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D. A. Davey

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REVIEW

Menopausal hormone therapy: a better and safer future

D. A. Davey

Faculty of Health Sciences, University of Cape Town, Western Cape, South Africa

ABSTRACT

Major advances in menopause hormone therapy (MHT) hold promise in the future of better and safer care for women at and after the menopause. The principal advances are: (1) the critical window or 'window of opportunity' in the 10 years or so after the menopause, during which the benefits of MHT in healthy women exceed any risks; (2) use of transdermal instead of oral administration of estrogen to reduce the risk of venous thromboembolism; (c) investigation of the use of oral micronized progesterone (MP) and vaginal MP to prevent endometrial hyperplasia and carcinoma without any increased risk of breast cancer and venous thromboembolism in postmenopausal women receiving estrogens; vaginal MP prevents endometrial proliferation in the short term but the long-term effects in MHT remain to be established; (4) investigation into the use of intrauterine levonorgestrel-releasing devices (LNG-IUDs), which are an attractive form of MHT in perimenopausal women, providing contraception and reducing uterine bleeding, although the risk of breast cancer with LNG-IUDs requires clarification. Women in the future can look forward to a symptom-free menopause and to safer and more beneficial MHT.

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MHT; estrogen; progesterone; progestins; oral; transdermal vaginal; intrauterine

Introduction

Major advances in menopause hormone therapy (MHT) hold promise in the years to come of better and safer care for women at and after the menopause. The principal advances are:

(1) The critical window hypothesis or 'window of opportunity' in the 10 years or so after the menopause, during which the benefits of MHT in healthy women exceed any risks;
(2) The use of transdermal instead of oral administration of estrogens to reduce the risk of venous thromboembolism (VTE);
(3) The use of oral and vaginal micronized progesterone (MP) with the aim of preventing endometrial hyperplasia and carcinoma in postmenopausal women receiving estrogens without any increased in the risk of breast cancer and VTE;
(4) The use of levonorgestrel (L-norgestrel)-releasing intrauterine devices (LNG-IUDs) to prevent endometrial hyperplasia and carcinoma in perimenopausal and postmenopausal women receiving estrogens without any increase in the risk of breast cancer and VTE;
(5) The use of low-dose estriol vaginal gel which may improve vaginal health and sexual function[1].

These measures, taken together or separately, can provide effective and safe MHT for women with menopausal symptoms and may reduce the incidence of cardiovascular disease (CVD) and osteoporosis in early postmenopausal women with less, and ideally no, increased risk of breast cancer or VTE. The measures taken together should also facilitate the long-term use of MHT when it is indicated.

The Women's Health Initiative (WHI) randomized, controlled trials (RCTS) of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) in postmenopausal women and of CEE-only in women with hysterectomy were stopped in 2002 and 2004, respectively, because the risks of treatment significantly exceeded the benefits[2,3]. The CEE + MPA trial found a significantly increased risk of breast cancer, VTE and CVD, and the CEE-only trial found a significantly increased risk of stroke and VTE. The publication of these findings resulted in a world-wide discontinuation of MHT. Over the last 10–15 years, continued investigations into different forms of MHT and into the pathophysiology of the menopause have led to a reappraisal of the role of MHT in the care of women at and after menopause.

The critical window hypothesis or 'window of opportunity'

The critical window hypothesis or 'window of opportunity' is based on the finding that MHT is beneficial in the years immediately after the menopause but may be deleterious when initiated 10 or more years after the menopause. It was first proposed to explain the difference between the findings of the WHI trials and of previous observational studies on coronary heart disease (CHD) and MHT[4]. The strongest support for the window of opportunity comes from mortality data in postmenopausal women who receive MHT. In the

