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Invited Review

Fertility preservation in gynecologic cancers

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HIGHLIGHTS

- Numerous effective fertility preservation options exist for women with gynecological malignancies.
- Conservative surgery is feasible in reproductive age women with gynecologic cancer.
- Embryo, oocyte and ovarian tissue freezing followed by autotransplantation are successful fertility preservation approaches.
- Special ovarian stimulation protocols exist for women with hormone sensitive cancers or for emergent fertility preservation.

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ABSTRACT

An increasing number of women in modern societies are delaying childbearing beyond the age of 35, and gynecologic cancers affect a significant proportion of reproductive age women who wish to preserve fertility for a future chance of childbearing. As a result, providing treatment options for fertility preservation in women with gynecologic cancer has become a crucial component of cancer survivorship care. In this review article, we discussed the current knowledge on fertility-sparing surgical approaches, as well as assisted reproductive technologies that can be utilized to preserve reproductive potential in women with cervical, endometrial, and ovarian cancer. A brief section on fertility preservation in pediatric gynecologic malignancies is also provided.

Contents

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1. Introduction

Although the incidences of most gynecologic malignancies peak substantially after the age of 50 years, a significant number of women encounter with a diagnosis of gynecologic cancer during reproductive age. According to the most recent Surveillance, Epidemiology and End Results (SEER) cancer statistics report based on the data between 2012 and 2016, the percentages for newly diagnosed uterine cancer, ovarian cancer, and cervical cancer under the age of 45 are 6.5%, 12%, and 36.5%, respectively [1]. Intertwined with the increasing sociodemographic transition toward women having first childbirth beyond age 35, reproductive aging, and gonadotoxic treatments, fertility issues have become more prevalent and complicated in women with cancer [2]. Considering the standard treatment strategies for gynecologic cancers, which involve surgical removal and/or ablative therapies of reproductive tract organs, the importance of preserving reproductive potential in this patient population has become more evident than ever before. Therefore, providing timely evaluation and treatment for available fertility preservation options without jeopardizing the cancer treatment has become an essential component of modern oncological care [3,4].

In this review article, we discuss the key topics from cancer therapies to BRCA mutations and to the timely referral that significantly determine the extent of the potential damage to the female reproduction and future success of preserving fertility. We then present an overview of currently available treatment strategies for fertility preservation in gynecologic malignancies including a section on the pediatric age group. We also briefly examine the debate on the use of GnRH analogs for the prevention of chemotherapy-induced ovarian damage. Finally, we present the current knowledge on the safety of pregnancy after cancer treatment and conclude with promising new technologies that may potentially transform the future of human reproductive science and clinical practice.

2. Impact of cancer treatment on fertility

Chemotherapy and radiotherapy have been successfully utilized in the treatment of several gynecologic malignancies. Alkylating agents, platinum derivatives, taxanes, anthracyclines, and antimetabolites are the most commonly used anti-neoplastic drugs for gynecologic cancers. The mechanism of activity of these chemotherapeutics and ionizing radiation is primarily based on the disruption of genomic synthesis and repair machinery in cancer cells. Causing extensive DNA damage that exceeds the cellular DNA repair capacity, anti-neoplastic agents ultimately lead to apoptotic cell death in cancer cells [5,6]. However, these therapies are usually non-selective to cancer cells, thus inducing concurrent damages in healthy tissues and organs. Following chemotherapy and radiotherapy, women are at increased risk of experiencing ovarian insufficiency and early menopause, as well as fibrosis, atrophy, and vascular injury in reproductive organs due to toxicity. The extent of their toxicity on reproductive organs, particularly to ovaries, depends on several parameters such as the age of the patient at the time of treatment, cumulative doses of chemotherapeutic agents and ionizing radiation, type of the chemotherapeutic regimen, and the application field of irradiation. Abdominal and pelvic radiation directly targeting ovaries can cause follicle depletion and ovarian failure. Furthermore, severe fertility issues can occur following radiotherapy due to endometrial and myometrial damage, fibrosis, and atrophy. Although it is often challenging to accurately determine the exact exposure of radiation to reproductive organs due to the scattering effect and locational variations of ovaries, potential doses for toxicity proposed based on the data collected from young patients who underwent total-body irradiation (TBI) before hematopoietic stem cell transplantation. While abdominopelvic radiation dose of <4 Gy does not appear to impair ovarian or uterine function, the risk of amenorrhea and ovarian damage significantly increases with doses exceeding 6–10 Gy. Wallace *et al.* developed a differential equation to model and predict the rate of follicle decline by age for a given dose of radiation. By solving the equation, one can estimate the number of remaining follicles after a specific dose of radiation and predict the risk of ovarian failure following radiotherapy [7]. Based on this model and data from clinical studies, total irradiation doses beyond 20 Gy is generally accepted as sterilizing due to immediate ovarian failure and severe uterine damage that cannot sustain pregnancy [8].

Among the anti-neoplastic drugs, alkylating agents such as cyclophosphamide pose the highest risk for ovarian toxicity and infertility [5,6]. Alkylating agents exert their cytotoxic activity via inducing DNA cross-linking and DNA strand breaks regardless of the proliferative state of the cell. Due to cell-cycle independent cytotoxic activity, alkylating agents target both growing follicles and dormant primordial follicles that constitute the ovarian reserve. Clinical trials in women with breast cancer have shown that other anti-neoplastic agents such as cisplatin and paclitaxel, which are also commonly used for the treatment of gynecologic malignancies, pose relatively moderate to low risk for infertility based on menstrual recovery rates post-chemotherapy [9]. Table 1 summarizes the characteristics of the commonly used chemotherapeutic agents and their potential effect on fertility.

