# ONCOFERTILITY: FERTILITY PRESERVATION IN CANCER PATIENTS

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## SUMMARY

*Gynecologic cancers are among the most common type of cancer in women. Previously, cancer treatment focused on eradicating the disease without paying particular attention to the patient's age of her future fertility plans. Advances in the field of oncology especially in early detection and treatment management, improved the prognosis of cancer patients. Therefore, in recent years quality of life after treatment became an important consideration for cancer patients. Today, fertility preservation (FP) plays a vital role in the management of gynecologic cancers. At the crossroads between gynecologic oncology and infertility lies a new field of medicine, namely oncofertility. The purpose of this review is to present the latest advances in oncofertility.*

***Key words:*** *fertility preservation, gynecologic oncology, infertility, oncofertility.*

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## ONKOFERTİLİTE: KANSER HASTALARINDA FERTİLİTE PREZERVASYONU

## ÖZET

*Kadınları etkileyen kanserler arasında jinekolojik olanlar büyük yer tutmaktadır. Geçmişte, kanser tedavileri hastanın yaşına ve ilerdeki fertilite planlarına bakılmaksızın, kanser hastalığını yok etmeyi hedeflemekteydi. Onkolojideki erken tanı ve tedavi yöntemlerindeki gelişmeler, jinekolojik kanser hastalarının prognozunu iyileştirmiştir. Bu sebeple, son yıllarda bu hastaların tedavi sonrası hayat kalitesi kayda değer bir unsur haline gelmiştir. Günümüzde fertilite prezervasyonu (FP), jinekolojik kanser yönetiminde önemli bir yere sahiptir.*
*Onkoloji ve infertilite bilim dallarının kesiştiği noktada doğan 'onkofertilite' dalındaki son gelişmeleri sunmak bu derlemenin temel amacıdır.*

***Anahtar kelimeler:*** *fertilite prezervasyonu, infertilite, jinekolojik onkoloji, onkofertilite*

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## INTRODUCTION

Among the cancers affecting women, gynecologic cancers have a significant role. Although these types of cancers are reported more frequently during menopause, they can also affect women in reproductive age. 8% of endometrium cancers, 12% of ovary cancers and 40% of cervical cancers can be reported in women of reproductive age[1].

In the past, the cancer treatment focused on, regardless of the age and fertility plans in the future, only counteracting cancer. However, thanks to early diagnosis and treatment protocols like Papanicoloau (Pap) smear, non-invasive scanning techniques, minimally invasive surgical procedures and advances in other treatments with antineoplastic agents and chemotherapy, diagnosis, treatment and survival rates of gynecological cancers have increased. Therefore, the fertility preservation (FP) of the patient and her desire to become a parent are now important for choosing and administrating the related treatment. In a survey among radical trachelectomy patients, 41% of them suggested that their childbearing desires are playing a significant role in their future[2]. As a result of advances in oncology treatment and high expectations of the patients, during recent years there has been a great improvement in FP. At the crossroads between gynecologic oncology and infertility lies a new field of medicine, namely oncofertility. The purpose of this review is to present the latest advances in oncofertility. The purpose of this review is to present the latest advances in oncofertility.

## CANCER TREATMENTS AFFECTING FERTILITY AND REPRODUCTION

### Surgical resection of vital reproductive organs

Surgical resection of organs like uterus, cervix, fallopian tubes and ovary has an important place in the treatment of malignancies. Furthermore, for the surgical staging of ovarian and uterine cancers, the pathologic evaluation of these organs are needed. However, in carefully chosen patients who have the fertility desire, staging and the surgical phases can be modified to preserve the reproductive function of the patient. When choosing a patient, ideal cancer phase, age of the patient (≤43), having no other fertility problems, having a desire to have a child and being concordant to monitoring are the important criteria.

According to the International Federation of Gynecology and Obstetrics' (FIGO), treatment approach in women for cervical cancer stage I-IIA is radical hysterectomy. However, in patients who want to preserve their fertility, with early stage squamous cell cervical cancer, a fertility preserving surgical approach can be considered. For women who have stromal invasion less than 3mm (FIGO stage IA1), a cervical conisation can be preferred. Similarly, there are also studies about conisation with successful results in women with adenocarcinoma diagnosis. Bisseling et al(3)performed conisation to 16 women with adenocarcinoma in micro invasive stage IA1, and reported that during the 72 month follow up period, no recurrences were detected. While performing conisation to stage IA1 squamous cell or cervical cancers with adenocarcinoma, it is important to leave a negative tumor area near excision border. Cervical cancers of FIGO stage 1A2-IB1 with an invasion more than 3mm, fertility preserving approach is radical trachelectomy, which is vaginally, abdominally, laparoscopically or robotically performed by removing all of the cervix and parametrium. For this operation, the criteria of the chosen patients are; (1) fertility desire, (2) concordance to the follow up, (3) not to have clear cell or undifferentiated histology, (4) have the suspicion of lymphovascular invasion FIGO stage IA1 or stage IA2-IB1 with a lesion less than 2cm, (5) not have the symptoms for pelvic lymph node metastasis. In these patients, it is reported that the preterm labor is twice higher. Hence, cerclage can be considered during antenatal follow ups.

