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Review

Pregnancy following treatment for malignancy

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Key content

- Increasing numbers of women are surviving cancer in childhood or early adulthood.
- Treatments for malignancy can cause long-term damage to a number of organs; this is frequently unappreciated by both patients and obstetricians.
- Pregnancy in women who have been exposed to treatments for cancer can be potentially problematic but most have a good outcome.
- A good understanding and initial assessment optimises the outcome for this group of women.

Learning objectives

- To understand the implications of previous cancer treatments.
- To be able to plan management for this group of women in pregnancy.

Ethical issues

- Should young survivors of malignancy be given improved information on the potential deleterious effects that their, often life-saving, treatment has had on other body systems?
- Should all female survivors of malignancy be offered routine prepregnancy counselling?

Keywords: cancer / chemotherapy / pregnancy / radiotherapy

Linked resource: Single best answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

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Introduction

There are estimated to be over 2 million survivors of cancer in the UK, and 33 000 survivors of childhood cancer; these numbers are likely to increase over the next few years.[1–3] Increasingly, women are presenting to obstetric services with a history of childhood cancer or, with advancing maternal age, of cancer in early adulthood (Figure 1).[4] The obstetric literature about previous malignancy predominantly concentrates on fertility issues following cancer therapies and on fertility-sparing surgery for gynaecological cancers, but provides little information on caring for women who undergo pregnancy with a distant history of cancer treatment.

Survivorship programmes

The overall goal of cancer treatments is to cure or control the cancer as far as possible. As increasing numbers of people are surviving cancer, the short- and long-term impact of a cancer diagnosis and its treatment is becoming clearer.

Survivorship programmes plan to address some of these issues. They aim to minimise the adverse effects of cancer treatments, inform patients about likely consequences, monitor and assess those living beyond cancer for further problems, and provide support.[3] Much of the work on survivorship programmes in the UK has developed from the National Cancer Survivorship Initiative.[1]

Many cancer survivors are unaware of the long-term consequences associated with their treatments or even which treatments they have had. The advent of 'end of treatment summary care plans' recommended by survivorship programmes should alleviate this; however, in the interim, a degree of 'guess work' relating to likely treatment used is necessary.

Treatments for malignancy and potential long-term consequences

Cancer therapies include surgery, radiotherapy, chemotherapy, biological therapy and hormone therapy. Depending on the cancer type, these can be used individually or for combination therapy. The destruction of healthy cells is a necessary by-product of these treatments. To address this, there is a continued emphasis on developing more targeted therapies that eradicate cancerous cells while sparing noncancerous ones; however, no current treatments can avoid damaging some healthy tissues.