3. BRCA mutations and ovarian reserve

BRCA1 and BRCA2 genes are members of the ataxia-telangiectasia-mutated (ATM)-mediated DNA damage signaling pathway and play an essential role in DNA double-strand break (DSB) repair, and mutations in these genes are associated with increased risk of breast and ovarian cancer [10]. In addition to cancer development, BRCA gene mutations are related to diminished ovarian reserve and accelerated reproductive aging [11–13]. Investigating the mechanisms underlying the ovarian aging process, we have demonstrated that mice with BRCA1 mutations accumulate DNA DBSs with an increased pace by aging in primordial follicle oocytes that constitute the ovarian reserve [11]. BRCA1 mutant mice had lower primordial follicles in their ovaries and also showed reduced litter size and poor embryo development. In parallel to these results in the mouse model, we also showed that affected women with BRCA1 mutations had lower serum anti-Müllerian hormone (AMH) levels compared to controls. Concordant with our results, Lin *et al.* reported that BRCA mutation carrier women experience menopause 3–4 years earlier than healthy controls [14]. Similarly, Philips *et al.* found 25% lower AMH concentrations on average in BRCA1 carriers compared to non-carriers [15]. Even though most studies found this association with BRCA1

Table 1
Chemotherapeutic agents commonly used in the treatment of adult and pediatric gynecologic cancers, their mechanism of action, and risk of infertility.

Chemotherapeutic agent	Class of anti-neoplastic drug	Mechanism of action	Cell cycle effect	Risk of infertility
Cyclophosphamide	Alkylating agent	DNA cross-link formation and double-strand breaks.	Cell cycle non-specific	High risk
Doxorubicin	Anthracyclines	Inactivation of DNA topoisomerase II, free oxygen radical formation, and induction of DNA double-strand breaks.	Cell cycle non-specific	Medium risk
Carboplatin Cisplatin	Platinum analogs	Intra- and inter-strand DNA cross-link formation by covalent binding to genome.	Cell cycle non-specific	Medium risk
Paclitaxel	Taxanes	Inhibition of cell division by disrupting microtubule formation during mitosis.	M phase	Low risk
Vincristine	Vinca alkaloid	Inhibition of tubulin polymerization and microtubule formation	M phase	Low risk
Dactinomycin	Antitumor antibiotic	Inhibition of mRNA transcription by binding to the transcription initiation complex	Cell cycle non-specific	Medium-low risk
Bleomycin	Antitumor antibiotic	Single and double strand DNA break formation via free oxygen radicals	G_2 – M phase	Low risk
Etoposide	Topoisomerase II inhibitor	Inhibition of DNA replication via blocking topoisomerase II activity	G_1 – S phase	Low risk
Methotrexate	Antimetabolites	Inhibition of de novo purine nucleotide synthesis by inactivation of dihydrofolate reductase.	S phase	Low risk
5-Fluorouracil		Inhibition of DNA synthesis and function via inactivation of Thymidylate synthase and alteration in RNA processing.	S phase	Low risk

(Modified from reference [9].)

mutations, one study found diminished ovarian reserve in BRCA2 mutation carriers [16].

Current evidence from clinical studies and animal experiments suggest that reproductive-age women with BRCA mutations are more prone to ovarian aging and vulnerable to chemotherapy-induced ovarian reserve loss. Therefore, clinicians should be more proactive in patients with germline BRCA mutations who wish to preserve fertility.

4. Counseling for fertility preservation

The American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM) have recently released updated practice guidelines for fertility preservation in women with cancer [3,4]. These guidelines strongly recommend clinicians to inform patients receiving therapies potentially toxic to ovaries and/or reproductive organs about the possible adverse effects of those treatments on future fertility and available fertility preservation options before the initiation of such treatments. Therefore, patients facing the risk of infertility due to planned oncological treatments should be promptly referred to a reproductive specialist who is particularly experienced in the field of fertility preservation. However, since the first ASCO practice guideline on fertility preservation published in 2006, studies have shown that less than half of the oncologists in the United States follow these guidelines and refer their patients under the risk of fertility loss to a fertility preservation specialist [17]. Similarly, Selter *et al.* recently reported that in 2016 only 5.5% of reproductive age women with lung, breast, colorectal or cervical cancer was evaluated for fertility preservation in the United States, and only 4.6% of those patients underwent a fertility preservation procedure [18].

Although oncologists are traditionally focused on providing the most effective cancer treatments to prolong patient lifespan and improve the quality of life, it should be emphasized that reproductive health is a crucial component of quality of life and it has become even much needed with growing cancer survival rates in the last two decades. Factors such as feeling distressed and overwhelmed at the time of diagnosis, lack of knowledge about available fertility preservation treatments, and concerns about the cost of treatments may cause limitations in referral and decision-making process. However, counseling for fertility preservation has been shown to significantly reduce long-term regret and dissatisfaction about fertility in women with cancer [19]. Hence, evaluation for fertility preservation should start as early as the planning for the cancer treatment. When the optimal fertility preservation procedure for the patient is decided, it can be typically completed in 2–3 weeks without causing a delay in the initiation of oncological treatment. For patients who need to start cancer treatment immediately, an increasingly effective fertility preservation option such as ovarian tissue cryopreservation and autotransplantation also exists [20–22]. We have previously shown that with early referral and intervention, a larger number of oocytes and embryos could be successfully collected and cryopreserved in women with breast cancer for future pregnancy [23]. Therefore, cancer care providers should be more attentive to fertility issues and collaborate with reproductive specialists to facilitate fertility preservation services for women with cancer.

