Hormone Therapy and Hemostasis

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The effect of hormones on the coagulation system has been a matter of controversy for many years. Until 1996, the conventional wisdom was that hormone therapy (HT) after menopause was not associated with a significant risk of thrombosis. To a large degree, this was presumed to be because the doses used in HT are many times lower than those used in oral contraceptives (OCs) (1), where it was known that there is a twofold to threefold increase in the risk of thrombosis. It appears clear now, that with standard-dose oral HT, there is a similar increased risk (approximately 2–3 fold), as reviewed in Chapter 36.

This increased risk was first consistently reported in a series of different epidemiologic studies in 1996 (2–4) and then reported in a randomized trial of HT and placebo in postmenopausal women with coronary disease (Heart and Estrogen/Progestin Replacement Study [HERS]) (5). It is probable that with aging and the lifelong increase in the extent of atherosclerosis and vascular damage, smaller hormonal influences (HT rather than OC use) can lead to a greater probability of thrombosis. Data from the Women's Health Initiative (WHI) provide the largest database on the risks of HT and estrogen therapy (ET) (6,7), at least for the doses and regimens studied, and these data will be reviewed here.

This chapter provides the basic information involved in coagulation and fibrinolysis, which was also discussed again in Chapters 34 and 36. It is clear that age, the type of ET and HT, and specifically the dose and the route of administration all influence the balance of factors reviewed later, and accordingly influence the level of risk. Inherited, albeit subtle thrombophilias, previously unrecognized, also substantially modify this risk. Finally, it must be accepted that there is not a good correlation between various changes in circulatory markers of the coagulation and fibrinolytic systems and the absolute risk of thrombosis.

I. HEMOSTASIS REVISITED

A review of hemostasis (8), while endorsing previous in vitro studies, notes variations in the sequential reactions that lead to blood clot formation in vivo. The process is very complex and has numerous coagulatory and fibrinolytic checks and balances. Fig. 35.1 depicts a simplified summary and will serve as a guide to some potential points of clinical relevance when prescribing HT.

Although the basic process is the same, arterial thrombosis differs from venous thrombosis: the former results in platelet-rich ("white") thrombi, whereas the low-blood-flow venous thrombosis is fibrin and red cell-rich ("red") and, as a consequence, is more liable to embolism (9). More importantly, thrombus formation is a key event in the origin and progression of atherosclerosis and, as will be discussed, may help to define the clinician's approach to cardiovascular health care in women.

II. VESSEL WALL

The endothelium, which is a semipermeable barrier between the blood and the deeper layers of the vessel wall, serves two main functions in hemostasis: it helps to regulate vascular tone, and it acts as an anticoagulant. The endothelium synthesizes vasodilators such as prostacyclin (PGI_2) and endothelium-derived relaxing factor (nitric oxide [NO]), as well as vasoconstrictors such as endothelin and platelet-activating factor (PAF) (see Fig. 35.1) (10). Prostacyclin and NO act synergistically to prevent platelet activation. Both factors are difficult to assay because they are either only locally active (NO) or are rapidly metabolized (PGI_2). Nevertheless, two studies have shown that nonoral estrogen in-

