Review Article

Fertility preservation in female cancer patients: the results, conclusions, improvement and prospects for the future of these women

Mustafa Zakaria[1], Mohamed Zarqaoui[2], Noureddine Louanjli[3], Nisrine En-Naciri[4], Mohamed Ennaji[5], Malak Jamil[6], Amal Kabit[7]

[1]*Consultant at IRIFIV Fertility Center, Morocco*
[2]*General Medical Coordinator, IRIFIV Fertility Center, Morocco*
[3]*Head of LABOMAC Laboratory of clinical Analysis and Assisted Reproductive Technology, IRIFIV Center, Morocco*
[4]*Senior Clinical Embryologist , Laboratory IVF, Morocco*
[5,6,7]*Senior Clinical Embryologist, IRIFIV Fertility Center, Morocco*

Fertility preservation is becoming extremely necessary to help improve the quality of living within female cancer survivors. Despite recommendations that suggest that there should be consideration of preservation fertility before cancer treatments start, there is a lack of regulation in this field. A variety of fertility preservation methods are available, and can be employed separately or together in the same patient to enhance medical performance and therefore to augment efficiency. Oocytes and fetal cryopreservation are indeed well known methods but have restrictions. Although currently perceived as experimental, ovarian tissue cryopreservation has a broader clinical application and the advantage to maintain longer the fertility option. Chemotherapy and radiotherapy have a huge effect on the reproductive potential and the process of fertility preservation should be implemented before these two treatments. The importance of fertility preservation has to be weighed against morbidity and mortality in relation with cancer. A multidisciplinary cooperation between oncologists and reproductive specialists is therefore necessary to increase knowledge and accessibility.

Keywords: Fertility preservation. Cancer and fertility treatment. Cancer Therapy and Fertility. Chemotherapy. Radiotherapy. FSS for ovarian tumors. ART results using Cryopreserved Gametes. Stimulation for Embryo or Mature Oocyte Cryopreservation. Cryopreservation of ovarian tissue.

Abbreviations: ICR: India Cancer Survivorship. FP: Fertility Preservation. ASRM: American Society Of Reproductive Medicine. SOF: Severe Ovarian Failure. POF: Premature Ovarian Failure. CT: Chemotherapy. DSP: Double-Stripe Separators. DXR: Doxorubicin. ESD: Effective Sterilizing Dose. TBI: Total Body Irradiation. FSS: Fertility Sparing Surgery. BOT's: Borderline Ovarian Tumours. BSO: Bilateral Salingo-Oopherectomy. USO: Unilateral Salingo-Oopherectomy. BC: Bilateral Cystectomy. CC: Contralateral Cystectomy. EOC: Epithelial Ovarian Cancers. NCCN: National Comprehensive Cancer Network. GCIG: Gynecologic Cancer Inter Group. OCCC: Ovarian Clear Cell Carcinoma. OHSS: Ovarian Hyperstimulation Syndrome. SERM: Selective Estrogen Receptor Modulator. E2: estradiol.

Introduction

Early cancer diagnosis and developed multimodality treatment are providing better cancer survival and focusing on 'quality of life' issues. Statistics from Europe and the US show that long-term survival is about 80 % in children and adolescents with diagnosed cancer. A new research approximated that 1 in 530 young adults among the age groups of 20 and 39 years is a childhood cancer survivor. Even in the developing countries like India cancer survivorship is growing rapidly (ICR) [1]. Unfortunately, lifesaving cancer treatments such as chemotherapy and radiotherapy harm the oocytes and reduce female fertility. Deletion of reproductive organs in gynecological cancers contributes to more reproductive damage. We can measure the severity of the issue by looking at global cancer statistics. In 2012, Globocan estimated 14.1 million of these cancer cases all over the world, of which 6.7 million were women. By 2035, it is expected that number would reach up to 24 million. The trend of avoiding childbirth has risen the number of women facing a diagnosis of cancer before they have completed their family. Development in the survival rates and existing data that do not indicate a rise in the threat of progression of cancer, good obstetric and neonatal outcomes of pregnancy in survivors, have led to a significant need for non-infertility [2]. Fertility preservation (FP) became the ' standard of care' for cancer survivors and patients who are at risk of diminished fertility. This article provides an overview of the different choices open to women for maintaining fertility. Even though infertility is a huge issue among survivors, the discussion about reproductive cancer treatment is barely mentioned before treatment begins. Therefore, referrals to reproductive medicine specialists for fertility

