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Fertility Preservation and Important Tips of Cancer in Adolescent and Young Adult (AYA)

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ABSTRACT

Cancer in adolescent and young adults (AYA) includes people who are diagnosed with cancer at the age of 15–39. One of the main concerns and consequences of AYA cancer treatment in both sexes is infertility. Premature ovarian failure (POF) is common in multimodal chemotherapy regimens. There is a significant difference in the sensitivity of the ovary to drugs.

In conclusion, in young cancer women, oophoropexy, infertility counseling, and embryo or oocyte cryopreservation should be considered. Medroxyprogesterone, oral contraceptive pill (OCP), or gonadotropin-releasing hormone (GnRH) should be prescribed in the risk of menorrhagia.

Keywords: Cancer, Young adult, Fertility preservation

Introduction

Adolescent and young adult (AYA) cancers are defined as those occurring in patients at the age of 15–39.

Excluding murder, suicide, or unexpected injuries, cancer is the most common cause of death in the AYA population. The most common cancers in AYA, which cover 95% of cancers in this age group, include lymphoma, melanoma, testicular, female genital malignancy, thyroid, bone and soft tissue sarcomas, leukemia, central nervous system (CNS), non-gonadal tumor mass, and breast cancers **(1–5)**.

One of the main concerns and consequences of AYA cancer treatment in both sexes is infertility. The effects of cancer treatment on fertility depend on the patient's age at the time of diagnosis and type of treatment, as well as the type, duration, and intensity of the chemotherapy dose. For example, young women with Hodgkin's lymphoma undergoing chemotherapy are at the risk of premature ovarian failure (POF) regardless of age at treatment. This risk is higher after chemotherapy with alkylating agents **(1, 6–8)**.

In a large prospective study of women aged 15–40 years with Hodgkin's lymphoma after chemotherapy with alkylating agents, there was an increased risk of 60% POF compared to patients (3–6%) without using alkylating agents **(6–8)**.

The issue of maintaining fertility in AYA patients has been less addressed. In one study, 231 reports of AYA patients with leukemia-lymphoma, sarcoma, breast, or testis cancers were reviewed. In a systematic study, it was reported that the following factors may influence the decision-making process of women with cancer:

1. Lack of knowledge of fertility preservation methods
2. Fear of the risk of reproductive treatments (such as delayed cancer treatment—hormone effects)
3. Not being referred by a cancer physician
4. Anxiety and excitement
5. Family support status
6. Financial issues **(9)**

Discussion about maintaining fertility should begin before cancer treatment. Many people with cancer do

not know the nature of their disease. In a study of 1928 adults treated for childhood cancer, 14% denied cancer, and 18% classified their treatment incorrectly.

In a study of unawareness of cancer treatment and its effect on fertility, it was found that about 1 in every 1,000 people under the age of 20 treated for cancer was unaware of their cancer treatment. Many of them had forgotten cancer treatment until their request for reproductive dysfunction **(1, 3, 6)**.

Premature Ovarian Failure

POF is common in multimodal chemotherapy regimens; for example, newer Hodgkin's regimens cause up to 50% POF that is not prevented by oral contraceptive pills (OCPs) and gonadotropin-releasing hormone (GnRH) therapy. In breast cancer, different regimens have different effects on POF. Maintaining fertility is important in AYA patients and should be part of their cancer treatment. The American Society of Clinical Oncology (ASCO) Guideline is for cancer therapists to refer to all new cancer patients at the time of diagnosis for fertility preservation. Before starting gonadotoxic treatment, the physician should discuss the risk of infertility and possible measures to maintain fertility with the patient. If possible, everyone who is newly diagnosed with cancer should consult an infertility specialist and endocrinologist if fertility is at stake **(6, 8–11)**.

Gonad dysfunction and fertility decline risk factors:

1. Chemotherapy with alkylating agents that maximize toxicity to the ovary (especially procarbazine and cyclophosphamide at the age of 13–20)

Some chemotherapy drugs have no effect on ovarian function, and some others cause permanent hypogonadism.

