# Iatrogenic menopause after treatment for cervical cancer

# IATROGENIC MENOPAUSE FOLLOWING TREATMENT FOR CERVICAL CANCER

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**HIGHLIGHTS:**

- Treatment for cervical cancer can result in an iatrogenic menopause.

- Iatrogenic menopause is associated with long-term morbidity and mortality.

- HRT can reduce these effects although compliance with treatment is a major challenge

- Non-HRT based interventions are needed for women who chose not to take HRT

**KEY WORDS**: Cervical Cancer; iatrogenic menopause; premature ovarian failure; radiotherapy; hormone replacement therapy

**INTRODUCTION**

Cervical cancer is typically a disease of young women with the incidence in the UK being highest amongst women aged 25 to 29 years (19.3/100,000 women) [1]. Many of women diagnosed with a 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 NHS 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 the majority of cases either due a bilateral oophorectomy as part of a hysterectomy, or chemoradiotherapy as either as 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 that survivorship and treatment-related sequelae are being brought more into the spotlight in an attempt to try 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 effect 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 the 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, 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 [6]. The underlying pathophysiology of this is likely to be hypoestrogenism contributing to enhanced progression of atherosclerosis [7, 8] and this risk can be reduced by commencing 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 DEXA scans performed 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 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 life-styles and are healthier before using HRT than women who do not [19] and therefore this may be a could be a confounding factor in trying to determine true causality [16]. Women with a premature surgical menopause also appear 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 impacting on their psychological wellbeing. However, a meta-analysis including studies that were mostly randomized controlled trials, concluded that HRT appears 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 along 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 appears 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 hemorrhagic 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 of fertility are also major contributory factors and cervical cancer survivors are at increased risk of developing sexual pain disorders [29]. The use of topical oestrogens (see Hormone Replacement Therapy and Cervical Cancer section) can help to alleviate these symptoms significantly.

## POPULATION CHARACTERISTICS

Women of screening age (25-64 years) diagnosed with a cervical cancer have been consistently shown to be less likely to attend when invited for routine cervical screening [1], and the proportion of cancers associated with non-compliance with the NHSCSP has increased significantly over the past two decades [30]. Failure to engage with a structured screening programme has been indentified as one of the major risk factors for developing a malignancy and this raises the concern that this population of women may continue this behavioural pattern after their diagnosis, being less likely to comply with treatment for their premature menopause. The reasons for such behaviour will of course be multi-factorial however it is known that the majority of women who develop a cervical cancer belong to the most deprived socioeconomic quintile [31], which raises the possibility that a lack of health education is a significant contributing factor. Social isolation and factors that result in a lack of engagement with health care, either due to alcohol abuse or a language barrier, have been shown to be associated with emergency routes of presentation for cervical cancer and advanced disease at diagnosis [32]. Smoking is also known to be more prevalent in the cervical cancer population as compared to the background population, which itself increases the risk of cardiovascular disease and osteoporosis.

## STRATEGIES FOR PRESERVING OVARIAN FUNCTION

Ovarian tissue is very sensitive to radiation with doses of only 6-15Gy, depending on fractionation, leading to permanent ovarian failure [33]. In many cases of cervical cancer it will be necessary for the ovaries to be irradiated as part of treatment since the incidence of metastasis, although lower in squamous carcinomas, is considerably higher in adenocarcinomas, 2.17% compared with 9.85% for stage IIB tumours [34]. Long-term

survival in women with ovarian metastasis is poor, 5-year survival of 46.6% for Stage IB and only 18.0% for Stage IIB, with a high distance relapse rate [34] and therefore it is important that women are appropriately selected and counselled if ovarian function is to be preserved.

In women with ovarian conservation, the determination of menopause and the decision to institute HRT is dependent primarily upon the menopausal symptoms (vasomotor symptoms, musculoskeletal symptoms, effects on mood, urogenital symptoms, reduced sexual desire). Further tests in the form of serum follicle-stimulating hormone (FSH) can be performed on two occasions at least four-six weeks apart to confirm the diagnosis of POF, however, it should be only used in women under 45 years of age [35]. Serum anti-Müllerian hormone (AMH) and antral follicle count by ultrasound scan are used to determine ovarian reserve for fertility treatment and are not recommended for diagnosis of premature menopause or menopause [35].

