Experience of the “Prof. Dr. Panait Sarbu” Hospital in Oncofertility among Breast Cancer Patients

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Rezumat

Experiența clinicii “Prof. Dr. Panait Sârbu” în oncofertilitate, în rândul pacienților diagnosticate cu cancer mamar

Introducere: Oncofertilitatea reprezintă un nou domeniu, dedicat pacienților aflați la vârstă fertilă care sunt diagnosticați cu o patologie neoplazică și care doresc să își completeze familia, după ce se depășește etapa de tratamente oncologice și proceduri chirurgicale. Având în vedere metodele noi de screening și tratament, majoritatea pacienților oncologici reușesc să supraviețuiască bolii, infertilitatea rămânând însă principalul efect secundar, pe termen lung al tratamentului. Paciente diagnosticate cu cancer mamar sunt candidate pentru preservarea fertilității, având în vedere asocierea agenților alchilanți în schema de chimioterapie. Aceștia cauzează infertilitate dependentă de doză, depleție foliculară, distrucție ovocitară, fibroză la nivelul corticalei ovariene și afectarea vascularizației ovarului (1). Spitalul “Prof. Dr. Panait Sârbu”, în cadrul proiectului “Newborn – Oncofertilitate”, este primul spital din România care efectuează proceduri de preservare a fertilității la pacienții oncologici.

Material și Metode: În cadrul programului “Newborn - Oncofertilitate” s-a adresat spitalului în scopul preservării fertilității un număr de 21 pacienți, dintre care 5 paciente diagnosticate cu neoplasm mamar. Medicii din cadrul spitalului, specializați în reproducere umană asistată au efectuat procedurile de preservare a fertilității, respectiv stimularea ovariană și prelevarea ovocitelor; ulterior materialul genetic a fost crioprezervat. Procedura a putut fi realizată în cadrul programului doar dacă pacientele au avut vârsta sub 35 ani, cazul a fost discutat anterior în cadrul comisiei oncologice și pacienta a primit avizul medicului oncolog.

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Discuții: S-a observat o predominanță a cazurilor de cancer mamar în rândul pacientelor care s-au adresat clinicii pentru preservarea fertilității. Pacientele care au corespuns condițiilor de înrolare în cadrul programului au urmat procedura de preservare a fertilității fără a fi întârziată începerea tratamentelor oncologice sau chirurgicale. Nu au existat reacții adverse pe durata stimulării ovariene. Materialul genetic a fost congelat prin metoda de vitrificare.

Cuvinte cheie: oncofertilitate, neoplasm mamar, crioprezervare, fertilitate

Abstract

Introduction: Oncofertility represents a new field, dedicated to patients at childbearing age who are diagnosed with a neoplastic disease and who want to have a biologic child after they complete the oncological and surgical treatment. Because of new screening and treatment methods, most patients survive the disease, but the main long-term complication remains infertility. Young women with breast cancer are candidates for preserving their fertility mostly because of the risk of chemotherapy-related infertility due to the alkylating agent, causing dose-dependent destruction of oocytes and follicular depletion and thus bringing cortical fibrosis and ovarian blood-vessel damage (1). “Prof. Dr. Panait Sârbu” hospital is the first medical facility in Romania which performs oncofertility procedures among breast cancer patients within the program “Newborn – Oncofertility”.

Material and Methods: Within the program run by our hospital 21 patients (13 men and 8 women) came for fertility preservation, including 5 patients diagnosed with breast cancer. Our specialists in reproductive medicine performed ovarian stimulation and oocyte pick-up, after which the genetic material was cryopreserved. The procedure could be performed only if the patients were under 35 years old, and provided the case had been previously discussed within the tumor board and the patient had received the oncological agreement.

Discussion: There was a slight predominance of breast cancer patients who addressed the clinic with a view for preserving their fertility and those who met the conditions could start the procedure immediately, without any delay when it comes to oncological or surgical treatments. There were no side effects during ovarian stimulation treatment. Oocytes or embryos were cryopreserved using the method of vitrification.

Key words: oncofertility, breast cancer, cryopreservation, fertility

Introduction

“Prof. Dr. Panait Sârbu” Hospital is the first state hospital in Romania which provided an oncofertility support, within the program carried out in collaboration with ASSMB, between November 2018 and October 2020. Thus, it is the only institution to have this kind of experience. The majority of the patients who address for preserving their fertility have been previously diagnosed with breast cancer.

