

# Fertility Preservation

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## ABSTRACT

Gonad cells (oocyte or spermatozoon) and tissues (ovary, testicle) are protected from gonadotoxic exposure to ensure the continuity of fertility due to medical interventions such as chemotherapy, radiotherapy, surgery, and the other non-oncological reasons. Depending on the progress of the cancer treatment, an increasing rate of patient survival has led to an increased importance of the fertility preservation concept. The currently used methods for fertility preservation are cryopreservation of the embryo, cryopreservation of the sperm and oocytes, ovarian transposition before radiotherapy, ovarian tissue freezing, GnRH analogue use, testicular tissue cryopreservation, and isolated spermatogonial stem cell transplantation, xenotransplantation, and some other methods of ongoing sperm maturation. Fertility patients and physicians are increasingly aware of the importance of protecting patients, increasing the knowledge and awareness of the society about the subject, and that this is an increasing contemporary problem.

**Keywords:** Fertility preservation, ovarian transposition, radiotherapy, ovarian tissue freezing, cryopreservation of oocytes, GnRH, testicular tissue cryopreservation, and isolated spermatogonial stem cell transplantation

## Introduction

Fertility protection is the preservation of ovary or embryos with oocytes or sperm, or the protection of ovaries from exposure to gonadotoxicity in order to ensure the continuity of fertility. Any condition that may cause a reduction in the reproductive capacity of women and men is an indication for the protection of fertility. Desire to delay fertility due to social reasons and cancer are the most common causes of patient admissions for the fertility protection (1).

In 2006, the term “oncofertility” was defined as a new subspecialty focusing on the future of reproduction for people with cancer who might face infertility as a result of chemotherapy, radiation or surgery. Oncofertility patients include pediatric, adolescent and young adult life stages, and the patients are 39 years of age and younger (2-4).

The increase in survival rates thanks to the advances in cancer treatment increased the importance of the concept of fertility protection. Medical interventions such as chemotherapy, radiotherapy and surgery have negative effects on ovarian reserve and may lead to premature ovarian failure and infertility. However, because of social, economic or technical barriers, only a part of all patients can be referred for consultation for fertility protection (5).

The protection of fertility is not limited to cancer patients. Similar to cancer, there are some autoimmune and hematologic systemic diseases treated with chemotherapy or radiotherapy (6). Sufficient orientation of patients about fertility preventive approaches, and increasing the knowledge and awareness of patients, their physicians and the society about this issue are emerging as a current problem with an increasing importance. There is a growing need for multidisciplinary centers that can be in contact with reproduction endocrinologists, medical and surgical oncologists, urologists, hematologists, general surgeons, family physicians and other related branches. In this compilation, it has been aimed to review the current knowledge about the treatment approaches in the protection of fertility.

## Current Treatments Applied for the Protection of Fertility

Embryo cryopreservation is the most commonly used method to protect fertility. This is followed by oocyte cryopreservation, ovarian tissue freezing and other methods.

A simplified scheme for the fertility protection options is shown in Figure 1 (5).

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**Cryopreservation of embryos (Freezing)**

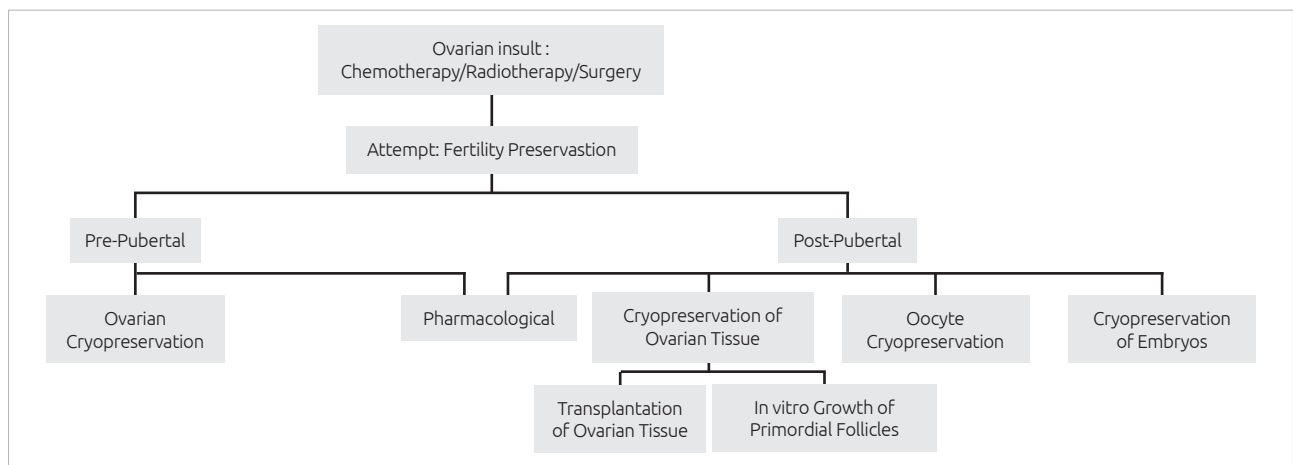
It is the most commonly used method which has been proven to be successful and reliable among the fertility protection approaches. The need for partner or donor sperm restricts the use of this method in children and adolescent population (3, 5, 7).

