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Review article

Reappraising 21 years of the WHI study: Putting the findings in context for clinical practice

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ABSTRACT

Menopausal hormone treatment (MHT) is recommended for the management of menopause symptoms. The Women's Health Initiative (WHI) placebo-controlled randomised study examined the effects of continuous combined or estrogen-only MHT on the risk of non-communicable diseases (NCDs) in post-menopausal women. The study was terminated prematurely after an interim analysis showed an increased risk of breast cancer diagnosis, which led to a rapid decrease in MHT use worldwide. Subsequently, limitations of the study design and its interpretation in the context of other clinical studies has contributed to a more nuanced appreciation of the risk–benefit profile of differing MHT regimens regarding risk associated with the class of progestogen prescribed, its pattern of prescription, duration of use and timing of initiation related to menopause onset. This review provides a contextual interpretation of the WHI placebo-controlled study and evaluates the impact of bioidentical MHT, with a focus on combined therapies containing micronised progesterone, on the risk of chronic NCDs in post-menopausal women.

1. Introduction

Vasomotor symptoms are associated with the perimenopause and onset of menopause. Perimenopause is the interval of irregular menstrual activity that directly precedes menopause [1], while menopause is the point in time when menstrual cycles permanently cease [2]. Estrogen deficiency associated with menopause can cause vasomotor (e.g. hot flashes, night sweats), physical (e.g. joint and muscular pain), psychological (e.g. sleep disturbances, anxiety and mood changes) and genitourinary (e.g. urinary symptoms, sexual dysfunction and vaginal dryness) symptoms. Symptomatic women may experience a worse sleep quality, lower health-related quality of life and an increased use of healthcare services than asymptomatic women [3,4].

Menopausal hormone treatment (MHT) improves menopausal symptoms by counteracting falling estrogen levels and is recommended for their management [5–8]. For women with an intact uterus, estrogen is combined with a progestogen to protect the uterus from endometrial cancer [8]. Women who have had a hysterectomy are prescribed estrogen alone [7].

The placebo-controlled Women's Health Initiative (WHI) study of

Abbreviations: BMD, bone mineral density; BP, blood pressure; CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; CRC, colorectal cancer; E2, 17β-estradiol; E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; ELITE, Early Versus Late Intervention Trial With Estradiol; EPIC, European Prospective Investigation into Cancer and Nutrition; ESTHER, Estrogen and Thromboembolism Risk; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HOPE, Health, Osteoporosis, Progestin, Estrogen; HR, hazard ratio; KEEPS, Kronos Early Estrogen Prevention Study; LDL, low-density lipoprotein; MHT, menopausal hormone treatment; MP, micronised progesterone; MPA, medroxyprogesterone acetate; NCD, non-communicable disease; OR, odds ratio; PEPI, Postmenopausal Estrogen/Progestin Interventions; RCT, randomised controlled trial; RR, relative risk; VTE, venous thromboembolism; WHI, Women's Health Initiative.

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conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) in post-menopausal women was terminated prematurely in 2002 after it reported an increased risk of breast cancer diagnosis, without beneficial cardiovascular effects [9]. Widespread media coverage resulted in a rapid decrease in the use of all types of MHT worldwide and a legacy of the WHI study has been a fear of cancer among some women, which has overshadowed its potential beneficial effects [3] and denied effective treatment for severe symptoms to many [10].

However, there has since been progress in understanding the risk–benefit profile of MHT in terms of the timing and duration of its use, and also in how bioidentical MHT may offer benefits over conventional non-bioidentical MHT [11]. This review considers potential issues in the interpretation of WHI study results and provides insights on the effects of bioidentical MHT options, particularly those containing micronised progesterone (MP), on risk of chronic non-communicable diseases (NCDs).

2. Methods

Our review primarily examines clinical studies of MPA vs MP published since the original WHI publications in 2002 [9] and analyses results from randomised controlled trials (RCTs), observational studies and review articles. Case reports, commentaries, editorials and congress abstracts were excluded. A background literature search focusing on MP and NCDs was conducted using PubMed and Google Scholar (last search date: August 2022) and the findings are discussed in this review.

