Article published online: 2020-12-31

Review Article

Fertility preservation in young patients with cancer

Virender Suhag, B. S. Sunita[1], Arti Sarin, A. K. Singh, Dashottar S.

Abstract

Infertility can arise as a consequence of treatment of oncological conditions. The parallel and continued improvement in both the management of oncology and fertility cases in recent times has brought to the forefront the potential for fertility preservation in patients being treated for cancer. Many survivors will maintain their reproductive potential after the successful completion of treatment for cancer. However total body irradiation, radiation to the gonads, and certain high dose chemotherapy regimens can place women at risk for acute ovarian failure or premature menopause and men at risk for temporary or permanent azoospermia. Providing information about risk of infertility and possible interventions to maintain reproductive potential are critical for the adolescent and young adult population at the time of diagnosis. There are established means of preserving fertility before cancer treatment; specifically, sperm cryopreservation for men and *in vitro* fertilization and embryo cryopreservation for women. Several innovative techniques are being actively investigated, including oocyte and ovarian follicle cryopreservation, ovarian tissue transplantation, and *in vitro* follicle maturation, which may expand the number of fertility preservation choices for young cancer patients. Fertility preservation may also require some modification of cancer therapy; thus, patients' wishes regarding future fertility and available fertility preservation alternatives should be discussed before initiation of therapy.

Key words: Fertility preservation, oncological management, young adults

Introduction

Cancer occurring between the ages of 15 and 30 years is 2.7 times more common than cancer occurring during the first 15 years of life, yet is much less common than cancer in older age groups, and accounts for 2% of all invasive cancers.[1] In India, about 5.8% of all cancer cases registered are in those aged 15 to 29 years in most urban cancer registries.[2,3] Cancer in adolescents and young adults (AYA) is unique in the distribution of the types that occur. Hodgkin lymphoma, melanoma, testicular cancer, female genital tract malignancies, thyroid cancer, soft tissue sarcomas, non-Hodgkin lymphoma, leukemia, brain tumors, breast cancer, bone sarcomas, and nongonadal germ cell tumors account for 95% of the cancers in this age group. The incidence of cancer in this age group increased steadily during the past quarter century.[1,3]

The combined 5-year survival rate for all cancers in young age group has improved from <50% in the 1970s to 80% today, and the 10-year survival rate is almost 75%. Thus, as a result of advances in treatment, almost 80% of children and adolescents who receive a diagnosis of cancer become long-term survivors.[4] Infertility can arise as a consequence of gonadotoxic treatment of oncological conditions. Improved cancer care associated with increased cure rates and long-term survival, coupled with advances in fertility treatment means that it is now imperative that fertility preservation is considered as part of the care offered to these patients.[5,6] This can only be approached within a multidisciplinary setting requiring close communication between surgical oncologists, radiation oncologists, medical oncologists, nursing staff, and reproductive health specialists during the development of a treatment plan. This structured interaction should enable the incorporation of fertility preservation into cancer management.[7,8] Algorithm for early referral and timely interventions for fertility preservation in young patients with cancer is given in Figure 1.[9-11]

Impact of Treatment on Fertility

Infertility is a major consequence of cancer therapy in both men and women.[12] The impact of cancer therapy on fertility is related to the age of the patient at treatment and is dependent on the duration, dose-intensity, and type of treatment. Alkylating agent–based chemotherapy is more harmful to the ovaries and testis than regimens containing non alkylating agents.[12,13] High doses of cranial radiotherapy (RT) can impair hypothalamic pituitary function, resulting in the deficiency of gonadotropin releasing hormone (GnRH) and impairment of fertility in both men and women. Gonadal exposure to low doses of radiation can cause oligospermia or azoospermia in men. Higher doses of radiation are associated with both ovarian and uterine dysfunction in women.[12,14]

Future fertility is an important concern for patients with cancer who are of reproductive age. Cancer related infertility can lead to long term distress and impaired quality-of-life in cancer survivors, especially for those who did not receive sufficient information on fertility preservation options before the start of their treatment. Even up to 10 years post treatment, the grief associated with interrupted childbearing continues to strongly affect quality-of-life. Importantly, a recent study demonstrated that women who received specialized counseling about reproductive issues reported less regret and greater quality-of-life.[15] Reproductive health has the potential to impact across physical, emotional, social, and spiritual well being of AYA cancer patients and encompasses a spectrum of issues related to fertility, sexuality, gynecologic health, urologic health, and family building.[16,17]

