Late reproductive effects of cancer treatment in children, young cancer survivors

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Abstract

The diagnosis of cancer in children, adolescents and young adults creates specific reproductive challenges for the patients and their families. Reproductive concerns range from perceived or actual alteration of body image to fulfilment of reproductive aspirations. Reproductive counselling is widely held to be a crucial component of pre-treatment work up, yet few patients actually receive these services. Hormone replacement therapy, although widely available, effective and beneficial, poses specific challenges in this group owing to their younger ages. Measures of ovarian reserve are reliable; however they are accessed by few and are not predictive of achieving a live birth. Only patients linked to reproductive services could benefit from the array of fertility preserving options available. Patients exposed to abdominal and pelvic radiotherapy can face further complications even after successful conception. Attendant psychological impacts, relating to genetic, structural and developmental effects on the off spring, warrant specific focus in counselling.

Keywords cancer survivors; chemotherapy; radiotherapy; reproductive and counselling

Introduction

Recent years have witnessed an increasing focus on the sexual and reproductive issues facing children, adolescents and young adults who have survived cancer and it is envisaged that this trend will continue. This category of patients has distinct reproductive health needs that require deliberate attention. In general, young people spend their adolescence forming and affirming their identity; sexual debut, romantic relationships, plans for marriage and having children are the norm. Among the patients with a previous cancer, the significant disruption caused by their experience means that survival and normality are the main concerns; normal milestones may be delayed or not achieved. Since its foundation in 1990, the Teenage Cancer Trust UK has provided valuable support for patients, carers and healthcare staff and remains a reliable medium for support and expertise.

It is pertinent that reproductive health and oncofertility form an integral part of counselling for this group of patients. Advances in cancer therapeutic technologies are impacting on survival and the trend to increasing longevity, especially amongst women in the developed world, means that more patients will present to health services with such needs. Whereas hormone replacement therapy could be met on a needs basis, fertility and its preservation are best addressed prior to treatment. Indeed, concerns regarding resulting delays in starting treatment should be balanced with timely consideration, counselling and liaison with patients and their family.

Certain modalities of treatment have specific impact on reproductive health owing to their mutagenic potential. Alkylating chemotherapy and irradiation depletes the ovarian reserve while radiotherapy and surgery may result in sterility and other physical limitations such as vaginal stenosis. In oncology these modalities are often employed in combination; if efforts are not deliberate, the consequences may be additive with implications for the quality of life of the survivors.

It is estimated that there are 33,000 cancer survivors living in the UK, where the cumulative risk of cancer before 15 years is one in 600, and 1500 new cases are diagnosed annually amongst the adolescent age group where cancers are rare. In Scotland, 3235 childhood cancers were recorded between 1987 and 2005 (130/year). A third of childhood cancers in the UK are leukaemia (mainly acute lymphoblastic leukaemia) with brain and spinal tumours constituting 25%. Another group of cancer patients are the young adults with gynaecological and breast cancers; in 2011 in the UK, 69.3%, 31.4%, 25.4% and 14.6% of newly diagnosed cancers of the cervix, breast, ovary and uterus respectively were in premenopausal women below 54 years. This group may require a range of reproductive health therapy with survival, disease recurrence and Quality of Life (QoL) implications.

The 5 year survival for all childhood cancers has increased in the past 50 years. In the 1960s this averaged 30% compared to 80% in 2001–2005. The survivors, however, showed higher rates of premature death and a range of physical, social, psychological and reproductive health problems. These effects may manifest soon after treatment or many years or decades thereafter. The consequent need for life-long care and follow up draws on the expertise of many disciplines and specialities.

Although the need for such structured, evidence based multidisciplinary long-term care is well enunciated in a recent European survey of experts, much fewer countries in Europe have national guidelines. Indeed, significant aspects of the care are based on a weak evidence base and more research is required. The recent SIGN (Scottish Intercollegiate guidelines network) guideline outlined the care of such patients in Scotland. In this review we use case-based discussions to highlight the present level of evidence as well as the scope of interventions available for the common reproductive health issues confronting survivors.

Case 1: premature ovarian failure (POF)

A 21 year old woman presents to her GP with secondary amenorrhoea, hot flushes and night sweats. She has been in remission for 5 years after chemotherapy for Hodgkin's lymphoma. She had seen the gynaecology team who explained that she was experiencing the symptoms of premature menopause and recommended cyclical combined hormone replacement therapy (HRT). On further questioning, she admits that she does not take the HRT as it makes her 'feel like an old woman'.

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The occurrence of amenorrhoea, elevated gonadotropins, with or without vasomotor symptoms of hot flushes and night sweats, in a woman 40 years or less is defined as premature menopause. This commonly occurs spontaneously in familial clusters with no obvious causes and is also seen in association with autoimmune diseases. Cytotoxic chemotherapy, especially with alkylating agents, pelvic radiotherapy, surgery and some infections have been known to cause or accelerate the condition. The precise mechanism leading to POF is not fully understood. Recently postulated aetiological agents include central regulators of cellular metabolism, proliferation and survival.