CONTACT D. A. Davey profdad@eject.co.za Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Western Cape 7925, South Africa

combined CEE + MPA and CEE-only arms of the WHI trials, the mortality in women age 50–59 years was significantly reduced (relative risk (RR) 0.7, 95% confidence interval (CI) 0.51–0.96) but in women aged 60–69 years was unchanged (RR 1.05, 95% CI 0.87–1.26)[5]. The mortality data for the WHI RCTs of CEE + MPA and CEE-only, including a cumulative 18-year follow-up, were re-analyzed in 10-year age groups and into the intervention and follow-up phases (fewer than 4% of women continued MHT after the trials were stopped). The all-cause mortality in the 50–59-year age group in the intervention phase was reduced (RR 0.69, 95% CI 0.51–0.94) and not significantly changed in the follow-up phase (RR 0.89, 95% CI 0.79–1.01)[6]. There was no apparent difference between the CEE + MPA and CEE arms of the WHI trial in overall mortality (RR 0.69, 95% CI 0.44–1.11 vs. RR 0.71, 95% CI 0.46–1.11) or in the CVD mortality (RR 0.77, 95% CI 0.33–1.79 vs. RR 0.81, 95% CI 0.32–2.04)[5,6].

An analysis of the pooled data from 30 trials found that the total mortality in postmenopausal women who initiated MHT before age 60 was significantly reduced (RR 0.61, 95% CI 0.39–0.95)[7]. A Cochrane review of 43 RCTs of MHT found that, in two RCTs of women with a mean age less than 60 and in the three RCTs in which MHT was started less than 10 years after the menopause, the mortality in those who received MHT was significantly reduced (RR 0.70, 95% CI 0.52–0.95)[8]. Both the International Menopause Society and the North American Menopause Society have endorsed the conclusion that the benefits of MHT outweigh its risks in healthy menopausal women who initiate MHT during the 'window of opportunity' in the 10 years after the menopause or before age of 60 years[9–12].

The reduction in mortality in women in the 10 years following the menopause is principally due to the reduction in the incidence of CHD. The Nurses' Heath Study found that postmenopausal women who began MHT near the menopause had a significantly reduced risk of CHD (RR 0.66, 95% CI 0.35–0.80) but women who commenced MHT 10 years or more after menopause did not[13]. The randomized, controlled Danish Osteoporosis study of 1006 healthy perimenopausal or postmenopausal women age 45–58 with vasomotor symptoms found a significant reduction in the primary composite endpoint of admission to hospital for myocardial infarction, heart failure or death in women who received estradiol 2 mg daily, and women treated with triphasic estradiol and norethisterone acetate had a RR of 0.48 (95% CI 0.26–0.87; $p = 0.015$)[14]. The 2015 Cochrane review of RCTs found that MHT initiated less than 10 years after menopause onset lowered the risk of CHD (RR 0.52, 95% CI 0.29–0.96) and also lowered the all-cause mortality (RR 0.70, 95% CI 0.52–0.95) but increased the risk of VTE (RR 7.14, 95% CI 1.11–2.73)[8].

The ELITE (Early versus Late Intervention) study was designed specifically to investigate the effect of estrogens and of age on the development of atherosclerosis measured by ultrasonography of the carotid artery intima-media thickness[15]. Compared with placebo, oral 17β-estradiol 1 mg daily significantly slowed carotid artery atherosclerosis in women within 6 years of the menopause but not in women who start estrogens more than 10 years post menopause. The difference between women who start MHT during the 'window of opportunity' and women who start MHT later probably relates to the difference in the state of the coronary blood vessels[16]. In younger menopausal women, estrogen increases vasodilation, decreases inflammatory cell adhesion and prevents the development of atherosclerosis in the coronary blood vessels. In older women, the estrogen receptors are less responsive and oral administration of estrogens may cause thrombosis or rupture of atherosclerotic plaques in the coronary vessels, resulting in myocardial infarction, heart failure or death.

Transdermal and oral MHT and venous thromboembolism

Estrogen and progesterone given orally are rapidly metabolized on first passage through the liver and may cause adverse effects on liver function including an increase in blood coagulation factors and an increased risk of VTE. Transdermal administration avoids the first-pass effect of estrogens on the liver and reduces the risk of VTE.

