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Review Article

Fertility preservation in women undergoing treatment for malignancies: a narrative review

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ABSTRACT

Incidence of cancer is increasing in young patients with simultaneous improvement in survival secondary to advances in cancer treatment. Fertility preservation in this young population is often overlooked in view of priority of cancer treatment, however it is important to avoid distress and provide a good quality of life in these young patients of child bearing age. Fertility might be affected due to systemic therapy like chemotherapy, radiotherapy and surgery involving reproductive organs. Timely referral to reproductive specialist during the narrow window after diagnosis and before starting cytotoxic treatment is required. Embryo and oocyte cryopreservation remains the gold standard with ovarian tissue cryopreservation and re-transplantation undertaken for special situations. Patients undergoing pelvic or abdominal radiotherapy benefit from ovarian transposition and ovarian shielding. Medical gonado-protection with Gonadotropin releasing hormone agonist during cytotoxic chemotherapy remains an area of controversy with conflicting results with recent consensus for use in premenopausal breast cancer patients. Patients requiring surgery for endometrial cancer, ovarian cancer or cervical cancer may be considered for conservative management including conservative surgery for early stage cancers with specific indications with the intent to allow patients to complete family. Adequate patient counselling for oncology outcomes and fertility preservation are required to enable the patients to take informed decisions to choose the unconventional path of cancer management and uncertainty involving pregnancy and live births.

Keywords: Fertility preservation, Young cancer patients, Fertility preserving cancer surgery, Conservative cancer management

INTRODUCTION

The incidence of cancer is increasing in the age group of 15-39 years and currently is 52.3 cases per 100,000. The common malignancies affecting this young population include carcinomas, lymphomas, melanomas, and central nervous system tumors.[1] With advances in treatment, the survival rates in this young population have improved significantly.[1] With trends of delayed child bearing, majority of these young patients have not completed their families when they are diagnosed with malignancy.

Anticancer therapies are associated with infertility and there is no absolute threshold at which infertility can occur, hence all these young patients who undergo anticancer treatment are at the risk of developing gonadal failure and infertility.[2] This can cause significant distress and negatively affect the quality of life.[2,3]

BARRIERS TO FERTILITY PRESERVATION

Less than half of the oncologists discuss fertility preservation (FP) with their patients.[4] There are certain barriers to FP.

Patient related barriers

Patients are too overwhelmed with the diagnosis of malignancy and are concerned with timely initiation of treatment. They are unaware about the effects of anticancer treatment on fertility or availability of FP methods. They fear passing their cancer diagnosis to their future children and the risk of having children with malformation or genetic aberrations.[5]

Physician related barriers

FP calls for a dedicated and detailed discussion with the physicians who are always working under time constraints. For an oncologist, optimal cancer treatment takes priority over FP who often presumes on behalf of patient about their FP choices based on their prognosis, family history, genetic syndromes, obstetrical history, and affordability.[4]

Financial barriers

All fertility preservations methods are expensive and are not covered in public funded schemes.[6]

PRETREATMENT FERTILITY COUNSELLING

All adolescent and young adults who are cancer patients need to be counselled about infertility resulting from cancer treatment and options of FP. Fertility counselling needs to be discussed as early as possible, once diagnosis is confirmed, during the staging workup and before the treatment starts, to help patients make informed decisions. Even a single cycle of chemotherapy affects the DNA integrity.[7]

Discussions should be documented and written information and/or online resources should be provided to all patients. Timely referral to reproductive specialist and genetic counselling should be provided.[2,8]

MARKERS OF FERTILITY

After 35 years, female fertility declines rapidly and women more than 30 years tend to commonly develop premature ovarian insufficiency (POI) after chemotherapy.