Toxic Effects of Chemotherapeutic Agents on the Ovary

A fixed number of primordial follicles present at birth form the ovarian reserve into puberty. Postpuberty, these primordial follicles contain single oocytes arrested in the prophase of the first meiotic division and are highly sensitive to cytotoxic drugs leading to cellular death. Follicular depletion has been shown to be physiologically age dependent, the maximum rate of depletion occurring around the age of 38 years when the

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.173175

Department of Radiation Oncology, HOD Radiation Oncology, Army Hospital (Research and Referral), [1]Department of Pathology, Base Hospital, New Delhi, India
Correspondence to: Dr. Lt. Col. Virender Suhag, E-mail: virendersuhag@gmail.com

How to cite this article: Suhag V, Sunita BS, Sarin A, Singh AK, Dashottar S. Fertility preservation in young patients with cancer. South Asian J Cancer 2015;4:134-9.

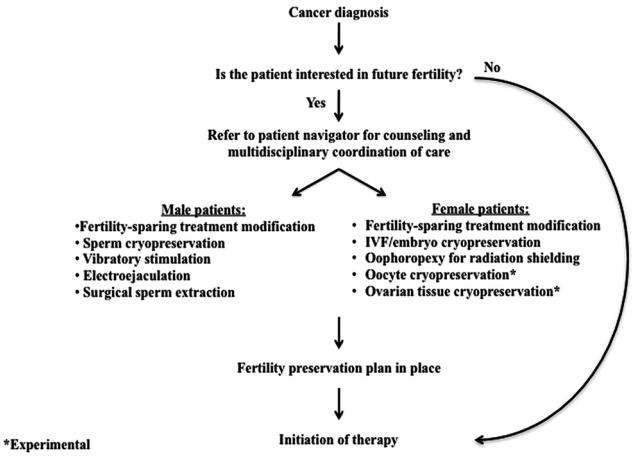

Figure 1: Algorithm for early referral and timely interventions for fertility preservation in young patients with cancer[9-11]

reserve is just about 10% the number present at menarche. The gonadotoxic effect is thus not just dependent on type and dosage of the cytotoxic drug employed but also on the age of the woman.

Cell cycle nonspecific agents like cyclophosphamide will destroy resting primordial cells as opposed to cell cycle specific agents like methotrexate which spare the rest primordial cells and as such are less gonadotoxic. Adriamycin and cyclophosphamide have a 38% ovarian failure rate in women aged over 40 years at 2 years postchemotherapy. Cyclophosphamide, methotrexate, and 5-fluorouracil, a classical breast cancer regime will render 71% of women over 40 years of age amenorrheic at 2 years.[5,18] The incidence of gonadal failure is dependent on age at diagnosis and the cumulative dose of alkylating agents. Among young women treated with adjuvant chemotherapy for breast cancer, the risk for chemotherapy related amenorrhea and premature menopause is significantly higher for those with newly diagnosed breast cancer treated with chemotherapy who are older than 35 years.[14,19]

Toxic Effects of Chemotherapeutic Agents on the Testis

Gonadal toxicity of the testis affects spermatogenesis more than it does testosterone production. This stems from the increased cytosensitivity of the germinal epithelium in comparison to that of the leydig cells. The germinal cell division is extremely high through increased meiotic and mitotic activity thus allowing for increased sensitivity to cytotoxic agents. Sexual maturation of the testis also influences the degree of gonadal damage experienced when exposed to cytotoxic drugs, the prepubertal testis being less susceptible than post pubertal testis. The extent to which spermatogenesis is affected is influenced by the type of cytotoxic agent and the dose to which it is exposed. The high, intermediate, and low risk of azoospermia in males and amenorrhea or premature ovarian failure in females after gonadotoxic oncological management are tabulated in Table 1.[5,10,14,16,18]