Recently an approach has been developed as an alternative treatment for radical trachelectomy, which is conisation after neoadjuvant chemotherapy (NACT) and pelvic lymph adenectomy and is performed generally in women in Europe with a larger cervical lesion and who want to preserve their fertility. The widest case series published by Maneo et al is belong to 21 women with the stage IB1 cervical cancer[3]. All the patients in this study have received conisation and pelvic lymph adenectomy after third round, cisplatin, paclitaxel and ifosfamide. On an average of 69 months follow ups, there was no recurrence detected. There were less preterm labors reported in ratip to the patients who received radical trachelectomy and the ones who received conisation.

In some cases, for the patients who will undergo radical hysterectomy and receive pelvic radiation therapy, a surgical approach can be required to preserve the ovary's function. For such purposes, in operations such as oophoropexy and ovarian transposition, ovary is hung to a place where no radiation is received. Ovarian veins, over the peritoneal oviduct are dissected and ovaries are hung in front of the psoas without creating tension. This operation has to be carried out just before the radiation therapy, and it can be either done abdominally or laparoscopically. The most frequent complication is the infarct of oviduct. This operation can protect the ovary from radiation therapy's adverse effects but not from chemotherapy.

As for patients with ovarian cancer, the preferred treatment is removing the oviduct and radical hysterectomy. However, for women who want to have children, it is possible to leave one ovary and the uterus. The chosen population for this, in general, is women who are in their twenties with germ cell ovarian cancer. In these women, even in the late stages, after unilateral salpingo-oophorectomy, omentectomy, peritoneal exemplification and pelvic lymph node exemplification pregnancy rates are high. As for women who are in the reproductive ages with the relatively less reported invasive epithelial cancers stage I, the conservative surgical approach has been reported with a better survival rate and pregnancy[4]. In addition, in the early stages of endometrial and cervical cancers, preservation of the ovary protects both the fertility and the endocrine function of the ovary. Endogenous ovary estrogen production also has protective characteristics. Therefore, an attention to the ovary preservation should be paid. The success of all these techniques depends on the detailed information about the patient. If the ovary is needed to be removed, gamete and/or embryo cryopreservation should be considered before the operation.

For endometrial cancer, the fertility preserving approach is not surgical but the hormonal methods. For the cancers with positive estrogen and progesterone receptors, treatment respond ratio is between 26 to 89%. Criteria for hormonal treatment patients: (1) having the grade 1 benign differential tumor, (2) not having lymphovascular invasion suspicion in the curettage sample, (3) no detected myometrial invasion via MR screening, (4) no metastatic disease reported in PET/CT screenings, (5) no adnexal mass was reported in CT or pelvic ultrasound (in women with premenopausal endometrial cancer, 29% could have ovarian cancer at the same time), (6) in endometrial biopsy or curettage samples the progesterone receptors has to be marked with immunohistochemicals. This treatment must be explained to the patient in detail with the related risks. The treatment methods used for this purpose are the intra uterine devices with megestrol acetate, medroxyprogesterone acetate and progesterone. 160 mg/day megestrol acetate or 600 mg/day medroxyprogesterone acetate is given to the patient for 3 weeks. After that the endometrial sampling is repeated, if the cancer is persistent or progressed, hysterectomy is suggested. If there is a regression, the treatment is continued for another 6 to 9 months. At the end of the treatment if there is no recurrence, conceiving is suggested to the patient and a close follow-up after labor. The duration of this treatment, the exact protocol about the dosage is still not clear and further research is required. Applying high dosages of progesterone with intra uterine devices and having no systematical adverse effects are definite advantages. Ramirez et al[3] performed progesterone treatment to 81 patients with endometrial cancer. 62 patients responded to the 12 week treatment, but in 15 of them the disease recurred and in 6 patient, residual cancerous tissue was reported in hysterectomy specimens. There were no responses in 19 patients. Women with endometrial cancer who are obese with polycystic ovarian syndrome and anovulation. Therefore, they could need assisted reproductive techniques, and the effects of hormonal changes are still unclear.

