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Cryopreservation Options to Preserve Fertility in Female Cancer Patients: Available Clinical Practice and Investigational Strategies from the Oncology Guidelines Point of View

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ABSTRACT

In recent years, advances in cancer treatment have improved the survival rate of cancer patients significantly. However, destructive damage to ovaries due to the therapies or cancer itself can cause different degrees of infertility in women of reproductive age that can affect their quality of life seriously. In this study, fertility cryopreservation options for female cancer patients in oncology guidelines were reviewed. Cryopreservation methods have a long history in reproductive biology and oncology. However, embryo and oocyte cryopreservation were the eligible restoration strategies in clinical oncology practice. Ovarian tissue cryopreservation (OTC) is the latest option recommended for fertility preservation in pre-pubertal and adult patients who cannot delay their treatment or in whom taking IVF hormones may have adverse effects on their cancer. Reports show that frozen-thawed ovarian tissue transplantation has led to more than 130 live births so far in patients, most of whom were cancer patients. Although OTC is indeed generally recognized as an investigational method, it is recommended in some important guidelines, such as ASCO 2018. Therefore, based on many clinical pieces of evidence , it is predicted that the investigational label will soon be removed, and OTC might be considered as one of the main fertility preservation options for female cancer patients in clinical oncology practice.

Keywords: Oncology Guidelines, Cancer Treatment, Fertility Preservation, Cryopreservation

INTRODUCTION:

The number of women of reproductive age with cancer is increasing every year (1). In recent years, improvements in cancer treatment, particularly chemo- and radiotherapy, have increased the survival rate of cancer patients (2). However, these treatments may cause a reduction in ovarian function and reserve. They may also result in a diminution of 5-10 years in the reproductive age or even lead to premature ovarian insufficiency (POI) (3, 4). Also, infertility after cancer treatment is one of the most important reasons for despair and decreased quality of life in female cancer survivals. Therefore, fertility preservation is one of the main concerns of young cancer patients (5). Hence, several guidelines have been developed by main oncology and fertility societies such as NCCN, ASCO, NICE, ESMO, and FertiPROTEKT to address this issue. The term "Oncofertility" has been officially incorporated in oncology since 2006 (6). Based on these guidelines, oncologists are required to discuss the risks of cancer or cancer treatment methods on the fertility of their female patients and to provide them with appropriate recommendations. However, there are still complaints among women who have been treated for cancer (7, 8). Providing these services and implementing fertility preservation guidelines in oncology requires an efficient and interdisciplinary team (9). Therefore, in many centers, especially in developing countries, still few female cancer patients may experience effective fertility preservation services (10). Depending on various parameters such as patients' age, marital status, feasibility of delay in cancer treatment, and treatment method, there are several options for fertility preservation in women. These options include oocyte, embryo, and ovarian tissue cryopreservation as well as in vitro maturation (IVM) of oocytes, ovarian tissue suppression, ovarian transposition (oophoropexy) or a combination of them (11). The role of cryopreservation techniques is much more prominent among these methods. In this study, cryopreservation techniques for fertility preservation in female cancer patients in all valid oncology guidelines were reviewed. In particular, we look at the latest option introduced in this field, ovarian tissue cryopreservation, which has a very promising clinical evidence.

METHODS:

Search strategy

In this study, published clinical practices, oncology guidelines, and recommendations on fertility preservation were searched manually and systematically in relevant websites such as NICE EUSOMA ASCO, NCCN, FertiPROTEKT as well as Google Scholar and PubMed from 2003 to 2019. Duplicates and guidelines irrelevant to fertility preservation in cancer patients were excluded. Search terms are listed in **Table 1**.

Table 1. Search terms for PubMed and Google Scholar.

No.	Database	Query	Number
1	PubMed	("Practice Guideline" [Publication Type]) AND "Fertility Preservation"[Mesh]	30
2	PubMed	("Fertility Preservation"[Mesh]) AND "Guideline" [Publication Type]	32
3	PubMed	"Fertility Preservation/standards"[Mesh]	38
4	Scholar	fertility preservation guidelines (all in title)	27
5	Scholar	fertility preservation AND oncology (all in title)	68

Table 2. Available guidelines for fertility preservation in cancer patients.