Additionally, evaluation for cancer susceptibility genes is an essential component of the counseling to provide individualized treatment and surveillance strategies. Molecular profiling and genetic counseling for women with hereditary cancer syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2 mutations) and Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC/Lynch Syndrome) (DNA mismatch repair gene mutations) should be provided. Women with BRCA1 or BRCA2 mutations have up to 46% lifetime risk of developing ovarian, tubal, and peritoneal cancers by the age of 70. The lifetime risks for gynecologic malignancies related to Lynch Syndrome are up to 60% and 12% for endometrial and ovarian cancers, respectively. Mutations in PTEN, TP53, and STK11 are also associated with a genetic predisposition to gynecologic cancers. Therefore, after completing childbearing, risk-reducing salpingo-oophorectomy for BRCA mutation carriers and hysterectomy with bilateral salpingo-oophorectomy for patients with Lynch Syndrome are strongly recommended.

5. GnRH analogs and ovarian protection

Ovarian suppression using GnRH analogs (GnRHa) to prevent ovarian reserve from chemotherapy-induced damage has been controversial due to conflicting results, methodological issues, and lack of biological plausibility. A key concern regarding the effectiveness of this approach is that dormant primordial follicles, which constitute the human ovarian reserve, do not express GnRH or gonadotropin (FSH, LH) receptors. Using FSH receptor-deficient mouse model to simulate the FSH suppression during GnRHa treatment, researchers have shown that cyclophosphamide induced significant loss of primordial follicles regardless of GnRHa use [24].

Clinical studies investigating the role of GnRHa use in ovarian protection from chemotherapeutic damage reported conflicting

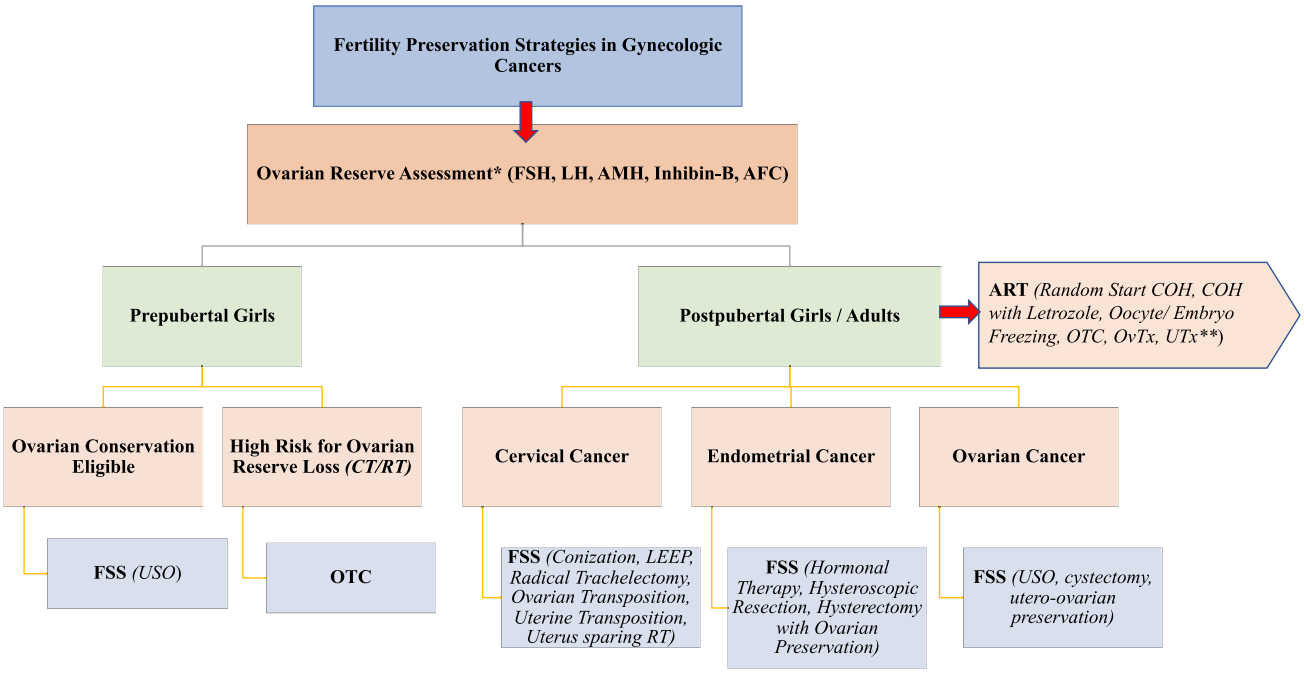

Fig. 1. An algorithmic approach to fertility preservation options in gynecologic cancers. (AFC, antral follicle count; AMH, anti-Müllerian hormone; ART, assisted reproductive technology; COH, controlled ovarian hyperstimulation; CT/RT, chemotherapy/radiotherapy; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FSS, fertility-sparing surgery; USO, unilateral salpingo-oophorectomy; OTC, ovarian tissue cryopreservation; OvTx, ovarian transplantation; UTx, uterine transplantation). *Ovarian reserve should be assessed not only to guide the fertility preservation strategy but also to be able to assess the extent of the damage to ovarian reserve after the completion of the cancer therapy. **Currently experimental procedure.

results. In studies involving women with breast cancer, some researchers suggested that GnRHa co-treatment may reduce chemotherapy-induced premature ovarian insufficiency (POI) in women <40 years of age [25]. However, these studies were criticized due to many weaknesses such as using poor ovarian reserve surrogates such as menstruation and confusing diminished ovarian reserve with ovarian failure [26,27]. Randomized clinical trials that used quantitative and reliable ovarian reserve surrogates such as the anti-Müllerian Hormone (AMH), which is the best available biomarker to detect changes in ovarian reserve and usually combined with antral follicle count (AFC), showed no benefit from GnRHa co-treatment for chemotherapy-induced ovarian reserve loss [28,29]. Given these reports showing no clear evidence for a protective effect of ovarian suppression during chemotherapy, we do not recommend GnRHa co-treatment as a fertility preservation option to women undergoing gonadotoxic treatments.

