POST-MENOPAUSAL OESTROGEN THERAPY

1. Exposure

'Post-menopausal oestrogen therapy' refers to the use of oestrogen without progestogen for women in the period around the menopause, primarily for the treatment of menopausal symptoms but increasingly for the prevention of conditions that become more common in the post-menopausal period, such as osteoporosis and ischaemic heart disease. Currently, it is mainly given to women who have had a hysterectomy, as treatment with oestrogen alone in women with a uterus increases the risk for endometrial cancer. In the past, women with a uterus were often prescribed post-menopausal oestrogen therapy, although predominantly in the United States. Post-menopausal therapy with combined oestrogen and progestogen is discussed in another monograph in this volume.

Post-menopausal oestrogen therapy can be administered orally, transdermally (by patch or gel), by injection or by implant. Local, topical preparations are also available for relief of urogenital symptoms. Annex 2 (Table 3) gives a list of common brands of post-menopausal oestrogen therapy, with their constituents and doses and examples of countries in which they are available. Post-menopausal oestrogen therapy can also be administered in combination with an androgen or with an anxiolytic, and examples of such brands and formulations are given in Annex 2 (Table 4).

1.1 Historical overview

Whether menopause is natural or induced surgically, women in this condition have long been known to suffer from problems such as hot flushes (or 'flashes') and urogenital atrophy and to have increased rates of fracture and cardiovascular disease, in comparison with pre-menopausal women. These problems are particularly severe in women who have a premature menopause. In 1895, Marie Bra suggested that ovarian secretions could be used to treat ovarian failure (Bush & Barrett-Connor, 1985), and the first therapeutic investigations of the administration of ovarian tissue for the relief of climacteric symptoms were reported in 1896. Subsequently, researchers and clinicians investigated the use of various ovarian, placental and urine extracts, implantation of ovarian tissue and oral administration of dried ovarian tissue (Kopera & van Keep, 1991).

The identification of the ovarian hormones allowed a more specific understanding of the factors that might be responsible for climacteric symptoms. Oestrone, oestriol and progesterone were identified in 1929, and oestradiol was identified in 1936 (IARC, 1979). The first synthetic oestrogens, diethylstilboestrol and ethinyloestradiol, were isolated in 1938 (Bush & Barrett-Connor, 1985).

Clinical use of oestrogen for women with premature surgical or natural menopause began in the 1930s (Stadel & Weiss, 1975; Kopera & van Keep, 1991). Campbell and Collip (1930) demonstrated the clinical efficacy of extracts of human placenta in relieving menopausal symptoms and deviations from the normal menstrual cycle, like dysmenorrhoea. Although a product containing these extracts was introduced onto the market, it was impractical to produce on a large scale (Stern, 1982); most oestrogen was therefore administered by injection or subcutaneous implant. The earliest use of an implant was reported by Bishop (1938), who administered oestrogen to women after oophorectomy.

