The rare homozygous protein C deficiency manifests in the neonate as *purpura fulminans* with widespread VTE and skin necrosis. A similar clinical presentation has been reported in heterozygous protein C–deficient adults after institution of warfarin therapy without simultaneous heparinization; this is called *warfarin-induced skin necrosis.* About one third of these patients are deficient in protein C on a hereditary basis, whereas the rest appear to have acquired protein C deficiency, possibly associated with vitamin K deficiency. Warfarin is a vitamin K antagonist that inhibits production of vitamin K–dependent protein C synthesis; and because of its short half-life, protein C levels rapidly fall before a decline in the levels of the procoagulant factors II, IX, and X. This imbalance shortly after starting warfarin favors a procoagulant state and may result in widespread microvascular thrombosis. Therefore, patients with active VTE should be fully anticoagulated with UFH or low-molecular-weight heparin (LMWH) before concurrent warfarin therapy is begun. UFH/LMWH should be continued until warfarin is therapeutic for at least 48 hours.

Inherited deficiency of protein S has similarly been implicated in warfarin-induced skin necrosis. Protein S deficiency is commonly acquired in acute illness. Protein S circulates in a free form and is bound by complement 4b (C4b)-binding protein; only free protein S is active as a cofactor for protein C. Because C4b-binding protein is an acute phase reactant, its increase with severe illness can decrease the level of free protein S. A similar effect is seen in normal pregnancy.

Short-term therapy for homozygous protein C deficiency or for doubly heterozygous protein C or S deficiency, especially in the setting of neonatal purpura fulminans, has included plasma or protein C concentrate with full-dose UFH anticoagulation. Functional and antigenic levels of AT, protein S, and protein C can be assessed to define whether functional deficiency is caused by a dysfunctional protein or by diminished synthesis. As with AT deficiency, initial heparin therapy followed by long-term treatment with warfarin has been successful in heterozygous protein C or S deficiency. As expected, both protein C and protein S levels are decreased during warfarin therapy; therefore, for adequate evaluation of protein C and S, the patient must not be taking warfarin when tested.

Venous Thrombosis: Acquired Risk Factors

Surgery and Medical Hospitalization

Medical and surgical illnesses convey increased thrombotic risk; these *acquired* risk factors are well accepted, even though the pathophysiologic features favoring thrombosis may be uncertain (Table 52-3). Stasis of blood flow is a clear risk factor for thrombus formation (e.g., VTE in immobilized inpatients). Other high-risk situations, including surgery (especially orthopedic) and trauma, are similarly associated with immobilization and stasis of lower extremity blood flow. When evidence of thrombosis is thoroughly sought, both surgery and trauma can be shown to be associated with extremely high (>50%) incidences of VTE. Fat embolism and tissue damage may also contribute to the risk for VTE with surgery and trauma, particularly in closed head injuries that result in massive tissue factor release. Prophylactic permanent or temporary inferior vena cava (IVC) filters are often placed in trauma patients to protect against PE, especially in high-risk patients for whom anticoagulation is contraindicated because of the increased risk for bleeding.

TABLE 52-3 ACQUIRED RISK FACTORS FOR THROMBOSIS

MEDICAL AND SURGICAL ILLNESSES	
Antiphospholipid antibody, lupus anticoagulant	Immobilization
Artificial heart valves	Malignancy
Atrial fibrillation (nonvalvular)	Myeloproliferative disorders with thrombocytosis
Congestive heart failure	Nephrotic syndrome
Hemolytic anemias (autoimmune hemolysis, sickle cell, thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria)	Orthopedic procedures
Hyperlipidemia	Pregnancy
	Trauma, fat embolism
MEDICATIONS	
	Heparin-induced thrombocytopenia
	Oral contraceptives, hormone replacement therapy
	Prothrombin complex concentrates

All hospitalized medical patients should be considered for venous thromboprophylaxis with LMWH. Bleeding risk attributes that argue against anticoagulation include thrombocytopenia, coagulopathy (with or without liver disease), and recent hemorrhage. Risk factors that most argue for prophylaxis include malignancy, prior VTE, immobilization, and thrombophilic conditions.

Pregnancy and Fetal Loss

Pregnancy is a hypercoagulable state associated with venous stasis; the risk for VTE during pregnancy and in the postpartum period for women with identified thrombophilia is about fivefold higher than it is for nonpregnant women. Pregnancy increases procoagulant proteins, including fibrinogen, vWF, and factors VII, VIII, and X, and decreases anticoagulants such as protein S and AT as well as fibrinolytic inhibitors such as PAI-1 and thrombin activator fibrinolysis inhibitor (TAFI). VTE can occur at any time during pregnancy or the puerperium. The risk of postpartum VTE is significantly higher in women with any of the following conditions: stillbirth, pre-term delivery, obstetric hemorrhage, caesarean procedure, medical comorbidities, or a prepregnancy body mass index greater than 30 kg/m^2.

Inherited maternal thrombophilia can compound the procoagulant state of pregnancy and predispose to both fetal loss and VTE in the mother. The principal inherited associated risk factors for fetal loss are FVL, the G20210A prothrombin mutation, AT deficiency, and protein C or protein S deficiency. The relative risk for fetal loss is markedly higher in those mothers with a history of prior VTE, although this particular risk appears to be restricted to the period after 9 weeks of gestation. In fact, inherited thrombophilia may be protective against fetal loss during the first 9 weeks, possibly by limiting oxygen toxicity to the early embryo. Therefore, recommended indications for evaluating the inherited thrombophilia risk in women seeking to become pregnant are a history of VTE or recurrent fetal loss after 9 weeks of gestation when no other specific cause (e.g., antiphospholipid syndrome) can be identified. Both AT deficiency and hyperhomocysteinemia have also been associated with placental abruption.

In the absence of an identified inherited thrombophilia or a diagnosis of antiphospholipid syndrome (discussed later), no