Review Article

Managing Pregnancy in Cancer Survivors

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Introduction

Cancer complicates about 1 in 2000 pregnancies, and the frequency has been rising in recent years.[1] Delay in first childbearing contributes significantly to a rise in this incidence. Cancer survivors are rapidly increasing in number due to earlier cancer diagnosis, aging of society and improvements in cancer treatments. In recent decades, there have been fewer miscarriages and premature births thus improving the obstetric outcome. Often, pregnancy after cancer treatment is safe for both the mother and baby. Here, in this review article, we discuss about the different facets of care of the pregnant lady who has undergone cancer treatment.

Interval between Pregnancy and Cancer Treatment[2,3,4]

A wait period of twelve months after finishing chemotherapy is advised by many organizations. Chemotherapy has a toxic effect on rapidly dividing cells and may damage the oocytes recruited for ovulation (the process of folliculogenesis takes around 12 months). Therefore, the rates of miscarriages and birth defects are more in pregnancies occurring soon after chemotherapy. Chemotherapy mediated immunosuppression may be a cause for small for gestational age fetuses and fetal growth restriction. There is no risk of preterm birth if pregnancy is planned one year after chemotherapy without radiation and two years after combined chemotherapy and radiation. Lifelong thyroid hormone replacement is given to thyroid cancer survivors. Hypothyroidism causes adverse feto-maternal outcomes thus, American Thyroid Association recommends postponement of pregnancy for 6-12 months after starting hormone replacement therapy. There is a risk of preterm birth in survivors of cancer cervix if conception occurs within one year of diagnosis. The chances of recurrence of breast cancer are maximum within 24 months after diagnosis, so women with breast cancer are advised against pregnancy for this time duration. Tamoxifen treatment is continued for 5 years in breast cancer, so breast cancer survivors need to avoid pregnancy for that time because of the risk of relapse/ poor outcome if tamoxifen is stopped. If women are willing to take this risk, interruption after 2 to 3 years of tamoxifen could be considered to allow pregnancy. Tamoxifen should be resumed following delivery in these patients.

Pre-pregnancy Counselling in Cancer Survivors

Depleted ovarian follicles causes premature ovarian failure and amenorrhea. Ovarian reserve in these patients is tested using Inhibin B, AMH and day 3 FSH. The uterine function, uterine blood flow, uterine cross-sectional area and endometrial thickness should be assessed by an ultrasound, prior to attempting a pregnancy. This may be valuable in predicting fertility in women at risk of uterine vascular insufficiency. A poor ovarian reserve can also be indicated by a small ovarian volume and a few number of antral follicles.[5] Certain germline mutations increase the risk of malignancy in the offspring. The BRCA 1 & 2 mutations increase the risk of breast and ovarian

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cancer, and mismatch repair genes (MLH1, MLH2, MSH6, PMS2) increase the risk of colorectal and endometrial cancer. All male and female cancer survivors with confirmed familial cancer syndrome should be offered genetic counselling. These patients can also be offered IVF and pre-implantation screening when planning a pregnancy.[6] At the time of the cancer diagnosis, the beginning of therapy, and once more at the conclusion of treatment and during follow-up, the patient should be informed about contraceptive counseling and the risks of infertility. A 2022 study emphasized the need for contraception as the rates of unplanned pregnancy were similar in both cancer survivors and the comparison group.[7] It is pertinent to discuss the risk of adverse pregnancy outcomes with the patient and the family and they should be informed that evidence does not support the survivors having an increased risk of congenital malformed fetuses. Cancer survivors treated with anthracyclines and chest irradiation should have a surveillance for cardiomyopathy in the pre-pregnancy period. If the survivors have a compromised left ventricular systolic function and the LVEF is < 30% before pregnancy, it is likely to further reduce during pregnancy and in postpartum. Pre-conceptional counseling should also emphasize choosing an acceptable delivery location and referring to a skilled obstetrical team.[8] Folic acid supplementation 400mcg should be started preconceptionally.

Contraception in Cancer Survivors[9]

Chemotherapy or radiation treatments may be teratogenic, so women are advised to avoid pregnancy during treatment. It is important to conceive in a period of optimum health, thus lies the importance of contraception. Permanent contraception may also be opted by some. Long-acting reversible contraception (LARC) with intrauterine devices (IUDs) or implantable contraceptives are more effective than short-term contraceptive methods, which include the use of estrogen and progestin with various delivery systems.

The various options of contraception are tabulated in Table 1.

