

Review

Emergency Fertility Preservation for Female Patients with Cancer: Clinical Perspectives

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Abstract. *To explore the new as well as the currently available options and strategies that can be used for emergency fertility preservation of female cancer patients, a systematic literature review was performed for all full-text articles published in PubMed in English language in the past 15 years according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Although under-utilized, several established, experimental and debatable options exist and can be used for emergency fertility preservation in females. Such options include emergency ovarian stimulation, embryo freezing, egg freezing, ovarian tissue freezing and autotransplantation, in vitro maturation, and ovarian protection techniques. This article describes and evaluates in detail the advantages and disadvantages of each option and suggests a new comprehensive multi-step strategy for emergency fertility preservation of female patients with cancer.*

Each year, millions of women worldwide are diagnosed with cancer. In the year 2012, the number of new cancer cases in women was approximately 1.2 million in the European Union, 0.7 million in the United States and 6.6 million worldwide (1). About 10% of those women were in their reproductive years. Due to recent advances in treatment, almost 90% of young women with cancer can survive when they are diagnosed-early (2). However, they may suffer from fertility loss due to irreversible reproductive damage caused by aggressive chemotherapy and radiotherapy (3-5).

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Almost one in 51 women will suffer from an invasive cancer by the age of 39 years and hence will receive cancer treatment. The most common forms of invasive cancer in women are breast (29%), lung (13%), colorectal (8%), uterine and cervical (6%) cancer, thyroid carcinoma (6%), lymphoma (4%), melanoma (4%), leukemia (3%), kidney (3%) and pancreatic (3%) cancer (2). Cancer treatments such as chemotherapy and radiotherapy act through inhibition of DNA function and cell division, resulting in cytotoxicity and cell damage (6). After chemotherapy and radiotherapy, the probability of conception in female cancer survivors is markedly diminished by 30-50%, with an increased risk of delivering pre-term and of babies with low birth weight (7-13). However, when reproductive organs are exposed to aggressive chemotherapy and radiotherapy, irreversible damage occurs leading to permanent loss of fertility (14-17).

Alkylating chemotherapy such as cyclophosphamide, ifosfamide and busulphan, in addition to ionizing radiotherapy to the abdomen and pelvis, or total-body irradiation are the most aggressive cancer treatments to the ovaries and uterus (18, 19). The degree of ovarian and uterine damage is related to the dose, site, and fractionation of the chemotherapy and radiotherapy, as well as the age of the patient at the beginning of treatment. Severe ovarian damage can lead to premature ovarian failure due to complete depletion of follicles and oocytes. Comparably, severe uterine damage can lead to recurrent miscarriage, pregnancy loss, preterm labor, and low birth weight due to disruption of uterine vasculature (20-23).

As the survival rate of young women with cancer is increasing, the need to develop effective and individualized fertility-preservation strategies is also increasing (24, 25). Unfortunately, the probability of female fertility loss increases tremendously when aggressive cancer treatment is immediately administered as in treatment of highly invasive malignancies. In such cases, developing an emergency fertility-preservation strategy becomes absolutely necessary (26, 27). The aim of the present article was to explore the new and the currently available options and strategies that can be used for emergency fertility preservation of female patients with cancer.

Materials and Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28), a systematic review of the literature in the past 15 years was performed for all full-text articles published in PubMed in English between 1 January 2000 and 31 December 2014 to explore the new and currently available options and strategies that can be used for emergency fertility preservation of female patients with cancer. Based on these inclusion criteria, the following electronic search strategy was performed in PubMed: (emergency female fertility preservation) OR female fertility preservation) OR oncofertility) AND female cancer patients) AND cryopreservation) AND full text[sb] AND ("2000/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[MeSH] AND English[lang] AND Female[MeSH Terms])).

The full-text articles identified from the initial search underwent screening for titles and abstracts, then were checked for eligibility according to the inclusion criteria. Only the full-text articles focusing primarily on the new and currently available options and strategies that can be used for emergency fertility preservation of female patients with cancer were included and fully reviewed. Data were extracted from the text, tables, graphs and references of the included articles.

