Fertility and pregnancy in cancer survivors

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Summary

Cancer survivors are increasing as improvements in cancer diagnosis and treatment translate to improved outcomes. As cancer survivors in their reproductive years contemplate pregnancy, it is important to understand the impact of cancer and its treatment on fertility and pregnancy outcomes. Cancer treatments such as chemotherapy and radiotherapy can affect patients' fertility, and strategies are available to help preserve the future fertility of survivors. The potential impact of previous cancer diagnoses and treatments on pregnancy and maternal and fetal outcomes needs to be assessed and discussed with survivors, with support from materno-fetal medicine specialists and high-risk antenatal services as needed.

Keywords

Oncology, cancer, high-risk pregnancy, materno-fetal medicine

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Introduction

As improvements in cancer diagnosis and treatment translate to improved outcomes, cancer survivors will continue to grow. At current rates, over three-quarters of children diagnosed with cancer will become survivors.¹ Many cancers diagnosed in adolescents and young adults (AYA), such as lymphoma, testicular and breast cancers, are also associated with good survival outcomes.² As these young survivors enter their reproductive years and contemplate pregnancy, it is important to understand the impact of cancer and its treatment on fertility and pregnancy outcomes (Table 1).

Impact of cancer treatment on fertility

Chemotherapy

Female fertility depends upon an intact hypothalamic-pituitary-ovarian axis, adequate ovarian follicle reserve and a normally functioning uterus, all of which may be affected by cancer treatment. Cytotoxic chemotherapy can damage the ovary and accelerate oocyte depletion, causing loss of hormone production and premature menopause.³ Ovarian damage from chemotherapy is related to patient age and ovarian function at the time of treatment, as well as the type, duration and cumulative dose of treatment. Older patients are more susceptible to ovarian damage from chemotherapy, due to smaller pre-treatment follicular reserve.⁴

It is often difficult to determine the toxicity of individual chemotherapy drugs, as most are given in multidrug combinations, often in association with radiotherapy. A cohort study of 10,938 male and female cancer survivors from the Childhood Cancer Survivor Study examined the relationship between 14 chemotherapy drugs and the likelihood of subsequent pregnancy and livebirth rates.⁵ These survivors did not receive cranial or gonadal radiotherapy. Compared to sibling controls, male survivors were 37% less likely to sire a pregnancy, while female survivors were 13% less likely to

become pregnant. Males treated with higher doses of alkylating agents, such as cyclophosphamide, ifosfamide and procarbazine, and DNA crosslinking drugs, such as cisplatin, were less likely to sire a pregnancy. For female survivors, busulfan, high-dose lomustine and high-dose cyclophosphamide were associated with reduced pregnancy rates. Little remains known about the gonadal toxicity of newer chemotherapeutic agents, such as taxanes, or targeted cancer therapies.

Alkylating agents, such as cyclophosphamide and procarbazine, are most likely to affect ovarian function.⁶ In a case control study of 1067 female cancers survivors diagnosed as teenagers, 42% of survivors were menopausal by age 31 compared to 5% of controls, with the relative risk of premature menopause increasing 27-fold in survivors who received both abdominal-pelvic radiotherapy and alkylating agents.⁷ A systematic review found that 21–71% of women aged under 40 who received cyclophosphamide-containing regimens for breast cancer became amenorrhoeic, with rates approaching 100% in older women.⁸ A single-institution study of women under 40 who received chemotherapy for lymphoma found that 31 women fell pregnant, 34 had primary ovarian failure and 19 retained relative fertility after 100 months' median follow-up. Women with ovarian failure were older at diagnosis and more likely to have received high-dose chemotherapy.⁹

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Table 1. Fertility and pregnancy-related problems in cancer survivors and associated cancer treatment factors.

Problem	Mechanism	Cancer treatment risk factors
Fertility-related problems		
Loss of ovarian function	Cytotoxic chemotherapy accelerates oocyte depletion, causing loss of hormone production and premature menopause	Alkylating agents are most likely to affect ovarian function More common in patients with older age at diagnosis and receiving high-dose chemotherapy
	Pelvic radiotherapy or total body irradiation causes accelerated oocyte depletion and premature ovarian failure	More common in patients diagnosed at older ages and receiving higher radiation doses
HPA dysfunction	Cranial irradiation causes HPA dysfunction and hypogonadism through GnRH deficiency	
Pregnancy-related problems		
Metabolic syndrome and GDM	Possibly related to hyperinsulinaemia associated with TBI, and/or growth hormone treatment for radiotherapy-related GnRH deficiency	
Cardiac dysfunction	Anthracycline chemotherapy may cause cardiac dysfunction, which may worsen during pregnancy	Risk of cardiotoxicity increases with higher total cumulative dose of anthracycline
Pre-term delivery and LBW	Uterine irradiation may reduce uterine volume and blood supply	Degree of uterine damage depends on total radiation dose, site of irradiation and patient age
Diminished lactation or failure to lactate	Cranial irradiation causes HPA dysfunction Breast irradiation affects lactational capacity of treated breast	