No.	Name	Organization	year
1	A strategy for fertility services for survivors of childhood cancer	British Fertility Society (BFS)	2003
2	Fertility: Assessment and Treatment for People with Fertility Problems	National Collaborating Center for Women's and Children's Health (UK)	2004
3	Recommendations on fertility preservation in cancer patients	American society of clinical oncology (ASCO)	2006
4	The effects of cancer treatment on reproductive functions: guidance on management	Royal Colleges of Physicians, Radiologists, and Obstetricians and Gynaecologists RCOG)	2007
5	Preservation of Fertility in Pediatric and Adolescent Patients with Cancer	American Academy of Paediatrics (AAP)	2008
6	Cancer, fertility and pregnancy—clinical recommendations for diagnosis, treatment and follow-up	European Society for Medical Oncology (ESMO)	2009
7	Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer	St. Gallen International Expert Consensus on the primary therapy of early breast cancer	2009
8	Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	European Society for Medical Oncology (ESMO)	2010
9	Fertility preservation in women—a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin's lymphoma and borderline ovarian tumors	FertiPROTEKT network	2011
10	Fertility preservation for AYAs diagnosed with cancer—guidance for health professionals	Clinical Oncological Society of Australia (COSA)	2011
11	Adolescent and young adult oncology	National Comprehensive Cancer Network (NCCN)	2012
12	Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer	International Society for Fertility Preservation (ISFP)	2012
13	Recommendations for the management of young women with breast cancer	The European Society of Breast Cancer Specialists (EUSOMA)	2012
14	Fertility—assessment and treatment for people with fertility problems (update)	National Institute for Health and Clinical Excellence (NICE)	2013
15	Survivors of childhood cancer	Scottish Intercollegiate Guidelines Network (SIGN)	2013
16	Recommendations on fertility preservation in cancer patients	American society of clinical oncology (ASCO)	2013
17	Cancer and fertility preservation in men, women and children	French Association for the Care of Oncological Support (AFSOS)	2013
18	Recommendations for the preservation of fertility in children and adolescents treated for cancer	French Society of Childhood Cancer (SFCE)	2013
19	Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion	Ethics Committee of American Society for Reproductive Medicine (ASRM)	2013
20	Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology	National Comprehensive Cancer Network (NCCN)	2016
21	Guidelines 2013 for the treatment of uterine body neoplasms	Japan Society of Gynecologic Oncology (JSGO)	2016
22	Uterine cancer guidelines: Recommendations for practice	British Gynaecological Cancer Society (BGCS)	2017
23	Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update Summary	American Society of Clinical Oncology (ASCO)	2018
24	ACOG Committee Opinion No. 747 Summary: Gynecologic Issues in Children and Adolescent Cancer Patients and Survivors	American College of Obstetricians and Gynecologists (ACOG)	2018

Data extraction

In all, our search revealed 24 guidelines for fertility preservation in cancer patients from 2003 to 2019. Despite the efforts made in this study, some guidelines may be missing, but given that there are all the important guidelines in the results, we are convinced that there is nothing important or option left out. The search results are listed in **Table 2**.

Embryo, oocyte, and ovarian tissue freezing are the most important introduced and clinically used cryopreservation options and restoration strategies for female cancer patients. The British Fertility Society (BFS) in 2003 and the American society of clinical oncology (ASCO) in 2006 published the first guidelines on fertility preservation in cancer patients in the UK and the USA, respectively. In those guidelines, except embryo freezing, other options were considered investigational for female cancer patients. Guidelines in the UK and the USA were updated several times until 2019 (**Table 1**). FertiPROTEKT in Germany (and German-speaking countries: Switzerland and Austria) and the European society of breast cancer specialists (EUSOMA) released their first guidelines for fertility preservation respectively in 2011 and 2012. NCCN, ISFP, NICE, NCCN, ASCO, ASRM, and other societies also have their first or subsequent guidelines between 2012 and 2019. For further display, all of the items in **Table 2** are displayed in a timeline in **Figure 1**. According to all of these guidelines, oncologists should inform their patients about the impact of cancer treatment on fertility and refer them to the relevant fertility preservation centers (12). The role of cryopreservation techniques is critical among fertility preservation methods. Overall, cryopreservation options for female can-