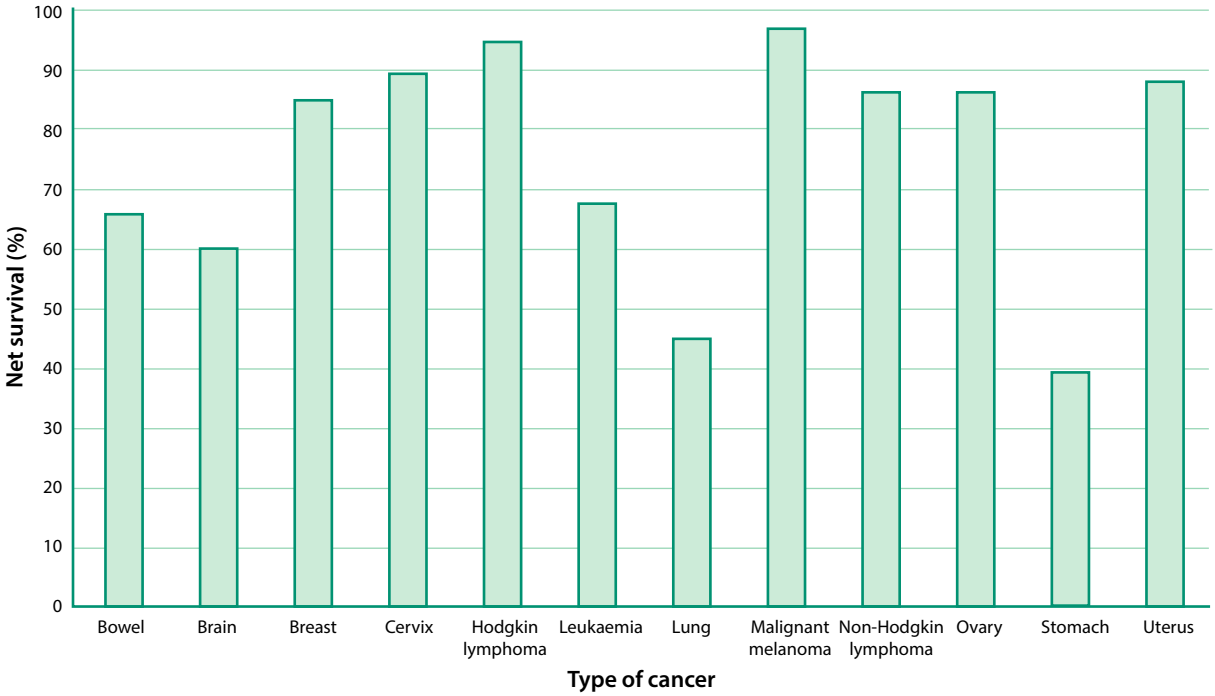

Figure 1. Five-year net survival for cancer diagnosed at age 15–39 years, 2007–2011. Adapted from Cancer Research UK.[4]

There is increasing awareness of the long-term consequences of cancer therapies; however, there remains a paucity of data in this area and certainly a lack of awareness by health professionals.[3] Long-term cohort studies, such as the North American Childhood Cancers Survivors Study[5,6] (CCSS) and The British Childhood Cancer Survivor Study[7] are beginning to fill this gap with long-term outcome data, albeit retrospective.[5] The CCSS is a retrospective cohort study looking at the outcome of 13 581 survivors of childhood cancers (leukaemia, central nervous system tumour, Hodgkin's disease, non-Hodgkin's lymphoma, Wilms' tumour, neuroblastoma, soft tissue sarcoma or bone tumour) diagnosed between 1970 and 1986 and comparing them with a cohort of siblings.[5,6] The British study is a similar large scale population-based cohort study following 17 981 survivors of childhood cancer diagnosed between 1940 and 1991.[7,8] Both survivor studies involved the completion of a questionnaire by the participants. These studies currently provide the best sources of observational data to counsel patients. However, current treatment regimens for cancer now include newer agents and biological therapies, the long-term effects of which are not as well studied.

Long-term consequences of cancer therapy can occur soon after treatment or can develop many years later. Physical consequences of cancer treatments range from symptoms affecting daily quality of life (for example, effects on bowel or urinary function), risks of long-term organ dysfunction or a second cancer. The CCSS has shown that survivors of childhood cancer are 3.3 times more likely to suffer with at least one chronic health condition compared with their siblings (95% CI 3.0–3.5).[6] In this study, 62.3% had at least one chronic medical condition.

Late consequences of cancer treatments relate more to the specific treatments used rather than the index cancer itself. Cancers such as Wilms' tumours that are treated with surgery alone are unlikely to produce clinically significant long-term consequences, whereas the risk is much higher with cancers requiring combined treatment with radiotherapy and chemotherapy and in those patients who have undergone bone marrow transplantation as part of their treatment for cancer.

Impact on maternal health

Long-term consequences of treatments for malignancy which may have particular relevance for obstetrics include the effects on cardiovascular, endocrine and respiratory function. Table 1 summarises the long-term consequences of chemotherapy agents, and Table 2 summarises the long-term effects of radiotherapy.

Cardiovascular

Many cancer therapies are known to have a long-term impact on cardiac function. In the CCSS cohort, cancer survivors were significantly more likely to report congestive heart

Table 1. Potential long-term consequences of chemotherapy agents

Drug class	Type of cancer	Potential long-term consequences
Anthracyclines	Haematological and breast malignancies	Cardiac dysfunction
Fluorouracil (5FU)		Cardiac
Taxanes	Breast cancer	Cardiac
Alklyating agents	Haematological malignancies	Diabetes
L-asparaginase	Acute lymphocytic leukaemia	Diabetes
Bleomycin	Hodgkin's lymphoma	Respiratory

Table 2. Potential long-term consequences of radiotherapy

Site of radiotherapy	Type of cancer	Potential long-term consequences
Cranial	Brain malignancies	Hypo-pituitary effects including growth hormone, thyroid
Neck	Thyroid cancer, Hodgkin's lymphoma	Thyroid dysfunction
Medistinum/ chest	Hodgkin's lymphoma, breast cancer	Cardiac and respiratory effects
Abdominal	Neuroblastoma, Wilms' tumour	Diabetes
Total body	Pre-bone marrow transplantation for leukaemia	All effects as above but at lower rates

failure, myocardial infarction, pericardial disease and valvular abnormalities than their siblings.[5] Similarly, in women followed-up after breast cancer, a higher incidence of heart failure and coronary artery disease has been reported.[3]

Anthracyclines have some of the strongest association with long-term cardiac consequences. Anthracyclines are used in the treatment of a variety of childhood tumours and those that can occur in early adulthood, such as haematological malignancies and breast tumours.[9] It is estimated that approximately 50% of childhood cancers were treated with anthracyclines between 1974 and 1990.[10] These patients are now of reproductive age.