Corresponding Author:
Mustafa Zakaria, MD General Practitioner, MSc of Reproductive Biology, Clinical Pathology and Assisted Reproductive Technology, Consultant at IRIFIV Fertility Center, Casablanca, Morocco; E-mail: dr.mustafazakaria@gmail.com

Received date: August 15, 2020; **Accepted date:** August 22, 2020; **published date:** August 31, 2020

preservation possibilities are few and far between. The literature shows a lower degree of psychological distress in patients receiving data linked to their sexual and reproductive health compared to those who did not obtain the information. Making an informed decision decreases genital remorse. Worldwide, oncology organizations have recognized the necessity of reproductive counseling. The American Society of Clinical Oncology (2006) proposes that "as part of education and informed consent leading up to cancer treatment, oncologists should treat the prospect of infertility with patients treated during their reproductive years and prepare to explore options for sustaining potential fertility or referring patients to reproductive specialists [3, 4, 5]. " The ASRM Practice Committee calls on mental health professionals and genetic counselors to be available to guide and help patients in decision making. Genetic counselors are required to address the potential threats to offspring and the currently available genetic testing.

Cancer and fertility treatment

The key elements of treating cancer are radiotherapy and chemotherapy. Such life-saving treatments, however, can endanger fertility. The degree of genital damage depends on the age of the patient, dosage, duration and type of factor used in the treatment. Many patients suffer from acute ovarian failure (AOF) which means they lose ovarian function during or shortly after cancer treatment. Some may acquire ovarian function after completing their cancer treatment, they will have an early menopause or menopause before reaching 40 years old [6, 7]. A higher risk of ovarian failure in cancer survivors is associated with aging at treatment and exposure to radiation therapy for the abdomen, pelvis, spine and alkylation factors.

Cancer Therapy and Fertility

Chemotherapy and radiotherapy are now the essential elements of cancer treatments. Depending on the agent used, the dosage given, and the patient's age, both can negatively affect the ovary. Chemotherapy Chemotherapeutic drugs work by interrupting processes of vital cells and disrupting the natural cycle of cell proliferation, so no doubt they have such a devastating effect on the germ cells. They end up causing DNA abnormalities as well as oxidative damage in somatic and germ cells. Persistent double-stranded, unrepaired DNA breaks trigger apoptotic death in oocytes. Genetic effects on the oocyte cause early embryonic mortality and aneuploidy [8, 9]. Ovarian effects the clinical effect of chemotherapeutic drugs on the ovary is variable ranging from no effect to complete ovarian atrophy. The resulting damage depends on the type of chemotherapy agent used, the dose given, the patient's age and her baseline ovarian reserve. The prepubertal ovary is less prone to harm from chemotherapeutic agents, while older women have lower ovarian reserves and are therefore more vulnerable to premature ovarian failure (POF) [10]. Decrease in ovarian reserve takes place due to apoptosis of growing follicles and activation of the rest follicle with subsequent apoptosis, resulting in a burn-out effect. Fibrosis of stromal blood vessels adds to the ovarian damage. The clinical manifestation of this follicular loss ranges from a complete amenorrhea to premature menopause and varying degree of infertility [11].

Chemotherapy (CT)

Chemotherapy drugs work by disrupting vital cell processes and halting the reproductive cycle of the natural cells. Sadly, this process is not limited to cancer cells alone, but can be entirely catastrophic for gonads being active in the metabolism. Cytotoxic agents generate DNA abnormalities and oxidative damage in somatic cells as well as germ cells, contributing significantly to programmed cell death.