Radiotherapy Effects on Fertility in Female Patients

Hypothalamic, pituitary and pelvic radiation, with or without alkylating agents, have been associated with acute ovarian failure and premature menopause. Total body irradiation and abdominal and pelvic RT have been shown to cause uterine dysfunction. Radiotherapy effects on the female are dose-dependent. The application of 14.3 Gray to an ovary in a woman over 30 years of age will usually render her irreversibly infertile and menopausal.[5,20] A dose of 6 Gray to the ovary of a woman <30 years of age is usually reversible, but ultimately, will bring the menopause forwards. Thus the female is not only concerned with issues regarding fertility but also with hormone production, as both seem to be equally affected by radiotherapy.[5]

Although the uterus is relatively resistant to radiotherapy, there is no doubt that uterine irradiation is harmful and even if fertility is conserved, uterine irradiation will result in poor implantation.[5,20,21] This appears to be due to a number of factors including reduced uterine volume and blood flow which have been demonstrated to result in increased mid trimester losses, preterm labor, and intrauterine growth retardation.[18] The vagina is relatively radio resistant, however, irradiation of this organ carries with it the risk of loss of lubrication and stenosis which may result in physical impairments to fertility as well as major psychosexual issues.[5,22]

Effect of Radiotherapy on Male Patients

The effect of radiotherapy on male fertility is also dose-dependent. The application of >6 Gray to testes will result in irreversible azoospermia. At levels of 3.5 Gray, sterility does occur, but this is reversible although commonly such recovery will take 18 to 24 months. Treatment age and normal pre-treatment sperm count influence the recovery rate. In the prepubertal male, irradiation >20 Gray to the Leydig cells of the testis will cause significant damage in terms of testosterone production but in the post pubertal male a level of >30 Gray is required to cause this level of damage.[5,23]

Fractional radiotherapy to testes for treatment of carcinoma *in situ* of the testis usually involves high doses of radiotherapy which lead to permanent azoospermia. Interestingly, the Leydig cells of the testis seem far more resistant to radiation effect and therefore testosterone production is usually less impaired in patients receiving even relatively high dosages of radiotherapy relative to its effects on sperm production. In addition, libido and erection will usually remain normal in the male and its sterility that is the main concern. However, it is not unusual for patients who have had pelvic irradiation to suffer from erectile dysfunction as a long term complication. This may in part be explained by radiation induced vascular disease leading to reduced blood flow in the pelvic and penile vessels.[5,24]

Modified Surgical Procedures for Gynecological Malignancies

A radical trachelectomy is a viable option for early stage cervical cancer. In a prospective study of 212 women who underwent radical vaginal trachelectomies, 66% of women attempting to conceive achieved pregnancy. Of those who conceived, 45% reached full term, 25% delivered between 28 and 36 gestational weeks, and 5% delivered before 28 gestational weeks.[25] Although fertility does not appear to be impaired, women opting for trachelectomy should be counseled that preterm delivery is a potential obstetric complication. In tumors <2 cm, the cervical cancer recurrence rate is 2–6% after

**Table 1: Risk of azoospermia in males and amenorrhea/premature ovarian failure in females after gonadotoxic oncological management[5,10,14,16,18]*

Risk	Treatment in males	Treatment in females
High risk	Total body irradiation	Radiation treatment of whole abdomen or pelvis with ≥6 Gy in adult women, ≥15 Gy in prepubertal girls and >10 Gy in post pubertal girls
	Radiotherapy of testicular ≥25 Gy men, ≥6 Gy prepubertal boys	Full body radiation
	Alkylating chemotherapy (including cyclophosphamide ≥75 g/m^2)	Alkylating chemotherapy (including cyclophosphamide ≥75 g/m^2 women <20 years old)
	HDT with stem cell support	HMAS
	Protocols for the treatment of lymphoma containing procarbazine: BEACOPP†, COPP, MOPP	Protocols for treating lymphoma that contain procarbazine: BEACOPP†, COPP, MOPP
	Irradiation of the brain≥40 Gy	Radiation of the brain ≥40 Gy
Intermediate risk	BEP for testicular cancer	FEC: 30-39 years old
	Cisplatin	Radiation treatment of whole abdomen or pelvis at 10-15 Gy in prepubertal girls, 5-10 Gy in post pubertal girls
	CHOP	CHOP
	Carboplatin <2 g/m^2	Cisplatin
		Radiation of the central nervous system ≥25 Gy
Low risk	ABVD	Doxorubicin and/or cyclophosphamide in women aged 30-39
	OEPA	
	Radiation treatment of the testicles from 02 to 07 Gy	FEC in women aged <30
		ABVD
		Anthracyclines
		Cytarabine

