Hormone replacement therapy: prothrombotic vs. protective effects

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Abstract

Hormone replacement therapy (HRT) is associated with reduced risk of coronary heart disease (CHD) and stroke in observational studies; however the possibility of confounding by other risk factors requires prospective assessment of its risks and benefits in randomised controlled trials. The HERS trial of oral HRT in secondary CHD prevention observed an early increased risk of myocardial infarction (MI) and venous thromboembolism (VTE) with HRT: the latter risk has been confirmed by other prospective and case-control studies, and a past history of VTE or MI is now a contraindication to oral HRT. Other prospective randomised trials of HRT, CHD and stroke are in progress. Potential prothrombotic effects of oral HRT (but probably not transdermal HRT) include increased plasma factors VII and IX, activated protein C resistance and C-reactive protein; and decreased antithrombin, protein C and S, and tissue factor pathway inhibitor. Potential protective effects of HRT include decreased blood pressure, lipids, glucose intolerance, fibrinogen, viscosity and plasminogen activator inhibitor; and increased endothelial function. The overall balance of prothrombotic and protective effects varies with HRT preparations and individual women: and may be clarified by ongoing large randomised trials and case-control studies (and substudies of trials).

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Introduction

Menstruating women have a lower risk of coronary heart disease (CHD) than men, and this relative risk reduction is attenuated following the menopause. The “protective” effect of the menopause has been refuted (1). Observational studies suggest that HRT use is associated with reduced risk of CHD and mortality (2,3), however such studies are biased due to confounding, in that HRT users have fewer CHD risk factors than non-users (4). Hence, the effects of HRT on CHD, stroke, and venous thromboembolism require prospective assessment of risks and benefits in randomised controlled trials.

Recent RCT results and a meta-analysis have shown that oral HRT use is associated with increased risk of venous thromboembolism (VTE) (5) as well as of stroke and breast cancer (6). Hence, physicians should not prescribe conventional oral HRT for women at increased risk of VTE, CHD or stroke. However, HRT reduces not only perimenopausal symptoms, but also the risk of osteoporosis and bone fractures, hence it is important to (a) establish the mechanisms through which conventional oral HRT might increase thrombotic risk (VTE, CHD, or stroke); and (b) establish whether or not alternative HRT preparations (e.g. low dose oral, or transdermal) or selective (o)estrogen receptor modulators (SERMs, e.g. raloxifene) may preserve their anti-symptomatic and anti-osteoporotic effects, while avoiding increase in thrombotic risk.

Prothrombotic effects

Increased coagulation factors

Like COC preparations, oral HRT preparations increase the levels of several coagulation factors, especially factors VII and IX (7-9). Use of combined oestrogen-progestogen HRT reduces the increase in factor VII observed with unopposed oestrogen HRT (9,10); but this is not explained by the differential effects of these HRT preparations on triglyceride levels (9). The increase in factor VII is similar for both fasting and postprandial plasma levels; but increases in activated factor VII are controversial (11,12). While there is overall little epidemiological evidence that increased factor VII levels are associated with venous or arterial thrombosis, there is increasing interest in factor IX levels and thrombosis (13).

Decreased coagulation inhibitors

Like COC preparations, oral HRT preparations decrease the levels of several coagulation inhibitors, including antithrombin, proteins S and C, and tissue factor pathway inhibitor (TFPI) (7-9; 13-15).

Increased activated protein C resistance

A possible effect of oestrogens on activated protein C (APC) resistance was suggested by reports of increased APC resistance during pregnancy or COC use in the mid-1990's. In the first epidemiological study of APC resistance in a large sample of the general population, current HRT users were observed to have a similar level of increased APC resistance to current COC users (16,17). In the same study, APC resistance was also associated with increasing age, obesity, and increased factor VIIIc levels (as well as the factor V Leiden mutation); hence we hypothesised that APC resistance was a potential

common biological pathway through which all these risk factors for VTE might promote venous thrombosis (16,17). Since 1997, we confirmed that APC resistance was associated with oral HRT use in a larger epidemiological study (18); while several other groups have confirmed that oral HRT use is associated with increased APC resistance in randomised controlled trials (19-21). One study of 12 patients with a "negative" result was not powered to detect an effect of oral HRT on APC resistance (22).

