REVIEW ARTICLE

Menopausal hormone therapy and risk of venous thromboembolism: The story so far

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Abstract

Menopausal hormone therapy (MHT) is known to increase the risk of venous thromboembolism (VTE), which includes deep vein thrombosis, pulmonary embolism, and less frequently cerebral vein thrombosis, but the absolute risk for a given patient is very low. After starting MHT, the risk of VTE seems to be at its highest, declining to the non-HRT user baseline level of risk after stopping. Whether estrogen-only or estrogen-progestin HRT combination is linked to a similar risk of VTE is unclear from the available evidence. The aim of this study is to evaluate the risks of developing VTE in relation to different types as well as different modes of administration of MHT through a database search including PubMed, MEDLINE, Google Scholar, Cochrane Library, and others in order to provide the women carers with the up-to-date and evidence-based guidelines and recommendations while counseling the post-menopausal women enquiring on use of hormonal therapies either to alleviate the menopausal symptoms or to prevent the long-term sequelae of estrogen deficiency. *(Afr J Reprod Health 2024; 28 [3]: 122-129)*

Keywords: Menopausal hormone therapy, post-menopausal women, estrogen, combined estrogen and progestogen, Venous thromboembolism

Résumé

On sait que l'hormonothérapie ménopausique (MHT) augmente le risque de thromboembolie veineuse (TEV), qui comprend la thrombose veineuse profonde, l'embolie pulmonaire et, moins fréquemment, la thrombose veineuse cérébrale, mais le risque absolu pour un patient donné est très faible. Après le début du MHT, le risque de TEV semble être à son plus haut niveau, diminuant jusqu'au niveau de risque de base des non-utilisatrices de THS après l'arrêt. Les preuves disponibles ne permettent pas de savoir si un THS à base d'œstrogène seul ou d'association œstroprogestative est lié à un risque similaire de TEV. Le but de cette étude est d'évaluer les risques de développer une TEV par rapport à différents types ainsi qu'à différents modes d'administration du MHT grâce à une recherche dans des bases de données comprenant PubMed, MEDLINE, Google Scholar, Cochrane Library et autres afin de fournir aux femmes les soignants avec les lignes directrices et recommandations à jour et fondées sur des preuves tout en conseillant les femmes ménopausées qui se renseignent sur l'utilisation de thérapies hormonales, soit pour soulager les symptômes de la ménopause, soit pour prévenir les séquelles à long terme d'une carence en œstrogènes. *(Afr J Reprod Health 2024; 28 [3]: 122-129).*

Mots-clés: Hormonothérapie ménopausique, femmes postménopausées, œstrogènes, association œstrogène et progestative, thromboembolie veineuse

Introduction

Venous thromboembolism (VTE), either deep vein thrombosis (DVP), pulmonary embolism (PE), or, less frequently, cerebral venous thrombosis (CVT), is a rare condition that affects women before the menopause however, following menopause, its frequency sharply rises[1]. VTE is a major factor in the burden of cardiovascular disease among postmenopausal women and may result in serious impairment or death[2]. VTE risk factors include constitutional traits (age, overweight, obesity) and genetic background (thrombogenic mutations, protein deficiencies). Additionally, HT use is a significant environmental factor that affects the risk of VTE in women[3].Concern over the link between hormonal therapy and venous thromboembolism (VTE) was first voiced in women using oral contraceptives (OC) 50 years ago[4]. Evidence rapidly showed a strong positive link between OC dose and VTE risk in addition to a clear correlation between OC and VTE[5]. Since postmenopausal hormone replacement therapies (MHT) normally had far lower levels of hormones than OC, similar concerns regarding HRT as a cause of VTE were not addressed[6]. However, current hormone therapy for menopause has been linked to a definite rise in the risk of venous thromboembolism (VTE)[7–11]. However, randomized controlled trials (RCTs) and observational studies both revealed a 2- to 3-fold higher risk of venous thromboembolism (VTE) with oral menopausal HT[12]. Comined estrogen-progestin preparations are usually associated with higher risks of VTE compared to estogen-only therapy, according to research[7–10,13], also increased risks are associated with oral compared to transdermal therapy[14–16]. This review investigates the magnitude of VTE risks associated with MHT use, stratified by type, dosage,duration, route of administration, and influenced other risks of the hormone used.