*Most authors classify various chemotherapy regimens into high, intermediate and low risk for causing azoospermia/amenorrhea, there is no consensus on absolute doses of most of the individual drugs in these groups. †BEACOPP=Bleomycin, vincristine, cyclophosphamide, doxorubicin, etoposide, and procarbazine, HDT=High-dose therapy, BEP=Bleomycin, etoposide, cisplatin, FEC=Cyclophosphamide, epirubicin, fluorouracil, OEPA=Vincristine, etoposide, prednisone, doxorubicin, ABVD=Doxorubicin, bleomycin, vinblastine and dacarbazine, CHOP=Cyclophosphamide, doxorubicin, vincristine, prednisone, COPP=Cyclophosphamide, vincristine, procarbazine, prednisolone, MOPP=nitrogen mustard, vincristine, procarbazine, prednisone, HDT=High-dose chemotherapy, HMAS=High-dose melphalan chemotherapy with stem cell support

a radical trachelectomy, making it an oncologically acceptable procedure as well.[18,26] The recurrence rate after a modified radical hysterectomy varies from 0.1% to 5% depending on stage, and a recent case control study of 137 women who underwent vaginal radical trachelectomy matched with radical hysterectomy controls demonstrated a 5-year recurrence free survival rate of 95% and 100%, respectively.[27,28]

For early stage endometrial cancers, a systematic review of 45 studies including 391 participants with complex atypical hyperplasia or grade 1 adenocarcinoma treated with progestin therapies was conducted. Not surprisingly, endometrial hyperplasia had a significantly higher likelihood of responding to hormonal therapy (66%) than did grade 1 endometrial carcinoma (48%). Reproductive outcomes were similar, with 41.2% of those with hyperplasia and 34.8% with carcinoma conceiving, resulting in 117 live births.[29]

In the case of ovarian malignancy, a conservative surgical approach to borderline ovarian tumors does not appear to affect survival. However, conservative surgery should be reserved for cases of stage 1A grade 1 epithelial ovarian cancer after adequate staging with careful follow up.[18,30] All these options underscore the need for gynecologic oncologists to work in conjunction with reproductive endocrinologists to determine the applicability of fertility sparing approaches and to counsel patients regarding their future fertility potential.

Fertility Preserving Techniques in Women

Oophorexy and embryo cryopreservation after *in vitro* fertilization (IVF) are the two established options for fertility preservation in women.[14,18,31,32] Oophorexy involves surgically displacing the ovaries out of the planned radiation field to minimize ovarian damage and has been shown to preserve ovarian function. It should be considered for all female patients who will be receiving RT and may be performed either during cancer surgery or in a separate surgical procedure. These ovarian transpositions can be carried out both laparoscopically or at laparotomy and there have been suggestions that lateral transposition may be more protective than median transposition of the ovaries. Techniques have been described to relocate the ovaries to the paracolic gutters, behind the uterus, or to anterolateral positions above the umbilicus.[5,18,33,34]

If cancer therapy can be delayed long enough for a cycle of oocyte stimulation (especially for patients with low and intermediate risk Hodgkins Lymphoma and low grade sarcomas), the possibility of embryo cryopreservation should be discussed. Embryo cryopreservation after IVF has been highly successful in women younger than 40 years. However, this method requires a male partner or sperm donor. Mature oocyte cryopreservation and ovarian tissue grafting and freezing are emerging techniques for fertility preservation in young women. They are still considered investigational and their efficacy is unclear. Mature oocyte cryopreservation is a potential alternative for single women, but, like embryo cryopreservation, requires hormone stimulation.[4,14,16] Ovarian tissue grafting does not require hormonal stimulation, and therefore no long delay in treatment is necessary. However, this procedure would not be considered appropriate for some women (e.g., those with a malignancy in whom reimplantation of malignant cells could occur with grafting).[32,35,36]