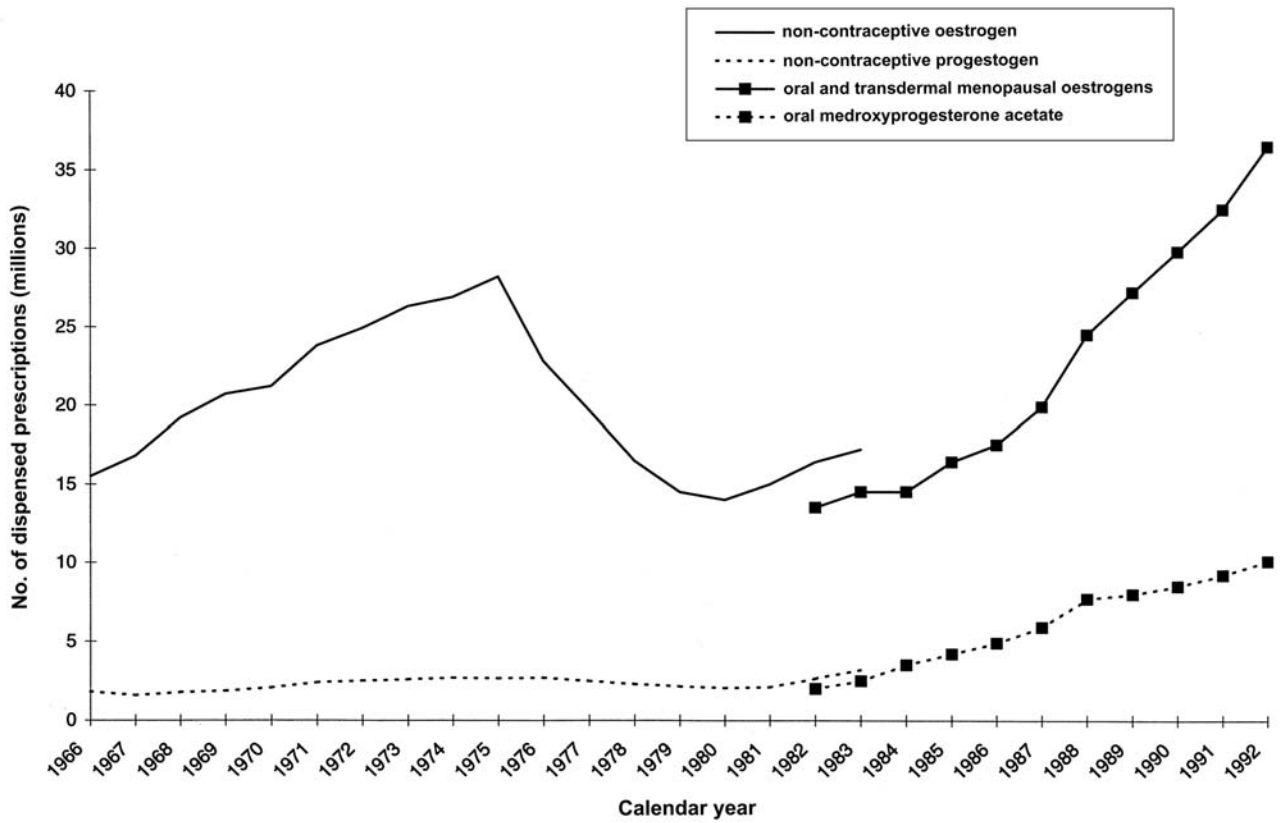
Clinical trials of conjugated equine oestrogens from the urine of pregnant mares were initiated in 1941 (Stern, 1982). In 1943, these preparations became available in the United States for use as oral post-menopausal oestrogen therapy and were introduced onto the market in the United Kingdom in 1956 (Godfree, 1994). Over the following years, post-menopausal oestrogen therapy began to be used less for women who had had a premature menopause than for women who had had menopause at a normal age, although women who had undergone a hysterectomy or an oophorectomy have been consistently more likely to receive post-menopausal oestrogen therapy than women who have had a natural menopause (Brett & Madans, 1997). The indications for use also widened, from short-term treatment for menopausal symptoms to longer-term treatment for the prevention of osteoporosis and cardiovascular disease; some clinicians advocated near-universal prescription for women after the menopause (Schleyer-Saunders, 1973).

Use of post-menopausal oestrogen therapy became widespread in the United States in the 1960s: the number of women using it was estimated to have increased by 240% between 1962 and 1967 (Bush & Barrett-Connor, 1985), such that approximately 13% of women in the United States aged 45–64 used post-menopausal oestrogen therapy (Stadel & Weiss, 1975). Figure 1 gives the estimated numbers of prescriptions for non-contraceptive oestrogens and progestogens from the National Prescription Audit in the United States (Kennedy *et al*., 1985; Wysowski *et al*., 1995) between 1966 and 1992. The dose of oral oestrogen prescribed decreased over the period 1975–83, as did the use of injectable post-menopausal oestrogen therapy (Kennedy *et al*., 1985). By 1992, transdermal oestradiol accounted for 15% of post-menopausal oestrogen therapy prescriptions in the United States (Jewelewicz, 1997).

In the United Kingdom, around 2% of English women aged 40–64 were using post-menopausal hormonal therapy during the period 1980–87, the prevalence rising rapidly to reach 22% by 1994. The majority of these prescriptions were for combined oestrogen–progestogen therapy (Townsend, 1998).