VTE is the most common adverse effect of MHT. The risks of VTE in the CEE + MPA arm of the WHI progressively increased with increasing age: for age 50–59, RR = 2.27 (95% CI 1.19–2.43; for age 60–69, RR = 4.28 (95% CI 2.38–7.72); and for age 70–79, RR = 7.46 (95% CI 4.32–14.38)[17]. In the CEE-only arm, for age 50–59 the RR for VTE was 1.22 (95% CI 0.62–2.42); for age 60–69, RR = 1.3 (95% CI 0.86–2.00); and for age 70–79, RR = 1.44 (95% CI 0.86–2.44)[2]. In a meta-analysis of 31 RCTs of estrogen-only and estrogen + progestin MHT, mainly of oral administration, the risk of VTE in all ages combined was increased (RR 2.05; 95% CI 1.44–1.72) and the risk of VTE with estrogen–progestin combinations was double that with estrogen only (RR 2.02, 95% CI 1.39–2.92)[18].

The Estrogen Thromboembolism Risk (ESTHER) case–control study published in 2003 provided the first evidence that oral but not transdermal estrogens increase the risk of VTE in postmenopausal women. The RR of VTE in oral MHT users compared with non-users was 3.5 (95% CI 1.86–6.8), but in transdermal users the RR was 0.9 (95% CI 0.5–1.6). The RR of VTE with oral vs. transdermal use was 4.0 (95% CI 1.9–8.3)[19]. The finding of an increased risk of VTE with oral estrogens and oral estrogens plus progestins but no increase with transdermal estrogens has since been confirmed in seven observational studies (Table 1).

There have been no large RCTs of oral vs. transdermal administration of estrogens in MHT but there is substantial observational evidence that the risk of VTE in postmenopausal women is increased by estrogens given orally but is not increased by estrogen administered transdermally.

The clinical findings are supported by the pathological findings that orally administered estrogens have a prothrombotic effect and increase plasma levels of factor IX and C-reactive protein due to the first-pass effect on the liver[27,28]. Estrogens given orally also decrease the levels of tissue plasminogen activator antigen and plasminogen activator inhibitor activity. Estrogens administered transdermally have no detrimental effect on blood coagulation factors[29,30].

Table 1. Relative risk (RR) of venous thromboembolism (VTE) in oral vs. transdermal estrogens in menopause hormone therapy (MHT).

Name of study	Year	Type of study	Number of subjects	Age range (years)	Number of subjects with VTE	Number of controls	RR of VTE		
							Oral vs. non-users[a]	Transdermal vs. non-users[a]	Oral vs. transdermal[a]
ESTHER[19]	2003	Case–control	536	45–70	155	381	3.5 (1.8–6.8)	0.9 (0.5–1.6)	4.0 (1.9–8.3)
ESTHER[20]	2007	Case–control	881	45–70	271	610	4.2 (1.5–11.6)	0.9 (0.4–2.1)	
E3N cohort[21]	2010	Cohort	80 308	59–74	549		1.7 (1.1–2.8)	1.1 (0.8–1.8)	Homogeneity $p = 0.01$
UK GP Practice Research[22]	2010	Nested case–control	955 582	50–79	23 505	231 652	E only 1.49 (1.37–1.63) E + P 1.54 (1.44–1.65)	E only 1.01 (0.89–1.16) E + P 0.96 (0.77–1.10)	
NHS Record Linkage[23]	2012	Survey	1 058 259	PM	2 200		E only 1.42 (1.21–1.66) E + P 2.07 (1.86–2.31)	E only 0.82 (0.64–1.06) E + P 1.06 (0.68–1.65)	
MEGA[24]	2013	Case–control		50+	1 082	1 468	E only 0.6 (0.3–1.02) CEE + MPA 4.0 (1.8–8.2) E + NETA 3.9 (1.5–10.7)	Non-oral MHT 1.1 (0.6–1.08)	
TEHS[25]	2016	Case–control			838	891	E only 1.31 (0.78–2.21) E + MPA 2.94 (1.67–5.36) E + NETA 2.25 (1.50–3.40)	E only 0.90 (0.35–2.23) E + P 1.16 (0.41–3.03)	
Insurance claims US[26]	2016	Matched cohort	5 102	50+	Transdermal MHT 274	Oral MHT 316			Transdermal vs. oral VTE 0.42 (0.19–0.96) CVD 0.81 (0.67–0.99)