Results

A total of 308 full-text articles were identified from the initial search. Almost 60% of these articles were published in the past five years. After screening titles and abstracts, all 308 full-text articles were checked for eligibility according to the inclusion criteria. Only 251 full-text articles focusing primarily on the new and currently available options and strategies that can be used for emergency fertility preservation of female patients with cancer were included and fully reviewed. The PRISMA flow diagram of the systematic review process is illustrated in Figure 1.

Regarding fertility preservation of female patients with cancer, many guidelines and recommendations have been published by the American Society of Clinical Oncology (ASCO) (29, 30), European Society for Medical Oncology (ESMO) (31, 32), American Society for Reproductive Medicine (ASRM) (33-35), International Society for Fertility Preservation (ISFP) (36-39), Fertility Preservation Network (FertiPROTEKT) (40), and US Oncofertility Consortium (41, 42). Some of these guidelines were not identified in the initial search. However, the final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Although under-utilized, several established, experimental and debatable options exist and can be used for emergency fertility preservation of female patients with cancer (29-42). Such options include emergency ovarian stimulation, embryo freezing, egg freezing, ovarian tissue freezing and autotransplantation, *in vitro* maturation, and ovarian protection techniques (43-45). In this section, we describe and evaluate in detail the advantages and

disadvantages of each option from a clinical perspective. We also suggest a new comprehensive multi-step strategy for emergency fertility preservation of female patients with cancer that can be carried out by oncologists, gynecologists and reproductive biologists.

Emergency Ovarian Stimulation

In cases of emergency fertility preservation, conventional ovarian stimulation is not preferred as it may take up to several weeks. Conventional ovarian stimulation may also result in ovarian hyperstimulation syndrome that would require further treatment leading to a delay of primary cancer therapy. In addition, conventional ovarian stimulation is contraindicated in patients with estrogen-sensitive tumors, such as breast and endometrial cancer, as it is associated with high levels of serum estradiol (46-53).

Recently, some alternative ovarian stimulation protocols within a two-week time frame have been attempted and shown promising results for emergency fertility preservation in patients with breast cancer and hematologic malignancies. Examples of these alternative protocols are luteal-phase or random-start protocol (54-57) and follicular-phase protocols using letrozole (aromatase inhibitor) (58-63) or tamoxifen (selective estrogen receptor modulator) (64, 65). Although promising, women with cancer showed lower response to ovarian stimulation in comparison to healthy age-matched women according to a recent meta-analysis (66). Consequently, extrapolation of conventional *in vitro* fertilization, embryo freezing, and egg freezing results to female patients with cancer should be done with caution (67, 68). After successful emergency ovarian stimulation, mature oocytes can be retrieved for further embryo freezing or egg freezing options.

Embryo Freezing

Embryo freezing is the first established cryopreservation method for female fertility preservation and is still considered the gold-standard option. It involves cryopreservation of *in vitro*-fertilized mature oocytes *via* slow freezing or vitrification (29-42). Nevertheless, vitrification is now more preferred due to a better post-thaw survival rate (69-71). As an emergency fertility-preservation procedure, embryo freezing requires emergency ovarian stimulation as described above, mature oocyte retrieval, and fertilizing sperm for *in vitro* fertilization. Therefore, it is not suitable for prepubertal girls or single women refusing sperm donation (29-42). In healthy women, the live birth rate per frozen embryo transfer is ~30% (72-74). However, in women with cancer, the live birth rate per frozen embryo transfer is reduced to ~15%, without any increased risk for congenital abnormalities (75).