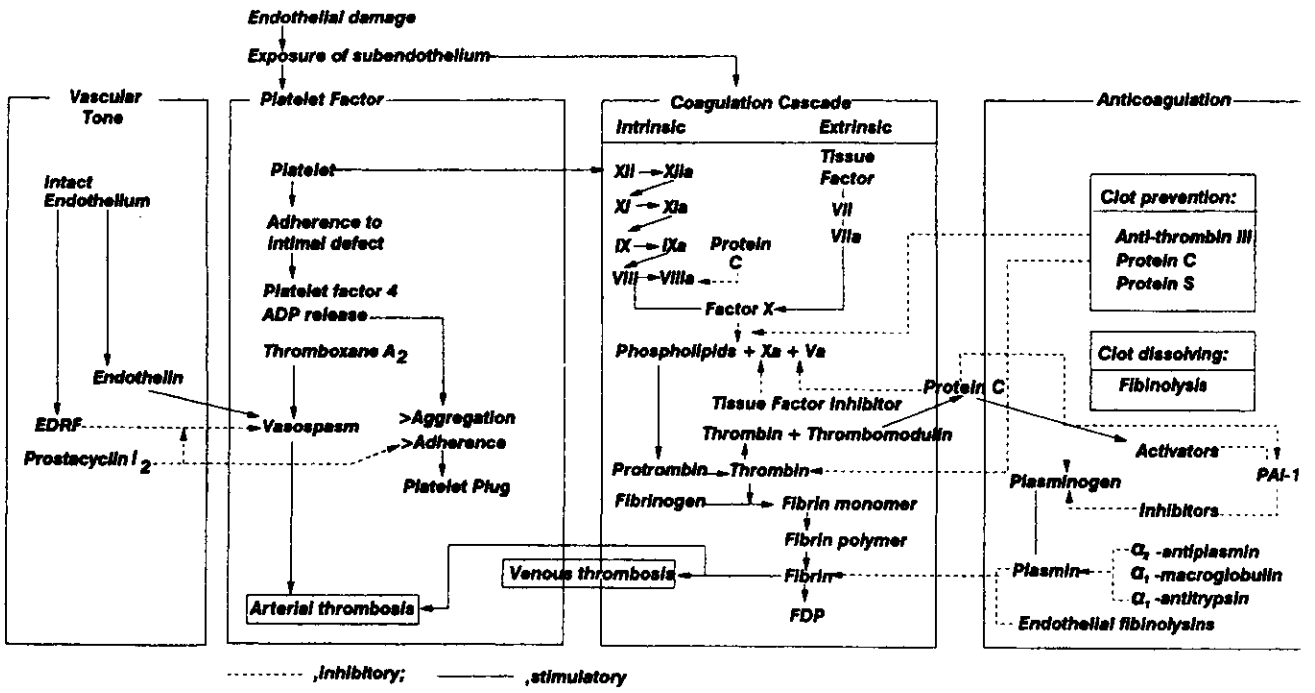


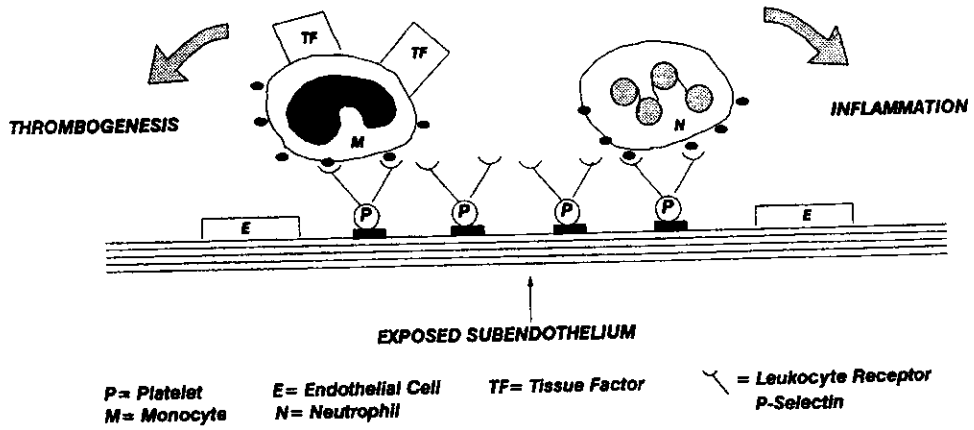
FIGURE 35.1 The integrated relationship between four systems (vascular tone, platelet activity, coagulation, and fibrinolysis) is depicted in separate pa els showing their interrelationships, both stimulatory (solid lines) and inhibitory (dashed lines). ADP, adenosine diphosphate; EDRF, endothelium deriv relaxing factor; FDP, fibrinogen-degradation products; PAI-1, plasminogen activator inhibitor-1.

creases plasma levels of both nitric oxide and prostacyclin (11,12). The serum estradiol level ranged between 80 and 120 pg/mL. A further study involving oral estradiol and norethindrone reported a 21% increased production in prostacyclin but no change in the potent vasoconstrictor, endothelial release (13). The endothelium also inactivates other known vasoactive substances such as serotonin and bradykinin (14). Blood flow—a major determinant of intimal damage—depends on the balance among these various vasoactive substances, many of which are influenced by HT.

The healthy endothelium prevents thrombosis in at least three ways. It synthesizes thrombomodulin, a protein that is an endothelial receptor for thrombin. The resulting complex activates protein C (see later), the primary inhibitor of factor Va and VIIIa (15); the intact endothelium is a surface anticoagulant. The cells consist of glycoproteins and proteoglycans such as heparin sulfate, the main cofactor to antithrombin III (the most potent endogenous anticoagulant). The glycoproteins emit a negative charge that propels platelets and prevents initiation of the intrinsic arm of the coagulation cascade (16); tissue plasminogen activator (t-PA) is continuously synthesized and secreted by endothelial cells and as such regulates the fibrinolytic activity of blood (17). This function may be a major contributor to the prevention of coronary artery disease (CAD). The activity of t-PA is enhanced by progestins (see later discussion).

