

CHAPTER 59: Connective Tissue Disorders

Owing to the great vascularity incident to pregnancy, the various pelvic joints always show a somewhat increased motility. In rare instances, particularly when the pelvis is contracted in the lower portion, spontaneous rupture of the symphysis pubis or one or both sacro-iliac joints has been observed.

—J. Whitridge Williams (1903)

INTRODUCTION

The principal concerns in the 1st edition of *Williams Obstetrics* with disorders of the joints were the obstructed pelvis caused by rickets. There is no mention of the arthritides complicating pregnancy. And of course, immune-mediated disease had not yet been elucidated.

Connective tissue disorders, which are also termed **collagen** vascular disorders, have two basic underlying causes. First are the *immune-complex diseases* in which connective tissue damage is caused by deposition of immune complexes. Because these are manifest by sterile inflammation—predominately of the skin, joints, blood vessels, and kidneys—they are referred to as rheumatic diseases. Many of these immune-complex diseases are more prevalent in women, for example, systemic lupus erythematosus (SLE) and rheumatoid arthritis. Second are the *inherited disorders* of bone, skin, cartilage, blood vessels, and basement membranes. Some examples include Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome.

IMMUNE-MEDIATED CONNECTIVE TISSUE DISEASES

These disorders can be separated into those associated with and those without autoantibody formation. The *rheumatoid factor (RF)* is an autoantibody found in many autoimmune inflammatory conditions such as SLE, rheumatoid arthritis, systemic sclerosis (scleroderma), mixed connective tissue disease, dermatomyositis, polymyositis, and various vasculitis syndromes. The *RF-seronegative spondyloarthropathies* are strongly associated with expression of the human leukocyte antigen B27 (HLA-B27) antigen and include ankylosing spondylitis, psoriatic arthritis, Reiter disease, and other arthritis syndromes.

Pregnancy may mitigate activity in some of these syndromes as a result of the immunosuppression that also allows successful engraftment of fetal and placental tissues. These changes are discussed in detail in [Chapters 4 \(Iron Metabolism\)](#) and [5 \(Amnion\)](#). One example is pregnancy-induced predominance of T2 helper cells compared with cytokine-producing T1 helper cells ([Keeling, 2009](#)). Pregnancy hormones also alter immune cells. Namely, **estrogens** upregulate and androgens downregulate T-cell response, and **progesterone** is immunosuppressive ([Cutolo, 2006](#); [Häupl, 2008a](#); [Robinson, 2012](#)).

In contrast, immune-mediated disease may contribute to obstetrical complications. One longitudinal cohort study found that unrecognized autoimmune systemic rheumatic disorders are associated with significant risk for preeclampsia and fetal-growth restriction ([Spinillo, 2016](#)). In this study, the prevalence of unrecognized rheumatic arthritis was 0.4 percent, and was 0.3 percent each for SLE, Sjögren syndrome, and antiphospholipid syndrome.

Last, some immune-mediated diseases may either be caused or activated as a result of prior pregnancies. To explain, fetal cells and free fetal DNA are detectable in maternal blood beginning early in pregnancy ([Simpson, 2013](#); [Sitar, 2005](#); [Waldorf, 2008](#)). *Fetal cell microchimerism* is the persistence of fetal cells in the maternal circulation and in organs following pregnancy. These fetal cells may become engrafted in maternal tissues and stimulate autoantibodies. This raises the possibility that fetal cell microchimerism leads to the predilection for autoimmune disorders among women ([Adams, 2004](#)). Evidence for this includes fetal stem cells engrafted in tissues in women with autoimmune thyroiditis and systemic sclerosis ([Jimenez, 2005](#); [Srivatsa, 2001](#)). Such microchimerism has also been described in women with SLE and those with rheumatoid arthritis-associated HLA alleles ([da Silva, 2016](#); [Lee, 2010](#); [Rak, 2009a](#)). Conversely, engrafted maternal cells may provoke autoimmune conditions in a woman's offspring ([Ye, 2012](#); [Stevens,](#)

2016).

SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus is a heterogeneous autoimmune disease with a complex pathogenesis that results in interactions between susceptibility genes and environmental factors (Hahn, 2015). Immune system abnormalities include overactive B lymphocytes that are responsible for autoantibody production. These result in tissue and cellular damage when autoantibodies or immune complexes are directed at one or more cellular nuclear components (Tsokos, 2011). In addition, immunosuppression is impaired, including regulatory T-cell function (Tower, 2013). Some autoantibodies produced in patients with SLE are shown in Table 59-1.

TABLE 59-1

Some Autoantibodies Produced in Patients with Systemic Lupus Erythematosus (SLE)

Antibody	Prevalence (%)	Clinical Associations
Antinuclear (ANA)	84–98	Best screening test, multiple antibodies; a second negative test makes SLE unlikely
Anti-dsDNA	62–70	High titers SLE-specific; may correlate with disease activity, nephritis, and vasculitis
Anti-Sm (Smith)	25–38	Specific for SLE
Anti-RNP	33–40	Not SLE-specific, high titers associated with rheumatic syndromes
Anti-Ro (SS-A)	30–49	Not SLE-specific; associated with sicca syndrome, predisposes to cutaneous lupus, neonatal lupus with heart block, reduced risk of nephritis
Anti-La (SS-B)	10–35	Associated with anti-Ro
Antihistone	70	Common in drug-induced lupus
Antiphospholipid	21–50	Lupus anticoagulant and anticardiolipin antibodies associated with thrombosis, fetal loss, thrombocytopenia, valvular heart disease; false-positive test for syphilis
Antierthrocyte	60	Direct Coombs test, may develop hemolysis
Antiplatelet	30	Thrombocytopenia in 15%; poor clinical test

dsDNA = double-stranded DNA; RNP = ribonucleoprotein.

Data from Arbuckle, 2003; Hahn, 2015.

Almost 90 percent of SLE cases are in women, and its prevalence in those of childbearing age approximates 1 in 500 (Lockshin, 2000). Accordingly, the disease is encountered relatively frequently during pregnancy. The 10-year survival rate is 70 to 90 percent (Tsokos, 2011). Infection, lupus flares, end-organ failure, hypertension, stroke, and cardiovascular disease account for most deaths.

Genetic influences are implicated by a higher concordance with monozygotic compared with dizygotic twins—25 versus 2 percent, respectively. Moreover, frequency in patients with one affected family member is 10 percent. The relative risk of disease rises if there is inheritance of the “autoimmunity gene” on chromosome 16 that predisposes to SLE, rheumatoid arthritis, Crohn disease, and psoriasis. Susceptibility genes such as

HLA-A1, -B8, -DR3, -DRB1, and -TET3 explain only a portion of the genetic heritability (Tsokos, 2011; Yang, 2013). Interestingly, even maternal exposure to fetal genes elevates susceptibility to SLE development. A case-control study found that a child's HLA-DRB1 genotype increases the risk of SLE in the mother (Cruz, 2016). Furthermore, neonatal lupus erythematosus has been reported in an infant conceived via oocyte donor to a mother with autoimmune disease with circulating anti-Ro and anti-La antibodies (Chiou, 2016).