**Chemotherapy**

Since the chemotherapeutic agents damages the oocytes, they have destructive effects on a woman's future fertility potential. The extent of this damage depends on three factors: type of the drug, dosage of the drug and age of the patient. Type of the drug is the most important parameter in ovarian failure. For example, alkylating agents like cyclophosphamide have a high risk of leaving toxic effects on ovaries and possibility of amenorrhea occurrence increases. These agents were used more commonly in ovarian cancers in the past, but today they are used more in gestational trophoblastic diseases. In general, medium-risk agents like platinum, taxol and doxorubicin are used in gynecological malignancy treatments. Many studies on humans found

out that these drugs affect fertility on a medium level risk, but lately the studies on animals show that they might cause gonadal toxicity more than expected. There is a need for extensive research about how the agents are effective on the future of the fertility. Future findings, regardless of which chemotherapeutic agent is used, should provide detailed information to the women at their reproductive ages.

In ovarian failure progress, the age of the patient is also crucial. The gametogenesis cannot be formed in the fetus after 20 weeks and as the patient ages, the number of follicles reduces. For this reason, during chemotherapy, the risk of ovary failure is higher in older patients. The prepubertal adolescents have more primordial follicle reserve. Therefore, they are more resistant to the sterilization effects of chemotherapy. This phenomenon can be explained better with breast cancer patients. The occurrence of ovarian failure is 50% in the breast cancer patients over 40 years old and this rate is 30% in the patients under 35 years old [5]. Finally, when evaluating a patient's ovary failure, the drug dosage is also considered. Especially the high dosages of the high-risk drugs can be damaging the ovaries more extensively. Even in younger cancer patients, the reduced ovary reserve and increased follicular FSH levels point out faster oocyte atresia and reduced oocyte quality. Hence, after chemotherapy treatment, reproduction ratio reduces significantly[6].

Even though the toxic effects of chemotherapeutic agents on the ovary's function, it is reported that there were no difference in maternal morbidity ratio in gestation after cancer treatments. Even so, some agents cause permanent damages on specific organs can result in maternal complications. Hence, potential adverse effects should be reviewed on the basis of the drug. In general cardiovascular complications like arrhythmia, dilated cardiomyopathy, and coronary artery vasospasm are reported after using anthracyclines (daunorubicine, doxorubicin, idarubicin, epirubicin and mitoxantrone). In patients who have used these drugs and wanted to conceive, evaluation with electrocardiogram and echocardiogram are necessary. Some researchers even ask for radio-nucleotide angiocardiogram and twenty-four-hour Holter monitorization. If there is a significant decrease in ventricular function, conceiving is inadvisable[7]. In germ cell tumor treatment in adolescents, the routinely used bleomycin can cause pulmonary fibrosis. In pregnant women, there is a risk of hypoxemia and when this is combined with pulmonary disease, there could develop maternal as well as fetal (pre-eclampsia, IUGR and low birth weight) risks. Therefore, women who used this drug should take pulmonary function tests and when their test results are not normal, a close follow-up during their pregnancies is important. In kids and young adults, when treating a gynecological malignancy, the commonly used platinum is nephrotoxic. Although the renal complications, which can occur while using these drugs are acute, there can be chronic renal failure in a few patients. Since the pregnancy worsens the existing renal conditions, having kidney function tests (serum metabolic panel and 24 hour urine collection) before gestation is necessary, because it is well documented that the women with kidney disease have more complications (like pre-eclampsia, IUGR and stillbirth) during their pregnancies[8]. In general assisted reproductive techniques are used for the conception of cancer patients. Therefore, multiple delivery by caesarean rates are high[9]. Hence, maternal and fetal close follow-up is important for such patients.