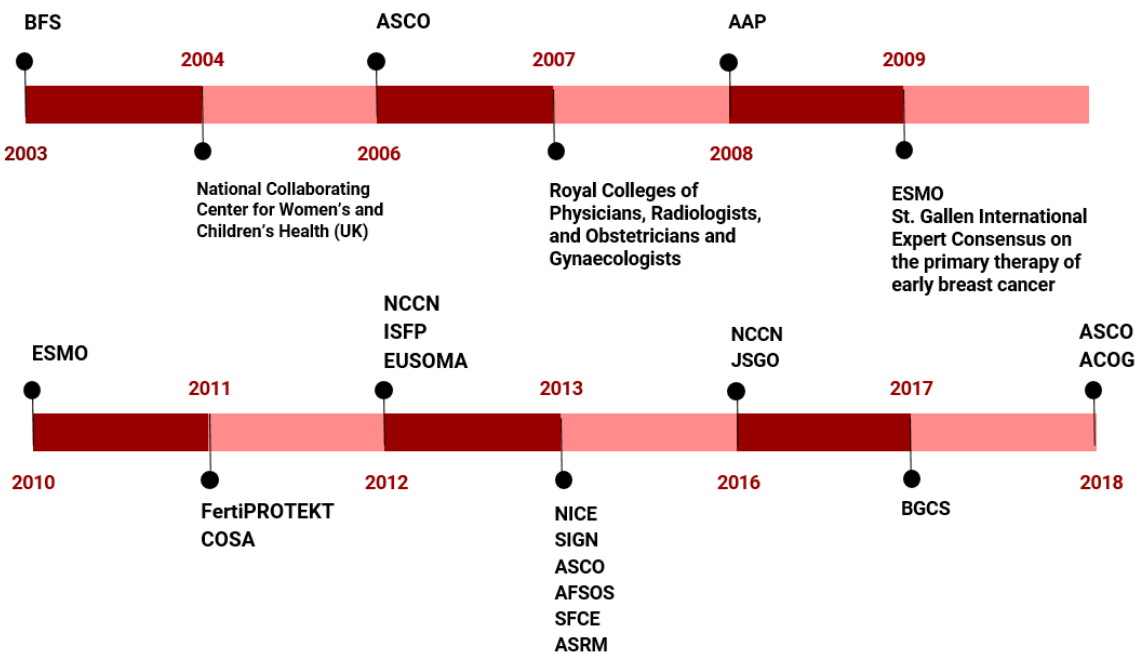

Figure 1. Timeline of fertility preservation guidelines from 2000 to 2019.

cer patients are as follows:

Embryo Freezing

According to the ASCO 2006, 2013, and 2018 and all other guidelines, embryo cryopreservation option is consistently considered eligible clinical technique for fertility preservation in female cancer patients (13). The first IVF baby, Louise Brown, was born in 1978. Zoe Leyland, the first baby from an embryo frozen after IVF, was born in Australia in 1984 (14). Therefore, embryo cryopreservation has been in progress for more than 30 years since the first years of fertility preservation technology (15). This option is broadly available, and adequate evidence is available to confirm its efficacy (16). According to ovarian stimulation protocols, this procedure requires female patients to undergo at least one hormone therapy cycle (10-14 days injection of stimulating hormones) for the superovulation of their ovaries. Therefore, this procedure is only recommended to post-pubertal, married women, and those who have adequate time before starting cancer treatment (17). Thus, when delaying cancer treatment is impossible, it is recommended not to wait for the next menstrual cycle to induce ovulation, and performing random-start stimu¬lation protocol is recommended (18). In a recent study, frozen than fresh embryo transfer protocols showed a higher percentage of implantation (46.8% vs. 42.0%) and ongoing pregnancy rates (52.0% vs. 45.3%) (19). It was estimated that more than half a million babies are born after frozen-thawed embryos worldwide (20). Embryo formation and freezing need a partner sperm. So, there are ethical and legal concerns about the fate of embryos if the patient dies or is divorced. In this situation, unfertilized oocyte cryopreservation and ovarian tissue freezing are alternative approaches for fertility preservation (15).