3. WHI critique

The WHI was performed with only one type of oral continuous combined MHT: CEE (0.625 mg/day) plus MPA (2.5 mg/day) [9], yet the results were applied to all types of MHT performed with different estrogens, progestins and routes of administration. In 2002, the WHI authors reported that CEE + MPA in post-menopausal women aged 50–79 years (mean 63.2 years) increased the risk of invasive breast cancer, coronary heart disease (CHD), stroke and venous thromboembolism (VTE) (Table 1) [9]. Subsequently, limitations of the study design and the interpretation of its outcomes were raised [12]. Five major concerns relating to the WHI results as originally published are summarised below.

1. A focus on relative rather than absolute risks may have caused some misunderstanding about the degree of conferred outcomes. WHI authors reported a relative risk of CHD and breast cancer of 1.29 and 1.26, respectively, in the CEE + MPA group compared with the placebo group, which some misinterpreted as a 29 % chance of developing CHD and a 26 % chance of being diagnosed with breast cancer with MHT exposure [9,12,13].
2. The reported risks were based on unadjusted 95 % confidence intervals (CIs). Further analyses based on adjusted CIs demonstrated that changes in the risk for breast cancer and CHD were not statistically significant [13].
3. Confounding factors, such as a decrease in events in the placebo group and a high dropout rate, may have contributed to the 5-year peak in CHD and VTE observed in women allocated to receive CEE + MPA [13].
4. Several factors limit the validity of the findings of the WHI study as a randomised placebo-controlled study. Participants were allowed to choose whether to continue their assigned treatment or undergo diagnostic procedures post-randomisation, the rate of unblinding in the CEE + MPA group was 45 %, and warnings were sent to participants about the detection of increased risks of myocardial infarction, stroke and pulmonary embolism during the study [13].
5. Women in the WHI study were 12–15 years past the onset of menopause and were thus not representative of post-menopausal women with symptoms who may benefit from MHT [13]. Only 30 % of participants were <60 years old, but the results were generalised to other ages [12]. Results from other studies such as the Kronos Early Estrogen Prevention Study (KEEPS) demonstrate that MHT has a beneficial risk–benefit ratio in younger women and those close to menopause [10,14–16].

Table 1
Relative and absolute risk or benefit in CEE + MPA arm of the WHI study in healthy post-menopausal women (N = 16,608, placebo and study group) [9].

Health event	RR vs placebo group at 5.2 years (95 % CI)	Increased AR per 10,000 women/ year	AR reduction per 10,000 women/ year
Myocardial infarction	1.29 (1.02–1.63)	7	ND
Stroke	1.41 (1.07–1.85)	8	ND
Breast cancer	1.26 (1.00–1.59)	8	ND
Thromboembolic events	2.11 (1.58–2.82)	18	ND
Colorectal cancer	0.63 (0.43–0.92)	ND	6
Hip fractures	0.66 (0.45–0.98)	ND	5

AR, absolute risk; CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate, ND, no data; RR, relative risk; WHI, Women's Health Initiative.
Adapted from Rossouw et al. [9].

4. Effect of WHI: changes in MHT prescribing

Following the publication of the WHI results in 2002, MHT use fell from 29 % in 2001 to 10–11 % in 2005 among women aged 50–74 in the UK [17]. A large decline in use was also observed in the USA (46 %) and Canada (28 %), among other countries [18].

5. Bioidentical MHT differs from CEE and MPA used in the WHI

The WHI study examined the effects of CEE + MPA [9] but other forms of MHT exist, such as bioidentical MHT [19–22]. Bioidentical hormones have an identical molecular structure to endogenous hormones. Compounded bioidentical MHT, unlike conventional bioidentical MHT, is not subject to quality control or good manufacturing standards [23]. This review focuses on conventional bioidentical MHT. Below, we briefly describe how bioidentical MHT differs from CEE and MPA.

5.1. Different estrogens for MHT

The types of estrogen used in MHT vary in chemical structure, contents, pharmacokinetics and pharmacodynamics [19,20].