NCCN guidelines on Adolescent and Young Adult (AYA) Oncology, Version 2.2024: For those who have been cancer-free for at least six months and have no history of hormonally mediated malignancies, chest radiation, anemia, osteoporosis, or venous thromboembolism, using any form of contraception is advised. IUDs is the preferred first-line contraceptive

Table 1: Contraceptive options in cancer survivors

Type of Cancer	Intra-Uterine devices (IUDs)			Progesterone only contraception	Combined hormonal contraception (CHC)
GESTATIONAL TROPHOBLASTIC DISEASE					
Decreasing or undetectable β-hCG levels	MEC 3			MEC 1	MEC 1
Persistently elevated β-hCG levels or malignant disease	MEC 4			MEC 1	MEC 1
BREAST CANCER					
Family history of cancer	MEC 1			MEC 1	MEC 1
Current breast cancer	Cu-T MEC 1			MEC 4	MEC 4
	LNG-IUS MEC 4				
Past breast cancer and no evidence of current disease for 5 years	Cu-T MEC 1			MEC 3	MEC 3
	LNG-IUS MEC 3				
ENDOMETRIAL CANCER		I	C	MEC 1	MEC 1
	Cu-T	MEC 4	MEC 2		
	LNG-IUS	MEC 4	MEC 2		
OVARIAN CANCER		I	C	MEC 1	MEC 1
	Cu-T	MEC 3	MEC 2		
	LNG-IUS	MEC 3	MEC 2		
HEPATOMA	Cu-T MEC 1			MEC 3	MEC 4
	LNG-IUS MEC 3				

MEC: Medical Eligibility Criteria by WHO; LNG-IUS: Levonorgestrel Releasing Intrauterine System; Cu-T: Copper T containing Intrauterine Device; I: Initiation, C: Continuation

option for females with a history of breast cancer. An LNG-IUS may be preferable for those treated with tamoxifen as it may reduce tamoxifen-induced endometrial changes without increasing the risk of breast cancer recurrence. The US CDC advises against using CHCs in individuals of reproductive potential who have active cancer or who have undergone cancer treatment within the last six months due to the risk of venous thromboembolism related with their usage.

Fathering a Child after Cancer Treatment

All males receiving gonadotoxic therapy should get infertility risk counseling. A testicular biopsy can be done in prepubertal boys, prior to initiation of oncologic treatment. The sample can be cryopreserved and used for Spermatogonial Stem Cell Transplantation (SSCT) later in life. In a study, a slightly increased risk of congenital malformations was found in children fathered by men diagnosed with TGCC (Testicular Germ-Cell Cancer). However, there was no additional risk increase brought on by radiotherapy or chemotherapy as the risk was the same in both pregnancies before and after paternal cancer treatment.[10] Male cancer survivors are advised by medical professionals to wait two to five years following treatment before having children. Despite the fact that sperm continue to be produced for several months after the beginning of cytotoxic therapy, pregnancy should be avoided during this time due to a higher risk of genetic damage to the sperm. Recovery of spermatogenesis may itself take 2- 5 years.[11]

Concerns about bearing a Child after Cancer Treatment

Cancer survivors may have a lot of concerns about childbearing.

1. **Risk of children getting cancer:** Around 5% of all cancers are hereditary and many of them are associated with germline mutations. These cancers develop at a much younger age. The common amongst them being BRCA 1&2 (increased risk of breast and ovarian cancer), HNPCC (increased risk of colon, endometrial, gastric cancer), MEN 2a (increased risk of medullary thyroid cancer, pheochromocytoma, and hypoparathyroidism). Genetic counselling is offered in confirmed cases.
2. **Risk of cancer recurrence:** The risk of breast cancer recurrence or mortality is not increased by pregnancy in women with low-risk breast cancer. Lee et al. found that women who became pregnant after breast cancer did not have a different risk of recurrence and death, compared with those who did not become pregnant after breast cancer treatment.[12] Thus, breast cancer is no longer a contraindication to pregnancy, however a wait period of 2 years is recommended (as discussed before). Contrarily, PABC (Pregnancy Associated Breast Cancer) has a significant risk of recurrence because it is particularly sensitive to the hormonal environment of pregnancy. Women having a history of melanoma or Hodgkin lymphoma appear to be unaffected by pregnancy in terms of recurrence rates or illness survival. Planning a pregnancy in breast cancer survivors on tamoxifen, requires stopping the drug, which can increase the risk of relapse.
3. **Issues regarding infertility:** Any of the treatment modalities can lead to male or female infertility. Options of fertility preservation should be discussed prior to treatment.
4. **Uncertainty:** There is an uncertainty regarding relapse, recurrence, survival and concerns for raising the child, in the cancer survivors. Proper pre-conceptional counselling and psychotherapy might be of help in such cases.

