childbearing, fertility preservation is of even greater importance. While spontaneous conception is achieved in more than 75% of women after conservative management (2, 6), oocyte or embryo cryopreservation and ovarian tissue cryopreservation (OTC) are viable options for patients who do not wish to conceive immediately (9, 10). OTC has proved to be a valuable strategy in prepubertal patients and those who cannot delay anticancer treatment. Autologous transplantation of frozen-thawed ovarian fragments onto the remaining ovary or inside a specially created peritoneal pocket has resulted in more than 130 live births worldwide, with success rates in the region of 40% (11).

However, safety issues surrounding reimplantation of ovarian tissue from cancer patients have been a bone of contention for many years. Various studies have analyzed the risk of reintroducing malignant cells upon frozen-thawed ovarian tissue transplantation, which could induce recurrence of the primary tumor. The presence of malignant cells in ovarian tissue has indeed been established in leukemia patients, and the risk of reintroducing malignant cells

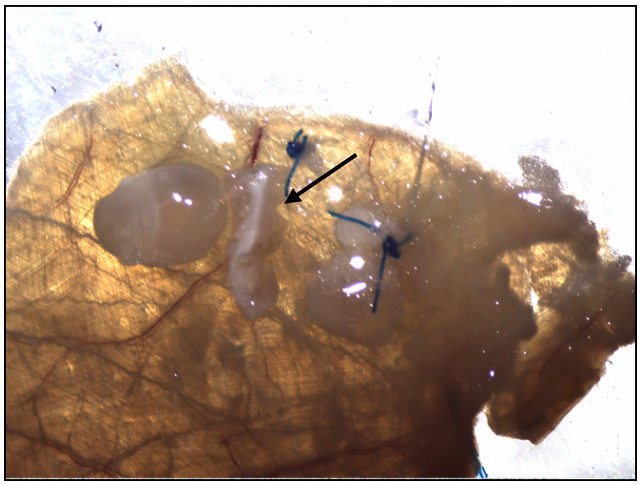
upon grafting demonstrated, rendering reimplantation of ovarian tissue from leukemia patients unsafe (12, 13).

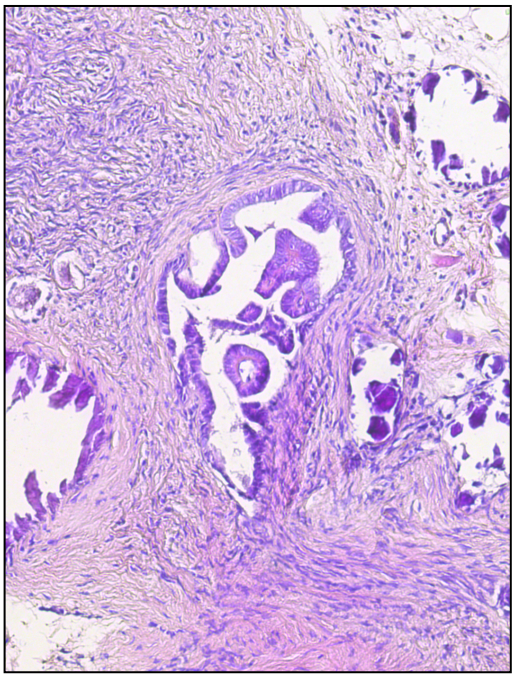
Similar concerns about safety have also been raised in case of ovarian tissue reimplantation in BOT patients for two main reasons:
1)BOTs are tumors that arise from the very same organ that will later be preserved for reimplantation, thereby increasing the chances of cryopreserving premalignant cells together with the tissue.
2)BOTs present as bilateral disease in up to 40% of cases already at diagnosis, and recurrence on the contralateral ovary is commonly observed after unilateral adnexectomy, indicating the presence of microscopically occult BOT cells in an ovary originally thought to be healthy at diagnosis.

For these reasons, the risk of reintroducing malignant cells in BOT patients was evaluated in 2017, with the findings of this experimental study subsequently published in Human Reproduction (14). Minimal residual disease in frozen-thawed ovarian tissue from women with BOTs was invesigated by immunohistochemistry, quantitative reverse transcription polymerase chain reaction and long-term (5 months) xenografting to immunodeficient mice using disease-specific molecular markers (cytokeratin 7 and mucin 1). This panel of tests, involving sensitive and specific techniques, revealed BOT cells able to survive after transplantation in the cryopreserved ovarian tissue of 1 of 11 patients (9.1%, Figure 1). This study thus proves that preimplantation analysis is a fundamental prerequisite before ovarian tissue transplantation and, in case of positive results, the procedure should be discouraged.
Concerning ovarian cancer, the literature reports four cases of OTC and subsequent transplantation in ovarian cancer patients (15-18). Successful pregnancies and live births were obtained in three patients, while in one woman, hormonal activity never resumed after ovarian tissue transplantation. Cancer relapse occurred in one patient (16) who underwent oophorectomy for a granulosa cell tumor and, concomitantly, prophylactic removal of the contralateral ovary for ovarian tissue cryopreservation. Nine years later, reimplantation of the tissue was requested and performed. After low-dose stimulation and in vitro fertilization, two embryos were transferred, ultimately leading to the birth of healthy twins. During the elective cesarean section, macroscopic tumor dissemination was detected at the level of the diaphragm and peritoneum, but not in the graft sites.

To conclude, excluding the development of new BOTs or ovarian cancer from reimplanted ovarian tissue is not 100% possible. For this reason, patients with BOTs or ovarian cancer seeking to achieve motherhood by means of ovarian tissue transplantation could undergo laparoscopic removal of their grafted tissue after pregnancy, in order to prevent disease recurrence or de novo development.

Figure 1: Ovarian tissue (arrow) from a BOT patient after long-term xenografting to mice (left); BOT lesion in ovarian tissue (right).





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