CEE, the type of estrogen therapy assessed in the WHI study [9], is used to manage early menopausal symptoms such as hot flashes and insomnia [24]. 17β-Estradiol (E2) is produced by the ovaries and is the major biologically active estrogen in humans [20]. CEE contains estrone, equilin, equilenin and other components, each conjugated to a sulphate group different from E2 [19]. CEE components primarily bind to estrogen receptor (ER) β [25]. In contrast, E2 binds to ERα, causing a conformational change in the estrogen response elements and the recruitment of co-activators and co-repressors that moderate the transcriptional activity and gene expression of the target cells [20].

Recent forms of MHT may contain the bioidentical E2, with different formulations containing different doses [26]. CEE and E2 have different effects on the liver as CEE stimulates angiotensinogen and sex hormone-binding globulin (an indirect index of venous thrombosis risk) 3.5-fold and 3.2-fold more than E2, respectively [27].

5.2. Bioidentical and synthetic progestogens for MHT

Progestogens used with estrogen in MHT include synthetic progestogens, hereafter referred to as progestins, and MP, also known as P4

[21]. The molecular structure of MP is chemically and biologically identical to that of endogenous progesterone, so MP is often termed 'natural' [28]. Synthetic progestins are structurally related to progesterone (e.g. MPA, medrogestone) or testosterone (e.g. norethynodrel, levonorgestrel) [28].

MP and synthetic progestins bind to progesterone, androgen, mineralocorticoid and glucocorticoid receptors with different affinities. Their affinity for each receptor type determines their biological effects [21,22,24]. MPA and MP have comparable progestogenic and anti-estrogenic actions. In addition, MPA has small androgenic effects and no notable anti-mineralocorticoid activity while MP demonstrates effective anti-androgenic and anti-mineralocorticoid activity [21]. Moreover, MPA, unlike MP, antagonises nitric oxide production, which has a cardioprotective effect, by cardiovascular endothelial cells [29]. Table 2 describes the biological activities of natural progesterone and progestins.

6. The impact of bioidentical MHT on the risk of chronic NCDs

Studies evaluating bioidentical MHT suggest that some may have a protective effect against certain chronic NCDs and a trend for a better safety profile than preparations containing CEE or progestins [30]. Table 3 summarises the findings described in this review article.

6.1. Cancer

6.1.1. Breast cancer

In the CEE + MPA arm of the WHI study, the risk of breast cancer was reported to be increased (hazard ratio [HR] 1.26, 95 % CI 1.00–1.59) when the study was terminated prematurely after a mean follow-up of 5.2 years. However, in those allocated to receive combined MHT who did not have prior MHT exposure, the risk of breast cancer diagnosis was not elevated [9]. In 2003, Million Women Study reported an increased risk of developing breast cancer in post-menopausal women aged 50–64 years given CEE + MPA for a total duration of use <5 years (relative risk [RR] 1.62, 95 % CI 1.34–1.96; $p < 0.0001$) [31].

Some subsequent studies suggest that the use of MP may be associated with a lower risk of developing breast cancer than MPA used in the WHI. A meta-analysis including two cohort studies reported that breast cancer risk was lower with MP than with progestins when combined with estrogen (RR 0.67, 95 % CI 0.55–0.81; $p < 0.0001$) in post-menopausal women (mean age 59 years) [22]. These findings were supported by a case-control study in women aged ≥50 years from the UK Clinical Practice Research Datalink. Only progestins were associated with a greater risk of developing breast cancer (odds ratio [OR] 1.28, 95 % CI 1.22–1.35), the OR with MP being 0.99 (95 % CI 0.55–1.79) [32]. The Collaborative Group on Hormonal Factors in Breast Cancer 2019 reanalysis of observational studies also reported that short-term use for up to 5 years of combined preparations containing MP is not associated with an increased risk of diagnosis but that a longer duration of exposure is. However, the number of breast cancer events for this latter risk estimate was too small to be reliable [33].