Pathophysiology of hormone-induced VTE

There are numerous theories as to how different hormones may cause VTE (Table 1). Oral contraceptives containing oestrogen are known to raise the levels of several coagulation proteins in the blood, including von Willebrand factor, fibrinogen, factors II, VII, VIII, and X. Additionally, oestrogen increases C4b binding protein, which subsequently combines with protein S, a naturally occurring anticoagulant, to lower the level of circulating free protein S[17]. Acquired protein C resistance and subsequent increased thrombosis risk would be the result of combined reduced free protein S level along with decreased tissue factor pathway inhibitor[18]. Although it depends on the type, synthetic progestins included in oral contraceptives are not linked to the onset of thrombosis[19,20]. Contrary to how oestrogen affects secondary hemostasis, increased VTE while taking testosterone is thought to be caused by a less well-understood mechanism. However, the proposed mechanism for venous thrombosis is thought to be primarily related to the effects of increased hematocrit and the resulting increase in serum viscosity. Testosterone is known to increase arterial thrombosis through accelerated atherosclerosis and possibly due to increased platelet aggregation[21]. The fact that many patients receiving testosterone therapy with VTE also have normal haemoglobin levels raises the possibility that additional mechanisms—like testosterone being converted to 17b-estradiol—may be at work[22]. A 2018 systematic review and meta-analysis included more than 2200 patients in six randomised controlled trials and 1.2 million patients in five observational studies, found no evidence of an increased risk of VTE in testosterone users (OR 1.41; 95 % CI 0.96-2.07), despite the fact that the included studies had a significant amount of heterogeneity and moderate bias[23] A retrospective cohort study included in the analysis also found no link between testosterone delivery method (such as injection, oral delivery, or transdermal patch) and VTE, despite the fact that this one study did show an overall rise in cardiovascular events, hospitalizations, and deaths in testosterone injection users compared to testosterone gel users[24].

Analysis of VTE risk by type of hormone

There is conflicting evidence regarding whether estrogen-only HT and combined estrogen/progestin HT carry distinct VTE hazards. Both have been separately analysed in a number of studies of the thromboembolic risk of HT. For instance, Douketis et al. showed that estrogen/progestin increased the relative risk of VTE by 2.7 (95% CI 1.4-5.1) while oestrogen alone did not (RR 1.2, 95% CI 0.6-2.6)[25]. When compared to estrogen-only use, Smith et al. discovered that combined hormonal therapy had an odds ratio of 1.6 (95% CI: 1.1-2.3) for VTE[26]. In a

large prospective study, Sweetland et al. discovered that among current oral HT users at the time of last contact, combined estrogen-progestin users had a significantly higher risk of VTE than estrogen-only users (RRs 2.07 vs. 1.42; $P_{heterogeneity} < 0.0001$), with a relative risk estimate of 1.46 (1.23-1.72) for the direct comparison of combined HT vs. estrogen-only HT. The same study revealed that among users of oral estrogen-progestin HT, use of preparations containing medroxyprogesterone acetate (e.g. Provera) was associated with a significantly higher risk of VTE than preparations containing norethisterone/norgestrel (RRs 2.67 vs. 1.91; $P_{heterogeneity} = 0.0007$)[27]. However, the LITE researchers found that the relative risks for oestrogen and progestin (1.6, 95% CI, 1.0-2.6) and oestrogen alone (1.6, 95% CI, 1.1-2.4) were comparable[28]. Although it may have lacked the necessary strength, the prematurely ended WISDOM trial failed to discover a difference in VTE risk between combination and estrogen-only HRT[29]. The Women's Health Initiative (WHI) discovered that women taking estrogen/progestin replacement had a higher risk of VTE[30] than those on just oestrogen[31]. Last but not least, the Estrogen

Table 1. Mechanism of thrombosis by hormone type

Hormonal therapy	Mechanism of thrombosis
Estrogen	Increased circulating coagulation factors including fibrinogen and factors II, VII, VIII, and X Increased C4b binding protein, which in turn decreases circulating levels of free protein S, a natural anticoagulant, leading to increased resistance to activated protein C
Testosterone	Potentially increased hematocrit leading to increased serum viscosity Adipose tissue conversion of testosterone to 17β-estradiol, in turn leading to the coagulation changes seen with estrogen therapy

(Adapted from www.co-hematology.com Volume 27 Number 5 September 2020).