HPA: hypothalamic-pituitary axis; GnRH: gonadotropin-releasing hormone; GDM: gestational diabetes mellitus; TBI: total body irradiation; LBW: low birth weight.

Radiotherapy

High-dose cranial radiotherapy can cause dysfunction of the hypothalamic-pituitary axis (HPA) and lead to hypogonadism through gonadotropin-releasing hormone (GnRH) deficiency.⁴ Gonadotropin deficiency can result in delayed puberty in children or amenorrhoea in women and can be treated with hormone replacement therapy.³

Gonadal exposure to pelvic radiotherapy or total body irradiation (TBI) can cause accelerated depletion of oocytes and premature ovarian failure. Oocyte depletion after radiotherapy is proportional to the number of primordial follicles at time of treatment (related to patient age) and radiation dose. Ovarian failure has been reported in 90% of women after TBI and up to 97% of women treated with abdominal irradiation as children.³ Furthermore, pelvic radiotherapy can affect uterine volume and function, likely due to damage to uterine vasculature and muscular elasticity. While hormone therapy has been investigated as treatment to improve uterine function, it has not demonstrated effectiveness in achieving normal uterine growth and development.³

Fertility preservation strategies

In vitro fertilisation (IVF) and embryo preservation are well-established treatments for infertility, but challenges are associated with their use in cancer survivors. The time required for IVF cycles may delay cancer treatment, and although newer random-start ovarian stimulation techniques can reduce this time considerably, it remains a prohibitive delay in aggressive malignancies such as acute leukaemia. IVF entails hormonal stimulation to produce mature oocytes, which can theoretically promote the growth of hormone-sensitive cancers. Embryo cryopreservation requires a male partner

to donate sperm. Oocyte cryopreservation is an alternative to embryo freezing, and success rates with this approach are improving.⁴

Orthotopic ovarian transplantation involves excising all or part of an ovary for freezing and subsequent re-grafting after cancer treatment. This strategy minimises delays in commencing treatment, but is associated with risks of laparoscopic surgery, and in rare cases, introduction of recurrent cancer when the ovary is reimplanted.¹⁰ A retrospective series of orthotopic ovarian transplantation in 74 women reported pregnancies in 28% and deliveries in 23% of patients. Success rates were higher in women who were younger at the time of cryopreservation.¹¹

Another surgical procedure for fertility preservation in women undergoing radiotherapy is oophoropexy, which refers to surgical transposition of ovaries outside a pelvic radiation field. This has resulted in successful pregnancies when performed in girls and young women before treatment for Hodgkin lymphoma.¹² In premenopausal women who underwent oophoropexy before surgery and radiotherapy for gynaecological cancers, ovarian function was preserved in 65%, as assessed by patients' symptoms and serum hormone levels.¹³

Gonadal shielding can be used to reduce scatter radiation to both male and female reproductive organs but is only possible with selected radiation fields and anatomy.⁴ Case reports have described ovarian function preservation in women who underwent ovarian shielding during TBI for stem cell transplantation.¹⁴

GnRH agonists and antagonists have been utilised to protect ovarian function during chemotherapy. These agents may act by suppressing gonadotrophin levels to prevent primordial follicles from maturing and becoming vulnerable to chemotherapy; decreasing utero-ovarian perfusion to reduce ovarian exposure to chemotherapy; directly activating GnRH receptors on ovaries and protecting undifferentiated germline stem cells.¹⁵ A meta-analysis of randomised, controlled

trials investigated whether the use of luteinising hormone-releasing hormone agonists (LHRH) agonists during chemotherapy affected subsequent fertility in premenopausal breast cancer patients. LHRH agonists were found to be associated with significantly reduced risk of premature ovarian failure (OR 0.36, $p < 0.001$), lower rates of amenorrhoea at one year (OR 0.55, $p < 0.001$) and higher rates of pregnancy (OR 1.83, $p = 0.041$).¹⁶ These findings should be interpreted with caution, however, as studies could not control for desired or attempted pregnancy and duration of follow-up is limited. At present, ovarian suppression cannot be endorsed as a replacement for other fertility preservation strategies.