6. Fertility preservation strategies in gynecologic cancers

In gynecologic cancers, fertility preservation strategies include fertility-sparing surgical approaches and assisted reproductive technologies (ART). The optimal strategy may vary in each patient based on the type and stage of malignancy, age at diagnosis, ovarian reserve status, available time from diagnosis to initiation of cancer treatment, and the type of planned cancer treatment. Hence, a personalized strategy with a multidisciplinary approach including the gynecologic surgeon, oncologist, and the reproductive specialist is crucial to provide the best treatment option to the patient. An algorithmic approach for fertility preservation strategy in gynecologic cancers is demonstrated in Fig. 1.

6.1. Cervical cancer

Cervical cancer is the second most common gynecologic malignancy in the United States with an estimated 13,170 new cases in 2019, and approximately 36.5% of those are women under age 45 years [1]. Although, the standard treatment for FIGO stage I-IIA disease is radical hysterectomy, *uterus-preserving* surgery such as loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) can be performed in reproductive age women with stage IA1 disease. The risk of recurrence after CKC in patients with stage IA1 disease and with no lymphovascular space invasion (LVSI), negative endocervical curetting after excision, and negative surgical margins was reported <0.5% [30]. The 5-year survival rates were also found comparable in patients under age 40 years who underwent hysterectomy and cervical conization, 99% vs. 98%, respectively [31]. However, in patients with positive LVSI, the risk of recurrence may increase up to 9%; hence, an additional thorough pelvic lymph node dissection and sentinel node mapping are recommended in those cases [32]. For stage IA2-IB2 cervical cancer, Bogani *et al.* recently reported 94% five-year disease-free survival and 97% overall survival rates in patients who underwent conization combined with pelvic node dissection via laparoscopy [33].

Radical trachelectomy with pelvic lymphadenectomy is another option for preserving uterus in early stage cervical cancer and can be performed via abdominal (AT), vaginal (VT) or minimally invasive methods such as laparoscopy or robotic surgery. In a recent meta-analysis, AT was found to be associated with a longer operative time compared to radical hysterectomy. However, no difference was observed in the five-year overall survival and disease-free survival rates between two groups suggesting that AT can be safely offered to women who wish to preserve fertility [34]. In a multicenter study, Cao *et al.* reported better pregnancy outcomes in the VT group compared AT (39.5% vs. 8.8%; $P = 0.003$). However, the recurrence rate was significantly higher in patients who underwent VT (0 in AT vs. 9.8% in VT, $P = 0.035$) [35]. Alternatively, for stage IB disease, neoadjuvant three courses of platinum-based chemotherapy combined with conservative surgery is proposed as an efficient fertility-sparing treatment [36]. Regarding the advanced cervical cancer with tumor size >2-cm, neoadjuvant chemotherapy

and abdominal radical trachelectomy reported as feasible strategies, however, there is limited experience and increased risk of recurrence (17%) that complicates the oncological safety of uterine preserving procedures in these cases. Therefore, these options should be offered in only selected patients [36].

Uterine preserving surgery enables to retain a functional uterus that can sustain a pregnancy. However, it should be noted that cervical excisional procedures are related to a significant increase in obstetric complications such as preterm delivery and prematurity due to loss of anatomical support and physiological function of the cervix [36].

For patients undergoing pelvic radiotherapy, ovarian transposition, and uterine transposition following radical trachelectomy to an upper abdominal location far from the irradiation field have been successfully described [37,38]. Laparoscopic ovarian transposition technique has been reported to have a success rate of 88.6% for preservation of ovarian function [37]. Though these techniques may significantly reduce the direct impact of ionizing radiation, studies have shown that the protective efficiency of these methods can be limited due to altered blood flow and scattered radiation. In addition, a secondary surgery is required in most cases to reposition the transposed organs to their original location in the pelvic cavity. Alternatively, high-precision modern radiation therapy methods such as MRI-guided brachytherapy can be utilized to reduce the scattering effect of radiation and selectively target uterine cervix, preserving healthy uterine corpus from radiation damage [39].

6.2. Endometrial cancer

The standard surgical management of the disease is total hysterectomy with bilateral salpingo-oophorectomy, and when appropriate sentinel lymph node mapping and pelvic/para-aortic lymphadenectomy may be combined in certain cases. Among the affected women, 6.5% are of age < 45 years that may wish to preserve fertility. Currently, there are limited *uterine preserving* strategies in fertile women with endometrial cancer, which include hormonal therapy with progestins and hysteroscopic resection of the tumor. Progestin therapy is considered for patients with grade 1 (well differentiated) endometrial adenocarcinoma without any sign of LVSI or myometrial invasion on the imaging via magnetic resonance imaging (MRI) or transvaginal ultrasound [40]. Importantly, these patients should be monitored with endometrial sampling every 3 to 6 months for treatment response, and high-risk histological subtypes or higher stages of disease are not considered for conservative management [41]. Progestin therapy regimens include oral use of megestrol acetate (160 mg daily) or medroxyprogesterone acetate (600 mg daily), and levonorgestrel-releasing intrauterine device (L-IUD). Recently Greenwald *et al.* reported no differences in all-cause mortality and cancer-specific mortality between patients who received progestin therapy (n = 161) versus who received primary surgery (n = 6178) after 15 years of follow-up [42]. Moreover, L-IUD was found to achieve a higher response rate compared to oral progestin therapy [43].

Hysteroscopic resection of the tumor in combination with progestin therapy is another strategy to be considered in this patient population [44]. However, the success of this approach is currently limited to case reports and case series [45]. Hence, it is unknown whether hysteroscopic tumor resection would provide improved oncological and reproductive outcomes.

Recently, studies have shown that preserving ovaries at the time of hysterectomy in early-stage endometrial cancer might be a safe option that does not increase the risk of cancer recurrence and prevents menopause-associated morbidity by retaining ovarian endocrine function [46]. Because these patients cannot achieve natural pregnancy, IVF procedure followed by embryo transfer to a gestational carrier is an option that might be offered. Additionally, though still an experimental method, *uterine transplantation* procedure recently resulted in livebirths and might be considered in selected cases [47].

