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The Women’s Health Initiative study, first published in 2002, raised concerns about the overall health benefit ratio of menopausal Hormone Therapy (HT). The original publication suggested more harm than benefit, showing increased risk of coronary heart disease, stroke, breast cancer, and venous thrombosis. The concern caused to patients and medical practitioners resulted in a significant drop in the number of women taking HT. Subsequent publications from WHI and re-analyses of other studies, such as the Nurses Health Study, have highlighted that in younger recently menopausal women, there is in fact a decrease in overall coronary heart events and a 30% decrease in overall mortality in users of HT.

The WHI study investigated the use of an oral estrogen, conjugated equine estrogen (CEE), in hysterectomized patients and used with medoxyprogesterone acetate (MPA) in non-hysterectomized patients. The surprising results in the original WHI publication lead to an increased focus on alternative ways of using HT. These included using lower doses, using different estrogens and progestins, and using estrogen transdermally instead of orally.

This paper will focus on the potential health advantages of transdermal over oral estrogen.

In South Africa, transdermal HT is available in the form of patches and gels. Both estrogen only and combined estrogen/progestin patches are available. If the transdermal estrogen is used in non-hysterectomized patients, the progestogen has to be provided separately as a tablet.

The major benefits of transdermal estrogen are as a result of it not undergoing hepatic first pass metabolism. A large amount of the estrogen administered orally, be it CEE or estradiol, is converted to estrone during absorption though the gut wall. It is then further metabolized in the liver. During this process it has a significant effect on clotting factors that lead to an increase in thrombosis risk. It also affects lipoproteins and other cardiovascular risk markers. Transdermal estrogens, by avoiding hepatic first pass metabolism, do not have these effects.

**Effect on thrombosis**

Oral estrogens affect many clotting factors during hepatic first pass metabolism, but the major effects leading to increased thrombosis risk are the effects on coagulation inhibitors and on thrombin:

- Oral estrogen negatively affects coagulation inhibitors. Antithrombin (AT III) levels are decreased by oral estrogen. Oral estrogen also increases Activated Protein C (APC) resistance. APC is a potent thrombosis inhibitor and by increasing resistance to this protein, its thrombosis inhibitory activity is markedly decreased.
- Oral estrogens increase the rate of thrombin production and increase peak levels of thrombin, again resulting in an increase in thrombosis risk.

Numerous studies, as well as WHI, have confirmed the increased risk of thrombosis with oral estrogens.

In the WHI estrogen and progestin arm, the relative risk (RR) of thrombosis was doubled compared with placebo (RR 2.06 CI 1.57-2.70). Importantly, the effect of other risk factors for thrombosis such as age, weight and Factor V Leiden were enhanced by E/P therapy. In patients aged 60-69 years the RR was 4.28, in obese patients it was 5.69, and in patients who were Factor V Leiden positive it was 6.69.

In a recent meta-analysis of observational studies, the RR of thrombosis for oral estrogen was 2.5 (CI 1.9-3.5), whilst for transdermal estrogen it was 1.2 (CI 0.9-1.7).

A case control study (155 patients and 381 controls) compared transdermal and oral estrogen as regards risk for deep vein thrombosis and pulmonary embolus. Transdermal estrogen did not increase the risk for either condition. Adjusted odds ratios for DVT were 3.2 and 0.8 for oral and transdermal E. For pulmonary embolism they were 3.8 and 0.8 respectively.

A further case control study, the Estrogen and Thrombo-Embolism Risk (ESTHER) study supported these findings with the risk being doubled for oral estrogen and not increased with transdermal estrogen. This study also looked at the effect on patients with additional risk factors for thrombosis. As with the WHI study, the increased risk of thrombosis was compounded in patients with prothrombin mutations and in obese patients. There was no compounding of the risk with transdermal estrogen. The Menopause Estrogen and Veins (MEVE) cohort study looked at whether oral and transdermal estrogen further increased risk of thrombosis in patients with a previous deep vein thrombosis. There was no compounding of the effect with transdermal estrogen (RR 1 CI 0.4-2.4) whereas with oral estrogen it was dramatically increased (RR 6.4 CI 1.5-27.3).
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Stroke