In conventional assisted reproductive techniques (ART), controlled ovarian stimulation therapy initiated in the first days of menstruation requires approximately 2 weeks. Moreover, since the women who are admitted may be in any period of their menstrual cycle, this period can be extended up to 6 weeks and some patients give up fertility preservation with the concern that this will cause delay in cancer treatment. In the current literature, there are studies suggesting that ovarian stimulation can be started safely and effectively at any time of the menstrual cycle. Despite the prolongation of stimulation and the increased total gonadotropin dose, there is no differ-

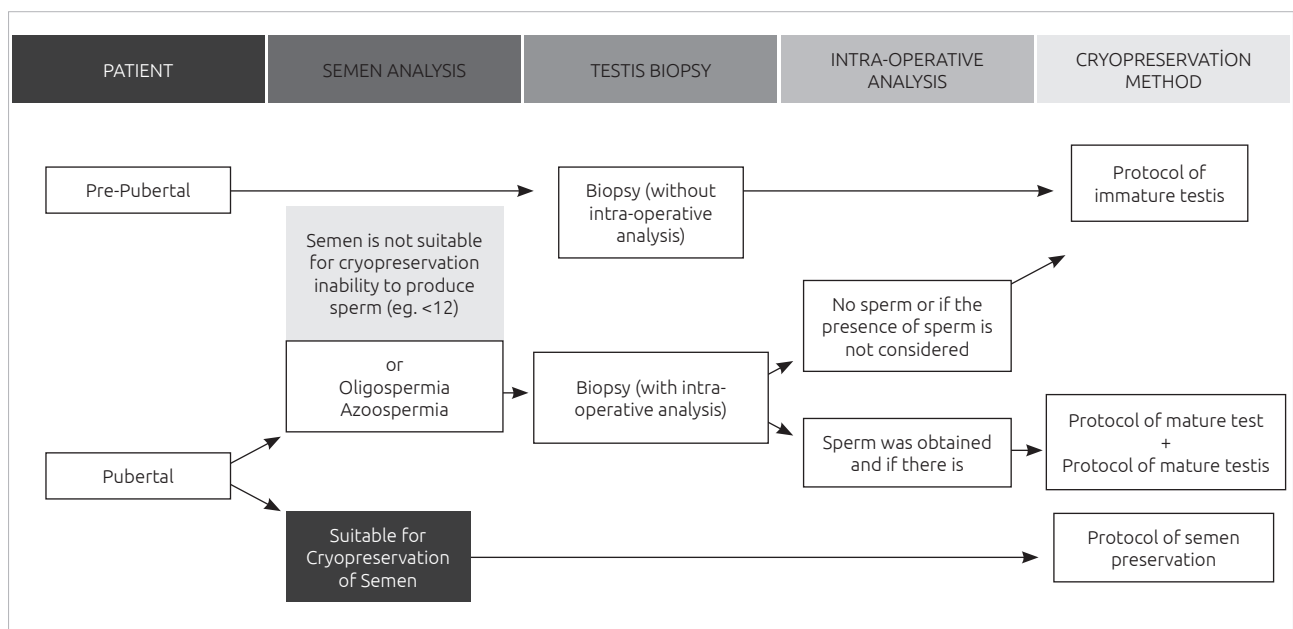
ence in terms of the number and quality of oocytes obtained. This option should be discussed with all patients who are in the reproductive period and will receive gonadotoxic therapy (7).

**Oocyte Cryopreservation (Freezing)**

Since there is not any partner requirement, it is the first choice in patients who are not married or who do not consider embryo freezing to be ethical and religiously appropriate (8). While the oocyte freezing procedure had previously been considered to be experimental, with the bulletin published in 2013 by the American Society of Reproductive Endocrinology (ASRM), it was accepted as not experimental, but a method that should be routinely presented to patients with an indication for fertility protection (9). Although slow freezing or vitrification can be used for oocyte freezing, the number of studies showing that the vitrification method has a higher success rate has increased in recent years. In this method, the



**Figure 1. A simplified schema for the fertility protection options in women (5)**



**Figure 2. Current methods for fertility protection in man (3)**

most important factors affecting the success rate are the age of the patient while the eggs are frozen and the number and quality of the frozen oocytes. Live birth rates for all ages are different according to the number of thawed eggs and the method of freezing. While the possibility of live birth in a 30-year-old woman who has 6 oocytes to thaw is 10.5%, the possibility of live birth in a 40-year-old woman who has 6 oocytes to thaw is 5,4%.