The optimal oncofertility care for young female cancer patients is described in several evidence-based national and international clinical practice guidelines (2-5). Because

many of methods of preserving fertility are still considered experimental, the only method we applied was ovarian stimulation with oocyte or embryos cryopreservation.

The main reason for infertility in breast cancer patients is the need for chemotherapy, which include an alkylating agent such as busulfan, cisplatin, cyclophosphamide, ifosfamide and melphalan. The dosage and treatment duration also impact the patient's fertility but the age remains a significant factor. Fertility in younger women, who have a larger pool of follicles, may be able to withstand stronger doses and longer treatment durations when compared to older women.

Guidelines recommend that the oncologist should discuss the potential loss of fertility with all female cancer patients and, if desired, offer a referral to and counselling by a fertility specialist. Information about fertility loss related to cancer treatment should be provided, regardless of a female cancer patient's reproductive age, parity, disease type or severity (5). Those who survive without losing their fertility will not be able to attempt pregnancy in the short run either, because they will have to receive continuous tamoxifen therapy for up to 5 years, who does not appear to have permanent effects on fertility but is teratogenic and must be held before and during pregnancy, or because of the uncertainty regarding the safety of pregnancy shortly after the breast cancer is diagnosed. By the time these patients are allowed to attempt pregnancy, many more of them will be in premature menopause or suffer from infertility because of further diminishing of ovarian reserve with aging. After that, the patient decides whether she wants to undergo fertility preservation methods, if there is no oncological contraindication.

Material and Methods

Between November 2018 – October 2020 five patients with breast cancer addressed to our human reproductive departament in order to preserve fertility. The organisation of patients in categories can be seen in *Table 1*.

Initially, all patients had a first consultation with one of our fertility specialists, discussed the possibility of fertility preservation, of a gynecological exam as well as of an endovaginal ultrasonography. All patients needed oncological approval and paraclinical investigation before starting the treatment.

The primary paraclinical investigations were:

- Complete blood count, coagulation panel, basic metabolic panel, thyroid panel, D-dimers, hepatitis, sifilis and HIV panel, smear test and vaginal swabs test.
- Serum estradiol, progesteron and LH levels before starting the stimulation, in the fifth day of treatment and at the time of trigger shot for oocyte maturation.

Depending on the hormone levels and follicle sizes, we scheduled visits every 4-5 days, until the day of hCG or GnRH agonist trigger administration. We started the stimulation independent of the menstrual cycle phase, within 2-3 days of the initial consultation, without any delay in oncological treatment.

Ovarian stimulation treatment was done with gonadotropins, the dose was adjusted based on the patients's age, body mass index and ovarian reserve, estimated by antral follicle count.

The main substances used in treatment were:

- gonadotropins;
- GnRH antagonist;
- aromatase inhibitor;
- hCG or GnRH agonist for oocyte maturation;
- we often associated anticoagulants also, because of the hipercoagulopathy status that exists in oncological patients and especially during stimulation therapy, therefore this population is more likely to require therapeutic anticoagulation during ovarian stimulation. We prescribed low molecular weight heparin, daily, last dose was administered 16-18 hours prior to oocyte pick-up and resumed 12 hours after the procedure.

The average duration of stimulation therapy was 10 days, till the largest ovarian follicles (leading follicles) reached at least 18 mm in diameter by ultrasound examination.

Table 1. Patients with breast cancer who underwent oncofertility procedure in our hospital

Age	Previous birth	BRCA mutation	Days of stimulation	Number of oocytes retrieved	Cryopreserved material	Familiar cancer
33	No	Neg	11	20	14 embryos	Yes
21	No	Neg	9	5	5 oocytes	Yes
33	No	Unknown	9	10	10 oocytes	Yes
32	No	Unknown	10	6	2 embryos	No
33	No	Neg	13	4	4 oocytes	Yes

The final maturation was triggered with hCG (6500 UI), dual trigger or with GnRH agonist alone (triptorelinum, 0,1-0,3 mg) if the patient was at risk of ovarian hyperstimulation syndrome. Oocyte retrieval was done under transvaginal ultrasound guidance 36 hours after final maturation induction.

In the embryology laboratory after stripping the cumulus cells, the oocyte cryo-preservation was done on the same day. For embryos cryo-preservation, intracytoplasmic sperm injection (ICSI) was performed. The embryos were cryopreserved on day 5.