III. PLATELET FACTOR

Platelets circulate in blood in an inactive resting fori When they are exposed to the subendothelial layers, platele develop pseudopodia, attach to the injured surface, and b come highly adherent (Fig. 35.2) (8). The binding is dete mined by various surface receptors that complex with specii ligands such as von Willebrand factor. The bound platele degranulate and expose receptors for factor VIII, factor and P-selectin (18). Neutrophils and monocytes bind to tl P-selectin receptor and participate in the inflammatory r sponse; in addition, the monocytes secrete tissue factor, tl initiator of the extrinsic coagulation cascade (see Fig. 35.1 Platelet aggregation is enhanced by modifying and sensiti ing their surface receptors to adhesive proteins, such as f brinogen. The platelet membrane also releases arachidon acid. Arachidonic acid is metabolized to thromboxane A which in turn promotes further platelet aggregation and loc vasoconstriction. The net result is a platelet plug with fibr formation, the first necessary step to permanent hemostas and wound healing (9). Aspirin inhibits cyclo-oxygenase a tivity in both platelets (thereby reducing thromboxane acti ity), as well as endothelial prostacyclin synthesis. Howeve the process is more prolonged in platelets (±2 days) and short lived in the endothelium (±6 hours). It is for this re son that low-dose intermittent aspirin use optimizes its ant



...ription of the initiation of blood coagulation and formation of the platelet plug within a blood vessel, involving both thrombogenesis

...ential (19). Two studies have confirmed that ...both combination oral treatment (conjugated ... [CEE] with medroxyprogesterone acetate ...17β-estradiol and norethindrone acetate and ...strogen (17β-estradiol plus MPA) decreased ...gation (20) and the cellular reactivity of plate...cytes (21). A positive effect of ET on platelet ...be reported decrease in thromboxane metabo...ite to both acutely administered intravenous ...long-term estrogen replacement therapy (ET) ...pellets (12).

...everal reports, as noted previously, have shown ...platelet aggregation with ET/HT, there has ...gation that the reverse is true with more plate...aggregation. This may relate in part to the ...studied, with women with cardiovascular ill... altered platelet activities. Indeed even here the ...e effect appears to be no overall change in ...aggregation (21a).

AGULATION-AGULATION

...ation system has built-in checks and balances ...in healthy individuals) inappropriate throm...serve the ability to help breach disruptions in ...culature. This is achieved by three mecha... procoagulant factors circulate in an inactive ...and hence coagulation, only occurs at the ... The process is thus localized to a relatively ...minimal damage; second, the activated coagu...ered and their activity modulated by naturally ...coagulants. Third, both coagulants and anti... present in concentrations far in excess of the ...need. As a consequence, when statistically sig-

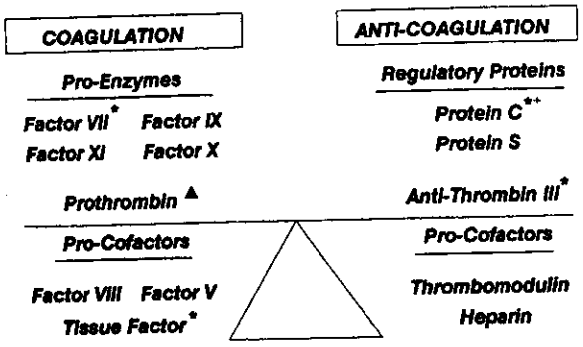


FIGURE 35.3 Balance between factors involved in coagulation and anti-coagulation. *, systemic tests of possible clinical value; ▲ best prognostic indicator (fragment 1.2); prothrombin 2021A; +, factor V Leiden.

nificant alterations in plasma levels of activated zymogens occur, for example, in response to HT, they usually have little or no clinical impact (22,23).

Factors involved in blood coagulation are summarized in Fig. 35.1. Based on in vitro studies (8), activation of factor X to Xa links the intrinsic and extrinsic pathways of the coagulation cascade and leads to the conversion of prothrombin (a vitamin K-dependent hepatic protein) to thrombin, which is the catalyst for the fibrinogen-fibrin reaction (see Fig. 35.1). The partial thromboplastin time (PTT) is a dynamic test that assesses the interrelated response of the intrinsic system; the prothrombin time (PT) is a measure of the activity of the extrinsic arm of the coagulation cascade. It has been noted that patients with hereditary factor XII deficiency, for example, have increased PTT but no bleeding diathesis, indicating that this factor is not important for the formation of a blood clot. Thus, the PTT is a test of dubious value (8). Tissue factor (a normal constituent of the surface of nonvascular cells) and stimulated monocytes activate coagulation. The physiologic