## **Ovarian transposition**

Ovarian transposition, moving the ovaries out of the pelvic radiation field, has been used for half a century in order to preserve ovarian function in patients with pelvic malignancies requiring pelvic irradiation. Different surgical techniques have been developed with the minimal access route, laparoscopic or robotic, being favoured due to a shorter recovery time [36]. It is not a widely used technique since it is felt that even with modern radiotherapy techniques, such as IMRT, ovaries will still receive enough radiation to induce menopause. Most of the reports in the literature are case series from single institutions and include a selected population of young, premenopausal patients with stage IB-IIA cervical tumours with a need for primary or adjuvant radiotherapy. A systematic review and meta-analysis of the outcomes of ovarian transposition in gynaecological cancers found that it was associated with the preservation of ovarian function [37] and successful pregnancy outcomes have also been reported [38], however metastases in transposed ovaries and recurrence have been

reported [39]. Although this technique would not be suitable for all and care must be taken with case selection since non-squamous histology, stage and unaffected peripheral stromal thickness have been shown to be significantly associated with an increased risk of recurrence [40], it may prevent the onset of menopause in a proportion of cases as well as opening up the possibility for oocyte retrieval and pregnancy through surrogacy [41].

## Ovarian tissue preservation

There are various options available to young women with regard to preserving ovarian tissue for future fertility treatment.  These include cryopreservation of embryos, mature and immature oocytes and of ovarian tissue. For post pubertal women all options are potentially available but for pre-pubertal girls or women for whom it is imperative to start cancer treatment immediately ovarian tissue cryopreservation is the only potential option.

Embryo freezing is a well established technique used routinely in IVF cycles and achieves a pregnancy rate of on average 30% [42]. It requires time for controlled ovarian hyperstimulation and egg collection, therefore potentially delaying the start of treatment by 2-3 weeks. It is also dependent upon the presence of a partner and stable relationship since the consent of both partners is required for the subsequent use of the embryos. Additionally, in the case of cervical cancer where the uterus will be irradiated, a surrogate will be needed in order to carry the pregnancy.

Oocyte cryopreservation is another option for single woman or those not in a stable relationship. Although the success rates are less than embryo cryopreservation, with the advancing cryopreservation techniques such as vitrification there is improvement in the

pregnancy rates achieved by this procedure [43]. Similar to embryo cryopreservation it requires time for controlled ovarian hyperstimulation and egg collection.

Ovarian tissue preservation is an evolving technique provided by very few centres in the UK and within research context. While only 24 live births have occurred worldwide as a result of this treatment, with the increasing survival from childhood malignancy and women's expectation of fertility preservation it seems likely to become an established option. The issue of the quantity of ovarian cortex to be removed, strips of cortex [44] or even the whole ovary [45], needs to be decided upon in accordance with the type of cancer treatment planned, the potential for metastatic dissemination and the risk of premature ovarian failure. Once the patient has recovered from their treatment and is disease free the ovarian tissue can be reimplanted, either in the pelvis (orthotopic) or at a distant site (heterotopic). Pelvic implantation to date has either been onto the remaining ovary (if present) by removing a piece of cortex to expose the medulla and allow a site of angiogenesis [46, 47], or using a two stage procedure a peritoneal window is made in the broad ligament and a vascular bed created before reimplanting tissue [48]. These techniques may not be possible after treatment for cervical cancer due to the effect of radiotherapy on the vasculature, thereby favouring a heterotopic site, the most common being the abdomen or forearm, but there are no pregnancies to date using this technique. There is consistent evidence that ovarian function is restored using heterotopic transplantation and has an expected duration of function of 4-5 years [46, 49-51]. It also has the advantages of avoiding invasive procedures, easy recovery of oocytes, and avoidance of injury in patients with severe pelvic adhesions [50-52]. In order to reduce the risk of tumour recurrence, techniques such as vitro maturation of oocytes from ovarian tissue or transplantation of isolated primordial follicles on an alginate gel matrix are being developed and are possible options for the future [53].