Discussions

Independent of the type of ovarian stimulation treatment, all patients received an aromatase inhibitor, letrozole (2.5 or 5 mg/ daily, depending of the ovarian reserve), because a high estrogen level is not considered safe for breast cancer patients and because estradiol levels can exceed 2,500-3000 pg/mL during stimulation, which is 10 times higher than peak levels of estrogen in a natural cycle. Estradiol's levels have been found to be even lower than in natural cycle (6), an important target, especially in estrogen sensitive breast cancer. Letrozole was continued during the whole period of stimulation. Therefore we have hypothesized that it can be safely used in patients with breast carcinoma undergoing fertility preservation. The use of letrozole did not affect the length of stimulation or the total gonadotropin doses (7). In patients who developed allergic reaction to letrozole, anastrozole can be used, but it has been shown to be inferior to letrozole in inhibiting aromatase activity. Moreover, letrozole may require 2 days before reaching to a significantly aromatase inhibition level, anastrozole requires 2 weeks. Therefore, specialist's advice is to start letrozole before administration of rFSH (8). Also, restart letrozole administration after the oocyte retrieval and keep it until the estradiol level is less than 50 pg/mL. Letrozole results in increased ovarian androgen levels, which

may have positive effects on early follicular growth (9). Recommendation is to use aromatase inhibitor even in estrogen negative receptor patients (10).

Because there is an urgent need to start cancer treatment, we applied a random-start protocol of stimulation, where a patient can be stimulated regardless of the menstrual cycle phase, which allows patients to initiate cancer treatment 2 weeks after first presentation for fertility preservation. Studies comparing stimulation in oncology patients with follicular to luteal phase starts revealed similar number of oocytes obtained (11). Usually random-start protocol requires a longer length of ovarian stimulation and a higher doses of gonadotropin used (7).

High frequency of pathogenic mutations BRCA 1 or 2 genes in young females diagnosed with breast cancer should be taken into consideration, according to childbearing before prophylactic oophorectomy. Women with BRCA mutation have poorer stimulation cycle outcomes with higher dose of gonadotropins, lower number of oocyte and embryo yield, they lose ovarian reserve faster and accumulate more DNA damage (12). Because DNA repair declines with age, oocytes accumulation of genetic damage increase with age. Here's why women with BRCA mutation are more likely to lose ovarian reserve after chemotherapy, so they need to be strongly counseled about fertility preservation (13).

For oocyte pick-up is better to use GnRh agonist than hCG, firstly to avoid hyperstimulation risk and so that the patient can begin neoadjuvant chemotherapy immediately, without a positive pregnancy test.

Conclusions

Oncofertility counselling in young breast cancer patients should be one of the basic elements of complex patient care, therefore our purpose was to develop safe ovarian stimulation methods and to perform in vitro fertilization in breast cancer patients who want to preserve their fertility by embryo or oocyte cryopreservation before chemotherapy.

The oocyte cryopreservation may be an option for patients without a partner. With the use of cryoprotectants and cryotools in combination with rapid cryopreservation techniques (vitrification) and fertilization with ICSI, multiple clinics have reported increasing pregnancy rates using cryopreserved and warmed oocytes (14,15).

Studies that have examined pregnancy outcomes in cancer survivors have found no statistically significant increase in congenital malformations or malignant neoplasms in the resulting offspring (16).

Most of our patients have family history of cancer, here we included first and second degree relatives, so genetics may play a role in cancer development in young adults.

Generally, in the past, pregnancy outcomes in cancer patients were scarce, but with new technology of oocytes and embryos vitrification, results can be similar to that achieved with fresh embryos in non-cancer patients (17).

Limitations, Reasons for Caution

The oncofertility program held in our hospital provided funding for 300 patients, however, only 21 patients accessed it, even though we organized an information campaign in other hospitals. Barriers were identified into the professional environment (lack of awareness on infertility regarding oncological patients, lack of knowledge about hospital's program and sometimes even a disagreement on who is responsible for discussing oncological treatment-related infertility) and into patient's level (they focus on surviving cancer, resources or higher age) and a need to start immediate cancer therapy.

Author's Contributions

All authors contributed equally to the paper.

Conflict of Interest

The authors declare no conflicts of interests.

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