The diagnosis of POF has impact on the physical, endocrine, reproductive and psychosexual health of the patient and is a major quality of life issue, especially in cancer survivors who may live most of their adult lives in this state. Treatment and preventive measures seek to mitigate these effects with a view to normal live without altered risk of recurrence or secondary cancers.

Notwithstanding the limitation to our understanding of its pathogenesis, depletion of primordial follicles of the ovary appears to be key to various aetiological pathways. These follicles provide both reproductive and endocrine function with secondary skeletal and cardiovascular health implications. The female human has the highest number of these follicles at around 20–22 weeks of intrauterine life. These begin to decline in quantity and later functional ability such that at birth the number is about 2 million. At puberty, the mean number of primordial follicles is about 600,000. With each ovulation, a number of these follicles are recruited but only one or two mature and culminate in ovulation with the remainder undergoing atresia. There is progressive depletion with each cycle, until the natural menopause at about the age of 52 years in the UK, when the number of follicles is about 1000.

The rate of depletion of follicles is accelerated by cytotoxic chemotherapy, irradiation, surgery, genetic disorders, infections and immunological disorders. A similar effect is seen in spermatogenesis among male cancer survivors. Down regulation of the hypothalamic, pituitary, ovarian axis at the time of exposure to chemotherapy has been shown to reduce the risk of POF and other reproductive consequences of these treatments.

Clinical presentation is variable; in the overt case, elevated FSH levels are associated with secondary amenorrhoea, and vasomotor symptoms of hot flushes and night sweats (with or without genitourinary symptoms). In occult cases, patients may present with unexplained infertility with normal gonadotropin levels. The occurrence of unexplained infertility with elevated gonadotropins is called biochemical ovarian insufficiency. The progress of patient in this spectrum is equally variable and often patients have an intermittent course. Complete depletion of the follicles results in amenorrhoea, elevated FSH >30 IU/Liter, and infertility. If this occurs prior to puberty, in childhood cancer survivors and in patients with genetic disorders, abnormalities of growth like short stature, decreased bone density may be affected; other aspects of puberty such as thelerche (breast development), puberche and adrenerche (adrenal development particular to puberty) can also be affected, with resultant patient and parental anxiety and psychosocial implications.

The diagnosis should always be based on history and examination. A urinary pregnancy test will exclude pregnancy; other causes can be excluded by thyroid function tests, autoantibody screening and karyotyping, especially if there is primary amenorrhoea. Gonadotrophin levels are elevated with low levels of oestradiol and progesterone. Tests for ovarian reserve using antral counts and antimullarian hormone will be considered below. Ovarian biopsy is not recommended. Patients should be monitored for bone mineral density with annual dual energy X-ray absorptiometry (DEXA).

The diagnosis of POF is an indication for HRT, and this should continue until the mean age of menopause in a given population. Health benefits of HRT are well established; HRT alleviates vasomotor symptoms, maintains or improves bone health and is cardioprotective in the long term. In cancer survivors, additional concerns with respect to therapy are the age of patients and the risk of recurrence. Young patients are challenged by having to take treatment that is ordinarily the remit of the elderly, and the older patients in the spectrum consider regular withdrawal bleeding with some combined preparations to be a nuisance. Survivors of breast and endometrial cancers traditionally considered oestrogen sensitive are appropriately concerned about recurrence.

For this young patient with an intact uterus, cyclical combined therapy is considered appropriate; in addition to the known benefits it sits well with younger patients that normally treasure regular period-like bleeding. Concerns related to the preparation are also not uncommon. Substitution of this preparation with a combine oral contraceptive (COCP) could be considered owing to the intermittent clinical course of the condition necessitating the need for contraception to avoid unwanted pregnancy. Concern regarding the use of COCP for HRT by some endocrinologists is probably more relevant for older patients owing to higher steroid doses in the pill and the consequent implications for breast cancer, cardiovascular and venothrombotic disease. In the younger patients higher dose preparations may be required to control the menopausal symptoms.

Older patients in whom regular menstruation is not a priority may be more amenable to continuous combined preparation. Where fertility and vasomotor symptoms are a concern, the use of HRT may affect fertility treatment. In this regards, alternative therapy and non-hormonal treatment for vasomotor symptoms may be preferable while fertility treatment is underway although the effectiveness and safety profile is not well documented.

In patients without a uterus, oestrogen can be administered orally or topically without the need for progesterone. In this patient, topical oestrogens could be combined with oral progesterone or progesterone administered locally as in an intrauterine system (IUS).

Patients with persistent low libido despite adequate HRT may benefit from androgen treatment with methyl testosterone. This can be administered orally or via subcutaneous implantation.

General measures include diet and calcium supplementation. Management of these symptoms is very challenging for the young patients, their family; effective counselling and collaboration within a multidisciplinary context is required.

Prevention of antral follicular damage during treatment in adolescent and young adult patients with established hypothalamic, pituitary and ovarian function is achieved by down regulation using gonadotrophin releasing hormone analogues. Shielding and surgical transposition of the ovaries outside a