Table 1: Estimated risk of gonadal dysfunction to cytotoxic drugs Source

High risk	Medium risk	Low risk
Busalfan	Cisplatin	Vincristine
Chlorambufil	Doxarubicin	Methotrexate
Cylophosphamide	Carboplatin	Dactinomycin
Dacarbazine		Mercaptapur
Melphalan		Vinblastine
Nitrogen mustard		
Procarbazine		

A. Ovarian effects: Follicular cell death and fleshy vascular fibrosis result in diminished ovarian reserve. Additionally, the remaining follicles are activated and subject to subsequent apoptosis, resulting in a "combustion" effect. The degree of ovarian harm is linked to the dosage and method of chemotherapy factor used (Table 1), the age of the patient and primary ovarian reserve, since a woman is born with a restricted number of eggs depleted by time [12, 13, 14]. Genital toxicity is significantly higher when alkylation factors like cyclophosphamide, followed by other drug families, are responsible for the highest life expectancy ratio for ovarian failure. Though older women have less ovarian reserves and are therefore more prone to experience early ovarian failure (POF). Clinical features differ significantly from complete menopause to early menopause and various levels of infertility (Table 2).

Table 2: Risk of permanent amenorrhea in women treated with chemotherapy and radiotherapy (ASCO Guidelines)

High Risk > 80%	External radiotherapy that includes the pelvic region CMF, CEF, CAF x 6 cycles. Women > 40 years old (CMF: cyclophosphamide, methotrexate and fluorouracil CEF: cyclophosphamide, epirubicin, fluorouracil CAF: cyclophosphamide, doxorubicin, fluorouracil)
Intermediate Risk	CMF, CEF, CAF x 6 cycles. Women 30–39 years old AC x 4 in women > 40 years (Doxorubicin/cyclophosphamide)
Low Risk < 20%	CMF, CEF, CAF x 6 cycles in women < 30 years old AC x 4 in women < 40 years old
Very Low Risk or no risk	Vincristine Methotrexate Fluorouracil
Unknown Risk	Taxanes Oxaliplatin Irinotecan Monoclonal Antibodies (trastuzumab, bevacizumab and cetuximab) Tyrosine-Kinase Inhibitors (ertolinib, imatinib)

B. Effect on eggs: the non-DNA double-stripe separators (DSP) activate the apoptosis processes in the eggs. Animal studies have demonstrated that certain cytotoxic medications are mutagenic and deformed to the urinary cells that are exposed during maturity. The risk of maximal mutation usually happens during the ripening stage of eggs and minimum during inactivity. The ripening period in humans takes for 6 months. It is also advised that pregnancy be postponed for 6 months until toxic gonadal treatments have been completed. No considerable increase in miscarriage, congenital malformations, genetic abnormalities or malignant tumors was detected when pregnancy took place long after completion of treatment. It is wise to conduct fertility maintenance techniques such as eggs and fetal preservation before a CT scan, but if postponement is inevitable, waiting 6 months after treatment is compulsory [15, 16]. FP should not be executed between the cycles of treatment. The exact safe period from completion of treatment to collection of eggs has not been determined for preservation.

Cytotoxic drugs and their action on the ovary: A group of different drugs are made below:

1. Alkylation factors have a very serious impact and are responsible for the highest age-adjusted odds ratio for ovarian failure rates. 2. Platinum compounds like cisplatin cause damage to DNA. They present an average menopause risk. 3. Anthracycline antibiotics such as doxorubicin (DXR) induce oxidative stress. With this group of medications, the risk of menopause and fertility is medium to low. In 1995, Mailhes reported that DXR administration in female mice is responsible for dominant killer mutations and chromosomal abnormalities in mature / pre-ovulatory eggs in female mice [17, 18] 4. Vinca alkaloids do not appear to increase the risk of ovarian failure, although animal experiments show a high rate of chromosomal abnormality in eggs. 5. Metabolites such as methotrexate and 5FU do not appear to affect ovaries based on the current limited data available. Methotrexate is commonly used to treat ectopic pregnancy without any effect on subsequent fertility. 6. Taxis - The available data are controversial with some studies showing an increased risk of ovarian failure. Other studies indicate that there is no increased risk. 7. Targeted biological treatments (Herceptin, Tamoxifen, Rituximab) are anti-cancer treatments derived from organisms. These agents are designed to interfere with specific molecules that are expressed by tumors (herceptin or tamoxifen), or act via the immune system (rituximab). Fertility risk data for these drugs are limited but since they target specific cells, it is believed that the risk should be low. They are generally given as an adjuvant treatment for 5 years or more after cancer treatment, but this delay may in itself pose a risk of fertility [19, 20].