WHI\textsuperscript{13} showed an increase in ischaemic stroke risk with the use of oral estrogen (RR 1.31 CI 1.02-1.68). This increase in risk was present in all age groups. A meta-analysis of 28 RCT’s\textsuperscript{14} showed a similar increase (RR 1.29 CI 1.13-1.47). A nested case control study\textsuperscript{15} comparing transdermal and oral estrogen found an increased risk similar to that seen in WHI with oral estrogen (RR 1.28 CI 1.15-1.41). The increased risk was seen with all doses. With transdermal estrogen there was no increased stroke risk (RR 0.95 CI 0.75-1.20). The risk was, however, dose dependent. When administered in "usual" or low doses (≤50µg) the RR was 0.81 (CI 0.62-1.05). With higher doses the risk was increased (RR 1.89 CI 1.15-3.11).

Coronary Heart Disease

There are no significant clinical studies comparing oral and transdermal estrogen as regards coronary heart disease. A Danish cohort study did, however, suggest a lower risk for myocardial infarction with unopposed transdermal estrogen than with unopposed oral estrogen. The RR with the use of oral estrogen was 0.98 (CI 0.90-1.96) whereas with transdermal estrogen it was 0.62 (CI 0.42-0.93). The difference between the two forms of therapy was significant (p=0.04)

There are numerous differences in cardiovascular intermediate endpoints which point to advantages with transdermal estrogen use, particularly in higher risk patients. Oral estrogens have some beneficial effects on lipoproteins in that they decrease total and LDL cholesterol and increase HDL cholesterol.\textsuperscript{17} Triglyceride levels are, however, increased with oral estrogen and this may be of significance in patients with the metabolic syndrome which in itself is a high risk factor for coronary heart disease. Small particle LDL levels are also increased with oral estrogen\textsuperscript{18} and this decreases the oxidative susceptibility of LDL which would be considered a negative effect. This does not occur with transdermal estrogen. Similar to oral estrogen, transdermal estrogen lowers total and LDL cholesterol, but unlike oral estrogen, it lowers triglycerides.\textsuperscript{19}

Other differences between oral and transdermal estrogen suggest that transdermal estrogen has a better cardiovascular profile. Oral estrogen increases the inflammatory marker C reactive protein (CRP).\textsuperscript{20} This is another effect of hepatic first pass metabolism. Raised CRP is, however, an independent risk factor for cardiovascular disease in women.\textsuperscript{21} Transdermal estrogen does not increase CRP levels. Oral estrogen also increases another acute phase protein, serum amyloid A (SAA), which is an adverse risk factor in postmenopausal women.\textsuperscript{22} Transdermal estrogen does not have this effect.

Other advantages of transdermal estrogen

Effect on breast tissue

There are no clinical studies comparing oral and transdermal estrogen as to their effect on breast cancer. A prospective randomized clinical study on 77 women randomized to receive either sequential CEE/MPA or transdermal estradiol gel/micronized progesterone showed less breast cell proliferation and therefore less breast density with the transdermal estrogen/micronized progesterone regimen.\textsuperscript{23} It has also been shown that the above two regimes differ in their effect on gene regulation with the transdermal estrogen /micronized progesterone regime again having a more favourable profile.\textsuperscript{24}

Effect on hepatic proteins

The increase of Sex Hormone Binding Globulin (SHBG) seen with oral estrogen use lowers free testosterone levels. This can have a negative impact on libido. This is not seen with transdermal estrogen. Patients complaining of a low libido whilst using oral estrogen should be changed to a transdermal preparation.

Thyroid Binding Globulin (TBG) levels are also increased with oral estrogen and a change in thyroid replacement dose may be needed. Again this is not seen with transdermal preparations.

Conclusions

The discussion above shows that transdermal estrogen has some clear advantages over oral estrogen, particularly in higher risk patients such as the older woman who wishes to continue with HT, patients with mild hypertension, diabetes or metabolic syndrome, smokers, and in obese patients. Given the many advantages of transdermal administration we should offer this form of HT as a first choice to all patients being considered for HT. In so doing we may lower the risk of adverse events and further increase the benefit vs risk profile with the use of HT in our management of menopausal patients.

References

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