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Editorial

HRT after endometrial cancer – Is it safe?

Endometrial cancer is the most common gynaecological malignancy in the western world. In Denmark with a population of 5.6 mio., 4718 women got endometrial cancer from 2005 to 2011 incl. Most were postmenopausal, but 0.9% less than 40 and 5.3% less than 50 years [1].

Endometrial cancer surgery includes total hysterectomy and bilateral salpingo-oophorectomy (BSO), and consequently may result in premature surgical menopause. BSO is performed because of risk of ovarian metastases, co-existent ovarian cancer and because oestrogen from the ovaries may increase the risk of recurrence.

Premature surgical menopause increases the risk of cardiovascular and neurological diseases, bone fractures and impaired sexual function [2]. Hormone Replacement Therapy (HRT) reverses some of these risks. Even postmenopausal women may experience return of climacteric symptoms after BSO, especially if on HRT prior to diagnosis. All women may experience symptoms of atrophic vaginitis, not least following local radiation (brachytherapy).

HRT after endometrial cancer is generally not recommended, since most endometrial cancers are oestrogen dependent, 80% being endometrioid adenocarcinomas [1,3].

The fear that HRT increases the risk of recurrence is mainly based on theoretical considerations. In a recent meta-analysis, Shim et al. reviewed the scientific background [4]. Based on one randomized and five observational studies, a total of 896 HRT users and 1079 controls, no significant increased risk of recurrence was found in endometrial cancer survivors using HRT (19 recurrences) compared to the control group (64 recurrences).

In the only prospective randomized controlled study available, 1236 women were randomized to placebo or oestrogen tablets and 41% (oestrogen) and 50% (placebo) were compliant with the medication for the entire three years [5]. The study was closed prematurely after publication of the Women's Health Initiative study, when it became apparent that the goal of achieving 2108 subjects could not be reached. The majority of the enrolled patients had well differentiated endometrioid adenocarcinomas, 91% had less than 50% myometrial invasion and the absolute recurrence rate was as could be expected low (only 2.1% i.e. 1.9% ($n = 12$) on placebo and 2.3% ($n = 14$) in the oestrogen group with no significant difference).

Oestrogen only (ERT) was used in the randomized and in one case–control study. Combined oestrogen and progestin only (cHRT) was used in one prospective matched cohort. The remaining three observational studies used mixtures of cHRT and ERT. In the observational studies the pooled OR for recurrence was 0.19 (95% CI: 0.08–0.46; $P = 0.943$). A subgroup analysis revealed that ERT was not associated with cancer recurrence (OR: 0.35; 95% CI: 0.06–2.10; $P = 0.054$ and cHRT was associated with a significant negative association (i.e. protective effect) with an OR: 0.23 (95% CI: 0.08–0.66; $P = 0.824$). All studies included women in stage I and II and only one study also provided data on 4 stage III women in each study arm.

Although the combined results of the available evidence indicate that HRT after surgery for endometrial cancer may be safe, we are still left with more questions than answers.

The non-randomized studies include three retrospective case–control studies done in the seventies and eighties with 44–62 women on HRT, one retrospective matched cohort study (75 women in each group) and one prospective matched cohort study (50 per group). In the latter two attempts were made to match for treatment type and no significant differences were found, but still in the retrospective study 65% in the no-treatment group had lymph-nodes removed versus 56% of those treated with conjugated equine estrogens with (49%) or without (51%) progestin. There were two recurrences on HRT and 11 in the no-treatment group in the retrospective cohort. In the prospective study all participants in the active group got cHRT – but no recurrences were found reflecting that 88% had stage I cancers and 94% were grade 1 or 2.

In all of these trials the active treatment was systemic. There are no data available on low dose local vaginal oestrogen therapy. Likewise there are no data on different doses and types of HRT and although the meta-analysis indicates that cHRT may be the better option compared to ERT, the only randomized study included ERT only. No studies compare ERT and HRT sequentially (scHRT) or continuous combined (ccHRT), although it has been shown that ERT and scHRT increase the risk of endometrial cancer whereas ccHRT may reduce it [3]. On this background in the absence of data one may prefer to use ccHRT when treating women with a history of endometrial cancer.

The majority of recurrent endometrial cancers are found in the vaginal vault, especially in women who have not received brachytherapy. This may be of concern when treating with local low dose oestrogen although systemic oestrogen values are not beyond normal postmenopausal range. No data exist on local therapy. Considering the prevalence of dry vaginas after BSO and possibly brachytherapy, such data are urgently needed.

The available studies included patients with very low risk of recurrence and an excellent survival. However low risk patients are also those with the most oestrogen dependent tumours. Only two studies, the randomized and the retrospective cohort, included

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a few women with serous and clear-cell carcinomas, (a total of 27 in the two studies combined equally distributed). These are more malignant, less oestrogen dependent types, but no data are available on whether ERT/HRT may be an option after surgery for these patients.

In conclusion the total risk of recurrence after low risk endometrial cancer is very low with or without HRT. The data on which to base a recommendation for ERT or cHRT are frail and indication of cHRT being preferable to ERT is only available from non-randomized studies. No data are available on local oestrogen therapy. There are no data on non-endometrioid adenocarcinomas, and one can only speculate whether oestrogen treatment increases the risk of recurrence of these more malignant types.

However the current evidence suggests that most women suffering from severe climacteric symptoms after endometrial cancer treatment may be offered relief from symptoms without major increase in risk of recurrence.

Contributor

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