

Hormonal Therapies and Venous Thrombosis

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INTRODUCTION

Hormones have an impact on coagulation through some mechanisms which are well known although not completely understood.

Women ongoing hormonal replacement therapy (HRT) also displayed a trend toward hypercoagulable state and venous thromboembolism [1].

On the other hand, the use of oral contraceptives containing oestrogen and progestin is associated with a small but clinically significant increased risk of venous thrombosis [2].

Exposure and dose of estrogens seem to be the main determinant, whereas progestins seem to reverse the prothrombotic effect of oestrogens.

HORMONE REPLACEMENT THERAPY

The association between hormone replacement therapy (HRT) and venous thromboembolism (VTE) was matter of discussion until '90 years. Although an increased incidence of thrombotic events has been always described in population taking HRT, several reports did not find significant association between both conditions until 1996 [3, 4]. However, beginning from 1996 most and most Authors found a significant association between HRT and VTE in several types of clinical studies (i.e. observational studies, case-control studies, prospective and follow up studies) [5-7]. Moreover, the association between HRT and venous thrombosis was underlined in the first year both for deep vein thrombosis and pulmonary embolism if women ongoing HRT were compared to non-users [8]. Probably first studies failed to demonstrate this topic because a different design and different magnitude of studies; moreover, old studies frequently did not have objective diagnostic methods for VTE [8]. Most studies showed that thrombotic risk is highest in the first year of use of HRT, while other studies showed that thrombotic risk persists also in following years [9]. From a pharmacological point of view there are no difference between the administration of HRT (i.e. transdermal or *per os*) nor for single oestradiol administration or for combined hormonal therapies [10].

Prothrombotic effects of HRT are related to several actions. Low doses of oestradiol are associated with less activation of coagulation, including TFPI and APC Resistance, and inflammatory markers if compared with regular dose: low dose and conventional dose formulations had similar effects on C reactive protein [11, 12]; however also the increase synthesis of clotting factors as to the decreased synthesis of clotting inhibitors as to an acquired form of activated protein C resistance are involved in the hypercoagulable state of women ongoing HRT [1]. As confirm of this trend to hypercoagulable state, markers of thrombin generation are frequently increased in women taking HRT: increased levels of prothrombin fragments 1+2, TAT complexes and D-dimer have been found in several studies [13]. Furthermore the increase in these markers was higher in women who subsequently developed recurrent VTE.

On the other hand, actually there are few references and indication to test thrombophilia before to begin HRT. This may be related to several factors as the adult age of users HRT or the combined risk with other risk factor for arterial thrombosis (e.g. smoking, diabetes, hypertension dyslipidemia) or the use of any type of pharmacological thromboprophylaxis for any reason (recent surgery, aspirin use and so on), as cost/effectiveness of thrombophilia testing as cost/benefit of thrombophilia testing. So further studies are needed to analyse the usefulness of thrombophilia testing for women on HRT or candidate to HRT to prevent VTE.

ORAL CONTRACEPTIVE USE

The association between oral contraceptives (OC) and VTE is well known since 1960. OC, in fact, are the more common acquired and transient thrombotic risk factor in young women [2]. Initially the prothrombotic action was attributed to the oestrogen [14], while also the prothrombotic action of progestins is relevant [15]. Thereafter, differences between the prothrombotic actions of several progestins were underlined in several studies; third generation of OC were found to be more thrombogenic than first and second generation because the prothrombotic action of desogestrel or gestogene [16].

The prothrombotic action of OC is based on the increase of synthesis of clotting factors as to the decrease of synthesis of clotting inhibitor as to an acquired form of activated protein C resistance [17]. The appearance of acquired activated

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protein C resistance seems to be stronger if third generation OC were taken [18].

Furthermore, the interaction between OC use and inherited thrombophilia greatly increases the risk of venous thromboembolism as recently demonstrated also by the RIETE registry [19, 20].

On the other hand great interest has been raised on the role of thrombophilia testing for women taking OC or candidate to take pill for any reason because the incidence of thrombotic events seems to be rare if compared to the number of women ongoing pill and because thrombotic complication may occur independently from the presence of inherited thrombophilia.

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