role has been identified for prophylactic anticoagulant therapy with recurrent pregnancy loss.

### Oral Contraceptives and Hormone Replacement

Oral contraceptive use conveys an increased risk for VTE, and a similar increased risk is seen early after institution of hormone replacement therapy in postmenopausal women. Concomitant heterozygosity for FVL synergistically increases the risk for VTE in women who take oral contraceptives or hormone replacement therapy. Cigarette use in women using oral contraceptives also increases the risk of thrombosis, possibly through increased platelet reactivity mediated by increased thromboxane synthesis. On the arterial side, epidemiologic evidence clearly points to smoking as the main cardiovascular risk factor. Paradoxically, most data suggest a protective role for hormone replacement therapy in cardiovascular disease. As discussed previously, acquired APC resistance and decreases in the levels of both free and functional protein S occur with oral contraceptive use.

### Other Prothrombotic Disease States

As described earlier, thrombosis in nephrotic syndrome is associated with loss of AT through the kidneys. Hemolysis is a general prothrombotic state that appears to be mediated through blood cell destruction, perhaps through increased exposure to procoagulant membrane phospholipids; hemolysis with thromboembolic complications has been observed in patients who have artificial heart valves, sickle cell disease, and other hemolytic anemias, including Coombs-positive autoimmune hemolytic anemia. In the case of paroxysmal nocturnal hemoglobinuria (PNH), complement activation may directly mediate platelet activation, and therapy with the complement inhibitor eculizumab has significantly decreased the rate of thromboembolic disease in PNH.

Platelet activation and clearance appear to be the primary prothrombotic manifestations of heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura (TTP). Although chronic disseminated intravascular coagulation (DIC) is classically associated with certain malignancies such as mucinous adenocarcinoma and promyelocytic leukemia, in that setting, known as Trousseau syndrome, there is an increased risk in malignancy for VTE that is not related to DIC. Indeed, VTE occurs in a wide spectrum of malignancies, including lung, breast, gastrointestinal, and any metastatic solid tumor. However, when idiopathic VTE occurs in a cancer-free individual, an intensive work-up to find an occult malignancy is not warranted and has not been shown to improve subsequent cancer-related morbidity or mortality. However, once a cancer diagnosis is established in patients with prior VTE, they are at increased risk for subsequent VTE events, especially if the FVL or G20210A prothrombin mutation is present. LMWH prophylaxis after malignancy-associated VTE achieves superior prevention compared to warfarin, possibly because of better maintenance of an anticoagulated state. In the special case of myeloproliferative disorders (e.g., essential thrombocythemia), abnormal platelet physiologic mechanisms causing hyperaggregability are often present and require platelet-specific inhibition (See Hypercoagulability and Platelet Disorders).

### Antiphospholipid Antibody Syndrome

Another acquired prothrombotic disorder is the antiphospholipid antibody syndrome (APS). APS is a primary disorder, unlike the occasional association of lupus anticoagulant or antiphospholipid antibodies with other autoimmune diseases such as systemic lupus erythematosus (SLE). The etiologic connection with SLE has not been fully defined, but replacement of the host immune system after hematopoietic stem cell transplantation for refractory SLE has the potential to eradicate the lupus anticoagulant and thromboembolic risk. All of the manifestations of APS are related to hypercoagulability, including recurrent venous or arterial thrombosis, thrombocytopenia caused by microcirculatory platelet clearance, and recurrent fetal loss resulting from placental vascular insufficiency. Serologic markers of APS include *anticardiolipin antibodies, anti–$\beta_2$-glycoprotein I antibodies*, and *lupus anticoagulants.* The Sydney Consensus Criteria for Antiphospholipid Syndrome is the current standard for diagnosis of APS. Diagnosis requires both the clinical criterion of radiologically or pathologically confirmed thrombosis or thrombosis-related fetal loss and the laboratory criterion of positive tests on two or more occasions at least 12 weeks apart. Anticardiolipin and anti-glycoprotein antibodies are detected by enzyme-linked immunosorbent assay (ELISA), whereas lupus anticoagulants are defined by correction of prolonged phospholipid-dependent clotting tests (most commonly hexagonal phase partial thromboplastin time [PTT] or Russell viper venom clotting time), with addition of excess phospholipid. Therefore, *lupus anticoagulant* is a misnomer; its presence predisposes the patient to clotting rather than to bleeding, and the risk for thrombosis is highest when a lupus anticoagulant is detectable. Another misleading aspect of this nomenclature is that phospholipid-reactive antibodies are actually directed against phospholipid-binding proteins in plasma (e.g., $\beta_2$-glycoprotein I antibody, annexin V, prothrombin). Anti–$\beta_2$-glycoprotein I antibody is detected by immunoassay, and high titers of this marker are also correlated with thromboembolic risk.

In patients with recurrent pregnancy loss in the context of APS, LMWH during pregnancy can help reduce further miscarriages.

## Hypercoagulability and Platelet Disorders

Essential thrombocythemia and polycythemia vera are clonal myeloproliferative disorders associated with mutations in the *JAK2* gene. They are wholly (essential thrombocythemia) or partially (polycythemia vera) characterized by thrombocytosis, and patients with these disorders are at increased risk for thrombosis. Platelet aggregometry in these disorders often shows abnormal responses, especially to epinephrine and ADP; however, the abnormal aggregation does not correspond to either bleeding or thrombosis risk. Patients with polycythemia vera in particular have a high incidence of thrombosis in the mesenteric, portal, and hepatic venous circulation.

Thrombotic complications, both arterial and venous, occur in essential thrombocythemia, even in young patients. The risk of arterial thrombosis in essential thrombocythemia (and probably also in primary myelofibrosis and polycythemia vera) is most increased by a history of previous thrombosis or the