**Radiation**

In comparison with chemotherapy, the radiation does not only damage ovaries, but also damages uterus and hypothalamic-pituitary axe. Abdominal pelvic and total body irritation have detrimental effects on ovary follicles depending on the dosage. When the ovarian failure ratio of the radiation dosage ≤300 cGY is 11%, this rate increases to 50% with the dosage of >300 cGY. Therefore, oophoropexy or ovary transposition should be carried out in such cases. In addition, the treatment effect also depends on the age. Consequently, it is reported that a single dosage radiotherapy is more toxic than divided dosages. Radiation has a three dimentional effect on the uterus. Firstly, by breaking the uterus vesiculation the cytotrophoblast invasion could be blocked. By decreasing the fetoplacental circulation, this condition causes fetal growth restriction [10]. Secondly, radiation causes myometrial fibrosis. Reduced uterus elasticity and volume cause preterm birth. And lastly, radiotherapy could damage the endometrium. This causes abnormal decidualization and placental confinement becomes harder. Hence, increased rates of placenta accreta and percreta could be reported[10,11]. Pregnant women who have received either pelvic or abdominal radiation are in high risk

and they should be followed up closely during their gestation periods. Therefore, for reviewing the placenta the utilization of ultrasound and/or MRI and for monitoring the fetal growth the utilization of ultrasound series and to evaluate the fetal health utilization of antenatal tests are important. Even though the preterm birth is reported frequently in these patients, there is still no reliable tests for initial diagnosis. Breast and thorax radiation could cause cardiac complications like pericarditis, pancarditis, cardiomyopathy and valve damage[12,13].Therefore, an electrocardiogram and echocardiogram are important. If any kind of anomaly is to be found, an intense antepartum and intrapartum evaluation are essential.

The main doubts of the women who want to conceive after cancer treatment are the congenital and structural anomalies that could occur in their children. Hence, many researchers studied congenital anomaly incidence after chemotherapy and radiation[14]. Although, there were no increased risks[15,16], it is likely that the patients could still have doubts as many agents used in cancer treatments affect vital processes of embryo and photogenesis like DNA, cell division and cellular metabolism. In addition, the fetus gender ratio of the cancer patients was studied and no significant difference was reported. This circumstance refutes the argument of X-attached mutation of the cancer treatments[17]. Lastly, there was no increase of malignancy risk for the cancer patient's children except for the cancers with genetic syndromes (i.e. FAP, HNPCC, retinoblastoma, Li-Fraumeni syndrome)[18].

## FERTILITY PRESERVATION (FP) APPROACHES

### Embryo and oocyte cryopreservation

In addition to surgical modifications to preserve reproductive organs for fertility, in recent years, developments are made in the assisted reproductive techniques. Thus, the hope of staying fertile after cancer treatment has increased for the women who are diagnosed with cancer. The two-most successive techniques are embryo and oocyte cryopreservation. Noyes et al carried out oocyte cryopreservation successfully before or during the cancer treatment in 50 cancer patients[19]. Both oocyte and embryo cryopreservation have been used for nearly 20 years. Embryo cryopreservation, a type of in vitro fertilization (IVF), has being carried out since the birth of the first baby with this technique in 1984[20]. The success and the effectiveness of the technique are proven by bringing more than 200,000 babies into the world since the first time it was carried out. The first baby brought into the world with the oocyte cryopreservation was in 1986[21]. However, in comparison with embryo cryopreservation, the oocyte cryopreservation did not spread like as quickly. The main factor of this may be the specific fragility and instability of the oocyte. In the beginning, these factors have limited the usage of this technique and its speed of development. With the somewhat recent developments in Italy, in 1998 and the live births reported in series with oocyte cryopreservation led improvements in this technique[22,23]. Subsequently, at the end of 90's, oocyte cryopreservation covered a lot of ground. Today, results show that oocyte cryopreservation data is equivalent to the IVF[24-26]. In addition, in a recent study, 900 babies who were born with oocyte cryopreservation were evaluated and no difference was found in terms of genetic anomaly risk in comparison with the babies who were born naturally[27]. However, many reproductive medicine societies like the American Society for Reproductive Medicine (ASRM) still consider the oocyte cryopreservation as an "experimental" approach, but they are supporting these approaches for FP in cancer patients[28]. Both oocyte and embryo cryopreservation provide equivalent FP ratio, but for women without a partner the oocyte cryopreservation is a more suitable solution. Oocyte cryopreservation, which does not require sperm, could provide reproductive autonomy to the patient. In addition, if the cancer was not cured, the ethical and psychological burden of the oocyte cryopreservation on the cancer patient is less than a frozen embryo.