Table 2
Biological activities of natural progesterone and progestins. The level of activity of these compounds depends on their tissue concentration and binding affinity to the receptors [21].

	PR	Anti-E	EST	AND	A-A	A-M	$GABA_A$
Progesterone	+	+	−	−	+	+	+
Drospirenone	+	+	−	−	+	+	−
Dydrogesterone	+	+	−	−	−	−	−
MPA	+	+	−	±	−	−	−
Levonorgestrel	+	+	−	+	−	−	−

A-A, antiandrogenic; A-M, antimineralocorticoid activity; AND, androgenic; anti-E, antiestrogenic; EST, estrogenic; $GABA_A$, positive modulation of γ-aminobutyric acid type A receptor; MPA, medroxyprogesterone acetate; PR, progestogenic.
+ denotes effective, ± slightly effective and − not effective.
Adapted with permission from Piette [21].

Table 3
Impact of MHT on the risk of chronic NCDs and associated risk factors. Risk is described as RR, OR or HR.

	CEE + MPA	Estrogen + progestin	Estrogen + MP
Breast cancer	HR 1.26 [9]	OR 1.28 [32]	RR 0.67 [22] OR 0.99 [32]
CRC	HR 0.63 [9] HR 0.72 [59]	RR 0.74 [60] RR 0.86 [61] HR 1.15 [62]	HR 1.02 [62]
Endometrial cancer	HR 0.63 [9]	ND	HR 1.80[c] [63] HR 2.42[a,c] [37] HR 1.96[b,c] [37]
CHD	HR 1.29 [9]	OR 0.68 [41]	ND
VTE	HR 1.41 [9]	ND	OR 0.70 [53] HR 0.70 [54]
Bone health	HR 0.66 [9,32]	• Vertebral fractures RR 0.66 [58] • Non-vertebral fractures RR 0.87 [22,58]	ND

CEE, conjugated equine estrogen; CHD, coronary heart disease; CRC, colorectal cancer; E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MHT, menopausal hormone treatment; MPA, medroxyprogesterone acetate; MP, micronised progesterone; NCD, non-communicable disease; ND, no data; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.
[a] As reported in the EPIC study.
[b] As reported in the E3N study.
[c] Sequential MHT.

6.1.2. Colorectal cancer

The WHI study reported a reduced risk of colorectal cancer (CRC) in post-menopausal women given CEE + MPA (HR 0.63, 95 % CI 0.43–0.92) [9]. Meta-analyses suggest that MHT may reduce the risk of CRC, regardless of the type of estrogen and progestogen used [34,35].

6.1.3. Endometrial cancer

In the WHI study, continuous combined CEE + MPA was linked with a significant reduction in the risk of endometrial cancer (HR 0.63, 95 % CI 0.43–0.92) [9]. The REPLENISH trial, which randomly allocated 1835 post-menopausal women to continuous daily use of oral MP (100 mg) with E2 (0.5 mg or 1 mg) or placebo, found no association of the former with endometrial hyperplasia after 1 year of allocated treatment [36].

Randomised studies evaluating endometrial outcomes in women prescribed sequential MHT containing MP for a median duration of exposure of 15 (range 2–36) months suggest that with an adequate dose of oral or vaginally administered MP but not transdermal, it is as effective as progestins in the prevention of abnormal endometrial biopsies, hyperplasia or unscheduled bleeding [30,37].

However, in the long-term (>5 years) this may not be the case. While continuous combined MHT with progestins has been associated with a reduced risk of endometrial cancer risk with a longer duration of use, data regarding the impact of sequential or continuous combined MHT with MP is limited [37,38]. A significantly increased, duration-dependent risk was reported with MP-containing regimens in both the European Prospective Investigation into Cancer and Nutrition (EPIC)

(HR 2.42, 95 % CI 1.53–3.83) and Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N) (HR 1.96, 95 % CI 1.41–2.73) prospective cohort studies but while the former suggests administration was probably predominantly sequential, the timing of MP administration was not recorded in the latter [37,39].