Radiotherapy

The effects of radiotherapy are seen not only on the ovary but the uterus as well.

A. Ovarian effects: The human oocyte has an approximated median lethal dose (LD50) of < 2 gray (Gy) and is extremely sensitive to radiation. The 'fertility window 'is evaluated by the dose of radiation to the ovaries, the number of current primordial follicles or ovarian reserve and age of the patient at the time of treatment (Table 3) [21, 22]. The dose of fractionated radiotherapy [Gy] at which premature ovarian failure usually arises after treatment in 97.5% of patients is considered the effective sterilizing dose (ESD). ESD significantly reduces with increasing age, being 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3 Gy at 30 years, with only 6 Gy being requested to trigger permanent ovarian failure in women over 40. Ovarian failure has been revealed in 90 % of patients following TBI (10-15.75 Gy) and in 97% of females treated with total abdominal irradiation (20-30 Gy) during childhood.

Table 3: Radiation induced ovarian damage by dose and age

Age of treatment (years)	Effective sterilizing dose(Gy):loss of 97.5% of follicles
0	20.3
10	18.4
20	16.5
30	14.3
40	11.3

B. Uterine effects: Uterine growth begins at puberty and is finalized almost seven years after menarche, i.e. around the age of twenty, a rise in uterine blood flow is observed during puberty too. Exposure to radiation led directly to reduce vascularity, fibrosis and hormone dependent endometrial insufficiency which consequently lead to adverse reproductive outcomes. Direct radiation also reduces the uterine volume and ended up causing complete endometrial atrophy. In adults, an exposure to total body irradiation (TBI) of 12Gy is linked with important uterine damage. In childhood, radiation doses of > 25Gy directly into the uterus seem to induce irreversible damage. Reulen et al 2009 observed increased rates of infertility, miscarriage, preterm labor, intrauterine growth retardation and low birth weight, especially if conception took place within one year of radiotherapy [23, 26]. Chiarelli et al 2000 reported

an increase in perinatal mortality although this group found no rise in spontaneous abortions or birth defects. It was suggested that patients receiving > 45 Gy during adulthood and > 25 Gy during childhood should be advised to avoid attempting pregnancy, but there is no clarity about the radiation dose to the uterus above which pregnancy would not be sustainable. Successful delivery has been reported in a patient of Ewing 's sarcoma who obtained sterilizing pelvic radiotherapy (54 Gy) and 40 weeks intensive high-dose chemotherapy. Endocrine milieu accomplished after transplantation of cryopreserved ovarian cortical tissue resulted in follicular development and uterine growth shown on sequential ultrasound examination in colorectal cancers radiation damage to the gonads and uterus is inevitable, therefore ovarian transposition and fertility preservation techniques should be highly recommended.

