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EMAS position statement: Managing menopausal women with a personal or family history of VTE

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ABSTRACT

Introduction: Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a serious cardiovascular event whose incidence rises with increasing age.
Aims: To formulate a position statement on the management of the menopause in women with a personal or family history of VTE.
Material and methods: Literature review and consensus of expert opinion.
Results and conclusions: Randomized controlled trials have shown an increased risk of VTE in oral hormone therapy (HT) users. There are no randomized trial data on the effect of transdermal estrogen on VTE. Recent observational studies and meta-analyses suggest that transdermal estrogen does not increase VTE risk. These clinical observations are supported by experimental data showing that transdermal estrogen has a minimal effect on hepatic metabolism of hemostatic proteins as the portal circulation is bypassed. A personal or family history of VTE, especially in individuals with a prothrombotic mutation, is a strong contraindication to oral HT but transdermal estrogen can be considered after careful individual evaluation of the benefits and risks. Transdermal estrogen should be also the first choice in overweight/obese women requiring HT. Observational studies suggest that micronized progesterone and dydrogesterone might have a better risk profile than other progestins with regard to VTE risk. Although these findings should be confirmed by randomized clinical trials, they strongly suggest that both the route of estrogen administration and the type of progestin may be important determinants of the overall benefit-risk profile of HT.

1. Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a serious event in both men and women. In women, its incidence is uncommon in premenopausal women but rises significantly after the menopause with increasing age [2–4]. The absolute risk is small being around 0.5 per 1000 before the age of 50 while it rises after 50 with an absolute risk of 2–3 per 1000 over 60 years in women not taking HT [2,3]. VTE risk factors include genetic [1] and acquired factors [5,6]. Moreover VTE risk varies throughout a woman's life, with hormonal exposure underlying this risk. Several studies have shown that longer exposure to endogenous estrogen is associated with an increased VTE risk [7,8]. Also this varying risk may depend on exogenous estrogen use including combined oral contraceptives and postmenopausal hormone therapy (HT).

Randomized trials have shown that women who were given oral HT had a 2- to 4-fold increase in the risk of VTE as compared to non users with the highest risk occurring in the first year of use [7,9–13]. In the Women's Health Initiative (WHI) study, pulmonary

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embolism was the main contributor to the burden of cardiovascular disease and accounted for more than 60% of the potentially fatal events due to HT [10–13]. On the other hand, there is growing evidence that the route of estrogen administration significantly affects the VTE risk associated with HT. Recent meta-analyses [14,15] suggest that transdermal estrogen does not confer any additional risk of a VTE event in postmenopausal women.

Hormone therapy is classically contraindicated in women with a personal history of VTE. Nevertheless, recent data suggest that the various types of HT (according to the route of estrogen administration or the type of progestin) have different actions on hemostatic variables. Accordingly, HT might still represent an option in the management of menopause in women with a higher risk for VTE. In any case, such decisions require individual assessment. Moreover, other non-estrogen based options can be used. They have been reviewed in the EMAS position statement on managing the menopause in the context of coronary heart disease [16]. Raloxifene has no effect on climacteric symptoms and is associated with an increased risk of VTE [17]. Tibolone does not increase VTE risk in women over 60 with osteoporosis [18]. There are no data regarding tibolone in women with a personal history or at high risk of VTE. There have been no controlled studies regarding the risk of VTE with nutritional supplements that have estrogen-like properties such as phytoestrogens and the risks associated with their use are unknown [16].

The aim of this position statement is to examine the role of HT on VTE risk in postmenopausal women.

2. Venous thromboembolism and hormone therapy

The risk of VTE has been examined in large randomized controlled trials evaluating the efficacy and safety of HT. Oral conjugated equine estrogen (CEE) given in association with medroxyprogesterone acetate (MPA) was the major combination that was evaluated in most of the large trials. The Heart and Estrogen/progestin Replacement Studies (HERS I and II) found an overall 2.1-fold increase in VTE risk over the 6.8 years of follow-up (95% CI, 1.28–3.40) [7,8]. In the Women's Health Initiative, a randomized controlled trial of 16,608 postmenopausal women aged 50–79 years, a two-fold risk of VTE with combination HT was confirmed [10,11,13].

Review of studies reporting oral CEE-only HT reveal a modest increase of VTE risk of 1.3-fold, but there is large variability in study design with small numbers of patients enrolled. Data from the Women's Health Initiative study concerning the 10,739 women without an uterus indicate that the risk of VTE in women receiving oral CEE given alone is increased during the first 2 years of use (hazard ratio 1.32), but is still less than that with the MPA combination [12]. There are no data regarding VTE risk and low dose vaginal estradiol or estriol. Since systemic estrogen levels, when recommended dose regimens are used, do not exceed the postmenopausal range and the hepatic first-pass is avoided it is unlikely that vaginal administration confers an extra risk.

