inducing a flare. Randomized, placebo-controlled clinical trials have helped to guide hormonal therapy in women with SLE.

A multicenter, randomized trial revealed that oral contraceptive therapy does not increase the risk of SLE flares in women with mild or stable SLE disease activity. However, this is not generalizable to all SLE women, particularly those whose disease is active or severe and those with prior thrombotic events or APAs. An effective form of birth control is necessary for young, sexually active women with SLE, especially those on teratogenic medications. Physicians must carefully discuss the risks and benefits of birth control with SLE patients.

Hormonal therapy is a controversial topic regardless of SLE status. However, it is of particular interest in SLE because some women reach menopause prematurely. In a clinical trial of hormonal therapy in SLE patients with mild or stable disease with no prior thrombotic events, APAs, or gynecologic or breast cancers, no SLE patients had severe clinical flares, but 20% did have mild to moderate flares. These findings suggest that brief (1-year) hormonal therapy may be considered for alleviating menopausal symptoms in a subset of SLE women.

Bone Health

SLE patients have higher rates of low bone mineral density, osteoporosis, and fractures than do healthy age-matched subjects. The increased risk is accounted for by traditional risk factors, such as female sex, white or Asian race, older age, and low body weight, and by SLE-associated factors. Fatigue and articular symptoms due to SLE may limit physical activity, leading to loss of bone strength.

Therapies commonly used for SLE contribute to overall loss of bone health. Corticosteroids reduce bone mass and are an independent risk factor for fractures in women with SLE. Cyclophosphamide use can lead to premature ovarian failure, another risk factor for osteoporosis. Lupus disease damage, regardless of steroid use, leads to low bone mineral density. SLE patients are advised to avoid sun exposure, which can lead to low 25-hydroxyvitamin D levels and insufficient absorption of calcium.

Because of SLE-specific risk factors for low bone mineral density, prevention of osteoporosis is extremely important (see Chapter 75). Although osteoporosis screening guidelines for SLE patients are the same as for the general population, bone density scans should be considered for patients with premature menopause and those who are or will be on chronic (>3 months) corticosteroids.

Cardiovascular Disease

As survival and therapies for SLE have improved and patients are living longer, CVD has emerged as a leading cause of morbidity and mortality. SLE patients are 5 to 10 times more likely than healthy individuals to have a coronary event. More striking, premenopausal women between 35 and 44 years of age are more than 50 times as likely as healthy women to have a myocardial infarction.

Autopsy series reveal atherosclerotic heart disease as the underlying mechanism of CVD in SLE. The cause of premature atherosclerosis in SLE is multifactorial and includes inflammatory mediators, SLE-related factors (e.g., premature menopause, corticosteroid therapy, disease activity), and traditional cardiovascular risk factors.

Although no firm cardiovascular management guidelines exist for SLE patients, the 2011 updated guidelines from the American Heart Association for prevention of CVD in women included (for the first time) autoimmune diseases (i.e., SLE and rheumatoid arthritis) in the increased-risk category. Physicians should consider premature atherosclerotic CVD and aggressively evaluate SLE patients with typical and atypical cardiac symptoms, regardless of age and sex.

Secondary Antiphospholipid Syndrome

APS is a disorder characterized by recurrent vascular thrombosis or recurrent pregnancy loss, or both, in the setting of APAs (Table 79-5). Lupus anticoagulant is part of the antiphospholipid laboratory panel and is paradoxically associated with thrombosis and recurrent pregnancy loss. The term *lupus anticoagulant* is a misnomer because the in vitro anticoagulant effect reflects the prolonged activated partial thromboplastin time (aPTT), but the term does not indicate a diagnosis of SLE or an increased risk of bleeding.

Diverse proteins binding to APAs have been recognized. APS is considered primary if it occurs in isolation and secondary if it occurs in conjunction with other autoimmune diseases. There are no major differences in severity or clinical consequences between primary and secondary APS. The reported prevalence of various APAs in SLE ranges from 16% to 55%. SLE patients with APAs have an increased risk of thromboembolism and pregnancy complications and have a higher prevalence of pulmonary hypertension, Libman-Sacks endocarditis, and neurologic complications. The term *catastrophic APS* has been coined to describe patients who exhibit multiple microthromboses, are positive for APAs, and often have a life-threatening illness resulting in multiorgan failure that can be clinically indistinguishable from sepsis or thrombotic thrombocytopenic purpura.

Treatment for APS is tailored to the patient and the clinical manifestations. For patients with vascular thrombosis, indefinite anticoagulation is usually prescribed as prophylaxis against recurrence. Warfarin is the usual drug of choice for long-term therapy, with a target of an international normalized ratio (INR) between 2 and 3. Higher INR levels (3 to 4) are not more effective and are associated with bleeding complications. Unfractionated and low-molecular-weight heparin is also an effective anticoagulant for APS and is used for patients who suffer recurrent events while on warfarin therapy or patients who are or plan to become pregnant.

Malignancy

A multicenter international cohort (SLICC) of more than 16,000 SLE patients reported an increased risk of malignancy among them compared with the general population. Most striking was a fourfold increased risk of non-Hodgkin's lymphoma. Other hematologic, vulvar, lung, and thyroid cancers were described with increased frequency, whereas breast and endometrial cancers were observed less than expected in SLE patients compared with the general population. Malignancy risk appears to be highest early in the disease course, but risk remains elevated throughout a patient's lifespan. Although lymph node