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This article discusses why some of the Women’s Health Initiative (WHI) Randomised Clinical Trial conclusions are now considered to be exaggerated.

Introduction

The release of data from The Women’s Health Initiative (WHI) Randomised Clinical Trial (RCT) of the use of Hormone Replacement Therapy (HRT) in postmenopausal women in July 2002 led to a period of protracted debate, disagreement and confusion about the role of HRT and its real risks and benefits.

The WHI HRT RCT comprised two placebo-controlled arms. Much has been written about the WHI. Suffice to say, they were well-designed, well-conducted RCTs aiming to examine the effects of HRT on older postmenopausal women. The problems lay in the interpretation of results.

In the Trial, 10,739 women who had had a hysterectomy were randomised to receive conjugated estrogens (CE) 0.625mg daily, or placebo. In the second arm of the Trial, 16,608 women with an intact uterus were randomised to receive placebo, or CE 0.625mg plus medroxyprogesterone acetate (MPA) 2.5mg daily. Their age

Take Home Messages

- HRT should not be initiated in older women, HRT is not for every woman and estrogen therapy is safer than estrogen plus MPA therapy.
- Most guidelines have found that HRT is the most appropriate treatment for menopausal symptoms.
- Estrogen-only therapy for three years in postmenopausal women with an intact uterus led to an increased incidence of endometrial hyperplasia and atypia, the addition of a progestin or micronised progesterone prevented such changes.
- There is now general consensus amongst medical experts that the original claims of harm reported in the WHI were exaggerated and vary with the age of women and the type of progestogen used.
range was fifty- to seventy-nine years and the mean age of the study population was sixty-three years.2

The Estrogen and Progestin arm of the Trial was stopped prematurely in July 2002 because of ‘adverse outcomes’.3 These results were controversial, and the following fourteen years have seen several re-analyses of the WHI data seeking to resolve differences apparently seen between this RCT and other studies.4,5 Data from these publications pointed to a different risk: a benefit profile for younger women using HRT compared to older users, and also for users of CE only, compared to users of CE and MPA. These findings were confirmed with the publication of long-term follow-up data of both arms of the WHI.6 The WHI long-term follow-up showed that, for women aged fifty- to fifty-nine years, or within ten years of their last menstrual period who were using combined HRT, there was no significant increased risk of coronary heart disease (CHD), stroke, pulmonary embolus or breast cancer. Venous thromboembolic risk was increased, as was expected for those taking oral HRT. The results from long-term follow-up of the estrogen-only arm of the WHI were even better. There was a statistically significant reduction in the risk of coronary heart disease and breast cancer, no increased risk of stroke or pulmonary embolus and a small increase in the risk of venous thrombosis.

Overall, the health outcomes for women using CE-only therapy in the WHI Trials were superior to those using combined CE/MPA therapy. Thus, the important messages to come from the WHI are that HRT should not be initiated in older women, HRT is not for every woman and that estrogen therapy is safer than estrogen plus progestogen therapy. Or perhaps we should say that estrogen therapy is safer than estrogen plus MPA, because it has become evident that the adverse effects seen with MPA do not apply to all progestogens.

Progestogens

The term ‘progestogen’ is used to describe compounds that bind to progestosterone receptors and exert similar effects. The term includes natural progestosterone and synthetic progestins. Synthetic progestins are further divided into subgroups, depending on whether they are structurally related to progestosterone or to testosterone.8 Synthetic pregnane derivatives include medroxyprogesterone, megestrol acetate, chloradimone and cyproterone, whilst nor pregnane derivatives include nomegestrol acetate, nesterone, promegestone and trimegestone. Testosterone-derived progestins include the original progestin, norethindrone (norethisterone), ethynodiol, norethynodrol and levonorgestrol. Dydrogesterone is one of a group of compounds called ‘retroprogesterones’ and these are structurally very similar to progesterone except that the methyl group at C10 is in the alpha orientation, rather than the beta orientation seen with progesterone. The clinical effects of dydrogesterone are very similar to progesterone.