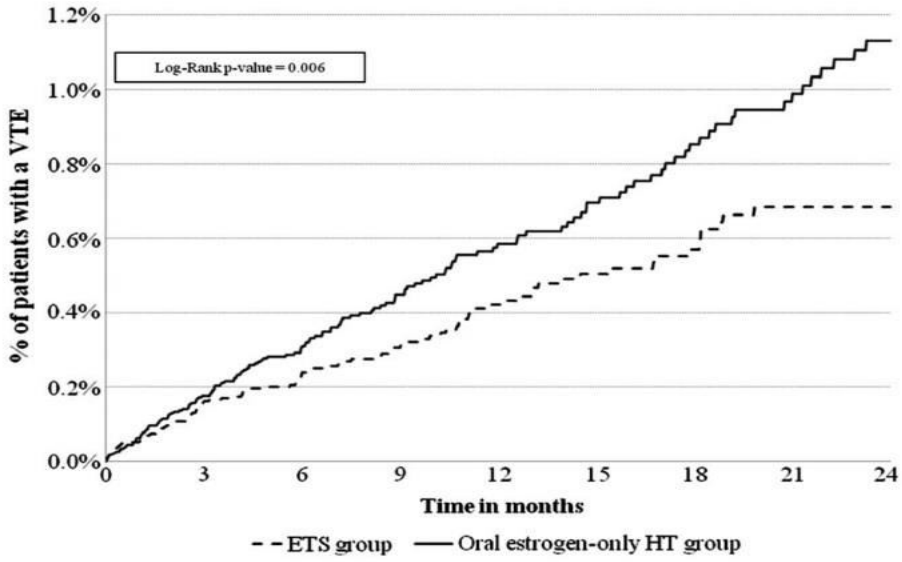

Figure 1: Kaplan-Meier rates of VTE. ETS, estradiol transdermal system; HT, hormone therapy; VTE, venous thromboembolism. (Adapted from Menopause, Vol. 25, No. 11, 2018)[44].

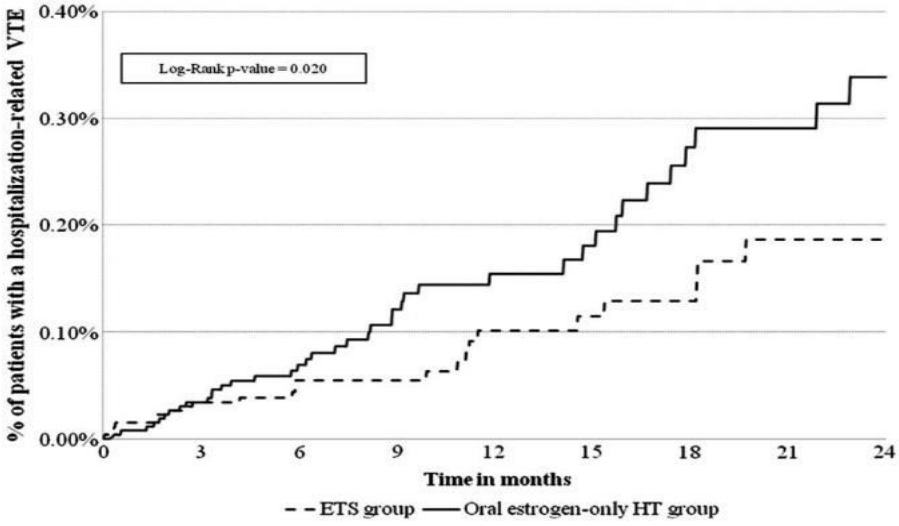

Figure 2: Kaplan-Meier rates of hospitalization-related VTE. ETS, estradiol transdermal system; HT, hormone therapy; VTE, venous thromboembolism. (Adapted from Menopause, Vol. 25, No. 11, 2018)[44].

and Thromboembolism Risk study (ESTHER) researchers did not discover that the addition of progestins to oral estrogens raised the incidence of VTE any more, with the exception of norpregnane progestin derivatives[32]. Only two French studies have so far looked into the VTE risks associated with the various pharmacological groups of progestogens. The data collectively demonstrated that norpregnane derivatives, nomegestrol acetate or promegestone, are more thrombogenic, with a two to three times larger thrombotic risk than with other derivatives; in contrast, micronized progesterone appeared to be safe with regard to thrombotic risk[33,34].