6.3. Ovarian cancer

Preservation of fertility in ovarian cancer stands more challenging compared to cervical and endometrial cancers as the origin of the disease involves the source of oocyte reserve. However, there still exist some options for ovarian preservation in reproductive age patients with early stage disease (FIGO stage IA-IB), borderline ovarian tumors (BOTs) or germ cell and sex-cord stromal tumors. Unilateral salpingo-oophorectomy (USO) appears as a safe treatment for unilateral BOT, and when both ovaries are involved and complete resection is achievable, ovarian cystectomy should be preferred to preserve ovaries [48,49]. In a recent systematic review, conservative management of early-stage BOTs was associated with a lethal recurrence of 0.5% and a pooled estimate for spontaneous pregnancy rate of 54%. In advanced stage BOTs, the spontaneous pregnancy rate was 34% and the risk of lethal recurrence was 2% [49].

For early-stage (IA-IB) invasive epithelial ovarian cancer uteroovarian preserving surgery with complete peritoneal staging and systematic pelvic/para-aortic lymphadenectomy has also been shown to be a therapeutically safe option with successful reproductive outcomes [50,51]. However, for grade 3 and stage IC disease, the safety of this procedure is still unclear and should be carefully evaluated.

6.4. Assisted reproductive technologies

When ovarian reserve loss appears inevitable due to the planned gonadotoxic chemotherapy/radiotherapy or surgical removal of ovaries, assisted reproductive technologies (ART) such as controlled ovarian hyperstimulation (COH) cycle followed by oocyte and embryo cryopreservation can be successfully performed to preserve fertility prior such treatments. COH can be defined as carefully monitored stimulation of ovaries using gonadotropins to induce the development of multiple follicles in the same cohort. A major concern regarding the conventional COH protocols is the elevated circulating estradiol levels due to the development of multiple large follicles at once that can worsen oncological outcome in estrogen-sensitive cancers. Hence, we have developed safer ovarian stimulation protocols that provide high oocyte and embryo yields using anti-estrogenic drugs such as Tamoxifen and Letrozole, which can be used alone or in combination with lower doses of gonadotropins [52]. In endometrial cancer patients, we successfully demonstrated the use of letrozole COH protocol with embryo freezing [53]. In breast cancer patients, we have also shown the safety of these protocols after short and mid-term follow-up [54]. Also, contrary to the traditional COH initiation at follicular phase, we introduced “Random Start Ovarian Stimulation” concept that ovarian stimulation can be initiated regardless of the menstrual cycle phase without reducing the yield of oocytes and embryos [55]. With random-start ovarian stimulation, an adequate number of oocytes can be successfully retrieved in less than two weeks, particularly when emergency fertility preservation is needed.

Embryo and oocyte cryopreservation are established ART procedures; however, when there is no sufficient time for a COH cycle, patients can be offered ovarian tissue cryopreservation (OTC) and subsequent autotransplantation (OvTx) procedure [20]. OTC enables the preservation of a large number of follicles embedded in the ovarian cortex and can be performed at any time of the menstrual phase. Frozen-thawed ovarian cortical tissues can be successfully transplanted after completion of oncological treatment. Since our first success in 2000, we have developed advanced

orthotopic and heterotopic ovarian transplantation techniques using robotic surgery and decellularized extracellular matrix scaffolds to improve surgical dexterity, and graft viability, respectively [21,22,56–59]. In a recent video report, we demonstrated step-by-step heterotopic transplantation of ovarian tissue to lower abdominal wall using robotic surgery in a patient who underwent OTC at the time of hysterectomy with bilateral salpingo-oophorectomy due to endometrial cancer at the age of 32 years [21]. Ovarian graft function resumed 15 weeks after the operation and the patient is currently undergoing IVF treatment for embryo freezing to be transferred to a gestational carrier. Though OvTx is still considered experimental, we found in a recent meta-analysis that this procedure achieved 37.7% cumulative livebirth rate per women and as a result it is being placed among the established ART methods by many countries including the U.S. [60].

One concern regarding this procedure is the risk of reimplantation of occult tumor cells in the cryopreserved ovarian tissue. However, studies in ovarian samples from patients with non-metastatic breast, bone, and soft tissue tumors did not show any sign of cancer cells in cryopreserved ovarian tissues [61,62]. Hence, in early-stage endometrial and cervical cancers without ovarian involvement, the risk of reintroducing cancer cells after OvTx appears to be very unlikely. Nonetheless, histological evaluation of frozen-thawed ovarian samples for malignant cells before the transplantation is recommended in all cases.

7. Fertility preservation in pediatric gynecologic malignancies

Pediatric gynecologic tumors are very rare and can be classified into three main groups: sex-cord stromal carcinomas (SSCs) (granulosa and Sertoli-Leydig cell tumors), rhabdomyosarcomas of the vagina and cervix, and ovarian germ cell tumors (GCTs). SSCs and GCTs are the most common ovarian tumors in the pediatric population and fertility-preserving surgery with complete surgical staging is the standard of care. Cisplatin-based chemotherapy regimens PEB (cisplatin+etoposide+bleomycin) and PEI (cisplatin+etoposide+ifosfamide) are widely used for stage II or higher SSCs. For GCTs, based on recent case series showing the efficiency of oncological treatment and maintaining reproductive function, PEB protocol is usually recommended [63].

Because complete surgical resection is often not feasible for rhabdomyosarcomas of the vagina and cervix, the standard treatment approach is chemotherapy (VAC protocol; vincristine+dactinomycin+cyclophosphamide) and radiotherapy followed by local excision if necessary [64]. Due to the risk of gonadal toxicity and ineligibility for oocyte/embryo freezing, the only available ART option for prepubertal girls with gynecologic malignancies is OTC from the unaffected ovary for future OvTx.