2. High-dose transcranial radiation that can reduce pituitary-hypothalamic function

3. Radiotherapy of the uterus and ovaries

4. Age

5. Dose of the drug

6. Diversity between people (12, 13)

Ovarian Differences in Response to Chemotherapy

There is a significant difference in the sensitivity of the ovary to drugs. In some women, the function of the ovaries remains normal, but some others develop permanent hypogonadism. The probability of POF in childhood cancer survivors is 8–10% **(7, 14, 15, 17)**.

Mechanism of Chemotherapy Drug Effects on the Ovary

Mostly, evolving follicles (granulosa-theca cells) are affected, and resting oocytes are less affected. In the case of alkylating agents, which have the most impact on ovarian failure, the effect of the drug is on DNA breakage; thus, it affects both resting and dividing cells **(6, 16)**.

The First Recommendation for Fertility Preservation in AYA (15–39 years) Cancer Patients

Oophoropexy should be considered in all female patients who are to receive radiotherapy.

The ovaries are surgically removed from the radiation field, which is done during cancer surgery or in a separate operation. Oophoropexy can be done by laparoscopy just before radiation. Of course, the success rate of this method is also not agreed upon. Oophoropexy immediately prior to radiotherapy reduces the chance of surgical failure and its return to its original position. The surgeon can also cryopreserve one ovary and transpose another ovary before radiotherapy.

Causes of failure of oophoropexy treatment in maintaining ovarian function:

1. Scatter radiation

2. Vascular dysfunction during surgery

3. Radiation dose

4. Patient's age

5. Shield while radiation **(8, 17–25)**

The Second Recommendation for Fertility Preservation in AYA Cancer Patients

Embryo or oocyte cryopreservation should be discussed with the patient if you can delay the treatment as much as an oocyte stimulation cycle. Particularly, in patients with a low and moderate risk of Hodgkin's lymphoma, low-grade sarcoma, and breast cancer, embryo cryopreservation is a proven and effective method of maintaining fertility. The reason is that the fertilized egg tolerates the freezing process better than the oocyte. Sometimes we do not have the time (it takes two to three weeks) **(8, 22–25)**.

Embryo Cryopreservation Time

Ovarian stimulation after chemotherapy is not recommended, and in these cases, it should be delayed for six months. The patient must have a partner unless she accepts the use of a donor.

Using mature oocyte cryopreservation, it should be noted that, in studies, frozen oocytes in vitro fertilization (IVF) have 21% success, whereas fresh oocytes have 61% success.

Cryopreservation is recommended for people without a partner who do not want to have a donor. The oocyte has more water and is more sensitive to freezing. Some studies consider success as a fresh oocyte. On the other hand, estrogen-sensitive tumors may be stimulated by these two methods. In one study, the use of letrozole combined with FSH protects breast cancer patients from the harmful effects of estrogen **(21, 22)**.

The Third Recommendation for Fertility Preservation in AYA Cancer Patients

Ovarian tissue cryopreservation can be considered if available. The advantage of this method is that it is implanted in later stages and does not require ovarian stimulation. This is a research method, and by selecting that person, it enters the research protocol.

Ovarian tissue cryopreservation criteria:

1. Under 35 years without children

2. At least 50% risk for POF after treatment

3. Not a high-risk ovarian cancer (genetically)

Ovarian cryopreservation is a research method, and evidence supporting the efficacy and safety of ovarian tissue cryopreservation is low. This method is not suitable for cancer patients and the potential for implantation of malignant cells into the graft exists. Although ovarian cryopreservation is still considered a research method, it is a fertility preservation method if available **(8, 19–20)**.

Fourth Recommendation for Fertility Preservation in AYA Cancer Patients

In chemotherapy protocols, which may have prolonged thrombocytopenia and risk of menorrhagia, administration of medroxyprogesterone, OCP, or GnRH can be used but does not preserve ovarian function and only controls menorrhagia **(8, 18–22)**.

