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Mini-Review

Reproductive Options in Ovarian Tumours

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Abstract

Fertility preservation has emerged as a crucial theme for oncologic patients due to improving survival rates. Nowadays, both Oncology and Reproductive Medicine societies recommend informing all reproductive-aged cancer patients about potential fertility loss and an early referral to infertility specialists. Ovarian tumours are particularly challenging as they affect the organ to be preserved. Fertility preservation techniques like oocyte-freezing and ovarian tissue cryopreservation can be considered. Shared decision-making involving comprehensive risk-benefit discussions, in a multidisciplinary setting, is imperative for personalized approaches to fertility preservation. In conclusion, proactive fertility preservation counselling and tailored strategies, considering tumour characteristics and patient preferences are vital for optimizing outcomes in women with ovarian tumours.

Keywords

Ovarian neoplasms; fertility preservation; fertility sparing surgery; ovarian tissue cryopreservation; oocyte-freezing.

Introduction

Due to increasing survival rates in oncologic patients, fertility preservation (FP) has now become a relevant topic. The American Society of Clinical Oncology (ASCO) guideline states that all cancer patients of reproductive age - pre-pubertal girls and fertile-age women - whose oncologic treatment might harm their reproductive potential, should be referred to an infertility specialist as early as possible [1].

Ovarian tumours are, among all gynaecological cancers, the ones who raise more questions, considering that the damaged organ is the same one to be preserved. Regardless of the histological type or prognosis, all the available treatments for ovarian neoplasms, from surgery to chemotherapy, can harm a woman's fertility.

As far as surgery is concerned, generally, in low-stage tumours, it is recommended to conduce a fertility sparing surgery (FSS) with the purpose of preserving fertility [2]. Most of the literature reports encouraging pregnancy rates, after this type of surgery, in women with ovarian tumours [3,4,5], with discrepant results in epithelial tumours, as live-birth rates vary from 13% to 96% [6,7]. However, in any case, to perform FSS, an appropriate surgical staging and adequate and regular follow-up is warranted.

Nearly 1/3 of the patients diagnosed with borderline ovarian tumours are under 40 years old. A FSS should be considered in these cases – cystectomy or unilateral adnexectomy (if serous or mucinous subtype, respectively) plus peritoneal staging [8]. The 5-year survival rate with this approach seems to be the same as with radical surgery. Even considering that some data point out higher recurrence rates in FSS, according to European Society for

Medical Oncology (ESMO) guidelines, even in stage II and III, FSS should be considered [9].

Germ cell tumours are the most common ovarian tumours in preadolescent girls, but only contribute to 5% of all ovarian cancers [10]. The FSS consists of unilateral adnexectomy, with complete surgical staging (examination of the omentum and ganglia and resection, if needed, plus peritoneal washing) [11]. According to the literature, although there aren't many studies in advanced stages, this surgery might be considered in any stage, as both recurrence and global survival rates match radical surgery ones [12]. This might be explained given the high chemosensitivity of these tumours. A recent systematic review describes an 8,7% recurrence risk, regardless of tumour stage, if conservative surgery is done in germ-cell tumours [13].

In sex cord-stromal neoplasms, a unilateral adnexectomy might also be offered, while the need for lymphadenectomy is still controversial. FSS is recommended in stage IA, and according to some authors, also in stage IC [2].

From all the malignant epithelial tumours, only 10% occur in women under age 40. Unilateral adnexectomy and complete surgical staging is advisable in stage IA, low-grade tumours, in serous, endometrioid and mucinous expansile subtypes [9]. According to National Comprehensive Cancer Network (NCCN) guidelines, it can be offered in stage I and low-grade epithelial tumours, as recurrence and survival rates are similar to radical surgery [2]. A recent systematic review recommends bilateral adnexectomy, with eventual preservation of the uterus in IA high grade, IC1 and IC2 [8].

Even if FSS is decided, to increase these women's chances ofachieving their reproductive desire, they should be referred to a reproductive-counselling appointment to discuss FP options. The most common FP techniques are oocyte-freezing and ovarian tissue cryopreservation (OTC). The live-birth rate for each cryopreserved egg is 3 to 6% and nearly 30% after cryopreserved ovarian tissue transplantation (OTT) [12]. This last technique also allows endocrine function to be restored in nearly 90% of cases [12,13,14].

As far as oocyte-freezing is concerned, although it cannot be used in pre-pubertal girls, this technique promotes woman's reproductive autonomy, with less ethical and religious questions than other possible methods, and – particularly important in ovarian and hematologic cancer – with no risk of reintroducing malignant cells in the body. Some of the limitations that were associated with oocyte freezing have been overcome thanks to new strategies. Nowadays, with random-start ovarian stimulation protocols, there is no need to delay any oncological treatment longer than two weeks – the time needed from stimulation to follicular function. In estrogen-dependent tumours, stimulation with letrozole might be a safe option, with similar effectiveness. Ex-vivo follicular punction may also be done, but with lower rates of success. This approach implies an optimal coordination between oophorectomy and follicular puncture, to avoid meiotic disruption caused by temperature variation and ischemia. However, it should be considered that women with ovarian tumours seem to have a lower response to ovarian stimulation, with a lower oocyte yield, compared to other tumours [15]. In the literature, there are some reports of live birth after oocyte freezing in ovarian tumours [16,17,18].