8. Pregnancy after cancer

A significant concern regarding fertility preservation in women with cancer is the safety of ART and pregnancy following cancer treatments. Azim *et al.* reported that patients who became pregnant after breast cancer treatment found to have better overall survival and less risk of recurrence than the control group suggesting the safety of pregnancy after cancer treatment [65]. Regarding gynecologic malignancies, though current data is limited to a few case reports or case series, ART seems to not have any adverse effect on disease-free survival. Furthermore, using estrogen-reducing ovarian stimulation protocols such as letrozole may provide a protective effect in estrogen-sensitive gynecologic cancers.

9. Conclusions and future prospects

Despite several challenges preserving reproductive capacity in women with gynecologic cancer is achievable without compromising survival. Hence, an individualized multidisciplinary approach and timely referral to a reproductive specialist is crucial for achieving best results for girls and women desiring to preserve their fertility. In addition to the currently available ART options limited to selected patients, there are several new techniques in the horizon, and if successfully developed, may significantly transform the field of fertility preservation. Prevention of chemotherapy-induced ovarian damage by antiapoptotic/cell preserving agents [66], stem cell technologies [67], *in vitro* oogenesis using induced pluripotent stem cells (iPSCs) [68], *in vitro* primordial follicle growth [69] and 3-D printed ovarian matrices to be populated by human primordial follicles ("artificial ovary") [70] are among these promising advances that may be translated into clinical practice in the near future.

Author contribution

E.T. conceived the concept of the manuscript. E.T. and K.O. wrote the manuscript and approved for submission.

Declaration of competing interest

The authors declare no conflicts of interest.

References

[1] N. Howlader, A.M. Noone, M. Krapcho, D. Miller, A. Brest, M. Yu, et al., SEER Cancer Statistics Review, 1975–2016, National Cancer Institute, 2018.
[2] S. Bhasin, C. Kerr, K. Oktay, C. Racowsky, The implications of reproductive aging for the health, vitality and economic welfare of human societies, J. Clin. Endocrinol. Metab. (2019), https://doi.org/10.1210/jc.2019-00315.
[3] K. Oktay, B.E. Harvey, A.H. Partridge, G.P. Quinn, J. Reinecke, H.S. Taylor, et al., Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update, J. Clin. Oncol 36 (2018) 1994–2001.
[4] Ethics Committee of the American Society for Reproductive Medicine, Electronic address Aao. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion, Fertil. Steril. 110 (2018) 380–386.
[5] G. Bedoschi, P.A. Navarro, K. Oktay, Chemotherapy-induced damage to ovary: mechanisms and clinical impact, Future Oncol. 12 (2016) 2333–2344.
[6] R. Soleimani, E. Heytens, Z. Darzynkiewicz, K. Oktay, Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise, Aging (Albany NY) 3 (2011) 782–793.
[7] W.H. Wallace, A.B. Thomson, F. Saran, T.W. Kelsey, Predicting age of ovarian failure after radiation to a field that includes the ovaries, Int. J. Radiat. Oncol. Biol. Phys. 62 (2005) 738–744.
[8] J.Y. Wo, A.N. Viswanathan, Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients, Int. J. Radiat. Oncol. Biol. Phys. 73 (2009) 1304–1312.
[9] E. Taylan, K.H. Oktay, Current state and controversies in fertility preservation in women with breast cancer, World J Clin Oncol 8 (2017) 241–248.
[10] R. Roy, J. Chun, S.N. Powell, BRCA1 and BRCA2: different roles in a common pathway of genome protection, Nat. Rev. Cancer 12 (2011) 68–78.
[11] S. Titus, F. Li, R. Stobezki, K. Akula, E. Unsal, K. Jeong, et al., Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans, Sci. Transl. Med. 5 (2013) 172ra21.
[12] W. Lin, S. Titus, F. Moy, E.S. Ginsburg, K. Oktay, Ovarian aging in women with BRCA germline mutations, J. Clin. Endocrinol. Metab. 102 (2017) 3839–3847.
[13] K. Oktay, J.Y. Kim, D. Barad, S.N. Babayev, Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks, J. Clin. Oncol. 28 (2010) 240–244.
[14] W.T. Lin, M. Beattie, L.M. Chen, K. Oktay, S.L. Crawford, E.B. Gold, et al., Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California, Cancer 119 (2013) 1652–1659.
[15] K.A. Phillips, I.M. Collins, R.L. Milne, S.A. McLachlan, M. Friedlander, M. Hickey, et al., Anti-Mullerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations, Hum. Reprod. 31 (2016) 1126–1132.

