Endometrial cancer in the Million Women Study

The Million Women Study (MWS) has now reported on the effect of various hormone replacement therapy (HRT) regimens on the risk of endometrial cancer (*Lancet* 2005;364:1543–51). Compared with never-users of HRT, the risk of endometrial cancer was reduced in those who had last used continuous combined estrogen/progestogen preparations (relative risk 0.71 [95% confidence interval (CI) 0.56–0.90]; $p = 0.005$), was increased with last use of tibolone (1.79 [1.43–2.25]; $p < 0.0001$) and estrogen only (1.45 [1.02–2.06]; $p = 0.04$), and not significantly altered with last use of cyclic combined estrogen and progestogen preparations (1.05 [0.91–1.22]; $p = 0.5$). The women's body mass index (BMI) significantly affected these associations, such that the adverse effects of tibolone and estrogen only were greatest in non-obese women and the beneficial effects of combined therapy were greatest in obese women. The authors' interpretations of these findings are that estrogens and tibolone increase the risk of endometrial cancer, but progestogens counteract the adverse effect of estrogens on the endometrium, with the effect being greater the more days every month that they are added to estrogen and the more obese that women are.

Although this paper was just concerned with endometrial cancer, the authors also added in the data about the increase in breast cancer, on which the previous publication reported (*Lancet* 2003;362:419–27), and concluded that, when endometrial and breast cancers are added together, there is a greater increase in total cancer incidence with use of combined HRT, both continuous and cyclic, than with the use of other therapies.

It is difficult to know how to interpret this new report as the validity of the methodology of MWS has been questioned by many commentators, especially Shapiro (*Climacteric* 2004;7:3–7) and Whitehead and Farmer (*Endocrine* 2004;24:187–93) with criticisms, including:

- The study population is not truly representative of the general population of the UK
- Treatment ascertainment was made only at the initial questionnaire so that prior treatments were not known and many women will have changed types, doses and regimens during and before enrolment in the study
- The risk of endometrial cancer persists for many years after cessation of hormone therapy, which does not happen with breast cancer
- It is widely considered that the previous MWS findings on breast cancer risk with HRT were an overestimation
- Tibolone may be prescribed selectively to women experiencing bleeding problems who would also be at greater risk of endometrial cancer [This was a similar concern in the breast cancer study as tibolone is considered to cause less changes in breast density than conventional combined HRT regimens and was shown to have been prescribed selectively for this purpose (Velthuis-te Wierik *et al*. *Climacteric* 2004;7:197–209).]
- Details of the histology of the endometrial cancers have not yet been reported and will be most important for proper evaluation of the clinical implications of this study. An earlier report of four cases of endometrial cancer in patients using tibolone had indicated that the adenocarcinoma developed from an atrophic

epithelium (Yazigi *et al*. *Gynecol Oncol* 2004;93:568–70), which is different from the more common transition through hyperplasia that occurs with unopposed estrogen.

Nevertheless, many of the findings are not unexpected. In particular, the protective effect of progestogen and the apparent reduction in the risk of endometrial hyperplasia and carcinoma have been reported in several prospective and observational studies. Obesity is well known as a risk factor for both endometrial and breast cancer and the inverse relationship with endometrial cancer in women taking HRT preparations in this report is quite striking and not readily explained.

The most surprising finding, however, is of the significantly and greatest increase in risk of endometrial cancer associated with the use of tibolone. This preparation was used by 9% of MWS subjects and has been used widely in Europe especially and has been available in the UK since 1991, but is not licensed in North America. It is a unique synthetic steroid which has now been classified as a STEAR (selective tissue estrogen and androgen regulator) and is known to have estrogenic, androgenic and progestogenic activity. In the endometrium, it is specifically converted to its Δ4-metabolite, which has no estrogenic activity, so the endometrium is not stimulated. Many studies have confirmed that women using this preparation generally have an atrophic endometrium, so it is surprising that this report indicates such a different outcome and highly significant risk for endometrial cancer. However, as with the previous report on breast cancer, there is uncertainty about the validity of drawing such conclusions.

The initial questionnaire that all the subjects completed on entry to the MWS asked for details about the current use of therapy and the total duration of HRT usage, but made no enquiry about previous therapies and duration of use, and only 48% of the women were apparently exclusive users of tibolone.

It must also be questionable whether it is biologically plausible that, after an average of 5.2 years of use of HT, that the current or last users of tibolone should produce 86 carcinomas from 28,028 women. Nevertheless, although the relative risk suggests a 79% increased risk of endometrial cancer, when this is converted into absolute figures the excess of endometrial cancer risk in 1000 women over a 5-year period is only three cases.

Undoubtedly, this report will receive unjustified exposure in the media around the world and further inappropriate comments about the dangers of hormone therapy. In reality, this study should not alter the clinical practice and management of postmenopausal women taking hormone therapies. For each individual woman, the perceived risks and benefits need to be assessed on a regular basis and any abnormal bleeding should be investigated appropriately. Endometrial cancer is a relatively rare condition in postmenopausal women and, in the MWS, the incidence rate for non-users of HRT was about 3 per 1000 women over a 5-year period. The use of hormone therapy, and in particular tibolone or unopposed estrogen, may slightly increase that risk but, with appropriate monitoring and investigation of abnormal bleeding, the risk can be minimized and needs to be put into perspective with the benefits and risks for other life-threatening conditions related to life-style and alternative factors.

For further guidelines on the use of hormone treatment of women in the menopausal transition and beyond, see *Climacteric* 2004;7:333–7.

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