Gonadotropin releasing hormone agonists have been used as ovarian protectors during chemotherapy. Although some

investigators have reported that GnRH agonist administration before and during combination chemotherapy may preserve post-treatment ovarian function in women with breast cancer younger than 40 years, others have observed no protection of the ovarian reserve in young women with advanced stage HL treated with GnRH and escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone chemotherapy.[37,38] A more recent systematic review and meta analysis suggests that although GnRH with chemotherapy in premenopausal women is associated with higher rates of spontaneous resumption of menses and ovulation, it is not associated with improvement in pregnancy rates.[39] Additional studies are required to confirm these findings. Menstrual suppression does not protect the ovaries. Medroxyprogesterone or oral contraceptives may be used in protocols that are predicted to cause prolonged thrombocytopenia, and thus present a risk for menorrhagia.[14] An overview of fertility sparing strategies in young females and males with cancers is given in Table 2.[9-11]

Strategies for Fertility Preservation in Young Males

Sperm cryopreservation remains the obvious choice for males capable of producing a semen sample. This is mainly achieved through masturbation, but can also be achieved through testicular biopsy and testicular sperm extraction and epididymal aspiration of sperms. Sperm collection should be carried out prior to treatment to avoid collection of potentially abnormal DNA containing cells. However, young males will only start producing sperm cells suitable for cryopreservation around the age of 12 to 13 years. Certainly sperm retrieval should be offered to patients in whom the risk of infertility is high, but there is now a good evidence base to suggest that if the testicular volume is < 10 ml, it is very unlikely that the patient will demonstrate any significant spermatogenesis. Thus, sperm retrieval should be limited to males where testicular volume is > 10 ml and samples should ideally be produced by ejaculation. In the situation where young males are unable to ejaculate, then rectal electro stimulation, testicular or epididymal aspiration may be offered and can be successfully undertaken. Sperm banking can then be done with the expectation that the semen can be used at a later date. At present, the later use of stored sperm is likely to require assisted conception methods like intracytoplasmic sperm injection to optimize the likelihood of successful fertilization.[4,5,7,13,15,35]

Ideally, three pre-treatment samples should be drawn a few days apart. Samples are then stored in liquid nitrogen at minus 196° centigrade in two separate locations for 10 years. Each sample undergoes a standard diagnostic semen analysis and is assessed against standard criteria. Prescreening is required and the patients are checked for Hepatitis B and C, Syphilis, HIV and cytomegalovirus. Although positive results will not preclude a patient from undertaking sperm storage, a positive result will determine the batching and isolation required for semen storage. Appropriate documentation as per institutional policy is a mandatory requirement. Approximately, 50% of sperm stored will be lost during the preservation and storage process. Potential damage to cryopreserved sperm includes osmotic injuries from cryoprotective agents, hypothermic injury, and oxidative damage.[5]

Recommendations

Several international professional organizations, including The American Society of Clinical Oncology, the National Comprehensive Cancer Network and American Society of Reproductive Medicine periodically issue guidelines for research, clinical practice, and social and ethical implications related to fertility preservation in cancer patients.[7,9-11,31,40,41] The guidelines specify that oncologists should be prepared to either "discuss fertility preservation options or refer patients who are interested to reproductive specialists." Referral to reproductive specialists such as reproductive endocrinologists, gynecologists, urologists, or andrologists is a critical step toward providing patients with cancer the information needed to make decisions about the use of fertility preservation services or other family building options. Reproductive specialists can provide patients with a personalized assessment of fertility risks, in-depth information about fertility preservation and other family building options, and counseling and support related to the physical and psychosocial impact of cancer treatment on fertility.[15]