The fall in the number of prescriptions of oestrogen in the United States corresponded to scientific reports and growing public awareness of the elevated risks for endometrial cancer of women using post-menopausal oestrogen therapy who had not had a hysterectomy (Smith *et al*., 1975; Ziel & Finkle, 1975). Thereafter, the prescription rates for such therapy in the United States began to rise but more frequently in combination with a progestogen (Hemminki *et al*., 1988; see the monograph on 'Post-menopausal oestrogen–progestogen therapy'). Administration of unopposed therapy to women with a uterus

Figure 1. Estimated numbers of dispensed prescriptions (in millions) of non-contraceptive oestrogens and progestogens in the United States, 1966–92



Adapted from Kennedy *et al.* (1985) and Wysowski *et al.* (1995)
The estimates for 1966–83 are for prescribed oestrogens and progestogens other than those that are part of an oral contraceptive, and the estimates for 1982–92 are for the more specific categories of oral and transdermal menopausal oestrogens and oral medroxyprogesterone acetate (the most commonly prescribed menopausal progestogen in the United States).

continued, predominantly in the United States, with the recommendation that the endometrium be monitored (e.g. American College of Physicians, 1992). A more substantial shift in consciousness in the United States occurred in 1995, with the publication of the results of a trial that showed the occurrence of adenomatous or atypical endometrial hyperplasia in 34% of women receiving 0.625 mg of unopposed conjugated equine oestrogens daily (Writing Group for the PEPI Trial, 1995). Subsequently, the protocol of the nationwide Women's Health Initiative trial of post-menopausal hormonal therapy was amended so that women with a uterus could be randomized to receive only combined oestrogen–progestogen therapy or placebo (Finnegan *et al*., 1995).

Oestrogen–androgen combinations accounted for an estimated 14% of non-contraceptive oestrogen prescriptions in the United States in 1966, but this had fallen to less than 2% in 1983 (Kennedy *et al*., 1985). The number of oestrogen–androgen prescriptions then began to increase again, from 0.1 million in 1982 to 0.8 million in 1992 (Wysowski *et al*., 1995). Oestrogen in combination with a tranquillizer represented an estimated 3% of non-contraceptive oestrogen prescriptions in the United States in 1975, falling to less than 1% of prescriptions in 1983 (Kennedy *et al*., 1985).

Outside the United States, use of post-menopausal oestrogen therapy was generally uncommon until the late 1970s and 1980s and was prescribed mainly to women who had had a hysterectomy (although very few data are available about international use before the 1980s). In Europe, women with an intact uterus have been treated with combined oestrogen–progestogen therapy since the early 1970s (Maddison, 1973).

Transdermal post-menopausal oestrogen therapy became available in the mid-1980s.

1.2 Post-menopausal oestrogen therapy preparations

The main oestrogens used in oral post-menopausal oestrogen therapy are conjugated equine oestrogens, oestradiol and oestradiol valerate, although esterified oestrogens, mestranol, oestriol and oestropipate, are also used. Oestriol is more commonly used in Scandinavia (Persson *et al*., 1983; Stadberg *et al*., 1997). The appropriate dose of oestrogen varies with the indication for therapy; for menopausal symptoms, it can be raised until a minimum effective dose is found. The usual oral dose of conjugated equine oestrogens is 0.625–1.25 mg daily, and the usual oral dose of oestradiol is 0.5–4.0 mg daily (British Medical Association, 1997). For prevention of osteoporosis, the United Kingdom guidelines stipulate minimal doses of 0.625 mg/day oral conjugated equine oestrogens, 2 mg/day oral oestradiol or 0.050 mg/day oestradiol by patch, and not all types of oestradiol patches are specifically licensed for this indication (Anon., 1996).

Oestradiol can also be administered transdermally via a gel or patch, which avoids the first-pass effect of the liver, where a substantial proportion of orally administered oestrogen is deactivated, thus providing more constant blood hormone concentrations than oral preparations. In addition, because it does not cause the peaks and troughs in hormone concentration characteristic of oral medication, a lower overall dose of oestrogen can be given by transdermal administration (Williams & Stancel, 1996). Transdermal doses of oestradiol range from 0.025 mg to 0.1 mg per 24 h (British Medical Association, 1997). The

patches available initially consisted of a central oestradiol reservoir and an external adhesive ring, while in those developed more recently oestradiol is distributed throughout the adherent part of the patch (Anon., 1996). The patches are applied to a clean, non-hairy area of the skin, generally below the waist, and are reapplied every three to four days at a different site.

The available implants consist of crystalline pellets of oestradiol which are inserted subcutaneously under local anaesthesia and provide continuous oestrogen therapy for several months (Anon., 1996). Implants containing 50 mg oestradiol provide effective concentrations for approximately six months, and those containing 100 mg may last for up to nine months (Studd, 1976).

Oestrogen combined with androgen is usually taken orally but can also be given by implant. The usual indication for this type of therapy is menopausal symptoms accompanied by loss of libido (British Medical Association, 1997; Reynolds, 1998). A combination of esterified oestrogen and the anxiolytic chlordiazepoxide (given as 5–10 mg daily) is available in the United States for menopausal symptoms accompanied by anxiety (Reynolds, 1998).

