FERTILITY PRESERVATION COUNSELING OF FEMALE CANCER PATIENTS

L. DEL PUP1, A. BORINI2, R. FISICHELLA3, F. PECCATORI4

1Gynecological Oncology Department, National Cancer Institute, Aviano, Pordenone, Italy
2Tecnobios Procreazione, Centre for Reproductive Health, Bologna, Italy
3Department of Surgery, University of Catania, Policlinico Universitario “G. Rodolico”, Catania, Italy
4Division of Gynecologic Oncology, European Institute of Oncology, Milan, Italy

Abstract: Fertility information is a priority for young cancer female patients, but provision of such information is often inadequate. Health care providers should be prepared to discuss the negative impact of cancer therapy on reproductive health and to explain the use of fertility preservation methods to all patients even if they are not interested at the time of treatment. Fertility preservation might be offered without the risk of delaying cancer treatments, only if there is a prompt referral and an effective network between oncologists and reproductive endocrinologists.

Early fertility counseling may increase patient’s chances of receiving appropriate information and improve the success of fertility preservation. Development of local clinical guidelines and educational activities should be encouraged. Indications and contraindications, limits and controversies of the fertility sparing techniques are reviewed in order to help the oncologist to effectively counsel cancer patients.

KEY WORDS: Cancer, Infertility, Fertility preservation, Gn-RH analogues, Ovarian tissue, Oocyte or embryo cryopreservation, Fertility sparing surgery, Ovarian transposition, Counseling, Quality of life.

INTRODUCTION

The majority of children, adolescents, and young adults diagnosed with cancer will eventually become long-term survivors. Thus, the long-term adverse effects of the treatments received are becoming more important. In female cancer survivor, chemotherapy induced ovarian damage substantially impairs quality of life (QoL), leading to premature ovarian failure and infertility.

Traditionally, oncologists have focused more on providing the most effective treatments available, and less on the patient’s QoL. Nowadays, all physicians treating young patients with cancer should take more in consideration the adverse effects of antibilastic therapies on fertility and how to minimize them\(^1\). Moreover, they should be knowledgeable about fertility preservation options and should be ready to discuss these options\(^2,3\) with their patients.

Discussions about the potential gonadotoxic effects of therapies and decisions about fertility preservation options should be presented to all patients when a cancer treatment is planned, with timely and complete information.

FERTILITY COUNSELING

Reproductive concerns are particularly relevant for those patients who have a high maternity desire prior to cancer, are childless at the time of diagnosis, and have a high probability of iatrogenic infertility due to cancer treatment. Cancer diagnosis
may reduce the desire to have children in 6-13% of patients, but it may increase it in 19-24% of them. Among cancer survivors, 76% of those without children and 31% of those who are already parents wish to have children in the future. This suggests that there may be a need for more formalized intensive counseling both prior to and after cancer treatment to aid patients in resolving or managing psychosocial sequelae resulting from unplanned infertility. The percentage of cancer survivors having reproductive concerns is reported in Table 1.

The possible impact of anticancer treatment on fertility and menstrual function should be addressed in all cancer patients in reproductive age. As showed in recent studies, the potential iatrogenic loss of fertility, which also means loss of a potential child, has a profound impact on young women and sometimes may be more stressful than the cancer diagnosis itself. An early discussion facilitates the planning of a fertility preservation technique.

Discussing fertility issues at the time of diagnosis provides the patient and her family with the reassurance that the oncology team believes in a future of survival and even of acceptable QoL. A well-organized network between oncologists and reproductive specialists with expertise in fertility preservation methods is the first step to be accomplished during the management of fertility issues in cancer patients. While none of the fertility preservation options currently available provides total reassurance regarding future fertility, the fertility counseling itself may have a positive psychological impact. In a study including 1,041 cancer women aged 18-40 years, counseling about reproductive loss and fertility preservation has been associated with less regret and greater QoL for survivors, even though 96% of patients did not put in place any active strategies to preserve fertility.

The loss of reproductive potential as a consequence of anticancer treatment negatively impacts on QoL in young survivors.