A progestogen is essential when prescribing HRT for women with an intact uterus to protect the endometrium from unopposed stimulation by estrogen. Estrogen alone may be used in women following a hysterectomy. The Postmenopausal Estrogen and Progestogen Intervention Study9 (PEPI) provided the most compelling evidence for this. It showed that whilst estrogen only therapy for three years in postmenopausal women with an intact uterus led to an increased incidence of endometrial hyperplasia and atypia, the addition of a progestin or micronised progesterone prevented such changes and the results were then identical to placebo.

WHI Outcomes for Estrogen-only and Estrogen Plus Progestin RCTs

The WHI RCTs are the largest RCTs examining the effects of HRT in postmenopausal women. These RCTs showed clearly that there were differences in cardiovascular outcomes between the CE only and the CE/MPA arms of the study. The original papers showed an increased risk of CHD for CE/MPA (HR 1.29; 95% CI 1.02-1.63), compared to a trend toward reduced risk for CE alone10 (HR 0.91; 95% CI 0.75-1.12), which was maintained with long-term, follow-up7 and achieved statistical significance for the fifty- to fifty-nine-year-old age group1 (HR 0.65; 95% CI 0.44-0.96). The risk of venous thromboembolic disease was also greater for users of CE/MPA compared to users of CE11 (HR for CE 1.34; 95% CI 1.01-1.77), (HR for CE/MPA 2.09; 95% CI 1.59-2.74).

There was also a difference in breast cancer risk for users of CE alone compared to CE/MPA. CE/MPA use resulted in an increased risk1 of borderline significance (HR 1.26; 95% CI 1.00-1.59) whilst use of CE alone resulted in a non-significant decrease in risk12 (HR 0.77 95% CI 0.59-1.01) that became significant with long-term follow-up13 (HR 0.77; 95% CI 0.62-0.95).

Overall, the health outcomes for women using CE-only therapy in the WHI Trials were superior to those using combined CE/MPA therapy.

Differing Effects with Different Progestogens

At first, the difference seen in risk with CE alone compared to CE/MPA was thought to be a class effect regarding the progestogen, meaning it would apply to all women using combined estrogen plus any type of progestogen therapy. However, subsequent research has shown there are significant differences in health outcomes depending on which progestogen is used in combined HRT.
Please review full Product Information before prescribing. Full Product Information is available from Besins Healthcare (ph 1800 BESINS, e-mail medinfo.au@besins-healthcare.com).

**Prometrium**

**Indications**: menstrual irregularities; adjunctive use with an oestrogen in postmenopausal women with an intact uterus.

**Contraindications**:
- known allergy/hypersensitivity to progesterone or excipients;
- severe hepatic dysfunction;
- undiagnosed vaginal bleeding;
- known missed abortion/ectopic pregnancy;
- mammary/genital tract carcinoma;
- thromboembolic disorders;
- thrombophlebitis;
- cerebral haemorrhage;
- porphyria.

**Clinically Significant Precautions**: not a treatment for premature labour; should only be used during first trimester of pregnancy by vaginal route (pregnancy Cat A); not a contraceptive; discontinue if unexplained visual loss/changes, proptosis, diplopia, papilloedema, retina vascular lesions or migraine; use caution in conditions affected by fluid retention and history of depression, diabetes, hepatic dysfunction, migraine, photosensitivity and during lactation; increased risk of breast cancer and venous thromboembolism with oestrogen concomitant therapy (refer oestrogen PI); may cause drowsiness; may affect laboratory test results.

**Clinically Significant Interactions**: caution with P450 enzyme inducers and inhibitors; may increase antidiabetic medication; bioavailability may be reduced by smoking and increased by alcohol abuse.

**Very Common and Common Adverse Effects**: menstrual disturbances; headache.

**Dosage and Use**: take capsules (100mg/200mg) orally, OD at bedtime without food.

**Hormone Replacement Therapy**:
- 200 mg/d for 12d (d15-d26) of the cycle; or 100mg can be given from d1-d25.
- Secondary amenorrhoea: 400mg/d for 10d. Ovulation disorders/anovulation: 200-300mg for 10d (d17-d26, inclusive). HRT, hormone replacement therapy.