Despite the potential value of this consultation, studies suggest that only about half of oncologists report routinely referring patients of childbearing age to reproductive specialists.[15,42-44] Several factors have been identified to account for this discrepancy, including lack of knowledge, uncertainty about the success of fertility preservation methods, and language or cultural barriers. The success of fertility preservation measures depends upon early and open communication with patients, flexibility in scheduling appointments and procedures for both cancer care and fertility preservation, and the presence of a multidisciplinary oncofertility team that can see patients and discuss their cases on short notice.[7] Key to this approach is a recognition that cancer patients are interested in information regarding fertility, and that early intervention and discussion are critical to ensure future reproductive success. These recommendations identify sperm cryopreservation and embryo cryopreservation as the options known to be most successful.[7,9,10]

Practice Guidelines for Asian Countries

- The oncologists must provide information about risk of infertility and possible interventions to maintain reproductive potential to all young adult patients and their parents at the time of diagnosis
- In selected cases, the cancer therapy should be modified to help fertility preservation without affecting the overall treatment outcome
- Close communication between oncologists and reproductive specialists should be encouraged. Reproductive specialists should be encouraged to attend tumor boards and multidisciplinary care clinics for newly diagnosed patients
- All cancer hospitals should enforce a multidisciplinary structured interaction between oncologists, nursing staff, and reproductive health specialists early in course to ensure incorporation of fertility preservation into cancer management
- The concept of early referral and timely interventions for fertility preservation in young patients with cancer should be incorporated in training and teaching curriculum of oncology residents
- All discussions and interventions must be documented in medical case records of the patients

Table 2: Fertility preservation options for young women and men diagnosed with cancer[9-11]

Options in young females			Options in young males		
Option	**Definition**	**Comment**	**Option**	**Definition**	**Comment**
Embryo banking	Harvesting eggs, IVF and freezing of embryos for later implantation	Need partner or donor sperm	Sperm cryopreservation (S) after masturbation	Freezing sperm obtained through masturbation	Outpatient procedure Approximately three samples collected a few days apart
Egg banking (experimental)	Harvesting and freezing of unfertilized eggs for IVF and implantation after cancer treatment	May be useful for single women or those averse to embryo creation	Sperm cryopreservation (S) after alternative methods of sperm collection	Freezing sperm obtained through testicular aspiration or extraction, electro-ejaculation under sedation, or from a post-masturbation urine sample	Testicular sperm extraction-outpatient surgical procedure
Ovarian tissue banking (experimental)	Freezing of ovarian tissue and re-implantation of tissue or *in vitro* maturation of follicles and fertilization of eggs after cancer treatment	Tissue not suitable for transplant if high risk of ovarian metastases; highly unlikely live birth by *in vitro* fertilization	Gonadal shielding during radiation therapy (S)	Use of shielding to reduce the dose of radiation delivered to the testicles	Only possible with selected radiation fields and anatomy Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs
Radiation shielding	Use of shielding to reduce scatter radiation to ovaries	Does not protect against effects of concurrent chemotherapy	Testicular tissue cryopreservation Testis xenografting Spermatogonial isolation (I)	Freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation in animals	Outpatient surgical procedure
Ovarian transposition	Surgical repositioning of ovaries away from radiation fields	OPD procedure or in conjunction with gynae oncosurgery	Testicular suppression with GnRH analogues or antagonists (I)	Use of hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy	Studies do not support the effectiveness of this approach
Radical trachelectomy	Surgical removal of cervix with preservation of uterus	For early stage carcinoma cervix			
Ovarian suppression (experimental)	GnRH analogs or antagonists used to suppress ovaries	Does not protect against radiotherapy			
Donor embryos	Embryos donated by a couple	Donor embryos available through IVF clinics or registered agencies			
Donor eggs	Egg donated by a woman	Patient may choose donor based on various characteristics			
Gestational surrogacy	Woman carries pregnancy for another woman or couple	Legal status as per the law of the state			

S=Standard, I=Investigational, IVF=*In vitro* fertilization, GnRH=Gonadotropin-releasing hormone, OPD=Outpatient department

- All countries should have clear-cut guidelines regarding fertility preservation and must enforce strict compliance.

