

Oncofertility: Realizing a Couples' Dream of Parenthood

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ABSTRACT

Oncofertility is an emerging field, merging oncology and reproductive endocrinology. Any woman facing a cancer diagnosis is devastated especially if she is young. Young women diagnosed with cancer face an additional burden of compromise of future fertility. Oncofertility aims to explore and expand fertility options to address reproductive concerns of young women with cancer diagnosis. This review aims to highlight the available and emerging options for young women diagnosed with gynecological cancers to enable them to realize their dream of parenthood.

Keywords: Oncofertility, Cancer, Young, Reproductive, Fertility preservation

INTRODUCTION

Earlier, cancer treatment was aimed to eradicate the disease. The woman's age and her desire for future conception did not receive much attention. Oncological advances such as Papanicolaou (Pap) smear and non-invasive radiological techniques have led to early detection of gynecological cancers. Prognosis of women after early detection of cancers has dramatically improved. Minimally invasive gynecologic oncological surgeries, state of the art radiotherapy technology and use of newer chemotherapeutic agents have contributed significantly towards improvement in survival of cancer patients. Quality of life issues are now being increasingly addressed for cancer patients. Fertility preservation has in the recent years received much attention. Oncofertility is an emerging specialty at the crossroads between gynecologic oncology and reproductive medicine.

"To believe in something, and not to live it, is dishonest" - Mahatama Gandhi

Life dreams are a stimulus for new learning. Most couples have a shared life dream. Parenthood is one such dream, every couple wishes to realize. Cancer

treatment can compromise reproductive functions of both men and women. The aim of this review is to highlight the available and emerging fertility preservation options for young women receiving treatment with gynecological cancers from an oncologist's perspective.

Oncofertility: The Unmet Need

The concept of oncofertility applies to both gynecological and non-gynecological cancers. Gynecological cancers are the most common cancers in women. In India, approximately 23,438 adolescents and young adults (15-39 years of age) are being diagnosed with gynecological cancers and 8,748 succumb to these deadly cancers.¹ Cancer diagnosis in young women can be devastating. There are varied concerns – emotional, reproductive, sexual and financial. The field of oncofertility was developed in 2006 with an aim of preservation, expansion and restoration of the reproductive future of cancer patients.² This enables young women to have a maximal chance to make an optimal decision without any significant impact and delay in the oncologic outcome. An Oncofertility Consortium was established by Prof TK Woodruff and funded by a National Institute of Health Roadmap Grant.³ This consortium is meeting the urgent need of providing information to cancer patients and developing options concerning their fertility.

Role of Gynecologist in Oncofertility Care

Gynecologists have been the primary care providers for women's health. Reproductive age women are

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usually examined by them.⁶ They also coordinate referrals to oncologists, perform clinical decision making and provide emotional support to these young women.⁷ Thus, a gynecologist is an invaluable component in oncofertility. They advice women, providing them knowledge and refer them for fertility concerns throughout their cancer treatment.⁵ There exists a considerable gap in patient care especially with regards to information on fertility preservation. Oncologists often are unable to bridge this gap due to several reasons.^{4,8} First, they deal cancer with utmost priority and are unwilling to delay cancer treatment. Secondly, they believe that addressing reproductive concerns will cause anxiety of the woman and her family. Thirdly, there most oncologists are uncomfortable in discussing fertility preservation options due to lack of training. Cultural, religious and linguistic barriers may also exist. Discussion with unmarried women about fertility preservation may be a challenging task. A gynecologist is in a better position to do so.

Female Reproductive Axis – Impact of Cancer Therapy

Multimodality approach is adopted in cancer treatment. Surgery, radiotherapy and chemotherapy either alone or in combination are used for cancer treatment. For being able to conceive, a woman must have a functioning neuroendocrine system, healthy pool of ovarian follicles and a receptive uterus. Uterus supports embryo implantation as well as fetal growth and development. The extent of impact of cancer treatment on reproductive axis of a woman is unpredictable.