Fertility Sparing Surgery for Ovarian Tumors

Borderline ovarian tumours (BOT's): are a heterogeneous group of non-invasive epithelial ovarian tumours that occur at a younger age, approximately 30% of BOT affect women under 40 years of age. They present in early stage and are frequently associated with infertility. They are less aggressive than malignant ovarian tumours and have a good prognosis. Since younger women are affected, fertility preservation needs to be considered when planning treatment. Traditional management of BOT is total hysterectomy with bilateral salingo-oopherectomy (BSO) with surgical staging. The fertility sparing surgery offered is dependent on the stage of disease, histology, and preexisting ovarian reserve. Unilateral salingo-oopherectomy (USO) or cystectomy(C) with extensive staging is performed and patient is kept under surveillance. Rate of recurrence after cystectomy is as high as 25%, three times more than with oophorectomy. A recent meta-analysis of 39 studies that included 5105 women having BOT concludes that USO is advisable in the case of mucinous BOT to reduce recurrence rate [27, 28, 29]. For bilateral BOT, which are almost always serous, a more conservative approach to bilateral cystectomy (BC) should be prioritized because there was no significant difference in the rate of recurrence compared to USO with contralateral cystectomy (CC). Among the patients undergoing C, BC, USO and USO+CC, the pooled recurrence predictions were respectively 25.3%, 25.6%, 12.5% and 26.1% The cumulative pregnancy rate was 55.7% with 45.4% for USO and 40.3.0% for C in their study. Malignant ovarian tumours: Hysterectomy, BSO and pelvic and para-aortic lymphadenectomy with omentectomy and peritoneal biopsies are the standard treatment for ovarian cancer. Non-epithelial malignant ovarian tumours, especially germ-cell tumours, do well with fertility-sparing surgery. Approximately 2.7% of patient's epithelial ovarian cancers (EOC) are younger than 40 years old and present with stage I disease. FSS has also been tried for early stage epithelial ovarian malignancy [30, 33]. Prerequisites for conservative surgery involve well-differentiated unilateral disease, with no sign of extra-ovarian metastasis. In a series of 572 women with stage I epithelial ovarian cancer, there were no differences in 5-year overall survival or disease-free survival between women who had undergone radical hysterectomy and those who had undergone fertility-sparing surgery. A detailed discussion with patients discussing the risk of recurrence is important and full understanding of this potential threat should be provided. The National Comprehensive Cancer Network (NCCN) guidelines for treatment recommend that fertility-sparing surgery can be conducted in all patients with epithelial ovarian cancer in stage IA and IC. The Gynecologic Cancer Inter Group (GCIG) consensus review maintains the point of view that FSS is not advised for stage IC, ovarian clear cell carcinoma (OCCC). A recent study by Miyamoto et al 2013 reported that early stage OCCC survival outcomes are similar to other histological types, and such patients may be offered FSS.

ART results using Cryopreserved Gametes

Data on pregnancy and live birth rates from gamete cryopreservation in cancer patients are scarce. Live birth rates similar to non-oncological patients have been reported using cryopreserved embryos. Successful oocyte freezing requires a skilled embryologist, as human oocytes are highly prone to ice crystal formation and damage by cryoprotectants. An overall survival rate of 85.2% (95% CI 83.2-87.2) was reported by Cobo et al 2015 [34, 36]. The author also estimated an oocyte-to-baby rate of 6.5%, the probability increases progressively with a plateau being reached at twenty-five.

Ovarian Stimulation for Embryo or Mature Oocyte Cryopreservation

The preferred protocol is the antagonist protocol with a GnRH agonist trigger for oocyte maturation, as it is shorter and decreases the risk of ovarian hyperstimulation syndrome (OHSS). To avoid delay in CT, a random start protocol has been introduced where OS is started at any time of the menstrual cycle without compromising the outcome. GnRH antagonist starts when the leading follicle reach a size of 12-14mm during controlled ovarian stimulation. Normal follicular growth and development is observed despite the increased progesterone levels seen in the luteal phase or a spontaneous LH surge, which may occur when the initial lead follicle reaches maturity. Literature suggests that age is the only factor that contributes to a decrease in the number of oocyte recovered in oncological patients, though there are concerns about a pre-existing reduced ovarian reserve in patients with BRCA mutations and lymphoma. Oocyte recovery rates are lower in women who have undergone prior gonadotoxic therapy due to reduced ovarian reserve [37, 39]. Supraphysiological estradiol (E2) levels achieved during OS, have raised concerns in hormone sensitive cancers. This has been addressed effectively by the addition of letrozole an aromataze inhibitor, along with gonadotrophins during OS [40, 42]. It is given from the start of OS in a dose of 2.5-

5mg daily and continued till after oocyte retrieval, until the E2 levels normalize. Use of Letrozole does not appear to affect the oocyte number or fertilization rate. Tamoxifen, a selective estrogen receptor modulator (SERM) is used routinely in BC patients to reduce recurrence. It has also been used during OS in hormone sensitive breast cancer patients, a follow up of 10 years has not shown an increase in recurrence rate in these patients.

