Continuous combined hormone replacement therapy and its effects

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The cessation of menstruation at the menopause is a great relief for most women. Hormone replacement therapy (HRT) in sequential regimens re-creates a monthly cycle and period-type bleeds, which are a major cause for dissatisfaction, especially for older, postmenopausal women. Continuous combined therapy aims to provide the benefits of HRT without cyclical bleeding.

While the benefits of hormone replacement therapy (HRT) are becoming increasingly well established and accepted, it is self-evident that women will not achieve such effects if they do not continue with HRT for long enough. Compliance or continuance is surprisingly poor, with up to 40% of women stopping therapy within 8 months, and few continuing for more than 1 or 2 years (Ryan et al, 1992).

The main reasons for discontinuing HRT include cyclical, period-type bleeding, fear of cancer, unacceptable or unexpected side-effects such as breast tenderness and premenstrual syndrome (PMS)-type symptoms, and weight gain. Reaching the menopause brings welcome relief from menstruation, but is often particularly troublesome during the perimenopausal years. It is not surprising, therefore, that bleeding induced by sequential HRT is considered unsatisfactory by most women.

After the menopause, the endometrium will still respond to oestrogen and progesterone in a similar way to the cyclical ovarian hormone production during the premenopausal fertile years, and the endometrium breaks down and bleeds when the levels of progesterone in particular decrease at the end of each month. Sequential regimens of HRT are intended to mimic the ovarian cycle, whereas continuous combined therapy (CCT) provides the same dose of oestrogen and progestogen every day without a break so that there is no cycle. The continuous daily progestogen is the fundamental difference between these regimens, and it is the implications of this that will form the basis of this review.

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BLEEDING AND THE ENDOMETRIUM

In sequential regimens the progestogen is intended to prevent endometrial hyperplasia and carcinoma, and to produce a regular, controlled and predictable bleed. This bleed is similar to normal menstruation, but it is not widely appreciated that no more than 50% of the functional layer of the endometrium is shed, thus a 'medical curettage' cannot be the sole mechanism by which progestogens prevent hyperplasia.

The biochemical and morphological changes in the endometrium which are induced by progestogen (Whitehead et al, 1981) are maintained as long as progestogen is administered. If this is continuous, the proliferative effect of oestrogen will be prevented, and the endometrium should become atrophic. This was the rationale for the introduction of CCT, since without any cycle or a progestogen withdrawal phase, and with no tissue to be shed, there should not be any bleeding (Mattsson et al, 1982). The benefits should be the same as for sequential therapy.

Although the main aim of CCT is to avoid cyclical bleeding, all studies of CCT have found a high incidence of bleeds, particularly in the first 3 months, varying from 50 to 80%. This occurs more often in women who are within 1 year of the menopause, rather than in postmenopausal women, probably as a result of some residual ovarian activity.

However, the bleeds are usually light and are often only intermittent spotting. With time it becomes less, so that few women are bleeding after 12 months (Mattsson et al, 1982; Magos et al, 1985; Archer et al, 1994; Udoff et al, 1995). The development of low dose combinations, with 1 mg oestradiol or equivalent, may cause less bleeding (Baerug et al, 1998). The gonadomimetic hormone tibolone is specifically converted in the endometrium to its' Δ 4-metabolite, which has no oestrogenic activity, so the endometrium is not stimulated. One comparative study with CCT does

suggest a lower incidence of bleeding or spotting (Hammar et al, 1998).

Several studies have confirmed that an atrophic endometrium is achieved with CCT in 90–100% of women, even after only 3 months of treatment, with daily doses of progestogen as low as 0.35 mg norethisterone acetate, or 2.5 mg medroxyprogesterone acetate (MPA). After 1 year of treatment with conjugated equine oestrogens (CEE) 0.625 mg and MPA 2.5 or 5.0 mg daily, Woodruff and Pickar (1994) found endometrial hyperplasia without atypia in less than 1% of women, which is lower than the background rate in postmenopausal women.

Wells (1996) reported on a series of women who had complex endometrial hyperplasia while taking standard sequential oestrogen/progestogen regimens. This was converted to normal endometrium after 9 months of CCT. These data suggest that the continuous progestogen in CCT may provide better protection of the endometrium, which is particularly important for long-term therapy.