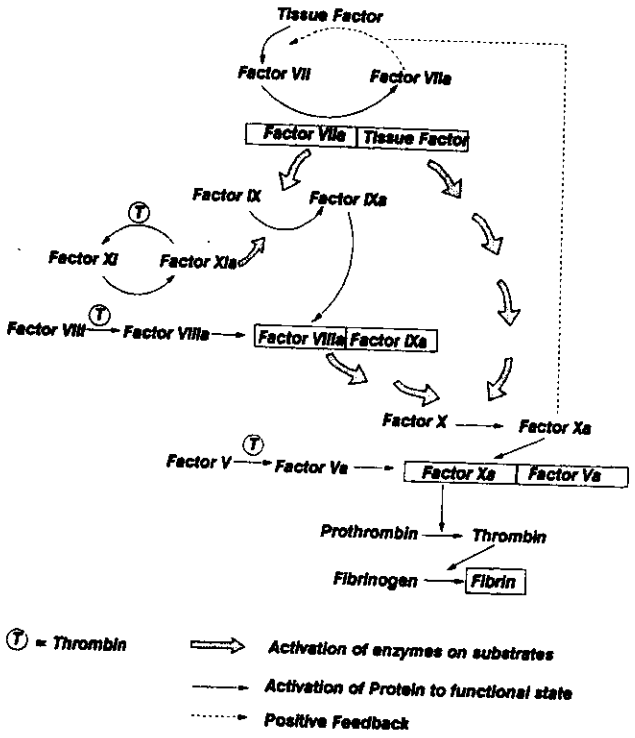


FIGURE 35.4 Pathway of coagulation involving factors from tissue and the cascade toward fibrin formation.

pathway of blood coagulation appears to bypass the first steps of the intrinsic pathway and is summarized in Fig. 35.4. Coagulation hinges on the formation of a tissue factor-activated VII-a complex that in turn converts factor IX to IXa and factor X to Xa (24). Activated factors VIIIa and IXa further catalyze the X-to-Xa conversion. Activated factor Xa, together with activated factor Va, mediates the conversion of prothrombin to thrombin in the presence of phospholipids and calcium (8). Thrombin, when free in solution, promotes clotting by converting fibrinogen to fibrin, by activating platelets, and, by positive feedback, stimulating the activation of factors XI, VIII, and V (see Fig. 35.4). By contrast, thrombin has a local anticoagulant effect (10,25). When thrombin forms a complex with thrombomodulin on the endothelial surface, it inhibits blood clotting by activating protein C (15). The latter is a zymogen formed in the liver and is vitamin K dependent. Protein S, another vitamin K-dependent protein, is a cofactor for protein C (26). Protein C also initiates fibrinolysis by activating plasminogen and neutralizing plasminogen activator inhibitor (9) (PAI-1) (see Fig. 35.1). Resistance to activated protein C has been discovered as a hereditary trait in individuals who develop venous thromboembolism without apparent cause. This is referred to as *factor V Leiden* and is said to occur in approximately 20% of patients with venous thromboembolism. In one study, the risk of recurrent venous thromboembolism in carriers of this mutation was increased with a hazard ratio of 2.4 compared with patients without this condition (27).

Antithrombins are inhibitors of thrombin and other coagulation proteases (28). Antithrombin III, which is the most important, probably accounts for at least 50% of the natural fluidity of blood. The action of antithrombin III is catalyzed by heparin and, in its complex form, neutralizes thrombin instantly (29). Antithrombin III also inhibits other enzymes in the coagulation cascade, such as activated factors Xa, XII, XI, and X (15). However, its main efficacy as a natural anticoagulant is thought by some to be the prevention of factor Xa generation and the activation of prothrombin. A deficiency of antithrombin III is associated with an increased liability of thrombosis (30). The level at which antithrombin III deficiency would cause thrombosis is not known, but it would probably have to be reduced to approximately 50% of its normal activity. This estimate is based on the plasma levels of antithrombin III in families who have congenital antithrombin III deficiency. Not all individuals with antithrombin III deficiency experience thrombosis. As with protein C deficiency, thrombosis usually occurs in conjunction with other events such as trauma and surgery. Reliable assays are now available for the measurements of antithrombin III and protein C levels.

