Three cases of endometrial cancer associated with "bioidentical" hormone replacement therapy

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We describe three women who developed endometrial cancer after taking "bioidentical" hormone replacement therapy (HRT) to relieve menopausal symptoms. Although pharmaceutical HRT is a well established and tested therapy, little is known about the quality control, safety and efficacy of bioidentical HRT. Women should be advised to avoid bioidentical HRT, and those who continue to use it should receive regular endometrial surveillance. **(MJA 2007; 187: 244-245)**

Clinical records

Patient 1

A 71-year-old non-diabetic woman had been on some form of hormone replacement therapy (HRT) since the age of 49 years. She took oral oestrone sulfate 1.25 mg daily and medroxyprogesterone acetate 10 mg for at least 10 days a month for 8 years. For the next 2 years, she used a 3.2% compounded topical progesterone cream (at a daily dose of "one level spoonful"). In December 1997, she had some irregular vaginal bleeding, which was investigated by diagnostic hysteroscopy and curettage. The tissue diagnosis was atrophic endometritis.

Between June 1998 and July 2002, she used "bioidentical" HRT as troches. Each troche contained: oestradiol, 1.75 mg; progesterone, 300 mg; testosterone, 4.5 mg; and dehydroepiandrosterone (DHEA), 5 mg. The initial dose was half a troche per day, dissolved in the mouth.

Between July 2002 and December 2004, she used one-eighth of a troche in the morning and one-quarter in the evening. Each troche contained: trieste (oestrone, oestradiol, oestriol), 3.0 mg; progesterone, 400 mg; testosterone, 1.5 mg; and DHEA, 5 mg.

Early in 2004, she presented with several episodes of vaginal bleeding, and an ultrasonic scan revealed a thickened endometrial lining (combined thickness, 18 mm; normal for a postmenopausal woman is < 5 mm). Hysteroscopy confirmed a grossly abnormal endometrium with abnormal vascularisation. Curettage revealed a grade 2 endometrioid carcinoma. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The final diagnosis was stage IA, grade 2 endometrial cancer.

Patient 2

A 59-year-old non-diabetic woman, who had been menopausal from age 51 years, used "bioidentical" HRT as troches containing oestradiol, progesterone, testosterone and DHEA (doses unknown) from November 2001. From May 2003, she had noted continuous vaginal bleeding. An ultrasonic scan showed that the endometrial thickness was 19 mm. Diagnostic curettage in July 2003 confirmed a diagnosis of complex endometrial hyperplasia with atypia. She was referred to the Gynaecological Cancer Centre at the Royal Hospital for Women in September 2003, and underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The final diagnosis was stage IB, grade 2 endometrial cancer.

Patient 3

A 54-year-old non-diabetic woman presented with irregular vaginal bleeding. She had been using troches made by a compounding chemist for several years (precise time unknown). This treatment had been commenced while she was still menstruating. The troches had contained varying doses of DHEA, oestrone, oestradiol, oestriol and progesterone (doses unknown). The troches were posted to her by mail and she was monitored by telephone conversations with a nurse.

A pelvic ultrasound revealed a thickened endometrium; hysteroscopy and curettage showed a polypoid lesion at the fundus. Histopathology revealed grade 2 endometrial cancer. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, and the final diagnosis was stage IA, grade 2 endometrial cancer.

Discussion

Pharmaceutical HRT is a well established and tested therapy for the relief of menopausal symptoms such as hot flushes.[1] The risks, benefits and adverse effects of pharmaceutical HRT have been established in large randomised controlled trials such as the Women's Health Initiative study.[2] For example, unopposed oestrogen is known to be associated with an increased risk of endometrial carcinoma,[3] so a progestin is added to prevent this complication. Pharmaceutical progestins, when used appropriately, are very effective in preventing endometrial carcinoma.[3] Pharmaceutical medications undergo rigorous quality control, safety and efficacy testing. In Australia, pharmaceutical medicines are regulated by the Therapeutic Goods Administration.

In contrast to this, compounding chemists can "hand make" pharmaceuticals in novel delivery systems. Currently, these compounds are not directly regulated by the Therapeutic Goods Administration. Thus, little is known about the quality control, pharmacokinetics, safety and efficacy of these treatments. Compounded hormone replacement therapy is often termed "bioidentical" HRT. Typically, bioidentical HRT contains three oestrogens (oestrone, oestradiol and oestriol), progesterone, and androgens such as testosterone and DHEA, and is usually given either as cream rubbed onto the skin or as troches. Often, bioidentical HRT is monitored using blood or salivary levels of sex hormones. If the dose of progesterone is insufficient to prevent oestrogen-induced endometrial hyperplasia, then these treatments might cause endometrial carcinoma.

When testing new HRT regimens, endometrial assessment is one of the most important safety endpoints. The usual method used for evaluating the endometrium in HRT trials is endometrial biopsy (usually performed every 6–12 months). In its guidelines to the pharmaceutical industry, the United States Food and Drug Administration recommends endometrial biopsies at the beginning and

end of an HRT trial.[4] Sometimes ultrasound can give additional useful information (endometrial thickness, polyps, fibroids etc). The current "gold standard" test for endometrial assessment is hysteroscopy and curettage.

The three cases reported here raise the possibility that the oestrogen component of the troche was significantly absorbed but the dose of progesterone was inadequate, thereby causing endometrial hyperplasia. The North American Menopause Society has produced a useful discussion paper on bioidentical HRT,[5] and it should be noted that the Australasian Menopause Society does not recommend the use of bioidentical HRT.[6,7] Until this therapy has been properly tested, it may be prudent not to advocate bioidentical HRT and to perform endometrial surveillance (eg, annual transvaginal ultrasound and endometrial biopsies) on women who, despite counselling, continue to use bioidentical HRT.

Competing interests

John Eden is a consultant for Wyeth, AstraZeneca, Arkopharma, and Lawley Pharmaceuticals.

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References

1 MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. *Climacteric* 2004; 4: 58-74.
2 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
3 Gambacciani M, Monteleone P, Sacco A, Genazzani AR. Hormone replacement therapy and endometrial, ovarian and colorectal cancer. *Best Pract Res Clin Endocrinol Metab* 2003; 17: 139-147.
4 Center for Drug Evaluation and Research. Guidance for industry. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms — recommendations for clinical evaluation [draft guidance]. Rockville, MD: CDER, 2003. http://www.fda.gov/cder/guidance/5412dft.pdf (accessed Jul 2007).
5 North American Menopause Society. Understanding the controversy: hormone testing and bioidentical hormones. Proceedings of the Postgraduate Course prior to the 17th Annual Meeting of the North American Menopause Society. Nashville, Tennessee; 2006; 11 Oct. http://www.menopause.org/edumaterials/PG06monogrpah.pdf (accessed Jul 2007).
6 Australasian Menopause Society. Bioidentical hormones (troches) advice to consumers [media release]. 29 Nov 2003. http://www.menopause.org.au/public/media_detail.asp?ID=38 (accessed Jul 2007).
7 Australasian Menopause Society. Bioidentical hormones (troches) advice for doctors [media release]. 29 Nov 2003. http://www.menopause.org.au/public/media_detail.asp?ID=39 (accessed Jul 2007).

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