World Cancer Research Journal WCRJ 2014; 1 (2): e211

FERTILITY PRESERVATION COUNSELING OF FEMALE CANCER PATIENTS

L. DEL PUP[1], A. BORINI[2], R. FISICHELLA[3], F. PECCATORI[4]

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

Absract: *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 antiblastic 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

Corresponding Author: Lino Del Pup, MD; E mail: ldelpup@cro.it

may reduce the desire to have children in 6-13% of patients, but it may increase it in 19-24% of them[4]. Among cancers survivors, 76% of those without children and 31% of those who are already parents wish to have children in the future[4].

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[2,5]. 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[6]. 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[7,8]. An early discussion facilitates the planning of a fertility preservation technique.

Discussing fertility issues at the time of diagnosis provides also 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 preservations 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[9].

TABLE 1. PERCENTAGES OF CANCER SURVIVORS HAVING SPECIFIC REPRODUCTIVE CONCERNS5.

Reproductive Concerns Scale	%
Loss of control over reproductive future	40
Discontent with number of children	30
Inability to talk openly about fertility	27
Illness affected ability to have children	18
Sad about inability to have children	15
Frustrated ability to have children affected	13
Angry ability to have children affected	11
Mourned loss of ability to have children	11
Concerns of having children	11
Guilt about reproductive problems	8
Less satisfied with life because of problem	8
Less of a woman	6
Blame self for reproductive problems	6
Others are to blame for reproductive problems	4

The loss of reproductive potential as a consequence of anticancer treatment negatively impacts on QoL in young survivors[10,11].

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[12], 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[13].

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%[14]. 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[15].

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 chemotherapy toxicity on the gonads[16]. 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[17-21], 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[22].

A 2012 meta-analysis[23] 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[24] 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[25].

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 chemotherapy-associated gonadotoxicity[17] 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 uteroovarian perfusion, 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 antiapoptotic molecules such as sphingosine-1 phosphate (S-1-P).
- GnRHa may protect the undifferentiated germline stem cells, which ultimately generate de novo primordial follicles.
- GnRHa in contrast to embryo and oocyte cryopreservation, could theorically 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.

Criticism to GnRHa use is based on these considerations. Primordial follicles initiate follicle growth through an unknown mechanism, which is not gonadotropin dependent. There is some controversy regarding the existence of GnRH receptors on the human ovary, whereas GnRH receptors have clearly been detected in the rat ovary. The response may thus not be similar across species. If the sole mechanism of gonad protection with GnRHa are through the suppression of gonadotropins, especially FSH, then treatment would not be expected to protect the primordial follicle population that represents the ovarian reserve.

Some pre-pubertal children receiving gonadotoxic chemotherapy may eventually have POF. As younger patients have a larger ovarian reserve a decreased frequency of immediate amenorrhea does not mean that the gonads are unaffected by the chemotherapy, but simply that they have a sufficient number of oocytes not to demonstrate immediate ovarian failure[26].

The hypo estrogenic state induced by GnRHa may have negative effects in breast cancer patients by arresting tumors cells in G0 phase and making them less responsive to chemotherapy.

At present, despite encouraging reports, the benefits and long-term effects of GnRHa co-treatment are still unclear and the controversy will only be resolved by further prospective randomized clinical trials. Nevertheless this simple and relatively safe strategy is still too often used. Therefore, GnRHa co-treatment for prevention of chemotherapy-induced gonadotoxicity should be offered to patients only with appropriate informed consent in an institutional review board approved investigational protocols.

EMBRYO CRYOPRESERVATION

Embryo cryopreservation is still the most efficient method to preserve future fertility because of reasonable post-thaw survival, implantation, and delivery rates. Because the efficacy of in vitro fertilization (IVF) is dramatically reduced after even one round of chemotherapy, IVF should be performed before chemotherapy. Embryo freezing is predominantly suitable for sexually mature women needing a partner or a sperm donor for egg fertilization. In some countries it has legal limitations. For example, it was not allowed in Italy since 2004 even if now it is permitted again.

After embryo freezing, success rates of transfer of thawed embryos are currently similar to those of fresh embryos if they remain intact after thawing, and this treatment can lead to a 59% pregnancy rate and a 26% live birth rate[27].

Embryo cryopreservation is an established technique that is available for fertility preservation if: 1) a small delay in the initiation of chemotherapy or radiotherapy is acceptable; 2) a partner sperm is available (or a donor outside Italy); 3) ovarian hyper-stimulation can be safely performed; 4) this technique is chosen knowing its better efficiency and the alternatives, and 5) there are no ethical or legal limitations

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[28].