V. FIBRIN FORMATION AND FIBRINOLYSIS

The introduction of t-PA therapy into clinical practice emphasizes the importance of fibrinolysis in maintaining intimal health and vascular patency. Fibrinogen is a dimer with three polypeptide chains: α, β, and γ. Thrombin acts on the α and β chains and produces two molecules of fibrinopeptide A and two molecules of fibrinopeptide B. This leaves a large residue molecule known as *fibrin monomer*, which spontaneously polymerizes into non-stable fibrin polymer. These are cross-linked in the presence of calcium and activated factor XIII to form the stable insoluble clot, fibrin (9). This process is vital to survival and is nature's way of preserving the integrity of the vascular tree subsequent to injury so that healing and normal function of the area concerned can be restored and maintained.

Fibrin formation is regulated by the process of fibrinolysis, which involves the enzymatic degradation of fibrin and fibrinogen by plasmin (9). Plasmin is formed from plasminogen, a β-globulin synthesized by the liver (25). The biologic activity of plasmin, and hence fibrinolysis, is determined by activators and inactivators of plasminogen and plasmin inhibitors (see Fig. 35.1). Fibrinolysis is initiated by either factor XIIa or urokinase plasminogen activator (intrinsic pathway) or tissue-type plasminogen activator (t-PA), the extrinsic pathway (31). Tissue plasminogen activator, which is produced by the endothelial cells and released into the circula-

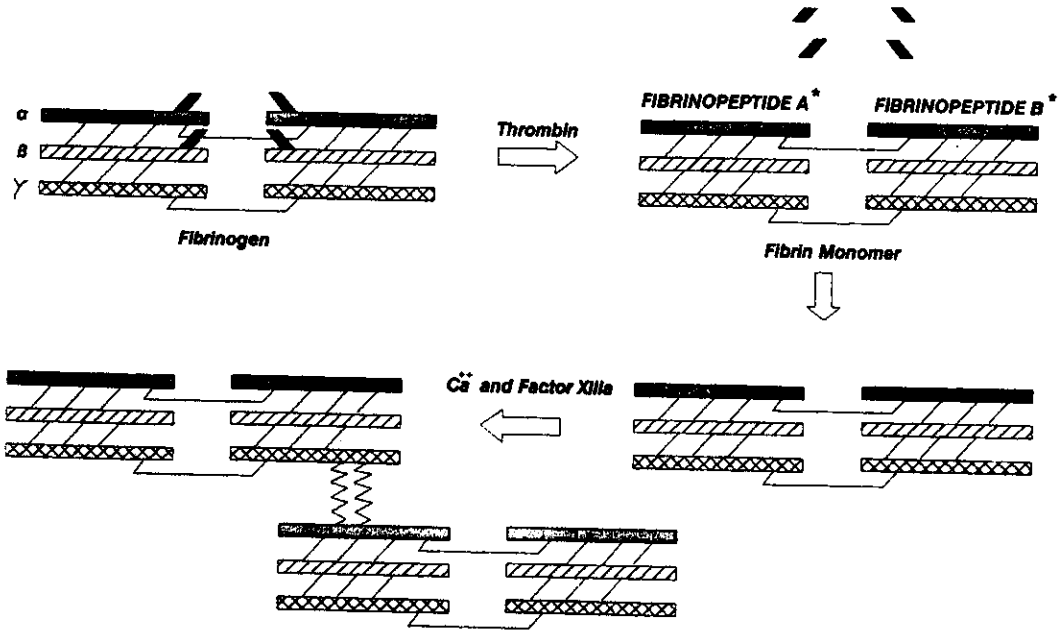


FIGURE 35.5 Diagrammatic depiction of how fibrin polymer forms. Asterisks depict potential markers for thrombosis.

e presence of fibrin binds together with plasmino-
erate plasmin, and thus fibrinolysis (17). Fibrin acts
ubstrate and a cofactor to plasminogen activity.
plasminogen activator is inhibited by plasminogen
hibitor type 1 (PAI-1) (32). PAI-1 is produced by
s and endothelial cells. The balance between t-PA
is said to be the major determinant of the sponta-
nolytic activity of blood (32). Both fibrinogen and
significantly reduced by combination transdermal
lus MPA, and the mean plasma estradiol level was
e 138 pg/mL (33). In another study, conjugated
done and in combination with MPA) significantly
lasma PAI-1 antigen levels (34). In this study,
l estrogen had very little effect on PAI-1.
d, plasminogen has to bind to fibrin in order to
l to plasmin. The binding takes place at the so-
ne-binding" sites on the plasminogen molecule.
ch glycoprotein has an affinity for these sites and
re, control the amount of biologically available
nogen (35). Estrogen decreases plasma histidine-
rotein and may, therefore, enhance fibrinolysis
nous progestins and estrogen (37) are associated
ed plasminogen activity (5). Three main plasmin
exist: α_2-plasmin inhibitor; α_2-macroglobulin,
s quickly and as a competitive plasmin inhibitor;
rypsin, which reacts more slowly but more firmly.
wo proteases also inhibit thrombin and as such
cting functions: they prevent clot formation by
g thrombin, and they encourage fibrin and fi-
egrity by inhibiting plasmin. Their overall effect on thrombogenesis is not known. Antiplasmin inhibitor (α_2-plasmin inhibitor) is said to inhibit 35% of the plasmin generated from plasminogen (38). It acts in two ways: direct inactivation of plasmin and blockage of plasminogen binding to fibrin. Pharmacologic lowering of a_2-plasmin inhibitor levels can be viewed as a positive side effect because the net effect will result in increased fibrinolysis.

