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Overview

Iatrogenic Menopause After Treatment for Cervical Cancer

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Abstract

The ever-improving prognosis of women diagnosed with cervical cancer has meant that survivorship and treatment-related sequelae are being brought more into the spotlight in an attempt to try to reduce morbidity and improve women's long-term health. However, there are many issues surrounding an iatrogenic menopause in cervical cancer, a variety of potential management options and barriers to treatment. Women who have become menopausal under the age of 45 years as a result of cervical cancer are significantly less likely to start hormone replacement therapy (HRT) or continue it long term as compared with those who have undergone a surgical menopause for a benign reason. High profile media reports raising concerns about the safety of HRT use have left many women reluctant to consider HRT as a therapeutic option for menopausal symptoms and many are seeking to use complementary/alternative medicine, including non-pharmacological interventions, to alleviate symptoms. The benefits of HRT in this population have been shown to reduce these effects, although adherence to treatment regimens is a challenge due to poor compliance, which is in part due to the fear of a second malignancy. The development of non-HRT-based interventions to ameliorate menopausal symptoms and reduce the long-term health consequences are needed for women who choose not to take HRT.

Key words: Cervical cancer; hormone replacement therapy; iatrogenic menopause; premature ovarian failure; radiotherapy

Statement of Search Strategies Used and Sources of Information

This article is not a systematic review. Experts in the fields relating to the different aspects of the topic have written each of the sections and have used Medline as their primary source of information and references.

Introduction

Cervical cancer is typically a disease of young women, with the incidence in the UK being highest among women aged 25–29 years (19.3/100 000 women) [1]. Many women diagnosed with cervical cancer will have early stage, microscopic disease (stage IA) and will be successfully treated with local excision, thereby preserving their fertility and ovarian function. However, data from the National Health Service Cervical Screening Programme (NHSCSP) Audit of Invasive Cervical Cancer 2009–2013 document [1] reports that 67.7% of women under 25 years and 53.1% of women 25–49 years had at least stage IB disease at diagnosis, which would result in loss of fertility and iatrogenic menopause in a high proportion of cases, either due to a bilateral oophorectomy as part of a hysterectomy or chemoradiotherapy, as either primary or adjuvant treatment. Although cervical cancer accounts for only 1% of cancer cases in the UK, the issue of iatrogenic menopause as a consequence of treatment for cervical cancer, given the age distribution of the cases, is not inconsiderable and the number of women affected is increasing year on year.

The improvement in the prognosis of women diagnosed with a cervical cancer as a result of the addition of concomitant chemotherapy to radiotherapy [2] has meant

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that survivorship and treatment-related sequelae are being brought more into the spotlight in an attempt to try to reduce morbidity and improve women's long-term health. The aim of this article is to review the issues surrounding iatrogenic menopause in cervical cancer, potential management options and barriers to treatment. Other malignancies that require pelvic radiotherapy can also result in ovarian failure and many of the issues that affect cervical cancer patients can be extrapolated to them, although the risks and management would need to be determined on an individual basis.

Premature Ovarian Failure

The management of an early menopause should have two goals: firstly to alleviate the woman's symptoms, typically vasomotor and mood disorders and secondly to reduce the risk of long-term health consequences, which can result from hypoestrogenaemia, in particular the cardiovascular and bone effects. Women who have undergone premature ovarian failure (POF) due to oncological treatment are subject to a sudden onset of menopause, which is often more severe than physiological menopause [3], with the onset of symptoms within days of surgery and within 12 weeks after starting radiotherapy. The stress of undergoing a cancer diagnosis can also cause menopausal symptoms to become more severe [4].

Cardiovascular Disease

POF can lead to earlier than expected serious health consequences contributing to increased morbidity and mortality, even in women who have not had to undergo cancer treatment, including cardiovascular disease, osteoporosis, cognitive impairment, including dementia and parkinsonism, psychological effects, impaired sexual function and subfertility. Bilateral oophorectomy has been associated with increased cardiovascular risk and premature death, with the younger the age at oophorectomy the greater the increase in risk [5]. In those with POF under the age of 40 years, the increased risk of mortality from ischaemic heart disease is up to 50% higher compared with those with a menopause at the age of 52–55 years [6]. The underlying pathophysiology of this is probably hypoestrogenism contributing to enhanced progression of atherosclerosis [7,8] and this risk can be reduced by starting oestrogen replacement [9].

Osteoporosis

One of the biggest risks of POF is osteoporosis and this is associated with a significantly elevated fracture risk and the morbidity that accompanies this [10]. Analysis of dual energy X-ray absorptiometry (DEXA) scans carried out at diagnosis of POF show 3.6% of women have bone density within the osteoporotic range and 25.9% have osteopenia [11]. Oestrogen therapy is the most effective intervention for preventing bone loss in women with POF [11] and hormone replacement therapy (HRT), even low dose regimens, reduces the risk of osteoporosis and subsequent fractures [12,13]. Additional measures, including regular weight-bearing exercise, a calcium-rich diet with consideration of calcium and vitamin D supplementation if deficient, have also been shown to be beneficial.

Neurological and Cognitive Effects

There is evidence that women who have undergone an early menopause without oestrogen replacement have an increased risk of dementia or reduced cognitive function [14]. Evidence to date suggests that there may be a neuroprotective effect of oestrogen on the brain and that the effect may be age-dependent [15,16]. Several observational studies have found that women who have used HRT after their menopause have better cognitive functions than controls [17,18]. However, women who choose to use HRT after the menopause have, in general, higher education, healthier lifestyles and are healthier before using HRT than women who do not [19] and therefore this may be a confounding factor in trying to determine true causality [16]. Women with a premature surgical menopause also seem to have an increased risk of parkinsonism compared with controls and the risk is increased with younger age at oophorectomy [20].

Although HRT is advocated in the management and treatment of psychological and cognitive symptoms associated with the menopause [21] it is debatable whether depression is the direct result of the loss of oestrogen in menopausal women or arises as a result of other menopausal symptoms [22,23]. Longitudinal studies indicate that mood symptoms may be a result of menopausal women experiencing vasomotor symptoms, sexual dysfunction and poor-quality sleep [23–25], thereby affecting their psychological wellbeing. However, a meta-analysis including studies that were mostly randomised controlled trials, concluded that HRT seems to be effective in reducing depressed mood among menopausal women (overall effect size for HRT was 0.68) [26].

Sexual Function

Dyspareunia due to vaginal atrophy is a common and distressing consequence of POF and together with loss of libido can lead to significant sexual dysfunction. A systematic review of studies suggested that vaginal dryness, pain, bleeding and severe dyspareunia were all prominent issues of sexual dysfunction and that in terms of treatment modality, radiotherapy seems to be associated with worse quality of life and sexual function [27]. Pelvic radiation can lead to epithelial sloughing, ulcer formation and necrosis. This effect can progress on to vaginal wall thinning, adhesions, fibrosis and ultimately vaginal stenosis [28]. The bladder is similarly affected and therefore common symptoms are urgency and haemorrhagic cystitis.

The loss of ovarian function due to adjuvant therapy affects androgen secretion and therefore can lead to low libido. Psychological factors such as low self-esteem and loss

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