Cancer therapies target the hypothalamic-pituitary-gonadal (HPG) axis. The ovary is highly susceptible to all forms of cancer treatment. Women are born with approximately two million primordial follicles. This pool is non-renewable and decreases to 500,000 at the onset of menarche. By age 37 years, the number of ovarian follicles decreases to 25,000 and at the onset of menopause reaches approximately 1,000. Any cancer treatment hastens the decline of follicle pool.⁹ Uterus is more resistant than ovaries to chemotherapy and radiotherapy. Uterine age is not primarily associated with menopause. The devastating impact on fertility of a young woman with cancer depends on her age, specific cancer type and fertility status prior to start of cancer treatment.¹⁰ Major long term negative effect of cancer therapy are premature ovarian failure, premature menopause and subsequent infertility.

Women receiving cancer treatment must be counseled that their fertility may be threatened but they may never loose it. Contraception during cancer treatment must be discussed. After the completion of cancer treatment, she may regain her natural fertility. A woman's sense of sexuality may be diminished due to vaginal dryness, hot

flushes, bodily changes, sexual dysfunction, loss of identity and attractiveness.

The upfront treatment of gynecological cancers including ovary, fallopian tube, endometrial and early stage cervical cancer is surgery. Surgical staging is an essential part of clinicopathologic assessment and determination of the need for adjuvant treatment in ovarian and endometrial cancers.

The reproductive consequences of radiotherapy depend on dose, site, duration of exposure, frequency of treatments, whether administered in isolation or in combination with chemotherapy.^{11,12} Radiotherapy damages the growing ovarian follicles especially the actively dividing cells. Primordial follicles are more resistant to radiation induced damage. The dose required to destroy half of immature human oocytes is less than 2 Gy.¹³ Total abdominal radiation with 20-30 Gray and total body radiation with 15 Gray can lead to nearly total loss of ovarian function in about 90% women.¹⁴ Radiation targeting the cranium or chemotherapy can alter hypothalamus and pituitary function.¹²

Radiotherapy on the other hand reduces uterine volume and elasticity, damages the uterus musculature and decreases its vascularity.¹¹ There are reports of miscarriages, placental abnormalities, preterm births and delivery of low birth weight infants in women conceiving after radiotherapy.

Ovary is a chemosensitive organ. Alkylating agents are more gonadotoxic than the other available chemotherapeutic agents. They produce DNA breaks and target primordial ovarian follicles for death along with compromising stromal cell function.¹⁵ Follicle destruction results in impaired ovarian hormone production in addition to uterine dysfunction. Gamete loss may or may not occur. Chemotherapy does not have any negative impact on the uterus.

Assessment of Reproductive Function

The functional potential of the ovary is defined as ovarian reserve.¹⁶ This reflects the number and quality of oocyte within the ovary. Assessment of ovarian reserve prior to initiation and after completion of cancer treatment is beneficial especially in young women. Pretreatment assessment allows prediction of vulnerability of a woman to cancer therapies. This may further emphasize the need for adopting a fertility preservation approach. Post-treatment, ovarian reserve assessment indicates whether the couple should adopt natural fertility methods or rely on fertility preservation option. Several tests have been developed to assess ovarian reserve. No single predictive marker has been advocated.

Currently, the markers used for assessment of ovarian reserve are Anti-Mullerian hormone (AMH) and antral

follicle count (AFC).^{17,18} AMH is a hormone produced by granulosa cells of the developing ovarian follicles.¹⁹ AMH level is unaffected by the day of menstrual cycle, oral contraceptive use or pregnancy. AMH level inversely correlates with the number of antral follicles. AFC can be determined by counting the number of 2-10 mm diameter follicles on transvaginal ultrasound.²⁰ Together, AMH and AFC correlate to ovarian age and remaining ovarian reserve. Measurement of these parameters is critical to assess the need for fertility preservation decision making. Other tests such as day 3 estradiol, FSH and inhibin-B may also be used to evaluate a woman's fertility status.

Fertility Sparing Surgery (FSS) in Women with Gynecologic Cancers

The care of young women with gynecological cancers is both challenging and complex. A thorough understanding of the procedures available is essential to improve their overall quality of life. FSS requires highly skilled gynecological oncologists. These women therefore need to be managed in specialist cancer centers. A summary of fertility preservation strategies in young women receiving cancer treatment is depicted in Table 1.