**Ovarian sparing radiotherapy techniques**

Advanced intensity modulated radiotherapy (IMRT) techniques (such as RapidArc, Tomotherapy and Volumetric Arc therapy) are being rapidly adopted by UK radiotherapy centres for the chemoradiotherapy treatment of cervical cancer. Such techniques have dosimetric benefits and the ability to create sharp dose gradients and limit the total dose received by certain organs at risk. Ovarian preservation with IMRT techniques is technically challenging due to the poor visualisation of the ovaries at the time of planning and that they are inevitably incorporated into the high dose clinical target volume (CTV). Ovarian transposition prior to chemoradiotherapy may result in a reduced dose to these structures provided that the ovaries are transposed away from the nodal planned target volume (PTV).

Current recommendations for IMRT treatment of cervical cancer recommend including the entire uterus within the CTV since there is no clear fascial plane separating the cervix and both structures contain continuous lymphatics. Whether to include the whole uterus however remains a controversial topic amongst experts since trachelectomy for early stage disease has opened up a fertility sparing option. It must be noted that patients treated with chemoradiotherapy typically have more advanced disease and therefore such benefits are unlikely to be translated into this group. Caution must therefore be exercised in such cases and patients enrolled into clinical trials where available.

**HORMONE REPLACEMENT THERAPY AND CERVICAL CANCER**

Cervical cancer is not a hormone dependant cancer although a number of studies have shown that oestrogen and progesterone receptors are found in the cervix and in a proportion of tumours [54-56]. Despite oestrogen and progesterone receptors being expressed in 39% and 33% of adenocarcinomas [54], exogenous oestrogen has not to date been shown to be associated with an increased risk of developing squamous cell carcinoma when compared to

HPV positive controls [56-58]. Several studies even noted a reduction in squamous cell carcinoma rates in women on HRT [59, 60], but this is likely to be because of increased screening compliance as a result of regular medical review.

The association between HRT and cervical adenocarcinoma is however less clear with two studies reporting a positive association [56, 59]. Jaakkola et al. [59], noted that risk was associated with duration of exposure with almost a 3 fold increase in risk after 10 years of use, although a causal mechanism for this remains to be identified and it is possible that the findings are as a result of confounding factors. Importantly neither oestrogen nor progesterone receptor expression have to date been shown to significantly influence disease-free and overall survival in cervical adenocarcinomas [54] and several studies actually reported improved survival rates with expression [55, 61].

There is only one randomised, controlled trial in the literature investigating the effect on HRT on survival for women treated with radiotherapy alone or combined with surgery for a stage I/II cervical cancer [62]. No significant difference in cervical cancer recurrence or in overall survival was seen at the end of 5-years between women who took HRT and those who did not therefore women using HRT should be reassured that HRT does not appear to cause an increase in recurrence of cervical cancer.

Oestrogen containing HRT has been shown to be effective in managing menopausal symptoms after radiotherapy for cervical cancer with a reduced incidence of post-radiotherapy complications [62]. Any complications that were present were milder and of shorter duration when compared with those women in the control group who did not receive HRT, $p < 0.01$) [62].

Topical oestrogens are highly effective at relieving urogenital symptoms related to vaginal atrophy [63]. There is minimal systemic absorption through the atrophic mucosa as studies have shown an initial rise in unconjugated plasma oestradiol but within two weeks of treatment this has declined to postmenopausal levels [64, 65]. Other methods of improving sexual function are using water and oil based lubricants and if there is narrowing and shortening of the vagina, dilators may be helpful.

## HORMONE REPLACEMENT THERAPY REGIMENS

### Route of delivery and Preparations

There are many different HRT formulations and preparations, for example transdermal patch, transdermal gel, oral tablet and vaginal ring. The preparations may contain oestrogen only, a progesterone only or be a combination both hormones. The choice of preparation or combination of preparations will be dependent on the individual patient, on her individual clinical situation and her personal preferences.

