Female fertility loss and preservation: threats and opportunities

M. Salama, K. Winkler, K. F. Murach, B. Seeber, S. C. Ziehr & L. Wildt*

Department of Gynecological Endocrinology and Reproductive Medicine, Innsbruck Medical University, Innsbruck, Austria

Received 4 May 2012; revised 25 July 2012; accepted 31 August 2012

Background: Ovarian aging and cytotoxic treatments are the most common causes for fertility loss in women. With increasing numbers of young female survivors following cytotoxic cancer treatments, the issue of fertility preservation has assumed greater importance.

Methods: We review the literature on the causes of female fertility loss as well as the recent advances in fertility preservation options and strategies that might be of interest to oncologists. Currently, several methods and techniques exist for fertility preservation of female patients with cancer including embryo freezing, ovarian protection techniques, oocyte cryopreservation, ovarian tissue cryopreservation followed by autotransplantation, and recently in vitro culture of ovarian tissue, follicles, and oocytes. Each method or technique has advantages and disadvantages related to current success rate, required delay in cancer treatment, sperm requirement, and risk of reintroducing cancer cells.

Results: To date, embryo freezing is the only established method successfully and widely used for fertility preservation of female patients with cancer. The other methods are promising but still considered experimental.

Conclusion: Patient awareness, physician knowledge, early counseling, costs management, international registry, interdisciplinary networks, and research development are necessary to improve the current care in the field of female fertility preservation.

Key words: autotransplantation, cancer, cryopreservation, fertility preservation, in vitro maturation, ovary

background

Ovarian aging and cytotoxic treatments are the most common causes for fertility loss in women. According to recent reports, ~700,000 women are newly diagnosed with cancers every year in the United States. About 8% of these women are under the age of 40 years and are at the risk of fertility loss following aggressive cytotoxic treatments [1]. Advances in the diagnosis and treatment of many childhood, adolescent, and adult malignancies have increased the cure and survival rates dramatically [2, 3]. With increasing numbers of female survivors at a young age, the issue of developing fertility preservation methods and strategies before chemotherapy and radiotherapy has become increasingly important [4, 5]. In this article, we review the causes of female fertility loss as well as the recent advances in fertility preservation options and strategies that might be of interest to oncologists.

Female fertility loss results from marked depletion of oocytes, which may be a physiological (natural) or pathological (premature) phenomenon [6]. Physiological or natural fertility loss occurs for all women at menopause due to aging. For most women, menopause occurs around age 50, when the quantity and quality of oocytes have markedly declined [7–9]. Pathological or premature fertility loss occurs before the age of 40 years and is induced mainly by aggressive cytotoxic treatments necessary for malignant or autoimmune diseases. Other causes of premature fertility loss include surgery such as bilateral oophorectomy for benign or malignant indications, autoimmune conditions, X-chromosome abnormalities, autosomal genetic conditions, and environmental hazards [6, 10].

Cytotoxic treatments act mainly through prevention of cell division and inhibition of DNA function. When ovaries are exposed to aggressive cytotoxic treatments such as chemotherapy and radiotherapy, gonadotoxicity occurs with irreversible follicular and oocyte damage resulting in premature ovarian failure (POF) [11, 12]. Alkylating chemotherapy such as cyclophosphamide and busulfan, as well as ionizing radiation to pelvis or abdomen, or total body irradiation, are the most gonadotoxic treatments and lead to subsequent POF in almost all cases [13–15]. Risks of permanent amenorrhea with currently used chemotherapy and radiotherapy regimens...
are summarized in Table 1 [16]. In addition to sustaining ovarian damage, adult survivors of childhood cancers may suffer from poor reproductive outcomes such as preterm birth and spontaneous abortion due to the disruption of the uterine vasculature and subsequent uterine damage following pelvic and abdominal irradiation [17]. The most common forms of malignant diseases in women that may occur during prepubertal, adolescent, and reproductive years and require cytotoxic treatments are leukemias, lymphomas, other hematologic malignant conditions, breast and cervical cancers, sarcomas, brain cancer, renal cancer, and bone cancer [18, 19]. Autoimmune diseases in women usually occur during the reproductive years, and some of them require similar cytotoxic treatments such as rheumatoid arthritis and systemic lupus erythematosus [20–22].

methods
Several methods and techniques are described in the literature to preserve fertility of female patients with cancer. Each method or technique has advantages and disadvantages related to current success rate, required delay in cancer treatment, sperm requirement, and risk of reintroducing malignant cells.