No randomized trial has examined the relationship between transdermal HT and the risk of VTE. However, several large cohort studies and meta-analyses have been published.

- The first study was the ESTHER study [19], a multicenter case–control study of VTE among postmenopausal women aged 45–70. Oral but not transdermal HT was associated with an increased risk of VTE, the odds ratio for VTE in current users of oral and transdermal ERT compared with non-users being 3.5 (95% CI 1.8–6.8) and 0.9 (0.5–1.6), respectively.
- More recently, 4 other large observational studies [20–23] also reported the same results as the ESTHER study. A meta-analysis [15] including those latest studies confirms that oral but not transdermal estrogens increased the risk of VTE in postmenopausal women. This analysis therefore suggests that transdermal estrogen might be well tolerated with respect to VTE risk.

In addition, the risk of VTE was also found to be influenced by the type of progestin. In the ESTHER study, further results suggested that preparations containing norpregnane derivatives were more thrombogenic than those containing micronized progesterone or pregnane derivatives [24]. In the larger E3N study [20], there was no increase in VTE risk when transdermal estrogen was administered with micronized progesterone or dydrogesterone. Risk estimates were slightly, but not significantly, higher if estrogens were associated with pregnane derivatives or norethisterone acetate. In contrast, a significantly increased VTE risk was found when estrogen was combined with norpregnane derivatives (HR: 1.8; 95% CI 1.2–2.7). In a recent large nested case–control study using the UK general practice research database on women aged 50–79 [22], pregnane derivatives were associated with a slightly higher VTE risk (HR:1.72; 95% CI 1.52–1.94) than nortestosterone derivatives (HR:1.48; 95% CI 1.37–1.60).

Until recently, there were no data on the relationship between the dose of estrogens and the risk of VTE. However, the data from the observational study using the UK general practice research database suggest that the risk of VTE might be lower when using lower oral estrogen doses as compared to higher ones [22]. In contrast, there was no difference in VTE risk with transdermal estrogen whatever the dose [19,22].

Differential effects of HT on hemostatic variables by route of estrogen administration may explain the difference in VTE risk between oral and transdermal estrogen users. Oral estrogens result in a hepatic first-pass effect which may contribute to impair the biosynthesis and clearance of proteins involved in hemostasis. Randomized trials have consistently shown that oral but not transdermal estrogens activate the coagulation cascade and increase fibrinolytic potential [25–27]. Oral, not transdermal, estrogen increases plasma concentrations of the prothrombin activation peptide (F1 + 2) [26,27]. A lower antithrombin concentration has also been shown in oral but not transdermal estrogen users. Similarly, increased thrombin generation, which is a marker of hypercoagulability has been found in oral, but not transdermal HT users [27]. Furthermore the rise in estrone synthesis by the liver following oral estrogen administration might contribute to this increase in thrombin generation [28].

Numerous reports also support for a role of oral estrogen on the protein C system. Activated protein C (APC) is an important natural anticoagulant which reduces the final process of coagulation. APC resistance has been described in patients at high risk for thrombosis and it was initially related to the factor V Leiden mutation. In the absence of factor V Leiden, a reduced response to APC is associated with an increased VTE risk. Acquired APC resistance has been reported in oral contraceptive users [29,30]. Several randomized trials [27,31,32] have also found that oral but not transdermal estrogen induce APC resistance in postmenopausal women.

With regard to the type of progestin, two randomized trials have previously shown that micronized progesterone combined with transdermal estrogen did not increase APC resistance or prothrombin activation peptide (F1 + 2) concentrations in contrast to oral estrogen [26,27]. On the other hand, a more recent study [33] shows that norpregnane derivatives (both nomegestrol acetate and promegestone) together with transdermal estrogen induce APC resistance compared to nonusers or users of transdermal estrogens combined with micronized progesterone. In addition, prothrombin activation peptide (F1 + 2) concentrations were higher in users of transdermal estrogens combined with norpregnane derivatives

than in nonusers. Therefore, the findings showing that transdermal estrogen together with micronized progesterone is not associated with increased APC resistance is likely to support the epidemiological data suggesting that such combinations may have a safer risk profile than other progestins with regard to VTE risk.

3. HT and women at high VTE risk

3.1. Women with personal history of VTE

HT is contraindicated in women with a personal history of VTE. Several reports have reported an important excess risk in postmenopausal women taking oral HT compared to non users. A recent French study (Menopause, Estrogen and Venous Events (MEVE)) nevertheless suggests that again use of transdermal estrogen may be well tolerated with regard to VTE recurrence [34]. This study included 1023 postmenopausal women with a personal history of VTE who were followed over an average 80 months after stopping anticoagulant therapy. Use of transdermal estrogens was not associated with an increased risk of recurrent VTE (hazard ratio 1.0; 95% CI 0.4–2.4) as compared to non users. In contrast, women using oral estrogens had an increased risk of recurrent VTE (hazard ratio 6.4; 95% CI 1.5–27.3). The difference between both routes of estrogen administration was significant ($p = 0.02$). Even though these data need further confirmation because of the small numbers of exposed cases in the MEVE study, they are likely to further support transdermal HT as a safer option for women at high risk for VTE.

