Journal of Steroid Biochemistry & Molecular Biology 142 (2014) 76–82

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Hormone replacement therapy and venous thromboembolism

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ARTICLE INFO

Article history:
Received 31 January 2013
Received in revised form 23 May 2013
Accepted 26 August 2013
Available online 3 September 2013

Keywords:
Hormone replacement therapy
Deep venous thrombosis
Venous thromboembolism, Pulmonary embolism, Factor V Leiden

ABSTRACT

Hormone replacement therapy (HRT) for post-menopausal women is known to promote venous thromboembolism (VTE), i.e., deep venous thrombosis and pulmonary embolism, though the absolute risk for a given patient is very small. The risk of VTE appears to be greatest soon after the initiation of HRT and returns to the baseline level of risk of non-HRT users after discontinuation. There is inconsistent data about whether estrogen-only or combined estrogen–progestin HRT are associated with similar VTE risk. Retrospective analyses suggest that transdermal HRT is not as prothrombotic as oral HRT, though this has not been evaluated in randomized clinical trials. Increasing age and weight further promote HRT's VTE risk. Some studies have investigated whether prothrombotic combinations may increase HRT's VTE risk and there is evidence that Factor V Leiden may do this. However, no benefit to screening prospective HRT users has been described, yet. Advanced proteomic and genomic studies may hold promise in the future for better elucidating which HRT users are at highest risk for VTE. Presently, physicians and prospective HRT users should discuss the potential risks and benefits for the individual patient, acknowledging there is no way to fully mitigate the risk of VTE.

This article is part of a Special Issue entitled 'Menopause'.

Contents

1. Introduction

Concern about the relationship between the use of hormonal therapies and venous thromboembolism (VTE), including deep venous thrombosis (DVT), pulmonary embolism (PE) and less commonly cerebral venous thrombosis (CVT), was first raised 5 decades ago in women taking oral contraceptives (OC) [1]. Evidence quickly demonstrated a definitive correlation between not only OC and VTE but also demonstrated a strong positive correlation between OC dose and VTE risk [2]. Efforts to reduce the OC dose of estrogens and progestins followed thereafter. Similar concerns about postmenopausal hormone replacement therapy (HRT) as a cause of VTE were not raised because HRT typically contained much lower doses of hormones than OC [3]. Early studies evaluating the possible relationship between HRT and VTE had negative findings. Three of these were small case-control studies. These included the Boston Collaborative Drug Surveillance Program (RR 2.3 95% CI, 0.6–8.0), Petitti et al. (RR 0.7 95% CI 0.2–2.5), and Devor et al. (RR 0.6 95% CI 0.2–1.8) [4–6]. Devor et al. included the greatest number of

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http://dx.doi.org/10.1016/j.jsbmb.2013.08.016

incident VTE – 121 cases – in a study based at a single academic medical center [5]. Additional VTE risk factors such as immobilization, central cather placement, malignancy, and post-operative state were highly prevalent in the acutely ill population evaluated in this study, which may not reflect the general population at risk from HRT and accordingly may have obscured HRT's apparent thrombogenicity. Nachtigall et al. performed a double-blind trial between 1969 and 1978 that randomized long-term institutionalized women to estrogen with cyclic progesterone, or to placebo [7]. While no increased risk was demonstrated, the overall incidence of VTE in the entire population approached 20% – far more than would be normally expected, again indicating that this was a population whose comorbidities may have obscured HRT's prothrombotic risk. Finally, the Postmenopausal Estrogen/Progrestin Intervention (PEPI) trial was a randomized double-blinded placebo-controlled study that compared conjugated equine estrogen either alone or with different progestins at different dosing schedules [8]. PEPI did not show significant differences in VTE between the different study groups but was underpowered because of its relative small size (825 participants) and brief follow-up of three years.

The results from studies adequately powered to fully assess the relationship between HRT and VTE started to become available in 1996. These analyses included both retrospective and prospective designs, and often differed in their basic methodologies. Despite this heterogeneity, a 2–3-fold increase in VTE risk was consistently demonstrated (Table 1). Studies included analysis of a single health insurance plan whose members were admitted with idiopathic VTE [9], an Italian analysis of hospital admissions [10], a population-based analysis of data from a single health maintenance organization in Washington State [11], and hospital admission analyses from France [12–14], and the UK [15]. Prospective cohort studies examining this association include the Nurses' Health Study [16], the Oxford-Family Planning Association analysis [17], an international multi-center study based in Canada, Italy, and the Netherlands [18], the Longitudinal Investigation of Thromboembolism Etiology (LITE) [19], and the Iowa Women's Health Study [20].