To date, embryo freezing is the only established method that is successfully and widely used for female fertility preservation [23–25]. The other methods for female fertility preservation are promising but still considered more or less experimental due to their debatable success rates, and include ovarian protection techniques, oocyte cryopreservation, ovarian tissue cryopreservation followed by autotransplantation, and recently in vitro culture of ovarian tissue, follicles, and oocytes [26–28]. Though experimental, all female fertility preservation methods mentioned above except in vitro culture of ovarian tissue and follicles, are currently used in clinical practice and have resulted in healthy live births [23–28]. This section reviews the recent advances in each female fertility preservation option and discusses its advantages, disadvantages, and future directions.

ovarian protection
The risk of ovarian damage following chemotherapy and radiotherapy may be reduced (depending on the type of cancer) using some surgical and nonsurgical protection methods to enable future pregnancy and childbirth [29–31].

Surgical protection is defined as prophylactic transposition of the ovaries away from the field of pelvic irradiation (oophoropexy). The most common indications of oophoropexy are Hodgkin’s disease, cervical and vaginal cancer, and pelvic sarcomas [32–35]. Oophoropexy may be carried out by laparotomy, laparoscopy, or robotic surgery [36]. Commonly, ovaries are transposed medially behind the uterus, or laterally outside the radiation field. The most simple and effective method is laparoscopic lateral ovarian transposition [37].

The success rate of oophoropexy is affected by the degree of scatter radiation, vascular compromise, age of the patient, dose of radiation, shielding of the ovaries, and if concomitant chemotherapy is used. A recent review showed that laparoscopic ovarian transposition in women <40 years old may be associated with preservation of ovarian function in up to 88.6% of cases [38]. After oophoropexy, spontaneous pregnancy is possible. If pregnancy cannot be achieved, oocyte retrieval and in vitro fertilization (IVF) is an option especially when ovaries were transposed to an abdominal position [39, 40]. Nonsurgical protection includes ovarian suppression by GnRH analogs and use of fractionated doses of chemotherapy and radiotherapy, as well as pelvic shielding.

GnRH analogs act on the pituitary to suppress gonadotropin secretion and consequently suppress the ovaries and make them hypothetically less sensitive to cytotoxic treatments. Therefore, GnRH analogs may provide some ovarian protection in adult females during chemotherapy [41, 42]. However, the results of using GnRH analogs for ovarian protection are still contradictory and need further investigations particularly in patients with breast cancer [43–48].

embryo freezing
To date, embryo freezing is the only established method successfully and widely used for fertility preservation in female patients with cancer. Embryo freezing has a very good post-thaw survival rate of 35%–90% and live birth rate of 27.7% per frozen embryo transfer [49, 50]. Studies have shown any increased risk of birth defects in babies conceived using frozen embryos compared with those born of naturally conceived pregnancies from mothers of a similar age [26, 51, 52].

Embryo freezing requires ovarian stimulation to retrieve mature oocytes and a sperm from a male partner or sperm donor for IVF. After IVF of the retrieved mature oocytes, embryos are then frozen for future use. Embryo freezing can be done at the 2, 4, or 8 cell or blastocyst stages either by conventional slow freezing or by vitriication (ultrarapid freezing). Vitriication is gradually replacing slow freezing of embryos due to a better post-thaw survival rate [53–55].

Conventional ovarian stimulation may require up to several weeks. Therefore, this procedure may not be an option for women with highly aggressive malignancies that require immediate cytotoxic treatment such as leukemia, some lymphomas, and sarcomas [36, 57]. Recently, random-start-controlled ovarian hyperstimulation for emergency fertility preservation has shown promising results [38].