Anti mullerian hormone (AMH) and antral follicle count (AFC), determined on transvaginal ultrasound are taken as markers of ovarian reserve. Assessment of pre-treatment ovarian function, through AMH levels, helps to predict post-treatment recovery of ovarian function.[9] For women with reduced ovarian reserve (AMH <0.5 ng/ml and AFC <5) FP needs to be individualized.[10]

Menstruation might return within 3 months to 2 years after chemotherapy, however return of menstruation is not an indicator for fertility. Around 40% of women aged 35 years who resume normal menstruation following cancer treatment experience infertility due to severely diminished ovarian reserve.[11]

CAUSES OF INFERTILITY

Infertility in cancer patients can be caused by systemic chemotherapy, radiation to the pelvis and/ or abdomen and surgery that involves the reproductive organs.

Chemotherapy

Treatment with the commonly used combination chemotherapies typically advance a woman's reproductive age by around 10 years. Chemotherapy causes a reduction in ovarian reserve which may result in infertility and POI. If chemotherapy affects the maturing follicles it leads to temporary sterilization however if primordial follicle pool is affected, it may result in permanent sterilization.[12]

Most alkylating agents, conditioning chemotherapy for bone marrow transplant (BMT) and Total Body Irradiation (TBI) are considered high risk, platinum and anthracyclines are considered medium risk while vinca alkaloids, antimetabolites, topoisomerase inhibitors, antitumor antibiotics are considered low risk for gonadal toxicity and infertility.[2,7,12] The infertility risk from taxanes, targeted therapies, immunotherapy (including immune check point inhibitors) trastuzumab, vascular endothelial growth factor inhibitors (VEGFi) remain unknown.[12,13]

Endocrine treatment is not known to affect fertility but because of the long-prescribed duration, fertility declines due to natural ovarian aging.[14] In women with hormone receptor-positive breast cancer, prescribed 5-10 years of adjuvant endocrine therapy, safety of temporary interruption of endocrine therapy on cancer outcomes is not clearly known. Results from the multicentre, prospective POSITIVE trial showed that 3-year recurrence rate is not affected with upto 2 years interruption in endocrine therapy. In women who consider this option, informed decisions should be made after counselling about the risks of recurrence and pregnancy outcomes.[14] Following delivery, adjuvant endocrine therapy should be resumed to complete the recommended duration of treatment.

Radiotherapy

Malignancies (e.g. lymphoma, Wilms, sarcoma) where radiotherapy is delivered to ilioinguinal and abdominal region or irradiating gonads such as acute leukaemia or gonadal tumours can cause acute gonadal failure and infertility. Radiation therapy (RT) causes a reduction in the number of ovarian follicles and adversely affects the uterine and endometrial function. The gonadotoxic effect of RT is dependent on the radiation field, total dose and fractionation schedule. The risk of infertility from radiation therapy increases with age, adult patients being more sensitive to radiation than adolescents or children. Increased fractionation of radiation dose is one of the techniques used to reduce the fertility risk.[15]

The gonads are one of the most radiosensitive cells and a radiation dose of ≤2 Gy can decrease the ovarian reserve by 50%. Permanent infertility is seen with doses >6 Gy.[16] Radiation causes decreased uterine size and elasticity; myometrial fibrosis and necrosis; endometrial atrophy; blood supply alteration; the cervix becomes atrophic and loses elasticity; implantation is hindered and pregnancy has been considered unviable at doses >25 Gy to uterus.[17]

Surgery

Surgical management for ovarian cancer, endometrial cancer and cervical cancer involves the removal of either the ovaries and fallopian tubes or uterus or all, which may impair the reproductive potential.

FERTILITY PRESERVATION PROCEDURES

Oocyte and embryo preservation

The most commonly used FP procedures and considered the 'gold standard' are embryo and oocyte cryopreservation.[2,8] These procedures require an available period of about 2 weeks prior to starting any cancer treatment for oocyte stimulation and retrieval to take place. Flexible ovarian stimulation protocols are available which are independent of the menstrual cycle and prevent delay.[2,7,8]