Eventually, prospective randomized double-blinded placebo-controlled data from the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) removed remaining doubt about the link between HRT and VTE [21,22]. Following the publication of these studies, the Women's International Study of Long Duration Estrogen After Menopause (WISDOM) was a double-blinded randomized controlled trial of estrogen-alone, combined estrogen/progestin therapy, or placebo that was prematurely terminated after the results of the HERS and WHI studies became available [23]. Despite the fact that the study only accrued one-quarter of its target participants, for whom a median of only 12.8 months of follow-up was accrued for combined HRT users, a strong trend toward increased VTE risk was demonstrated. Calculated VTE incidence rates were 84.3 versus 35.3 per 10,000 women-years for those assigned to HRT and placebo respectively, corresponding to a hazard ratio of 2.39 (95% CI, 0.62–9.24, $P = 0.19$).

Citing safety concerns, Høibraaten et al. prematurely closed a double blind randomized controlled trial of combined HRT in women who had previously experienced unprovoked VTE [24]. In this study 71 women were assigned to HRT and 69 to placebo and the study was terminated after approximately 480 days of follow-up in each group because of recent publications positing a convincing link between HRT and VTE. Despite the limited follow-up, 8 participants in the HRT group (10.7%) versus 1 in the placebo group (2.3%) experienced recurrent VTE ($p = 0.04$). The authors made the important observation that in the HRT group all events occurred within 261 days of treatment (5 occurred after less than 4 months of treatment), whereas the single placebo-associated event occurred after 413 days of treatment.

2. Comparative risks of estrogen-only versus estrogen–progestin HRT

Several studies of the thromboembolic risk of HRT have included separate analyses of estrogen-only and combined estrogen/progestin HRT, and there is inconsistent data regarding whether they confer different risks. For example, Douketis et al. demonstrated that estrogen/progestin led to an increased relative risk of 2.7 (95% CI 1.4–5.1) in VTE, whereas estrogen alone did not (RR 1.2, 95% CI 0.6–2.6) [18]. Similarly, Smith et al. found that combination hormonal therapy had an odds ratio of 1.6 (95% CI 1.1–2.3) of VTE compared to estrogen-only use [11]. On the other hand, the LITE investigators calculated similar relative risks for estrogen/progestin (1.6, 95% CI, 1.0–2.6) and estrogen alone (1.6, 95% CI 1.1–2.4) [19]. The prematurely terminated WISDOM trial also did not find a difference in VTE risk between combination and estrogen-only HRT, though it may have been insufficiently powered to do so [23]. Jick et al. calculated the relative VTE risk to be 4.1 (95% CI, 1.6–7.6) in estrogen-alone users versus 2.4 (95% CI, 0.8–7.3) in combination HRT users and noted that the confidence intervals overlapped [9]. The WHI found an increased risk of VTE in women taking estrogen/progestin replacement [21], but not in those taking estrogens alone [25]. The latter population solely included women who had undergone hysterectomy, whereas the former had not. Accordingly, attempting to interpret the WHI data to answer this question is speculative at best because of this important difference. Finally, the ESTHER investigators did not find that the addition of progestins to oral estrogens further increased VTE risk, with the exception of norpregnane progestin derivatives [12]. At this point available data comparing the VTE risk of unopposed estrogen versus combination therapy are inconclusive. Indeed, a recent meta-analysis did not find a difference in the thrombogenicity of estrogen-only versus estrogen/progestin HRT (HR 2.2, 95% CI, 1.6–3.0, and HR 2.6, 95% CI, 2.0–3.2, respectively) [26].

Authors of many of the above studies performed further analysis on the timing of HRT-induced VTE and found that the increased risk is largely confined to the first year of use, though not all available studies stratified the data this way (Table 1, reviewed in Canonico 2008). Similarly, some studies found that prior HRT users no longer had increased risk of VTE. Analogous data regarding the heightened VTE risk in the first year of use, and return to baseline risk following the discontinuation of therapy, exist for VTE secondary to hormonal contraceptives [27].

3. Effect of age and weight on HRT's VTE risk

Age has been demonstrated to be one of the strongest VTE risk factors in many scenarios, and similar data exist for users of HRT. For example, compared with placebo users in the sixth decade in the WHI, combination HRT users in the sixth, seventh and eighth decades of life had a VTE risk of 2.27 (95% CI, 1.19–4.33), 4.28 (95% CI, 2.38–7.22) and 7.46 (95% CI, 4.32–14.38), respectively [21]. An analogous though less pronounced effect of age was seen in the estrogen-only arm of the WHI [28]. The HERS II study evaluated the effect of age on VTE by comparing women older or younger than 65 years of age. Age greater than 65 was associated with increased VTE risk in HRT users compared to placebo users in univariate analysis (HR 1.9, 95% CI, 1.0–3.6) but not in multivariate analysis [29]. Age was not analyzed as a pontentiator of VTE risk in other studies of HRT.

Obesity is also an established VTE risk factor [30]. In the WHI, VTE risk increased in both overweight (body mass index