All patients with newly diagnosed cancer should be assessed and receive the information regarding the risk of treatment-related infertility. Those interested in fertility preservation should be referred to a specialist. Furthermore, the previous contraindication of pregnancy in breast cancer survivors should be reconsidered after the publication of a number of studies that ultimately demonstrated that pregnancy does not worsen prognosis even in endocrine responsive breast cancer. An active fertility counseling makes a huge psychological difference: in a 2009 study by Rippy et al, there was a higher rate of pregnancy than expected and the positive attitude of the physicians team towards pregnancy reduced the fear of pregnancy after breast cancer and the elective abortion rate.

An informed choice whether to access any available fertility preservation strategy can only be made after a proper discussion of risks, success rates and costs. On the other hand, being some fertility preservation strategies still experimental and difficult to access in many centers, it is mandatory for oncologists and gynecologists to conduct more research in this important field.

Fertility counseling should include a detailed description of all the available techniques to preserve fertility which are appropriate for each individual patient including procedures, timing, possible complications, expected results. It is mandatory to make clear to the patient what is well-known and what is still experimental about these techniques. In some cases, more than one technique can be applied at the same patient or, when chemotherapy can be postponed, more cycles of ovarian stimulation can be performed to store a larger number of oocytes or embryos, thus increasing the chances of future pregnancies. Some circumstances, such as thromboembolic risk or severe abdominal adhesions, may increase complications or contraindicate a technique and must be taken into consideration during fertility counseling.

The percentage of patients that opt for oocyte/embryo or ovarian tissue cryopreservation after fertility counseling varies from 4% to over 50%. A better understanding of the factors influencing their choice will help physicians to improve the quality of fertility counseling.

The choice between the available fertility preservation strategies for young women candidates to cancer treatments depends on several factors: patient’s age and ovarian reserve, type of planned cancer treatment, whether she has a partner, the time available, and the possibility that cancer has metastasized to her ovaries.
The main available fertility preservation techniques for young cancer patients are: temporary ovarian suppression; embryo cryopreservation; cryopreservation of oocytes; cryopreservation of ovarian tissue. Among the cryopreservation techniques, to date, cryopreservation of embryos and of mature oocytes are the only strategies that have shown reliable results, while the others are still in the experimental phase. Long term follow-up of cancer patients that underwent one or more fertility preservation strategies at the time of cancer diagnosis and treatment is recommended.

GONADOTROPIN-RELEASING HORMONE AGONIST CO-TREATMENT WITH CHEMOTHERAPY

The rationale for the use of gonadotropin-releasing hormone agonist (GnRHa) to reduce the gonadal toxicity of chemotherapy is the observation that cytotoxic drugs mostly affect tissues with a rapid cellular turnover. Because chronic administration of GnRHa decreases FSH secretion and suppresses gonadal function, it has been hypothesized that it may reduce chemotherapeutic toxicity on the gonads. Unfortunately, the vast majority of clinical studies investigating gonadal protection by GnRHa during chemotherapy have been small, retrospective, and uncontrolled. A significant number of these studies used resumption of menses as a surrogate marker for fertility and many reported a higher frequency of menstrual cycles in women who have received GnRHa, but none has demonstrated a beneficial effect regarding fertility recovery.

Following encouraging findings in animal models, the first nonrandomized studies with short-term follow-up suggested a protective role for GnRHa co-treatment, but these studies have been criticized for their lack of randomization, different follow-up periods for treatment and control groups, and the use of ovarian failure as the endpoint, which may not reflect the decrease in primordial follicle count in response to chemotherapy in young women.

A 2012 meta-analysis evaluated the role of GnRHa in the prevention of chemotherapy-induced premature ovarian failure (POF), pooling data of a total of seven randomized clinical trials involving 745 premenopausal patients randomly assigned to receive chemotherapy or chemotherapy plus GnRHa. Five trials have been carried out in breast cancer patients and two trials in lymphoma patients. The pooled odds ratio estimate for chemotherapy induced POF was 0.46 (95% CI: 0.3-0.72) showing an important benefit of this strategy in reducing the gonadal toxicity of cytotoxic therapy in premenopausal cancer patients.

Another meta-analysis designed to assess the efficacy of GnRHa administration to prevent chemotherapy-induced ovarian toxicity specifically in premenopausal breast cancer women have pooled data from five randomized clinical trials, with a total of 528 patients. Significantly fewer women treated with GnRHa during chemotherapy have experienced post-treatment POF (RR: 0.40; 95% CI: 0.21-0.75). However, both treatment groups had similar rates of resumed menses (RR: 1.31; 95% CI: 0.93-1.85) and spontaneous pregnancy (RR: 0.96; 95% CI: 0.20-4.56).

