

POST-MENOPAUSAL OESTROGEN– PROGESTOGEN THERAPY

1. Exposure

Post-menopausal oestrogen–progestogen therapy involves administration of the oestrogens described in the monograph on ‘Post-menopausal oestrogen therapy’ accompanied by a progestogen or progesterone to women around the time of the menopause, primarily for the treatment of menopausal symptoms but also for the prevention of conditions that become more common after the menopause, such as osteoporosis and ischaemic heart disease. The progestogen can be administered orally or transdermally and either continuously or at various intervals. Intermittent progestogen administration causes withdrawal uterine bleeding, while continuous therapy generally does not. In ‘peri-menopausal hormonal therapy’, the components are not specified but are usually oestrogen with or without a progestogen. Annex 2 (Table 5) gives examples of brands of post-menopausal oestrogen–progestogen therapy. Progestogens that can be given in combination with the oestrogens are listed in Annex 1, with their constituents, doses, routes of administration and the names of some countries in which the brands are available; Annex 1 also gives the chemical formulae and some information on indications for use.

1.1 Historical overview

The earliest forms of hormones used for the treatment of ovarian failure or after oophorectomy were natural extracts of ovarian tissue, placenta and urine from pregnant women and thus contained both oestrogen and progestogen, as well as other substances. Crystalline progesterone was first identified in 1934, and shortly afterwards experimental treatment of women with injected oestrogen and progesterone began (Hirvonen, 1996). In the decades that followed, however, menopausal symptoms were treated mainly with oestrogen alone rather than with combined oestrogen–progestogen therapy.

Oral progesterone equivalents did not become readily available until the 1940s, when Russell Marker synthesized diosgenin from extracts of the Mexican yam. Further experimentation yielded the synthesis of norethisterone (norethindrone) by Carl Djerassi in 1950 and norethynodrel by Frank B. Colton in 1952. These compounds were named progestogens (or progestins) owing to their progesterone-like actions (Kleinman, 1990). They were ultimately used in combined oral contraceptives (see section 1 of the monograph on ‘Oral contraceptives, combined’ for details), developed in the late 1950s.

During the 1960s and early 1970s, most hormonal therapy was used in the United States (particularly in California) and took the form of post-menopausal oestrogen therapy,

without progestogen. At that time, some clinicians, especially those in Europe, prescribed oestrogen–progestogen therapy, primarily for better control of uterine bleeding during treatment, as post-menopausal oestrogen therapy sometimes causes irregular bleeding in women with a uterus (Maddison, 1973; Studd, 1976; Bush & Barrett-Connor, 1985). Figure 1 of the monograph on ‘Post-menopausal oestrogen therapy’ shows the estimated numbers of prescriptions of non-contraceptive progestogens and medroxyprogesterone acetate in the United States between 1966 and 1992.

Studies linking post-menopausal oestrogen therapy with increased rates of endometrial cancer were first published in 1975 (Ziel & Finkle, 1975). These led to a rapid decrease in prescription of such therapy in the United States and the recommendation by many clinicians and researchers that progestogen be added to oestrogen when treating post-menopausal women with an intact uterus, as this had been shown to attenuate the risk of endometrial cancer associated with the use of oestrogen alone (Bush & Barrett-Connor, 1985; Kennedy *et al.*, 1985). In Europe, when post-menopausal hormonal therapy was indicated for women with an intact uterus, it became accepted practice to administer combined oestrogen–progestogen therapy; post-menopausal oestrogen therapy was still given to hysterectomized women. In the United States, some clinicians continued to prescribe post-menopausal oestrogen therapy to women with a uterus, following guidelines to monitor the endometrium (American College of Physicians, 1992), although increasing prescription of progestogens was noted after 1975 (see Figure 1 in the monograph on ‘Post-menopausal oestrogen therapy’). In the United States in 1980, approximately 5% of the Premarin®, the commonest oestrogen sold, was accompanied by oral Provera®, the commonest progestogen, while in 1983 this figure had risen to 12% (Kennedy *et al.*, 1985). In the United Kingdom, prescription of oestrogen–progestogen therapy increased throughout the late 1970s and early 1980s, until in 1984 almost equal amounts of oestrogen alone and oestrogen–progestogen therapy were used (Townsend, 1998).

