REVIEW

Prevention and treatment of venous thromboembolism during HRT: current perspectives

Hannelore Rott

Coagulation Center Rhine-Ruhr,
Duisburg, Germany

Abstract: Many large trials in the past 15 years have proven an increased risk of vascular complications in women using oral, mostly non-bioidentical, hormone therapy. The risk of vascular complications depends on the route of administration (oral versus transdermal), age, duration of administration, and type of hormones (bioidentical versus non-bioidentical). Acquired and/or hereditary thrombophilias (eg, factor V Leiden, prothrombin mutation G20210A, and others) lead to a further increase of risk for venous thromboembolism, stroke, or myocardial infarction. Therefore, bioidentical hormone therapy via the transdermal route seems to be the safest opportunity for hormone replacement therapy, although large trials for bioidentical hormone therapy are needed.

Keywords: hormone replacement therapy, stroke, myocardial infarction, thrombophilia, bioidentical hormone therapy

Introduction

Five major classes of human steroid hormones are known: estrogens, progestogens, androgens, mineralocorticoids, and glucocorticoids. The term "progestogen" refers to both the natural progesterone and synthetic compounds that have progestogenic activity similar to that of progesterone. The term "progestin" generally refers to synthetic progestogens. The term "progesterone" refers to the naturally occurring human molecule.[1–3] Estrogens and progestogens are most commonly prescribed for the treatment of perimenopausal and menopausal symptoms such as hot flashes, night sweats, emotional lability, poor concentration, and sleep disturbance.

The endogenous estrogens found in humans include estradiol (E2), estriol (E3), estrone (E1), and their conjugates. The human ovary produces E2 and E1, whereas E3 is formed through 16α-hydroxylation of E1 and E2. Before menopause, the predominant estrogen in circulation is E2, secreted by the ovaries. E1 is found in highest concentration after menopause and is converted from E2 and adrenal androstenedione in adipose tissue. E3 is short-acting and the least potent estrogen, and it is not converted, unlike E1, into E2. E2 has the highest affinity for both estrogen receptors (alpha and beta); E1 binds only to estrogen receptor alpha (which is located in breast cancer cells and the endometrium); and E3 binds weakly to both receptors.

Progesterone in a nonpregnant woman is secreted by the ovaries and adrenal glands. Progestogens are needed in hormone replacement therapy (HRT) to prevent endometrial hyperplasia or neoplasia when estrogen is administered. In "classic" HRT, mostly synthetic progestins, such as medroxyprogesteronacetate (MPA), are used.[1] These synthetic progestins have different affinities for the progesterone receptor and

Correspondence: Hannelore Rott
Coagulation Center Rhine-Ruhr,
Koenigstr 13, 47051 Duisburg, Germany
Tel +49 203 3483 360
Fax +49 203 3483 3636
Email hannelore.rott@gzrr.de

they may also activate non-progesterone receptor steroid receptors in different tissues.[4]

Because of this, the most physiological way to apply HRT is to give bioidentical hormones transdermally without first-pass mechanism in the liver to avoid unphysiological changes and actions of the hormones, as described in the Oral non-bioidentical HRT and the risk of venous thromboembolism (VTE), stroke, and coronary heart disease (CHD) section.

What types of sex hormones are used in HRT?

One should keep in mind that there are many different types of sex hormones in use for HRT, including those that are partially synthetic, semisynthetic, derived from animal sources, or bioidentical (which means identical to the naturally occurring human hormones, bioidentical human hormones) (see Table 1).

The synthetic hormones, or those from animal sources, that are used in HRT do not contain the physiological amounts of E1, E2, and E3. The physiological proportion of E1, E2, and E3 in human blood is about 33% E1, 45% E2, 10% E3,

Table 1 Types of sex hormones used in hormone replacement therapy

Non-bioidentical estrogens, for example
Ethinyl E2
Esterified estrogens
Conjugated equine estrogens
Dienestrol
Mestranol
Bioidentical estrogens, for example
Estrone sulfate
Estropipate
Estradiol
Estriol
Progestins (non-bioidentical), for example
Medroxyprogesterone acetate
Norethindrone (acetate)
Norgestrel
Levonorgestrel
Desogestrel
Norgestimate
Megestrol acetate
Drospirenone
Etonogestrel
Medrogestone
Dydrogesterone
Progesterone (bioidentical)
Progesterone
Other
Tibolone

Note: Data from Moskovitz.[3]
Abbreviation: E2, estradiol.

and about 10% metabolites of E1 and E2.[5] E2 is the most potent human estrogen. The distribution of estrogens in non-bioidentical estrogens differs significantly from human estrogens; this is especially true for conjugated equine estrogens (CEE) (see Figure 1).