Fifth Recommendation for Fertility Preservation in AYA Cancer Patients

Some studies suggest that menstrual suppression with GnRH can protect ovarian function, but this evidence is insufficient. Therefore, this procedure is not recommended today for fertility preservation. A five-year randomized follow-up study showed that the GnRH administration had no significant effect on POF or subsequent pregnancy. Thus, although it is suggested that menstrual suppression with GnRH may protect ovarian function, further studies are needed.

Ovarian suppression with GnRH during chemotherapy can reduce chemotoxicity on the ovary. In animals, this effect is shown. In humans, the benefits of this method have been limited. Extensive studies have suggested that GnRH may be useful in maintaining the menstrual function, but there is no evidence that it can increase pregnancy chances after chemotherapy.

We do not recommend the GnRH method as the primary method of fertility preservation; it has not been shown to be equivalent to or better than the embryo or oocyte cryopreservation. If both of these are not possible, some may undergo GnRH during chemotherapy, but the patient should be aware that the benefit of this method is limited and cannot replace the existing methods such as embryo or oocyte cryopreservation. On the other hand, the possibility of reducing the effect of chemotherapy with GnRH has been raised, and its safety is not very certain.

Some authorities do not accept routine GnRH for ovarian preservation. However, it is used to prevent menorrhagia in women at risk of severe thrombocytopenia. GnRH therapy should be started at least two to three weeks before chemotherapy in order to have a chance of downregulation **(8, 21–25)**.

Summary of Fertility Preservation Recommendations in AYA Cancer Patients

Recommendations for oophoropexy, embryo or oocyte cryopreservation, ovarian tissue cryopreservation (research), menorrhagia prevention, ovarian suppression with GnRH (research) **(8, 17–20)**.

Conclusion

1. Oophoropexy should be considered immediately prior to radiotherapy

2. Infertility counseling and embryo or oocyte cryopreservation if we have a few weeks' time

3. Ovarian tissue cryopreservation: No need for ovarian stimulation

4. Prescribe medroxyprogesterone, OCP, or GnRH in cases at risk of menorrhagia

5. Menstrual suppression with GnRH, which its effect on maintaining fertility is unclear

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Conflict of Interest

Authors declared no conflict of interests.

References

1. Chan JL, Letourneau J, Salem W, et al. Regret around fertility choices is decreased with pre-treatment counseling in gynecologic cancer patients. J Cancer Surviv 2017 Feb 1;11(1):58-63. [DOI:10.1007/s11764-016-0563-2] [PMID] [PMCID]

2. Bleyer A, O'Leary M, Barr R, Ries L. Cancer Epidemiology in older Adolescents and Young Adults 15 to 29 Years of age, including SEER incidence and survival: 1975-2000. National cancer institute, NIH pub. No. 06-5767 2006.

3. Bleyer A, Budd T, Montello M. Adolescents and Young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer 2006 Oct 1;107(S7):1645-55. [DOI:10.1002/cncr.22102] [PMID]

4. Butow P, Palmer S, Pai A, et al. Review of adherence-related issues in adolescents and young adults with cancer. J Clin Oncol 2010 Nov 10;28(32):4800-9. [DOI:10.1200/JCO.2009.22.2802] [PMID]

5. Kondryn HJ, Edmondson CL, Hill J, Eden TO. Treatment non-adherence in teenage and young adult patients with cancer. Lancet Oncol 2011 Jan 1;12(1):100-8. [DOI:10.1016/S1470-2045(10)70069-3]

6. Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, Ginsberg JP, Kenney LB, Levine JM, Robison LL, Shnorhavorian M. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2016 May 1;17(5):567-76. [DOI:10.1016/S1470-2045(16)00086-3]

7. Metzger ML, Meacham LR, Patterson B, Casillas JS, Constine LS, Hijiya N, Kenney LB, Leonard M, Lockart BA, Likes W, Green DM. Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol. 2013 Mar 20;31(9):1239-47. [DOI:10.1200/JCO.2012.43.5511] [PMID] [PMCID]