6.2. Cardiovascular disease

6.2.1. Coronary heart disease

Initial data from the WHI study indicated an increased risk of CHD in women allocated to receive CEE + MPA (HR 1.29, 95 % CI 1.02–1.63) [9], likely because the treatment was given to asymptomatic women years after the onset of menopause [18].

Subsequent analysis showed that the use of continuous combined CEE + MPA in younger women (50–59 years) or those within 10 years of menopause onset reduces the risk of CHD [18,40].

A meta-analysis pooling data from 23 trials reported a decrease in CHD in MHT users aged <60 years (OR 0.68, 95 % CI 0.48–0.96), suggesting a preventive effect of MHT if started before atherosclerosis develops [41]. The study did not focus on bioidentical MHT and encompassed all forms. Regarding bioidentical MP, available data suggest a neutral effect on the vascular system [42].

6.2.2. Hypertension

In the WHI, women who received CEE + MPA demonstrated an increase of 1.5 mm Hg of systolic, but not of diastolic, blood pressure (BP) and showed a 5 % increased risk of developing hypertension after 2 years of treatment compared with those who received placebo [43].

Studies monitoring the effect of oral MP on BP in initially normotensive post-menopausal women, including the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, found no evidence of increased BP compared with untreated controls, placebo-treated controls or groups treated with estrogen only or progestogens plus estrogen [44]. Notably, the REPLENISH trial, which examined the impact of E2 combined with MP on BP in post-menopausal women with a uterus, found no clinically meaningful change in systolic or diastolic BP between baseline and month 12 [45,46]. Moreover, a study examining the effects of daily administration of 1000 mg of percutaneous estradiol gel plus MP 100 mg on haemodynamics in post-menopausal women found no significant change in systolic or diastolic BP from baseline at 12 weeks [47].

6.2.3. Lipid metabolism

The WHI reported no significant difference in triglyceride levels between women given CEE + MPA and those given placebo after 1 year. Levels of total cholesterol and low-density lipoprotein (LDL) fell significantly while high-density lipoprotein (HDL) rose in the active treatment group compared with control [48].

Combined MHT in post-menopausal women can decrease HDL cholesterol (HDL-C) levels. However, treatment with oral MP alone or its addition to estrogen therapy induces significantly smaller changes in HDL-C metabolism than progestins [49]. The PEPI trial showed that oral CEE (0.625 mg/day) combined with MP (200 mg/day for 12 days/month) increased HDL-C by 4.1 mg/dL, while the addition of MPA blunted this effect (1.20–1.60 mg/dL) [44,49].

Bioidentical MHT appears to have a protective effect on lipid metabolism. The REPLENISH trial showed no significant changes in lipid parameters with daily oral 1-mg E2/100-mg MP capsules compared with placebo [45]. Serum concentrations of total cholesterol and LDL decreased significantly in post-menopausal women receiving percutaneous E2 (1.5 mg/day for 3 months) combined with vaginal MP (200 mg/day for 14 days/month). The lipid-lowering effects were observed with E2 alone and administration of MP did not alter the response to E2 [50]. On the other hand, a significant decrease in HDL-C levels was observed in users of oral E2 + MP compared with hysterectomised users of E2 alone, but HDL-C levels largely returned to previous levels after the first two cycles [51].

6.2.4. Venous thromboembolism and stroke

The WHI investigators reported an HR of 1.41 (95 % CI 1.07–1.85) for stroke in women who received CEE + MPA [9]. Later evidence suggests, however, that younger women are at a lower risk of VTE and ischaemic stroke [10].

MPA is associated with an increased risk of VTE [52], whereas MP is not [9]. A systematic analysis suggests that MP has neutral effects on primary and recurrent VTE risk and ischaemic stroke risk when used as a component in combined MHT [42]. In addition, the placebo-controlled KEEPS, REPLENISH and Early Versus Late Intervention Trial With Estradiol (ELITE) trials, which assessed thromboembolic adverse events, reported no significant intergroup differences for VTE and stroke in women treated with MP [42]. The Estrogen and Thromboembolism Risk (ESTHER) study also found no association between MP and risk of VTE, reporting that the risk of developing an idiopathic VTE was not associated with MP (OR 0.70, 95 % CI 0.30–1.90) [49,53]. Furthermore, the REPLENISH trial showed no significant changes on coagulation parameters with daily oral 1-mg E2/100-mg MP compared with placebo from baseline to month 12 [10]. More recently, a retrospective real-world evidence study demonstrated that VTE rates were lower in women treated with 1-mg E2/100-mg MP (n = 2116) than in those treated with CEE + MPA (index treatment: n = 2998) after 2 years (HR 0.70, 95 % CI 0.53–0.92) [54].