[a]95% confidence intervals given in parentheses.
PM, postmenopause; E, estrogen; P, progestin; CEE, conjugated equine estrogens; MPA, medroxyprogesterone; NETA, norethisterone acetate; CVD, cardiovascular disease.

The combined clinical and pathological evidence on the risk of VTE provides good and sufficient reason for preferring the use of transdermal estrogens to oral estrogen in MHT in most, if not all, menopausal women.

Oral and vaginal micronized progesterone

Oral micronized progesterone

In postmenopausal women with an intact uterus receiving estrogen, the addition of progesterone or progestins is regarded as essential to prevent endometrial hyperplasia and carcinoma. The combination of a progestin with estrogen increases the risk of breast carcinoma and VTE and the risk varies with the type of progestin. Oral micronized progesterone (MP) has been claimed not to increase the risk of breast cancer. When administered orally, MP is rapidly metabolized in the intestinal mucosa and the liver, and the plasma levels of progesterone are very low when measured by specific liquid chromatography and mass spectrometry (LC-MS)[31].

Oral administration of MP 100 mg daily results in peak levels of less than 2.2 ± 3.06 ng/ml measured by LC-MS. With the doses of MP currently used clinically, the concentrations of MP in the plasma may be insufficient to prevent endometrial hyperplasia and carcinoma when estrogens are given in the short term but may increase the risk when given in the long term (more than 5 years)[32]. At the same time, the low plasma concentrations of MP following oral administration have may have a weak effect on breast tissue and may not increase the risk of breast carcinoma in the short term but may increase the risk in the long term.

The low plasma concentrations of MP may also have less effect on blood coagulation and on the risk of VTE. The claim that MP does not cause endometrial hyperplasia and carcinoma and is not associated with an increased risk of breast cancer and VTE, however, has been disputed and is discussed in the following sections.

Oral micronized progesterone, oral progestins, endometrial hyperplasia and carcinoma

After a review of 40 studies, an expert committee concluded that oral MP, if applied sequentially for 12–14 days/month at 200 mg/day, provides endometrial protection for up to 5 years[33]. In the European EPIC study of 115 474 postmenopausal women in Europe, the risk of endometrial carcinoma was increased both in current estrogen-only users (RR 2.52, 95% CI 1.77–3.57) and in current estrogen–progestin users (RR 1.41, 95% CI 1.08–1.83)[34]. In estrogen–progestin users, the risk of endometrial carcinoma depended on the type of progestin, the regimen – sequential or continuous – and duration of use. The risk of endometrial carcinoma was not increased in synthetic progestin users but was significantly increased in MP users (RR 2.42, 95% CI 1.53–3.8).

In an analysis of the 65 360 women in the French cohort of the EPIC study, the risk of endometrial cancer was increased in estrogen plus MP users (RR 1.80, 95% CI 1.38–2.34) compared with never users and increased with increased duration of use: <5 years, RR = 1.3 (95% CI

0.99–1.97), and >5 years, RR = 2.66 (95% CI 1.87–3.77). The risk of endometrial cancer with the use of estrogens and progestins other than MP was not increased[35].

In a systematic review of 28 studies, continuous combined estrogen–progestin therapy had a lower risk of endometrial cancer than sequential estrogen–progestin therapy. The risk of endometrial cancer was increased with MP given either continuously or sequentially[36]. The claim that oral MP can prevent the increased incidence of endometrial hyperplasia and carcinoma in postmenopausal women treated with estrogens has not been substantiated.