Early Stage Cervical Cancer

The standard treatment for women with early and locally invasive cervical cancer is radical hysterectomy and bilateral pelvic with or without paraaortic lymphadenectomy. Radiation or chemo-radiation has been utilized for those with locally advanced or metastatic disease. Several options for young patients with early stage disease who desire to preserve their ovarian function and fertility without

compromising their oncologic outcome exist. These include cone biopsy, large loop excision of the transformation zone (LLETZ), radical trachelectomy and ovarian transposition with or without pelvic lymphadenectomy. If fertility preserving options are used in patients with squamous lesions or adenocarcinoma of cervix, it is essential to have satisfactory margins free of disease.

Cervical conization is recommended for young patients with stage IA1 (stromal invasion \leq 3 mm and extension $<$ 7 mm) with no lympho-vascular invasion in whom the risk of nodal metastasis or recurrence is minimal. The reported survival at 5 years was 98% and 99% for those who underwent hysterectomy or conization respectively.²¹

Large Loop Excision of Transformation Zone (LLETZ)

LLETZ can be performed to treat stage IA1 cervical cancers instead of knife/laser cone biopsy. The use of diathermy can make pathological assessment difficult because of the heat artifact. The aim is to obtain a 2.5 cm depth of cervical tissue. One intact specimen may not be obtained which is a prerequisite for accurate pathological assessment.²²

Radical trachelectomy can be performed vaginally, abdominally or robotically with pelvic and/or para aortic lymphadenectomy.²³ Radical trachelectomy may be recommended in young women less than 40 years age, desirous of infertility, FIGO stage IA1 disease with lymphovascular invasion, stage IA2, or stage IB1 with small tumor size ($<$ 2 cm) in the absence of high risk histological features (e.g., clear cell, small cell neuroendocrine type, and glassy cell tumors) and no evidence of nodal metastasis. Successful pregnancies have been reported.²⁴

Table 1: Fertility preservation strategies in young women receiving cancer treatment

Treatment Modality	Disease Site	Strategy
Gynecologic cancer surgery	Early stage cervical cancer	Conization Large loop excision of transformation zone (LLETZ) Radical trachelectomy (RT) Neoadjuvant chemotherapy, conization and pelvic lymphadenectomy
	Early stage endometrial cancer	Hormonal (progestin) therapy
	Early stage ovarian cancer	Fertility sparing surgical staging
Radiotherapy	For early stage cervical cancer	Pelvic shielding Ovarian transposition Embryo cryopreservation Oocyte cryopreservation
Chemotherapy	For early stage ovarian cancer	Embryo cryopreservation Oocyte cryopreservation

Neoadjuvant Chemotherapy, Conization and Pelvic Lymphadenectomy

Neo-adjuvant chemotherapy has been used to reduce the tumor size in patient with $>$ 2 cm lesion prior to fertility-sparing surgery.²⁵ Maneo et al reported a series of 21 women with stage IB1 cervical cancer, mean tumor diameter 1.5 cm, treated with neoadjuvant chemotherapy followed by cold knife conization and pelvic lymphadenectomy.²⁵ No disease relapse was observed after median follow up of 69 months. Nine women attempted to conceive. Ten pregnancies occurred in 6 of these patients. There were 9 live infants and one miscarriage.²⁵ Post radical trachelectomy it is recommended to obtain cervical cytology, every 3 or 4 months for the first 3 years and every 6 months for the next 2 years. Colposcopy with or without endocervical curettage is recommended when cytology is abnormal.²⁶ Follow up cytology can be truly normal but frequently reported as abnormal, so good communication with an experienced cytopathologist becomes very important and critical to avoid an unnecessary surgery.

The decision to perform hysterectomy in patients once they have completed their family should be individualized.

Ovarian Transposition (OT) and Pelvic Shielding

OT is a procedure in which the ovaries and their blood supply are detached from the uterus and transposed to an area above the pelvis in the paracolic area. The rationale is to protect the ovaries from direct radiation exposure, hereby preserving ovarian function for future surrogate pregnancy by in vitro fertilization (IVF). Ovarian transposition can be performed in women with high risk early stage cervical cancer treated by radical hysterectomy that will require post-operative radiation or chemoradiation.²⁷ This procedure can be performed via laparotomy or by laparoscopy. If the woman has already undergone radical hysterectomy for cervical cancer, OT can be offered at a second sitting. After transposition the ovaries are marked with surgical clips to determine the location at radiotherapy planning. Potential risks include direct injury to ovarian vessels, torsion, cystic changes and mid-cycle extra pelvic abdominal pain. Only a few cases of occult metastatic cervical cancer to ovaries have been reported, most involving non-squamous lesions. Oocyte retrieval will eventually be performed by abdominal route instead of conventional transvaginal way. Pelvic shielding during radiation therapy using lead aprons can also be performed.

