

## Editorial

# Body-identical hormone replacement

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The adverse outcomes seen in the Women's Health Initiative (WHI)<sup>1</sup> were mainly due to an over-dosage of hormones in a relatively elderly population. However, fundamental differences exist between conjugated equine estrogens and 17 $\beta$ -estradiol and between medroxyprogesterone acetate and natural progesterone. It is likely that these differences also contributed to the adverse outcomes in the WHI, which were contrary to the cardiovascular benefits seen in previous observational trials. Recent studies of cardiovascular risk markers in younger women have been designed using predominantly estradiol and natural progesterone (transdermal and oral) as the primary interventions<sup>2,3</sup>. This Editorial accompanies four manuscripts in which the authors explore, through review of the literature and presentation of their own data, the effects that estradiol and progesterone can have, both in the physiological environment and also when replaced as transdermal estradiol and micronized oral progesterone.

### Progesterone

Synthetic analogs of progesterone known as progestins/progestogens were developed to make the hormone available orally before the process of micronization had been developed. Unfortunately, in addition to binding to the progesterone receptor, many of these compounds also bind to the glucocorticoid, mineralocorticoid and androgen receptors. This binding can lead to unwanted side-effects such as unfavorable glucose metabolism, fluid retention, acne and weight gain<sup>4</sup>. The natural progesterone molecule binds primarily to the progesterone receptors to produce the desired effect in the endometrium, i.e. secretory transformation. There is some weak binding to the mineralocorticoid receptor but there is an antagonistic effect which gives it mild diuretic properties.

### Transdermal estradiol

Synthetic forms of orally administered estradiol, e.g. valerate, are cleaved at an early stage during gastrointestinal absorption leading to delivery of bio-identical estradiol. The biological

effects of oral conjugated equine estrogens are complex and have still not been fully evaluated. However, there are some fundamental differences between oral and transdermally administered estradiol due to the avoidance of first-pass hepatic metabolism. In theory, this manifests in a more physiological systemic effect; factors of coagulation are not activated and neither is the renin-angiotensin-aldosterone cascade, thus reducing the risk of venous thrombosis and hypertension.

### Supplement papers

The first paper in this Supplement by Simon<sup>5</sup> explores the fundamental differences between transdermal and oral estrogens and hypothesizes that use of the transdermal route of administration of estrogen in the WHI study might have reduced some of the prothrombotic adverse events which were reported. He also emphasizes that menopause societies are now advising that natural progesterone may have more favorable metabolic and breast effects compared to synthetic progestogens.

The second paper by Mueck<sup>6</sup> explores in more detail the differential effects of transdermal estradiol and natural progesterone on the cardiovascular system. He discusses the lack of a procoagulant effect of transdermal estradiol, emphasizing the absence of thrombin generation and resistance to activated protein C. This may result in primary prevention benefits for myocardial infarction and diabetes, although larger studies would be desirable to confirm this. Natural progesterone also appears to have a beneficial cardiovascular effect; it does not attenuate the beneficial effects of transdermal estradiol in reducing insulin resistance and may have additional benefits on blood pressure.

The third paper by Gompel<sup>7</sup> explores the differential effects of progesterone and progestogens on the endometrium and the breast. Most data suggest that progesterone is equally effective as progestogens at protecting the endometrium from the proliferative effects of estrogen. However, there appear to be fundamental differences in how progesterone and progestogens behave in breast tissue. Natural progesterone has a

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pro-apoptotic effect on breast epithelial cells, whereas androgenic progestogens such as medroxyprogesterone acetate appear to have a proliferative effect, possibly through non-specific effects on the glucocorticoid receptors and gene expression. This might explain the small increased risk in breast cancer promotion when synthetic progestogens are combined with estrogen. Observational data such as the E3N cohort from the EPIC cohort<sup>8</sup> suggest that women using natural progesterone are not at increased risk of breast cancer; ideally, these data would be confirmed by long-term, randomized, prospective studies.

The final paper by Seifert-Klauss and colleagues<sup>9</sup> examines the physiological effects of natural progesterone on bone turnover in the premenopausal woman. Evidence suggests that higher progesterone levels in the luteal phase of ovulatory cycles may be associated with more bone formation and less bone resorption than anovulatory cycles in which progesterone levels are low. The group are now studying bone physiology in more detail to determine the precise impact of anovulatory

cycles on bone mineralization. This important work could have clinical applications in helping to predict which women approaching the menopause might be at increased risk of osteoporosis. A full understanding of this mechanism will also clarify the importance of the progesterone component of exogenous hormone therapy in both the prophylaxis and treatment of osteoporosis.

## Conclusion

In conclusion, the papers in this Supplement have demonstrated evidence that replication of the physiological hormonal environment with transdermal estradiol and natural progesterone can maximize the benefits and minimize the side-effects and risks of hormone therapy. It is time we moved away from the notion, often propagated by epidemiologists and the media, that HRT products have a single class effect.

## References

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33
2. Panay N, Fenton A. Bioidentical hormones: what is all the hype about? *Climacteric* 2010;13:1–3
3. Harman SM, Brinton EA, Cedars M, *et al.* KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12
4. Panay N, Fenton A. Alternative regimens for endometrial protection. Where are we now? *Climacteric* 2011;14:607–8
5. Simon JA. What's new in hormone replacement therapy: focus on transdermal estradiol and micronized progesterone. *Climacteric* 2012;15(Suppl 1):3–10
6. Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. *Climacteric* 2012;15(Suppl 1):11–17
7. Gompel A. Micronized progesterone and its impact on the endometrium and breast vs. progestogens. *Climacteric* 2012; 15(Suppl 1):18–25
8. Fournier A, Fabre A, Mesrine S, *et al.* Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol* 2008;26:1260–8
9. Seifert-Klauss V, Schmidmayr M, Hobmaier E, Wimmer T. Progesterone and bone: a closer link than previously realized. *Climacteric* 2012;15(Suppl 1):26–31