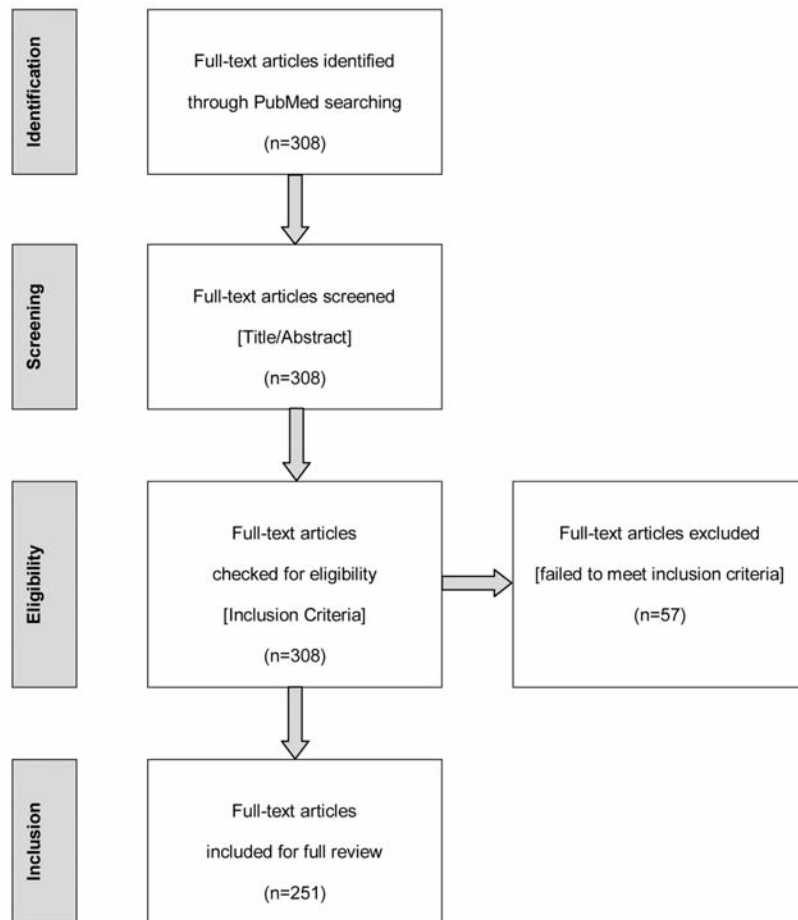


Figure 1. PRISMA four-phase flow diagram of identification, screening, eligibility and inclusion steps for this study.

Egg Freezing

Egg freezing is no longer considered an experimental cryopreservation method for female fertility preservation (35). It involves cryopreservation of mature oocytes *via* slow freezing or vitrification. However, vitrification is now more preferred due to a better post-thaw survival rate (69-71). As an emergency fertility-preservation procedure, egg freezing requires emergency ovarian stimulation as described above, and mature oocyte retrieval without the need for fertilizing sperm or *in vitro* fertilization. Therefore, it is still not suitable for prepubertal girls but may be suitable for single women refusing sperm donation and embryo freezing (29-42). In healthy women, the live birth rate per frozen oocyte is ~6% and continues to improve due to advances in vitrification protocols (76-79). However, in women with cancer, there exist not enough data on the outcome of egg freezing as the procedure was considered experimental for many years. To date, only few live births have been reported after oocyte vitrification in women with cancer (80-82). Until

enough data become available, the results of conventional egg freezing should be extrapolated with caution to female patients with cancer during counseling (35).

Ovarian Tissue Extraction

Ovarian tissue extraction involves surgical excision of at least half of one ovary *via* laparoscopy or laparotomy immediately before the beginning of cancer treatment. The extracted ovarian tissue can be transported within 24 h under special conditions to central cryobanks to be processed by more experienced teams (29-42). The extracted ovarian tissue can be either frozen for future re-transplantation (autotransplantation) or processed *in vitro* in an attempt to produce mature oocytes (*in vitro* maturation) (43-45).

Ovarian Tissue Freezing

Ovarian tissue freezing is still considered an experimental cryopreservation method for female fertility preservation

(29-42). It involves cryopreservation of surgically excised cortical ovarian tissues. Ovarian tissue freezing is performed *via* slow freezing as standard. However, vitrification of ovarian tissue was attempted in numerous research trials with promising results (83-87). After recovery from cancer and when pregnancy is desired, frozen ovarian tissue can be thawed and transplanted back into the same patient (autotransplantation) (88, 89).

Autotransplantation

Classically, frozen-thawed ovarian tissue is autotransplanted orthotopically to the remaining ovary or ovarian fossa. In the case of severe pelvic adhesions or poor pelvic vasculature due to previous irradiation, frozen-thawed ovarian tissue can be autotransplanted heterotopically to other sites such as the subcutaneous space of abdominal wall or forearm for subsequent ovarian stimulation, oocyte retrieval and *in vitro* fertilization. Following successful ovarian tissue freezing and autotransplantation, the ovarian function may resume two to nine months postoperatively and may last for up to seven years (90-93).