The transdermal as compared to the oral route has several advantages [35]. In particular, it does not appear to increase the risk of venous thromboembolism (VTE) compared to a significant increase with oral oestrogens [35]. Also, the risk of ischaemic stroke is slightly increased with oral, but not transdermal oestrogen [35]. Transdermal HRT in the form of gel or patches are preferable in women where drug bioavailability may be affected by concomitant medication, for example drugs for epilepsy or migraine and have been shown to be more cost effective than oral HRT [35]. Absorption levels have been shown to vary with the transdermal route and local skin reactions to patch adhesives mean that some women may have to switch to oral preparations.

Although there are some combined transdermal preparations commercially available, the

doses of oestrogen contained in them are sometimes not high enough to alleviate women's symptoms. Rather than increasing the dose of progesterone by giving two patches it is preferable as previously described to uncouple the two hormones to allow the dose of oestrogen to be titrated and using separate progesterone, such as medroxyprogesterone acetate or a micronized progesterone. This therefore avoids the need to increase the progesterone dose, and the adverse effects that are associated with it, for example bloating, mood changes, breast tenderness and skin problems. The type of progesterone can also be chosen depending on women's symptoms, C19 derived progestogens, for example norethisterone, are good for cycle control and reducing unscheduled bleeding, whereas the C21 derived progestogens, for example medroxyprogesterone acetate, dydrogesterone or micronized progesterone [66], are better for avoiding androgenic symptoms [67]. There is emerging evidence that micronized progesterones may be preferable with regard to breast cancer risk as compared to oral preparations [68] and they can be used orally or vaginally alongside transdermal or oral oestrogen-only preparations.

Subcutaneous oestrogen implants may be helpful in managing young patients who have severe symptoms. They are inserted every 5-6 months subcutaneously in the abdominal fat by a minor surgical procedure and appear to have a similar risk profile to transdermal oestrogens, although there is a risk of tachyphylaxis with prolonged use [69].

Low testosterone has been reported as a cause for low libido in women who have undergone POF. Transdermal testosterone gel or an implant have been used as treatments for this but they are currently unlicensed in women in the UK [35].

**Following hysterectomy**

In women who have undergone hysterectomy, oestrogen-only HRT can be instituted since they will not require a progesterone for endometrial protection.

**In women who have not had a hysterectomy**

Despite the endometrium being exposed to high doses (60+ Gy) of radiotherapy for cervical cancer, residual functional endometrium has been shown to persist after the completion of treatment [70, 71]. This residual endometrium can be stimulated by exogenous oestrogens [72] and therefore oestrogen-only HRT is not advised [70] since oestrogen-only HRT is a known risk factor for an endometrial malignancy [73] and a continuous combined 'no bleed' regime would be suitable for this population.

**NON-HORMONAL THERAPIES**

High profile media reports about the safety of HRT use have left many women reluctant to consider HRT as a therapeutic option for menopausal symptoms and in addition, a proportion of women are prevented from using HRT for medical reasons [74]. As a consequence, many women are seeking to use complementary and alternative medicine, including non-pharmacological interventions, to alleviate symptoms associated with the menopause [75]. There are a myriad of non-hormonal therapies that have been used to treat menopausal symptoms however the majority are only supported by individual anecdotal reports and not by clinical trial evidence [76]. In general, reviews of alternative and complimentary non-hormonal therapies indicate that large randomized placebo controlled trials are lacking and these therapies are not as effective as oestrogen at controlling vasomotor symptoms. The fact that there is a 50% improvement in symptoms with placebo highlights the requirement for large robust blinded randomised trials [77].