Early Stage Ovarian Cancer

Thorough surgical staging is the hallmark of treatment for early-stage ovarian cancers. Comprehensive staging determines surgical stage and is important in guiding adjuvant chemotherapy for patients with ovarian cancer. Some completely staged patients may not require further adjuvant therapy.

Comprehensive surgical staging (CSS) in early-stage ovarian carcinoma includes an adequate midline vertical incision, peritoneal washings, thorough exploration of the abdominal and pelvic cavities, biopsy of any suspicious lesions, random peritoneal biopsies, bilateral diaphragm sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymph node dissection and complete omentectomy. If a tumor of mucinous histology is suspected or noted on frozen section, an appendectomy should also be performed. The surgical staging of gynecologic malignancies relies heavily on the evaluation of the pelvic and paraaortic lymph nodes. The use of minimally invasive techniques for surgical staging of early ovarian cancer is associated with decreased morbidity.

Modified surgical staging (MSS) is comprehensive surgical staging with preservation of uterus and contralateral tube and ovary.²⁸ This is also often referred to as conservative

surgery or fertility sparing surgery (FSS). After completion of childbearing, completion surgery should be considered.

European Society of Gynecologic Oncology (ESGO) Task Force on fertility preservation in gynecologic cancers²⁹ has recommended the following common requirements to be fulfilled before considering conservative treatment for malignant ovarian tumors:

1. Discourage in women older than 40 years (too strong) because fertility results are poor in this age group.
2. Obtaining fully informed consent with potential oncological and obstetrical outcomes.
3. The woman should agree to comply with a thorough follow-up after the treatment.
4. A careful histological review of the ovarian tumor (and peritoneal spread if present) should be carried out by a designated gynecologic pathologist. High risk histologic tumor subtypes (clear cell, small cell) and other histological characteristics (tumor grade in case of epithelial ovarian cancer (EOC), presence of a micropapillary pattern or stromal microinvasion (SMI) in case of a serous borderline tumor, etc) must be determined.
5. A careful description of the abdominopelvic cavity (with an adequate description in the operative report) should be provided during initial surgery (and/or restaging surgery if performed).

Laparoscopy has been proposed for management of suspect adnexal masses³⁰ and for comprehensive surgical staging of early epithelial ovarian cancer.³¹ The primary concerns about application of laparoscopy include risk of spillage,³² tumor cell peritoneal dissemination with carbon dioxide pneumoperitoneum, port-site metastases and incomplete staging. A major concern is the possibility of encountering an unexpected ovarian malignancy during operative laparoscopy. Intra-operative cyst rupture upstages an unexpected ovarian cancer from stage IA to stage IC1. A gynecologic oncologist skilled in laparoscopy should perform a laparoscopic staging of ovarian tumors. Availability of a dedicated oncopathologist for accurate frozen section reporting is highly desirable. Post surgical management of early-stage ovarian cancer depends on its stage. Adjuvant chemotherapy is required in patients with FIGO stage IC (all grades), whereas observation is necessary in patients with FIGO stage IA and IB (grade 1 or 2). Obtaining an intact specimen is crucial for accurate evaluation of capsule infiltration.³³

Epithelial Ovarian Cancer (EOC)

A conservative approach should be considered only in case of early-stage EOC after a comprehensive surgical staging. An endometrial curettage (to exclude synchronous endometrial carcinoma) should be performed. A routine

biopsy of the contralateral ovary is not recommended²⁹ if a preoperative vaginal ultrasonography and an intraoperative assessment do not reveal any abnormalities. In young women with EOC, conservative surgery should be considered only in adequately staged patients, with a stage IA grade 1 (and probably 2) serous, mucinous or an endometrioid tumor, including a careful follow-up. Such an approach could also probably be discussed in stage IC grade 1 disease (except patients with stage IC3 disease due to positive cytology where radical treatment should be preferred).²⁹

Borderline Ovarian Tumor (BOT)