Despite the availability of fertility preservation strategies, their uptake may be suboptimal. A systematic review of care experiences of AYA cancer patients found variability in how often clinicians discussed fertility-related issues, with most young people receiving insufficient information about fertility preservation options or the impact of treatment on fertility.¹⁷ Possible barriers to adequate discussion include unfamiliarity and inexperience of clinicians around this topic and embarrassment discussing reproductive issues.¹⁸ To ensure that all patients have equitable access to fertility preservation, cancer clinicians must be equipped to routinely and comfortably discuss fertility issues with patients and to facilitate referral to fertility specialists. In Australasia, this imperative has been formalised in the Australasian Oncofertility Consortium Charter.¹⁹

Planning pregnancy after cancer

Assessing fertility after cancer treatment

In women, amenorrhoea due to premature ovarian failure clinically reflects depleted ovarian follicles. This can be confirmed with biochemical assessments of ovarian reserve such as follicle-stimulating hormone (FSH) or anti-Müllerian hormone (AMH). FSH levels reflect function in mature follicles, and women with impaired fertility often have elevated FSH in early follicular phase, despite healthy ovulatory cycles.¹ AMH is a hormone produced by granulosa cells of pre-antral and small antral follicles. Serum AMH correlates with age and ovarian follicular reserve and is a more reliable indicator of ovarian reserve than FSH.^{1,4}

Contraception

Women with preserved fertility after cancer treatment need to make informed decisions regarding contraception, in order to avoid or delay pregnancies until appropriate times. Hormonal contraception is not routinely recommended in women with a history of hormone receptor-positive breast cancer, in light of accumulating evidence of increased breast cancer risk associated with long-term hormonal contraception use.²⁰ Copper intrauterine devices are a highly effective, reversible, long-acting, hormone-free method that should be considered a first-line contraceptive option for women with previous hormone-sensitive cancers.²¹ However, cancer survivors are less likely to use effective contraception than the general population and are therefore at risk for unintended pregnancy, signifying an area in need of better education and counselling in survivorship care.²²

Family cancer syndromes and pregnancy

Improved understanding of family cancer syndromes has led to the identification of a number of germline genetic mutations that increase the risk of developing certain cancers and may be passed onto offspring. The most common and well-known of these include mutations affecting the BRCA1 and BRCA2 genes that increase the risk of breast and ovarian cancer, and mismatch repair genes

(MLH1, MLH2, MSH6, PMS2) that increase the risk of colorectal and endometrial cancer. All male and female cancer survivors who are confirmed to have a family cancer syndrome caused by an identified genetic mutation should receive genetic counselling, as IVF and pre-implantation screening can be offered to prevent the transmission of the pathogenic mutation to future offspring.

Impact of cancer treatment on pregnancy

Antenatal period

There are inconclusive data regarding whether previous cancer diagnoses and treatment are associated with higher rates of complications during pregnancy. A retrospective cohort study of 1989 female childhood cancer survivors found similar rates of maternal diabetes, pre-eclampsia and anaemia in the survivor population compared to 14,278 matched controls.²³

Long-term follow-up of patients from the National Wilms Tumour Studies reported that increasing dose of flank radiotherapy in female patients was associated with higher rates of pregnancy-associated hypertension, including pre-eclampsia.²⁴ Higher rates of pre-eclampsia and gestational diabetes mellitus (GDM) were noted in a population-based cohort study of 1894 women previously diagnosed with AYA cancers.²⁵ However, the association between radiotherapy and hypertension has not been consistently found in other studies of childhood cancer survivors.²⁶

Cancer survivors are at increased risk of metabolic syndrome, and female survivors of AYA cancer have higher rates of GDM than the general population. Increased risk of GDM appears to be associated with greater age at cancer diagnosis, chemoradiotherapy, tumours arising in the abdominal-pelvic region and certain diagnoses (e.g. central nervous system tumours and bone sarcomas).²⁵ The mechanism behind this increased GDM risk is unclear, but may be related to hyperinsulinaemia associated with TBI, growth hormone deficiency and subsequent growth hormone treatment after cranial irradiation, and treatment sequelae leading to decreased immune function and weight gain.^{25,27}