A recent review of 12 trials, both randomized and nonrandomized, in women with breast cancer has found the benefit of co-treatment with GnRHa to be uncertain in female fertility.

All these meta-analysis and reviews did not include the recently presented randomized SWOG trial, that was conducted in estrogen receptor negative breast cancer patients and demonstrated a 70% reduction of permanent amenorrhea in the GnRHa treated group (goserelin at least on the week prior to the first chemotherapy dose), with a significant two-fold pregnancy rate.

The mechanisms by which GnRHa could minimize chemotherapeutic associations are:

- The hypogonadotropic state generated by the GnRHa creates a pre-pubertal hormonal milieu that decreases the activity and so the rate of follicular apoptosis and degeneration.
- The hypoestrogenic state may decrease uterine-perfused, resulting in a decreased total cumulative exposure of the ovaries to the chemotherapeutic insult.
- Gonads contain GnRH-I and GnRH-II receptors the activation of which could decreases apoptosis.
- GnRHa may up-regulate an intragonadal anti-apoptotic molecules such as sphingosine-1 phosphate (S-1-P).
- GnRHa may protect the undifferentiated germine stem cells, which ultimately generate de novo primordial follicles.
- GnRHa in contrast to embryo and oocyte cryopreservation, could theoretically preserve the overall ovarian function and not only fertility. Furthermore, this technique can be performed in combination with cryopreservation strategies, thus increasing the chance of fertility recovery after cancer treatments. The GnRHa co-treatment with chemotherapy can thus be used as 1) the only strategy, if no other option is available and the patient is informed about its limits, particularly of the non yet demonstrated fertility protective effect, or 2) combined with other options.
Cryopreservation of unfertilized human oocytes

Fertility might be preserved by obtaining mature oocytes before gonadotoxic treatment for in-vitro fertilization and subsequent embryo implantation.

For women without a partner, cryopreservation of mature oocytes is an option, but subsequent pregnancy rates are lowered because these cells sustain more damage during the freeze-thaw process than do embryos.

The technique is also inappropriate for pre-pubertal patients, in whom all fertility preservation strategies remain experimental. Cryopreservation of oocytes can be applied also in patients without a male partner and in countries where embryo cryopreservation is prohibited. Since January 2013, cryopreservation of oocytes is no longer considered experimental. The embryo end egg cryopreservation techniques need a period of ovarian stimulation that could delay treatment. It may be offered when it is medically reasonable and safe to delay chemotherapy by 2 to 6 weeks because they require a phase of ovarian stimulation lasting about 9-15 days which is usually started at the onset of menses. To overcome the need to wait the onset of menses and allow more patients the chance of embryo/oocyte cryopreservation without delaying initiation of chemotherapy, there are some attempts with the initiation of ovarian stimulation in the luteal or late follicular phases. Preliminary experiences with these “emergency protocols” showed promising results in terms of oocyte recovery.

Use of “random-start antagonist protocols” is supported by the demonstration of up to three major follicle-recruiting waves during a normal menstrual cycle and it has challenged the concept that antral follicles observed in the luteal phase are mostly atretic.

These protocols have thus proved to be efficient for fertility preservation while shortening the delay to egg retrieval to about 2 weeks.

Vitrification techniques have improved oocyte survival and fertilization rates, approaching those reported for fresh oocytes. Overall pregnancy rates are still relatively lower than those with embryo-freeze-
In a recent meta-analysis of individual patient data, raw data from 1,805 women from 10 studies who underwent egg-freezing and attempted pregnancy have been reanalyzed. Using these data, the authors have been able to calculate specific success rates based on age, number of eggs, and method of freezing. The formula used can be found at http://www.i-fertility.net/index.php/probability-calculator. The efficacy depends on the number of recovered oocytes, so it could only be proposed only to patients below the age of 38-40 years and with the possibility to recover a sufficient number of oocytes (approximately 8-15).

The cryopreservation of human oocytes can be performed if: a) the laboratory is specifically highly competent on oocyte cryopreservation; b) even if a partner is not available; c) ovarian stimulation is possible and safe; d) other options are discussed and discarded; and e) the patient is properly conscious of results and risks.