Anthracyclines cause a dose-dependent decline in ejection fraction, which can result in a dilated cardiomyopathy, the pathophysiology of which is uncertain. The damage is felt to occur at the time of exposure but, most commonly, does not manifest until years after initial treatment. Cardiac sequelae are potentiated by mediastinal radiotherapy and other chemotherapy agents.[9,10] Asymptomatic anthracycline-induced cardiac dysfunction is described in up to 57% of those treated with the agents.[11]

While the effects of anthracyclines on cardiac function are the most well known, other chemotherapy agents have been associated with myocarditis, coronary artery disease, pericarditis, prolonged QT interval and other rhythm disturbances.[9] In addition, radiotherapy is associated with pericardial disease (pericardial effusions and pericarditis), coronary artery disease, valvular disease and cardiomyopathy.[10] Cardiac effects have also been reported with biologic agents used in the treatment of breast and haematological malignancies.[9,12]

Although some guidelines for monitoring those with exposure to potentially cardiotoxic therapies exist, such as those from the Scottish Intercollegiate Guidelines Network (SIGN), there is no consensus for frequency or mode of surveillance.[2,9,10]

Pregnancy is known to challenge the cardiovascular system with changes in cardiac output that can cause decompensation in women with established heart disease.[13] Case reports have described both dilated cardiomyopathy in pregnancy and peripartum cardiomyopathy in women previously treated with doxorubicin.[14,15] In a case series of 37 pregnant women with a history of treatment with doxorubicin in childhood, there were three admissions with cardiac deterioration in pregnancy involving two women (one woman was admitted with deterioration in both of her pregnancies).[16] In this study, there was a trend towards worsening fractional shortening on echocardiograms in those women who already had fractional shortening less than 30% before pregnancy, but this was not significant.[16] A Dutch study looked at 53 women treated at one centre with anthracyclines in childhood who went on to have a pregnancy. In this group, none of the women developed clinical heart failure; however, surveillance with echocardiograms was not routine practice so it is not possible to assess asymptomatic cardiac dysfunction.[17] Although they provide some reassurance, these studies are too small to be able to assess whether there is an increase in peripartum cardiomyopathy in women previously treated with anthracyclines.

In its long-term follow-up of survivors of childhood cancer guideline, SIGN provides one of the few recommendations for assessing cardiac damage in relation to pregnancy.[2] It recommends regular echocardiographical screening for those exposed to anthracyclines or who have received radiation to a field that includes the heart. For women who are pregnant or planning pregnancy, this does not need to be repeated if the woman has had a normal echocardiogram within the last 3 years.[2] Similarly, the Royal College of Obstetricians and Gynaecologists Green-top Guideline *Pregnancy and Breast Cancer* advises that women whose breast cancer was treated with adjuvant chemotherapy with anthracyclines should have

an echocardiogram to assess ejection fraction and fractional shortening in pregnancy; the impact of radiotherapy is not discussed.[18]

Endocrine

Endocrine dysfunction is one of the most common long-term consequences of cancer treatment.[19,20] The effects can be attributable to direct damage to the endocrine organ or secondary to effects on the pituitary axis. Both chemotherapy and radiotherapy are implicated and, like cardiotoxicity, effects are often most significant when both chemotherapy and radiotherapy have been used. The hypothalamus is particularly sensitive to the effects of radiation. Survivors of childhood cancers are more likely to develop endocrine consequences of treatment compared with those treated for cancer as an adult.[19]

Thyroid dysfunction can be seen following radiotherapy to the neck or the cranium and can occur a number of years after treatment. It has been estimated that 20–30% of those with neck irradiation will develop thyroid dysfunction.[19] Chemotherapy and bone marrow transplantation are additional risk factors. In the British Childhood Cancer Survivor Study, 7.7% reported hypothyroidism.[20] Those at highest risk were survivors of Hodgkin's disease (19.9%) and central nervous system tumours (15.3%). The use of radiotherapy to treat Hodgkin's lymphoma or central nervous system tumours was significantly associated with subsequent thyroid dysfunction.