Reproductive Outcomes in Cancer Survivors[8]

In the first livebirths of female survivors of Child, Adolescent or Young Adults (CAYA) cancers, there is no increased risk of malformations or altered sex ratios to suggest enhanced germ cell mutagenicity.[6] CAYA cancer survivors treated with radiotherapy in doses that expose the uterus, are more prone to adverse obstetrical outcomes such as miscarriage (moderate quality evidence), premature birth (high quality evidence), and low birth weight (high quality evidence). Thus high -risk obstetrical surveillance is recommended in such cases. The dose of radiation that exposes CAYA survivors to these risks is not clearly demonstrated. Radiation therapy to uterine-exposed volumes can harm the uterine vasculature, inhibit uterine muscle growth, and perhaps affect endometrial function due to poor blood flow. Poor implantation of the embryo and poor placental growth may hence occur. Miscarriage and fetal growth

restriction results from a reduced uterine elasticity and volume. Additionally, ovarian failure-related hormonal insufficiency may result in decreased uterine volumes. Although preceding radiation may not in and of itself enhance the risk for an elective C-section, these elevated obstetrical risks may affect the decision to perform one. Early initiation of chemotherapy or other cancer treatments in these patients may warrant labor induction or C-section.[13] myometrial fibrosis causes Impaired uterine distensibility and it can be associated with cervical incompetence contributing to the increased risk of pre-term birth.[6] Cardiomyopathy may be the cause of shortness of breath, fatigue and ankle swelling in CAYA cancer survivors.

Cancer survivors do not appear to be at a higher risk for stillbirth as compared to the general population.[14] There is a threefold risk of developing hypertension in pregnancy in survivors of Wilms tumor treated with abdominal radiotherapy.[14] Hyperinsulinemia associated with TBI (Total Body Irradiation) and/or growth hormone (GH) treatment for radiotherapy-related GnRH deficiency may lead to metabolic syndrome and gestational diabetes milletus. Cancer survivors who have undergone cranial or breast irradiation may experience diminished lactation or failure to breastfeed. Breast radiation reduces the irradiated breast's ability to produce milk, while radiation to the head produces HPA (Hypothalamic Pituitary Axis) dysfunction.[6] Abdominal and pelvic radiation has also been linked in several studies to a higher risk of perinatal mortality and postpartum hemorrhage.[6] A study of 232 female colo-rectal cancer patients documented increased rates of antepartum haemorrhage, caesarean delivery, low Apgar score, need for neonatal resuscitation and NICU admission compared to controls. Open but not laparoscopic cancer surgery in these colo-rectal cancer females was associated with increased risk of gastrointestinal obstruction, spontaneous abortion, antepartum haemorrhage, postpartum haemorrhage and prolonged hospital stay >5days.[6] Adverse pregnancy outcomes don't seem to be linked to prior chemotherapy treatment alone.[5] Among cancer survivors, absolute maternal mortality peripartum is still rare.[13] Although more common in these individuals than in the general population, venous thromboembolism cannot be identified as a specific cause of death.[13]

Effect of Pregnancy on Cancer Outcomes[6]

Pregnancy is safe for women who have had a history of breast cancer and has no negative effects on overall survival. Like breast cancer, melanomas are also diagnosed in women of childbearing years. According to a study, there was no statistically significant difference in overall survival between melanoma-diagnosed pregnant women and melanoma-diagnosed non-pregnant controls.

Obstetric Care after Trachelectomy[15,16]

Women with post-trachelectomy pregnancies are more frequently seen in obstetric practice as a result of earlier cervical cancer detection and an increase in the number of women having fertility-preserving surgery.

Contraception: Oral hormone contraceptive users don't seem to have a higher chance of developing cervical cancer. The use of combined hormone methods, subdermal implants and progesterone implants are given UK MEC category 2. The progesterone-only pill (POP) relies on the action of cervical mucus and since the cervix is removed, this action is lost rendering POPs an ineffective contraception. POPs are given MEC 1 category as per UK MEC criteria. Due to the difficulties in identifying the isthmic os and isthmic stenosis, the insertion of an IUCD is technically complex and demands expertise.