After orthotopic autotransplantation, spontaneous pregnancy can be expected or subsequent ovarian stimulation, oocyte retrieval and *in vitro* fertilization can be performed (94). Although an international registry is needed, at least 37 healthy babies have been born worldwide after ovarian tissue freezing and orthotopic autotransplantation without any increased risk for miscarriage or congenital abnormalities. In such cases, the live birth rate per transplant was roughly estimated to be ~30% (44). Heterotopic autotransplantation has not yet resulted in any reported live births, although it did result in a four-cell embryo (95), a biochemical pregnancy (96) and a clinical pregnancy (97). In comparison to autotransplantation, transplantation of fresh and frozen-thawed ovarian tissue between monozygotic twin sisters has been successful and resulted in healthy live births (44).

As an emergency fertility-preservation procedure, ovarian tissue freezing followed by autotransplantation may be the only suitable option for prepubertal girls although no babies have yet been born in women whose ovarian tissue was frozen before puberty (29-42).

Although promising, ovarian tissue autotransplantation carries the risk of re-introducing malignant cells in the case of ovarian carcinoma and malignancies that may metastasize to ovaries (29-42). The risk of re-introducing malignant cells depends mainly on the type and stage of the primary cancer at the time of ovarian tissue extraction. Several methods such as histological examination, immunohistochemistry, polymerase chain reaction and long-term xenotransplantation were used to assess the risk of re-introducing malignant cells with autotransplantation in different types of cancers. Overall, it is estimated that the risk of re-introducing

malignant cells is high in leukemia, moderate in gastrointestinal cancer, and low in breast cancer, sarcoma of the bone and connective tissue, gynecological cancer, and Hodgkin's and Non-Hodgkin's Lymphoma (98, 99). In such cases, *in vitro* maturation may be an alternative (100-102).

In Vitro Maturation

In vitro Maturation is an experimental strategy that involves *in vitro* culture of ovarian tissue, follicles or immature oocytes, hoping at the end to produce mature oocytes ready for fertilization (29-42).

In research settings, part of the fresh or frozen-thawed ovarian tissue may be processed *in vitro* through three sequential culture steps with the hope of producing mature oocytes ready for fertilization (103-107). Step one involves culture of cortical ovarian tissue pieces to enhance primordial follicles growth within 6-10 days. To develop further, growing follicles must be isolated from the ovarian cortex. Step two involves isolation and culture of growing ovarian follicles to produce fully-grown antral follicles within 30 days. To develop further, oocytes must be isolated from the antral follicles. Step three involves immature oocytes isolation and culture for about one to two days in an attempt to produce mature oocytes that can be either fertilized or frozen for future use (3). In humans, this three sequential culture step strategy has not yet resulted in any meiotically-competent mature oocytes ready for fertilization, although the concept has been successful in some animal species (108-110). In addition to this multistep *in vitro* strategy, long-term xenotransplantation of frozen-thawed human ovarian tissue can be used experimentally to enhance follicle and oocyte development (111, 112).

In clinical practice, immature oocytes might be retrieved transvaginally from stimulated or unstimulated ovaries at any time of the menstrual cycle and immediately before the beginning of cancer treatment (113-116). The retrieved immature oocytes can be cultured *in vitro* for about one to two days in an attempt to produce mature oocytes that can be either fertilized or frozen for future use (113-116). Recently, vitrification of immature oocytes has been attempted but with less promising results than vitrification of *in vitro*-matured oocytes (117, 118). In healthy women, *in vitro* maturation of oocytes has resulted in several hundred healthy babies, and the overall live birth rate per *in vitro* maturation cycle was almost half of that for conventional *in vitro* fertilization (119). Until enough data become available in the case of cancer, these results of oocyte *in vitro* maturation should be extrapolated with caution to female patients with cancer during counseling (120). Surprisingly, immature oocytes might be also retrieved *ex-vivo* during manipulation and further dissection of the excised ovarian tissue biopsies (121-123). Recently, the first live birth resulting from *in vitro*-

matured oocytes retrieved *ex-vivo* after oophorectomy in a patient with ovarian cancer was reported (124).

As an emergency fertility-preservation procedure, *in vitro* maturation is not recommended in prepubertal girls as the true potential for *in vitro* development of immature oocytes retrieved before puberty is uncertain (43) and needs further studies and research (125).