**<u>Dietary supplements</u>**

There are many dietary supplements that report to have a positive effect on menopausal symptoms however, the quality and proportion of active ingredients in many of these over-the-counter preparations is not known and therefore the effects will vary depending on manufacturer and their cannot be guaranteed [35]. Drewe et al., have conducted a systematic review examining the extensive evidence for non-hormonal treatments for menopausal vasomotor symptoms in women following a cancer diagnosis [78]. The most common supplement are the Isoflavones, which are found naturally in the Fabaceae family of legumes, for example soybeans, alfalfa and mung bean sprouts and red clover blossom. Genistein and daidzein are the main isoflavones in soy and have been evaluated in different doses in a variety of placebo-controlled trials. The results ranged from a reduction in symptoms to no difference compared to placebo, in particular in four studies in women with a breast cancer diagnosis [79-82]. A meta-analysis of six studies did indicate a reduction in the vasomotor symptoms after 12-16 weeks and 26 weeks of use, -0.97 (95% CI -1.82 to -0.12) and -1.22 (95%CI -2.02 to -0.42) [83]. Red clover contains the isoflavones formononetin and biochanin in addition to genistein and daidzein. A meta-analysis of their effect on the frequency of hot flushes showed no difference compared to placebo, -0.44 (95% CI -1.47 to 0.58) [83]. Black cohosh (Cimicifuga racemosa) is derived from a member of the buttercup family. A number of randomised trials have been conducted and a meta-analysis by Beer et al., [78] identified a significant effect as compared to placebo, in contrast to a Cochrane review published in 2012 [84]. NICE guidance does include support for isoflavones and black cohosh in the treatment of vasomotor symptoms however, it does advise that women should be made aware that the safety of individual preparations is unknown and they may interact with other medication [35]. Vitamin E succinate has also been proposed as a treatment and although a reduction of

the frequency of flashes has been seen the clinical impact appears to be minimal as compared to placebo [85, 86].

## **Pharmacological treatments**

Serotonin-norepinephrine and Selective serotonin reuptake inhibitors (SNRIs/SSRIs), clonidine and gabapentin are often used to control vasomotor symptoms but clonidine is the only one of these products licensed for this use. NICE guidance states that non-hormonal therapies should not be offered as the first line option for the management of vasomotor symptoms [35]. Clonidine (up to 50 mg TDS) has been the subject of a number of studies of varying quality. A meta-analysis of 4 trials demonstrated a benefit compared to placebo of - 0.95 (-1.44 to -0.47) for the 4-week trials and -1.63 (-2.76 to -0.50) for the 8-week trials [83]. The SNRI most commonly used is venlafaxine, especially in breast cancer patients [87], since it has a weak/negligible effect on cytochrome P450 unlike other SNRIs, for example fluoxetine and paroxetine, which are strong inhibitors of this enzyme system [88] and therefore reduce the efficacy of concomitant medication, in particular tamoxifen and other chemotherapeutic agents [89]. Venlafaxine can significantly reduce hot flushes and sweats and is used in doses up to 75 mg daily. A double-blind, placebo controlled trial of investigating venlafaxine and clonidine showed a significant reduction in hot flashes for both treatments compared to placebo [90]. The efficacy of venlafaxine has been shown to be not dissimilar to that of low-dose oral oestrogen, with a 48% reduction in the frequency of vasomotor symptoms compared to 53%, and is well tolerated, patient satisfaction of 52% compared to 69% for estradiol [91]. Gabapetin, in doses up to 900 mg per day, has been shown to reduce the frequency of flashes compared to placebo, 44-45% versus 15-29%, however is associated with a high level of reported adverse events, 50% compared to 27.6%

in the placebo group [92, 93].

## Non-pharmacological treatments

There are limited clinical data on non-pharmacological treatments such as behavioral interventions, exercise and acupuncture. Acupuncture has been found to be less effective than oestrogen in management of hot flushes but more beneficial than placebo. In their review, Daley, Stokes-Lampard and MacArthur [94] identified several large observational studies that demonstrated associations between exercise and lower rates of vasomotor symptoms. However, several smaller observational studies showed no association between exercise, menopausal symptoms and quality of life outcomes [94]. There is no supporting evidence from randomized controlled trials for the causal role of exercise in reducing vasomotor symptoms [74] yet exercise has been shown to have a significantly positive effect on quality of life and psychological symptoms [95] and appears to reduce the loss of bone mineral density in POF [96].

For mood and psychological symptoms recent NICE guidance recommends the use of cognitive behavioural therapy (CBT).  SNRIs and SSRIs have not been shown to be effective for mood disorders related to the menopause and are only indicated in women with clinical depression or anxiety disorders [35].