Progestins are synthetic progestogens, which are mostly used in HRT. The only bioidentical progestogen is progesterone (see Table 1).

Both estrogens and progestins/progesterone can be used orally, transdermally, intranasally, or intramuscularly.

Oral non-bioidentical HRT and the risk of venous thromboembolism (VTE), stroke, and coronary heart disease (CHD)

Table 2 shows the absolute risk of VTE in women with and without HRT.

Many large trials in the past 15 years, for example, the Women's Health Initiative (WHI) trial in 2002[6,7] and the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) trial,[8] showed a marked increase in the risk of VTE in women using oral non-bioidentical HRT. Of note, most of the women in these trials used oral CEE + MPA.

In the WHI trial, the risk of VTE in HRT patients was double that of patients in the placebo group;[6] in the Heart and Estrogen/progestin Replacement Study (HERS), the VTE risk was nearly threefold;[9] and, in the ESTHER study, the risk was fourfold[10] (see Table 3). VTE risk is much higher in women taking CEE than in women taking oral esterified estrogens.[11]

The risk of VTE while taking CEE + MPA increases with age. Compared with women between the ages of 50–59 years who were taking placebo, the risk associated with HRT was higher with age: hazard ratio (HR) of 4.28 for women aged 60–69 years and 7.46 for women aged 70–79 years. Compared with women who were of normal weight and taking placebo, the risk associated with taking estrogen + progestin was increased among overweight (HR 3.8) and obese women (HR5.61), respectively.[12] The VTE risk in oral HRT users is highest in the first year of use,[13,14] then declines, but remains on a higher level compared to nonusers. There is no elevated risk for past users of HRT after 6 weeks of stopping HRT.[15]

The risk of VTE recurrence is lower in women who developed VTE on estrogen replacement and then stopped the HRT. This shows that, in most women with VTE on HRT, the HRT was the main risk factor.[16]

A Free human estrogens

B Conjugated equine estrogens
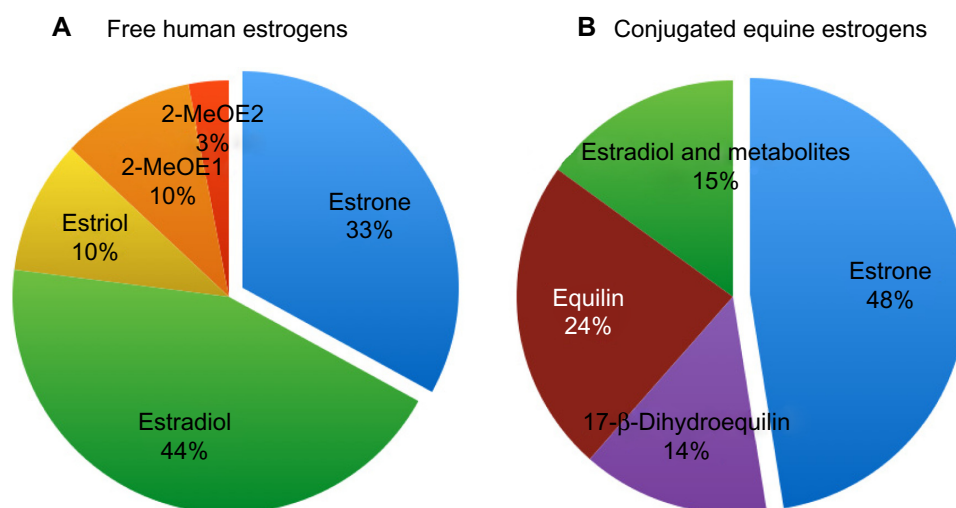
Figure 1 Distribution of estrogens in women and horses.
Notes: (**A**) Normal estrogen distribution in nonpregnant women. (**B**) Distribution of estrogens in pregnant horses.
Abbreviations: 2-MeOE1, 2-methoxyestrone; 2-MeOE2, 2-methoxyestradiol.