Ovarian-Protection Techniques

Ovarian-protection techniques are the surgical and non-surgical procedures that can be used as emergency fertility-preservation options before or during cancer treatment to protect the ovaries from the deleterious gonadotoxic side-effects of chemotherapy and radiotherapy (126).

Surgical ovarian-protection techniques include surgical transposition of ovaries (oophoropexy) away from the field of pelvic irradiation, as in the case of pelvic malignancies such as Hodgkin's lymphoma, cervical carcinoma, vaginal carcinoma and pelvic sarcoma (127). During oophoropexy, ovaries can be transposed either laterally towards the pelvic wall or medially behind the uterus (128, 129). Although under-used, oophoropexy can be carried out *via* laparotomy, laparoscopy, or even *via* robotic surgery. The most simple and successful technique is laparoscopic lateral oophoropexy (130-132). According to the guidelines of ASCO, the success of oophoropexy in protecting ovaries and preserving fertility is debatable and varies according to the dose, site, and type of pelvic irradiation, the age of the patient, as well as whether chemotherapy is combined. There is also the probability of re-migration of the transposed ovaries to their original positions during the course of radiotherapy (29, 30). Literally, oophoropexy does not protect ovaries from chemotherapy-induced gonadotoxicity. For this reason, it is not feasible to perform oophoropexy in female patients with cancer scheduled to receive chemotherapeutic treatments (29, 30).

Non-surgical ovarian protection techniques include the use of gonadotropin-releasing hormone (GnRH) analogs before and during chemotherapy, pelvic shielding during radiotherapy, and fractionation of the chemotherapy and radiotherapy doses (126).

GnRH analogs are commonly-prescribed medications in the field of gynecological endocrinology and reproductive medicine. However, the role of GnRH analogs in protecting ovaries before and during chemotherapy is still debatable (133-137). Some randomized trials, systematic reviews and meta-analyses showed a correlation between administration of GnRH analogs before and during chemotherapy and lower rates of premature ovarian failure in female cancer survivors (138-144). In fact, the mechanism of action of GnRH analogs and their direct and indirect effects on ovaries are not fully understood. It is known that GnRH analogs suppress gonadotropin secretion from the pituitary gland and hence suppress ovarian function indirectly (145, 146). Some

Table I. A new comprehensive multi-step strategy for emergency fertility preservation of female patients with cancer.

Option 1:	Emergency ovarian stimulation followed by embryo freezing/egg freezing.
Option 2:	Ovarian tissue extraction followed by ovarian tissue freezing and autotransplantation/ <i>in vitro</i> maturation.
Option 3:	Ovarian protection techniques including oophorectomy, gonadotropin-releasing hormone analogs, pelvic shielding, fractionated doses of chemotherapy and radiotherapy.
Firstly:	If feasible and not contraindicated, all options (1, 2 and 3) may be attempted consecutively.
Secondly:	If Option 1 is contraindicated or infeasible, Option 2 and Option 3 may be attempted consecutively.
Thirdly:	If Option 2 is contraindicated or infeasible, Option 1 and Option 3 may be attempted consecutively.
Fourthly:	If Option 1 and Option 2 are contraindicated or infeasible, only Option 3 may be attempted.

theories suggest that with administration of GnRH analogs before and during chemotherapy, the ovaries are suppressed and the number of primordial follicles entering the growing pool decreases and this may make them less sensitive to the gonadotoxic chemotherapeutic agents (147-148). Other theories suggest a direct protective effect of GnRH analogs on ovaries, including up-regulation of intraovarian anti-apoptotic molecules and protection of ovarian germline stem cells (147-148). GnRH analogs do not literally protect ovaries from radiotherapy-induced gonadotoxicity. For this reason, it is not feasible to use GnRH analogs in female patients with cancer scheduled to receive pelvic irradiation (29-42). According to ASCO, ESMO and ASRM guidelines published in 2013, GnRH analogs should not be relied upon as a fertility-preservation method (30, 32, 35).