In addition, due to conventional ovarian stimulation protocols and their resulting high serum estrogen levels and the risk of developing ovarian hyperstimulation syndrome (OHSS), ovarian stimulation may not be a suitable option for women with estrogen-sensitive cancers, such as breast and endometrial cancers or for women suffering from concomitant polycystic ovarian syndrome [59–61]. However, alternative controlled ovarian stimulation protocols with either tamoxifen (selective estrogen receptor modulator) or letrozole (aromatase inhibitor) have been successfully used apparently without adverse effects in patients with breast cancer [62–65].

Owing to its requirement for a sperm from a male partner or sperm donor for IVF, embryo freezing may not be an option for prepubertal and adolescent girls, nor for single women who refuse sperm donation for ethical or religious reasons. The same ethical issues may apply, when embryo donation, egg donation, gestational surrogacy, or adoption is offered [66–69].

oocyte cryopreservation
Oocyte cryopreservation may be an alternative to embryo freezing to avoid the need for a fertilizing sperm, in cases where a male partner or sperm donation are not available or refused. However, mature oocytes are more sensitive to cryoinjury than embryos due to their surface-area-to-volume ratio, high-lipid content, and the temperature-sensitive meiotic spindle [70–72].

Oocyte cryopreservation can be done either by conventional slow freezing or by vitriication. However, oocyte vitriication is associated with a better outcome due to relatively less cryoinjury. Exposure of oocytes to cryoprotectants induces hardening of the zona pellucida, necessitating that all oocyte cryopreservation protocols utilize intracytoplasmic sperm injection (ICSI) for fertilization [73–77].
Table 1. Risks of permanent amenorrhea with modern chemotherapy and radiotherapy adapted from the American Society of Clinical Oncology (ASCO) guidelines on fertility preservation in female patients with cancer [16]  

<table>
<thead>
<tr>
<th>Degree of risk</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| High risk (>80%) | - Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan  
|                | - External beam radiation to a field that includes the ovaries  
|                | - CMF, CEF, CAF × six cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin)  
| Intermediate risk | - CMF, CEF, CAF × six cycles in women age 30–39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin)  
|                | - AC × four cycles in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)  
| Lower risk (<20%) | - ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine)  
|                | - CHOP × four to six cycles (cyclophosphamide/doxorubicin/vincristine/prednisone)  
|                | - CVP (cyclophosphamide/vincristine/prednisone)  
|                | - Acute myeloid leukemia (AML) therapy (anthracycline/cytarabine)  
|                | - Acute lymphoblastic leukemia (ALL) therapy (multi-agent)  
|                | - CMF, CEF, CAF × six cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)  
|                | - AC × four cycles in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)  
| Very low or no risk | - Methotrexate, fluorouracil, vincristine, bleomycin, dactinomycin  
| Unknown risk (examples) | - Taxanes, oxaliplatin, irinotecan, monoclonal antibodies, tyrosine kinase inhibitors |

To date, more than 900 babies have been born after cryopreservation of the in vivo matured oocytes, with no major increase in complication rates including miscarriage or congenital abnormality [78]. The live birth rate per cryopreserved oocyte has recently improved from 2% to 6% due to advances in freezing and thawing protocols [79–83]. It is also recommended that more mature oocytes per cycle should be retrieved and cryopreserved to increase the success rate [84].

Similar to embryo freezing, oocyte cryopreservation requires ovarian stimulation to retrieve mature oocytes, and therefore, it has the same disadvantages as mentioned above [59–65]. Likewise this procedure is not an option for prepubertal girls but may be suitable for adolescent girls [66–69].

**ovarian tissue cryopreservation and autotransplantation**

Ovarian tissue cryopreservation and autotransplantation is a promising option in fertility preservation of female patients with cancer. This procedure allows immediate initiation of cancer treatment as it does not require prior ovarian stimulation nor sperm donation. Unlike embryo freezing and oocyte cryopreservation, ovarian tissue cryopreservation and autotransplantation may be the only possible option for prepubertal girls, women with estrogen-sensitive cancers, and women with highly aggressive malignancies where rapid initiation of treatment is required [26, 27, 85].

Removal of ovarian tissue can be done via laparoscopy or laparotomy immediately before cancer treatment. Usually 50% of one ovary is excised; however, excision of one whole ovary can be carried out when ovarian damage is highly expected due to pelvic irradiation or high-dose chemotherapy. If clinically reasonable, the other ovary is left in situ so that the patient can maintain the potential for natural fertility in the case of continued ovarian function after treatment [86]. Excised ovarian tissue can be transported in special thermoboxes to centralized cryobanks by commercial transportation within 24 h for final processing and cryopreservation [86, 87].