Oocyte Freezing

The first human birth from a frozen oocyte was reported in 1986 (Australia), resulting in the birth of twins by Prof. Christopher Chen in Australia, in 1986 (21). The hormonal preparation period is the same for both embryo and oocyte freezing methods. The only difference is that in the freeze-thaw oocyte cycles, the intracytoplasmic sperm injection (ICSI) does not occur. This technique remained clinically undeveloped until recently, and the frequency of applying this procedure has steadily increased in infertility treatment and oncology since October 2012 when the American society for reproductive medicine (ASRM) lifted the 'experimental' label from the oocyte freezing process (22). After the birth of more than 900 babies derived from this procedure, the experimental label was ultimately removed in ASCO 2013 and then in other oncology guidelines (23-25). This method is suitable for single women or those who do not prefer embryo freezing because of religious or ethical reasons. It has been reported that implantation and clinical pregnancy rates, respectively 40% and 55%, in the frozen oocytes is similar to fresh samples (19). The ASRM and society of assisted reproductive technology practice committee reported that the pregnancy rate for each cryopreserved oocyte is 4.5-12% (26).

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation (OTC) is another option for fertility preservation in cancer patients. The first human live birth as a result of ovarian cortex implantation was reported in 2004 in Belgium (27). According to ASCO 2013 guideline, OTC should be considered investigational. However, the ASCO 2018 guideline mentioned this option as a standard treatment in the future due to the rapid development of ovarian tissue freezing technique (28). Some researchers, such as Donnez et al., have dropped the experimental label from ovarian tissue cryopreservation techniques because of their extensive experience in this field (15, 27, 29-34). The reasons why OTC and transplantation stayed as an experimental protocol is the diver-

sity of options (vitrification or rapid freezing versus slow freezing, the whole ovary versus cortical strips transplantation, and orthotopic versus heterotopic transplantation) (25). The main motivation for this technique is to begin OTC before cancer treatment to restore the tissue after cancer recovery. Besides, ovary grafts may delay menopause in young women in their future life (35, 36). The advantage of the OTC method over egg and embryo freezing is that it is possible to be carried out without ovarian stimulation, and there is no need for sperm. Therefore, it is a suitable method for patients who cannot delay their cancer treatment as well as pre-pubertal girls. Another advantage of ovarian tissue freezing compare to oocyte and embryo cryopreservation is that at the time of freezing, hundreds of primordial follicles can be stored (37). The first use of cryopreservation in human ovarian tissue was performed over a long period of animal experimentation. Deanesly and Parrott, in 1954 and 1961 respectively, displayed that ovarian tissue can be successfully frozen in mice and can result in the birth of live pups with a normal lifespan and fertility after auto-transplantation (38-40). This technique was used in humans after the successful pregnancy was reported in sheep by Gosden et al. in 1994 (41). Indications for OTC include gynecological diseases (30), systemic disorders, autoimmune disease, ovarian tumors (42), genetic disorders such as Turner's syndrome (31), and endometriosis leading to premature ovarian insufficiency (POI) (32). However, it is believed that the most common reason for OTC is malignancies, such as leukemia, Hodgkin's lymphoma, and breast cancer (43, 44). Technical considerations are essential for freezing ovarian tissue (33, 34). The interest in frozen-thawed ovarian tissue transplantation is overgrowing.

Ovarian tissue transplantation

Oktay et al. firstly performed the transplantation of the frozen ovary in 1999 (45). The first successful transplantation of slow-frozen ovarian tissue was reported in Belgium by Donnez et al. in 2004, and the second live birth was reported in 2005 by Meirow et al. (46, 47) (**Figure 2**). Transplantation of ovarian tissue fragments can be performed to the pelvic or subcutaneous areas, respectively. One of the concerns about the transplantation of ovarian tissue is ischemia and follicular depletion that may occur until the formation of vessels in tissue if transplantation carries out without vascular reanastomosis (48). Transplantation of the whole ovary