Before the cancer treatment, oocyte and/or embryo cryopreservation could be carried out quickly in patients who want FP. In general, the needed duration is between two to four weeks. The reason of this intermittent duration is to consider the menstruation cycle (if there is a uterus) of the patient. Contraceptive pill usage does not pose an obstacle for the ovary's stimulation, because the treatment can begin while using the pill. In the USA, researchers of the Stanford School of Medicine, in a recent study on the duration of the initiation of treatment in breast cancer patients, found

no difference between women who are being treated for FP and who are not[29]. Noyes et al found the average treatment time for FP as 12±0.3 days[30]. Reproductive aged patients with endometrial cancer are especially suitable for cryopreservation. In general, endometrial cancer is associated with polycystic ovarian syndrome (PCOS). Such patients could respond vigorously to the ovary stimulation and produce oocytes in high numbers. Even though the ovary hyper-stimulation's effects over the cancer disease are not known precisely, fertility treatment of cancer patients can be carried out without any complications. In addition, the available treatment options for patients with cancer include spontaneous conception, ovulation induction ± intrauterine insemination or IVF (by using fresh or frozen gamete or embryo). Cervical cancers in which the radical hysterectomy ± ovarian transposition are possible, because of the damages of the hysterectomy on the ovarian functions[30], the oocyte collection should be carried out before the surgical approach, because the oocyte collection would be harder after the transpositioning.

**Usage of ganadotropine releasing hormone (GnRH) agonist for protecting the ovary**

According to some specialists, GnRH agonist usage can be feasible to protect the ovaries from the gonadotoxic effects of chemotherapy[31-34]. In general, a month before the chemotherapy treatment, GnRH agonist administration is carried out in different dosages (3.75mg/month - 11.25mg/3months). The 3.75mg/month dosage could be more suitable to cease immediately, if there is drug intolerance or FP occurs. The quick ovarian stimulation is not possible when using 3 month of high dosages, because their effects could sometimes last for 4 months.

Although there are many theories on how this treatment protects the ovary, the well accepted one belongs to Blumenfeld[32]. According to the Blumenfeld's theory, gonadotoxic chemotherapy increases FSH by killing ovarian follicles. Increased FSH causes the selection of primer follicles. These follicles join to the cell cycle again and killed by chemotherapy. GnRH agonists repress endogenous FSH/ pituitary extraction. Therefore, they slow down the oocyte atresia which was sped up after gonadotoxic treatment. Unfortunately, there are still no comprehensive studies that are randomized with a control group and measuring the gestation rates after cancer treatment with or without agonist. Because the existing research findings (Hodgkin patients) are retrospective and th control groups are inconsistent (i.e. different chemotherapeutic agents used, with patients in different stages of cancer, etc.), they present poor conclusions[35]. Although Huser et al concluded that the ovary is protected as a result of using GnRH agonist with chemotherapeutic agents, there were no statistically significant difference in premature ovarian failure after aggressive chemotherapy (BEACOPP)[33]. In a recent randomized study, in early stage breast cancer patients, the comeback ratio of menstruation and ovulation after treatment and ± GnRH agonist usage were compared[34]. In accordance with this study's results, GnRH agonist usage has increased the ratio of menstruation and ovulation comeback. In another recent study Oktay et al researched GnRH agonist and FSH usage in 74 breast cancer patients and as a result they obtained matured oocytes and embryo in increased numbers[36]. However, before recommending usage of GnRH agonist for FP, age of the patient, her ovarian reserve, her oncological treatment protocol, and her marital status (does she have a partner or not) should be taken into consideration. This kind of FP method could be more suitable for adolescents with healthy ovarian reserves. Extensive studies for the routine usage of GnRH agonist for FP in cancer treatments are still needed to establish its benefits.

## OVARIAN AND UTERINE TRANSPLANTATIONS

Since the beginnings of the 20$^{th}$ century, ovarian transplantation has been in practice and was performed in 50 cases with premature ovarian failure in the recent years[37]. A third of these patients became pregnant. This method is also carried out on women with cancer. Since the follicle number is high in younger women, the initial results are better.

As for uterus transplantation, until quite recently, successful results were limited to animal studies. However, on August 8$^{th}$, 2011, in Akdeniz University School of Medicine, Ozkan et al. carried out the first uterine transplantation from a cadaver. After the transplantation, the patient started to menstruate. Subsequently, a frozen embryo was transferred to the patient. However, the pregnancy was spontaneously aborted on 8 weeks gestational age.

## CONCLUSION

The diagnosis and the treatment of cancers are dynamic processes facing continuous improvements. In gynecological oncology, the adverse effects of the treatment of cancer in a woman can be the losing the ability conceive. Today, with the advances in the field of oncology, the survival ratio is increasing for malignancies, which could not be treated in the previous years. Therefore, an increasing number of women patients who have overcome the cancer, face the depressing reality of infertility, which might have detrimental effects on their quality of life. The studies in the field of oncofertility make progress on cancer patients to preserve their reproductive functions after the cancer treatment, while trying to find an answer to the basic desire of a human being, which is becoming a parent.

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