Cleavage of fibrin and fibrinogen produces a variety of fragments known as *fibrin* or *fibrinogen degradation products* (FDPs). FDPs have potent anticoagulant properties and may interfere with platelet activity as well.

VI. CLINICAL MARKERS OF THROMBOSIS

Given the complexity of hemostasis, it is not surprising that relatively few tests can predict individuals at risk for thrombosis (23,39). Only 15% to 20% of patients with hypercoagulability have an identifiable biochemical abnormality of their plasma proteins (8). Thrombosis is a localized event. Tests based on systemic venous blood samples are insensitive markers of changes occurring on the damaged vascular intima—especially when the latter involves arteries—and tests are performed on venous blood. Also, apart from the physiologic checks and balances of hemostasis, some factors can serve as a systemic procoagulant and a local vessel wall anticoagulant. For example, thrombin promotes coagulation by catalyzing activation of some zymogens (factors XI, VIII, and V) in the coagulation cascade (8), but it

stimulates the intact vascular endothelium to synthesize prostacyclin and NO and also promotes functions of t-PA, which together tend to inhibit platelet aggregation and vascular spasm while enhancing fibrinolysis (10,15,25).

Various studies have identified plasma fibrinogen, factor VIIc (which can be indirectly measured by the prothrombin time), and PAI-1, as markers of arterial thrombosis (39,40). More recently, elevated levels of fragment 1.2, which is derived from the conversion of PT to thrombin, has been correlated with a thrombotic tendency (41). This test is clinically available and may identify patients at risk for thrombosis. As noted, the PTT is probably of little clinical value, whereas the role of the PT as a measure of anticoagulation is being reevaluated. Native prothrombin antigen has been identified as the sole type of prothrombin in normal blood and can readily be distinguished from abnormal prothrombin, which may be synthesized, for example, in response to treatment with anticoagulants such as warfarin (8). Studies have shown that the adequacy of anticoagulation is better monitored if native prothrombin antigen levels are assayed instead of the PT (42). The effect of exogenous sex steroids on native prothrombin antigen is unknown.

Fibrinopeptides A and B, as well as various FDPs, do change in response to HT and may be an indirect sign of accelerated coagulation. In this context, the assay of the FDP, D-dimer, may be important. D-dimer, which is an FDP peptide with epitopes that cross-link with those found on activated fibrin, has been used as a marker of ongoing intervascular coagulation; for example, in patients with suspected pulmonary embolism (43). Although measurement of sensitive D-dimer has a clear place in the diagnosis of thromboembolic states, the sensitivity is not as high as once envisioned (only in the 80% range) (43a).

Reliable assays are available for antithrombin III and proteins C and S. Deficiencies of protein C, protein S, or antithrombin III are associated with thromboembolic disease and are used for screening tests in women with histories of previous thrombotic disease. These protein assays also have to be distinguished from the measurements of activity. Antithrombin III activity must be measured in plasma. Serum antithrombin III only quantifies the amount of antithrombin III left after clotting, not that consumed during clotting; therefore, it has no clinical relevance to the risk of inappropriate thrombus formation (22). Although activated protein C resistance is said to be present in at least 20% (or more) of patients with venous thrombosis and has been associated with an increased risk of thrombosis in women taking OCs (see later), routine testing for this factor prior to treating women with hormone replacement therapy (HRT) is both impractical and costly. Thus, if the prevalence of factor V Leiden is 2% and the positive predictive value of the assay is 44%, the cost of preventing one thromboembolic death is more than $44 million (44).

Currently the testing for genetic aspects of thrombophilia (i.e., evaluating polymorphisms and various mutations) has become extremely commonplace, particularly in wor who have recurrent miscarriages. Whether these tests truly meaningful for the risk of thrombosis in a postme pausal women in questionable, particularly without a fan history or a history of prior thrombosis.