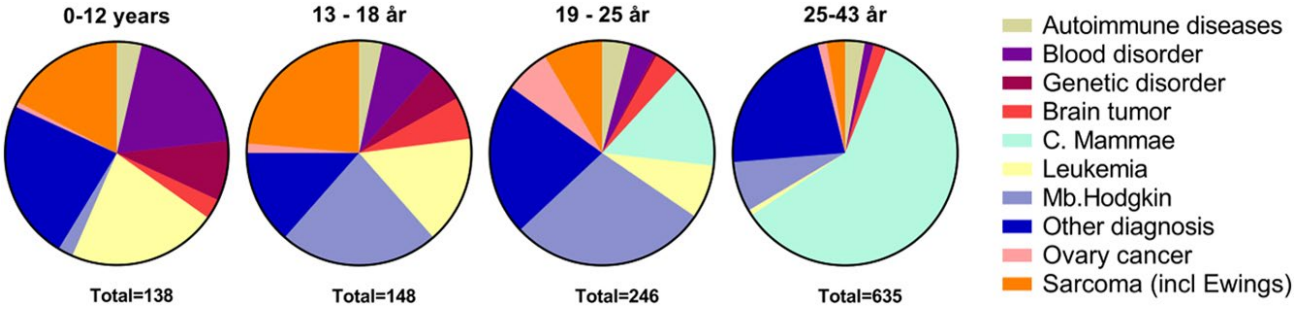

Figure 2. Diagnoses according to age at OTC in Denmark.

is a better option to overcome this problem (49). However, this approach leads to inadequate penetration of cryoprotectants into the large-sized ovary and vascular injury by ice crystals during cryopreservation (50). Angiogenic and anti-apoptotic factors can be used to enhance the revascularization of the implant (51). One of the concerns about grafted ovarian tissue for women with leukemia is the reseeding of cancer cells. Alternative options are required, such as IVM of follicles, stem cell reproductive technologies, and artificial ovary. However, all of these techniques are investigational. According to the reports from ovarian tissue transplantation in cancer survivors so far, only one case out of over 100 babies born worldwide showed transmission of malignant cells (52). Subsequently, successful pregnancies and live birth rates continue to climb steadily after frozen-thawed ovarian tissue transplantation (53-55). Since June 2017, over 130 live births have been reported from slow freezing of human ovarian tissue by specific machines or rate freezers and a few from manual vitrification (**Figure 3**) (56).

Based on these results, unlike oocyte and embryo cryopreservation, slow freezing remains the gold standard for ovarian tissue freezing. As shown in **Figure 4**, since the year 2004 that the first pregnancy was reported by Donnez until June 2017, the number of live births has continued to climb steadily.

Figure 5 summarizes the emergence of cryopreservation methods in reproductive biology and their subsequent adoption in oncology as a standard procedure.

Alternative approaches to fertility preservation

Although the focus of this study is on cryopreservation methods as they have a decisive impact on restoring fertility, here is a brief mention of other options for female cancer patients. Gonadal shielding throughout radiotherapy is another approach to fertility preservation in female cancer patients. The fixation of ovarian tissue away from the radiation area is another solution to help these patients (57). The controversial approach for fertility preservation is ovarian suppression with