Conclusion

As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise. Effective multidisciplinary team members consisting of oncologists, oncology trained nurses, social workers, reproductive endocrinology and infertility specialists, and embryologists are required to work together in order to achieve success.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bleyer A, Viny A, Barr R Cancer in 15- to 29-year-olds by primary site Oncologist 2006;11:590-601.
2. Arora RS, Alston RD, Eden TO, Moran A, Geraci M, O'Hara C, *et al*. Cancer at ages 15-29 years: The contrasting incidence in India and England Pediatr Blood Cancer 2012;58:55-60.
3. Kalyani R, Das S, Kumar ML Pattern of cancer in adolescent and young adults – A ten year study in India Asian Pac J Cancer Prev 2010;11:655-9.
4. Revel A, Revel-Vilk S Fertility preservation in young cancer patients J Hum Reprod Sci 2010;3:2-7.
5. Ajala T, Rafi J, Larsen-Disney P, Howell R Fertility preservation for cancer patients: A review Obstet Gynecol Int 2010;2010:160386.
6. Pavone ME, Hirshfeld-Cytron J, Lawson AK, Smith K, Kazer R, Klock S Fertility preservation outcomes may differ by cancer diagnosis J Hum Reprod Sci 2014;7:111-8.
7. Redig AJ, Brannigan R, Stryker SJ, Woodruff TK, Jeruss JS Incorporating fertility preservation into the care of young oncology patients Cancer 2011;117:4-10.