The human ovarian cortex contains the vast majority of the follicular reserve. Via cryopreservation of ovarian cortical strips, most of the primordial follicles are preserved as they resist cryoinjury due to their small size and low metabolic rate. Cryopreservation of ovarian cortical strips is routinely done via the slow freezing method, although vitrification is currently being developed in research settings [88–90]. Many reports using viability staining and xenografting have confirmed the survival and developmental potential of primordial follicles after cryopreservation and thawing using human cortical tissue [91–94].

When pregnancy is desired after recovery from cancer, the stored ovarian cortical strips are thawed and transplanted back into the same patient, to either an orthotopic or heterotopic site. Orthotopic sites include the remaining ovary or the ovarian fossa, whereas heterotopic sites include sites outside of these, such as the subcutaneous space of the forearm or the abdominal wall. Orthotopic transplantation is more successful and usually preferred, as it provides a more physiological environment for follicle and oocyte development in addition to the possibility of natural conception. Heterotopic transplantation necessitates future oocyte retrieval and IVF. Thus, heterotopic transplantation may only be indicated in cases...
where the pelvis is affected by previous irradiation or by severe scar formation [95–97].

Many reports have shown resumption of endocrine ovarian function in women after either orthotopic or heterotopic transplantation; however, follicular development and oocyte fertilization are not straightforward. To date, there are only 15 live births reported after human ovarian tissue cryopreservation and orthotopic autotransplantation [98–100]. Heterotopic transplantation in human has resulted in a four-cell embryo [101] and a biochemical pregnancy [102] but no live births to date. However, it has resulted in a live birth in monkeys [103].

Following orthotopic autotransplantation, the origin of the reported pregnancies (whether the oocyte stemmed from the transplanted tissue or from the remaining ovarian tissue) cannot be confirmed with complete certainty, as it is feasible that spontaneous conception from the remaining ovary could have occurred. This was the case in four spontaneous pregnancies and three live births following heterotopic subcutaneous transplantation of frozen banked ovarian tissue where a woman conceived naturally from an oocyte stemmed from the ovarian tissue left in situ [104].

Ovarian tissue cryopreservation and autotransplantation carries the risk of reintroducing malignant cells. This is especially a concern in ovarian cancer, hematological malignancies such as leukemia or in other malignancies that may metastasize to the ovaries, such as gastrointestinal and breast cancers [26, 27, 85]. Techniques such as preoperative imaging, biomarker screening, histological examination, immunohistochemistry, polymerase chain reaction, and xenografting can be carried out to minimize the risk of ovarian macro- and micro-metastasis [105–107].

Other disadvantages of ovarian tissue cryopreservation and autotransplantation include the limited life span of the ovarian grafts and the potential post-transplantation window of ischemia that is responsible for atresia of up to 70% of follicles. Some studies have therefore suggested the use of vascular ovarian grafts, angiogenic factors, and antioxidants to improve neovascularization and to prevent ischemia and subsequent follicular loss following transplantation [108–111].

Whole ovary cryopreservation via slow freezing or vitrification has been studied in human and several animal species [112–118]. Moreover, transplantation of cryopreserved whole or semi-ovary was successful in sheep and resulted in live births [112, 116, 117]. However, the major difficulties associated with cryopreservation and autotransplantation of the whole ovary are the very high follicular loss after transplantation as well as the greater risk of reintroducing malignant cells [119].

In addition to autotransplantation, fresh and frozen/thawed ovarian cortex transplantation between monozygotic twin sisters has been attempted resulting in restoration of ovarian function, successful pregnancies, and healthy babies [108, 120].

### multistep in vitro fertility preservation strategy

Many reports have suggested plausible in vitro methods for fertility preservation in humans based on an experimental multistep strategy including sequential in vitro culture of ovarian tissue, follicles, and oocytes (Figure 1). The aim of the multistep in vitro strategy is to produce mature oocytes ready for IVF without the need for ovarian stimulation. After IVF, embryos could be transferred in utero or frozen for later use [26, 121–123].