Clinical Manifestations and Diagnosis

Lupus is notoriously variable in its presentation, course, and outcome (Table 59-2). Findings may be confined initially to one organ system, and others become involved later. Or, the disease may first be multisystem. Frequent findings are malaise, fever, arthritis, rash, pleuropericarditis, photosensitivity, anemia, and cognitive dysfunction. At least half of patients have renal involvement. SLE is also associated with declines in attention, memory, and reasoning (Hahn, 2015; Kozora, 2008).

TABLE 59-2

Some Clinical Manifestations of Systemic Lupus Erythematosus

Organ System	Clinical Manifestations	Percent
Systemic	Fatigue, malaise, fever, weight loss	95
Musculoskeletal	Arthralgias, myalgias, polyarthritis, myopathy	95
Hematological	Anemia, hemolysis, leukopenia, thrombocytopenia, lupus anticoagulant, splenomegaly	85
Cutaneous	Malar (butterfly) rash, discoid rash, photosensitivity, oral ulcers, alopecia, skin rashes	80
Neurological	Cognitive dysfunction, mood disorder, headache, seizures, stroke	60
Cardiopulmonary	Pleuritis, pericarditis, myocarditis, endocarditis, pneumonitis, pulmonary hypertension	60
Renal	Proteinuria, nephrotic syndrome, renal failure	30–50
Gastrointestinal	Nausea, pain, diarrhea, abnormal liver enzyme levels	40
Vascular	Thrombosis: venous (10%), arterial (5%)	15
Ocular	Conjunctivitis, sicca syndrome	15

Modified from Kasper, 2015.

Identification of antinuclear antibodies (ANA) is the best screening test, however, a positive result is not specific for SLE. For example, low titers are found in normal individuals, other autoimmune diseases, acute viral infections, and chronic inflammatory processes. Several drugs can also cause a positive reaction. Antibodies to double-stranded DNA (dsDNA) and to Smith (Sm) antigens are relatively specific for SLE, whereas other antibodies are not (see Table 59-1). Although hundreds of autoantibodies have been described in SLE, only a few have been shown to participate in tissue injury (Sherer, 2004; Tsokos, 2011). Currently, microarray profiles are being developed for more accurate SLE diagnosis (Putterman, 2016).

Anemia develops frequently, and there may be leukopenia and thrombocytopenia. Proteinuria and casts are found in the half of patients with glomerular lesions. Lupus nephritis can also cause renal insufficiency, which is more common if there are antiphospholipid antibodies (Moroni, 2004). Other laboratory findings include false-positive syphilis serology, prolonged partial thromboplastin time, and higher RF levels. Elevated serum d-dimer concentrations often follow a flare or infection, but unexplained persistent elevations are associated with a high risk for thrombosis (Wu, 2008).

The diagnostic criteria for SLE are listed in Table 59-3. If any four or more of these 11 criteria are present, serially or simultaneously, the diagnosis of

lupus is made. Importantly, numerous drugs can induce a lupus-like syndrome. These include proton-pump inhibitors, thiazide diuretics, antifungals, chemotherapeutics, statins, and antiepileptics. Drug-induced lupus is rarely associated with glomerulonephritis and usually regresses when the medication is discontinued (Laurinaviciene, 2017).

TABLE 59-3

Clinical Criteria for Classification of Systemic Lupus Erythematosus

Clinical Manifestations
Skin
Oral ulcers
Alopecia
Synovitis
Renal: proteinuria, casts, biopsy
Neurological: seizures, psychosis, myelitis, neuropathies, confusional state
Hemolytic anemia
Leukopenia or lymphopenia
Thrombocytopenia
Immunological Manifestations
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid
Hypocomplementemia
Direct Coombs

ANA = antinuclear antibodies; dsDNA = double-stranded DNA; Sm = Smith.

Data from Hahn, 2015; Hochberg, 1997.

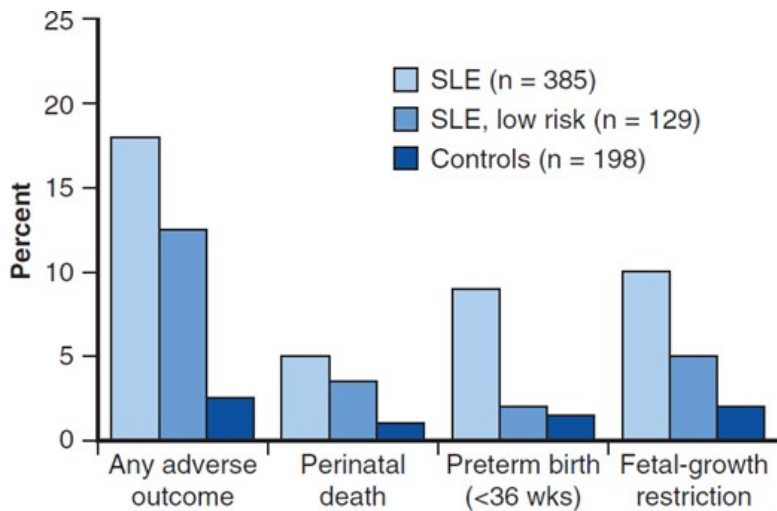
Lupus and Pregnancy

Of nearly 16.7 million pregnancies from 2000 to 2003 in the United States, 13,555 were complicated by lupus—an incidence of approximately 1 in 1250 pregnancies (Clowse, 2008). During pregnancy, lupus improves in a third of women, remains unchanged in a third, and worsens in the remaining third. Thus, in any given pregnancy, the clinical condition can worsen or *flare* without warning (Hahn, 2015; Khamashta, 1997).

Petri (1998) reported a 7-percent risk of major morbidity during pregnancy. In a cohort of 13,555 women with SLE during pregnancy, the maternal mortality and severe morbidity rate was 325 per 100,000 (Clowse, 2008). In a review of 13 studies with 17 maternal deaths attributable to SLE and lupus nephritis, all occurred in those with active disease (Ritchie, 2012). Results of a prospective cohort study of 385 women are shown in Figure 59-1.

FIGURE 59-1

Frequency of adverse pregnancy outcomes. All women with systemic lupus erythematosus (SLE) in the PROMISSE study are compared with a subset of low-risk SLE patients and with control patients without SLE. (Data from Buyon, 2015.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield. *Williams Obstetrics*, 25th Edition. Copyright © McGraw-Hill Education. All rights reserved.

During the past several decades, pregnancy outcomes in women with SLE have improved remarkably. For most women with inactive or mild/moderate SLE, pregnancy outcomes are relatively favorable. Women who have confined cutaneous lupus do not usually have adverse outcomes (Hamed, 2013). However, newly diagnosed SLE during pregnancy tends to be severe (Zhao, 2013). In general, pregnancy outcome is best in women for whom: (1) lupus activity has been quiescent for at least 6 months before conception; (2) there is no lupus nephritis manifest by proteinuria or renal dysfunction; (3) antiphospholipid syndrome or lupus anticoagulant is absent; and (4) superimposed preeclampsia does not develop (Peart, 2014; Stojan, 2012; Wei, 2017; Yang, 2014).