8. Gwede CK, Vadaparampil ST, Hoffe S, Quinn GP The role of radiation oncologists and discussion of fertility preservation in young cancer patients Pract Radiat Oncol 2012;2:242-7.
9. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, *et al*. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients J Clin Oncol 2006;24:2917-31.
10. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, *et al*. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update J Clin Oncol 2013;31:2500-10.
11. Lee SJ, ASCO Fertility Preservation Guidelines Committee Preservation of fertility in patients with cancer N Engl J Med 2009;360:2680-3.
12. Wallace WH, Anderson RA, Irvine DS Fertility preservation for young patients with cancer: Who is at risk and what can be offered? Lancet Oncol 2005;6:209-18.
13. Levine J, Canada A, Stern CJ Fertility preservation in adolescents and young adults with cancer J Clin Oncol 2010;28:4831-41.
14. Coccia PF, Altman J, Bhatia S, Borinstein SC, Flynn J, George S, *et al*. Adolescent and young adult oncology Clinical practice guidelines in oncology J Natl Compr Canc Netw 2012;10:1112-50.
15. Vadaparampil ST, Quinn GP Improving communication between oncologists and reproductive specialists to promote timely referral of patients with cancer J Oncol Pract 2013;9:300-2.
16. Vadaparampil ST, Hutchins NM, Quinn GP Reproductive health in the adolescent and young adult cancer patient: An innovative training program for oncology nurses J Cancer Educ 2013;28:197-208.
17. Murphy D, Orgel E, Termuhlen A, Shannon S, Warren K, Quinn GP Why Healthcare Providers Should Focus on the Fertility of AYA Cancer Survivors: It's Not Too Late! Front Oncol 2013;3:248.
18. Chhabra S, Kutchi I Fertility preservation in gynecological cancers Clin Med Insights Reprod Health 2013;7:49-59.
19. Agrawal S Late effects of cancer treatment in breast cancer survivors South Asian J Cancer 2014;3:112-5.
20. 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.
21. Critchley HO, Wallace WH Impact of cancer treatment on uterine function J Natl Cancer Inst Monogr 2005;34:64-8.
22. Liao L, Doyle J, Crouch NS, Creighton SM Dilation as treatment for vaginal agenesis and hypoplasia: A pilot exploration of benefits and barriers as perceived by patients J Obstet Gynaecol 2006;26:144-8.
23. Colpi GM, Contalbi GF, Nerva F, Sagone P, Piediferro G Testicular function following chemo-radiotherapy Eur J Obstet Gynecol Reprod Biol 2004;113 Suppl 1:S2-6.
24. Kiserud CE, Magelssen H, Fedorcsak P, Fosså SD Gonadal function after cancer treatment in adult men Tidsskr Nor Laegeforen 2008;128:461-5.
25. Speiser D, Mangler M, Köhler C, Hasenbein K, Hertel H, Chiantera V, *et al*. Fertility outcome after radical vaginal trachelectomy: A prospective study of 212 patients Int J Gynecol Cancer 2011;21:1635-9.
26. Schneider A, Erdemoglu E, Chiantera V, Reed N, Morice P, Rodolakis A, *et al*. Clinical recommendation radical trachelectomy for fertility preservation in patients with early-stage cervical cancer Int J Gynecol Cancer 2012;22:659-66.
27. Suprasert P, Srisomboon J, Charoenkwan K, Siriaree S, Cheewakriangkrai C, Kietpeerakool C, *et al*. Twelve years experience with radical hysterectomy and pelvic lymphadenectomy in early stage cervical cancer J Obstet Gynaecol 2010;30:294-8.
28. Beiner ME, Hauspy J, Rosen B, Murphy J, Laframboise S, Nofech-Mozes S, *et al*. Radical vaginal trachelectomy vs radical hysterectomy for small early stage cervical cancer: A matched case-control study Gynecol Oncol 2008;110:168-71.
29. Gunderson CC, Fader AN, Carson KA, Bristow RE Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: A systematic review Gynecol Oncol 2012;125:477-82.
30. Morice P, Denschlag D, Rodolakis A, Reed N, Schneider A, Kesic V, *et al*. Recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology about the conservative management of ovarian malignant tumors Int J Gynecol Cancer 2011;21:951-63.
31. Coccia PF, Pappo AS, Altman J, Bhatia S, Borinstein SC, Flynn J, *et al*. Adolescent and young adult oncology, version 22014 J Natl Compr Canc Netw 2014;12:21-32.
32. Resetkova N, Hayashi M, Kolp LA, Christianson MS Fertility Preservation for Prepubertal Girls: Update and Current Challenges Curr Obstet Gynecol Rep 2013;2:218-25.
33. Perri T, Ben-Baruch G, Davidson T, Beiner ME, Helpman L, Hogen L, *et al*. Use of titanium spiral tacks for long-term oophoropexy before pelvic irradiation Int J Gynecol Cancer 2014;24:1133-6.
34. Barahmeh S, Al Masri M, Badran O, Masarweh M, El-Ghanem M, Jaradat I, *et al*. Ovarian transposition before pelvic irradiation: Indications and functional outcome J Obstet Gynaecol Res 2013;39:1533-7.
35. Deepinder F, Agarwal A Technical and ethical challenges of fertility preservation in young cancer patients Reprod Biomed Online 2008;16:784-91.
36. Imbert R, Moffa F, Tsepelidis S, Simon P, Delbaere A, Devreker F, *et al*. Safety and usefulness of cryopreservation of ovarian tissue to preserve fertility: A 12-year retrospective analysis Hum Reprod 2014;29:1931-40.
37. Badawy A, Elnashar A, El-Ashry M, Shahat M Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: Prospective randomized study Fertil Steril 2009;91:694-7.
38. Behringer K, Wildt L, Mueller H, Mattle V, Ganitis P, van den Hoonaard B, *et al*. No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma Final results of a phase II trial from the German Hodgkin Study Group Ann Oncol 2010;21:2052-60.
39. Bedaiwy MA, Abou-Setta AM, Desai N, Hurd W, Starks D, El-Nashar SA, *et al*. Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: A systematic review and meta-analysis Fertil Steril 2011;95:906-14e1-4.
40. Johnson RH, Kroon L Optimizing fertility preservation practices for adolescent and young adult cancer patients J Natl Compr Canc Netw 2013;11:71-7.
41. Debono DJ, Kohnke JM, Helft PR Addressing Fertility in Patients With Advanced Cancer: How the Quality Oncology Practice Initiative Standards and ASCO Guidelines Facilitate Ethical Communication J Oncol Pract 2009;5:298-300.
42. Trost LW, Brannigan RE Oncofertility and the male cancer patient Curr Treat Options Oncol 2012;13:146-60.
43. Quinn GP, Vadaparampil ST, Lee JH, Jacobsen PB, Bepler G, Lancaster J, *et al*. Physician referral for fertility preservation in oncology patients: A national study of practice behaviors J Clin Oncol 2009;27:5952-7.
44. Forman EJ, Anders CK, Behera MA A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients Fertil Steril 2010;94:1652-6.