[16] L. Johnson, M.D. Sammel, S. Domchek, A. Schanne, M. Prewitt, C. Gracia, Antimullerian hormone levels are lower in BRCA2 mutation carriers, Fertil. Steril. 107 (2017) 1256–1265 (e6).
[17] G.P. Quinn, S.T. Vadaparampil, J.H. Lee, P.B. Jacobsen, G. Bepler, J. Lancaster, et al., Physician referral for fertility preservation in oncology patients: a national study of practice behaviors, J. Clin. Oncol. 27 (2009) 5952–5957.
[18] J. Selter, Y. Huang, L.C. Grossman Becht, K.L. Palmerola, S.Z. Williams, E. Forman, et al., Use of fertility preservation services in female reproductive-aged cancer patients, Am. J. Obstet. Gynecol. (2019), https://doi.org/10.1016/j.ajog.2019.05.009.
[19] N.A. Deshpande, I.M. Braun, F.L. Meyer, Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: a systematic review, Cancer 121 (2015) 3938–3947.
[20] E. Taylan, K. Oktay, Autologous transplantation of human ovarian tissue, in: P. Leung, E. Adashi (Eds.), The Ovary, 3 ed, Elsevier, 2019, pp. 493–500.
[21] K. Oktay, E. Taylan, T. Kawahara, G.M. Cillo, Robot-assisted orthotopic and heterotopic ovarian tissue transplantation techniques: surgical advances since our first success in 2000, Fertil. Steril. 111 (2019) 604–606.
[22] K. Oktay, E. Taylan, Y. Sugishita, G.M. Goldberg, Robot-assisted laparoscopic transplantation of frozen-thawed ovarian tissue, J. Minim. Invasive Gynecol. 24 (2017) 897–898.
[23] S. Lee, S. Ozkavukcu, E. Heytens, F. Moy, K. Oktay, Value of early referral to fertility preservation in young women with breast cancer, J. Clin. Oncol. 28 (2010) 4683–4686.
[24] F. Horicks, G. Van Den Steen, C. Gervy, H.J. Clarke, I. Demeestere, Both in vivo FSH depletion and follicular exposure to Gonadotrophin-releasing hormone analogues in vitro are not effective to prevent follicular depletion during chemotherapy in mice, Mol. Hum. Reprod. 24 (2018) 221–232.
[25] H.C. Moore, J.M. Unger, K.A. Phillips, F. Boyle, E. Hitre, D. Porter, et al., Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy, N. Engl. J. Med. 372 (2015) 923–932.
[26] K. Oktay, K. Rodriguez-Wallberg, P. Munster, Ovarian protection during adjuvant chemotherapy, N. Engl. J. Med. 372 (2015) 2268–2269.
[27] K. Oktay, E. Taylan, K.A. Rodriguez-Wallberg, G. Bedoschi, V. Turan, F. Pacheco, Goserelin does not preserve ovarian function against chemotherapy-induced damage, Ann. Oncol. 29 (2018) 512–513.
[28] I. Demeestere, P. Brice, F.A. Peccatori, A. Kentos, J. Dupuis, P. Zachee, et al., No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial, J. Clin. Oncol. 34 (2016) 2568–2574.
[29] P.N. Munster, A.P. Moore, R. Ismail-Khan, C.E. Cox, M. Lacevic, M. Gross-King, et al., Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer, J. Clin. Oncol. 30 (2012) 533–538.
[30] M. Kyrgiou, G. Koliopoulos, P. Martin-Hirsch, M. Arbyn, W. Prendiville, E. Paraskevaidis, Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis, Lancet 367 (2006) 489–498.
[31] J.D. Wright, R. NathavithArana, S.N. Lewin, X. Sun, I. Deutsch, W.M. Burke, et al., Fertility-conserving surgery for young women with stage IA1 cervical cancer: safety and access, Obstet. Gynecol. 115 (2010) 585–590.
[32] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines). Cervical Cancer (Version 4.2019).
[33] G. Bogani, V. Chiappa, D. Vinti, E. Somigliana, F. Filippi, G. Murru, et al., Long-term results of fertility-sparing treatment for early-stage cervical cancer, Gynecol. Oncol. 154 (1) (2019 Jul) 89–94.
[34] A. Prodromidou, C. Iavazzo, A. Fotiou, V. Psomiadou, A. Douligeris, G. Vorgias, et al., Short- and long term outcomes after abdominal radical trachelectomy versus radical hysterectomy for early stage cervical cancer: a systematic review of the literature and meta-analysis, Arch. Gynecol. Obstet. 300 (1) (2019 Jul) 25–31.
[35] D.Y. Cao, J.X. Yang, X.H. Wu, Y.L. Chen, L. Li, K.J. Liu, et al., Comparisons of vaginal and abdominal radical trachelectomy for early-stage cervical cancer: preliminary results of a multi-center research in China, Br. J. Cancer 109 (2013) 2778–2782.
[36] E. Bentivegna, S. Gouy, A. Maulard, C. Chargari, A. Leary, P. Morice, Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review, Lancet Oncol. 17 (2016) e240–e253.
[37] N.S. Moawad, E. Santamaria, A. Rhoton-Vlasak, J.L. Lightsey, Laparoscopic ovarian transposition before pelvic cancer treatment: ovarian function and fertility preservation, J. Minim. Invasive Gynecol. 24 (2017) 28–35.
[38] G. Baiocchi, H. Mantoan, M.J. Chen, C.C. Faloppa, Uterine transposition after radical trachelectomy, Gynecol. Oncol. 150 (2018) 387–388.
[39] P. Ghadjar, V. Budach, C. Kohler, A. Jantke, S. Marnitz, Modern radiation therapy and potential fertility preservation strategies in patients with cervical cancer undergoing chemoradiation, Radiat. Oncol. 10 (2015) 50.
[40] W.J. Koh, B.E. Greer, N.R. Abu-Rustum, S.M. Apte, S.M. Campos, J. Chan, et al., Uterine neoplasms, version 1.2014, J. Natl. Compr. Cancer Netw. 12 (2014) 248–280.
[41] A. Rodolakis, I. Biliatis, P. Morice, N. Reed, M. Mangler, V. Kesic, et al., European Society of Gynecological Oncology Task Force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients, Int. J. Gynecol. Cancer 25 (2015) 1258–1265.
[42] Z.R. Greenwald, L.N. Huang, M.D. Wissing, E.L. Franco, W.H. Gotlieb, Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer? Cancer 123 (2017) 1545–1554.