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[29,30]. 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[31-33].

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[34].

These protocols have thus proved to be efficient for fertility preservation while shortening the delay to egg retrieval to about 2 weeks[35].

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-freez-

ing, pregnancy rates and live births after thawing and fertilizing frozen eggs are currently reaching those obtained after embryo cryopreservation[30,36-38].

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-calc[39,40]. The efficacy depends on the number of recovered oocytes, so it could only 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[41]. The first reports by Oktay and colleagues[42] and Donnez and co-workers[43] 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 prevention strategy. Successful recovery of fertility and live births having been reported after re-transplantation of the tissue[43-45].

In pre-pubertal children facing gonadotoxic treatments, cryopreservation of gonadal tissue has also been undertaken for fertility preservation[46].

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[47-49].

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 neoplatic 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

2 Gy applied to the gonadal area may destroy up to 50% of the ovarian follicle reserve. Irradiation of the vagina is related to fertility and sexual issues due to loss of lubrication, anatomic impairment, and in some cases vaginal stenosis. Radiotherapy of the uterus in young women and girls causes tissue fibrosis, leading to restricted uterine capacity and blood flow. The damage to the uterus seems to be more pronounced in women who are younger at the time of radiotherapy. Impaired uterine growth during pregnancy and unfavorable pregnancy outcomes, including spontaneous abortion, premature labor, and low birth weight offspring, have been reported in women who had undergone radiotherapy to the uterus[50].

Transposition of the ovaries should be considered in case of: a) planned pelvic or whole body irradiation; b) unnecessary chemotherapy; c) unlikely ovarian cancer involvement; d) ovarian hyper-stimulation can be performed; and e) possibly in combination with ovarian tissue cryopreservation

FERTILITY-SPARING SURGERY

Preservation 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[51].

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 trachelectomy 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 trachelectomy has been performed in about two thirds of these cases, and approximately 300 pregnancies resulting in live births, half being premature, have been reported[52-55].

Abdominal trachelectomy has been undertaken in 485 cases, 38% attempted a pregnancy and 67 achieved a live birth (59.3%)[56].

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 trachelectomy 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[57,58].

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[2].

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 trachelectomy 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 future[59-61].

REFERENCES

1. Del Pup L, Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Sisto R. Fertility preservation methods for female neoplastic patients. Radiol Oncol 2006; 40: 175-181.
2. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagert K, Beck LN, Brennan LV, Oktay K; American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Onc 2006; 24: 1-15.
3. Robertson JA. Cancer and fertility: ethical and legal challenges. J Natl Cancer Inst Monogr 2005; 34: 104-106
4. Schover LR. Motivation of parenthood after cancer: a review J NAtl Cancer Inst Monogr 2005; 34: 2-5.
5. Wenzel L, Dogan-Ates A, Habbal R, Berkowitz R, Goldstein DP, Bernstein M, Kluhsman BC, Osann K, Newlands E, Seckl MJ, Hancock B, Cella D. Defining and Measuring Reproductive Concerns of Female Cancer Survivors. J Natl Cancer Inst Monogr 2005; 34: 94-98.
6. Rodriguez-Wallberg KA, Oktay K . Fertility preservation during cancer treatment: clinical guidelines Cancer Management and Research 2014; 6 105-117.
7. Schover LR. Patient attitudes toward fertility preservation. Pediatr Blood Cancer 2009; 53: 281-284.
8. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, Rosenberg R, Przypyszny M, Rein A, Winer EP. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004; 22: 4174-4183.
9. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012; 118: 1710-1717.
10. Loprinzi CL, Wolf SL, Barton DL, Laack NN. Symptom management in premenopausal patients with breast cancer. Lancet Oncol 2008; 9: 993-1001.
11. Tschudin S, Bitzer J. Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. Hum Reprod Update 2009; 15: 587-597.
12. Rippy EE, Karat IF, Kissin MW. Pregnancy after breast cancer: the importance of active counselling and planning. Breast 2009; 18: 345-350
13. Gracia CR, Jeruss JS. Lives in the balance: women with cancer and the right to fertility care. J Clin Oncol 2013; 31: 668-669.
14. Lawrenz B, Jauckus J, Kupka MS, Strowitzki T, von Wolff M. Fertility preservation in >1,000 patients: patient's characteristics, spectrum, efficacy and risks of applied preservation techniques. Arch Gynecol Obstet 2011; 283: 651-656.
15. Roberts JE, Oktay K. Fertility preservation: a comprehensive approach to the young woman with cancer. J Natl Cancer Inst Monogr 2005; (34): 57-59.
16. Del Mastro L, Giraudi S, Levaggi A, Pronzato P. Medical approaches to preservation of fertility in female cancer patients. Expert Opin Pharmacother 2011; 12: 387-396.
17. Blumenfeld Z, Eckman A. Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a. J Natl Cancer Inst Monogr 2005; 34: 40-43.
18. Blumenfeld Z, Avivi I, Linn S, Epelbaum R, Ben-Shahar M, Haim N. Prevention of irreversible chemotherapy induced ovarian damage in young women with lymphoma by a gonadotrophin releasing hormone agonist in parallel to chemotherapy. Hum Reprod 1996; 11: 1620-1626.
19. Blumenfeld Z, Avivi I, Ritter M, Rowe JM. Preservation of fertility and ovarian function and minimizing chemotherapy-induced gonadotoxicity in young women. J Soc Gynecol Invest 1999; 6: 229-239.
20. Blumenfeld Z, Shapiro D, Shteinberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. Lupus 2000; 9: 401-405.