Comprehensive surgical staging remains the standard of care for BOT's. BOT's are seen in younger women with 5 year survival rate of 95-97% in stage Ia. In stage II and III BOT's, the 5 year survival is 65-85%. These tumors tend to grow slowly. Young women with unilateral BOT's can be offered fertility sparing surgery. Bilateral BOT's can be managed by bilateral ovarian cystectomy at fertility sparing surgical staging. Conservative surgical techniques are associated with high recurrence rate. Ovarian stimulation after conservative surgery for BOT has a high recurrence rate of 19.4% in a study.³⁴ Women with BOT's treated by ovarian cystectomy alone have a higher rate of appearance of new lesion/recurrence. However, the mortality in this group remains low. Post-treatment reproductive performance after conservative treatment of BOT needs to be adequately studied. The prognostic significance of surgical approach (laparoscopy vs laparotomy) for BOT is currently inconclusive. Pelvic and para-aortic lymphadenectomy do not increase overall survival.

Malignant Ovarian Germ Cell Tumor (MOGCT)

Stage I MOGCT confined to one ovary can be managed with unilateral salpingo-oophorectomy. Fertility preservation is the standard of care in MOGCT. The intent is to remove the tumor intact and perform a modified surgical staging.³⁵ 90-95% of MOGCT's are curable with the use of postoperative systemic chemotherapy.³⁶

Early Stage Endometrial Cancer

Surgical staging is the cornerstone in the treatment of endometrial cancer. Meticulous patient selection is essential before offering a fertility preservation strategy in women with endometrial cancer. Very early stage endometrial cancer (confined to endometrium and grade 1) may be treated with progestins.³⁷ Various progestogenic regimens have been described in literature which include medroxyprogesterone acetate in 400-800 mg divided daily doses or megestrol acetate 160 mg daily. Data on use of levonorgestrel releasing intrauterine system in early stage endometrial cancer in young women is very limited. The dilemma

of establishing the correct stage exists with such an approach. Hysteroscopy, dilatation and curettage and contrast enhanced MRI may lead to underestimation of stage of disease. This conservative approach has a high recurrence rate. Recurrence rate of 47% between 7 and 36 months of follow up in a study by Ushijima et al after treatment with 600 mg medroxyprogesterone acetate daily for 26 weeks.³⁸ In a 3 year follow up of 28 women, 12 pregnancies and 7 normal deliveries were achieved. Progestin treatment is highly controversial and 10-29% women will have a coexisting ovarian cancer.^{39,40} There exists no consensus on the duration of progestin treatment. However, some authors have described the use of proestrogenic agents for 9-12 months. Ideal follow up is also not yet addressed. Before initiation of assisted reproduction techniques (ART), a hysteroscopy and endometrial biopsy is usually performed. Most studies have described endometrial sampling at 3 monthly intervals. After completion of family or failure of ART, surgical staging is recommended. Women must be informed that use of oral progestogens is not a standard treatment. They must be counseled regarding a high rate of recurrence and compromise in survival in order to preserve fertility.

Non-surgical Fertility Preservation Strategies

Fertility preservation in young women with cancer encompasses the full range of standard and experimental options. In the prepubescent patient, ovarian tissue cryopreservation is the only option and is still investigational. In younger women, it may occasionally be feasible to offer ovarian tissue retrieval and cryopreservation, ovarian stimulation and oocyte retrieval and/or IVF and embryo cryopreservation. Ovarian tissue freezing remains investigational. Surrogacy will be required to achieve a pregnancy if the uterus is removed. Assisted conception techniques would usually be undertaken in the window between primary surgery and the start of chemotherapy or radiotherapy. A working partnership with a fertility clinic should be established so that rapid referral can be made and the patient seen expeditiously to avoid delay. Despite recent advances and improving success rates with oocyte and embryo preservation, there are no guarantees that these methods will result in a successful pregnancy for any individual.

Embryo Cryopreservation

Embryo cryopreservation following IVF is a routine procedure in fertility clinics. Limited data exists on its success rates in the context of fertility preservation in women with gynecological cancers. This procedure is the gold standard in fertility preservation when partner or donor sperm is available. This process requires 10-14 days of ovarian stimulation with daily gonadotropin injections,

accompanied by frequent visits for ultrasound monitoring and blood work. Mature oocytes are harvested via transvaginal needle aspiration. The oocytes are fertilized with partner or donor sperm and cryopreserved after 3 or 5 days.

