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Venous and arterial thrombosis: epidemiology and risk factors at various ages

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Abstract

The incidence of both venous and arterial thrombosis increases exponentially with age in both men and women. Possible reasons include: increasing immobility, trauma, surgery and acute medical illness; increasing prevalence (and/or cumulative effects) of obesity, raised blood pressure, dyslipidaemia and glucose intolerance; increasing prevalence of atherosclerosis; and increasing circulating markers of inflammation (C-reactive protein, CRP) and thrombosis. While arterial thrombosis is less common in women, the relative risk for classical risk factors associated with myocardial infarction is at least as strong in women as in men, in prospective population-based studies using MONICA criteria (e.g. Scottish Heart Health Study, Reykjavik Study). Some of these risk factors (e.g. smoking, cholesterol, triglycerides) show decreasing hazard ratios with age. Ongoing studies of newer potential risk factors for venous and arterial thrombosis (e.g. homocysteine, haemostatic and inflammatory variables) should elucidate their roles in risk prediction, including thrombotic risks of sex hormones which have effects on these variables.

Keywords: Thrombosis; Epidemiology; Risk factors

1. Introduction

Oestrogen and selected (o)estrogen receptor modulator (SERM) therapies have made major global contributions to womens' health and social welfare over the past 40 years. Combined oral contraceptive (COC) preparations are highly efficient contraceptives, containing the population explosion and allowing women life choices. Hormone replacement therapy (HRT) with oestrogens (or with the SERM, raloxifene) alleviates menopausal symptoms and is effective in prophylaxis of postmenopausal osteoporosis. Another SERM, tamoxifen, is effective in secondary prophylaxis of breast carcinoma, and probably also in primary prophylaxis. These benefits are partly offset by increased risks of venous thromboembolism (VTE), stroke, and myocardial infarction; and recent studies have shown plausible biological mechanisms through which even low doses of oestrogens (or SERMs) may promote thrombotic risk.

To facilitate a balanced assessment of the impact of these treatments on the risks of venous and arterial thrombosis, one cannot rely only on the case-control studies and randomised controlled trials (RCT's) which estimate the *relative* risks of oestrogen therapy.

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It is important to estimate the *absolute* risks of venous and arterial thrombotic events at different ages, upon which the relative risks should be predicated [1]. It is also important to estimate the impact of *other classical risk factors* in individual women, so that they can be advised, as far as possible, of their baseline individual risks when oestrogen (or SERM) therapies are discussed. Finally, it is important to consider the impact of *newer risk factors* (such as thrombotic or inflammatory markers), through which oestrogen (or SERM) therapies may in part exert their prothrombotic effects.

2. Effects of age

The most important risk predictor for both venous and arterial thrombosis is age: the increases with age in incidence and prevalence of both conditions are exponential in both women and men.

Possible reasons for the increased risk of VTE with age include increasing immobility, obesity, trauma, surgery and medical illnesses. These potential mediators are interlinked. In a recent study, it was shown that increasing habitual physical activity in UK men aged 60–80 years was associated with decreasing plasma levels of thrombotic and inflammatory markers [2]. Such evidence links two arms of "Virchow's Triad": stasis and changes in the components of the blood. The acute increases in both venous stasis and circulating levels of thrombotic and inflammatory markers which follow acute trauma, surgery or medical illness are likely to accentuate the chronic effects of immobility, obesity and chronic illness; resulting in an increased risk of VTE with age.

Possible reasons for the increased risk of *arterial* thrombosis (coronary, stroke or limb) with age include: the increasing prevalence of atherosclerosis; the increasing prevalence (and/or cumulative effects) of "classical" risk factors including obesity, raised blood pressure, dyslipidaemia and glucose intolerance; and increasing circulating markers of inflammation, such as C-reactive protein (CRP) [3], and thrombotic and rheological variables [4–6].

The age effect on VTE is important when considering the relative risk of oral oestrogen therapies. The *relative* risk of COC and HRT/raloxifene/tamoxifen for VTE is about threefold in current users [7]. However, Table 1 shows that this relative risk is translated into very different *absolute* risks for women at different ages. In a typical COC user (age under 30) COC use increases the absolute risk of VTE from 5 to 15 (second generation) or 30 (third generation) per 100,000; which many women might perceive as negligible in relation to the benefits of COC. Table 1 also shows that the risk of VTE in pregnancy (which may be an alternative to use of highly-effective COC) is about double that of third generation COC's, and quadruple that of second generation COC's. When a women reaches the median age for menopause (about 50 years), her baseline risk for VTE has risen to 1 per 10,000; hence for the similar *relative* risk of VTE for oral HRT use as for COC use (three-fold) the *absolute* number of excess annual cases will be higher at this age: 1 per 5000 (although this may be perceived as negligible by many women in relation to the symptomatic benefits of HRT).

When a women reaches her sixties, her baseline annual risk of venous thromboembolism approaches 1 per 1000 (Table 1), and continued oral HRT use (e.g. prophylaxis of postmenopausal osteoporosis) increases her annual risk of VTE to about 1 in 300 (e.g. in recent randomised controlled trials of oral HRT in prevention of arterial thrombosis) [8]. At this level, many women may look to the several alternative approaches to reduce their risks of osteoporosis and of arterial thrombosis (e.g. regular exercise, reducing smoking

Table 1
Venous thromboembolism and age

Age (years)	Annual risk	Oral oestrogen effect
<30	5/100,000	COC 15–30/100,000 (pregnancy 50–75/100,000)
50 (mean age of starting HRT to prevent perimenopausal symptoms)	1/10,000	Oral HRT 3/10,000
60–70 (average age of developing VTE in general population)	1/1,000	Oral HRT (e.g. HERS) 3/1,000
>80	1/100	Not applicable

habit and alternative medications after discussion with their primary healthcare team).