Stimulation regimens increase serum estrogen levels and are a concern for estrogen sensitive breast and gynaecological tumors. Aromatase inhibitors or tamoxifen can be used to reduce estrogen levels. Fixed dose of letrozole 2.5 mg twice a day has been found to be more effective and reduces estrogen serum concentration by more than 50%.[18] A meta-analysis showed no increase in cancer recurrence after controlled ovarian stimulation in patients with hormone-receptor-positive breast cancer.[19]

Advantage of oocyte cryopreservation over embryo cryopreservation is that it can be carried out in single females without a partner and for women with ethical and religious issues with embryo cryopreservation. On the other hand, embryos are less sensitive to freezing and thawing procedures when compared to oocytes. [2,7,8] Women with a partner should be offered the option to cryopreserve unfertilized oocytes or to split the oocytes to attempt both embryo and oocyte cryopreservation. [2,7,8]

Live birth rate (LBR) after embryo cryopreservation ranges from 20% to 45% and LBR after oocyte cryopreservation is 50% in women ≤35 years old and 22.9% in women >36 years old.[20,21]

Ovarian tissue cryopreservation and reimplantation

Ovarian tissue cryopreservation and transplantation is an emerging technique which is effective in women under 35 years. Five percent of primordial follicles are lost during freezing and another two third are lost during revascularization. Ovarian retransplantation can be orthotopic (within the pelvis) or heterotopic (subcutaneous transplant).[7,8,22]

This is the only FP method for prepubertal girls, does not require time to undergo ovarian stimulation and can be used in patients with hormone dependent tumors. Ovarian stimulation can be combined with cryopreservation of ovarian tissue to increase the success rate in women receiving highly gonadotoxic treatments.[2,7]

However, it is recommended that ovarian tissue should be carefully analysed before grafting using immunohistochemistry and molecular markers, to rule out possibility of micrometastasis.[23] Genetic testing should be done before transplantation of cryopreserved tissue. LBR after ovarian tissue cryopreservation and reimplantation ranges from 18.2 to 40%.[23]

Medical gonado-protection

There is conflicting evidence to recommend gonadotopin releasing hormone analogue (GnRHa) as a method of FP. Use of medical gonado-protection using GnRHa induces hypogonadism before starting chemotherapy.[24] It may be considered in young women with breast cancer, starting 1 week before initiation of chemotherapy and continued for the duration of chemotherapy, recognizing the limitations, controversy, and potential risks.[24] Limited evidence exists on their protective effect on the ovarian reserve and the potential for future pregnancies as indicated by lack of recovery of AMH. No protective effect was seen for patients with lymphoma, radiation therapy, or for male gonads.[2]

In premenopausal breast cancer patients, of the 14 randomised trials, majority showed a statistically significant reduction in POI risk with concurrent administration of a GnRHa during systemic cytotoxic therapy. In an individual patient-level meta-analysis, the administration of a GnRHa during chemotherapy was associated with a significant reduction in POI rates [from 30.9% to 14.1%; odds ratio 0.38; 95% CI 0.26-0.57; p<0.001] and a higher number of post-treatment pregnancies [33 versus 20; incidence rate ratio 1.83; 95% CI 1.06-3.15]. Treatment effect was observed in both patients with hormone receptor-positive and -negative disease and irrespective of patient age, type and duration of chemotherapy.[24]

In premenopausal women with haematological malignancies, a recent meta-analysis showed no significant difference in POI rates [18.9% versus 32.1%; risk ratio (RR) 0.70; 95% CI 0.20-2.47] or post-treatment pregnancies (17 versus 18; RR 1.13; 95% CI 0.66-1.93) between patients that received chemotherapy alone and those with concurrent GnRHa.[25]

In premenopausal women with other solid tumours, only one randomised trial including 30 patients with ovarian

cancer is available. A significant reduction in POI rates (from 33.3% to 0.0%; P¼ 0.02) was observed with the use of a GnRHa during chemotherapy; post-treatment pregnancies were not reported.[26]