Cryopreservation of ovarian tissue (OTC)

OTC involves removal of ovarian cortical tissue rich in primordial follicles and cryopreservation by slow freezing or vitrification (a more recent technique) after tissue preparation. Collection of ovarian tissue and re-transplantation can both be performed laparoscopically. Re-implantation of tissue is preferentially to the ovary/pelvic cavity (orthotopic), however heterotopic transplantation (abdominal wall or fore-arm) can be carried out if required. Reports of pregnancies achieved after ovarian tissue transplantation are increasing and a live birth rate of 23% has been announced. Advantages of the procedure are that it can be done in patients requiring urgent chemotherapy, OS is not required, gonadal function is preserved and a subsequent spontaneous conception is possible [43, 47]. For heterotropic transplantations, IVF is required to achieve pregnancy. Success of transplantation depends on the patients age, baseline ovarian reserve and expertize of the surgeon and cryobiologist performing the procedure. Ovarian function usually resumes between 60–240 days post-transplant and would extend for up to 7 years. It is the only technique available for preserving fertility in pre-pubertal girls. Stern et al 2013 recently reported on the first ongoing pregnancy from a heterotopic implantation of ovarian tissue. Low follicular survival rate after ovarian transplantation, precludes its use in women over 40 years [48, 50]. The amount of ovarian tissue cryopreserved theoretically should be proportional to the risk of age-related decreased follicular reserve in younger patients. According to the current evidence, removal of both ovaries for cryopreservation is currently not justified without a high probability of inducing complete ovarian failure from the chemotherapy regimen. The procedure is still deemed experimental by ASRM, although it is approved as a standard FP procedure in Europe and Israel.

Conclusion

Fertility preservation has become the life expectancy and standard of care for patients at risk of losing their reproductive potential due to cancer treatment, immune diseases or genetic makeup. Fertility maintenance advice is mandatory, although many oncologists are still reluctant to refer patients to reproductive specialists. A number of techniques are available to maintain fertility and can be used individually or together in the same patient to increase efficiency. For eggs, embryo freezing is available after puberty, a well-established method. Before, chemotherapy requires a two-week period of time. In women where there is an urgent need to start a CT scan and in prepubescent girls, ovarian tissue freeze can be introduced. OTC requires double surgery, although it has the advantage of allowing spontaneous pregnancy and restoring endocrine secretion [51, 52]. With more deliveries reported, the trial result has been lost in some countries. Tissue screening of malignant cells before transplantation is of paramount importance. In the future maturation in the laboratory in the intestines, stem cell therapy may be effective agents for the prevention of vertigo to improve fertility care. A multidisciplinary approach is vital to delivering effective FP services.

References

1. Hudson MM, Reproductive outcomes for survivors of childhood cancer, Obstet Gynecol 2010; 116:1171–1183.
2. Ward E, De Santis C, Robbins A et al., Childhood and adolescent cancer statistics, 2014, CA Cancer J Clin 2014; 64:83 – 103.
3. Indian Cancer Registry. Consolidated Report of the PBCRs: 2001-2004. Available from: www.icmr.nic.in/ncrp/cancer_reg.htm, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. [Int J Cancer. 2015]
4. Quinn GP, Vadaparampil ST, Bell-Ellison BA et al., Patient-physician communication barriers regarding fertility preservation among newly diagnosed cancer patients. Soc Sci Med. 2008; 66:784–9.
5. Lee SJ, Schover LR, Partridge AH, Patrizio P et al., American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006; 24:2917–31.
6. 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.
7. Wallace WH, Thomson AB, Saran F, Kelsey TW, Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005; 62:738–44.
8. Chemaitilly W, Mertens AC, Mitby P et al., Acute ovarian failure in the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 91:1723-1728, 2006.
9. Green DM, Sklar CA, Boice JD, Jr, Mulvihill JJ et al., Ovarian failure and reproductive outcomes after childhood cancer treatment: Results from the Childhood Cancer Survivor Study. J Clin Oncol. 2009; 27:2374–81.
10. Sklar C, Reproductive physiology and treatment-related loss of sex hormone production, Med Pediatr Oncol 33:2-8, 1999.