Pre-conceptional: Counselling and risk assessment is done for women planning pregnancy. A preventive cerclage is inserted at the remnant cervix following RT (Radical Trachelectomy) to prevent premature deliveries. Multiple pregnancies should be avoided by elective Single Embryo Transfer (eSET) and doing IUI when monofollicular growth is documented on follicular monitoring.

Management of miscarriage in these patients: There is an increased rate of mid-trimester miscarriage (7-11%) and ascending infections and PPROM are the major causes. Expectant care and medical therapy without a surgical intervention should be taken into consideration for an early miscarriage following RT. For individuals who need D&E, the neocervix is dilated to Hegar size 7 (if necessary), preferably under ultrasound guidance, through the isthmic cerclage. When doing a surgical evacuation after a second trimester miscarriage, the cerclage might need to be

removed. Some studies also recommend hysterotomy to avoid lacerating the residual cervix and/or removing the cerclage and the decision is taken keeping the gestational age into consideration.

Antenatal Care and Management: Cervical (isthmic) incompetence, ascending infection, prematurity, PPROM and chorioamnionitis are more frequently observed in pregnancy post RT. A loss of mechanical, cellular, biochemical and immunological barrier in a neo-cervix is a cause. The risk of preterm delivery is around 45%. There is a difficulty in assessment of detection of labor as there is a painless dilatation of neo-cervix.

The frequency of visits can be every two weeks after 18 weeks. Serial isthmic or neo-cervical length scans to monitor isthmic shortening and funnelling is recommended at every antenatal visit (every fortnightly). Expertise is required for assessing the length of the neocervix. If prophylactic cerclage proves to be ineffective, the patients may need to undergo another cerclage depending on the gestational age. Transabdominal approach may be used even in early after first trimester. Urine culture is done at the first visit and later if symptomatic (some suggest doing urine culture in each trimester). Unnecessary cervical digital examination should be avoided. Limitation of activity can be advised. Bed rest is preferably avoided unless there is vaginal bleeding or a suspicion of early threatened labour. Sexual intercourse may be a source of infection; patients may be advised to consider avoiding coitus from 20 weeks onwards. Barrier contraception to be advised to prevent the risk of infection. Elective dental work during pregnancy is avoided to minimise risks of infection and preterm birth resulting from periodontitis. If there are signs of premature labor or if delivery seems impending, antenatal corticosteroids, fetal neuroprotection with magnesium sulphate and tocolysis should be given as per guidelines and protocols. The use of vaginal progesterones is debatable in these patients, but some recommend its use from 12 weeks until 36 weeks. Antibiotics should be started if premature rupture of membranes occurs and deliver as soon as possible.

Cervical cytology should be checked during and after pregnancy to detect recurrence.

Thromboprophylaxis with low-molecular-weight heparin is reserved for women with additional risk factors for venous thromboembolic disease.

Other Antenatal and Perinatal Considerations: The incidence of varices at the site of uterovaginal anastomosis is 14%–24%. It can lead to abnormal bleeding during pregnancy. Hemostasis in this case can be achieved by compression or argon laser. In women who have undergone RT, C-section should be the mode of delivery due to the sutured residual cervix. Care should be taken not to injure the urinary bladder or the uterine artery (if not ligated during RT), as there is an absent or poorly formed lower segment due to distortion following cervical amputation. A classical C-section should be avoided. Cerclage removal is not done at the time of C-section. The elective C- Section should be at 37 weeks or later, but one should be prepared for it any time after 34 weeks. Intra-abdominal adhesions make the surgery technically difficult prolonging the duration of the C-section causing damage to other vital organs. In the postpartum period, lochiometra could be a concern due to narrowing of the cervical canal. There are risks associated with preterm birth and prematurity. Timely administration of antenatal corticosteroids may improve outcomes in preterm neonates.

Obstetrical Care after Breast Cancer[3,17,18,19]

According to studies to date, a subsequent pregnancy is not likely to affect the outcome of the breast cancer, and, equally, a prior diagnosis of breast cancer will not necessarily affect the pregnancy outcome. Tamoxifen has a long half-life; therefore, doctors urge women using it to quit 3 months before trying to get pregnant. To prevent the need for imaging during pregnancy, they should have any necessary regular imaging before attempting to conceive. Given their low life expectancy and potential impact on their ability to receive effective treatment, women with metastatic disease should be counselled against becoming pregnant. Disease recurrence should be ruled out prior to conception. Information about disease recurrence and the necessary treatment should be given to the woman. A multidisciplinary approach is then needed. According to studies, pregnancy does not increase the risk of recurrence, even in hormone receptor-positive

breast cancer. According to a study, the prognosis for pregnant women after breast cancer was comparable to that of the non-pregnant group. The prognosis is good for women with a subsequent pregnancy after early-stage breast cancer. The published series reflect an improvement in treatment over recent decades.