Anthracyclines are a class of chemotherapy drugs typically used to treat sarcoma, breast and haematological malignancies. They are commonly associated with cardiotoxicity, which can present years after treatment. This is concerning due to the theoretical risk of cardiac decompensation in pregnancy. Although no safe dose has been established, higher total cumulative dose of anthracyclines is associated with increasing risk of cardiotoxicity.³ In a case series of women treated with anthracyclines in childhood, those with normal baseline cardiac function (defined as left ventricular systolic function $\geq 30\%$) had no change in cardiac function after delivery. However, those with impaired pre-pregnancy cardiac function had a non-significant deterioration in cardiac function on echocardiography and worse pregnancy outcomes, including more maternal and neonatal intensive care admissions, longer hospital stays and more induction of labour.²⁸ A cohort study investigated the incidence of clinical heart failure, defined as congestive heart failure with signs and/or symptoms requiring treatment, in women who became pregnant after treatment with anthracyclines. None of the women in this cohort developed anthracycline-induced clinical heart failure.²⁹ These data suggest that in general, women treated with anthracyclines are not at significant risk of developing clinically significant peri-partum heart failure, but those with cardiac dysfunction prior to pregnancy are at risk of adverse pregnancy outcomes and further deterioration in cardiac function.

Maternal and neonatal outcomes

A number of studies have investigated the effect of previous cancer therapy on pregnancy outcomes. Several cohort studies demonstrated no significant difference in the rate of congenital or chromosomal abnormalities in children of female childhood cancer survivors compared to controls.^{24,26,30,31} Furthermore, there is no increased risk of malformations or altered sex ratios in the first livebirths of female survivors of childhood and AYA malignancies to suggest increased germ cell mutagenicity.^{23,25}

The evidence for the association between miscarriage or spontaneous abortion and cancer treatment is mixed and varies with different patient cohorts and cancer treatments. A Canadian cohort study of 830 female childhood cancer survivors who received abdominal-pelvic radiotherapy and/or alkylating agents did not find an increased risk of spontaneous abortion.³⁰ However, the Childhood Cancer Survival Study, which reported on the outcomes of 4029 pregnancies in 1915 females, found non-statistically significant increases in miscarriage risk in patients whose ovaries were in the radiation field (RR: 1.86, $p=0.14$) or near the radiation field (RR: 1.64, $p=0.06$). This study also reported higher miscarriage rates in patients who received cranial irradiation (RR: 1.4) and craniospinal irradiation (RR: 2.22) compared to patients who received no radiotherapy.³² The British Childhood Cancer Survivor Study reported a marginal association between increased risk of miscarriage and abdominal irradiation (OR: 1.4, 95% CI: 1.0–1.9) based on questionnaires administered to 10,483 survivors with 7300 reported pregnancies.³³

Abdominal and pelvic radiotherapy for childhood cancer is consistently associated with increased risk of pre-term delivery and low birth weight (LBW) <2500 g, with odds ratios of up to 3.5 for pre-term delivery and 6.8 for LBW.^{23,24,26,30,32–34} The proposed mechanism for these findings is that childhood uterine irradiation leads to reduced adult uterine volume and blood supply, which may restrict fetal growth and the ability to carry pregnancies to term.³³ The degree of damage depends on total radiation dose, site of irradiation and patient age at time of treatment, with the prepubertal uterus possibly more vulnerable to the effects of irradiation.³⁵ Impaired uterine distensibility due to myometrial fibrosis can be associated with cervical incompetence, which may also contribute to the increased risk of pre-term birth.³ In some studies, abdominal and pelvic irradiation has also been associated with increased risk of perinatal death and post-partum haemorrhage.^{26,30}

On the other hand, there are few data suggesting that chemotherapy is associated with adverse pregnancy outcomes. A single-centre study of 40 patients in the Netherlands reported no difference in maternal or neonatal outcomes in women treated with chemotherapy, compared to controls.²⁶ In the Childhood Cancer Survival Study, the livebirth rate was not lower for patients treated with any particular chemotherapeutic agent.³² A study of female colorectal cancer (CRC) survivors showed a marginal association between chemotherapy and adverse maternal outcomes, and no evidence of a link between chemotherapy and adverse neonatal outcomes.³⁶