Local topical preparations are available in the form of creams, pessaries and vaginal tablets containing oestriol, oestradiol, conjugated oestrogens, dienoestrol or other oestrogens. They generally have low systemic absorption and are given for urogenital symptoms when systemic therapy is not required. They are not discussed further in this monograph.

1.2.1 *Patterns of use*

Menses cease normally around the age of 50, often preceded and accompanied by climacteric symptoms. Women who have had a hysterectomy often have earlier onset of symptoms, and those who have had pre-menopausal oophorectomy often develop symptoms soon after their operation. Treatment of climacteric symptoms with post-menopausal oestrogen therapy is generally begun around or before the age of menopause and continued until withdrawal of treatment does not lead to a return of the symptoms. Symptomatic treatment generally lasts for less than five years and often for one to two years. Longer-term treatment for the prevention of osteoporosis and other conditions may continue for 10 years or more.

Table 1 shows the prevalence of use of post-menopausal oestrogen therapy in selected international population-based studies. These studies are difficult to interpret and compare as they tended to involve regions within a country that are not necessarily representative of the nation as a whole, include different age groups and usually do not allow a distinction between post-menopausal oestrogen therapy and oestrogen–progestogen therapy. Use of post-menopausal oestrogen therapy varies enormously from country to country and may also show substantial variation within a particular country (Keating *et al*., 1997). This regional variation is particularly marked in the United States. No figures on prevalence of use are available for many countries. Use is generally considered to be low in most of Africa and Asia.

Table 1. Prevalence of use of post-menopausal hormonal therapy (HT) in selected studies, 1975–97

Country	Reference	Year(s)	Age group (years)	Current use (%)			Any use (%)		
				HT	Oestrogen alone	Oestrogen–progestogen	HT	Oestrogen alone	Oestrogen–progestogen
Australia	MacLennan *et al*. (1993)	1991	> 40	14			25		
Denmark	Pedersen & Jeune (1988)	1983	40–59	16			33	16	12
	Køster (1990)	1987	51	22			37	10	17[a]
	Oddens & Boulet (1997)	1994	45–65	18			31		
Finland	Topo *et al*. (1995)	1989	45–64	22					
France	Ringa *et al*. (1992)	1986–87	45–55[b]	8	3	3[a]			
Norway	Topo *et al*. (1995)	1981	45–55	9					
Sweden	Persson *et al*. (1983)	1980	50–54	9					
			55–59	6					
	Lindgren *et al*. (1993)	1988	55, 57, 59 and 65	10			20		
	Stadberg *et al*. (1997)	1992	46, 50, 54, 58 and 62	21			41		
	Hammar *et al*. (1996)	1995	55–56	35[c]			40[c]		
United Kingdom	Spector (1989)	Late 1980s	45–65				10		
	Sinclair *et al*. (1993)	1991	33–69[b]	9			16		
	Griffiths & Jones (1995)	1993	45–65	20			33		
	Lancaster *et al*. (1995)	1993	45–64	15					
	Banks *et al*. (1996)	1994–95	50–64	30			43		
	Porter *et al*. (1996)	NR	45–54	19					
	Kuh *et al*. (1997)	1993	47	18			25		
	Townsend (1998)	1987	40–64	3					

Table 1 (contd)

Country	Reference	Year(s)	Age group (years)	Current use (%)			Any use (%)		
				HT	Oestrogen alone	Oestrogen–progestogen	HT	Oestrogen alone	Oestrogen–progestogen
United States	Stadel & Weiss (1975)	1973–74	> 18[b]				51		
	Barrett-Connor *et al*. (1979)	1973–75	55–74	39					
	Egeland *et al*. (1988)	1983–84	40–52	6	4	1			
	Barrett-Connor *et al*. (1989)	1984–87	50–79	31					
	Harris *et al*. (1990)	1986–87	NR	32	26	6			
	Cauley *et al*. (1990)	1986–88	> 65	18	15	3			
	Derby *et al*. (1993)	1981–82	40–64	5					
	Derby *et al*. (1993)	1989–90	40–64	11					
	Nabulsi *et al*. (1993)	1986–89	45–64						
	Black			17	16	1	33		
	White			22	17	5	39		
	Johannes *et al*. (1994)	1981–87	45–61	12[d]					
	Handa *et al*. (1996)	1986–87	> 65	6			25		
	Salamone *et al*. (1996)	1991		17			45		
	Brett & Madans (1997)	1982–92	25–74[b]				45	31	14
	Keating *et al*. (1997)	1995	45–74[b]	38					