Chemotherapy, radiation therapy, or a combination of these treatments for breast cancer survivors do not raise the incidence of congenital abnormalities, single gene disorders, or chromosomal syndromes in their progeny. Few studies have demonstrated an increase incidence of low birth weight, preterm labor and an increased need of C-sections in these patients. Mothers can breastfeed from the unaffected breast, but due to the damage done by radiotherapy, it is very improbable that this will happen from the irradiated breast.

Pregnancy after Ovarian Cancer[20,21]

Conservative surgery for ovarian cancer should aim to prevent recurrence and it includes complete surgical staging, including pelvic/para-aortic lymph node sampling, multiple peritoneal biopsies, washings, and omentectomy. In one study, the pregnancy rate for patients trying to conceive was 51.7% for those with early-stage ovarian neoplasms who got suitable adjuvant chemotherapy and conservative surgical treatment. Additionally, among women who had documented live births, the obstetric, neonatal, and oncologic outcomes were positive and there was no evidence of any congenital defects in their children.

Normal pregnancy may cause high blood CA125 levels, which typically peak in the first trimester and return to normal range in the second. Thus, it is of limited value for substantiating a recurrence/ follow up during pregnancy. However, fluctuations in CA 125 levels may be of concern. Computed tomography (CT) could not be used as test in pregnancy and ultrasound or an MRI is an alternative evaluation tool. Ascites can develop rapidly at recurrence and relapse. Close examination of accumulation of ascites may lead to early diagnosis of recurrence.

Pregnancy after Endometrial Cancer/ Atypical Endometrial Hyperplasia[22,23]

The treatment for endometrial cancer and atypical endometrial hyperplasia is total hysterectomy. However, fertility preserving treatment may be opted by women with no children. Pregnancy is often encouraged as soon as possible (preferably by ART) after successful treatment of endometrial cancer (after complete remission, CR) for two reasons: there is a protective effect of changes in endogenous estrogen and progesterone during pregnancy, and the duration of response to hormonal therapy may be as low as 12-24 months. Many patients with early-stage endometrial carcinoma have been reported to have achieved successful pregnancies after conservative medical management. Because recurrence after successful fertility-sparing therapy of endometrial cancer is very high, prophylactic hysterectomy is usually performed once patient has given birth to a child. Until now, there are no data regarding how many pregnancies a woman could support after fertility-sparing therapy of early endometrial cancer. In a meta-analysis, the pregnancy rate was 34% in the group treated with progestins only (live birth rate of 20%), 18% in LNG-IUS group (live birth rate of 14%), and 40% in progestin plus LNG-IUS group (live birth rate of 35%). Successful pregnancies may be indicated by a normal BMI, a shorter time to CR, a prolonged three-month treatment, fewer hysteroscopy procedures, and a thicker endometrium, while relapse before pregnancy can negatively impact conception. Moreover, a successful pregnancy protects the endometrium while ART (Assisted Reproductive Techniques) does not increase the risk of recurrence. High hormone levels during pregnancy have the same effects as a highly successful progesterone treatment and it does not accelerate the growth of endometrial lesions. The decidual endometrium is totally exfoliated during birth and the puerperal process; this is analogous to curettage and has a therapeutic impact on endometrial lesions to, at least in some way, prevent relapse. Pregnancy also stops the PCOS induced vicious cycle of estrogen exposure in obese females. However, a follow-up interval of six months should be maintained for routine tumor follow-up during pregnancy. Counselling regarding optimal weight gain in pregnancy and the development of gestational diabetes, pre-eclampsia is important in these survivors.

Conclusion

A personalized preconception consultation and pregnancy surveillance is very helpful for CAYA cancer survivors. Targeted lower body and the uterus

radiation increases the risk of preterm birth and low birthweight, necessitating close monitoring of high-risk pregnancies. It is important to reassure the survivors that there is no elevated risk of congenital abnormalities. The numbers of pregnancies after cancer treatment are limited to produce evidence-based guidelines and further research and data is warranted in this field.

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