Lupus Nephritis

Active nephritis is associated with adverse pregnancy outcomes, although these have improved remarkably and especially if disease remains in remission (Moroni, 2002, 2005; Stojan, 2012). Of complications, women with renal disease have a high incidence of gestational hypertension and preeclampsia. Of 80 gravidas with SLE reported by Lockshin (1989), 63 percent of women with preexisting renal disease developed preeclampsia compared with only 14 percent of those without underlying renal disease. In a review of 309 pregnancies complicated by lupus nephritis, 30 percent suffered a flare, and 40 percent of these had associated renal insufficiency (Moroni, 2005). The maternal mortality rate was 1.3 percent. These findings were corroborated in a subsequent prospective study (Moroni, 2016b). In addition, a third of the 113 pregnancies were delivered preterm (Imbasciati, 2009; Moroni, 2016a). Wagner and coworkers (2009) compared outcomes of 58 women with 90 pregnancies and found that active nephritis was linked with a significantly higher incidence of maternal complications—57 versus 11 percent.

Most recommend continuation during pregnancy of immunosuppressive therapy for nephritis. New-onset nephritis or severe renal flare is treated aggressively with intravenous corticosteroids and consideration of immunosuppressive drugs or intravenous immunoglobulin (Lazzaroni, 2016).

Lupus versus Preeclampsia-Eclampsia

Chronic hypertension complicates up to 30 percent of pregnancies in women with SLE (Egerman, 2005). Also, as mentioned, preeclampsia is common, and superimposed preeclampsia is encountered even more often, and earlier, in those with nephritis or antiphospholipid antibodies (Bertsias, 2008). Preeclampsia and lupus nephritis share features of hypertension, proteinuria, edema, and renal function deterioration. However, the management is

distinct, as lupus nephritis is treated with immunosuppression, and severe preeclampsia/eclampsia requires delivery ([Lazzaroni, 2016](#)). It may be difficult, if not impossible, to differentiate lupus flare with nephropathy from severe preeclampsia if the kidney is the only involved organ ([Petri, 2007](#)). Central nervous system involvement with lupus may culminate in convulsions similar to those of eclampsia. One proposed schema for differentiating the two is shown in [Table 59-4](#). Management for preeclampsia-eclampsia is described in [Chapter 40 \(Preeclampsia\)](#).

TABLE 59-4

Some Distinctions between Lupus Flare and Preeclampsia Syndrome

Factor	Lupus	Preeclampsia
Clinical findings	Fatigue, headache, extra-renal signs (rash, serositis, arthritis)	Headaches, confusion, visual changes, convulsions
Blood pressure	Normal or high	High
Anemia	Hemolytic	Absent
Proteinuria	Present	Present
Creatinine	Normal or high	Normal or high
Transaminases	Normal	Normal or high
Complement	Decreased	Normal

Data from [Andreoli, 2012](#).

Management During Pregnancy

Lupus management consists primarily of monitoring fetal well-being and maternal clinical and laboratory status ([Lateef, 2012](#)). Pregnancy-induced thrombocytopenia and proteinuria resemble SLE disease activity, and the identification of a lupus flare is confounded by the increased facial and palmar erythema of normal pregnancy ([Lockshin, 2003](#)).

For SLE activity monitoring, various laboratory techniques have been recommended, but interpretation may be challenging. The sedimentation rate may be misleading because of pregnancy-induced hyperfibrinogenemia. Serum complement levels are also normally increased in pregnancy ([Appendix, Serum and Blood Constituents](#)). And, although falling or low levels of complement components C₃, C₄, and CH₅₀ are more likely to be associated with active disease, higher levels provide no assurance against disease activation. Our experiences and those of others suggest that clinical manifestations of disease and complement levels correlate poorly ([Lockshin, 1995](#); [Varner, 1983](#)).

Serial hematological studies may detect changes in disease activity. Hemolysis is characterized by a positive Coombs test, anemia, reticulocytosis, and unconjugated hyperbilirubinemia. Thrombocytopenia, leukopenia, or both may develop. According to [Lockshin and Druzin \(1995\)](#), chronic thrombocytopenia in early pregnancy may be due to antiphospholipid antibodies. Later, thrombocytopenia may indicate preeclampsia.

Urine is tested frequently to detect new-onset or worsening proteinuria. The fetus is closely observed for adverse effects such as growth restriction and oligohydramnios. Many recommend screening for anti-SS-A (anti-Ro) and anti-SS-B (anti-La) antibodies, because of associated fetal complications described subsequently. Antepartum, the fetus is surveilled as outlined by the [American College of Obstetricians and Gynecologists \(2016a\)](#) and described in [Chapter 17 \(Fetal Movements\)](#). Unless hypertension or evidence of fetal compromise or growth restriction develops, pregnancy is allowed to progress to term. Peripartum corticosteroids in “stress doses” are given to women who are taking these drugs or who recently have done so.

Pharmacological Treatment

There is no cure for SLE, and complete remissions are rare. Approximately a fourth of pregnant women have mild disease, which is not life threatening, but may be disabling because of pain and fatigue. Arthralgia and serositis can be managed by nonsteroidal antiinflammatory drugs (NSAIDs). However, chronic or large intermittent dosing is avoided due to related oligohydramnios or ductus arteriosus closure ([Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs](#)). Low-dose aspirin can be used throughout gestation. Severe disease is managed with corticosteroids such as prednisone, 1 to 2 mg/kg/d orally. After the disease is controlled, this dose is tapered to a daily morning dose of 10 to 15 mg. Corticosteroid therapy can lead to gestational diabetes.

Immunosuppressive agents such as azathioprine are beneficial for active disease. These are usually reserved for lupus nephritis or disease that is corticosteroid resistant. Azathioprine has a good safety record during pregnancy ([Fischer-Betz, 2013](#); [Petri, 2007](#)). Its recommended daily oral dose is 2 to 3 mg/kg. Teratogenic medications to be avoided include mycophenolate mofetil, methotrexate, and cyclophosphamide ([Götestam Skorpén, 2016](#)). However, cyclophosphamide can be considered in the second or third trimester for severe disease ([Lazzaroni, 2016](#)). In some situations, mycophenolate is the only treatment that achieves disease stability. In these cases, counseling is essential regarding fetal risks described in [Chapter 12 \(Immunosuppressant Medications\)](#) ([Bramham, 2012](#)).

Antimalarials reduced dermatitis, arthritis, and fatigue ([Hahn, 2015](#)). Although these agents cross the placenta, hydroxychloroquine is not associated with congenital malformations. Because of the long half-life of antimalarials and because discontinuing therapy can precipitate a lupus flare, most recommend their continuation during pregnancy ([Borden, 2001](#)).

When severe disease supervenes—usually a lupus flare—high-dose glucocorticoid therapy is given. [Petri \(2007\)](#) recommends pulse therapy consisting of methylprednisolone, 1000 mg given intravenously over 90 minutes daily for 3 days, then a return to maintenance doses if possible.