21. Blumenfeld Z. Ovarian rescue/protection from chemotherapeutic agents. J Soc Gynecol Investig 2001; 8: S60-S64.
22. Sonmezer M, Oktay K. Fertility preservation in female patients. Hum Reprod Update 2004; 10: 251–266
23. Del Mastro L, Levaggi A, Poggio F, et al. Role of temporary ovarian suppression obtained with GNRH analogue in reducing premature ovarian failure (POF) induced by chemotherapy in premenopausal cancer patients: a meta-analysis of randomized studies. ESMO Congress 2012. Ann Oncol 2012; 23: Suppl 9 (abstract: 1551PD).
24. Yang B, Shi W, Yang J, Liu H, Zhao H, Li X, Jiao S. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials. Breast 2013; 22: 150-157.
25. Turner NH, Partridge A, Sanna G, Di Leo A, Biganzoli L. Utility of gonadotropin-releasing hormone agonists for fertility preservation in young breast cancer patients: the benefit remains uncertain. Ann Oncol 2013; 24: 2224-2235.
26. Falcone T, Bedaiwy MA. Fertility preservation and pregnancy outcome after malignancy. Curr Opin Obstet Gynecol 2005; 17: 21-26.
27. Marrs RP, Greene J, Stone BA. Potential factors affecting embryo survival and clinical outcome with cryopreserved pronuclear human embryos. Am J Obstet Gynecol 2004; 190: 1766-1771.
28. Porcu E, Fabbri R, Damiano G. Oocyte cryopreservation in oncological patients. Eur J Obstet Gynecol Reprod Biol 2004; 113(Suppl. 1): S14-S16.
29. ISFP Practice Committee, Kim SS, Donnez J, Barri P, Pellicer A, Patrizio P, Rosenwaks Z, Nagy P, Falcone T, Andersen C, Hovatta O, Wallace H, Meirow D, Gook D, Kim SH, Tzeng CR, Suzuki S, Ishizuka B, Dolmans MM. Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet 2012; 29: 465-468.
30. Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology Mature oocyte cryopreservation: a guideline. Fertil Steril 2013; 99: 37-43.
31. Michaan N, Ben-David G, Ben-Yosef D, Almog B, Many A, Pauzner D, Lessing JB, Amit A, Azem F. Ovarian stimulation and emergency in vitro fertilization for fertility preservation in cancer patients. Eur J Obstet Gynecol Reprod Biol 2010; 149: 175-177.
32. Sönmezer M, Türkçüo lu I, Co kun U, Oktay K. Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles. Fertil Steril 2011; 95: 2125.e9-11.
33. Bedoschi GM, de Albuquerque FO, Ferriani RA, Navarro PA. Ovarian stimulation during the luteal phase for fertility preservation of cancer patients: case reports and review of the literature. J Assist Reprod Genet 2010; 27: 491-494.
34. Baerwald AR, Adams GP, Pierson RA. A new model for ovarian follicular development during the human menstrual cycle. Fertil Steril 2003; 80: 116-122.
35. von Wolff M, Thaler CJ, Frambach T, Zeeb C, Lawrenz B, Popovici RM, Strowitzki T. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril 2009; 92: 1360-1365.
36. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril 2006; 86: 70-80.
37. Practice Committee of American Society for Reproductive Medicine; Practice Committee of Society for Assisted Reproductive Technology. Ovarian tissue and oocyte cryopreservation. Fertil Steril 2008; 90(Suppl 5): S241-S246.
38. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online 2009; 18: 769-776.
39. Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. Fertil Steril 2013; 100: 492-499. e3.
40. Oktay K, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. N Engl J Med 2000; 342: 1919.
41. Oktay K, Buyuk E, Veeck L, Zaninovic N, Xu K, Takeuchi T, Opsahl M, Rosenwaks Z. Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. Lancet 2004; 363: 837-840
42. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, Martinez-Madrid B, van Langendonckt A. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004; 364: 1405-1410.
43. Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM. Children born after autotransplantation of cryopreserved ovarian tissue. a review of 13 live births. Ann Med 2011; 43: 437-450.
44. Oktay K, Türkçüo lu I, Rodriguez-Wallberg KA. Four spontaneous pregnancies and three live births following subcutaneous transplantation of frozen banked ovarian tissue: what is the explanation? Fertil Steril 2011; 95: 804.e7-e10
45. Rodriguez-Wallberg KA, Borgstrom B, Sheikhi M. Lundqvist ML, Hovatta O. Cryopreservation of oocytes and gonadal tissue in a large fertility preservation programme at a teaching hospital. Hum Reprod 2010; 25(Suppl 1): i104.
46. Dolmans MM, Luyckx V, Donnez J, Andersen CY, Greve T. Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue. Fertil Steril 2013; 99: 1514-1522.
47. Greve T, Clasen-Linde E, Andersen MT, Andersen MK, Sørensen SD, Rosendahl M, Ralfkiaer E, Andersen CY. Cryopreserved ovarian cortex from patients with leukemia in complete remission contains no apparent viable malignant cells. Blood 2012; 120: 4311-4316.
48. Rosendahl M, Greve T, Andersen CY. The safety of transplanting cryopreserved ovarian tissue in cancer patients: a review of the literature. J Assist Reprod Genet 2013; 30: 11-24.
49. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, Yasui Y. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 2009; 27: 2374-2381.
50. Wallberg KA, Keros V, Hovatta O. Clinical aspects of fertility preservation in female patients. Pediatr Blood Cancer 2009; 53: 254-260.
51. Plante M, Gregoire J, Renaud MC, Roy M. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. Gynecol Oncol 2011; 121: 290-297.
52. Li J, Li Z, Wang H, Zang R, Zhou Y, Ju X, Ke G, Wu X. Radical abdominal trachelectomy for cervical malignancies: surgical, oncological and fertility outcomes in 62 patients. Gynecol Oncol 2011; 121: 565-570.