Discussion

A Suggested Multi-step Strategy for Emergency Fertility Preservation of Female Patients with Cancer. Offering emergency fertility preservation strategies to female patients with cancer requires interdisciplinary oncofertility team of oncologists, gynecologists and reproductive biologists with sufficient knowledge, skills and experience. Although under-utilized, several options exist and can be used for emergency fertility preservation of female patients with cancer. However, each of these options has advantages and disadvantages and may not be suitable for all cases. Additionally, many other factors play important roles in that decision-making process. Such factors include access and

Table II. Three major options for emergency fertility preservation of female patients with cancer.

Characteristic	Option 1	Option 2	Option 3
Methods	Emergency ovarian stimulation followed by embryo freezing/egg freezing.	Ovarian tissue extraction followed by ovarian tissue freezing and autotransplantation/ <i>in vitro</i> maturation.	Ovarian protection techniques such as oophorectomy, gonadotropin-releasing hormone analogs, pelvic shielding, fractionated doses of chemotherapy and radiotherapy.
Status	Established	Experimental	Debatable
Contraindications	1–Emergency ovarian stimulation is contraindicated in prepubertal girls. 2–Embryo freezing may be refused by single women who do not accept sperm donation.	1–Autotransplantation of frozen-thawed ovarian tissue is contraindicated in ovarian carcinomas and malignancies that may metastasize to ovaries. 2– <i>In vitro</i> maturation is not recommended in prepubertal girls.	1–Oophorectomy and pelvic shielding are not feasible when chemotherapy is used. 2– Gonadotropin-releasing hormone analogs are not feasible when radiotherapy is used.

cost of treatment, type and stage of cancer, age, general health condition, reproductive function and ovarian reserve of the patient, as well as the desire to have children. After evaluation of all these factors, an emergency fertility-preservation strategy can be individually tailored to each case in order to be effective.

In Table I and II, we suggest a simple and comprehensive multi-step strategy that might help oncologists, gynecologists and reproductive biologists in the complex decision-making process of developing effective emergency fertility-preservation strategies for female patients with cancer.

In our suggested multistep strategy, three major options are highlighted. Option 1 includes emergency ovarian stimulation followed by embryo freezing/egg freezing. Option 2 includes ovarian tissue extraction followed by ovarian tissue freezing and autotransplantation/*in vitro* maturation. Option 3 includes ovarian-protection techniques such as oophorectomy, GnRH analogs, pelvic shielding, fractionated doses of chemotherapy and radiotherapy. According to the most recent guidelines and recommendations, Option 1 is considered established, while Option 2 is considered experimental and Option 3 is considered debatable (29-42). Firstly: If feasible and not contraindicated, all options (1, 2 and 3) may be attempted consecutively. Secondly: If Option 1 is contraindicated or infeasible, Option 2 and Option 3 may be attempted consecutively. Thirdly: If Option 2 is contraindicated or infeasible, Option 1 and Option 3 may be attempted consecutively. Fourthly: If Option 1 and Option 2 are contraindicated or infeasible, only Option 3 may be attempted.

If the suggested multi-step strategy unfortunately fails or is infeasible or impossible, third party reproduction, such as embryo donation, egg donation and surrogacy or even

adoption, can be considered later as alternative strategies, depending on the legal, ethical, social and religious status in each country (149-151). In this context, it is important to mention that third-party reproduction is now offered as cross-border reproductive care in many Centers worldwide as addressed by the European Society of Human Reproduction and Embryology (152) and ASRM (153).

Conclusion

When immediate initiation of cancer treatment becomes essential, development of an emergency fertility-preservation strategy becomes necessary. Although under-utilized, several established, experimental and debatable options exist and can be used for emergency fertility preservation of female patients with cancer. Our systematic literature review highlighted three major options: (i) emergency ovarian stimulation followed by embryo freezing/egg freezing, (ii) ovarian tissue extraction followed by ovarian tissue freezing and autotransplantation/*in vitro* maturation, and (iii) ovarian-protection techniques. All these options, except *in vitro* maturation of ovarian tissue and follicles, have resulted in healthy live births. However, each option has advantages and disadvantages and may not be suitable for all cases. This is why the emergency fertility-preservation strategy must be individualized in order to be effective. Accordingly, we suggest a simple and comprehensive multi-step strategy that might help oncologists, gynecologists and reproductive biologists in such a complex decision-making process. Patient awareness, early counseling and proper coordination between oncofertility team members are the key factors for success in any emergency fertility-preservation strategy for female patients with cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

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