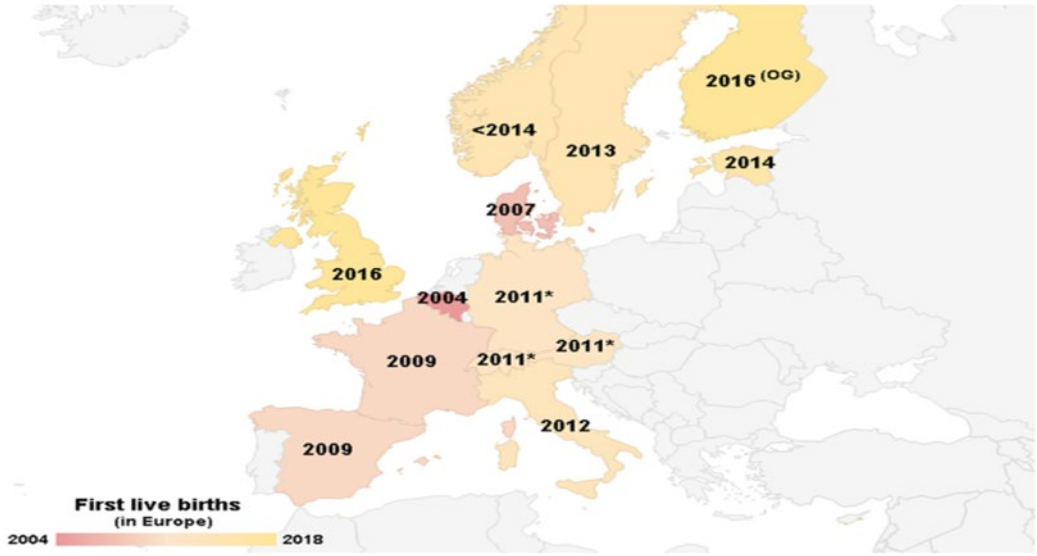

Figure 3. A case report and follow-up of the first live birth after heterotopic transplantation of cryopreserved ovarian tissue in Eastern Europe. BMC Women's Health volume 19, Article number: 65 (2019)

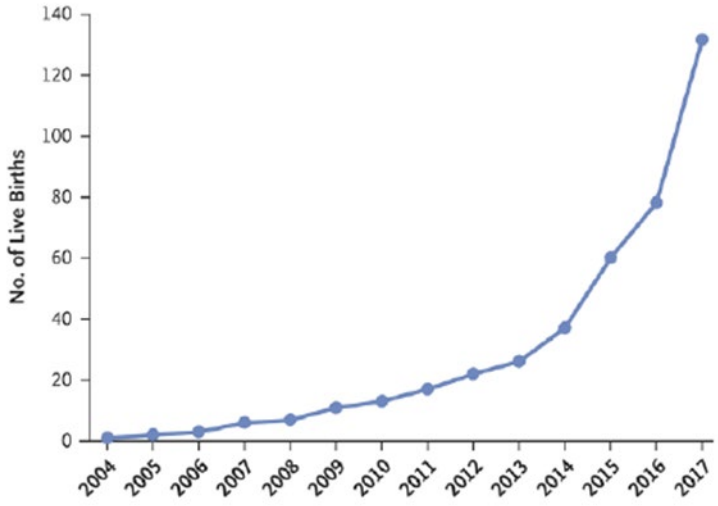

Figure 4. Total live birth rates after frozen-thawed ovarian tissue transplantation.

preservation of the ovarian follicle dormant by gonadotropin-releasing hormone (GnRH) agonists or antagonists during chemotherapy. AMH is an agonist that is produced by granulosa cells in growing follicles and directly inhibits the initiation of primordial follicle activity (58). Conservative gynecologic surgery is an alternative option of fertility preservation in women with cervical cancer.

Family planning and building

Embryo or oocyte donation or gestational surrogacies are other alternative options that assisted reproductive technology (ART) can make available to cancer survivors if patient-specific fertility preservation strategies are missed or not operationalized. However, adoption

Figure 5. Timeline of cryopreservation options for maintaining fertility in female cancer patients for years 2000 to 2019.

is the ultimate choice for such patients.

DISCUSSION:

The area of ART is progressing rapidly, with various laboratory techniques being developed. The field of cryopreservation is one of those techniques. Female cancer patients of reproductive age should be informed about the gonadotoxic effects of chemotherapy or radiotherapy, and oncologists should refer them to relevant specialists for appropriate consultation and intervention (59). Improvements in cancer treatment have increased the survival rate of cancer patients. Infertility is one of the critical problems following cancer treatment that affects their quality of life seriously (2). The importance of the issue of fertility preservation has also led to the publication of dozens of articles and guidelines in recent years that have well explained the available strategies in reproductive biology and oncology. Also, the term "Oncofertility" has been officially incorporated in oncology since the year 2006. Oncofertility refers to an interdisciplinary field that bridges oncology, reproduction, and women's health research to explore and expand options for the reproductive future of cancer patients. Clinical care for such patients may include fertility preservation before medical interventions as well as family planning, complex contraception, and hormonal management across the cancer survivors' lifespan. The Oncofertility Consortium is an international, multi-institutional group that assesses the impact of cancer and its treatment on reproductive health, founded in 2007 by Dr. Teresa Woodruff at Northwestern University (6). The consortium later formed national physicians cooperative (NPC) and global partners network (OCGPN) and continued to foster international and interdisciplinary collaborations. There are many developing countries from Africa and Latin America (such as Egypt, Tunisia, Brazil, Peru, and Panama) within OCGPN. Many national fertility preservation societies and networks were also formed in South Korea, Japan, India, Australia, and other countries outside the US and EU trying to explore the barriers and opportunities associated with oncofertility practice.