Oral micronized progesterone, oral progestins and breast cancer

Breast carcinoma is the most common carcinoma in women and an increase in the risk of breast cancer is the most serious risk associated with MHT. The WHI trial of CEE + MPA was terminated prematurely because of the increased risk of breast cancer (RR 1.26, 95% CI 1.00–1.59)[2]. In the CEE-only arm of the WHI trial, in contrast, the risk of breast cancer was decreased (RR 0.77, 95% CI 0.59–1.01)[3].

The Million Women Study reported that the risk of breast cancer was increased both in estrogen–progestin users (RR 2.00, 95% CI 1.88–2.12) and in estrogen-only users (RR 1.30, 95% CI 1.21–1.45) and that the increase in risk for combined estrogen–progestin users was significantly greater than in estrogen-only users[37].

The UK Generations Study of 58 148 menopausal women followed for 6 years (median 5.4 years) found that the risk of breast cancer was increased in current estrogen plus progestogen users (RR 2.74, 95% CI 2.05–3.6) but was not increased in estrogen-only users (RR 1.00, 95% CI 0.66–1.54)[38].

In the first report of the French cohort of the E3N-EPIC study in 2005, in 54 548 postmenopausal women with a mean duration of use of MHT of 2.8 years, the risk of breast cancer was found not to be significantly increased with MHT with MP (RR 0.9, 95% CI 0.7–1.2) but was increased with MHT containing synthetic progestins (RR 1.4, 95% CI 1.2–1.7)[39]. In a later report of the E3N study in 2009, the risk of breast cancer was found to be increased with MHT with MP if MHT was initiated in the 3-year period following onset of the menopause and continued for 5 or more years (RR 1.54, 95% CI 1.28–1.86) but was not increased if initiated after 3 years (RR 1.00, 95% CI 0.68–1.47)[40].

A separate French CECILE case–control study of 1555 menopausal women (739 cases and 816 matched controls) found that, compared with never use, the risk of breast cancer was increased with current use of estrogen plus synthetic progestins for 4 or more years (RR 2.07, 95% CI 1.26–3.39) but was not increased with estrogen plus MP for the same period (RR 0.79, 95% CI 0.37–1.71)[41].

A number of factors influence the increase in risk of breast cancer associated with MHT including the interval between the menopause and starting MHT (gap time), duration of MHT, and body weight and body mass index; the interpretation of the effect of MP and progestins on risk of breast cancer may be difficult. It has been suggested that the low plasma concentrations of MP given orally may have a weak effect on breast tissue and may not increase the risk of breast carcinoma over short periods, but may increase the risk with longer periods of 5 years or more[32]. MHT is usually initiated for the relief of menopausal symptoms within a year or so of the menopause and it is often necessary to continue MHT for more than 5 years. An increased risk of breast cancer with oral MP given for 5 years or more cannot be ruled out, and a possible reduction in risk of breast cancer with MP cannot be regarded as a reason for preferring MP to progestins in MHT in the light of the increased risk of endometrial hyperplasia and carcinoma with MP.

Oral micronized progesterone, progestins and venous thromboembolism

Most studies have shown an increased risk of VTE with MHT with combined estrogen and progestin compared with estrogen only, and the risk appears to vary with different progestins. In the CEE + MPA arm of the WHI trial, the risk of VTE in women age 50–59 was increased (RR 1.27, 95% CI 1.19–4.33), but in the CEE-only arm the risk was not significantly increased (RR 1.22, 95% CI 0.62–2.42)[2,3].

The UK NHS record linkage study reported that the risk of VTE was significantly greater for estrogen–progestin than for oral estrogen-only therapy (RR 2.07, 95% CI 1.86–2.31 vs. RR 1.42, 95% CI 1.21–1.66). The risk of VTE with MPA was greater (RR 2.67, 95% CI 2.25–3.17) than with other progestins (RR 1.91, 95% CI 1.69-2.17), heterogeneity = 0.0007[23].

A Dutch study found that the risk of VTE was increased with oral CEE and MPA (RR 4.0, 95% CI 1.8–8.2) and with oral estradiol plus norethisterone acetate (RR 3.9, 95% CI 1.5–10.7) compared with oral estrogen-only MHT and that there was no significant difference between the progestins[24].