The use of oral non-bioidentical HRT is associated with an overall 29% increase in the risk of ischemic stroke. The severity of stroke (poor functional outcome, death, disability, or dependency) increased with oral non-bioidentical HRT, with a nonsignificant increase of fatal stroke.[17] Tibolone, an oral synthetic steroid hormone similar to norethisterone and with estrogenic, progestogenic, and androgenic effects, also leads to an excess risk of stroke (odds ratio [OR] 2.18).[18]

Oral CEE in combination with MPA was associated with an HR of 1.24 for CHD and not a protection against cardiac diseases, as was initially expected.[19] In postmenopausal women who had survived a myocardial infarction, the oral use of 2 mg E2 valerate did not reduce the overall risk for further cardiac events.[20] Women, who initiated hormone therapy (CEE) after hysterectomy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. The

risk for stroke was increased in this study regardless of years since menopause.[21] In a group of women aged 45–58 years who were treated with either 2 mg oral E2 + norethisterone acetate, or in cases who had undergone hysterectomy with oral E2 alone, there was a significantly reduced risk of mortality, heart failure, and myocardial infarction.[22]

Given the above results, the type of oral HRT, for example CEE + MPA versus E2 (which is a natural hormone) + progestogen of different types might be very important in terms of the risk of vascular complications. Of note, HRT with oral CEE + MPA did not have clinically meaningful effects on health-related quality of life.[23]

The main reason for the increased risk for vascular complications in oral HRT is primarily the estrogen component; the progestin only modifies this risk, as is already known to be the case with oral contraception.[24] The amount of coagulation activation also seems to be dependent on the estrogen dosage used.[25]

High endogenous levels of sex hormones of E2 and testosterone in the general population are not associated with increased risk of VTE.[26]

Only one study of testosterone application in women and cardiovascular disease exists, and no increased risk of cardiovascular disease could be found in women prescribed testosterone tablets, injections, or implants.[27]

Transdermal HRT and the risk of VTE

Sex hormones can be given easily via a transdermal route as a patch or gel/cream.

Table 2 Absolute risk of VTE in peri- and postmenopausal women with and without HRT

Age	Absolute risk of VTE without HRT	Absolute risk of VTE with HRT (oral estrogen + progestin)
50–59 years	0.8	2.27
60–69 years	1.9	4.28
70–79 years	2.7	7.46

Notes: Annualized rate/1,000 person years. Data from Chushmann et al.[12]
Abbreviations: HRT, hormone replacement therapy; VTE, venous thromboembolism.

Table 3 Risk for VTE, stroke, and CHD in women using oral, non-bioidentical hormone replacement therapy

Risks	HERS[9]	WHI trial[6,7]	WISDOM study[8]	ESTHER study[10]
VTE	RH 2.89	HR 2.13	HR 7.36	OR 4.2
Myocardial infarction or death from CHD	RH 0.99	HR 1.29	Significant increase	Not detected
Stroke or cerebral vascular accident	Not detected	HR 1.41	No increase	Not detected

Note: Data from Rossouw et al,[6] Anderson et al,[7] Vickers et al,[8] Hulley et al,[9] and Canonico et al.[10]
Abbreviations: CHD, coronary heart disease; HERS, Heart and Estrogen/progestin Replacement Study; HR, hazard ratio; OR, odds ratio; RH, relative hazard; VTE, venous thromboembolism; WHI, Women's Health Initiative; WISDOM, Women's International Study of long Duration Oestrogen after Menopause.