In nonpregnant subjects, antihypertensive therapy often includes an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker. For pregnancy, these should be changed to safer fetal options such as calcium-channel blockers, alpha methyldopa, or labetalol ([Cabiddu, 2016](#)).

Perinatal Mortality and Morbidity

Adverse perinatal outcome rates are significantly elevated in pregnancies complicated by SLE. Among these are preterm delivery, fetal-growth restriction, stillbirth, and neonatal lupus syndrome ([Madazli, 2014](#); [Phansenee, 2017](#)). Perinatal outcome rates worsen in mothers with a lupus flare, significant proteinuria, or renal impairment and in those with chronic hypertension, preeclampsia, or both ([Lazzaroni, 2016](#)). Adverse outcomes are also more common in women with neuropsychiatric lupus ([de Jesus, 2017](#)). Reasons at least partially responsible for adverse fetal consequences include decidual vasculopathy with placental infarction and decreased perfusion ([Hanly, 1988](#)).

Neonatal Lupus Syndrome

This is characterized by newborn skin lesions—lupus dermatitis; a variable number of hematological and systemic derangements; and occasionally congenital heart block ([Hahn, 2015](#)). Cutaneous manifestations can be present in 30 to 40 percent of infants and appears at 4 to 6 weeks of age ([Silverman, 2010](#)). These are usually associated with anti-SS-A and SS-B antibodies, and approximately 40 percent of women with SLE are positive for these ([Buyon, 2015](#)). Thrombocytopenia and hepatic involvement are seen in 5 to 10 percent of affected infants.

In a review of outcomes in 91 infants born to women with lupus, eight of these were possibly affected—four had definite neonatal lupus and four had possible disease ([Lockshin, 1988](#)). Cutaneous lupus, thrombocytopenia, and autoimmune hemolysis are transient and clear within a few months ([Zuppa, 2017](#)). This is not always so for congenital heart block, discussed next. In subsequent offspring, the recurrence risk for neonatal lupus may near 25 percent ([Julkunen, 1993](#)).

Congenital Heart Block

Fetal and neonatal heart block results from diffuse myocarditis and fibrosis in the region between the atrioventricular (AV) node and bundle of His. Congenital heart block develops almost exclusively in fetuses of women with antibodies to the SS-A or SS-B antigens ([Buyon, 1993](#)). Even in the presence of such antibodies, however, the incidence of fetal myocarditis is only 2 to 3 percent but rises to 20 percent with a prior affected child ([Bramham, 2012](#); [Lockshin, 1988](#)). Fetal cardiac monitoring is performed between 18 and 26 weeks' gestation in pregnancies with either of these antibodies. The cardiac lesion is permanent, and a pacemaker is generally necessary. Long-term prognosis is poor. Of 325 infants with cardiac

neonatal lupus, nearly 20 percent died, and of these, one third was stillborn ([Izmirly, 2011](#)).

Maternal administration of corticosteroids, plasma exchange, or intravenous immunoglobulin does not reduce the risk of congenital heart block. Maternal corticosteroid administration for treatment congenital heart block is controversial, is currently not recommended, and is discussed further in [Chapter 16 \(Tachyarrhythmias\)](#). Although this therapy to treat fetal heart block has not been studied in randomized trials, some evidence suggests that early fetal exposure to the mother's corticosteroid treatment for SLE may mitigate fetal myocarditis. Namely, [Shinohara and coworkers \(1999\)](#) reported no heart block in 26 neonates whose mothers received corticosteroids before 16 weeks' gestation as part of SLE maintenance therapy. By contrast, 15 of 61 neonates with heart block were born to women in whom corticosteroid therapy was begun after 16 weeks for an SLE exacerbation.

There are reports that maternal treatment with [hydroxychloroquine](#) (Plaquenil) is associated with a lower incidence of fetal heart block ([Izmirly, 2012](#)). Research in this area is ongoing.

Long-Term Prognosis and Contraception

The survival rate for women with SLE is 95 percent at 5 years, 90 percent at 10 years, and 78 percent at 20 years ([Hahn, 2015](#)). In general, women with lupus and chronic vascular or renal disease may limit family size because of morbidity associated with the disease and greater risks for adverse perinatal outcomes. For contraception, combination oral contraceptives did not increase the incidence of lupus flares in two large multicenter trials ([Petri, 2005](#); [Sánchez-Guerrero, 2005](#)). Progestin-only implants and injections provide effective contraception with no known effects on lupus flares ([Sammartino, 2014](#)). Concerns that intrauterine device (IUD) use and immunosuppressive therapy lead to greater infection rates in these patients are not evidenced-based. Notably, comorbid antiphospholipid antibodies are a contraindication to hormonal methods. Tubal sterilization may be advantageous and is performed with greatest safety postpartum or whenever SLE is quiescent.

ANTIPHOSPHOLIPID SYNDROME

This syndrome is an autoantibody-mediated acquired thrombophilia with recurrent thrombosis or pregnancy morbidity as part of its clinical constellation ([Moutsopoulos, 2015](#)). Specifically, antiphospholipid syndrome (APS) is diagnosed in women with persistently positive serum tests for antiphospholipid antibodies *and* with arterial and/or venous thromboses or obstetrical morbidity. Antibodies include lupus anticoagulant, anticardiolipin antibody, and anti- β_2 glycoprotein-I antibody.

Phospholipids are the main lipid constituents of cell and organelle membranes. There are proteins in plasma that associate noncovalently with these phospholipids. Antiphospholipid antibodies are directed against these phospholipids or phospholipid-binding proteins ([Giannakopoulos, 2013](#); [Tsokos, 2011](#)). This antibody group may be of IgG, IgM, and IgA classes, alone or in combination. Antiphospholipid antibodies are most common with SLE, other connective tissue disorders, and APS. However, a small proportion of otherwise normal women and men have low levels of these antibodies.

The stimulus for autoantibody production is unclear, but it possibly is due to a preceding infection. The pathophysiology encountered is mediated by one or more of the following: (1) activation of various procoagulants, (2) inactivation of natural anticoagulants, (3) complement activation, and (4) inhibition of syncytiotrophoblast differentiation ([Tsokos, 2011](#)). Clinically, these actions lead to arterial or venous thromboses or to pregnancy morbidity. Virtually every organ system may be affected.

Central nervous system involvement is one of the most prominent clinical manifestations. In addition to cerebrovascular arterial and venous thrombotic events, there may be psychiatric features and even multiple sclerosis ([Binder, 2010](#)). Renovascular involvement may lead to renal failure that can be difficult to differentiate from lupus nephritis ([D'Cruz, 2009](#)). Peripheral and visceral thromboses are also a feature. For example, [Ahmed and associates \(2009\)](#) reported a postpartum woman who developed spontaneous cecal perforation following a mesenteric vessel infarction. Obstetrical complications encompass recurrent pregnancy loss and placental dysfunction reflected by fetal-growth restriction, stillbirth, preeclampsia, and preterm birth. Treatment using [aspirin](#), anticoagulation, and close monitoring has increased live birth rates to more than 70 percent in these women ([Schreiber, 2016](#)).