NR, not reported
[a] 2% progestogen only
[b] Post-menopausal women only
[c] Oestriol users excluded
[d] Any use during study period

In the United States, the sales of non-contraceptive oestrogens increased from around 16 million per year in 1966 to around 36 million in 1992 (Kennedy *et al*., 1985; Wysowski *et al*., 1995). Use of post-menopausal hormonal therapy is more common in southern and western United States than in other regions (Keating *et al*., 1997). In England, a 10-fold increase in the estimated proportion of women using post-menopausal oestrogen therapy was seen in the period 1987–94, with less than 1% of women using oestradiol or conjugated oestrogens in 1987 and 10% in 1994 (Townsend, 1998). Table 1 shows that the prevalence of post-menopausal hormonal therapy in the mid-1990s was about 20% in the age group 45–64. In Scandinavia, use of post-menopausal hormonal therapy increased throughout the 1980s and early 1990s, Norway appearing to have consistently lower rates of use than Sweden, Finland and Denmark (Topo *et al.,* 1995). Sales of post-menopausal hormones (mainly oestradiol compounds cyclically or continuously combined with progestogens) have risen in Sweden since the 1970s, with a clear acceleration and doubling of use rates since the beginning of the 1990s (National Corporation of Pharmacies, 1997). Use of post-menopausal hormonal therapy in general appears to be also relatively common in Australia (MacLennan *et al.*, 1993).

Estimates based on sales data for 1991–92 show that enough post-menopausal hormonal therapy was sold to supply 20% of 45–70-year-old women in the United States (assuming only long-term use), 9–16% of women in Scandinavia and the United Kingdom, 7% in France, 5% in Belgium, 4% in the Netherlands, 3% in Austria and less than 1% of women in this age group in Italy and Spain (Jolleys & Olesen, 1996). Use of post-menopausal hormonal therapy is low in Japan (Nagata *et al.,* 1996).

The post-menopausal oestrogen therapy used in the United States is predominantly conjugated equine oestrogens, Premarin® being the single most commonly prescribed proprietary medicine overall in 1995 (Reynolds, 1998). The oestrogen composition of Premarin® is shown in Table 2. In Scandinavia and the United Kingdom, oestradiol is the oestrogen therapy most commonly prescribed for the menopause (Persson *et al*., 1997a; Townsend, 1998). Studies from Sweden show that 15–20% of current users of post-menopausal hormonal therapy take oestriol (Persson *et al*., 1983; Stadberg *et al*., 1997).

Women taking post-menopausal oestrogen therapy differ from women who do not take it in a number of ways; most notably, they are more likely to have had a hysterectomy and/or oophorectomy (Cauley *et al.*, 1990; Derby *et al.*, 1993; MacLennan *et al.*, 1993; Brett & Madans, 1997). Hysterectomy not only increases the likelihood that a woman will take post-menopausal hormonal therapy in general but also affects the type of therapy taken. Lancaster *et al.* (1995) reported from their general practice-based study in the United Kingdom that, of women taking post-menopausal hormonal therapy, 96% of those with a hysterectomy were taking oestrogen alone and 96% of women without a hysterectomy were taking combined oestrogen and progestogen. As post-menopausal oestrogen therapy is increasingly reserved for women who have had a hysterectomy, the relative use of oestrogen and combined oestrogen and progestogen therapy increasingly reflects the prevalence of hysterectomy in a population. Several studies have shown that, in comparison with non-users, post-menopausal oestrogen therapy users are more likely to have

Table 2. Oestrogen composition (as sulfates) of Premarin®

Oestrogen	% of total
Oestrone sulfate	42
8-Dehydrooestrone sulfate	18
Equilin sulfate	17
17α-Dehydroequilenin sulfate	10
Equilenin sulfate	4.3
17α-Dehydroequilin sulfate	3.4
17α-Oestradiol sulfate	2.4
17β-Oestradiol sulfate	1.5
17β-Dehydroequilin sulfate	0.7
17β-Dehydroequilenin sulfate	0.7

From Li *et al.* (1995)

taken the oral contraceptive pill in the past and to suffer from more severe menopausal symptoms (Sinclair *et al.*, 1993; Handa *et al.*, 1996; Persson *et al.*, 1997a). The relationship between post-menopausal oestrogen therapy and factors such as education, alcohol consumption, smoking and parity is not consistent from study to study.