Ovarian failure following cancer treatment: current management and quality of life

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BACKGROUND: There is a lack of evidence regarding current screening practices for incipient ovarian failure in young women following gonadotoxic therapy and the most appropriate form of estrogen replacement. This study examined the (i) prevalence and management of ovarian failure and (ii) quality-of-life implications of early menopause (EM). METHODS: A medical case note audit for 288 women with a history of gonadotoxic therapy (aged 18–50 years) was conducted. Self-reported quality-of-life data were obtained from 178 (62%). RESULTS: Ovarian screening was recorded in 44% of medical case notes, and ovarian failure was documented for 35%. From the self-reported data, 89/178 (50%) women reported experiencing an EM/ovarian failure. Worse menopausal symptoms were negatively associated with both sexual activity (pleasure \( r = 0.29, P < 0.01 \), discomfort \( r = 0.50, P < 0.001 \)) and habit \( r = 0.22, P < 0.05 \)) and general quality of life \( P = 0.01 \). Hormone replacement therapy is the most commonly prescribed estrogen preparation; however, 34% of women with EM/ovarian failure reported not taking any replacement therapy. CONCLUSIONS: Given the extent and impact of menopausal symptoms, further work is needed to establish systems for screening ovarian function and to determine appropriate and effective management of ovarian failure.

Keywords: ovarian failure; cancer; quality of life; early menopause; gonadotoxic therapy

Introduction

Ovarian failure is common in young women treated for cancer with gonadotoxic therapy. This has most commonly been described in survivors of breast cancer (Bines et al., 1996; Walsh et al., 2006; Partridge et al., 2007), childhood cancers (Chemaitylly et al., 2006; Lantinga et al., 2006; Sklar et al., 2006) and Hodgkin’s lymphoma (Clark et al., 1995; De Bruin et al., 2007). Ovarian failure experienced during treatment may be temporary or permanent. Women whose ovarian function resumes will often have depleted ovarian follicle reserves that can lead to premature menopause occurring months or years after treatment completion (Sklar et al., 2006; De Bruin et al., 2007). Rising cancer survival rates have led to an increased interest in managing premature menopause in this patient group (Chen and Manson, 2006; Verschuuren et al., 2006; Royal College of Physicians, 2007). However, there is a lack of evidence concerning current screening practices for incipient ovarian failure or the most appropriate method for estrogen replacement.

Estrogen replacement following premature ovarian failure is important to prevent or ameliorate potentially serious effects, including osteoporosis, as well as psychosocial and psychosexual well-being. Premature menopause is associated with worse health-related quality of life (HR-QOL) in breast cancer survivors (Ganz et al., 1998, 2000). Menopausal symptoms, particularly vaginal dryness and dyspareunia, are associated with worse sexual functioning (Ganz et al., 1998, 2000; Carmack Taylor et al., 2004; Wenzel et al., 2005). Although estrogen therapy may be useful, current replacement regimens are not always efficient in alleviating symptoms (Moadel et al., 1995; Madalinska et al., 2006).

To date, most research has focused on estrogen replacement in older post-menopausal women and there is little evidence regarding the most appropriate or adequate replacement for...
younger cancer survivors, whether that be hormone replacement therapy (HRT) or the oral contraceptive pill (OCP). There are well-documented concerns about providing long-term HRT for post-menopausal women (Rossouw et al., 2002; Beral, 2003) and also for treating women with estrogen responsive tumours (particularly breast cancer) because of cancer risks (Runowicz, 1996; Col et al., 2005). However, these studies do not raise questions about the safety of estrogen-containing medication for younger women without breast cancer, though most commentators consider it appropriate to replace estrogen in young women with premature ovarian failure (Committee of Safety of Medicines, 2003). Essentially, the optimum estrogen preparation for young women, the route of administration (whether oral or transdermal) and preferred dose remain open questions (Leung et al., 2004; Mah et al., 2005).

The aims of our study therefore were to:
(i) audit hospital case notes of a cohort of at-risk women to determine the prevalence of screening for ovarian dysfunction, extent of ovarian failure and prescribed estrogen replacement;
(ii) describe women’s self-reports of menopausal status and symptoms;
(iii) determine the impact of premature menopause and menopausal symptoms on women’s sexual activity and HR-QOL;
(iv) describe views of women experiencing an early menopause (EM) towards estrogen replacement, including perceived advantages and disadvantages and current use.