8. Haukvik UKH, Dieset I, Bjoro T, et al. Treatment-related premature ovarian failure as a long-term complication after Hodgkin's lymphoma. Ann Oncol. 2006 Sep 1;17(9):1428-33.. [DOI:10.1093/annonc/mdl149] [PMID]

9. Bramswig JH, Riepenhausen M, Schellong G. Parenthood in adult female survivors treated for Hodgkin's lymphoma during childhood and adolescence: a prospective, longitudinal study. Lancet Oncol 2015 Jun 1;16(6):667-75. [DOI:10.1016/S1470-2045(15)70140-3]

10. De Bruin ML, Huisbrink J, Hauptmann M, Kuenen MA, Ouwens GM, van't Veer MB, Aleman BM, van Leeuwen FE. Treatment-related risk factors for premature menopause following Hodgkin lymphoma. Blood, J Am Soc Hematol. 2008 Jan 1;111(1):101-8. [DOI:10.1182/blood-2007-05-090225] [PMID]

11. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, Robison LL, Sklar CA. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metabol. 2006 May 1;91(5):1723-8. [DOI:10.1210/jc.2006-0020] [PMID]

12. Blumenfeld Z, Zur H, Dann EJ. Gonadotropin-releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. Oncol. 2015 Nov;20(11):1283. [DOI:10.1634/theoncologist.2015-0223] [PMID] [PMCID]

13. Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, Levaggi A, Giraudi S, Lambertini M, D'Alonzo A, Canavese G. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun 1;40(5):675-83. [DOI:10.1016/j.ctrv.2013.12.001] [PMID]

14. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, Fischer D, Sommer HL, Conrad B, Ortmann O, Fehm T. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41. [DOI:10.1200/JCO.2010.32.5704] [PMID]

15. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, Francis PA, Goldstein LJ, Gomez HL, Vallejos CS, Partridge AH. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. New Eng J Med. 2015 Mar 5;372(10):923-32. [DOI:10.1056/NEJMoa1413204] [PMID] [PMCID]

16. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J clin oncol 1996;14:1718-1729. [DOI:10.1200/JCO.1996.14.5.1718] [PMID]

17. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American society of clinical oncology clinical practice guideline update. J Clin Ocnol 2013;31:2500-2510. [DOI:10.1200/JCO.2013.49.2678] [PMID] [PMCID]

18. Waimey KE, Duncan FE, Su HL, et al. Future directions in oncofertility and fertility preservation: a report from the 2011 oncofertilty consortium conference. J Adolesc young adult oncol 2013;2:25-30. [DOI:10.1089/jayao.2012.0035] [PMID] [PMCID]

19. Terenziani M, Piva L, Meazz C, et al. Oophoropexy: a relevant role in preservation of ovarian function after pelvic irradiation. Fertil steril 2009;91:935 e 915-936. [DOI:10.1016/j.fertnstert.2008.09.029] [PMID]

20. Oktay K, Turan V, Bedoschi G, et al. Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer. J clin oncol 2015;33:2424-2429. [DOI:10.1200/JCO.2014.59.3723] [PMID] [PMCID]

21. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo- banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum reprod 2010;25:2239-2246. [DOI:10.1093/humrep/deq146] [PMID]

22. Rienzi L, Romano S, Albricci L, et al. Embryo development of fresh 'Versus' vitrified metaphase ii oocytes after ICSI: a prospective randomized sibling-oocyte study. Hum reprod 2010;25:66-73. [DOI:10.1093/humrep/dep346] [PMID] [PMCID]

23. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk andwhat can be offered? Lancet Oncol 2005;6:209-218. [DOI:10.1016/S1470-2045(05)70092-9]

24. Barton SE, Najita JS, Ginsburg ES, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the childhood cancer survivor study cohort. Lancet Oncol 2013;14:873-881. [DOI:10.1016/S1470-2045(13)70251-1]

25. Mature oocyte cryopreservation: a guidline. Fertility and sterility 2013;--:37-43 [DOI:10.1016/j.fertnstert.2012.09.028] [PMID]

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