The SIGN guideline for the long-term follow-up of survivors of childhood cancer recommends annual thyroid function tests for survivors of childhood cancer who have received radiotherapy to the neck, spine or brain.[2]

The impact of thyroid dysfunction on reproductive health is well described.[21] As such, although no formal guidelines exist for antenatal screening for thyroid dysfunction in women with a history of malignancy, it would seem prudent to offer this to women at high risk, especially those women with a history of neck or cranial irradiation. Thyroid function tests should be interpreted cautiously. Primary hypothyroidism can be diagnosed by raised thyroid stimulating hormone; however, with secondary (central) hypothyroidism, the thyroid stimulating hormone level will be low or normal with inappropriately low free T4 levels.

Although not as frequent a problem as thyroid dysfunction in cancer survivors, diabetes and the metabolic syndrome are also seen more often than in the background population. The cause is felt to be multifactorial and risk appears to be greatest after cranial, abdominal or total body irradiation and the use of alkylating agents.[22] In the CCSS, survivors were 1.8 times more likely than the sibling group to report diabetes (95% CI 1.3–2.5, $P<0.001$).[22] This effect is independent of obesity. Given that this can occur a number of years after treatment, it may be that diabetes would be first detected in pregnancy. There are no data on whether the risk of gestational diabetes is higher and no recommendations on screening this group. However, consideration should be given to additional screening for gestational diabetes in women with a history of cranial, abdomen or total body irradiation and to those treated with alkylating agents. For example, in the UK, where glucose tolerance tests are not universally recommended, it may be prudent to consider offering them to this group of women.

Other endocrine consequences of treatments for malignancy include hypopituitarism, growth hormone deficiency and syndrome of inappropriate anti-diuretic hormone deficiency. Effects on reproductive hormones will impact on the ability to conceive rather than ongoing management in pregnancy.

Effects on bone mineral density are also long-term medical consequences of cancer treatment; this is unlikely to have great significance within the obstetric population.

Respiratory

A number of chemotherapeutic agents, including bleomycin (commonly used in the treatment of Hodgkin's lymphoma), are associated with subsequent pulmonary disease, such as pneumonitis, recurrent pneumonia and pulmonary fibrosis; often this will be symptomatic but subclinical pulmonary fibrosis can also occur. Radiotherapy to the chest and total body irradiation are also implicated in pulmonary disease. Pulmonary function tests may help in detecting women who may be at risk of respiratory compromise and the authors would recommend them in pregnancy to all women who have been treated with bleomycin in the past. In the CCSS, there was a (self) reported 3.5% cumulative incidence of lung fibrosis 20 years post initial cancer diagnosis.[23] In contrast, a much higher incidence was found in a Dutch cohort study of 220 childhood cancer survivors; 44% had a pulmonary function impairment on pulmonary function testing.[24]

Thrombotic risks

There is a well-described association between venous thrombosis and malignancy and, therefore, many women with a previous history of malignancy will also have had a venous thrombotic event. If there is a previous history of venous thrombotic events, consideration needs to be given to the risk of recurrent thrombosis during pregnancy and these women require careful risk assessment by an obstetric haematologist. While the risk of malignancy has been removed, these women may still require thromboprophylaxis with heparin, depending on their individual risk assessment.

Recurrence or secondary malignancy

Women are often concerned about the risk of recurrence of malignancy in pregnancy, especially when cancer treatment is relatively recent. Advice is often given to defer pregnancy

until after the highest risk of recurrence, for example, with breast cancer a wait of 2 years after treatment is recommended.[18] Women should be reassured that, in the unlikely event of a recurrence, many treatments can be safely used in pregnancy.

Survivors of childhood cancer are at risk of a secondary malignancy as a result of the treatment they have received. This risk is associated with both the use of radiotherapy and chemotherapy. Subsequent cancers can occur in any location.[2] Women should be advised to have a low threshold for reporting new symptoms and medical professionals for instigating investigation in this instance.

Other effects

The management of many malignancies often involves blood and/or platelet transfusion support. Complications from this include infection with blood-borne viruses and the development of red cell antibodies. All women are routinely screened for red cell antibodies and blood-borne infections in pregnancy; women who have been previously transfused should be counselled that their risk of these is slightly higher. If red cell antibodies are present, a discussion regarding the risk of developing haemolytic disease of the newborn is required and the antibodies should be followed-up as recommended by national guidance, including referral to fetal care units if clinically indicated.[25]

Women who have undergone allogeneic bone marrow transplantation (haematopoetic stem cell transplantation) as part of their treatment for malignancy have often received very high doses of chemotherapy and in some cases total body irradiation. The long-term complications of this will vary depending on the treatment regimen used but the impact on maternal health includes all of the complications previously described. Chronic graft versus host disease (cGVHD) is an immunoregulatory disorder that shares features of autoimmunity and immunodeficiency and is a particular long-term complication of allogeneic haematopoetic stem cell transplantation. It occurs in 40–50% of related allografts and up to 70% of matched unrelated transplants.[26] Although cGVHD can occur at any site or in any organ, the most frequently affected are skin, nails, mouth, eyes, female genitalia, gastrointestinal tract, liver, lungs, muscles, fascia and joints. Disease can be localised but in some cases is widespread, causing significantly debilitating symptoms.