The Women’s Health Initiative trial of post-menopausal hormonal therapy was begun in the United States in 1992. In this trial, women with a uterus could be randomized to post-menopausal oestrogen therapy with monitoring of the endometrium, reflecting a proportion of clinical practice at the time (Finnegan *et al.*, 1995). In 1995, the results of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial showed adenomatous or atypical endometrial hyperplasia in 34% of women receiving 0.625 mg unopposed conjugated equine oestrogens daily (Writing Group for the PEPI Trial, 1995). The protocol of the Women’s Health Initiative trial was therefore amended so that women with a uterus could be randomized to receive only combined oestrogen–progestogen therapy or placebo (Finnegan *et al.*, 1995). No figures on the prevalence of post-menopausal oestrogen–progestogen therapy after this publication are available, but it is expected that use will increase relative to that of post-menopausal oestrogen therapy.

1.2 Post-menopausal oestrogen–progestogen therapy preparations

The oestrogens used in post-menopausal oestrogen–progestogen therapy are described in the monograph on ‘Post-menopausal oestrogen therapy’ and in Annex 1; the proges-

togens used in oestrogen-progestogen therapy are derived from 17 α -hydroxyprogesterone and 19-nortestosterone, although progesterone itself is sometimes used. Tibolone is a centrally acting compound with both oestrogenic and progestogenic actions. Of the 17 α -hydroxyprogesterone derivatives, medroxyprogesterone acetate is the most widely used; dydrogesterone is also available. Of the 19-nortestosterone derivatives, norethisterone, norethisterone acetate, norgestrel and levonorgestrel are used in post-menopausal oestrogen-progestogen therapy. Progesterone is now administered orally in a micronized form but was given by injection in the past (British Medical Association, 1997).

In the commonest treatment regimen, the oestrogen component is taken daily orally or transdermally, usually at a constant dose, with a progestogen given for 10–14 days per month, causing withdrawal bleeding. A typical dose of progestogen is 5–10 mg medroxyprogesterone acetate orally, daily for 10–14 days. Preparations are also available in which the progestogen is given every three months, causing quarterly bleeding. Another widely used regimen is a constant dose of oestrogen taken daily continuously, accompanied by continuous progestogen. A typical continuous progestogen dose would be about 2.5 mg medroxyprogesterone acetate orally per day (British Medical Association, 1997). The continuous progestogen can also be given transdermally as 0.25 mg norethisterone acetate per 24 h; this regimen usually does not result in withdrawal bleeding (Cameron *et al.*, 1997). Tibolone is given orally, continuously and does not usually result in bleeding, except if treatment is started within 12 months of the woman's last menstrual period (British Medical Association, 1997).

In some countries, primarily in Europe, a progestogen is sometimes given alone for the treatment of menopausal symptoms. A progestogen can also be given in the form of a levonorgestrel-releasing intrauterine device, accompanying oral or transdermal oestrogen, to deliver the progestogen directly to the endometrium (British Medical Association, 1997). This system is not widely licensed for use as post-menopausal oestrogen-progestogen therapy.

1.2.1 *Patterns of use*

Like post-menopausal oestrogen therapy, combined oestrogen-progestogen therapy is started around the time of the menopause and can be used for both short- and long-term treatment. Table 1 in the monograph on 'Post-menopausal oestrogen therapy' shows the prevalence of current and any use of post-menopausal hormonal therapy in selected studies internationally, with post-menopausal oestrogen therapy and oestrogen-progestogen therapy use shown in the studies in which they were reported separately; very few studies mentioned use of post-menopausal oestrogen-progestogen therapy. In the United States, post-menopausal oestrogen-progestogen therapy was being used currently by 1–5% of women aged 45–64 and had ever been used by 14% of a nationally representative sample of post-menopausal women aged 25–76 in the late 1980s. In Denmark, 12% of 40–59-year-old and 17% of 51-year-old women had ever used post-menopausal oestrogen-progestogen therapy in 1983 and 1987, respectively. In Sweden, combined oestradiol-progestogen use (usually with levonorgestrel or norethisterone acetate) became popular in the

early 1970s and is now standard practice. Thus, the increase in the sales of replacement hormones in Sweden since the early 1990s almost entirely entails progestogen-combined regimens. In England, prescription data showed that an estimated 1% of women aged 40–64 used post-menopausal oestrogen–progestogen therapy in 1989, compared with an estimated 11% of women in 1994. About 1% of women in this age group were using tibolone in 1994 (Townsend, 1998).

In a study of general medical practices in the United Kingdom in 1993, 96% of women with a hysterectomy who were taking post-menopausal hormonal therapy were taking oestrogen alone, and 96% of women who had not undergone hysterectomy were taking combinations of oestrogen and progestogen (Lancaster *et al.*, 1995).