For premenopausal women with malignancies other than breast cancer, GnRHa may be considered as an option to potentially reduce POI risk, after informed discussion with the patients. GnRHa should not be considered as an equivalent or alternative for FP but can be offered along with cryopreservation techniques or when they are not possible. Advantages are its suitability for premenopausal patients of all ages, non-invasive nature and low health risk.[2,24]

Ovarian transposition and ovarian shielding

Ovarian transposition (OT) or oophoropexy and gonadal shielding are indicated in women <40 years of age who are scheduled to receive pelvic RT.[27]

For OT ovaries are surgically removed away from the field of radiation, mobilised with its vascular pedicle and the location is marked with radio-opaque clips to allow identification of the transposed ovary. OT can preserve ovarian function in 50–80% of cases.[27,28] Hwang et al demonstrated that fixation more than 1.5 cm above iliac crest was the most important factor for intact ovarian function. The procedure is usually done as close to treatment as possible to prevent remigration of ovaries.[29] OT is the only available method for children undergoing pelvic or abdominal RT and may prevent premature menopause in patients not requiring FP.[2,7]

Gonadal shielding during RT by lead blocks reduces the RT dose to 4-5 Gy. The minimum free margin should be 2 cm in order to reduce the risk of gonadal irradiation due to variable position of ovaries in different phases of the menstrual cycle. Accurate placement of shielding requires ultrasound guidance or placement of markers to ensure that ovaries are well positioned within the shielded region. In a meta-analysis, from 19 studies, the average of correctly positioned shields was noted to be 34%.[30]

Drawback of OT and gonadal shielding is that they only block direct radiation exposure but ovaries are not always protected from scattered radiation, hence these procedures should be supplemented with other FP procedures.[27]

BRCA MUTATIONS

Patients with BRCA1 and BRCA2 mutations are at an increased risk of developing breast and ovarian cancer, have a reduced ovarian reserve, a decreased baseline AMH level, at higher risk of developing POI and need to undergo prophylactic bilateral oophorectomy before the age of 40 years.[31]

Patients with a hereditary cancer syndrome have a 50% risk of transmitting the mutated gene to their children. Oocyte or embryo cryopreservation in these women are the preferred options for FP. These techniques facilitate the use of preimplantation genetic diagnosis (PGD). Ovarian transplantation can be offered in BRCA positive patients, but the ovarian tissue must be completely removed after subsequent pregnancy.[32]

Table 1: Fertility preservation procedures available for female cancer patients.

Procedure	Patient population
Embryo cryopreservation	Patients with partner
Oocyte cryopreservation	For single females
Ovarian tissue cryopreservation	For pre-pubertal girls, lack of time for ovarian stimulation, for hormone sensitive tumors to avoid estrogen surge during ovarian stimulation
Medical gonadoprotection (GnRHa)	For breast cancer patients undergoing chemotherapy
Ovarian transposition	For patients undergoing pelvic or abdominal radiation

FERTILITY PRESERVATION IN GYNAECOLOGICAL MALIGNANCIES

Ovarian cancer

Fertility-sparing surgery in ovarian cancer consists of preserving the uterus with or without preservation of the contralateral annex. It may include unilateral or bilateral salpingo-oophorectomy associated with collection of peritoneal lavage, omentectomy and biopsy of any peritoneal alteration.[33,34]

Fertility-sparing surgery can be considered in cases of: stage IA epithelial with low grade histology (G1–G2) and borderline ovarian tumours; malignant ovarian germ cell tumours and sex cord stromal histology. Unilateral salpingo-oophorectomy is the treatment of choice for young patients with early-stage tumours and may be considered in selected cases of advanced disease; and it can be individually considered in patients with stage 1C1 tumours with intraoperative rupture of the tumour capsule and negative peritoneal cytology.[33,34] Complementation of surgery is recommended after the end of pregnancy for patients with invasive epithelial disease, and is not necessary for non-epithelial and borderline tumors. Oocyte cryopreservation is indicated for patients who will be receiving adjuvant chemotherapy.[2]