**REFERENCES**:

**PBS Information**: This product is not available on the PBS.
Micronised Progesterone and Its Relevance to the Management of the Menopause

Reasons for this are the differing effects on enzyme systems and hepatic synthesis, but also include the differences in receptor binding of progestogens. Progesterone binds primarily to progesterone receptors and there is very minor binding to anti-mineralocorticoid receptors. Dydrogesterone behaves in a similar manner. In contrast, the progestins commonly used in Australia bind to other receptors. Medroxyprogesterone acetate binds not only to progesterone receptors but also to glucocorticoid receptors, whilst norethisterone binds to progesterone, estrogen and androgen receptors.14

**Differing Breast Cancer Risks with Different Progestogens**

Differences in receptor binding give rise to different clinical effects. In vitro, tests have shown that breast cancer cells stimulated by growth factors show a four-fold reduction in the apoptosis/proliferation ratio (net proliferation) when exposed to medroxyprogesterone acetate, whereas other progestins have minimal effect. A study of the effect of progesterone combined with estradiol showed this combination reduced human breast cell proliferation and increased apoptosis compared to estradiol alone or in combination with medroxyprogesterone acetate.15

A systematic review and meta-analysis of breast cancer risk with different progestogen17 reported a statistically significant reduction in breast cancer risk for users of estrogen plus micronised progesterone.

The largest single observational study looking at the effects of different progestogens on breast cancer risk found that women who used estrogen plus micronised progesterone had no increased risk of breast cancer18 (RR 0.9; 95% CI 0.7-1.2). However, women using estrogen plus other progestins had an increased risk of breast cancer (RR 1.4; 95% CI 1.2-1.7). A systematic review and meta-analysis of breast cancer risk with different progestogens17 reported similar findings with a statistically significant reduction in breast cancer risk for users of estrogen plus micronised progesterone (RR 0.67; 95% CI 0.55-0.81).

**Differing Cardiovascular Risks with Different Progestogens**

Similar findings pertain to cardiovascular risk factors. It is well known that oral estrogens increase risk of venous thromboembolic events11 and that this risk is attenuated by the use of non-oral therapy. The WHI RCT found the risk of venous thromboembolism was greater for CE/MPA than for CE alone.11 Two large French observational studies also found a lower venous thromboembolism risk for users of micronised progesterone compared to synthetic progestins. In the ESTHER Study,18 venous thromboembolism risk was not increased for users of transdermal estrogen (RR 0.9; 95% CI 0.4-2.1) or transdermal estrogen plus micronised progesterone (RR 0.7; 95% CI 0.3-1.9), whereas risk was increased for users of transdermal estrogen plus synthetic progestins (RR 3.9; 95% CI 1.5-10). In the E3N Study,19 which examined 549 cases of venous thromboembolism over 811,643 patient-years, there was no increase in risk for users of transdermal estrogen with micronised progesterone (RR 0.9; 95% CI 0.6-1.5), whereas the risk was increased with transdermal estrogen plus synthetic progestins. The PEPI Study9 found that the beneficial effects of estrogen on lipoproteins were attenuated by the addition of MPA, whereas this attenuation was significantly reduced by a combination of CE and micronised progesterone. A study measuring flow mediated dilatation (FMD) in recently menopausal non human primates receiving oral CE HRT found a significant increase in FMD with estrogen use. This was reduced to non-significant change by the addition of medroxyprogesterone acetate in a dose-related manner.21

Taken together, this data suggests better outcomes for women using estrogen plus micronised progesterone compared to estrogen plus a synthetic progestin. Indeed, in a hypothetical calculation of what may have been the WHI results had the participants used transdermal estrogen plus micronised progesterone,22 it was estimated there would be a reduction in risk of venous events.