Increased coagulation activation markers

Studies of the effects of HRT on coagulation activation markers (e.g. prothrombin fragment F1 + 2, thrombin-antithrombin (TAT) complexes, fibrin D-dimer) have shown variable results; this is not surprising in view of their skewed distributions, wide inter-and intra-individual variations, and the effect of venepuncture and *ex vivo* activation on F1 + 2 and TAT levels. However, overall oral HRT appears to increase circulating levels of these activation markers (7-9,12,14,15,17,23-25). To date, increased coagulation activation markers have been associated with increased APC resistance (21) – as in the general population (17) and during pregnancy (26) – and also with decreased TFPI levels in women with previous VTE (25).

Increased C-reactive protein and proinflammatory cytokines

Recent observational and prospective studies have shown that oral HRT is associated with increased plasma levels of C-reactive protein, possibly due to oestrogen-induced upregulation of pro-inflammatory cytokines such as interleukin-6 (IL-6) or tumour necrosis factor alpha (TNF-α) (18,28-32).

Table 1. Potential prothrombotic and antithrombotic effects of oral HRT.

Prothrombotic	
Increased coagulation factors, e.g. VII, IX	
Decreased coagulation inhibitors, e.g.	antithrombin Protein S Protein C Tissue factor pathway inhibitor
Increased activated protein C (APC) resistance	
Increased coagulation activation markers	
Increased C-reactive protein and interleukin-6	
Antithrombotic	
Decreased	blood pressure lipids glucose intolerance fibrinogen viscosity plasminogen activator inhibitor type 1
Increased endothelial function	

Antithrombotic effects

Several potential antithrombotic effects of HRT have been reported (Table 1), including decreases in blood pressure, lipids (including lipoprotein (a), glucose intolerance, and endothelial dysfunction (6, 7). Decreases in fibrinogen, viscosity and plasminogen activator type 1 (PAI-1) are most relevant to this review.

Several epidemiological studies have reported reduced fibrinogen levels in HRT users (7, 8); however such studies are susceptible to confounding (4) and more recent studies have not confirmed a fibrinogen-lowering effect (12, 14, 23-25). Lower fibrinogen levels, as well as lower lipoprotein levels, may contribute to the lower plasma viscosity levels in HRT users (18, 33, 34).

As with COC, oral HRT consistently lowers PAI-1 levels, as well as t-PA antigen levels (reflecting circulating PAI-1 – t-PA complexes) (7, 8, 12, 18, 22-24, 35-37).

The relevance of these antithrombotic effects is unknown, because there is no evidence from RCT's that HRT reduces the risk of either arterial or venous thrombosis (5, 6).

Which prothrombotic effects explain the prothrombotic risk of oral HRT?

There is now no doubt that oral HRT increases the risk of VTE, by a factor of 2-3 (5, 6). Oral HRT increases plasma levels of factor IX and APC resistance; and decreases levels of coagulation inhibitors such as antithrombin (17, 18). Each of these variables has been associated with increased risk of VTE in case-control studies; and was shown to further increase the risk of VTE in HRT users (38). The supra-additive effect of

HRT use and APC resistance was confirmed to be due to the factor V Leiden mutation in a subsequent report from the same study (38, 39) and in a separate study (40). Hence it seems reasonable to suggest that HRT use increases the risk of VTE by multiple prothrombotic effects, including its effect on APC resistance. In view of the possible effects of inflammation on VTE, the supra-additive association of plasma CRP levels with VTE and HRT use (42) is also of interest.

The prothrombotic and proinflammatory effects of oral HRT may also be relevant to the increased risk of stroke (and possibly of coronary heart disease) associated with its use in randomised controlled trials (6). The increased risk of stroke may partly reflect "paradoxical" thromboembolism from the venous circulation through right-to-left intracardiac shunts (e.g. patent foramen ovale, atrial septal defect). The relevance of the prothrombotic and proinflammatory effects of oral HRT to arterial thrombosis requires further study (32).

Transdermal versus oral HRT

Overall, the literature suggests that transdermal HRT does not induce the same prothrombotic and proinflammatory effects as oral HRT (7-8, 12, 18, 23). This probably reflects the lack of a "first-pass" effect of oral HRT on hepatic metabolism (18). A preliminary report from the ESTHER case-control study of HRT and VTE in France suggests that transdermal HRT is not associated with VTE, in contrast to oral HRT (43). Transdermal HRT may therefore be considered in women who are at increased risk of VTE (44). The relative risks of arterial thromboembolism for transdermal versus oral HRT require further study.

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