Oocyte Cryopreservation

Mature oocyte cryopreservation is an alternative option for women who do not have partners or who are unwilling to use donor sperm. It is technically challenging and requires ovarian stimulation, with the resultant potential delay in cancer treatment. It may be contraindicated if the tumour is thought to be hormone sensitive although there are no scientific data on this. In October 2012, American society of Reproductive Medicine (ASRM) published an official guideline stating that mature oocyte cryopreservation should no longer be considered experimental and can be recommended with appropriate counseling to patients receiving gonadotoxic therapies for cancer.⁴¹

In-vitro Maturation (IVM)

IVM is the process of maturing immature oocytes in the laboratory.⁴² After retrieval, these oocytes are cultured in the laboratory to achieve both nuclear and cytoplasmic maturation followed by cryopreservation. Immature oocytes can be collected from the ovaries during both the follicular and luteal phases. Because no gonadotropin injections (or very few) are used, the procedure can be done expeditiously. This option will be useful for women in whom exposure to exogenous hormones is undesirable and in whom chemotherapy cannot be delayed.⁴³

Oocyte vitrification may offer increased success rates in comparison with slow freezing, but is limited by the number of oocytes that can be obtained. This technique has been recommended by NICE fertility (draft) guidance⁴⁴ but only carries a 3–5% chance of resulting in a successful pregnancy per frozen egg.

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is another experimental method for fertility preservation and is the only option for prepubescent girls. This procedure involves laparoscopic surgery to obtain ovarian cortical biopsies containing healthy follicles. The biopsies are cryopreserved and then reimplanted after the patient is disease-free. Orthotopic reimplantation occurs in the pelvic cavity, while heterotopic reimplantation occurs in an area outside the pelvic cavity, such as the forearm. It can be performed without significant delay but success rates from its use remain debatable.⁴⁵ The concern with this procedure is the potential for reintroducing cancer cells, which could lead to recurrence of malignancy after reimplantation.⁴⁶

The field of ovarian tissue and oocyte retrieval and storage is fast changing and expert advice and help from fertility specialists needs to be sought in order to give the patient the best chance of future childbearing. Despite these advances, a recent study showed that in USA only 4% of women treated for cancer take steps to preserve their fertility⁴⁷ with only 61% being counseled on the risk of cancer treatment to fertility by their oncology team despite receiving therapies that could reduce their fertility.⁴⁸ These studies did not include patients with gynecological cancers and although gynecologists are much more likely to be aware of fertility issues, there seems to a huge potential to improve this statistics.

Ovarian suppression with Gonadotropin Releasing Hormone (GnRH) agonists is a non-invasive method in which follicles are preserved from gonadotoxic agents by inhibitory effects of these agonists on stimulatory effect of FSH. Use of GnRH analogs (for suppression of LH and FSH production) for ovarian chemoprotection is experimental and controversial and should only be used in randomized controlled trials.⁴⁹ As proposed by American Society of Clinical Oncology (ASCO) until good evidence is supported by randomized clinical trials these women interested in the use of GnRH agonists should be encouraged to participate in clinical trials.

CONCLUSIONS

Oncofertility is an emerging field of science developed to explore and expand fertility preservation options for young cancer patients, helping them understand these options better. A team based approach is needed to provide clinical care and ensure an optimal outcome balancing cancer care and reproductive function. Oncologists, reproductive endocrinologists and gynecologists work together along with clinical psychologists and counselors in this entire fertility preservation process. Preservation of fertility in men may be easier with the banking of sperms before treatment but for the women, storage of the gametes is technically very complex with limited success. Fertility preservation in reproductive-age women with cancer remains an important but underrepresented topic. Specific fertility preservation strategies exist for women facing gynecologic surgery, pelvic radiation and/or chemotherapy. Recent advances in the field of ART have made oocyte cryopreservation, in addition to embryo cryopreservation, an established and accepted option. Despite of the negative impact of cancer treatment on female reproductive axis, there exist numerous fertility preservation options for young women with cancers. The quality of life in these young women can be greatly improved. A young woman's sexuality, body image, reproductive functions are negatively effected by cancer

diagnosis. However, oncofertility opens up an arena for realization of a couples' dream of parenthood.

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