Both estrogens and progestogens have very good bioavailability when given transdermally. Another advantage of giving estrogens transdermally is the avoidance of the so-called first-pass mechanism in the liver. In the first-pass mechanism, which occurs only when steroid hormones are given orally, the structure of the hormones can change due to metabolizing effects, leading to formation of unphysiological molecules and activation of receptors of other steroid hormones. One possible consequence, among others, is a hypercoagulable state and a sometimes greatly reduced concentration of the drug, with the necessity of much higher doses needed orally in comparison to transdermal administration. With oral HRT, coagulation activation occurs (eg, higher levels of coagulation factor VII, greater thrombin generation peak levels, higher endogenous thrombin potential, higher level of prothrombin fragment 1.2)[28] and anticoagulants decrease (eg, antithrombin, protein C, protein S, tPA);[29,30–32] an acquired APC resistance phenotype can also occur.[33] Thrombin generation is significantly increased in women who use HRT orally (Table 4). This may be mediated by the first-pass metabolism of E1, the main metabolite of E2, because plasma E1 levels are higher in women taking oral estrogen.[34] The level of high-density lipoprotein cholesterol can increase[35] and the level of lipoprotein(a) decrease[36] while patients are on oral HRT, but this has obviously no clinical protective effect against arterial complications, as shown in the Oral non-bioidentical HRT and the risk of venous thromboembolism (VTE), stroke, and coronary heart disease (CHD) section.

In a multicenter case-control study in postmenopausal women in France, oral use of estrogen (E2, mean dose 1.5 mg)

Table 4 Changes in coagulation and metabolic parameters in users of oral versus transdermal hormone replacement therapy (HRT)

Coagulation parameter	Oral HRT	Transdermal HRT
D-dimer	Increase	No change
Protein S	Decrease	No change
Antithrombin	Decrease	No change
APC ratio	Decrease	No change
Thrombin generation	Increase	No change
Factor VII	Increase	No change

Abbreviation: APC, activated protein C.

was associated with a fourfold risk of VTE, especially when combined with norpregnane derivatives, whereas E2 via the transdermal route showed an OR of 0.9 for VTE.[10,37]

Roach et al showed that non-oral HRT did not increase the risk of VTE, but oral HRT did, by fourfold.[38] Another nested case-control study came to the same conclusion, with a relative risk of VTE of about 1.5 for oral estrogen use and no increase of VTE risk for transdermal use of estrogen.[39] The same was true in another study from 2011 involving around 54,000 women and comparing transdermal with oral estrogen use. The incidence ratio for VTE in transdermal users was 0.72.[40]

Intranasal application of E2 + norethisterone is also not associated with an activation of the coagulation system.[41]

Thrombophilia and HRT

For the absolute risk of VTE in women over 49 years, see Table 5.[12]

The condition of thrombophilia can be hereditary (eg, factor V Leiden (FVL) mutation; prothrombin mutation G20210A [PTM]; deficiencies of antithrombin, protein C, or protein S; elevated lipoprotein[a]; non-O blood group[42]); acquired (obesity, smoking, varicosis, chronic inflammatory bowel disease, rheumatic diseases, intake of corticosteroids, antiphospholipid syndrome, hyperhomocysteinemia, elevated factor VIII levels, surgery, cast, etc);[43] or, often, a combination of both.

In a case-control study in women aged 45–64 years, the relative risk of idiopathic VTE in HRT users showed a significant association with APC resistance (OR 4.06), low antithrombin levels (OR 3.33), low protein C levels (OR 2.93), or high D-dimer levels (OR 3.84). D-dimer levels rose in patients on oral HRT,[44] but transdermal HRT had no effect in this regard.[30] Carriers of APC resistance/FVL who used oral HRT had a 13-fold increase of VTE risk.[45] Two other studies found similar results, with an OR of about 14 for women with FVL + oral HRT compared to women assigned to placebo.[46,47]

In another study in postmenopausal women with idiopathic VTE, the combination of either FVL or PTM and oral estrogen was associated with a 25-fold increased risk of VTE compared with non-users without mutation.

FVL or PTM alone without oral estrogen use showed ORs of 3.4 and 4.8, respectively for VTE; however, the risk for women with prothrombotic mutation using transdermal estrogen was similar to that of women with a prothrombotic mutation who were not using estrogen.[48]

For the other known hereditary thrombophilias, such as deficiencies of antithrombin, protein C, and protein S or elevation of lipoprotein(a), no data exist for the VTE risk in HRT users; the same is true for the acquired thrombophilic disorder antiphospholipid syndrome. This may be due to the rarity of these conditions (see Table 5).

Combined hereditary risk factors, eg, the combination of non-O blood group and either FVL or PTM, further increases the risk of VTE and myocardial infarction.[49]

In a study from 2001, in which postmenopausal women received mainly esterified oral estrogens, the risk of nonfatal myocardial infarction was increased eleven-fold in women with PTM compared with women without HRT and the wild-type genotype.[50]

There are no further data regarding the roles of specific thrombophilias and HRT on the risk of CHD or stroke.