Endometrial cancer

Endometrial cancer is predominantly a disease of postmenopausal women; however, 6.4% cases occur in the age group of 20 to 44 years.[35] In these age groups, tumors

are generally well differentiated, around 10% are associated with lynch syndrome and the risk of synchronous ovarian cancer is 4-25%.[36] FP, if desired, is indicated for patients with endometrioid carcinomas, stage IA grade 1 tumours without myometrial invasion. In women harbouring copy number high p53abn tumors, conservative therapy is not indicated.[37]

High doses of oral medroxyprogesterone (400–600 mg/day) or megestrol acetate (160-320 mg/day) and a levonorgestrel IUD at a dose of 52mg can be used alone or in combination with systemic progestogen, with the combination considered preferrable for fertility preservation.[38] Hysteroscopic resection of the tumor and adjacent endometrium preceding LNG-IUD or progestogen has better rates of complete response.[38] Other medications like GnRHa (for obese patients), aromatase inhibitors, metformin and lifestyle changes should be incorporated in the management.[39] Most studies have a median time of 4-6 months for regression. A positive estrogen receptor and progesterone receptor status is associated with a more favourable outcome while presence of risk factors, like obesity, insulin resistance, polycystic ovarian syndrome may require a longer treatment time. Hence, 6–12 months is the recommended duration of therapy for a complete response. If there is no response or progression after 6–12 months, radical surgery is suggested.[37] Complete response rates range from 48% to 96%, highest complete response rates are obtained with the combination of hysteroscopic resection followed by progestin treatment which varies from 90% to 95.3%.[39,40]

Two consecutive complete response endometrial biopsies with a minimal interval of 3 months are necessary to consider the success of the fertility sparing treatment and to recommend pregnancy. A 3 to 6-month follow-up biopsy is required until pregnancy or until definitive surgery is performed.[37] Assisted reproduction techniques can facilitate and shorten the time required to achieve pregnancy and decreases the risk of relapse. Pregnancy rates vary from 32-53% and live birth rates from 28-69.4%. Definitive surgical treatment consisting of total hysterectomy with or without bilateral salpingo-oophorectomy and surgical staging is recommended after completion of childbearing.[37]

Cervical cancer

Conservative surgical treatment for FP in cervical cancer patients consists of conisation or radical trachelectomy. Conisation includes a cone biopsy, which is excision of a cone or wedge-shaped piece of the uterine cervix including the transformation zone with negative margins.[41] Radical trachelectomy includes en bloc removal of the cervix, upper vagina, and parametria while leaving the uterine body and fundus in situ.[42]

FP is indicated in patients with early cervical cancer with squamous, adenocarcinoma, and adenosquamous histologies. Conization with margins free of tumor and free of high-grade squamous intraepithelial lesion (HSIL) for stage IA1 without lymphovascular space involvement (LVSI); radical trachelectomy with pelvic lymphadenectomy for stages IA1 with LVSI, IA2 and IB1 (up to 2 cm), depth of invasion <10 mm with or without LVSI; or IB2 lesions >2 cm, with use of neoadjuvant chemotherapy to reduce tumour size followed by radical trachelectomy and pelvic lymphadenectomy may be considered on an individual basis, although long-term safety studies are lacking.[41]

The prospective ConCerv study compared simple hysterectomy with conization and pelvic lymphadenectomy in stage IB1 patients. The recurrence and 5-year mortality rates of radical trachelectomy were 3-6% and 1.6-5%, respectively and was similar to radical treatment.[43] Infertility after radical trachelectomy occurs in 14-41%. First trimester abortion is comparable to that of the general population, second trimester miscarriage is more frequent. Prematurity occurs in 28-38% of pregnant women and, before 32 weeks in 12%, resulting from premature rupture of membranes secondary to cervical insufficiency.[42] Cerclage can be performed at the same surgical time. Pregnancy rates range from 55-65.8% and the rate of live newborns is 70%. There is no indication of radical treatment after pregnancy.[42]

Literature indicates that 20–44% of patients with stage IB2 disease require adjuvant treatment post-radical trachelectomy.[42] Other fertility-sparing surgeries like OT may be considered for patients needing adjuvant or definitive radiation for carcinoma cervix. This may be preceded by cryo-conservation of oocytes or ovarian tissue and limitation of the radiation dose received by ovaries. Use of a surrogate mother will be required, as uterine dysfunction after pelvic radiation therapy preclude to carry a pregnancy to term.