While the majority of data regarding pregnancy and birth outcomes after cancer treatment is based on follow-up of childhood cancer survivors, two population-based cohort studies from Western Australia report on outcomes in adult and young adult populations. One of these studies identified 1894 women who were diagnosed with cancer between ages 15–39 and subsequently completed a pregnancy ≥ 20 weeks. Compared to controls, cancer survivors had higher rates of threatened abortion (<20 weeks), caesarean delivery, premature birth 20–36 weeks, LBW <2500 g, neonatal distress indicated by low Apgar score at 1 min, neonatal resuscitation and neonatal intensive care (NIC) admission. However, there was no increase in rates of congenital abnormalities, perinatal deaths, antepartum haemorrhage, premature rupture of membranes or failure of labour to progress.²⁵ A study of 232 female CRC patients again

illustrated increased rates of antepartum haemorrhage, caesarean delivery, low Apgar score, need for neonatal resuscitation and NIC admission compared to controls. Open but not laparoscopic cancer surgery was associated with increased risk of gastrointestinal obstruction, spontaneous abortion, antepartum haemorrhage, postpartum haemorrhage and prolonged hospital stay >5 days.³⁶

Breastfeeding

For women who carry successful pregnancies after cancer treatment, breastfeeding may be affected by previous radiotherapy. In a retrospective review of female survivors treated with prophylactic cranial irradiation for acute lymphoblastic leukaemia in childhood, the majority (83%) of survivors with offspring reported minimal or no breast changes during pregnancy, and failure to lactate postpartum. This failure to lactate is likely related to deficiencies in the hypothalamic-pituitary-ovarian axis resulting from cranial irradiation.³⁷

Whole breast radiotherapy is standard of care for women who undergo limited surgery (wide local excision or ‘lumpectomy’) as curative treatment for early breast cancer. A case series based on a survey of clinicians reported that 34% of women who became pregnant after surgery and radiotherapy lactated from the irradiated breast and 24.5% were able to breastfeed successfully.³⁸ In a retrospective study of premenopausal women who underwent breast-conserving surgery and radiotherapy, lactation occurred in 10 of 17 women. While volume was significantly diminished in 80% of the treated breasts, lactation occurred in the contralateral breast of all patients.³⁹

Effect of pregnancy on cancer outcomes

The decision to fall pregnant is a difficult one for women with preserved fertility after cancer treatment, as they must weigh up the relative risks of cancer recurrence with the likelihood that their reproductive years have been shortened by cancer treatment. Pregnancy is a particularly complex issue for women diagnosed with breast cancer before completing their families, as the risk of recurrence in hormone receptor positive breast cancer can extend for a decade or longer after diagnosis, and treatment protocols now entail up to 10 years of extended adjuvant hormonal therapy.⁴⁰ There are fears that hormonal changes associated with pregnancy may increase the risk of breast cancer recurrence and compromise patients’ long-term survival.^{41,42} To address this question, Azim et al. conducted a meta-analysis of 14 studies examining the impact of pregnancy on the overall survival of women with history of breast cancer.⁴¹ Women who became pregnant following breast cancer diagnosis had a 41% reduced risk of death compared to women who did not become pregnant. Subgroup analysis revealed no difference in survival between women who became pregnant and those who were not pregnant and relapse-free. This suggests a selection bias whereby women who remained well and relapse-free were more likely to choose to become pregnant.⁴¹ Nevertheless, this information is reassuring in providing evidence that pregnancy in women with previous breast cancer is safe and does not compromise overall survival.

Like breast cancer, melanomas are not uncommonly diagnosed in women of childbearing years. There have been concerns that hormonal changes during pregnancy may influence melanoma outcomes. Historically, studies have reported that women diagnosed with melanoma during pregnancy had poorer survival than non-pregnant women diagnosed with melanoma.⁴³ However, a recent registry-based cohort study of Swedish women showed no statistically significant difference in overall survival between 185 pregnant women diagnosed with melanoma and 5348 age-matched non-pregnant controls diagnosed with melanoma.⁴⁴

Conclusion

While cancer treatment may disrupt patients' gonadal function, strategies are available to help preserve the future fertility of survivors. As the number of survivors with preserved fertility increases, they should be counselled on the safety of pregnancy with respect to congenital abnormalities and cancer outcomes, as well as areas of increased risk such preterm delivery after abdominal-pelvic radiotherapy. More research is required in pregnancy and birth outcomes of survivors diagnosed and treated as adults, as most data are based on follow-up of childhood cancer survivors. While there are guidelines regarding processes for fertility preservation, currently no guidelines exist delineating how best to manage cancer survivors who fall pregnant. It is important to comprehensively assess these patients' cancer diagnosis, treatment history and associated risks. Due to the potential complexity of some patients' care needs, they should be reviewed by materno-fetal medicine specialists and managed in high-risk antenatal services as appropriate.

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