The multistep in vitro strategy could be an alternative to ovarian tissue cryopreservation and autotransplantation to overcome the limited life span of ovarian grafts as well as the risk of reintroducing malignant cells. Moreover, the multistep in vitro strategy does not require ovarian stimulation with its potential complications such as OHSS and delay in cancer treatment.

As ‘step one’ of the proposed multistep in vitro strategy, fresh or cryopreserved-thawed tissue slices of human ovarian cortex would be cultured in vitro to allow for growth of follicles from the primordial to the preantral stage. As ‘step two’, preantral follicles could then be isolated enzymatically and/or mechanically and further cultured individually in vitro in a two- or three-dimensional environment. As ‘step three’, when the follicles have reached the antral stage, oocyte granulosa cell complexes would be retrieved and cultured to induce oocyte in vitro maturation (IVM). Finally, in vitro matured oocytes could be either cryopreserved or fertilized to produce embryos. After IVF, embryos can be directly transferred in utero or cryopreserved for further use. The critical points and details of these three in vitro steps or procedures will be discussed below.

### in vitro culture of ovarian tissue

By culturing human ovarian cortex, many primordial follicles enter the growing pool over short culture periods of 6–10 days [124, 125].

To overcome difficulties in nutrients diffusion, as well as gas and metabolites exchange, human ovarian cortex should be cut and cultured as small thin pieces or slices. The other advantage of culturing small pieces or slices of human ovarian cortex is the maintenance of not only the organizational structure of the ovarian tissue but also the interactions between the follicle and surrounding thecal and stromal cells [124–126].

Disadvantages of human ovarian tissue culture include ischemia in the interior of the tissue with no possibility of revascularization in vitro. Another disadvantage to this technique is the inability to follow-up and clearly measure follicles within the tissue by light microscopy over the culture period. In addition, follicle integrity and oocyte survival are only maintained for a relatively short period. Therefore, to develop further, follicles and oocytes must be released from the ovarian stromal environment [26, 124, 125].

Various reports have confirmed follicle survival and growth as well as hormone production after in vitro culture of fresh and/or frozen-thawed human ovarian cortical tissue [89, 124, 127–129]. Two approaches have been successfully used to this end, including culture on the conventional two-dimensional surface, and culture in three-dimensional gels or extracellular matrix [127, 130–132].

### in vitro culture of ovarian follicles

The aim of in vitro culture of ovarian follicles is to produce mature oocytes ready for fertilization [26, 121, 122, 133–135]. The production of mature oocytes and live offspring has been achieved in mice following the long-term culture of oocytes in primordial and preantral follicles isolated from both fresh and cryopreserved ovarian tissue [136–140]. In contrast, in nonrodent species, large animals, and humans, the complete in vitro growth and maturation of follicles and oocytes may be achieved only through a multistep strategy that closely mimics the conditions present in the ovary in vivo. In this approach, primordial follicles growth is initiated in situ by culturing ovarian cortical. Afterward, isolated preantral follicles are grown in vitro to the antral stage followed by isolation and IVM of the oocytes [124, 125, 141–144].

Two approaches have been successfully used for in vitro culture of isolated follicles, including two- and three-dimensional culture systems. With two-dimensional culture systems, isolated follicles may attach and grow on to a two-dimensional surface, resulting in the migration of granulosa cells away from the oocyte leaving the oocyte naked and vulnerable. With three-dimensional culture systems, isolated follicles are embedded or encapsulated into biologic or synthetic matrices to maintain their three-dimensional architecture during growth that occurs in all directions as in vivo [145–147].

Both approaches have produced live offspring in mice. In contrast to three-dimensional culture systems, two-dimensional culture systems appear to be less successful in supporting normal follicular development in large animals or humans. However, to date, no meiotically competent human oocytes have been produced using either two- or three-dimensional follicle
culture systems [148–150]. Recently, alginate hydrogel three-dimensional culture systems have shown very promising results especially in large animals and in the human. In rhesus monkeys, alginate hydrogel supported preantral follicle growth to the antral stage and, for the first time, promoted oocyte maturation to the MII stage [141]. In human, alginate hydrogel supported *in vitro* development of preantral follicles into large antral stages within 30 days but there was no evidence of producing fertilizable development of the IVM babies [157].