A small proportion of these patients develop the *catastrophic antiphospholipid antibody syndrome (CAPS)* or *Asherson syndrome*. This is defined as a rapidly progressive thromboembolic disorder simultaneously affecting three or more organ systems or tissues ([Schreiber, 2016](#)). It has a high mortality rate from activation of a cytokine storm. In half of cases, a "triggering" event is identified.

Specific Antiphospholipid Antibodies

As mentioned, several antibodies in APS are directed against a specific phospholipid or phospholipid-binding protein:

1. β_2 -Glycoprotein I—also known as apolipoprotein H—is a phospholipid-binding plasma protein that inhibits prothrombinase activity within platelets and inhibits platelet aggregation (Giannakopoulos, 2013). Thus, its normal action is to limit procoagulant binding and thereby prevent coagulation cascade activation. Logically, antibodies directed against this glycoprotein would reverse its anticoagulant activity and promote thrombosis. This is important from an obstetrical viewpoint because β_2 -glycoprotein I is expressed in high concentrations on the syncytiotrophoblast surface. Complement activation may contribute to its pathogenesis (Avalos, 2009; Tsokos, 2011). Teleologically, this seems appropriate because the decidua intuitively should be a critical area to prevent coagulation that might lead to intervillous space thrombosis. Another possibility is that β_2 -glycoprotein I may be involved in implantation, and this glycoprotein may result in pregnancy loss via an inflammatory mechanism (Iwasawa, 2012; Meroni, 2011).
2. *Lupus anticoagulant (LAC)* is a heterogeneous group of antibodies directed against phospholipid-binding proteins. This antibody group induces prolongation in vitro of the prothrombin, partial thromboplastin, and Russell viper venom times. Thus, paradoxically, this so-called anticoagulant is actually powerfully thrombotic in vivo.
3. *Anticardiolipin antibodies (ACAs)* are directed against one of the many phospholipid cardiolipins found in mitochondrial membranes and platelets.

Antibodies against Natural Anticoagulants

Some antiphospholipid antibodies are also directed against the natural anticoagulant proteins C and S (Robertson, 2006). Another is directed against the anticoagulant protein annexin V, which is expressed in high concentrations by syncytiotrophoblast (Giannakopoulos, 2013). Testing for these other antibodies is not recommended (American College of Obstetricians and Gynecologists, 2017). However, some studies have evaluated these nonconventional antiphospholipid antibodies in women who clinically meet APS criteria but do not have the classic antibody profile. In one study, treatment of women with these nonconventional antibodies offered some benefits, such as a lower pregnancy loss rate (Mekinian, 2016).

Clinical features shown in Table 59-5 provide indications for testing. By international consensus, APS is diagnosed based on laboratory and clinical criteria found in Table 18-5. First, one of two clinical criteria—which are vascular thrombosis or certain pregnancy morbidity—must be present. With laboratory criteria, elevated levels of LAC, ACA, and anti- β_2 -glycoprotein I should be confirmed on two occasions 12 weeks apart. The diagnosis can be further stratified based on the number of these tests that are positive (Miyakis, 2006).

TABLE 59-5

Some Clinical Features of Antiphospholipid Syndrome

Venous thrombosis—thromboembolism, thrombophlebitis, livedo reticularis
Arterial thrombosis—stroke, transient ischemic attack, Libman-Sacks cardiac vegetations, myocardial ischemia, distal extremity and visceral thrombosis and gangrene
Hematological—thrombocytopenia, autoimmune hemolytic anemia
Other—neurological manifestations, migraine headaches, epilepsy; renal artery, vein, or glomerular thrombosis; arthritis and arthralgia
Pregnancy—preeclampsia syndrome, recurrent miscarriage, preterm delivery, fetal-growth restriction, fetal death

Data from Giannakopoulos, 2013; Moutsopoulos, 2015.

Tests for LAC are nonspecific coagulation tests. The *partial thromboplastin time* is generally prolonged because the anticoagulant interferes with conversion of prothrombin to *thrombin* in vitro. Tests considered more specific are the *dilute Russell viper venom test* and the *platelet neutralization*

procedure. There is currently disagreement as to which of these two is best for screening. If either is positive, then identification of LAC is confirmed.

[Branch and Khamashta \(2003\)](#) recommend conservative interpretation of results based on repeated tests from a reliable laboratory that are consistent with each clinical case. Only approximately 20 percent of patients with APS have a positive LAC assay alone. Thus, ACA enzyme-linked immunosorbent assay (ELISA) testing should also be performed. Efforts have been made to standardize ACA assays, however, these remain without international standards ([Adams, 2013](#)). For each APS test, interlaboratory variation can be large, and agreement between commercial kits is poor.

Pregnancy and Antiphospholipid Antibodies

As noted, nonspecific low levels of antiphospholipid antibodies are identified in approximately 5 percent of normal adults ([Branch, 2010](#)). When [Lockwood and coworkers \(1989\)](#) first studied 737 normal pregnant women, they reported that 0.3 percent had LAC and 2.2 percent had elevated concentrations of either IgM or IgG ACAs. Subsequent investigations confirmed this, and taken together, they totaled almost 4000 normal pregnancies with an average prevalence for antiphospholipid antibodies of 4.7 percent. This is similar to that for normal nonpregnant individuals ([Harris, 1991](#); [Yasuda, 1995](#)).

In women with high ACA levels, and especially when LAC is identified, risks for decidual vasculopathy, placental infarction, fetal-growth restriction, early-onset preeclampsia, and recurrent fetal death are increased ([Saccone, 2017](#)). Some of these women, like those with SLE, also have a high incidence of venous and arterial thromboses, cerebral thrombosis, hemolytic anemia, thrombocytopenia, and pulmonary hypertension ([American College of Obstetricians and Gynecologists, 2017](#); [Clowse, 2008](#)). In 191 LAC-negative women with APS, women with antibodies to cardiolipin and β_2 -glycoprotein I had significantly higher miscarriage rates than if either one alone was positive ([Liu, 2013](#)). Women with higher titers tend to have more adverse outcomes ([Hadar, 2017](#)).

Pregnancy Pathophysiology

It is not precisely known how antiphospholipid antibodies cause damage, but it is likely that their actions are multifactorial. Platelets may be damaged directly by antiphospholipid antibody or indirectly by binding β_2 -glycoprotein I, which causes platelets to be susceptible to aggregation ([Giannakopoulos, 2013](#)). One theory proposes that phospholipid-containing endothelial cell or syncytiotrophoblast membranes may be damaged directly by the antiphospholipid antibody or indirectly by antibody binding to either β_2 -glycoprotein I or annexin V ([Rand, 1997, 1998](#)). This prevents the cell membranes from protecting the syncytiotrophoblast and endothelium. This exposes the basement membrane, to which damaged platelets can adhere and form a thrombus.

[Pierro and associates \(1999\)](#) reported that antiphospholipid antibodies decreased decidual production of the vasodilating prostaglandin E_2 . Diminished protein C or S activity and greater prothrombin activation may also be contributory ([Zangari, 1997](#)). Evidence also supports that thrombosis with APS stems from activation of the tissue factor pathway ([Amengual, 2003](#)). Finally, uncontrolled placental complement activation by antiphospholipid antibodies may play a role in fetal loss and growth restriction ([Holers, 2002](#)).