### **Cryopreservation of Ovarian Tissue (Freezing)**

The method of freezing and storing ovarian tissue is offered as an option in selected patients, especially in those who are in prepubertal period or in whom radiotherapy or chemotherapy should not be delayed. In addition, freezing ovarian tissue seems to be an effective method for preserving too many follicles and preserving hormonal function (11).

Cryopreservation of ovarian tissue requires surgical intervention. It is the preparation of cortical strips with a thickness of 0.3-2 mm by taking the ovary or a portion of the ovary with laparoscopy or laparotomy before cancer treatment. These small parts are frozen with one of the slow-freezing or vitrification methods and stored. The thawing and transplantation of the tissue can occur after years (12). The first live birth after the auto-transplantation of ovarian tissue in humans was reported by Donnez et al. (13). It was reported that 13 live births took place with cryopreserved ovarian tissue in 2011, and 24 live births took place after 60 re-transplantations in 2013 worldwide (14, 15). This application may have risks of re-implantation or recurrence of malignant cells that may be present in the frozen tissue. Especially in hematological cancers such as leukemia and lymphoma, there is a risk of malignant cell in the ovary. Another risk is the possibility that ischemia develops after transplantation and the graft does not function (16).

Currently, ovarian tissue freezing is an experimental method. It is a laborious procedure that requires two surgical procedures. The data on its efficacy, safety and outcomes are inadequate, and more studies are needed. However, it appears to be useful in selected patient groups. The fact that the procedure is carried out by an experienced team is one of the important factors that increase the success.

### **Transposition of the Ovary**

It is the surgical removal of the ovaries from the radiation area in order to protect the ovaries from the gonadotoxic effect of radiation in patients with pelvic malignancies and requiring pelvic irradiation. The procedure that was first performed with laparotomy in 1958 is performed using laparoscopic and robotic techniques nowadays. The procedure is performed just before radiotherapy (17). Severe damage to ovarian DNA and iatrogenic ovarian failure, early menopause, need for long-term hormone replacement therapy and infertility can be encountered after pelvic radiation. The ovarian function can be preserved at a rate of 70% with the transposition of the ovary before radiotherapy (18).

### **Using GnRH Analogues**

The use of GnRH analogues during chemotherapy is among the latest strategies for fertility protection. However, in randomized controlled studies conducted on whether or not this approach protects the ovarian tissue against chemotherapy damage, it is emphasized that the results are not compatible and are controversial, and that more research is needed (19). In the Prevention of Early Menopause Study (POEMS) (20), it was reported that the use of GnRH analogues during chemotherapy decreased the incidence of ovarian failure, increased pregnancy rates and increased disease-free and overall survival rates significantly, but the effect has not been clearly explained (20). In the randomized controlled study called as the Prevention of Menopause Induced by Chemotherapy (PROMISE) (21), it was observed that the use of Triptorelin and Goserelin during chemotherapy significantly decreased the development of ovarian failure (21). In the POEMS; while ovarian failure occurred in only 22% of patients who received chemotherapy, this rate decreased statistically significantly up to 8% in the group receiving GnRH agonists with chemotherapy. In the PROMISE study, similarly, this ratio is 8,9% and 25,9% (21).

In a recent study conducted on human ovarian tissue, it was shown that GnRH bound to its receptors but did not activate anti-apoptotic mechanisms and did not protect ovarian tissue against gonadotoxic chemotherapy agents such as cyclophosphamide and cisplatin (3, 21, 22). Since the results of randomized controlled trials are contradictory, there is insufficient evidence for the safety of ovarian suppression using GnRH analogues in combination with chemotherapy. For this reason, although GnRH agonists are considered as an experimental fertility protection method, there is excessive menstrual bleeding due to chemotherapy and therefore, it is recommended to be applied as protection for other conditions (22).

### **Cryopreservation of Sperm and Testicular Tissue in Male Patients**

Testicles can also be negatively affected by chemotherapeutic agents and radiotherapy, and spermatogenesis is impaired. Sperm cryopreservation is the first option for fertility protection in adolescent men. Since chemotherapy will increase DNA damage in sperm, pretreatment procedure should be performed (3). In the prepubertal period; experimental treatments that can be applied when it is not possible to obtain sperm are testicular tissue cryopreservation and isolated spermatogonial stem cell transplantation, xenotransplantation and in vitro sperm maturation. In males after puberty; sperm cryopreservation, testicular sperm extraction and cryopreservation is the surgical acquisition of sperm with percutaneous epididymal sperm aspiration, testicular sperm aspiration and microepididymal sperm aspiration, and the storage of the obtained sample after freezing (3, 21, 22). Current methods used for fertility protection in males are shown in Figure 2 (3).