In addition to mutations in Factor V resulting in activa protein C resistance (APC), mutation searches may also clude those involving the prothrombin gene (G20210A) a in methylene-tetrahydrofolate reductase (MTHFR) Cb7 Current clinical assays are able to detect both homozyg and heterozygous states. However, these assays are of du ous value, particularly without a strong family or perso history of thrombosis, and are not recommended for scre ing women before considering ET or HT.

VII. COAGULATION AND CLINICAL SYNDROMES

The association between accelerated coagulation, venc thrombosis (both superficial and deep), and the potential pulmonary embolism is well recognized and will not discussed further. Less well-recognized is the key role thrombosis and fibrin formation in the origin and progr sion of atherosclerosis, as well as the pathogenesis of acu CAD and associated syndromes. This has been reviewed the past (6). In brief, subsequent to injury of the corona artery endothelium, macrophages and lipids accumulate the site of epithelial denudation. The macrophages initia changes that involve the intima and lead to platelet adhesi and the release of various growth factors. This results smooth muscle cell proliferation, hypertrophy and migr tion, and the formation of foam cells, characteristic of t mature atherosclerotic plaque. These lesions appear in mc children by the age of puberty (45); however, many regre and it is only in the third decade of life that the lipid-ri plaques are covered by a fibrotic cap with focal areas of m crothrombi formation (46). Fibrin and fibrin-related pro ucts have been found in the intimal section of these lesio and are typical of a mature atherosclerotic plaque (47).

Angiographic studies have shown that the intimal lesio responsible for subsequent myocardial infarction often ha mild (50%) to moderate (70%) stenosis (48). Thus, recurre mural thrombi-associated with fissuring and disruption established plaque-rather than sudden occlusive events m be responsible for much of the unstable angina and eventu myocardial infarctions seen in clinical practice (49). Th clinical impact of mural thrombosis is self-evident. The e ficacy of thrombolytic therapy when treating patients wi acute myocardial infarction is well established. The inhib tion or prevention of atherosclerosis by prophylactic ant thrombin or fibrinolytic therapy is less clear. Two unrelate (and speculative) observations suggest a potential role f preventive subclinical anticoagulation: pigs with homoz gous von Willebrand disease are resistant to thrombosis an

spontaneous atherosclerosis (50). Lower-dose aspirin prophylaxis is very effective in preventing coronary thrombosis (51). By inhibiting platelet adhesion at sites of vascular damage, aspirin may prevent microthrombosis and the subsequent evolution of atherosclerosis.

The role of sex steroids in the pathogenesis of the intimal thrombosis and atherogenesis has not been established, but a potential relationship is seen. Apolipoprotein (a), a glycoprotein that is part of the Lp(a) molecule, is structurally similar to plasminogen (52). In vitro studies have demonstrated competition between apolipoprotein (a) and plasminogen for the latter's endothelial binding sites (53). By interfering with plasmin generation and clot lysis, endothelial thrombosis results. Lp(a) is also a potent and independent atherogenic moiety. It is absorbed into the arterial intima, where it accumulates in macrophages and is eventually degraded into foam cells, the precursor of arterial plaque (54). Lp(a) also binds to and immobilizes intimal fibrin and promotes plaque formation by the previously discussed thrombin hypothesis. The effect of exogenous estrogen on plasma levels of Lp(a) is variable (55), but some studies have reported a 50% reduction in plasma levels (56). Inconsistency among various studies may be caused by the initial plasma Lp(a) value. Estrogen decreases elevated Lp(a) but has little apparent effect on normal plasma Lp(a) levels. Progestins and, to a lesser extent, exogenous estrogen increase plasma plasminogen antigen and plasminogen activity (5,31). The net potential may be intimal protection via estrogen, because of inhibition of Lp(a) absorption and foam-cell formation, and reduced levels of plasma apolipoprotein (a). This could then free endothelial plasminogen receptors to respond to progestin-stimulated endothelial fibrinolysis if progestins are administered. A recently published study adds some credence to this hypothesis. After 1 year of combination HRT-either estradiol valerate plus MPA or transdermal estrogen plus MPA-significant reductions were noted in plasma levels (compared with baseline) of PAI-1 activity, Lp(a), with corresponding increases in t-PA antigen and the percent of plasminogen (57).

As reviewed here and elsewhere, hormonal therapy causes an increase in fibrinolytic activity, for example an increase in plasminogen, while at the same time changes also occur in markers of procoagulation.