Impact of age and weight on MHT-associated VTE risk

Age has been shown to be one of the major risk factors for VTE in various settings, and similar information is available for HRT users. For instance, 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, compared to placebo users in the sixth decade of the WHI trials[35]. In the estrogen-only arm of the WHI, a comparable but less apparent effect of age was observed[36].In the HERS II trial, women older or younger than 65 years of age were compared to determine the impact of age on VTE. In univariate analysis, age greater than 65 was associated with increased VTE risk in MHT users compared to placebo users (HR 1.9, 95% CI, 1.0-3.6), but not in multivariate analysis[37]. In addition, obesity is a recognised risk factor for VTE[38]. When compared to placebo users in the normal weight group, VTE risk increased in MHT users in the WHI trials, in both overweight (body mass index (25-30 kg/m2)) and obese (body mass index >30 kg/m2),where (HR 3.8, 95 % CI, 2.08–6.94 and 6.61, 95% CI, 3.12–10.11, respectively)[30]. Although the Iowa Women's Health Study discovered a comparable rise in VTE risk in overweight and obese women, it did not examine whether this was specifically true of HRT users[39]. Additionally, the ESTHER showed that people with a BMI greater than 30 kg/m2 had an increased chance of developing VTE[40].

Analysis of VTE risk by route of hormone administration

The effects of HT using oral versus transdermal oestrogen alone or in conjunction with progestogen relative to nonusers have been examined in previous case-control studies of VTE in postmenopausal women. The Estrogen and Thromboembolism Risk (ESTHER) research, for instance, assessed the effect of progestogens and the route of oestrogen administration on the risk of developing VTE[41]. The ESTHER study's authors reported that the odds ratios for VTE in post-menopausal women treated with oral and transdermal oestrogen compared with nonusers were 4.2 (95% CI, 1.5-11.6) and 0.9 (95%

CI, 0.4-2.1) respectively. They came to the conclusion that oral, but not transdermal, oestrogen was linked to an increased risk of VTE[41]. Recently, the results of a large population-based case-control study involving 23,505 postmenopausal VTE cases matched with 231,562 controls recruited from the General Practice Research Database of the United Kingdom between 1987 and 2008 were published by Renoux *et al*. The risk of VTE was higher for users of oral oestrogen (RR ¼1.49; 95% CI, 1.37-1.63) and oral estrogen-progestogen (RR ¼ 1.54; 95% CI, 1.44-1.65), the authors found. However, the risk was not increased by current use of transdermal oestrogen alone (relative risk [RR] 1.01; 95% CI, 0.89-1.16) or combined with a progestogen (RR ¼ 0.96; 95% CI, 0.77-1.20)[42].Using data from 80,308 postmenopausal women followed for an average of 10.1 years, Canonico et al. also demonstrated that transdermal estrogens did not increase the risk of VTE compared to nonuse (hazard ratio: 1.1; 95% CI 0.8–1.8), but oral oestrogen did (hazard ratio: 1.7; 95% CI 1.1–2.8). These studies' findings support the hypothesis that a transdermal oestrogen formulation may be less likely to cause thrombosis than oral oestrogen[43]. Laliberte' et al., found that after adjustment for confounding factors, estradiol transdermal system(ETS) was associated with a statistically significant risk reduction for VTE and hospitalization-related VTE by 33% and 62%, respectively, compared with the oral estrogen-only HT cohort[44]. (Figure 1&2). The safety of vaginal estrogens, which are frequently used to treat atrophic vaginitis, was explicitly assessed in a recent systematic review. The use of vaginal oestrogen is not anticipated to increase the risk of cardiovascular events or venous thromboembolic events because it bypasses the liver's first-pass metabolism, according to the authors[45]. Additionally, since vaginal estrogens use a considerably lower amount of oestrogen than the vaginal ring, it is anticipated that there will be a lesser risk of thrombosis[46].