In a Swedish study, the risk of VTE in combined estrogen–progestogen users was double that of estrogen-only users (RR 2.18, 95% CI 1.21–3.92, $p = 0.009$). The risk was increased by both medroxyprogesterone acetate (MPA) (RR 2.94, 95% CI 1.67–5.36) and norethisterone acetate (RR 2.25, 95% CI 1.50–3.40) and there was no significant difference between the progestins[25].

It has been claimed that the risk of VTE is less with MHT with MP than with other progestins. In the E3N study of 80 308 postmenopausal women with 549 cases of incident VTE, the risk for VTE was not significantly increased with the use of estrogens combined with MP (RR 0.9, 95% CI 0.6–1.5), nortestosterone derivatives (RR 1.4, 95% CI 0.7–2.4) or pregnane derivatives including MPA (RR 1.3, 95% CI 0.9–2.0), compared with oral estrogens only but was increased with norpregnane derivatives combined with estrogens (RR 1.8, 95% CI 1.2–2.7)[21].

In the four studies of transdermal estrogens with oral MP or progestins, the risk of VTE was not increased[20,23–25]. The use of transdermal rather than oral estrogens in all women receiving MHT would obviate any possible increased risk of VTE with all types of progestins as well as with MP and is another good reason for using transdermal estrogens in

preference to oral estrogens in all perimenopausal and postmenopausal women.

Vaginal micronized progesterone

Vaginal administration of MP has been investigated in women having embryo implantation to provide luteal support and ensure an adequate secretory endometrium. MP administered vaginally is preferentially absorbed by the endometrium and only a small proportion enters the general circulation[42,43]. This first-pass effect in the uterus has been confirmed *in vivo* and *in vitro*[31,44–46]. Vaginal administration of MP 90 mg daily resulted in mean peak levels of 10.5 ± 0.46 ng/ml, with adequate levels lasting more than 24 h. The concentrations of progesterone in endometrial tissue after vaginal administration of 90 mg MP are twice those following intramuscular administration of 80 mg progesterone[46].

The effect of MP administered vaginally on the endometrium in postmenopausal women receiving estrogens has been investigated using transvaginal ultrasound (TVUS) and endometrial biopsy in a number of short-term studies (1–3 years)[33]. All the studies of endometrial thickness using TVUS found that the thickness was unchanged or reduced. Six studies investigated the effect of vaginal MP administered for at least 1 year and performed endometrial biopsies at baseline and after 1 year. All the endometrial biopsies were reported as inactive or atrophic, proliferative or secretory endometrium and none were reported as hyperplastic or neoplastic.

In the ELITE RCT of estrogen, in postmenopausal women with an intact uterus, MP (45 mg) was administered vaginally in the form of a 4% vaginal gel applied sequentially once daily for 10 days in each 30-day cycle and the results were analyzed after a median of 5 years[15]. The study was not designed to evaluate the effect of vaginal MP on the endometrium, but all serious adverse effects were recorded. In the women who initiated MHT less than 6 years since the menopause, there was one uterine cancer in the group treated with estrogen and vaginal MP and none in the placebo and vaginal MP group. In women who initiated MHT more than 10 years after the menopause, there was one uterine cancer in the estrogen and vaginal MP group and two in those who received placebo and vaginal MP. There was no evidence of an adverse effect from the vaginal MP over the median 5-year period.

The high concentration of progesterone in the endometrium with vaginal MP should prevent endometrial hyperplasia and carcinoma in postmenopausal women receiving estrogen. An expert panel of gynecological endocrinologists in 2016 concluded that, when combined with estrogens, vaginal MP may provide endometrial protection if applied sequentially for 12–14 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3–5 years[33]. There have been no studies of the effect of vaginal long-term MP on the risk of endometrial hyperplasia and carcinoma in postmenopausal women receiving estrogens. The long-term use of vaginal MP requires further investigation. Patient acceptability of the vaginal administration of MP in the long term also needs to be investigated.