The effectiveness of OTC with subsequent grafting was acknowledged by the American Society for Reproductive Medicine, considering it as a safe and clinically accepted technique in 2019 [19].

Among of the advantages of OTT are the fact that it is the only technique available for pre-pubertal girls, there is no need to delay any oncological treatment, doesn't require hormonal stimulation, and might restore both endocrine function and follicular activity, allowing posterior spontaneous pregnancies.

The first live birth after OTT, with OTC in 1997 due to a Hodgkins Lymphoma, was published in 2004 [20].

A successful case of a woman undergoing iatrogenic menopause after treatment for a stage IIIb squamous cell carcinoma of the cervix, with OTT into the forearm was published in 2003 [21]. Subsequent confirmation of endocrine function and follicular activity was described. Nowadays, fragments of ovarian cortex are transplanted via abdominal surgery into the remaining ovary (orthotopic transplant) or into a peritoneal pouch (heterotopic transplant) in the adnexal region.

According to the literature, the main factor conditioning the success of OTT is the number of primordial follicles in the fragments, bearing in mind that 50 to 90% degenerate following the ischaemia that occurs after transplantation and before revascularisation. A recent systematic review found no significant differences in transplantation outcomes (time of ovarian function's restoration and pregnancy rate) regarding the size of ovarian tissue grafts [22].

The literature regarding FP techniques in women with ovarian cancer is scarce. The largest cohort with OTT in ovarian tumours includes 10 cases of OTC in ovarian malignant tumours and from 29 cases in germ cell and borderline tumours. Of these 39, posterior ovarian cortex transplantation was done in five women, one case in a malignant tumour and four in germ cell and borderline tumours. There were no recurrences, and the overall pregnancy rate was 18,4% in all patients (n=399), with no specific data on women with ovarian tumours [23].

The largest cohort, with a detailed description on histologic

type and pregnancy rates, concerning OTT in ovarian cancer is form a French European Society of Gynaecological Oncology certified centre. Nearly 45% of the cases were malignant (19/43) and FP techniques were not advisable in only five cases. Cryopreservation was done in 25 women, 19 performing oocyte-freezing and 5 OTC. Oocyte freezing was offered after surgery, with an average time after surgery of five months. Nearly half of women had more than 10 oocytes yield. No OTT was performed so far. The pregnancy rate in this population of women wishing to conceive was 80%. In 38 women, there were nine pregnancies and four live births, two of them occurred spontaneously. There were no recurrences in women with malignant tumours. In 20% of women with borderline tumours submitted to ovarian stimulation the tumour has recurred. However, the literature described no contraindication in hormonal stimulation in borderline tumours [24].

The most controversial issue in OTT is the possibility of reintroducing neoplastic cells in some tumours, namely, in ovarian cancer. According to the literature, a higher risk of implantation of malignant cells and, therefore, tumour recurrence, after OTT might be seen in leukaemia, Burkitt's lymphoma and neuroblastoma, so cryopreservation is contraindicated. As far as ovarian contralateral tumours or borderline tumours are concerned, the reported risk is between 0,2 and 11%, so, even if highly controversial, some authors are in favour of OTT in benign and borderline ovarian tumours and in selected cases of ovarian carcinoma IA. OTT remains contraindicated in women with BRCA mutations.

To decrease the risk of re-implantation of malignant cells, some strategies might be considered. The analysis of part of the cortex of the fragments to be cryopreserved and their entire ovarian medulla by histopathology, immunohistochemistry and, if possible, the exclusion of the presence of tumour-specific molecular markers are fundamental. Moreover, two techniques are being studied: in vitro follicular maturation – which enables the use of the primordial follicles present in the ovarian fragments – with research going on to find the best growing matrix; and the artificial ovary – introducing primordial follicles into a decellularized tissue matrix – which has been successful in rodents, with the restoration of endocrine function, follicular activity and even live births [24].

It is therefore considered pertinent to encourage cryopreservation of normal ovarian cortex in children and women of childbearing age with ovarian tumours, with the goal of a safer use in a few years. However, every decision regarding these techniques should be shared with the patient, with all the risks and benefits comprehensively explained.

Conclusion

Clinicians should refer all pre-pubertal girls and women of reproductive age with ovarian tumours who have not completed their reproductive project, to a reproductive counselling appointment. The decision regarding the use of FP methods should be shared, with all risks and benefits explained in a multidisciplinary setting discussing pros and cons and choosing the best approach to each patient situation and needs. The approach should be personalised according to the tumour's histological type, stage, suggested oncological treatment and ovarian reserve. Considering the pregnancy rates, recurrence risk and survival rates after FSS in ovarian cancer, it is worthy to provide this type of surgery in low-stage ovarian cancer, if adequate staging and follow-up are guaranteed. As far as FP methods are concerned, OTT has promising results in several tumours, but more data and strategies are needed to increase the safety in women with ovarian cancer.

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