Inherited thrombophilias' effect on MHT-related VTE risk

The multiplicative risk of VTE associated with OC usage in women with hereditary thrombophilias is well-established, particularly for the Factor V Leiden (FVL) and Prothrombin 20210 (PT20210) variants, which are prevalent in around 5% and 2% of Caucasian populations, respectively[47]. Clinicians may be able to treat non-carriers with greater assurance if they are able to identify either of these mutations in women with personal or family history of VTE[47].The researchers demonstrated that there was a positive relationship between HRT-induced VTE and (1) increasing degrees of activated Protein C resistance, (2) elevated levels of Factor IX, and (3) decreasing levels of antithrombin, an endogenous anticoagulant, in a large population-based study using age-matched inpatients who were admitted for diagnoses thought to be unassociated with HRT use as a control group. The odds ratio for VTE raised to 153 when all three of these conditions were present at the same time (95% CI, 23.5, 1001)[48]. The ORs for VTE were 3.9 (95% CI, 1.3-11.2) in carriers of the FVL, 3.2 (95% CI, 1.7-6.0) in HRT users, and 15.5 (95% CI, 3.1-76.7) in HRT users who were heterozygous for the FVL. The authors came to the conclusion that HRT use and FVL had independent effects that multiplied each other to raise the risk of VTE[48]. The lack of any MHT users in this study's prevalence of PT20210 precluded investigation. It is likely that the correlation between activated Protein C resistance and MHT-induced VTE in this study was unique to FVL carriers, even though the authors did not state it explicitly. This is because the prothrombotic effect of FVL is typically assessed by quantifying activated Protein C resistance. FVL heterozygosity was not linked to a significantly higher risk of VTE in Hibraaten's placebo-controlled research of providing HRT to women with previously unprovoked VTE (RR 1.4, 95 percent CI, 0.4-5.3)[49]. Prothrombotic factors, such as FVL, PT20210, the methylene tetrahydrofolate reductase C677T polymorphism, and several less common clotting factor polymorphisms/mutations thought to be procoagulant, were evaluated in a nested case-control analysis of all the women in the WHI who developed VTE (n = 147). In terms of statistical significance, only FVL was associated with the incidence of VTE[35]. The incidence of VTE was only statistically significantly correlated with FVL. FVL carriers who were randomised to MHT had a comparable OR of 6.69 (3.09-14.49), whereas those who were FVL negative had an OR of 2.24 (95% CI, 1.45-3.47) for incident VTE. The researchers calculated that the annual risk of VTE for FVL carriers using MHT would be roughly 0.8%.According to the 2005 analysis of the

ESTHER trial data, oral HRT usage plus the presence of either FVL or PT20210 significantly elevated the incidence of VTE compared to non-users who had neither mutation (OR, 25.5; 95% CI, 6.9-95.0)[50]. These higher risks were not observed among transdermal HRT users who were carriers of either of these mutations. The investigators could not discover a positive interaction between the two (p = 0.7), despite the fact that the VTE risk was lower in HRT users who did not carry either FVL or PT20210 (4.3 [95% CI, 2.6-7.2] vs. 25.5 in carriers using oral HRT)[50]. In conclusion, there is strong evidence connecting MHT to prothrombotic alterations in the coagulation system, particularly elevated levels of fibrinolysis indicators. However, we do not yet have enough data to identify which hypercoagulable conditions place people at the greatest risk for HRT-induced VTE. The most prevalent inherited hypercoagulable state is FVL, and while there is evidence that it increases VTE risk when combined with HRT, there is currently no proof of a positive interaction between the two[47].

Conclusion

Menopausal hormone therapy (MHT) is known to increase the risk of venous thromboembolism (VTE), which includes deep vein thrombosis, pulmonary embolism, and less frequently cerebral vein thrombosis, but the absolute risk for a given patient is very low. VTE risk factors include constitutional traits (age, overweight, obesity) and genetic background (thrombogenic mutations, protein deficiencies). Additionally, HT use is a significant environmental factor that affects the risk of VTE in women. Whether estrogen-only or estrogen-progestin HRT combination is linked to a similar risk of VTE is unclear from the available evidence. However, randomized controlled trials (RCTs) and observational studies both revealed a 2- to 3-fold higher risk of venous thromboembolism (VTE) with oral menopausal HT. Users of combination estrogen-progestin medication had higher risks than users of estrogen-only therapy, according to research, also using oral as opposed to transdermal therapy[14–16]

Conflict of interests

The authors claim they have no conflict of interests.

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