There have been two reports of endometrial cancer in women taking CCT, and in all of the cases there were predisposing factors, such as previous atypical endometrial hyperplasia or prolonged use of unopposed oestrogen therapy (Leather et al, 1991; Comerci et al, 1997). There are no reports of endometrial cancer developing in women from a normal endometrium while taking CCT.

TREATMENT COMBINATION OPTIONS

Initial reports on CCT were with oral regimens, either in a fixed dose combination such as oestradiol 2 mg with norethisterone acetate 1 mg, or with varying dose combinations, particularly of the progestogen, to obtain optimum prevention of bleeding (Magos et al, 1985). With the rapid expansion in the number of hormone preparations and routes of administration of oestrogen and progestogen, there are now many different options for providing CCT (*Table 1*). In the UK there are six fixed dose proprietary preparations (*Table 2*) and the gonadomimetic tibolone. This is a synthetic hormone that has oestrogenic, androgenic and progestogenic activity, and effects that are similar to CCT (Moore, 1999).

CARDIOVASCULAR DISEASE RISK FACTORS

The increasing prevalence of cardiovascular disease in postmenopausal women is associated with an unfavourable change in the blood lipid profile after the menopause, and in particular a rise in total cholesterol levels. Oestrogen replacement therapy causes a favourable change in the lipid profile, and this may contribute up to 30% of the total benefit in reducing cardiovascular disease risk. Progestogen derivatives of 19-nortestosterone have been shown to adversely affect the beneficial oestrogenic effect on serum lipoproteins (Hirvonen et al, 1981), and mainly for this reason there has been some reluctance to accept that CCT could be a suitable regimen for long-term HRT.

However, several studies with different combinations of oestrogen and progestogen have demonstrated a significant reduction in total cholesterol and in low density lipoprotein (LDL) cholesterol levels, with little difference between the different combinations (Christiansen and Riis, 1990; The Writing Group for the PEPI Trial, 1995; Speroff et al, 1996). The main effect of progestogens seem to be to blunt the rise of high density lipoprotein (HDL) cholesterol that is induced by oestrogen alone, but the reduction of the LDL fraction may be greater so that overall there is considered to be a beneficial effect. A raised serum triglyceride level is also an independent risk factor for coronary heart disease, and this tends to rise after the menopause and to be increased further by oral oestrogen. Studies of CCT with MPA have shown

TABLE 1.
Options for routes of administration of oestrogen and progestogen in continuous combined regimens

Oestrogen	Tablet
	Skin patch or gel
	Subcutaneous pellet implant
	Vaginal ring*
Progestogen	Tablet
	Skin patch
	Vaginal gel
	Suppository
	Intrauterine device*

*under development or not yet licensed for this purpose in the UK

TABLE 2.
Period-free therapy

Type	Brand®	Oestrogen	Progestogen	Formulation
Continuous combined therapy	Climesse	oestradiol 2 mg	norethisterone 0.7 mg	Tablets
	Kliofem	oestradiol 2 mg	norethisterone 1 mg	Tablets
	Kliovance	oestradiol 1 mg	norethisterone 0.5 mg	Tablets
	Elleste Duet conti	oestradiol 2 mg	norethisterone 1 mg	Tablets
	Premique	CEE 0.625 mg	MPA 5 mg	Tablets
	Evorel conti	oestradiol 50 μg	norethisterone 170 μg	Patches
Gonado-mimetic	Livial		tibolone 2.5 mg	Tablets

CEE = conjugated equine oestrogens; MPA = medroxyprogesterone acetate

variable effects and either little change or a slight increase, although norethisterone can significantly reduce the levels of triglyceride (Christiansen and Riis, 1990; Speroff et al, 1996).

There is no evidence that CCT alters systolic or diastolic blood pressure, or causes weight gain (Christiansen and Riis, 1990; The Writing Group for the PEPI Trial, 1995).