3.2. Women with a prothrombotic mutation

Factor V Leiden and the prothrombin G20210A mutation are the 2 most common genetic defects associated with an increased risk for VTE. A familial history of VTE or a personal history of VTE in the post-partum or with oral contraceptive use usually represent medical conditions which might lead to screening for those thrombogenic mutations.

The effect of HT on VTE risk in women bearing such mutations was investigated in case-control studies [35,36] and both WHI trials. Overall, the presence of the factor V Leiden mutation or prothrombin G20210A mutation increased the risk of VTE by more than 3-fold (pooled odds ratio 3.3, 2.6 to 4.1). The joint effect of thrombogenic mutations and oral estrogen use among postmenopausal women further enhanced the risk of VTE (odds ratio 8.0, 5.4 to 11.9) compared with women without mutations not taking estrogen. In a multicenter case–control study of VTE among postmenopausal women [1], a 25-fold increase in VTE risk was found in those who both carry a prothrombotic mutation and use oral estrogen, compared with nonusers without a mutation. In contrast, current use of transdermal estrogen did not confer additional risk in women who carry a prothrombotic mutation.

Again, transdermal estrogen administration seems safer than oral estrogen administration with respect to VTE risk, even in women carrying a prothrombotic mutation. These data may have potential implications to minimize the excess risk of VTE among women who require HT. However, the safety of transdermal estrogen has still to be confirmed in randomized trials among carriers of prothrombotic mutations.

3.3. Obese women

Obesity is another condition which has been associated with an increased risk of VTE. In the placebo arm of the WHI, obese women had a 2.9 fold increased risk of VTE compared to their lean counterparts. Use of oral HT has been univocally associated with an increased risk of VTE in overweight/obese postmenopausal women. This increased risk ranges from a factor of 4–6 in randomized trials such as the WHI [11] to a factor of 10–20 in the large E3N observational study [20] in overweight and obese women, respectively. On the other hand, no increased risk with transdermal estrogen was found in observational studies that have specifically examined the relationship between excess weight/obesity and HT use according to the route of estrogen administration [6,20].

The EMAS position statement in managing obese postmenopausal women can be reviewed in a previous issue of the journal [37]. When HT is required, the lowest estrogen dose using the transdermal estrogen route should be preferred.

4. Conclusions

In summary, while HT still remains the most effective therapy to counteract the climacteric symptoms associated with the menopause, VTE is one of the major harmful effects associated with oral HT. Transdermal estrogen appears safer than oral estrogen with regard to VTE risk and should be the first choice in overweight/obese women.

In most cases, a personal history of VTE represents a contraindication to HT. Screening for a prothrombotic mutation is not recommended in the general postmenopausal population. When HT is required, such screening could be discussed especially, when there is a personal history of VTE in the postpartum or after use of oral contraceptive or a familial history of VTE. Oral HT is contra-indicated in case of thrombogenic mutations and in women at high VTE risk. Transdermal estrogen could be used after an extensive risk-benefit evaluation when any other treatment option is unsatisfactory. There is no evidence that low dose vaginal estradiol or estriol used at the recommended doses are contraindicated. A body of concordant data suggest that micronized progesterone and dydrogesterone have an overall better risk profile than other progestins not only with regard to thrombotic risk but also breast cancer [38,39]. Therefore, in women with an intact uterus, micronized progesterone or dydrogesterone should be preferred in combination with transdermal estrogen [40]. Regular follow up by a specialist service is recommended as well as regular re-evaluation of the benefit-risk balance of HT.

5. Summary recommendations

- VTE risk rises in postmenopausal women with increasing age.
- Thrombogenic mutations and excess weight/obesity are additional risk factors in postmenopausal women.
- There is compelling evidence from randomized controlled trials that use of oral estrogen given either alone or in combination with progestins increases VTE risk in postmenopausal women.
- Although there is no randomized controlled trial on transdermal estrogens, numerous data (both epidemiological and biological) suggest that transdermal estrogen is safer than oral estrogen with regard to VTE risk.
- Transdermal HT should be the first choice in overweight/obese postmenopausal women.
- A personal history of VTE and in some cases, a familial history of VTE (if associated with a prothrombotic mutation) are strong contraindications to oral HT. When HT is required, transdermal estrogen can be considered after careful individual evaluation of the benefits and risks.
- Micronized progesterone or dydrogesterone are the preferred progestins for non-hysterectomized women.

Competing interests

None declared.

Provenance

EMAS position statement.

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