## BARRIERS TO HRT USE

Women who have become menopausal under the age of 45 years as a result of cervical cancer are significantly less likely to start HRT or continue it long term as compared to those who have undergone a surgical menopause for a benign reason [97]. Everhov et al. [97], identified that less than 46% of women who would be expected to have started HRT were prescribed it

at or near the recommended dose (≥75%) and although women under 40 years were more likely to use HRT than women aged 40 to 45 years, 56% versus 33%, the rates fell to 21% and 20% by 5 years following treatment. The reasons for such low HRT usage are likely to be multi-factorial and suggest a lack of awareness of the benefits of HRT following an iatrogenic menopause for cervical cancer both amongst the patient and their clinician.

## Second malignancies

One of the main concerns raised with the prolonged use of HRT is the increased risk of breast cancer. The Women's Health Initiative (WHI) study, which included women aged 50 to 79 years, identified that combined oestrogen and progestin HRT increases the risk of incident breast cancer in healthy postmenopausal women [98]. A more recent study however recruiting women aged 45 to 58 years who have recently become postmenopausal and started on HRT appear to have a reduced risk of mortality with no increase in cancer, VTE or stoke risk [99]. The WHI study findings have been extrapolated by the media and general public to mean that HRT use at any age is associated with an increased breast cancer risk and consequentially this has had a dramatic on HRT usage [100], although the absolute risks and associations are poorly understood and the study actually demonstrated a drop in breast cancer risk with oestrogen only HRT use [101]. The evidence for women undergoing a premature menopause is that they do not have an increase breast cancer risk but should instead continue HRT until the age of the natural menopause [102]. The concern that HRT usage will increase the risk of breast cancer in the treated cervical cancer population is therefore not grounded and some studies have actually indentified a reduced risk in this population [103, 104], which is likely to be due to the effect of an early menopause.

Cases of endometrial carcinoma following treatment for cervical cancer have been reported even without additional oestrogenic stimulation and therefore, although the risk is low, suspicious symptoms should always be investigated. The avoidance of oestrogen-only HRT does not appear to be followed in clinical practice with only half of HRT prescribed to this population containing a progestogenic component [97]. This may be due to a lack of awareness amongst clinicians of a potential association but does need to be considered especially in women with additional risk factors for developing an endometrial malignancy, in particular obesity.

Second malignancies have been reported following radical radiotherapy to the pelvis for cervical cancer [105] but the estimated excess of cases is low, a relative risk of 1.1 for developing a malignancy in tissues surrounding the cervix exposed to high radiation levels [106]. The risk does increase with time, Rodriguez identified that 35 years following radiotherapy treatment the risk of developing a colon cancer was higher in women who received radiotherapy compared to those that did not, 6.5% versus 2.5%, and 3.7% versus 0.8% for a rectal cancer [107]. Radiation-associated uterine malignancies are more likely to be of higher grade and stage as compared to spontaneous cancers and as a result carry a poorer prognosis [108]. Several studies have identified an increased association with a second primary lung malignancy [104, 109], however this is likely to be a reflection of the smoking behaviour in this population and reinforces the importance of smoking cessation advice and support following a cervical cancer diagnosis.

**Medical professionals**

Another potential barrier to HRT usage in this population is a lack of understanding as to the long-term implications of POF and the role of HRT following cervical cancer treatment by the medical team. Oncologists have their focus primarily on achieving the greatest survival with the lowest treatment-associated morbidity and there may be a role for specialist gynaecological endocrinology input in order to optimise POF management. There is also the challenge of ensuring that women continue with HRT following discharge from routine hospital follow up, typically after 5 years, since general practitioners will be unfamiliar with such prolonged HRT use, up to the age 50 years, and be under the misconception that this results in an increased breast cancer risk.

**CONCLUSIONS/RECOMMENDATIONS**

Iatrogenic menopause as a result of treatment for cervical cancer is associated with significantly increased long-term morbidity and mortality. 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 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 chose not to take HRT.

**CONFLICT OF INTEREST**

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