**OVARIAN TISSUE CRYOPRESERVATION**

Ovarian tissue consisting of germ cells can be removed and stored before gonadotoxic treatment. After patients are cured, this tissue might either be returned to patients via auto-transplantation or matured in vitro to produce offspring by in-vitro fertilization. Ovarian tissue can be removed by the use of multiple biopsy samples from the ovary or by oophorectomy. Removal of ovarian cortical strips can be done laparoscopically and produces tissue that is rich in primordial follicles. Cortical strips and biopsies are ideal because the tissue survives cryopreservation and undergoes revascularization on return, although most primordial follicles are lost.

Autologous transplantation of this tissue aims to restore natural fertility and also maintain sex-steroid production. The feasibility of this process has been shown in sheep and other mammals, with both the return of ovarian hormonal activity and the subsequent production of offspring. After such success in animals, evidence of ovulation after orthotopic transplantation in a woman has been reported. The first reports by Oktay and colleagues and Donnez and co-workers showed that ovarian function could realistically be preserved after sterilizing treatment, although the continuing intermittent ovulation in the Donnez study raises questions as to whether pregnancy clearly resulted from the grafted tissue. Till now around 28 babies are born using this fertility preservation strategy. Successful recovery of fertility and live births having been reported after re-transplantation of the tissue.

In pre-pubertal children facing gonadotoxic treatments, cryopreservation of gonadal tissue has also been undertaken for fertility preservation.

Retrieval of ovarian tissue may be performed by laparoscopy, can be planned shortly after diagnosis of malignant disease has been established, and does not require hormonal stimulation. This technique of fertility preservation remains experimental and several issues remain to be clarified, but perhaps the greatest concern is the potential to return malignant cells back to patients after they are cured.

This factor is of particular importance in patients with hematological malignant disease. Oocyte maturation in vitro, followed by assisted reproduction, would eliminate this risk.

Techniques to mature oocytes artificially, even from early stages of development, have yielded some success in mice. At present, little is known about the support needed for this process to take place in human tissue, and the clinical potential of this technique will need to be established.

Candidates to ovarian tissue cryopreservation are cancer patients who:

1. Wish to be pregnant in the future or who do not exclude such possibility;
2. Have a realistic chance of long-term survival;
3. Still have at least a certain amount of follicles, possibly not damaged by previous treatments;
4. Accept, must be performed and don’t have surgical contraindications to laparoscopy;
5. Have a low risk of primary tumor re-implantation or ovarian cancer;
6. Cannot use ovarian hyper-stimulation, because of neoplastic and/or thrombotic risk;
7. Need to start chemo/radiotherapy as soon as possible and who have not enough time to wait for In Vitro Fertilization (IVF) cycles;
8. Don’t yet have a partner or have him but cannot do ovarian stimulation;
9. Are well informed about all the options and their risks;
10. Choose ovarian cryopreservation conscious that it is still experimental;
11. Have ethical concerns regarding ovulation induction and oocyte retrieval or other options.

**TRANSPOSITION OF THE OVARIES**

Patients who receive pelvic irradiation might have their ovaries shielded or removed from the radiation field, a procedure known as oophoropexy, which can be undertaken laparoscopically. Although ovarian function can be preserved in 50% of cases, ischemia and scattered radiation induced uterine and ovarian damage will reduce the chances of a successful pregnancy. A dose of about...
have been published, a vaginal approach to radical tracheectomy, with preservation of the contralateral ovary, and bilateral salpingo-oophorectomy, with preservation of the uterus. Of course, after the latter two procedures, assisted reproductive technology or cryopreservation of at least a part of an ovary and/or of the uterus can be done in certain neoplastic situations. Optimal cancer therapy should supersede fertility preservation as a primary objective.

Young women presenting with borderline ovarian tumors may be offered a single oophorectomy, and this procedure appears to be safe with regard to oncologic outcome. Ovarian neoplasms candidates for fertility-sparing surgery are ovarian tumors of low malignant potential, malignant ovarian germ cell tumors and ovarian sex cord-stromal tumors. Fertility-sparing surgery may be an option for invasive epithelial ovarian cancer patients who have early-stage disease. The procedure remains highly controversial and patient must be well informed about risks.