**oocytes in vitro maturation**

Oocyte IVM involves *in vitro* culture of immature oocytes to produce mature oocytes ready for IVF. The immature oocytes can be retrieved clinically from stimulated or unstimulated ovaries or experimentally from extracted ovarian tissue biopsies or from *in vitro* cultured follicles [151–155].

As it does not require the conventional ovarian stimulation, oocyte IVM avoids OHSS and delay in cytotoxic treatment. Therefore, this technique is considered very suitable for patients having polycystic ovaries as well as for patients seeking fertility preservation [156, 157]. This method is menstrual cycle independent, with the possibility to retrieve immature oocytes in the follicular phase or even in the luteal phase, providing a time saving option for many patients [158–161].

Commonly, ICSI has been practiced more than IVF in IVM cycles to minimize the risk of zonal hardening during the *in vitro* culture period [162–164].

Regarding cryopreservation of the *in vitro* matured oocytes, vitrification is currently preferred to slow freezing. The live birth rate following vitrification of *in vitro* matured oocytes is still lower than *in vivo* matured oocytes [165]. Vitrification of immature oocytes at germinal vesicle (GV) stage was also evaluated with no differences seen in the survival rates compared with the vitrification of *in vitro* matured oocytes. However, the potential of oocyte maturation is reduced by vitrification of immature oocyte at GV stage [157].

Approximately the overall live birth rate per cycle of IVM is half of that for traditional IVF. Follow-up studies seem reassuring and have reported no increased risks regarding the pregnancies, deliveries, and the health and development of the IVM babies [157].

**integration of the different female fertility preservation options**

Preserving fertility of a young female patient with cancer is a complex decision not only for the patient, but also for her oncologist and gynecologist [166]. Therefore, oncofertility—an emerging discipline at the intersection of oncology and fertility—has recently developed to help young female patients with cancer in the decision-making process of fertility preservation [167, 168].

To this end, some tools and guidelines have been developed such as the American Society of Clinical Oncology (ASCO) guidelines published in 2006 [16] and the decision tree developed by Woodruff and coworkers in 2010 (Figure 2) [169]. Briefly, once cancer is diagnosed, the patient must be asked about her desire for future fertility. If the patient is not interested in fertility preservation, cancer therapy can proceed. However, if the patient is interested in attempting to preserve future fertility, the next steps involve both patient counseling and coordination of care. A fertility preservation plan can be tailored to an individual’s circumstances and integrate both established and experimental fertility preservation options [170–172]. The different options for fertility preservation, third-party reproduction, and adoption (depending on national legislation) that can be offered to female patients with cancer are summarized in Table 2 [16, 78, 173]. In 2010, the survey for preservation of adolescent reproduction demonstrated pediatric oncologists’ motivation to preserve fertility in patients with pediatric cancer according to ASCO guidelines. However, barriers to both gamete cryopreservation and referral to fertility specialists were cited especially in female pubertal patients [174].

For a wider and comprehensive vision of the emerging oncofertility field, some national and international interdisciplinary networks were recently established to advance the fertility preservation options for young female and male cancer survivors, and promote communication between researchers, clinicians, patients, and the public. Examples of such networks are the Oncofertility Consortium in the United States [25] and the FertiPROTEKT Network in Europe [28].

**results**

Several methods exist for fertility preservation in young female patients with cancer before chemotherapy and radiotherapy. However, embryo freezing is the only established method successfully and widely used. All other methods are promising but still have to be considered as experimental. More studies are still required to improve the outcome of ovarian protection techniques, oocyte cryopreservation, ovarian tissue cryopreservation, autotransplantation, and the *in vitro* culture of ovarian tissue, follicles, and oocytes. All preservation methods mentioned above, except *in vitro* culture of ovarian tissue and follicles, are currently used in clinical practice and have resulted in healthy live births.