There are many long-term observational studies on the effects of HRT on cardiovascular disease, but none of them have contained data on CCT. However, a recently reported randomized placebo-controlled secondary prevention (HERS) study assessed the effect of CCT with CEE 0.625 mg and MPA 2.5 mg daily on the risk of myocardial infarction (Hulley et al, 1998). The women had a mean age of 68 years and proven coronary artery disease, and were studied for just over 4 years.

Overall, there were no significant differences between the placebo and CCT group in the occurrence of non-fatal myocardial infarction, although the incidence was significantly greater in the treatment group during the first year. Subsequently, there were fewer events in years 4 and 5, producing a statistically significant favourable time trend. Analysis of the time trend suggested a possible late benefit of treatment, and it is very regrettable that the study was not continued for a further 6–12 months, which might have demonstrated a definite benefit from CCT.

This study also found a significant excess risk of venous thrombosis in the CCT users (relative risk 2.9, 95% confidence intervals 1.50–5.58) which is similar to other recent reports for HRT (Daly et al, 1996). The HERS study has received much critical analysis, and in particular it is not clear what relevance the findings have for postmenopausal women who do not have coronary artery disease. Current use of HRT is thought to provide approximately a 50% reduction in coronary heart disease risk, but the long-term effects will not be established until after further larger and more powerful prospective randomized controlled trials. These are currently underway, but will not report for several years.

OSTEOPOROSIS

One of the commonest reasons for women to want to take HRT in the long term is to prevent osteoporosis. The prevention of bone loss by oestrogen and combined sequential regimens of HRT is well established. Some progestogens, particularly norethisterone, can have an independent effect in preventing bone loss in postmenopausal women (Abdalla et al, 1985). When used in CCT regimens, there may be an additive effect to that of oestrogen, thus increasing the benefits for bone protection and the initial replacement of bone loss (Christiansen and Riis, 1990).

BREAST CANCER

None of the various reports on HRT and the risk of breast cancer have any or sufficient data on CCT regimens to indicate if there is any difference from unopposed oestrogen or sequential oestrogen and progestogen regimens. The HERS study was not powerful enough, but hopefully the other ongoing studies will provide satisfactory data on this aspect as well as for cardiovascular disease. It is unlikely that the continuous progestogen will alter the overall slightly increased risk with long-term use in postmenopausal women, and women should be counselled accordingly.

COMPLIANCE

CCT is most suitable for women who are at least 1 year postmenopause, when symptom control is less important than long-term benefits, although flushes and sweats are relieved by CCT (Baerug et al, 1998). Side-effects of sequential oestrogen/progestogen HRT are often a result of the progestogen component, and are similar to those of PMS. Each month these problems may be triggered by the introduction of the 10–12-day phase of progestogen.

With CCT there is no cycle or change in hormone levels, so that PMS-type side-effects seem to be less of a problem. However, the continuous progestogen may still cause breast tenderness and abdominal bloating, and if these do not resolve after the initial weeks of treatment, a lower dose may be more satisfactory (Baerug et al, 1998). The main advantage of CCT, however, should be the absence of period-type bleeds, and this does improve compliance compared to the monthly sequential regimens (Dören et al, 1995).

FUTURE

The future will see more lower dose combinations that should further improve compliance, and will be particularly suitable for older postmenopausal women who do not need the same dose as women around the time of the menopause. Development of intrauterine progestogen-releasing devices, vaginal rings and transdermal systems will provide further options and greater long-term acceptability.

Treatment strategies for long-term therapy are changing because of the increased risk of breast cancer with long-term HRT use, and evidence that the benefits on bone and cardiovascular protection are soon lost on cessation of treatment. Treatment for several years following the menopause will

provide symptom relief and some bone and heart protection, but the main risks of coronary heart disease and osteoporotic fractures are in women over the age of 70 years. Starting or resuming HRT over the age of 60 years with a low dose CCT regimen seems to be a good option. **HM**

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KEY POINTS

- Continuous combined therapy:
  - Provides similar benefits to sequential regimens but without the problems of a cycle.
  - Maintains an atrophic endometrium.
  - Is period-free but not always bleed-free.
  - Has less premenstrual syndrome-type side-effects.
  - Shows improved long-term compliance.
  - Allows low dose combinations for older women.
  - Has a lack of long-term data.