Hence, age is of fundamental importance when assessing the *absolute* risk of both arterial and venous thrombosis in individual women when considering oestrogen or SERM therapy. While the media tend to concentrate on potentially misleading statistics such as relative risks, it is important for healthcare professionals to concentrate on absolute risks. For example, in healthy young women without risk factors for cardiovascular disease, COC use has almost negligible thrombotic risk.

3. Effects of other risk factors: venous thromboembolism

About 50% of episodes of VTE are "idiopathic", occurring without a clear, clinically-identifiable cause such as congenital thrombophilias, obesity or intercurrent illnesses including trauma, surgery, acute medical illness, immobility (e.g. paralysis), cancer or chronic inflammatory diseases [9]. To minimise the risk of VTE, evaluation of all women prior to prescription of oral oestrogen or SERM therapy should include: past or family (first degree relative) history of VTE, obesity (body mass index) and chronic diseases. Since oral oestrogen (or SERM) appears to be the causal factor for VTE, women at increased risk for VTE should be advised to consider less thrombogenic alternatives, such as the progestogen-only pill for oral contraception or transdermal HRT [9].

Women scheduled for elective major surgery should be advised to discontinue oral oestrogen or SERM therapy several weeks beforehand [9]. It is essential that alternative, effective contraception be provided for COC users [9]. Screening for congenital thrombophilias prior to COC prescription is neither clinically-effective nor cost-effective [10]. Screening for congenital thrombophilias prior to oral HRT prescription may be more clinically- and cost-effective [11]: a formal study is currently in progress.

4. Effects of other risk factors: arterial thrombosis

Premenopausal women have lower risks of arterial thrombosis (coronary, cerebral or limb) compared to premenopausal men [12]: possible mechanisms include higher levels of high-density lipoprotein cholesterol [13], and lower levels of haematocrit and blood or plasma viscosity [14]. However, the "postmenopausal increase" in risk of coronary heart disease (CHD) in women may be a myth [15]; and a recent meta-analysis of randomised controlled trials of HRT to date suggests that HRT does not reduce either CHD risk or mortality, and increases the risk of stroke [8]. Hence observational studies of HRT, CHD, stroke and mortality may have been irretrievably biased, due to the multiple associations of HRT use with risk factors for CHD and stroke [8].

Since oral HRT may increase the risk of CHD and stroke, its use is now contraindicated in women with previous history of arterial thrombotic events [16]. In addition, women should be assessed for risk factors for arterial thrombosis (as well as for VTE) prior to prescription of oestrogen or SERM therapies.

There is less information on risk factors for arterial thrombosis in women compared to men. Prospective epidemiological studies have been severely biased towards men—perhaps because women have fewer "premature" events, which has been the traditional focus of prospective studies. To correct this bias, prospective studies should include women as well as men; should include sufficient numbers, and continue follow-up, to allow comparison of women with men; and should use internationally—agreed criteria, such as those of the WHO—MONICA Study [17]. To date, the Scottish Heart Health Study [18] and the Reykjavik Study [19] have provided information that classical CHD risk factors (e.g. smoking, blood pressure, cholesterol) are at least as strong predictors of CHD in women as in men. It would therefore be anticipated that the increased risk of CHD and stroke in women prescribed oral HRT (or SERMs) might be minimised by a formal calculation of such risk [20], followed by appropriate advice on reduction in these risk factors [20]. Such procedures would follow the experience with COC use, in which the increased risk of CHD and stroke is minimised by risk factor assessment and correction (see Chapter by Farley and Schmidt, this volume).

Some of these classical CHD risk factors (e.g. smoking, cholesterol, triglycerides) show decreasing hazard ratios with age, in women as well as in men

[19]. Nevertheless, they continue to confer important increases in absolute risk of CHD.

Moving on from classical CHD and stroke risk factors (smoking, blood pressure, cholesterol) to more recently established risk predictors, it is appropriate to examine the potential roles of risk factors which oral oestrogens (or SERMs) may increase, such as triglycerides, C-reactive protein, proinflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), and haemostatic variables such as fibrin D-dimer. Triglycerides have a higher impact on CHD risk in women than in men [19], which may be relevant to the increase in triglycerides induced by oral oestrogens. Oral HRT increases CRP levels, possibly due to oestrogen stimulation of IL-6 or TNF-α; however, the relative roles of these variables in prediction of CHD in women require further study [21]. The effects of oral oestrogens on thrombotic variables [22] may be as relevant to risks of CHD and stroke, as to risks of VTE: again, further study is required. The lesser effects of transdermal HRT on thrombotic and inflammatory variables [22] and on risk of VTE [23] may also be relevant to risks of CHD and stroke.

5. Conclusion

Recent publications which confirm and extend knowledge on the increased relative risks of venous and arterial thrombosis in women taking oral oestrogens have focussed interest on the baseline absolute risks of thrombotic disorders in women at different ages. Formal calculation of these absolute risks in individual women facilitates decisions on alternative therapies and empowers patient choices.

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