Materials and Methods

Patients
This was a cohort study of women treated with gonadotoxic therapy at a regional cancer centre in Sheffield, UK serving a population of 1.5 million. For inclusion into the study, patients had to be female, aged 18–50 years, treated for a malignancy with either gonadotoxic chemotherapy (e.g. vinblastine, cyclophosphamide and chlorambucil) and/or radiotherapy rendering them at risk of ovarian failure (radiotherapy fields including groin, inverted Y abdomen, pelvis, cranio-spinal, spinal, abdominal and total body). Patients were also required to have completed a minimum of 2 years after the treatment without relapse, English speaking and able to provide informed consent. Exclusion criteria: history of breast cancer. Ethics approval was obtained from the local Research Ethics Committee.

Audit
Between August 2005 and September 2006, patients were identified from hospital databases and outpatient clinic lists in Sheffield, UK. A standard pro forma was used to summarize medical data of eligible women from an individual’s entire medical case notes, independent of fixed time points. Information included diagnosis, treatment and duration, age at start and end of treatment, evidence of gonadotrophin and estradiol monitoring, evidence of ovarian failure, evidence of initiation of estrogen replacement, type of estrogen replacement, details of prescribing clinician (oncologist, haematologist, paediatrician, gynaecologist, surgeon) and whether more than one form of estrogen was used.

Survey
Patients were recruited between August 2005 and November 2006 at routine follow-up appointments (or by post if discharge had occurred). Those attending follow-up were introduced to the researcher by a member of the clinical team. The researcher explained the study and obtained informed consent. Women were then asked to complete the questionnaire either in clinic or at home (returned in a freepost envelope).

Measures
(i) Demographic information.
(ii) Late effects (Absolom et al., 2006): Participants were asked to indicate which of a list of 12 common late effects were currently experienced.
(iii) Menopausal symptoms [Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES), Fallowfield et al., 1999]: This 18-item endocrine subscale measures menopausal symptoms. Scores range 0–72, with higher scores indicating better endocrine functioning.
(iv) Sexual activity (Thirlaway et al., 1996): This measure generates basic descriptive information about sexual activity and 3 scores for those who are sexually active:
(a) pleasure (low score = low pleasure)
(b) discomfort (low score = more discomfort)
(c) habit (low score = less sexual activity than usual in the past month).
(v) HR-QOL (SF-36 version 2, Ware et al., 2000): 36-item questionnaire measuring 8 dimensions of health. Two overall scores can also be calculated which measure physical (physical component scale, PCS) and mental health (mental component scale, MCS).
(vi) Views about estrogen replacement therapy: Women were asked to report with whom they had previously discussed estrogen replacement with [general practitioner (GP), gynaecologist, cancer specialist or other], the most recent form of estrogen taken and why it was prescribed. An open question was used to determine women’s understanding of estrogen replacement, its purpose and perceived advantages and disadvantages.

Treatment of the data
Analyses were conducted using the Statistical Package for the Social Sciences version 11. Standardized measures were scored as described in original manuals or papers. Internal reliabilities of all scales were assessed with Cronbach’s alpha. t-Tests and Pearson correlations were used to measure differences and associations between clinical variables (e.g. age at diagnosis, time since diagnosis) and HR-QOL variables (sexual activity, menopausal symptoms and SF-36). t-Tests were also used to compare the study sample with age-matched UK normative data for the eight SF-36 subscales. Standard multiple regression was used to determine the demographic and clinical variables associated with SF-36 PCS and MCS.

Results
Audit sample
Figure 1 outlines the screening and participant recruitment process. The audit was completed for 288 patients (Table I). Primary cancer diagnoses included:
(i) haematological cancers (n = 184, e.g. leukaemia, lymphoma);
(ii) solid tumours (n = 61, e.g. osteosarcoma, squamous cell carcinoma);
(iii) primitive and other cancers ($n = 43$, e.g. germ cell tumours, medulloblastoma, rhabdomyosarcoma).

**Documentation of screening and extent of ovarian dysfunction, and prescribed estrogen therapy recorded in case notes**

Evidence of ovarian screening (gonadatrophins and/or estradiol) at least once during or after cancer therapy was documented in the case notes of 126 (44%) women. This monitoring was initiated by oncologist ($n = 77$, 61%); haematologist ($n = 14$, 11%); paediatric consultant in late effects ($n = 15$, 12%); endocrinologist ($n = 7$, 6%); gynaecologist ($n = 6$, 5%); GP ($n = 5$, 4%); it was not specified in 2 cases. Doctors recorded information on ovarian status in the notes of 157 women (54%). One hundred and one women (35%) were recorded as having ovarian failure and 56 (19%) as no ovarian failure. For the remainder ($n = 131$, 45%), no relevant information was documented.