11. Di Giacomo M, Barchi M, Baudat F, Edelmann W et al., Distinct DNA-damage-dependent and -independent responses drive the loss of oocytes in recombination-defective mouse mutants, Proc Natl Acad Sci U S A. 2005; 102:737–42. [PMC free article] [PubMed] [Google Scholar]

12. Higdon RE, Marchetti F, Mailhes JB, Phillips GL, The effects of cisplatin on murine metaphase II oocytes, Gynecol Oncol. 1992; 47:348–52. [PubMed] [Google Scholar]

13. Meirow D, Wallace WH, Preservation of fertility in patients with cancer, N Engl J Med. 2009; 360:2682. [PubMed] [Google Scholar]

14. Meirow D, Nugent D, The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update, 2001; 7:535–43. [PubMed] [Google Scholar]

15. Anderson RA, Themmen AP, Al-Qahtani A et al., The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer, Hum Reprod. 2006; 21:2583–92. [PubMed] [Google Scholar]

16. Meirow D, Nugent D, The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001; 7:535-543

17. Anderson RA, Themmen AP, Al-Qahtani A et al., The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer, Hum Reprod 2006; 21:2583-2592.

18. Meirow D, Lewis H et al., Subclinical depletion of primordial follicular reserve in mice treated with cyclophosphamide: clinical importance and proposed accurate investigative tool, Hum Reprod. 1999; 14(7):1903-1907.

19. Zavos A, Valachis A, Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis, Acta Oncol. 2016; 55(6):664-670.

20. Meirow D, Biederman H, Anderson RA et al., Toxicity of chemotherapy and radiation on female reproduction, Clin Obstet Gynecol 2010; 53:727-739.

21. Meirow D, Wallace WH, Preservation of fertility in patients with cancer, N Engl J Med. Vol 2009; 360:2682-3.

22. Di Giacomo M, Barchi M, Baudat F et al., Distinct DNA-damage-dependent and -independent responses drive the loss of oocytes in recombination-defective mouse mutants, Proc Natl Acad Sci U S A. 2005; 102:737–42.

23. Meirow D, Schiff E, Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data, J Natl Cancer Inst Monogr. 2005: 21-25.

24. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ et al., Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study, J Clin Oncol 2009; 27:2374-2381.

25. Chung K, Donnez J, Ginsburg E, Meirow D, Emergency IVF versus ovarian tissue cryopreservation: Decision making in fertility preservation for female cancer patients, Fertil Steril. 2013; 99:1534–42.

26. Mailhes JB, Important biological variables that can influence the degree of chemical-induced aneuploidy in mammalian oocyte and zygotes, Mutat Res 1995; 339:155-176.

27. Han HS, Ro J, Lee KS, Nam BH et al., Analysis of chemotherapy-induced amenorrhea rates by three different anthracycline and taxane containing regimens for early breast cancer, Breast Cancer Res Treat 2009; 115:335-342.

28. Anderson RA, Themmen AP., The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer, Hum Reprod 2006; 21:2583-2592.

29. Davis AL, Klitus M, Mintzer DM, Chemotherapy-induced amenorrhea from adjuvant breast cancer treatment: the effect of the addition of taxanes, Clin Breast Cancer 2005;6:421-424

30. Ganz PA, Land SR, Geyer CE Jr., Cecchini RS, et al., Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial, J Clin Oncol 2011; 29:1110-1116.

31. Wallace WH, Thomson AB, Saran F, Kelsey TW, Predicting age of ovarian failure after radiation to a field that includes the ovaries, Int J Radiat Oncol Biol Phys. 2005; 62:738–44.