Surgical procedures that would constitute fertility-sparing surgery for an ovarian malignancy include ovarian cystectomy, unilateral salpingo-oophorectomy, unilateral salpingo-oophorectomy plus hysterectomy, with preservation of the contralateral ovary, and bilateral salpingo-oophorectomy, with preservation of the uterus. Of course, after the latter two procedures, assisted reproductive technology (ART) would be necessary to achieve a pregnancy. The fertility sparing options for invasive cervical cancer are conization alone for stage IA1 or IA2 disease. Radical tracheectomy for stage IA2 or IB1 disease is a well-established surgical procedure for fertility preservation; nearly 1,500 cases have been published, a vaginal approach to radical tracheectomy has been performed in about two thirds of these cases, and approximately 300 pregnancies resulting in live births, half being premature, have been reported.

Abdominal tracheectomy has been undertaken in 485 cases, 38% attempted a pregnancy and 67 achieved a live birth (59.3%).

Cervical stenosis and sub-fertility are common after this type of surgery but, in general, the procedures appear to be safe, with no major complications and no higher risk of recurrence have been observed, in expert hands. Recent reports suggest that patients with stage I cervical cancer 2-4 cm in diameter may also be offered a radical tracheectomy in selected cases, after negative nodal metastasis findings following laparoscopic pelvic and para-aortic lymphadenectomy for staging or whenever para-aortic nodes are not involved and frozen sections taken intraoperatively have provided safe results. However, in these series, 45% of patients have required immediate hysterectomy or chemoradiotherapy owing to high-risk features on final pathology.

In addition, in vitro fertilization techniques may be employed prior to definitive therapy if time delays are not significant.

The optimal candidate for medical treatment of endometrial cancer is a woman of childbearing age who has a stage IA, grade 1, (without myometrial or cervical invasion), with recurrence rate of 30%-40% and 5% of recurrence during progesterone treatment. If such treatment is contemplated, it is recommended that a thorough hysteroscopy and curettage be performed to rule out a worse lesion prior to initiation.

Candidates for fertility-sparing surgery or therapies are:

1. Well informed patients with ovarian tumors of low malignant potential, malignant ovarian germ cell tumors, ovarian sex cord-stromal tumors; 2. Very selected cases of epithelial malignant ovarian cancers stage IA where one ovary could be saved and the patient understands the risks; 3. Stage IA1 or IA2 cervical cancer treated with conization alone or stage IA2 or IB1 where radical tracheectomy is performed, in a limited number of expert centers; 4. Selected cases of stage IA, low-grade, endometrial cancer treated with progestins, appropriately and closely followed.

**Egg O UTERUS DONATION**

Premature ovarian failure affects especially young female cancer patients who can only rely on egg donation. This technique has the highest effectiveness among fertility preservation options even for
women candidates to other fertility preventive options: cumulative pregnancy rates are over 60%, if embryos are of good quality.

Uterus donation is still anecdotal and it is a possibility for women who did hysterectomy or pelvic radiotherapy. Strong ethical and legal concerns are the main limits; these procedures are not allowed in Italy and in many other countries.

Candidates to egg or uterus donation are women who are affected by premature ovarian failure; did hysterectomy or pelvic radiotherapy and have neither ethical concerns nor legal limits to this procedures. A complete fertility preservation counseling should include a discussion of all the available strategies.

CONCLUSIONS

Fertility preservation is often possible and should always be proposed and discussed with women undergoing treatment for cancer. Despite the evidence that fertility loss in survivors of cancer is related to psychological distress and impaired QoL, many cancer patients of reproductive age still do not receive adequate information or referral to a reproductive specialist for fertility preservation. Oncologists should be prepared to counsel patients on this subject or they must refer patients to proper reproductive specialists. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning. These methods have psychological, ethical and legal aspects that should be fully discussed before choosing the most appropriate for each case. Some fertility preservation techniques are investigational, like ovarian cryopreservation or GnRHa co-administration. They must be performed in centers with the necessary expertise and within clinical trials. The field of fertility preservation is rapidly evolving, in particular because assisted reproductive technologies, as well as cryopreservation, transplantation, and in vitro culture methods, are developing rapidly, and new treatment options may be available in the near future69-61.

REFERENCES