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## References

1. TSRM Klavuzu-4. Üremenin korunması. Kasım 2015.
2. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016; 66: 271-89. [\[CrossRef\]](#)
3. Picton HM, Wyns C, Anderson RA, Goossens E, Jahnukainen K, Kliesch S, et al; ESHRE Task force on fertility preservation in severe diseases. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. *Hum Reprod* 2015; 30: 2463-75. [\[CrossRef\]](#)
4. Waimey KE, Duncan FE, Su HI, Smith K, Wallach H, Jona K, et al. Future directions in oncofertility and fertility preservation: A Report from the 2011 Oncofertility Consortium Conference. *J Adolesc Young Adult Oncol* 2013; 2: 25-30. [\[CrossRef\]](#)
5. Bedoschi G, Oktay K. Current approach to fertility preservation by embryo cryopreservation. *Fertil Steril* 2013; 99: 1496-502. [\[CrossRef\]](#)
6. Gidoni Y, Holzer H, Tulandi T, Tan SL. Fertility preservation in patients with non-oncological conditions. *Reprod Biomed Online* 2008; 16: 792-800. [\[CrossRef\]](#)
7. Boots CE, Meister M, Cooper AR, Hardi A, Jungheim ES. Ovarian stimulation in the luteal phase: systematic review and meta-analysis. *J Assist Reprod Genet* 2016; 33: 971-80. [\[CrossRef\]](#)
8. Pfeifer S, Goldberg J, Lobo R, Thomas M, Pisarska M, Widra E, et al. Practice Committee of American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. *Fertil Steril* 2013; 100: 1214-23. [\[CrossRef\]](#)
9. Pfeifer S, Goldberg J, McClure R, Lobo R, Thomas M, Widra E, et al. Practice Committees of American Society for Reproductive Medicine. Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertil Steril* 2013; 99: 37-43. [\[CrossRef\]](#)
10. Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertil Steril* 2013; 100: 492-9. [\[CrossRef\]](#)
11. Dittrich R, Hackl J, Lotz L, Hoffmann I, Beckmann MW. Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. *Fertil Steril* 2015; 103: 462-8. [\[CrossRef\]](#)
12. Meirou D, Roness H, Kristensen SG, Andersen CY. Optimizing outcomes from ovarian tissue cryopreservation and transplantation; activation versus preservation. *Hum Reprod* 2015; 30: 2453-6. [\[CrossRef\]](#)
13. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* 2004; 364: 1405-10. [\[CrossRef\]](#)
14. Donnez J, Dolmans MM, Pellicer A, Diaz-Garcia C, Sanchez Serrano M, Schmidt KT, et al. Restoration of ovarian activity and pregnancy after VOL. 103 NO. 2 / FEBRUARY 2015 467 Fertility and Sterility® transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. *Fertil Steril* 2013; 99: 1503-13. [\[CrossRef\]](#)
15. Donnez J, Dolmans MM. Preservation of fertility in females with haematological malignancy. *Br J Haematol* 2011; 154: 175-84. [\[CrossRef\]](#)
16. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. *Fertil Steril* 2012; 97: 134-40. [\[CrossRef\]](#)
17. Gubbala K, Laios A, Gallos I, Pathiraja P, Haldar K, Ind T. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. *J Ovarian Res* 2014; 7: 69. [\[CrossRef\]](#)
18. Mossa B, Schimberni M, Di Benedetto L, Mossa S. Ovarian transposition in young women and fertility sparing. *Eur Rev Med Pharmacol Sci* 2015; 19: 3418-25.
19. Turner NH, Partridge A, Sanna G, Di Leo A, Biganzoli L. Utility of gonadotropin-releasing hormone agonists for fertility preservation in young breast cancer patients: the benefit remains uncertain. *Ann Oncol* 2013; 24: 2224-35. [\[CrossRef\]](#)
20. Gerber B, Ortman O. Prevention of Early Menopause Study (POEMS): is it possible to preserve ovarian function by gonadotropin releasing hormone analogs (GnRH)? *Arch Gynecol Obstet* 2014; 290: 1051-3.
21. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA* 2011; 306: 269-76. [\[CrossRef\]](#)
22. Bildik G, Akin N, Senbabaoglu F, Sahin GN, Karahuseyinoglu S, Ince U, et al. GnRH agonist leuprolide acetate does not confer any protection against ovarian damage induced by chemotherapy and radiation in vitro. *Hum Reprod* 2015; 30: 2912-25.