53. Testa R, Ramirez PT, Ferreyra H, Saadi J, Franco G, Goldsman M, Perrotta M. Abdominal radical trachelectomy: a safe and feasible option for fertility preservation in developing countries. J Low Genit Tract Dis 2013; 17: 378-384.
54. Speiser D, Köhler C, Schneider A, Mangler M. Radical vaginal trachelectomy: a fertility-preserving procedure in early cervical cancer in young women. Dtsch Arztebl Int 2013; 110: 289-295.
55. Pareja R, Rendón GJ, Sanz-Lomana CM, Monzón O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy--a systematic literature review. Gynecol Oncol 2013; 131: 77-82.
56. Vercellino GF, Piek JM, Schneider A, Köhler C, Mangler M, Speiser D, Chiantera V. Laparoscopic lymph node dissection should be performed before fertility preserving treatment of patients with cervical cancer. Gynecol Oncol 2012; 126: 325-329.
57. Wethington SL, Sonoda Y, Park KJ, Alektiar KM, Tew WP, Chi DS, Leitao MM Jr, Jewell EL, Barakat RR, Abu-Rustum NR. Expanding the indications for radical trachelectomy: a report on 29 patients with stage IB1 tumors measuring 2 to 4 centimeters. Int J Gynecol Cancer 2013; 23: 1092-1098.
58. Lambertini M, Anserini P, Levaggi A, Poggio F, Del Mastro L. Fertility counseling of young breast cancer patients. J Thorac Dis 2013; 5(S1): S68-S80.
59. Borini A, Rebellato E. Focus on breast and ovarian cancer. Placenta 2008; 29: S184-S190.
60. The Practice Committee of the American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. Fertility and Sterility 2014; 101: 1237-1243.