The risk of VTE is significantly higher in patients administered oral compared with transdermal estrogen [42]. This was demonstrated in the E3N (oral: HR 1.7, 95 % CI 1.1–2.8; transdermal: HR 1.1, 95 % CI 0.8–1.8) [42] and ESTHER (oral: OR 4.2, 95 % CI 1.5–11.6; transdermal: OR 0.9, 95 % CI 0.4–2.1) [53] studies. The same association was found for risk of ischaemic stroke [42].

6.3. Insulin resistance and the risk of diabetes

The WHI reported a significant fall in insulin resistance in women treated with CEE + MPA compared with placebo after 1 year of follow-up (year 1 to baseline between-group difference − 0.22 ± 0.10, p = 0.03). After an average of 5.6 years of follow-up, the risk of developing diabetes was lower in the treatment group than in the placebo group [55]. Meta-analyses of RCTs confirm a beneficial effect of MHT on diabetes mellitus, although the results do not directly apply to MP as these analyses examined MHT as a whole [34]. Further studies are needed to identify the effect of MP on insulin resistance and the risk of diabetes.

6.4. Bone health

Osteoporosis results in a high risk of fractures, particularly in women aged >55 years [56]. The WHI study reported a decreased risk of hip fractures in post-menopausal women who received CEE + MPA (HR 0.66, 95 % CI 0.45–0.98) [9]. In the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial, in which post-menopausal women were administered daily CEE (0.3 mg, 0.45 mg or 0.625 mg) with or without continuous daily MPA (1.5 mg or 2.5 mg), women in the active treatment groups had significant gains from baseline in spine and hip bone mineral density (BMD) after 2 years [57].

Evidence supports the findings of the WHI that MHT may reduce the risk of fractures in women. A meta-analysis suggested that, in post-menopausal women, MHT of any type and route of administration tends to reduce the incidence of vertebral (RR 0.66, 95 % CI 0.41–1.07) and non-vertebral (RR 0.87, 95 % CI 0.71–1.08) fractures. MHT also appears to increase BMD at multiple sites (lumbar spine, forearm and femoral neck) [58].

7. Conclusions

The MHT regimen used in the continuous-combined arm of the randomised WHI study was associated with an increased risk of breast cancer and cardiovascular disease diagnosis, but also a reduction in the

risk of CRC, endometrial cancer and bone fractures. Data presented in this review suggest that combined preparations containing MP may have a better risk profile. However, some outcomes require further clinical trial evidence for definitive conclusions to be made. Overall, MHT appears to provide a better risk–benefit ratio if initiated closer to the time of onset of the menopause, and that the symptomatic benefits of MHT outweigh the risks of NCDs in the short term (i.e. with up to 5 years' exposure). Based on the findings of this review, future studies could shed light on the impact of differing bioidentical MHT estrogen (i.e. E2, CEE) and progestogen (i.e. MP or synthetic progestins) combinations on risk of NCDs by comparing the effects of bioidentical MHT in women pre vs post 10-year onset of menopause.

Contributors

Petra Stute made a substantial contribution to the conception and structure of the manuscript, and critical review of the important intellectual content.

Jo Marsden made a substantial contribution to the conception and structure of the manuscript, and critical review of the important intellectual content.

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Declaration of competing interest

PS has provided consulting services to Theramex and Astellas, has presented at conference for Theramex, Astellas, Besins Healthcare, Mylan, Labatec, Max Zeller & Soehne and Effik; and has received research project funding from EFFIK.

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