Complications from APS cannot be completely explained by thrombosis alone. Animal models suggest that effects are due to inflammation rather than thrombosis ([Cohen, 2011](#)). Some investigators hypothesize that APS-associated clotting is triggered as a “second hit” from innate inflammatory immune responses. These investigators recommend treatment with antiinflammatory agents ([Meroni, 2011](#)).

Adverse Pregnancy Outcomes

Overall, antiphospholipid antibodies are generally associated with higher rates of fetal wastage ([Chap. 18, Midtrimester Abortion](#)). In most early reports that describe these outcomes, however, women were included *because* they had had repeated adverse outcomes. Both antibody prevalence and miscarriage are common—recall that the incidence of antiphospholipid antibodies in the general obstetrical population is about 5 percent and early pregnancy loss approximates 20 percent. Accordingly, current data are too limited to conclude the exact risks for adverse effects of these antibodies on pregnancy outcomes. Fetal deaths, however, are more characteristic with APS than are first-trimester miscarriages ([Oshiro, 1996](#); [Roque, 2004](#)). Moreover, women with higher titers have worse obstetrical outcomes compared with those with low titers ([Hadar, 2017](#); [Nodler, 2009](#)).

When otherwise unexplained fetal deaths are examined, the data are mixed. One study measured ACA levels in 309 pregnancies with fetal death and found no differences in their frequency compared with levels in 618 normal pregnancies ([Haddow, 1991](#)). In another of women with recurrent

pregnancy loss, those with antiphospholipid antibodies had a higher rate of preterm delivery (Clark, 2007). In a case-control study of 582 stillbirths and 1547 live births, a three- to fivefold higher risk for stillbirth was found in women with elevated ACA and anti- β_2 -glycoprotein I levels (Silver, 2013). In women with antiphospholipid antibodies, adverse outcomes are more common in the presence of: (1) all three classic antiphospholipid antibody types, (2) comorbid SLE or systemic autoimmune diseases, and (3) prior thrombosis and pregnancy morbidity. Logistic regression found the probability of pregnancy failure was 93 percent with two or more antiphospholipid antibody types but was 63 percent for those with only one (Ruffatti, 2011).

Thrombosis Prevention in Pregnancy

Because of study heterogeneity, current treatment recommendations for women with antiphospholipid antibodies can be confusing. Therapy is directed at thrombosis prevention. As discussed, antiphospholipid antibodies are immunoglobulins that may be of G, M, or A classes. Those directed against the phospholipids (PL) are termed GPL, MPL, and APL, respectively. During testing, these are reported as semiquantified phospholipid binding-unit levels and expressed as negative, low-positive, medium-positive, or high-positive (American College of Obstetricians and Gynecologists, 2017). Of the three, higher titers for GPL and MPL anticardiolipin antibodies are clinically important, whereas low-positive titers are of questionable clinical significance.

As discussed in Chapter 52 (Acquired Thrombophilias), women with prior thromboembolic events who have antiphospholipid antibodies are at risk for recurrence in subsequent pregnancies. For these women, prophylactic anticoagulation with heparin throughout pregnancy and then for 6 weeks postpartum with either heparin or warfarin is recommended (American College of Obstetricians and Gynecologists, 2017). For those without prior thromboembolic events, recommendations for management from the American College of Obstetricians and Gynecologists (2017) and the American College of Chest Physicians (Bates, 2012) vary and are listed in Table 52-6. Some acceptable schemes include close antepartum maternal observation with or without prophylactic or intermediate-dose heparin, and some form of postpartum anticoagulation for 4 to 6 weeks. Sciascia and coworkers (2016) have presented preliminary salutary results with treatment with hydroxychloroquine.

Several trials have questioned the need for heparin for women with antibodies but no history of thrombosis (Branch, 2010). Although this is less clear, some recommend that women be treated if they have medium- or high-positive ACA titers or LAC activity and a prior second- or third-trimester fetal death not attributable to other causes (Dizon-Townson, 1998; Lockshin, 1995). Some report that women with recurrent early pregnancy loss and medium- or high-positive titers of antibodies may benefit from therapy (Robertson, 2006).

Described earlier (Antiphospholipid Syndrome), catastrophic antiphospholipid syndrome is treated aggressively with full anticoagulation, high-dose corticosteroids, plasma exchange, and/or intravenous immunoglobulins (Cervera, 2010; Tenti, 2016). If needed, rituximab may be added (Sukara, 2015).

Due to the risk of fetal-growth abnormalities and stillbirth, serial sonographic assessment of fetal growth and antepartum testing in the third trimester is recommended by the American College of Obstetricians and Gynecologists (2016a, 2017).

Specific Therapy in Pregnancy

There are other agents used to treat pregnant women with APS, but with no prior thromboembolic event. Aspirin, in doses of 60 to 80 mg orally daily, blocks conversion of arachidonic acid to thromboxane A_2 while sparing prostacyclin production. This reduces synthesis of thromboxane A_2 , which usually causes platelet aggregation and vasoconstriction, and simultaneously spares prostacyclin, which normally has the opposite effect. There appear to be no major side effects from low-dose aspirin other than a slight risk of small-vessel bleeding during surgical procedures. Low-dose aspirin does not reduce adverse pregnancy outcomes in antiphospholipid antibody-positive women without the complete APS syndrome (Amengual, 2015). Its use is recommended for women with SLE or APS (American College of Obstetricians and Gynecologists, 2016b).

Unfractionated heparin is given subcutaneously in dosages of 5000 to 10,000 units every 12 hours. Some prefer low-molecular-weight heparin, such as 40 mg enoxaparin (Lovenox) once daily (Kwak-Kim, 2013). With therapeutic dosing, measurement of heparin levels may be useful because clotting tests can be altered by LAC. The rationale for heparin therapy is to prevent venous and arterial thrombotic episodes. Heparin therapy also prevents thrombosis in the microcirculation, including the decidual-trophoblastic interface (Toglia, 1996). As discussed, heparin binds to β_2 -glycoprotein I, which coats the syncytiotrophoblast. This prevents binding of ACAs and anti- β_2 -glycoprotein I antibodies to their surfaces, which likely prevents cellular damage (Tsokos, 2011). Heparin also binds to antiphospholipid antibodies in vitro and likely in vivo. Aspirin plus heparin therapy is the most

efficacious regimen (de Jesus, 2014). However, heparin therapy is associated with several complications that include bleeding, thrombocytopenia, osteopenia, and osteoporosis. A description of various heparins and their adverse effects is found in Chapter 52 (Management).

Corticosteroids generally should not be used with primary APS—that is, without an associated connective tissue disorder. For women with SLE or those being treated for APS who develop SLE, corticosteroid therapy is indicated (Carbone, 1999). In such cases of secondary APS seen with SLE, the dose of prednisone should be maintained at the lowest effective level to prevent flares.