Evidence of prescribed estrogen was documented in the notes of 141 (49%) women. This included oral HRT ($n = 45$, 32%), transdermal HRT ($n = 6$, 4%), unspecified HRT

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**Table 1.** Demographic and clinical information for survey and audit participants.

<table>
<thead>
<tr>
<th></th>
<th>Survey, $n = 178$</th>
<th>Audit, $n = 288$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>38.5 (8.5)</td>
<td>38.5 (8.5)</td>
</tr>
<tr>
<td>Mean age at diagnosis, years (SD)</td>
<td>26.6 (10.1)</td>
<td>26.9 (10.1)</td>
</tr>
<tr>
<td>Mean time since end of treatment, years (SD)</td>
<td>10.4 (6.7)</td>
<td>11.1 (7.2)</td>
</tr>
<tr>
<td>Cancer diagnosis, $n$ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological cancers</td>
<td>128 (72)</td>
<td>184 (64)</td>
</tr>
<tr>
<td>Solid cancers</td>
<td>26 (15)</td>
<td>61 (21)</td>
</tr>
<tr>
<td>Primitive cancers</td>
<td>24 (14)</td>
<td>43 (15)</td>
</tr>
<tr>
<td>Marital status, $n$ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/partner</td>
<td>130 (73)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>26 (15)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>20 (11)</td>
<td></td>
</tr>
<tr>
<td>Employment status, $n$ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work, full-time</td>
<td>64 (36)</td>
<td></td>
</tr>
<tr>
<td>Work, part-time</td>
<td>63 (35)</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>19 (11)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>13 (7)</td>
<td></td>
</tr>
<tr>
<td>Disabled/long-term sick leave</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>
(n = 37, 26%), topical HRT (n = 2, 1%), oral contraception (n = 14, 10%), i.m. contraceptive injection (n = 2, 1%) and unspecified contraceptive (n = 35, 25%).

Survey sample
Of the audit sample, 279 women (97%, Fig. 1) were invited to complete the survey (one had moved overseas and eight were withdrawn by the consultant owing to either cognitive impairments or current acute mental health difficulties). Questionnaires were completed by 178 women (64%); 118 (66%) were recruited at follow-up clinics and 60 (34%) via postal recruitment. There were no differences in current age or time since the end of treatment between women who completed questionnaires and those who did not.

Women's self-reports of health and menopausal status
One hundred and twenty-eight (72%) women reported at least one late effect of their treatment (range 0–9, mean 2.15). The most common was EM (n = 86, 48%). In addition, three survivors of childhood cancer who reported estrogen deficiency were treated before menarche and never commenced normal menstruation. Of these 89 women, ovarian failure was documented in the medical records of only 61 (69%). The women experiencing an EM or ovarian failure were significantly older than those who were not (means 41.4 versus 35.4 years, P < 0.0001) and reported significantly more late effects (means 2.39 versus 0.94, P < 0.001). Other common late effects were difficulty conceiving (n = 83, 47%), weight gain (n = 39, 22%) and problems with sexual functioning (n = 31, 17%). Late effects increased with current age (r = 0.28, P < 0.001), and time since end of treatment (r = 0.19, P < 0.05), but not at diagnosis (r = 0.09, P = 0.24).

FACT-ES scores were compared with published data that primarily included women undergoing endocrine treatment for breast cancer (Fallowfield et al., 1999). Our study sample reported significantly worse menopausal symptoms than the breast cancer group (means 55.2 versus 59.7, P < 0.0001). The most commonly reported symptoms included irritability (29%); loss of sexual desire (29%); mood swings (27%); bloating and discomfort (27%) and headaches (26%). Older women reported worse menopausal symptoms (r = –0.18, P < 0.05). Menopausal symptoms were not related to age at diagnosis or time since end of treatment. Women experiencing EM/ovarian failure reported significantly worse menopausal symptoms (means 52.1 versus 58.2, P < 0.001) than those who were not.

The relationship between menopausal status, symptoms and sexual activity
One hundred and forty-eight women (83%) were married/in an intimate relationship and 128 of these (86%) were sexually active (Table II). After not having a partner, the most common reason for sexual inactivity was lack of sexual desire.