32. Holm K, Laursen EM, Brocks V, Muller J. Pubertal maturation of the internal genitalia: An ultrasound evaluation of 166 healthy girls, Ultrasound Obstet Gynecol. 1995; 6:175–81.

33. Laursen EM, Holm K, Brocks V, Jarden M et al., Doppler assessment of flow velocity in the uterine artery during pubertal maturation, Ultrasound Obstet Gynecol. 1996; 8:341–5.

34. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A et al., Radiotherapy at a young age reduces uterine volume of childhood cancer survivors, Acta Obstetricia et Gynecologica Scandinavica. 2004; 83(1):96–102.

35. Reulen RC, Zeegers MP, Wallace WHB, et al., Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study, Cancer Epidemiology Biomarkers and Prevention. 2009; 18(8):2239–2247.

36. Fenig E, Mishaeli M, Kalish Y, Lishner M. Pregnancy and radiation, Cancer Treat Rev. 2001;27:1–7

37. Chiarelli AM, Marrett LD, Darlington G et al., Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada, Am J Epidemiol. 1999; 150:245–54.

38. Teh WT, Stern C, Chander S, Hickey M et al., The impact of uterine radiation on subsequent fertility and pregnancy outcomes, Biomed Res Int. 2014; 2014:482968.

39. Rodriguez-Wallberg KA, Karlström PO, Rezapour M et al., Full-term newborn after repeated ovarian tissue transplants in a patient treated for Ewing sarcoma by sterilizing pelvic irradiation and chemotherapy, Acta Obstet Gynecol Scand. 2014 Dec 24.

40. Vasconcelos I, Mendes M de Sousa, Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk, Eur J Cancer. 2015 Mar; 51(5):620-31.

41. Kajiyama H, Shibata K, Mizuno M et al., Long-term survival of young women receiving fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery, Br J Cancer. 2011; 105:1288–94.

42. Okamoto A, Glasspool RM, Mabuchi S, Matsumura N, Nomura H, Itamochi H, et al., Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary, Int J Gynecol Cancer. 2014; 24:S20–S25.

43. Soares M, Sahrari K, Chiti MC et al., The best source of isolated stromal cells for the artificial ovary: medulla or cortex, cryopreserved or fresh?, Hum Reprod. 2015 Jul; 30(7):1589-98

44. Cakmak H, Katz A, Cedars MI, Rosen MP, Effective method for emergency fertility preservation: random-start controlled ovarian stimulation, Fertil Steril 2013 Aug 26

45. Lawrenz B, Fehm T, von Wolff M et al., Centers of FertiPROTEKT Network, Reduced pretreatment ovarian reserve in premenopausal female patients with Hodgkin lymphoma or non-Hodgkin-lymphoma--evaluation by using antimullerian hormone and retrieved oocytes, Fertil Steril. 2012 Jul; 98(1):141-4.

46. Oktay K, Kim JY, Barad D, Babayev SN, 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. 2010; 28(2):240–4.

47. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z, Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation, J Clin Oncol. 2005; 23:4347–53.

48. Meirow D, Raanani H, Maman E et al., Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies, Fertil Steril. 2014 Aug; 102(2).

49. Van der Ven H, Liebenthron J, Beckmann M, Toth et al., FertiPROTEKT network. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates, Hum Reprod. 2016 Sep; 31(9):2031-41.

50. Kim SS, Assessment of long term endocrine function after ovarian transplantation of frozen-thawed human ovarian tissue to the heterotopic site: 10 year longitudinal follow-up study, J Assist Reprod Genet 2012; 29:489–93.

51. Stern CJ, Gook D, Hale LG et al., First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy, Hum Reprod. 2013; 28:2996–9.

52. Huober-Zeeb C, Lawrenz B et al., Improving fertility preservation in cancer: Ovarian tissue cryobanking followed by ovarian stimulation can be efficiently combined, Fertil Steril. 2011; 95:342–4.

Review Article