Intravenous immunoglobulin therapy (IVIG) is controversial and has usually been reserved for women with overt disease—including CAPS or heparin-induced thrombocytopenia or both (Alijotas-Reig, 2013). It is used when other first-line therapies have failed, especially in the setting of preeclampsia and fetal-growth restriction. IVIG is administered by some in doses of 0.4 g/kg/d for 5 days—total dose of 2 g/kg. This is repeated monthly, or it is given as a single dose of 1 g/kg each month. Treatment is expensive, as one course costs more than \$10,000. A recent literature review found no benefits from adding IVIG to low-dose aspirin and low-molecular-weight heparin (Tenti, 2016). And, a Cochrane review found no improvement in the live birth rate for immunotherapy given to women with recurrent pregnancy loss (Wong, 2014). Trials are needed before application of this expensive and cumbersome therapy becomes widespread.

Immunosuppression with hydroxychloroquine may be beneficial with APS by reducing the risk of thrombosis and improving pregnancy outcomes in women with APS (Mekinian, 2015; Sciascia, 2016). Hydroxychloroquine is commonly used with low-dose aspirin in the treatment of women with antiphospholipid antibodies and SLE.

Statins have been examined due to their protective effects on endothelium. In a small trial in 21 women with APS who developed fetal-growth restriction or preeclampsia, the addition of pravastatin to low-dose aspirin and low-molecular-weight heparin improved placental blood flow, preeclampsia features, and pregnancy outcomes (Lefkou, 2016). Larger trials are needed.

Treatment Efficacy

Fetal loss is common in women with APS if untreated (Rai, 1995). Even with treatment, recurrent fetal loss rates remain at 20 to 30 percent (Branch, 2003; Empson, 2005; Ernest, 2011). Shown in Table 59-6 are pregnancy outcomes from 750 treated women with primary APS—the PREGNANTS study (Saccone, 2017). Participants were treated with low-dose aspirin and prophylactic low-molecular-weight heparin starting in the first trimester. Importantly, some women with SLE and antiphospholipid antibodies have normal pregnancy outcomes without treatment. Also, it is emphasized that women with LAC and prior bad pregnancy outcomes have had liveborn neonates without treatment.

TABLE 59-6

Pregnancy Outcomes (%) in 750 Women Treated for the Antiphospholipid Syndrome—the PREGNANTS Study

Outcome	Triple-Positive (n = 20)	Double-Positive LAC Negative (n = 90)	LAC Alone (n = 54)	ACA Alone (n = 458)	Anti-β ₂ Glycoprotein (n = 128)
Livebirth	30	43	80	56	48
Stillbirth	45	34	7	21	30
Preeclampsia ^a	55	54	11	34	48

ACA = anticardiolipin antibodies; LAC = lupus anticoagulant.

^aNonsevere only.

Data from Saccone, 2017.

In a manner similar to neonatal lupus syndrome (Perinatal Mortality and Morbidity), up to 30 percent of newborns demonstrate passively acquired antiphospholipid antibodies, and thus there is concern for their adverse neonatal effects (Nalli, 2017). One group found higher rates of learning

disabilities in these children (Tincani, 2009). Simchen and colleagues (2009) reported a fourfold greater risk for perinatal strokes. Of 141 newborns followed in a European registry, the rate of preterm birth was 16 percent; low birthweight, 17 percent; and later behavioral abnormalities in 4 percent of the children. There were no cases of neonatal thrombosis (Motta, 2012). A 7-year study of 26 women who had APS with 36 pregnancies reported three cases of autism spectrum disorder, all associated with persistent neonatal anti- β_2 -glycoprotein-1 IgG antibodies (Abisror, 2013).

RHEUMATOID ARTHRITIS

This chronic inflammatory disease stems from immunological dysfunction, and infiltrating T cells secrete cytokines to cause inflammation, polyarthritis, and systemic symptoms. The cardinal feature is inflammatory synovitis that usually involves the peripheral joints. The disease has a propensity for cartilage destruction, bony erosions, and joint deformities. Pain, aggravated by movement, is accompanied by swelling and tenderness. Extraarticular manifestations include rheumatoid nodules, vasculitis, and pleuropulmonary symptoms. Other complaints are fatigue, anorexia, and depression. The American College of Rheumatology criteria for rheumatoid arthritis diagnosis are shown in Table 59-7. A score of 6 or greater fulfills the requirements for definitive diagnosis.

TABLE 59-7

Criteria for Classification of Rheumatoid Arthritis

Factor	Criteria	Score
Joint involvement	1 large—shoulder, elbow, hip, knee, ankle	0
	2–10 large	1
	1–3 small—MCP, PIP, thumb IP, MTP, wrists	2
	4–10 small	3
	>10—at least 1 small	5
Serological testing	Negative RF and negative ACPA	0
	Low-positive RF or anti-CCP	2
	High-positive RF or anti-CCP	3
Acute-phase reactants	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
Duration of symptoms	Less than 6 weeks	0
	6 weeks or longer	1

ACPA = anti-citrullinated peptide antibody; CCP = cyclic citrullinated peptides; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IP = interphalangeal joint; MCP = metacarpophalangeal joint; MTP = metatarsophalangeal joint; PIP = proximal interphalangeal joint; RF = rheumatoid factor.

Criteria established in collaboration with the American College of Rheumatology and the European League Against Rheumatism. A score ≥ 6 fulfills criteria for diagnosis.

Data from [Aletaha, 2010](#); [Shah, 2015](#).

The worldwide prevalence of rheumatoid arthritis is 0.5 to 1 percent, women are affected three times more often than men, and peak onset is from 25 to 55 years ([Shah, 2015](#)). There is a genetic predisposition, and heritability is estimated at 15 to 30 percent ([McInnes, 2011](#)). Genome-wide associated studies have identified more than 30 loci involved in rheumatoid arthritis pathogenesis ([Kurkó, 2013](#)). There is an association with the class II major histocompatibility complex molecule HLA-DR4 and HLA-DRB1 alleles ([McInnes, 2011](#); [Shah, 2015](#)). Pregnancy provides a protection against rheumatoid arthritis development, and this may be related to HLA-disparate fetal microchimerism ([Guthrie, 2010](#)). Of other influences, cigarette smoking raises the risk of rheumatoid arthritis ([Papadopoulos, 2005](#)).

Management

Treatment is directed at pain relief, inflammation reduction, protection of articular structures, and preservation of function. Physical and occupational therapy and self-management instructions are essential. Until recently, [aspirin](#) and other NSAIDs were the cornerstone of therapy, but they do not retard disease progression. According to [Shah and St. Clair \(2015\)](#), [methotrexate](#) has become the preferred disease-modifying antirheumatic drug (DMARD). NSAIDs serve as adjunctive therapy but are important to pregnancy because [methotrexate](#) is contraindicated. Conventional NSAIDs nonspecifically inhibit both cyclooxygenase-1 (COX-1), which is an enzyme critical to normal platelet function, and COX-2, which mediates inflammatory

response mechanisms. Because gastritis with acute bleeding is an unwanted side effect common to conventional NSAIDs, the more specific COX-2 inhibitors have been recommended. However, their long-term use is associated with higher risk for myocardial infarction and major vascular events (Patrono, 2016).