Impact on obstetric outcomes

Over 8000 pregnancies in women who are survivors of childhood cancer are reported in the British and US survivorships studies.[8,27] Together with smaller observational studies, these have provided relatively reassuring data on pregnancy outcomes in the majority of women previously treated for malignancy.

Congenital anomalies

Cohort studies have consistently shown no association between parental cancer treatment and an increased rate of congenital anomalies.[16,28–30] In a Danish cohort of 3963 childhood cancer survivors (male and female), the prevalence of congenital anomalies in their children was not significantly different to those of their siblings (odds ratio 1.1, 95% CI 0.8–1.5).[30] Similar findings were seen in the CCSS data with an overall prevalence of congenital anomalies of 2.7% (similar to US population estimates of 3%).[29] Subgroup analyses of women by cancer type or treatment did not alter this finding.

Miscarriage, intrauterine growth restriction, prematurity and stillbirth

Miscarriage rates were increased in both the CCSS and the British Childhood Cancer Survivorship Study in women who had had pelvic radiotherapy (odds ratio 1.4 and 1.65, respectively).[8,27] It has been postulated that cranial radiotherapy could also increase the risk of miscarriage by interfering with the hypothalamic-pituitary axis; however, cohort studies have not found this to be a consistent finding.[8,27]

Considering growth restriction and prematurity, one retrospective cohort study using cancer and state birth records of 1898 survivors of childhood and adolescent cancer in the US identified a higher risk of prematurity (14–15% delivered before 37 weeks of gestation) but no association with small-for-gestational-age babies.[28] Both chemotherapy and radiotherapy were associated with an increased risk of prematurity. In the CCSS, again an association with prematurity but not small-for-gestational-age babies was seen but this appeared to be limited to women who had been treated with abdomino-pelvic radiotherapy.[31] In those women with the highest dose of radiotherapy to the uterus (>500 cGy), a significant association with small-for-gestational-age babies was seen. In the British Childhood Cancer Survivorship Study, an association with both prematurity and small-for-gestational-age was seen in cancer survivors, again this was limited to women who had been treated with abdomino-pelvic radiotherapy.[8]

Stillbirth rates do not appear significantly raised compared with the sibling groups used in cohort studies except, again, where women have received high-dose radiotherapy to a field involving the pelvic organs; in these women, stillbirth rates were significantly higher when radiotherapy was given before the menarche.[32]

Heritable cancer conditions

Some malignancies, such as those associated with the *BRCA* gene, are heritable. Appropriate genetic counselling should be offered in these cases.

Pregnancy plans

Pregnant women with a history of treatment for cancer in the past should be referred for consultant-led care. A detailed history should be taken, including the nature of the index malignancy, treatment given for this and any known long-term consequences of treatment she has already developed. It may well be that she is unsure of the exact nature of treatment; if so, and if further details cannot be obtained, a presumption may need to be made about the most likely treatment given for the particular malignancy involved. Baseline investigations will be guided by the history, but consideration should be given as to whether echocardiogram, thyroid function tests, a glucose tolerance test or respiratory function tests are needed.

Women should be advised about the slight increased risk of preterm birth and to present early if any symptoms of this occur. They can be reassured that the risk of congenital anomaly is not greater than in the general population. For women with a history of abdomino-pelvic radiotherapy or who have developed secondary medical conditions, growth scans may be appropriate.

An assessment of peripheral veins should be made because some women who have had extensive cancer treatment may have poor peripheral vasculature. Anaesthetic referral should be made in these cases and in cases where cancer treatments have been complicated by thrombosis or the development of red cell antibodies.

The future

As developments in oncology continue, it is likely that we will see an increasing number of women with a history of cancer within obstetric services. With the emphasis on survivorship programmes, women should be better informed about the treatment they have had and the consequences of this. Hopefully not only will there be improved evidence on caring for these women in pregnancy, but clinicians will also be more aware of the issues surrounding care.

Conclusion

The majority of women who present to obstetric services with a history of cancer will have a good pregnancy outcome. A thorough initial assessment and pregnancy plan will ensure that any consequences of their cancer treatment are addressed.

Contribution to authorship

SW initiated the proposal. Both SW and GS contributed to the literature search, drafting, revision and final approval of the article.

Disclosure of interests

The authors have no conflicts of interest to declare.

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