**conclusion**

With increasing numbers of young female survivors following cytotoxic cancer treatments, the issue of fertility preservation has assumed greater importance. Patient awareness, physician knowledge, early counseling, costs management, international registry, interdisciplinary networks, and research development
Figure 2. Decision tree for fertility preservation in female patients with cancer [169]. With the decision tree, the fertility preservation plan can be tailored to the patient's circumstances and integrate both established and experimental fertility preservation options.
Table 2. Different options for fertility preservation, third-party reproduction, and adoption that can be offered to female patients with cancer adapted from the American Society of Clinical Oncology (ASCO) guidelines on fertility preservation in female patients with cancer [16, 78]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ovarian protection (ovariopexy)</th>
<th>Gonadal shielding</th>
<th>Ovarian suppression</th>
<th>Embryo freezing</th>
<th>Oocytes cryopreservation</th>
<th>Ovarian tissue cryopreservation and autotransplantation</th>
<th>Oocyte in vitro maturation (IVM)</th>
<th>Third party reproduction (Embryo donation)</th>
<th>Oocytes donation</th>
<th>Gestational surrogacy</th>
<th>Adoption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Surgical repositioning of ovaries away from the radiation field</td>
<td>Use of shielding to reduce scatter radiation to the reproductive organs</td>
<td>Use of GnRH analogs to suppress ovaries</td>
<td>Ovarian stimulation, harvesting oocytes, IVF, and freezing of embryos for later implantation</td>
<td>Ovarian stimulation, harvesting and freezing of unfertilized oocytes</td>
<td>Freezing of ovarian tissue and implantation after cancer treatment</td>
<td>Harvesting of immature oocytes, IVM, and oocyte or embryo freezing</td>
<td>Embryos donated by a couple</td>
<td>Eggs donated by a woman</td>
<td>Woman carries a pregnancy for another woman or couple</td>
<td>Process that creates a legal parent–child relationship</td>
</tr>
<tr>
<td>Is it established or still experimental?</td>
<td>Established</td>
<td>Established</td>
<td>Experimental</td>
<td>Experimental</td>
<td>Experimental</td>
<td>Experimental</td>
<td>Established</td>
<td>Established</td>
<td>Established</td>
<td>Established</td>
<td>Established</td>
</tr>
<tr>
<td>Is it suitable for prepubertal girls?</td>
<td>Suitable</td>
<td>Suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
<td>Suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
<td>Not suitable</td>
</tr>
<tr>
<td>Does it require any delay in cancer treatment?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes, due to ovarian stimulation</td>
<td>Yes, due to ovarian stimulation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>When can it be carried out in relation to cancer treatment?</td>
<td>Before treatment</td>
<td>During treatment, in conjunction with radiotherapy</td>
<td>During treatment, in conjunction with chemotherapy</td>
<td>Before or after treatment</td>
<td>Before or after treatment</td>
<td>Before or after treatment</td>
<td>Before or after treatment</td>
<td>After treatment</td>
<td>After treatment</td>
<td>After treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Does not protect against gonadotoxic effects of chemotherapy</td>
<td>Does not protect against gonadotoxic effects of chemotherapy</td>
<td>Does not protect from radiation effects</td>
<td>Needs partner or donor sperm</td>
<td>May be attractive to single women or those opposed to embryo creation</td>
<td>Not suitable if high risk of ovarian metastases</td>
<td>Suitable also for patients with PCO</td>
<td>Legal status varies worldwide due to social or religious concerns</td>
<td>Legal status varies worldwide due to social or religious concerns</td>
<td>Legal status varies worldwide due to social or religious concerns</td>
<td>Legal status varies worldwide due to social or religious concerns</td>
</tr>
<tr>
<td>Success rates</td>
<td>~50% chance of success</td>
<td>Unknown; contradictory results reported</td>
<td>Live birth rate of 27.7% per frozen embryo transfer</td>
<td>Live birth rate of 2%–6% per frozen oocyte</td>
<td>Case reports of 15 live births to date</td>
<td>Half of that for traditional IVF</td>
<td>Unknown; higher than that of IVF transfers</td>
<td>Live birth rate of 40%–50% per cycle</td>
<td>Similar to IVF; approximately 30% per cycle</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

IVF, *in vitro* fertilization; GnRH, gonadotropin-releasing hormone; PCO, polycystic ovaries; NA, not applicable.
are necessary to improve the current care in the field of female fertility preservation.

disclosure

The authors have declared no conflicts of interest.

references


