Maturitas 82 (2015) 303–306

Contents lists available at ScienceDirect

Maturitas

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

Review article

Hormone therapy and risk of venous thromboembolism among postmenopausal women

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ARTICLE INFO

Article history:
Received 15 June 2015
Accepted 28 June 2015

Keywords:
Hormone therapy
Venous thromboembolism
Postmenopausal women

ABSTRACT

Despite a decrease in the use of postmenopausal hormone therapy (HT) over the last decade, many women are still prescribed this treatment, as it remains the most effective means of counteracting climacteric symptoms. Its use declined when it was shown that HT increases the risk of breast cancer, stroke and venous thromboembolism (VTE). Nevertheless, that benefit/risk ratio was established among women using oral estrogens alone or combined with a specific progestogen and it cannot necessarily be extrapolated to other HTs.

Oral estrogens increase the risk of VTE especially during the first year of treatment and past users revert to a similar risk as women who have never used them.

There is now growing evidence that VTE risk among HT users strongly depends on the route of administration. Indeed, transdermal estrogens, unlike oral estrogens, are not associated with an increased VTE risk and biological data support this difference between oral and transdermal estrogens. In addition, transdermal estrogens may not confer additional risk in women at high risk of VTE. Significant differences in thrombotic risk between HT preparations also relate to the concomitant progestogen. Studies have consistently shown that VTE risk is higher among users of combined estrogens plus progestogens than among users of estrogens alone. With respect to the different pharmacological classes of progestogens, two observational studies found that norpregnane derivatives are associated with an increased VTE risk, whereas micronized progesterone may be safe with respect to thrombotic risk. In conclusion, transdermal estrogens alone or combined with micronized progesterone may represent the safest alternative for women who require HT.

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http://dx.doi.org/10.1016/j.maturitas.2015.06.040
0378-5122/

1. Introduction

Venous thromboembolism (VTE), either deep-vein thrombosis (DVP) or pulmonary embolism (PE), is an uncommon disease before the menopause. Its incidence strongly increases after menopause [1]. VTE may cause significant disability and/or death and is an important contributor to the burden of cardiovascular disease among postmenopausal women [2].

Risk factors for VTE include genetic background (thrombogenic mutations, protein deficits) and constitutional factors (age, overweight, obesity). In addition, the use of hormone therapy (HT) is an important environmental determinant of VTE in women. PE, which can be fatal, is the main event attributable to HT use among young postmenopausal women, who now represent the most frequently treated population. However, this association has been observed among women treated with oral estrogens alone or estrogens combined with a specific progestogen. The combination is commonly used in the USA and there are important differences in medical practice between France and the USA, for instance. While oral estrogens are preferentially used in the USA, women in Southern European countries are more often prescribed transdermal estrogens. In addition, the progestogen added to estrogens also differs. In the USA, medroxyprogesterone acetate (MPA) is the most commonly used progestogen, while many progestogens are used in France, including the natural hormone, micronized progesterone. Therefore, the results from American studies cannot necessarily be extrapolated to other countries, using other types of treatments.

This brief review focuses on the relationship between VTE risk and HT use; it takes into account the route of estrogen administration and the type of progestogens.

2. Route of estrogen administration

2.1. Overall comparison

So far, the risk of first VTE among women taking oral estrogens has been investigated in 8 case-control studies [3–11], 6 prospective cohort studies [12–17] and 6 randomized controlled trials (RCT) [18–23] and the overall estimate is close to 2 and very significant. By contrast, an updated quantitative assessment of 5 case-control studies [4,6,7,9–11] and 3 cohorts [14,16,17] among women taking transdermal estrogens yielded an odds ratio for thrombosis close to one and not significant. In addition, the VTE risk is significantly lower among users of transdermal estrogens than among users of oral estrogens.

These results regarding the differential impact of oral and transdermal estrogens on VTE risk have biological support. While oral estrogens activate blood coagulation and induce activated protein C resistance (APCr), a validated surrogate marker of VTE, transdermal estrogens have no deleterious effect on haemostasis [24–26].

2.2. Characteristics of HT

Previous data have shown that past users of HT present similar VTE risks as women who have never used them, whatever the route of estrogen administration [27].

Based on observational studies of the duration of treatment separately for groups of users of oral and transdermal estrogens, the risk of VTE is the highest during the first year of treatment for women taking oral estrogen while there is no 'start' effect with the use of transdermal estrogens [5,7,11,17].

Similarly, there may be a dose effect with oral but not with transdermal estrogens, but because few studies have examined this there are not sufficient data to draw firm conclusions [5,7,16].

One study suggested that oral conjugated equine estrogens may be more thrombogenic than esterified estrogens [8]. The issue does not arise with transdermal devices that deliver only 17β-estradiol.

2.3. Women at high VTE risk

Women who have a baseline VTE risk factor and who use oral estrogens represent a group at high risk of VTE [28–30]. It has been suggested that transdermal estrogens do not confer additional VTE risk for women carrying a prothrombotic mutation, presenting an elevated BMI or a personal history of VTE [31–33]. These data suggest that transdermal estrogens are less thrombogenic than oral HT, and may even be safely used by women at high VTE risk who suffer from climacteric symptoms.

3. Different types of progestogens

3.1. Estrogens alone versus estrogens combined with progestogens

Comparison of VTE risk among women using estrogens alone and women using estrogens combined with progestogens shows that adding progestogens significantly increases the risk of VTE with both oral and transdermal treatments [7,9,10,14,16,17,34]. Nevertheless, this result does not take into account the different pharmacological classes of progestogens.

3.2. Impact of the different classes of progestogens

So far, the risk of VTE of the different pharmacological classes of progestogens has been investigated only in two French studies. Taken together, the data showed that norpregnane derivatives, either nomegestrol acetate or promegestone, are more thrombogenic, with a two to three times greater thrombotic risk than with other derivatives; in contrast, micronized progesterone seemed to be safe with respect to thrombotic risk [10,14].

This result has some biological support, in that a significant association between norpregnane use and APCr has been found in a cross-sectional study [35]. Nevertheless, further epidemiological and biological data are needed to confirm the potential thrombogenic role of norpregnane derivatives among postmenopausal women.

3.3. Few data regarding specific molecules

Except for micronized progesterone, which is the natural molecule, the only data on the impact of a specific molecule concern MPA, the most frequently used progestogen in USA. The effect of MPA on VTE risk has been evaluated both directly and indirectly [17,23,29,30]. Overall, the results consistently show that, when combined with oral estrogens, MPA seems to increase VTE risk relative to that of women who do not use progestogens.

These data suggest that the particular progestogen used is another important determinant of VTE risk, irrespective of the route