L-norgestrel-releasing intrauterine devices

Progestin-containing intrauterine devices (IUDs) offer an attractive way of delivering progestins to the endometrium and preventing endometrial hyperplasia and carcinoma in perimenopausal and postmenopausal women receiving estrogens. IUDs provide contraception and reduce the amount of blood loss in dysfunctional uterine bleeding, which is a common problem in perimenopausal women. An IUD containing levonorgestrel (L-norgestrel), marketed as Mirena, was introduced in 1990 and found to provide effective contraception for 5 years. The device contains 52 mg L-norgestrel and initially releases approximately 20 μg of L-norgestrel daily, declining to 14 μg daily after 5 years. In 2013, a smaller IUD, marketed as Skyla or Jaydess, containing 11 mg L-norgestrel and releasing approximately 10 μg L-norgestrel daily, declining to 5 μg daily, was introduced and found to provide effective contraception for 3 years. The use of both Mirena and Skyla in pre- and postmenopausal women has been extensively investigated in Finland. L-Norgestrel administered by an IUD acts directly on the endometrium and only a small amount enters the circulation. In a study of 110 premenopausal women using Mirena, the plasma levels of L-norgestrel, as measured by LC-MS, were 191 ± 71 pg/ml during the 1st year of use and 141 ± 59 pg/ml during the 5th year[46]. In a prospective, randomized, controlled study of 163 postmenopausal women using Mirena and receiving 2 mg estradiol valerate daily orally, the median plasma levels of L-norgestrel were 478 pg/ml at 12 months, as measured by radioimmunoassay (RIA) which measures metabolites as well as progesterone[47]. In the women using the Skyla IUD, the median L-norgestrel levels as measured by RIA were 185 pg/l at 12 months and were significantly lower than those in the women using Mirena. After 12 months of therapy, strong endometrial suppression was found in all 55 women using Mirena and in 46 out of 47 women who used Skyla. After 6 months of therapy, 54 out of the 55 women who used Mirena and 43 out of the 47 women who used Skyla had no bleeding.

It was anticipated that the very low circulating levels of progestin with IUDs releasing L-norgestrel would have little systemic effect and initial studies indicated that there was no increased risk of breast cancer. In a postmarketing study of 17 360 users of LNG-IUDs in Finland, the incidence of breast cancer was the same as that of the average Finnish female population between 30 and 54 years of age[48]. In a retrospective, population-based, case–control study in Finland and Germany comparing LNG-IUD versus copper-containing IUDs, there was no increased risk of breast cancer[49].

Two recent studies of LNG-IUDs have come to a different conclusion. In a case–control study of all Finnish women age between 50 and 62 years of age, the use of a LNG-IUD was associated with an increased risk of breast cancer (RR 1.45, 95% CI 1.9–1.77) and the risk was further elevated by the addition of estradiol (RR 2.15, 95% CI 1.72–2.68)[50]. The RR

estimates were corrected for confounders including age at first birth and parity, but age at menarche, age at menopause and body weight were not controlled.

A study of women aged 30–49 in Finland using a LNG-IUD for menorrhagia reported that, out of a cohort of 93 843 LNG-IUD users, a total of 2781 women were diagnosed as having breast cancer from the National Reimbursement Registry[51]. The incidence of breast and other cancer in LNG-IUD users was compared with the incidence in the general population. The standard incidence ratios of all cancers, except breast cancer, were found to be significantly reduced: endometrial adenocarcinoma (RR 0.5, 95% CI 0.35–0.70), ovarian cancer (RR 0.6, 95% CI 0.45–0.76), pancreatic cancer (RR 0.50, 95% CI 0.28–0.81) and lung cancer (RR 0.68, 95% CI 0.49–0.91). In contrast, the standard incidence ratio of breast cancer was significantly increased (RR 1.19, 95% CI 1.13–1.25).