Nineteen women were in a relationship but not sexually active (13%). Compared with sexually active women, these women were older at the time of study (means 43.3 versus 38.7, P < 0.05) and at diagnosis (means 33.3 versus 26.1, P < 0.01). Compared with women who were sexually active, sexually inactive women reported worse scores for FACT-ES menopausal symptoms (means 46.1 versus 56.0, P < 0.01) and more late effects (means 3.2 versus 2.0, P < 0.05). Compared with a healthy non-cancer sample aged 18–58 years (Atkins and Fallowfield, 2007), the current group reported worse median scores for pleasure (13 versus 16) and discomfort (4 versus 6) but not for habit (1 versus 1).

Women with EM/ovarian failure reported comparable scores for pleasure and habit but significantly worse scores for discomfort than women without (Fig. 2). Worse menopausal symptoms (FACT-ES) were significantly associated with worse scores for pleasure (r = 0.29, P < 0.01), discomfort (r = 0.50, P < 0.001) and habit (r = 0.22, P < 0.05).

The impact of menopausal status, symptoms and HR-QOL
Figure 3 shows the SF-36 subscale scores for the study sample in comparison with age-matched UK norms (Jenkinson et al., 1999). The sample reported significantly worse scores on all subscales except mental health. Women with EM/ovarian failure reported significantly worse scores on all SF-36 subscales than those without, with the exception of mental health.

To determine the impact of EM on HR-QOL, standard multiple regression analyses were conducted with the variables significantly associated with SF-36 PCS and MCS. The model for PCS (Table III) explained 29.9% of the variance. Fewer late effects and menopausal symptoms were positively associated with better physical health, as was being in a relationship. EM was not significantly associated with physical health.

The model for MCS (Table III) explained 37.5% of the variance. Again EM was not significantly associated.

Table II. Sexual activity.

<table>
<thead>
<tr>
<th>Reason for no sexual activity</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No partner</td>
<td>24 (51)</td>
</tr>
<tr>
<td>Not interested in sex</td>
<td>23 (49)</td>
</tr>
<tr>
<td>Too tired</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Physical problem</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Partner not interested</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Partner too tired</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Partner has physical problem</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other reason</td>
<td>10 (21)</td>
</tr>
</tbody>
</table>

Figure 2: Sexual activity subscale scores comparing women with and without EM/ovarian failure.
with MCS. Better mental health was associated with fewer menopausal symptoms and late effects, and younger age at diagnosis and questionnaire completion.

**Women's views of estrogen therapy and current use**

Of the women experiencing EM/ovarian failure, 58 (65%) had discussed estrogen therapy with their family doctor, 41 (46%) with a cancer specialist and 39 (44%) with a gynaecologist. Forty-three (48%) of the women with EM/ovarian failure were currently taking estrogen replacement. Twenty-five (28%) were using oral HRT, 10 (11%) HRT patch, 6 (7%) oral contraceptive, 1 (1%) was fitted with a hormone-releasing intrauterine device and taking oral HRT and 1 (1%) was using both oral and gel HRT. Thirty women (34%) were not taking any form of replacement and the current status of the remaining 16 (18%) could not be determined because questionnaire and medical record data were ambiguous.

Women taking estrogen replacement \( (n = 43) \) were significantly younger (38.8 versus 44.5 years, \( P < 0.01 \)) than those who were not \( (n = 30) \). They also reported fewer menopausal symptoms (54.9 versus 48.4, \( P < 0.05 \)) and better PCSs (48.6 versus 43.0, \( P < 0.05 \)).}

Seventy-six (85%) of the women experiencing EM/ovarian failure provided comments about their views of estrogen therapy. The most commonly reported advantages were protection against osteoporosis \( (n = 43, 48\%) \); replacement of hormones \( (n = 26, 29\%) \); relief of menopausal symptoms \( (n = 21, 24\%) \); improved emotional functioning \( (n = 15, 17\%) \). Thirty-four women (38%) reported the increased risk of cancers (particularly breast, \( n = 23, 26\% \)) as the main disadvantage. Further disadvantages included weight gain \( (n = 12, 13\%) \), emotional disturbances \( (n = 5, 6\%) \), risk of thrombosis \( (n = 3, 3\%) \), increased risk of strokes/heart attacks \( (n = 3, 3\%) \). Four women (4%) described difficulty finding an estrogen replacement which suited them. Nine women (10%) did not want to take replacement, having experienced severe side effects in the past or because they had been warned against it by health professionals because of the health risks.