**Conclusions of the National Institute for Health and Care Excellence (NICE) Guidelines**

- HRT improves bone density and reduces fractures
- Cardiovascular disease risk was not increased amongst normal users of HRT and may be reduced
- Venous thromboembolism risk was increased amongst oral, but not non-oral HRT users
- Breast cancer risk was not increased for users of estrogen, but was increased with long duration use in users of estrogen plus progestogen HRT
- Androgenic progestins might increase venous thromboembolism and breast cancer risks compared to natural progesterone.
thromboembolism, cardiovascular disease and breast cancer for women using that combination of HRT compared to that seen in the original trial.

**Endometrial Safety**

The primary reason for using a progestogen is to provide endometrial protection. Synthetic progestins were developed to provide a cheap, effective alternative to progesterone. Cheaper manufacturing costs and particle micronisation have allowed progesterone to again become an effective alternative to the synthetics. The largest RCT examining effects of progestogens9 on the endometrium found sequential micronised progesterone 200mg for twelve days per month was as effective at preventing endometrial hyperplasia as either sequential or continuous medroxyprogesterone acetate. A systematic review of forty studies21 also found endometrial protection from either oral or per vaginal progesterone. The recommended dose of micronised progesterone for women using it with standard dose estrogen therapy is 200mg daily for twelve to fourteen days per month as sequential hormone therapy. This is designed to give a regular withdrawal bleed upon stopping the progesterone. For post menopausal women wishing to avoid menstrual bleeding the recommended dose is 100mg daily. It has been suggested that the 100mg dose be taken for only 25 days per month and that this may result in less breakthrough bleeding. The advantages of such a regimen should be balanced against patient compliance issues.

**Recommendations**

Over the past year there have been several important papers published that help us all better understand the true place of HRT in treating peri- and post-menopausal women.

The first of these, The National Institute for Health and Care Excellence (NICE) Guidelines24 on menopause management was published in November 2015. This very comprehensive review of the literature concluded that HRT was the most appropriate treatment for menopausal symptoms; that HRT improved bone density and reduced fracture; that, in the normal target population, cardiovascular disease risk was not increased amongst users of HRT and may be reduced; that venous thromboembolism risk was increased amongst oral, but not non-oral HRT users; and that breast cancer risk was not increased for users of estrogen, but was increased with long duration use in users of estrogen plus progestogen HRT. It was also noted that androgenic progestins might increase venous thromboembolism and breast cancer risks compared to natural progesterone.
In early 2016, The International Menopause Society (IMS) published new guidelines on the management of midlife women’s health and menopausal hormone therapy. This comprehensive, evidence-based document (available from the www.imsociety.org) echoed the findings of The NICE Guidelines and had similar findings regarding health benefits and harms, particularly in the usual target population. Levels of evidence and good practice points accompanied the recommendations. Once again, it was noted that some synthetic progestins might increase both venous thromboembolic and breast cancer risks when compared to natural progesterone or dydrogesterone.

Similar conclusions have been reached in The Endocrine Society Guidelines on the use of menopausal hormone therapy.

Most recently, an update of The Global Consensus Statement on Menopausal Hormone Therapy has also been published. This document, much smaller and more concise than the other extremely detailed papers, summarises the place of menopausal hormone therapy in the 21st century.

There is now general consensus amongst medical experts that the original claims of harm reported in the WHI were exaggerated, vary with the age of women and the type of progestogen used and are also extremely uncommon when HRT is prescribed to women within ten years of their last menstrual period or when they are aged under sixty years.

Over the past decade, many women have been denied safe, appropriate treatment of their menopausal symptoms because of ‘misunderstanding’.

It is time for us, as clinicians, to acknowledge this and to ensure that our post-menopausal patients receive the treatment they deserve, namely effective, safe and evidence-based management. HRT is not for everyone, however for most women who experience troublesome symptoms when passing through the menopause transition, this option is valuable, safe and most effective.

Further Reading

Australian Menopause Society website

Jean Hailes for Women’s Health website
http://jeanhailes.org.au/

International Menopause Society website
http://www.imsociety.org/


Declaration

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The author competing interests statements can be viewed at www.healthed.com.au/monographs.

References

A list of references is included in the website version of this article. Go to www.healthed.com.au/monograph