VIII. HRT AND ARTERIAL THROMBOSIS: CLINICAL CONSIDERATIONS

An extensive literature exists on HT and its effect on hemostasis (58–62). Briefly stated, oral estrogens will induce an increase in the hepatic zymogens factors VII, X, IX, and II. However, most of the assays measure the inactive proenzyme, and the percent increase, although statistically significant in some studies, is invariably well within the physiologic range. It is highly unlikely that these changes have any biologic impact in vivo. Transdermal estrogen has a negligible influence on the hepatic zymogens (63) and is the preferable route of administering estrogen when procoagulant activity is increased; for example, immediately postsurgery. Of importance, recent data by Scarabin et al. (64) confirmed a thrombosis risk with oral estrogen but not with transdermal preparations. Consistent with the more recent data (2–4,64) standard HT is associated with a twofold to threefold increase in thrombosis risk. This has been extensively reviewed in Chapter 36. Of note, there is suggestive evidence that lower doses of ET or HT carries a lower risk (65), although there are no prospective randomized trials on this issue.

The existing data from the largest randomized trials shown an increased relative risk at the lower range of that in observational trials (i.e., closer to 2). This overall relative risk of venous thromboembolism (VTE) in WHI included women who were older (up to age 75 at study entry), who were obese, and who had other co-morbidities (one-third were hypertensive). Also at the beginning of the WHI HT trial, women with prior thrombosis were allowed to be enrolled. Even if that had not been the case, it is known that VTE risk with HT is observed earlier after initiation of HT and then decreases somewhat thereafter (Fig. 35.6).

The overall rate in the estrogen-alone (E-alone) trial of WHI was lower, with all the end points such as pulmonary embolism not being statistically increased (Fig. 35.7). This is noteworthy in that this cohort of hysterectomized women was more obese. However, the fact that 50% of this group had used ET or HT in the past may suggest that the exposed group were less susceptible to thrombosis, having been exposed earlier to this risk without having a thrombotic episode. Finally, it is also possible that there is a real difference in the risk of thrombosis with HT versus ET, with progestogens imparting an additional risk.

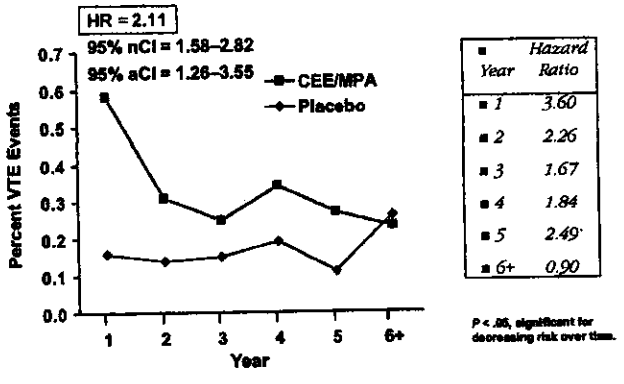


FIGURE 35.6 Annualized percentage of VTE events by year for women receiving CEE/MPA or placebo showing more events in the first year. (From ref. 6.)

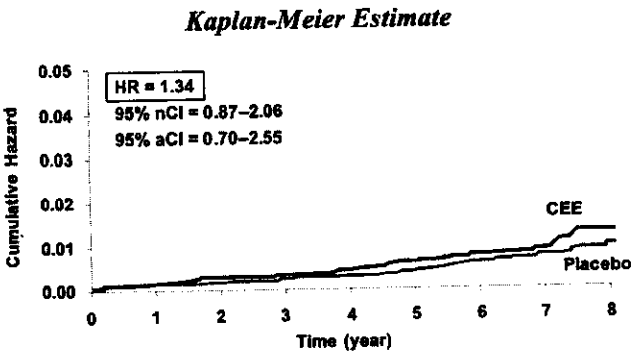


FIGURE 35.7 Cumulative hazard for pulmonary embolism by time, for women receiving CEE alone versus placebo. (From ref. 7.)

IX. CONCLUSION

Although the exact mechanisms of VTE risk with ET/HT are not known, in the absence of a known thrombophilia, it is clear that the VTE risk is twofold increased with standard-dose oral ET/HT. Additional factors are necessary to explain this risk in that measurement of circulatory procoagulant and fibrinolytic factors, although potentially altered by ET/HT, do not correlate well with this risk. Indeed, many of the procoagulant changes observed are statistical changes within the normal range of most laboratories. Lower oral doses and transdermal estrogen probably reduce this risk. Finally, the increase in VTE does not appear to alter mortality, and the overall prevalence is still quite low. For example, the risk of pulmonary embolism (PE), if increased twofold with HT, results in a risk of approximately 30–40 per 100,000 women per year. This rate is still lower than the rate of PE in pregnancy, which is approximately 60 per 100,000 women per year.

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