Uterine sparing radiation therapy of cervical cancer is a non-established approach because uterus and cervix are embryologically one unit with interconnected lymphatics.[41] High-precision modern radiation therapy techniques like IMRT, volumetric arc therapy and helical tomotherapy may allow uterine sparing chemoradiation to reduce the planned dose to the non-affected uterus to below 20-25 Gy.[17,41] With the use of MRI guided brachytherapy, dose to uninvolved corpus uteri can be reduced further. Whether this may preserve fertility, including the ability to carry a pregnancy to term after cancer treatment without compromised cancer control is fully unclear and great caution must remain.[17] It is therefore mandatory, to use this strategy for selected patients, strictly within prospective trials.

PREGNANCY OUTCOMES AFTER FERTIITY PRESERVATION

There is no particular time when it is considered optimal to allow patients to become pregnant following their cancer diagnosis. Timings should consider time to

completion of cancer treatment, risk of relapse, age, ovarian function and patient's wishes.[44] Ovarian reserve assessment should be undertaken at the earliest 12 months post-chemotherapy. An interval of at least 1 year following chemotherapy completion, 7 months after trastuzumab and 3 months after tamoxifen is suggested before attempting a pregnancy in order to reduce the risk of pregnancy complications.[2,44] Female cancer survivors have significantly reduced chances of post-treatment pregnancies compared with the general population, increased risk of developing obstetric and birth complications in terms of increased risk of prematurity (RR 1.56; 95% CI 1.37-1.77), low birth weight (RR 1.47; 95% CI 1.24-1.73), elective (RR 1.38; 95% CI 1.13-1.70) and emergency caesarean section (RR 1.22; 95% CI 1.15-1.30), assisted vaginal delivery (RR 1.10; 95% CI 1.02-1.18) and postpartum haemorrhage (RR 1.18; 95% CI 1.02-1.36).[45]

Table 2: Fertility preservation in gynaecological malignancies.

Site	Indications and oncology management	Definitive surgery after pregnancy
Ovarian cancer	Stage IA epithelial histology (grade 1 and grade 2): unilateral salpingo-oophorectomy along with collection of peritoneal lavage, omentectomy and biopsy of any peritoneal alteration	Complementation of surgery is recommended after the end of pregnancy for invasive epithelial disease, and not for non-epithelial and borderline tumors
	Stage IA/IC non epithelial germ cell tumor, sex cord tumor or borderline tumor: unilateral salpingo-oophorectomy along with collection of peritoneal lavages, omentectomy and biopsy of any peritoneal alteration	
Endometrial cancer	Stage IA grade 1 tumours without myometrial invasion: hysteroscopic tumor resection and adjacent endometrium followed by hormone therapy with high doses of oral medroxyprogesterone (400–600 mg/day) or megestrol acetate (160-320 mg/ day) and a levonorgestrel IUD at a dose of 52 mg can be used alone or in combination	Definitive surgery immediately after pregnancy
Cervical cancer	Stage IA1 without LVSI: conization with negative margins	Not indicated
	Stage IA1 with LVSI: radical trachelectomy with pelvic LND	
	Stage IA2, IB1 (T<2 cm) with or without LVSI: radical trachelectomy with pelvic LND	
	Patient's on adjuvant or definitive radiation/chemoradiation: ovarian transposition	

CONCLUSION

Fertility preservation for female cancer patients is feasible, however it involves following unconventional management protocols. It is important to let patients make informed decisions after being counselled about risks of cancer control and recurrence; and to counsel further that preserving gametes, embryos, or preserving fertility does not guarantee having a pregnancy after treatment.

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