**Discussion**

Despite being at risk of EM, evidence of ovarian screening was found for less than half of the audit sample. Among those screened, 101 (35%) were documented as having ovarian failure in the case notes. Of the 89 women self-reporting EM/ovarian failure, documented evidence in medical records was found for only 61. This disparity may reflect variation in follow-up of these patients and the priorities of the cancer physician. Further, recorded annotations in the case notes do not necessarily mean menopausal status was not discussed during a consultation, nevertheless the absence of documented evidence infers as such. However, we found that more women had discussed estrogen replacement with their family doctor. It is likely this occurs at the onset of menopausal symptoms and any subsequent tests or prescribed estrogen replacement is managed in primary care. It is also possible that some women experienced EM but did not seek any medical advice.

Our results suggest that more systematic screening of ovarian failure is required following cancer therapy.

Women’s self-reported menopausal symptoms were significantly worse than breast cancer patients treated with endocrine therapy (Fallowfield et al., 1999). The physical and mental health of the young women in our study was also significantly compromised compared with the general population. Of particular importance in this cohort of young women, menopausal symptoms were significantly associated with worse HR-QOL and sexual activity.

Although a number of variables may influence sexual functioning following cancer, in the current sample sexual desire and sexual discomfort were commonly reported and associated with worse menopausal symptoms. Atrophic vaginitis caused by estrogen deficiency is known to be associated with sexual dysfunction in cancer survivors (Ganz et al., 1998; Wenzel et al., 2005). At the very least, topical estrogens can alleviate symptoms, although evidence from our audit implies that few women used this form of medication. Health care professionals rarely discuss issues regarding sexual functioning with patients (Stead et al., 2003) and patients themselves may be reluctant to initiate discussions. Thus, problems will remain undetected unless a systematic approach to screening and assessment is implemented.
For women identified with ovarian failure, the audit indicated that oral HRT was prescribed most frequently, followed by unspecified estrogen replacement and then oral contraceptives. This was supported by the women’s reports of current estrogen replacement use. This contrasts with a report from a similar group of young women treated for hypopituitarism where OCP was the most frequent prescription (Mah et al., 2005). However, questions about the suitability of OCP have been raised because it does not contain appropriate drugs at the optimal dosage and results in menopausal symptoms during pill-free weeks (Verschuren et al., 2006). Also, oral estrogens are associated with metabolic changes due to first-pass metabolism through the liver (Leung et al., 2005). However, questions about the suitability of OCP have been raised because it does not contain appropriate drugs at the optimal dosage and results in menopausal symptoms during pill-free weeks (Verschuren et al., 2006). Also, oral estrogens are associated with metabolic changes due to first-pass metabolism through the liver (Leung et al., 2005).

According to self-reports, >30% of women experiencing EM/ovarian failure were not taking any form of estrogen therapy. This is a significant proportion of women and may in part reflect apprehension about estrogen replacement (Rossouw et al., 2002; Beral, 2003). Concerns centred on cancer risks, weight gain and emotional disturbances. These issues need to be addressed if women are to comply with treatment recommendations. In particular, reassurance is required that replacement therapy is restoring estrogen to within the reference interval for young women and as such, breast cancer risk should be no higher than in peers of comparable age who are naturally ovular.

Our study has a number of limitations. First, audit and patient’s self-report data were inconsistent. Medical records are not necessarily updated with regard to women’s menopausal status. This is especially relevant for the 34% of the survey sample recruited by post who were not receiving follow-up care. We were required to use women’s own accounts of their health status to identify those who were experiencing EM/ovarian failure. This is not ideal, especially for women taking OCP for contraceptive purposes where underlying ovarian failure may be masked. Further, some women had problems remembering specific details of estrogen preparations they were taking. Second, this was a single-centre study and our findings may not be representative of the management of similar patients in other institutions.

In summary, our findings indicate ovarian failure is a common problem that is not currently systematically screened or managed. The extent of menopause-related health issues in this cohort of young women of fertile years is of concern and warrants further attention to determine how best problems can be identified and managed. It is not clear why so many women appear not to use any form of estrogen replacement. This raises questions over fears surrounding the health risks associated with estrogen replacement and whether women receive adequate and informed information from health professionals about the replacement options available.

With increasing numbers of young women surviving cancer, the long-term management of estrogen deficiency needs to be addressed (Chen and Manson, 2006). Questions remain regarding who is most appropriate to deliver this service and the form of estrogen replacement most appropriate. In our centre, we intend to implement a planned protocol for follow-up, including late effects, that will involve a programme for multiple assessments, including for gonadotoxicity. Future research should aim to establish a more consistent and thorough programme of ovarian screening. How this should be organized and at what stage in the treatment and follow-up process merits further exploration and discussion.

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References


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