Bioidentical HRT (BHR)

The finding that the CCE + MPA arm, in particular, of the WHI study showed more risks than benefits for the patients led to a dramatically changed prescribing practice of HRT all over the world.[51] In USA, prescription of CEE + MPA has decreased by 63% between 2002 and now. A substantial number of patients expressed a loss of trust in information about HRT and in their physicians after publication of the WHI Trial. Furthermore, many women desire a "natural" alternative medication for treating menopausal symptoms. BHR may be one such alternative.

Endocrinologists define bioidentical hormones as compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body. This is only true for a few estrogens and for the only natural progestogen (progesterone) (see Table 1). The bioidentical hormones are usually derived from plant sources. Progesterone is available as oral micronized progesterone in oil or for vaginal use as gel or capsules. The micronized form of progesterone improves absorption of oral progesterone. The most common combinations for BHR include endogenous estrogen (mostly E2, E1, E3) and progesterone, preferably transdermally. Sometimes other ingredients, such as testosterone, are added. In Europe in particular, several bioidentical formulations for transdermal application are approved, for example E2 (oral 1–2 mg, or as a patch [25–100 µg/24 h]) and E3 (0.5–2 mg) for oral and transdermal or vaginal use. Natural micronized progesterone (100 mg capsule for oral or vaginal use) is also approved in most countries. Some small studies have shown favorable effects of BHR on myocardial ischemia and cardiovascular biomarkers.[52–54]

A recently published study showed a higher, doubled risk of VTE and possibly myocardial infarction in users of oral CEE compared to oral E2.[55] Another study showed a 2.5-fold risk for VTE in users of CEE, and the risk was much higher

Table 5 Thrombophilias and risk of VTE

Thrombophilia	VTE risk without HRT (OR)	VTE risk with HRT (OR)
Factor V Leiden mutation, heterozygous	5	13–25
Factor V Leiden mutation, homozygous	10	Higher than for heterozygous; thus far not sufficiently studied
Prothrombin mutation G20210A, heterozygous	3	13–25
Prothrombin mutation G20210A, homozygous	No data	Higher than for heterozygous; thus far not sufficiently studied
Prothrombin G20210A mutation, heterozygous + factor V Leiden mutation, heterozygous	4–15	No data
Congenital Protein S deficiency	5–11	No data
Congenital Protein C deficiency	3–15	No data
Congenital antithrombin deficiency	4–50, depending on type of AT deficiency (type I or II)	No data
Factor VIII elevation	5–8	No data
Antiphospholipid antibodies (lupus anticoagulants, anti-cardiolipin antibodies, anti-β2-glycoprotein I antibodies)	2–16, depending on antibody titer or combination thereof	No data
Hyperhomocysteinemia	Risk rises by 1.3 for each increase of 5 µmol	No data
Lipoprotein(a) >30 mg/dL	1.8	No data
MTHFR polymorphisms	Not elevated	No data

Abbreviations: HRT, hormone replacement therapy; OR, odds ratio; VTE, venous thromboembolism; MTHFR, methylenetetrahydrofolate reductase.

for women with hereditary thrombophilia (OR 9.1). In this study, the use of esterified estrogen was not associated with a higher risk for VTE without thrombophilia.[56]

BHR has also been demonstrated to cure typical menopausal symptoms[57–59] while lowering lipid levels.[60]

BHR, usually applied transdermally, seems to be a more physiological and safer alternative to classic HRT (eg, CEE + MPA), but large clinical studies are needed to confirm this.

Conclusion

Many different types of HRT exist (synthetic versus bioidentical, oral versus transdermal, etc), so the results, benefits, and risks of a particular type of HRT should not be assumed of other types of HRT.

The highest risk for vascular complications is associated with oral, non-bioidentical HRT, especially with oral CEE + MPA or with oral estrogens + synthetic progestins. Oral HRT shows an increased risk of vascular complications, while transdermal applications do not. Women with hereditary and/or acquired risk factors or a history of vascular complications should use transdermal and not oral HRT.

Transdermal BHR is possibly the best choice for any woman wishing to use HRT, but further studies on this option are needed.

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Disclosure

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