There are various options for fertility preservation for women undergoing cancer treatment. In this study, cryopreservation options for fertility preservation in female cancer patients in all valid oncology guidelines were reviewed. Our search revealed that there are at least 24 guidelines for maintaining fertility in cancer patients from 2003 to 2019. The guidelines are very similar. ASCO guidelines are based on evidence from large systematic reviews, and also are commonly cited by other oncology societies. Embryo and oocyte freezing are the standard and clinically established techniques for fertility preservation, while ovarian tissue cryopreservation and transplantation are yet investigational, but recommended (60). These options are described in more detail in the previous sections. Figure 5 summarizes the emergence of cryopreservation methods in reproductive biology and their subsequent adoption in oncology as a standard procedure.

OTC is a feasible option for fertility preservation in pre-pubertal girls with cancer and who do not have enough time or should not undergo ovarian stimulation hormone therapy (8). Unlike embryo and oocyte freezing that were originally used in infertility treatment, it seems that this option is more applicable to maintain fertility during cancer and other diseases treatment. Ovarian tissue freezing in humans is indeed a modified method of this technique for sheep ovarian tissue (41). Although the OTC method has been known and practiced for a long time and has lead to more than 130 cases of neonatal births, it has been investigational from the beginning. This technique is not widely used in infertility treatment or livestock industry, where there is much commercial incentive for cryopreservation. Sperm and embryo freezing methods have been used in modern animal husbandry for many years before en-

tering human infertility treatment in the 70th and 80th decades. The OTC method may result in hormonal balance or normalized feminine cycles as compared to the embryo and oocyte freezing. OTC is expected to become more applicable for women to maintain fertility after the usual years of menopause and to enable women to become pregnant at an older age.

Although the method of freezing eggs and embryos is very reliable and well known, as previously mentioned, they require several more conditions, including:

1- Coordination and referral of the cancer patient to the professional infertility center.

2- Requiring one to two weeks of hormone therapy, which may not be beneficial to the patient's cancer.

3- More ethical problems exist about the future of cryopreserved eggs or embryos and their subsequent use in the event of the patient's death or in case of divorce.

So it is well established that if all the facilities and expertise are in place, coordinating and introducing the patient to another discipline for embryo or egg freezing may simply delay cancer treatment for up to a month. OTC for future transplantation does not require ovarian stimulation cycle and can be performed immediately. This procedure can be performed in the cancer surgery room, and only the ovarian tissue is sent to the fertility center for freezing. However, the OTC is quickly becoming a routine method and seems to be able to address many of the major problems in fertility preservation and implementing oncology guidelines.

CONCLUSION:

According to all clinical practices and oncology guidelines, oncologists should inform their patients about the impact of cancer treatment on fertility and refer them to appropriate oncofertility centers for necessary guidance and action before the opportunity is missed. Embryo, oocyte, and ovarian tissue freezing are the main cryopreservation options and restoration strategies for female cancer patients. Oocyte and embryo freezing techniques are simpler, more reliable, and more conventional methods than ovarian tissue freezing. However, they require preparation process, specific conditions, and are more time-consuming. Ovarian tissue cryopreservation and re-transplantation are the feasible options for fertility preservation in pre-pubertal girls with cancer, and those who do not have enough time or who are contraindicated for hormone therapy for ovarian stimulation and egg collection. Endocrine function retrieval after reimplantation of frozen-thawed ovarian tissue is well recognized, and the live birth rate has been steadily increasing until now. Therefore, based on many clinical pieces of evidence and reports, it is predicted that the investigational label will soon be removed from this important cryopreservation option in oncology guidelines. Accordingly, it will be considered as an essential fertility preservation option for female cancer patients.

CONFLICT OF INTERESTS:

The authors declare that there is no potential conflict of interest in this article.

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