Hormonal therapy with patch or pill: How much does it matter?

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Counselling patients with climacteric complaints has become an increasingly difficult challenge in the “post-WHI-era”. On the one hand there are patients in the menopausal transition with a markedly impaired quality of life because of climacteric symptoms. Hormonal therapy (HT) is a very effective means of giving them relief of their complaints. On the other hand there may be severe side effects of this treatment such as stroke, myocardial infarction, breast cancer and last but not least thromboembolic events. Research in this field has to focus on therapies that minimize the potential risks of HT while improving the patients’ quality of life. We still do not know the exact mechanisms of many side effects of HT, and our knowledge is limited as to the optimal way of applying hormones.

Therefore, studies trying to explain the physiological changes induced by different ways of HT are of high value.

Since 1996 we know that HT leads to an elevated risk of thrombosis: Three different studies were published in a single issue of “The Lancet” showing a highly significant correlation between HT and venous thromboembolism (VTE) or pulmonary embolism (PE) (1–3). Two factors for the risk of thrombosis connected with HT could play a major role: first the possibly dilatatory effect of estrogens and progestogens upon (various) veins: dilatation of veins (especially the leg veins) may result in stasis, stasis may result in higher risk of thrombosis. The second risk factor seems to be the effect of estrogens upon liver specific pro-coagulatory proteins which is a dose-dependent phenomenon. So there might be a mechanical as well as a biochemical effect operative here.

For a long time, we thought that mainly the estradiol component of HT causes VTE or PE, but the two arms of the WHI-study taught us another lesson: The study-arm with conjugated equine estradiol plus medroxyprogesterone acetate (MPA) had a markedly higher incidence of venous thrombosis than the conjugated equine estradiol-mono arm (4, 5). Apparently the additional MPA added significantly to the known risk of VTE by oral estrogens. The exact mechanism of this is not known, but some authors think that it has to do with binding of MPA to the cortisol-receptor and thus activating a thrombin-responsive pathway. Owing to its glucocorticoid activity, MPA has been demonstrated to upregulate the thrombin receptor, the thrombin-induced production of tissue factor and pro-coagulation activity in the vessel wall (6).

In the ESTHER-study (7) women receiving transdermal hormones had no increased risk for VTE compared to the control group receiving no hormones at all. This pattern remained the same in obese patients and patients with coagulation factor defects (8, 9). On the contrary, women receiving oral estrogens had an about three- to four-fold higher risk for VTE, thus confirming the observation of former studies. The elevation of risk was even more pronounced for obese patients and for patients with mutations of the factor V or prothrombin gene (8, 9). The ESTHER-study is the only study to our knowledge that investigated the clinical endpoint VTE (and not only surrogate parameters such as coagulation factors) for transdermal versus oral estrogen therapy. It seems biologically reasonable that the transdermal route of estrogen application is connected with a low or even no risk for VTE by skipping the so called “liver first-pass effect” of orally applied estrogens. The conclusion of the ESTHER-study implies that women with an elevated risk for thrombosis (e.g. obesity, coagulation disorder) should favour the transdermal route of hormone application that will probably not or little affect their risk (10). How this translates into risk or no-risk for cardiovascular disease such as myocardial infarction or stroke remains completely unclear so far.

The HT regimens in the ESTHER study were quite heterogenous: about 10% of the women received estrogen only, about 90% estrogen plus progestagen. There is no exact information about which progestagens were used. To our knowledge, the study by Brosnan et al. (11) in this issue of Thrombosis and Haemostasis (see article beginning page 558) is the first one to investigate the difference between oral HT and transdermal HT with a given combination of norethisteroneacetate (NETA) and estradiol. Though the results are in favour of the transdermal route, the differences in coagulatory parameters between the oral and transdermal route of estradiol/NETA are less marked than one would have guessed and leave the question how this will translate into the incidence of the clinical endpoint for VTE.

There is an important topic to discuss concerning their results. As the authors quote, there are no measurements of estradiol or NETA concentrations in the serum in both groups. In our
clinical experience, the transdermal administration of 25 µg estradiol / 125 µg NETA has a less pronounced effect on climacteric symptoms than the oral administration of 1 mg estradiol / 0.5 mg NETA. Thus, it is questionable whether the two groups are really comparable with regard to the administered and bioavailable doses of sexual steroids.

In summary, although this trial raises the right questions, a number of issues remain unanswered. We still do not know to which degree the change of the investigated coagulation markers really influences the clinical endpoint of VTE. Future trials should call for objective measurements of hormone levels and investigate the different pro-coagulant potency of different progestins. It remains unclear whether there is a significant difference between MPA and NETA (or other progestins) in terms of their influence on VTE. In addition, it could be interesting to provide data on coagulation parameters with and without addition of progestins via the transdermal or the oral route. As the two arms of the WHI-study have shown (4, 5), the added progestin not only made a difference on thromboembolic disease but also on incidence of breast cancer and cardiovascular disease. So the focus of future research should address the effect of different progestin preparations on coagulation and their side effects in HT.

References