[43] C.C. Gunderson, A.N. Fader, K.A. Carson, R.E. Bristow, Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review, Gynecol. Oncol. 125 (2012) 477–482.
[44] C. Corzo, N. Barrientos Santillan, S.N. Westin, P.T. Ramirez, Updates on conservative management of endometrial cancer, J. Minim. Invasive Gynecol. 25 (2018) 308–313.
[45] I. Mazzon, G. Corrado, V. Masciullo, D. Morricone, G. Ferrandina, G. Scambia, Conservative surgical management of stage IA endometrial carcinoma for fertility preservation, Fertil. Steril. 93 (2010) 1286–1289.
[46] P. Jia, Y. Zhang, Ovarian preservation improves overall survival in young patients with early-stage endometrial cancer, Oncotarget 8 (2017) 59940–59949.
[47] G. Testa, G.J. McKenna, R.T. Gunby Jr., T. Anthony, E.C. Koon, A.M. Warren, et al., First live birth after uterus transplantation in the United States, Am. J. Transplant. 18 (2018) 1270–1274.
[48] S. Palomba, A. Falbo, S. Del Negro, M. Rocca, T. Russo, F. Cariati, et al., Ultra-conservative fertility-sparing strategy for bilateral borderline ovarian tumours: an 11-year follow-up, Hum. Reprod. 25 (2010) 1966–1972.
[49] E. Darai, R. Fauvet, C. Uzan, S. Gouy, P. Duvillard, P. Morice, Fertility and borderline ovarian tumor: a systematic review of conservative management, risk of recurrence and alternative options, Hum. Reprod. Update 19 (2013) 151–166.
[50] A. Ditto, F. Martinelli, G. Bogani, D. Lorusso, M. Carcangiu, V. Chiappa, et al., Long-term safety of fertility sparing surgery in early stage ovarian cancer: comparison to standard radical surgical procedures, Gynecol. Oncol. 138 (2015) 78–82.
[51] I. Zapardiel, M.D. Diestro, G. Aletti, Conservative treatment of early stage ovarian cancer: oncological and fertility outcomes, Eur. J. Surg. Oncol. 40 (2014) 387–393.
[52] K. Oktay, E. Buyuk, N. Libertella, M. Akar, Z. Rosenwaks, Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation, J. Clin. Oncol. 23 (2005) 4347–4353.
[53] A. Azim, K. Oktay, Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma, Fertil. Steril. 88 (2007) 657–664.
[54] A.A. Azim, M. Costantini-Ferrando, K. Oktay, Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study, J. Clin. Oncol. 26 (2008) 2630–2635.
[55] M. Sonmezer, I. Turkcuoglu, U. Coskun, K. Oktay, Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles, Fertil Steril. 95 (2011) 2125 e9–2125 e11.
[56] K. Oktay, G. Karlikaya, Ovarian function after transplantation of frozen, banked autologous ovarian tissue, N. Engl. J. Med. 342 (2000) 1919.
[57] K. Oktay, E. Buyuk, L. Veeck, N. Zaninovic, K. Xu, T. Takeuchi, et al., Embryo development after heterotopic transplantation of cryopreserved ovarian tissue, Lancet 363 (2004) 837–840.
[58] K. Oktay, G. Bedoschi, F. Pacheco, V. Turan, V. Emirdar, First pregnancies, live birth, and in vitro fertilization outcomes after transplantation of frozen-banked ovarian tissue with a human extracellular matrix scaffold using robot-assisted minimally invasive surgery, Am. J. Obstet. Gynecol. 214 (2016) 94 e1–9.
[59] E. Taylan, K. Oktay, Application of decellularized tissue scaffolds in ovarian tissue transplantation, Methods Mol. Biol. 1577 (2018) 177–181.
[60] F. Pacheco, K. Oktay, Current success and efficiency of autologous ovarian transplantation: a meta-analysis, Reprod. Sci. 24 (2017) 1111–1120.
[61] M. Sanchez-Serrano, E. Novella-Maestre, E. Rosello-Sastre, N. Camarasa, J. Teruel, A. Pellicer, Malignant cells are not found in ovarian cortex from breast cancer patients undergoing ovarian cortex cryopreservation, Hum. Reprod. 24 (2009) 2238–2243.
[62] M.M. Dolmans, Y. Iwahara, J. Donnez, M. Soares, J.L. Vaerman, C.A. Amorim, et al., Evaluation of minimal disseminated disease in cryopreserved ovarian tissue from bone and soft tissue sarcoma patients, Hum. Reprod. 31 (2016) 2292–2302.
[63] J.Y. Park, D.Y. Kim, D.S. Suh, J.H. Kim, Y.M. Kim, Y.T. Kim, et al., Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumors, Gynecol. Oncol. 137 (2015) 418–422.
[64] R.J. Andrassy, E.S. Wiener, R.B. Raney, D.M. Hays, C.A. Arndt, T.E. Lobe, et al., Progress in the surgical management of vaginal rhabdomyosarcoma: a 25-year review from the Intergroup Rhabdomyosarcoma Study Group, J. Pediatr. Surg. 34 (1999) 731–734 (discussion 4-5).
[65] H.A. Azim Jr., N. Kroman, M. Paesmans, S. Gelber, N. Rotmensz, L. Ameye, et al., Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study, J. Clin. Oncol. 31 (2013) 73–79.

[66] F. Li, V. Turan, S. Lierman, C. Cuvelier, P. De Sutter, K. Oktay, Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death, Hum. Reprod. 29 (2014) 107–113.
[67] Y.A. White, D.C. Woods, Y. Takai, O. Ishihara, H. Seki, J.L. Tilly, Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women, Nat. Med. 18 (2012) 413–421.
[68] C. Yamashiro, K. Sasaki, Y. Yabuta, Y. Kojima, T. Nakamura, I. Okamoto, et al., Generation of human oogonia from induced pluripotent stem cells in vitro, Science 362 (2018) 356–360.
[69] E.E. Telfer, Future developments: in vitro growth (IVG) of human ovarian follicles, Acta Obstet. Gynecol. Scand. 98 (2019) 653–658.
[70] M.M. Dolmans, C.A. Amorim, Construction and use of artificial ovaries, Reproduction (2019), https://doi.org/10.1530/REP-18-0536.