The authors of both of these studies indicating an increased risk of breast cancer in LNG-IUD users have cautioned on the possibility of selection bias. A random sample of Finnish women aged 15–64 in 1978–2002 found that LNG-IUD users had a higher socioeconomic position, were more often married, were less often overweight, were less often smokers, took more exercise and consumed alcohol slightly more often compared with non-users[51].

An increased incidence of breast cancer in LNG-IUD users, however, is plausible as progestins, including L-norgestrel, can act as promoters of breast cancer growth[32]. Women with LNG-IUDs *in situ* for at least 7 days have a low mean serum L-norgestrel level, as measured by LC-MS, but the variation in blood levels between individuals is large[52]. There is a rapid uptake of L-norgestrel in body fat and it has been suggested that a high concentration of L-norgestrel in breast fat may swamp the adjacent breast tissue and stimulate the development of occult breast cancers[53–55]. The risk of breast cancer in LNG-IUD users remains an open question.

Intrauterine devices are not suitable for all women and may not be the choice of some women. The presence of endometrial hyperplasia or polyps and uterine fibromyomata is usually regarded as a contraindication. The insertion of IUDs has to be performed by staff trained and skilled in the procedure and, in women more than 1 year postmenopause, cervical stenosis may prevent the insertion of IUDs. In a randomized trial, insertion of Mirena was reported as easy in 46.4% and as difficult in 21.4% of women. Insertion of the smaller Skyla was reported as easy in 70.4% and as difficult in 3.7% of women[47]. Paracervical block was used in 28.6% of the Mirena group and in 18.5% of the Skyla group. The long-term patient acceptability and safety of LNG-IUDs with continuous transdermal estrogen were assessed in a recent trial of 153 women followed up for over 10 years[56]. There were no cases of expulsion or of endometrial hyperplasia and the patient satisfaction was reported as high. It was suggested that, if started before the age of 60, the regimen could be advised for the lifelong prevention of cardiovascular, osteoporosis and other diseases. Until the possibility of an increased risk of breast cancer in LNG-IUDs is clarified, it is proposed that the use of LNG-IUDs be restricted to perimenopausal women with a specific indication for their use, namely contraception or dysfunctional uterine bleeding.

Conclusion

MHT is primarily given for the relief of menopausal vasomotor symptoms – hot flushes, night sweats and sleep disturbances. In the nationwide SWAN study in the USA, vasomotor symptoms were experienced by up to 80% of women, with a mean duration of symptoms of 7.6 years[57]. Moderate to severe vasomotor symptoms lasting 10 years or more are experienced by more than 30% of the women[58]. Vasomotor symptoms, moreover, are related to cardiovascular, bone and cognitive risks[59,60]. MHT is the 'gold standard' for treatment of women with vasomotor symptoms[9–12]. Advances in MHT over the last 10–15 years have altered the whole balance of risks and benefits of MHT and both the International Menopause Society and the North American Menopause Society have concluded that the benefits of MHT in current use exceed the risks in healthy symptomatic postmenopausal women when MHT is initiated within 10 years of the menopause or when younger than 60 years of age. The International Menopause Society and the North American Menopause Society have published detailed position statements on the benefits and risks of MHT and make the following key clinical points[9–12]:

(1) Hormone therapy is the most effective treatment for vasomotor symptoms and the genitourinary syndrome of the menopause and has been shown to prevent bone loss and fractures. MHT is an appropriate choice for healthy women in their fifties or within 10 years of the onset of the menopause.
(2) Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years and can be considered for continuation beyond aged 65 years for persistent vasomotor symptoms, quality-of-life issues or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risk.
(3) Individualization with shared decision-making and periodic re-evaluation to assess each individual woman's benefit–risk profile remains key.

The concept of 'the lowest dose for the shortest period of time' may be inadequate or even harmful for some women. A more fitting concept is 'appropriate dose, duration, regimen and route of administration'[8]. Women in the future can look forward to a symptom-free menopause and to safer and more beneficial MHT resulting in healthier and longer lives.

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ORCID

D. A. Davey http://orcid.org/0000-0002-0904-5462

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