In one systematic review, a higher rate of cardiac malformations was found in newborns exposed to NSAIDs in the first trimester (Adams, 2012). In addition, NSAIDs are associated with early spontaneous abortions, ductus arteriosus constriction, and neonatal pulmonary hypertension. Thus, risks versus benefits of these medications must be considered.

Glucocorticoid therapy in low-to-moderate doses is given to achieve more rapid symptom control. Of these, prednisone, 7.5 mg orally daily for the first 2 years of active disease, substantively reduces progressive joint erosions (Kirwan, 1995; Shah, 2015).

The American College of Rheumatology recommends several DMARDs that may reduce or prevent joint damage (Singh, 2016). Leflunomide, like methotrexate, is teratogenic (Briggs, 2015) (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Sulfasalazine and hydroxychloroquine are safe for use in pregnancy (Partlett, 2011). These, combined with COX-2 inhibitors and with relatively low-dose prednisone—7.5 to 20 mg daily—usually successfully treat flares. In one review of drug exposure, a fourth of women with rheumatoid arthritis took a DMARD within 6 months of conception (Kuriya, 2011). During pregnancy, 4 percent of 393 pregnant women were given a category D or X medication. Methotrexate was the most common—2.9 percent.

Biological DMARDs have revolutionized the treatment of rheumatoid arthritis. These include tumor necrosis factor alpha (TNF- α) inhibitors—infliximab, adalimumab, golimumab, certolizumab, and etanercept (Shah, 2015). Their use in pregnancy is limited, and fetal safety is a concern (Makol, 2011; Ojeda-Urbe, 2013). In one drug-exposure review, 13 percent of 393 women were given a biological cytokine-inhibiting DMARD—primarily etanercept (Kuriya, 2011). In another review of 300 exposures, no fetal effects were noted (Berthelot, 2009). A prospective study of 38 women found similar results (Hoxha, 2017). In 74 women exposed to adalimumab during pregnancy, no risks were identified (Burmester, 2017). There is also little known regarding pregnancy effects of anakinra, an interleukin-1 receptor antagonist, or of rituximab, an antagonist to the B-cell CD20 antigen.

Pregnancy and Rheumatoid Arthritis

In up to 90 percent of women with rheumatoid arthritis, their disease will improve during pregnancy (de Man, 2008). Animal studies suggest this may be due to regulatory T-cell alterations (Munoz-Suano, 2012). Even so, some women develop disease during pregnancy, and others become worse (Nelson, 1997).

A downside to this respite during pregnancy is that postpartum exacerbation is common (Østensen, 2007). This may stem from postpartum alterations in innate immunity (Häupl, 2008b). In one review, a postpartum flare was more common if women were breastfeeding (Barrett, 2000a). These same investigators followed 140 women with rheumatoid arthritis during 1 to 6 months postpartum (Barrett, 2000b). There was only a modest fall in objective disease activity, and only 16 percent had complete remission. They observed that although overall disease actually did not exacerbate postpartum, the mean number of inflamed joints rose significantly.

Some studies report a protective effect of pregnancy against developing new-onset rheumatoid arthritis. In a case-control study of 88 affected women, there was a protective effect of pregnancy in the long term, but the likelihood of new-onset rheumatoid arthritis was increased sixfold during the first 3 postpartum months (Silman, 1992). Pikwer and colleagues (2009) reported a significant reduction in the risk of subsequent arthritis in women who breastfed longer than 12 months.

These findings may reflect the interference of sex hormones with several putative processes involved in arthritis pathogenesis, including immunoregulation (Häupl, 2008a,b). First, Unger and associates (1983) reported that amelioration of rheumatoid arthritis correlated with serum levels of pregnancy-associated α_2 -glycoprotein. This compound has immunosuppressive properties. Second, Nelson and coworkers (1993) noted that amelioration of disease was associated with a disparity in HLA class II antigens between mother and fetus. They suggested that the maternal immune response to paternal HLA antigens may play a role in pregnancy-induced remission of arthritis. In addition to monocyte activations, there also may be T-lymphocyte activation (Förger, 2008).

Juvenile Rheumatoid Arthritis

This group of diseases is the most frequent cause of chronic arthritis in children and persists into adulthood. In 76 pregnancies of 51 affected

Norwegian women, pregnancy had no effects on clinical presentation, but disease activity usually became quiescent or remained so during pregnancy (Østensen, 1991). Postpartum flares were common as was discussed for rheumatoid arthritis. Joint deformities often developed in these women, and 15 of 20 cesarean deliveries were done for contracted pelvis or joint prostheses. Results from a summary of 39 Polish women with juvenile rheumatoid arthritis were similar (Musiej-Nowakowska, 1999).

This arthritis portends few adverse pregnancy outcomes. The risk for preterm birth is increased, but later fetal development is normal (Mohamed, 2016; Rom, 2014; Wallenius, 2014). Disease severity in early pregnancy was predictive of preterm delivery and fetal-growth restriction in a cohort study (Bharti, 2015). Another study of 190 pregnancies followed from first trimester to delivery found patients with low disease activity scores in the first trimester were likely to have low disease activity or remission in the third trimester (Ince-Askan, 2017). In a study of 1807 births, Remaues and associates (2017) reported increased incidences of preterm birth, fetal-growth restriction, and preeclampsia.

Primary treatment of symptomatic women during pregnancy is with aspirin and NSAIDs. These are used with appropriate concerns for first-trimester effects, impaired hemostasis, prolonged gestation, premature ductus arteriosus closure, and persistent pulmonary circulation. Low-dose corticosteroids are also prescribed as indicated. Gold compounds have been administered in pregnancy (Almarzouqi, 2007).

Immunosuppressive therapy with azathioprine, cyclophosphamide, or methotrexate is not routinely used during pregnancy. Only azathioprine is considered during early pregnancy because the other agents are teratogens (Briggs, 2015). As discussed in Management, DMARDs including sulfasalazine and hydroxychloroquine are acceptable for use in pregnancy.

If the cervical spine is involved, particular attention is warranted during pregnancy. Subluxation is common, and pregnancy, at least theoretically, predisposes to this because of joint laxity. Importantly, there are anesthesia concerns during endotracheal intubation.

Following pregnancy in women with rheumatoid arthritis and its juvenile form, contraceptive counseling may include combination oral contraceptives. These are a logical choice because of their effectiveness and their potential to improve disease (Farr, 2010). That said, all methods of contraception are appropriate.

SYSTEMIC SCLEROSIS—SCLERODERMA

This is a chronic multisystem connective tissue disorder of unknown etiology. It is characterized by microvascular damage, immune system activation leading to inflammation, and excessive deposition of collagen in the skin and often in the lungs, heart, gastrointestinal tract, and kidneys. It is uncommon, displays a 5-to-1 female dominance, and typically affects those aged 30 to 50 years (Meier, 2012; Varga, 2015).

This strong prevalence of scleroderma in women and its greater incidence in the years following childbirth give credence to the hypothesis that microchimerism is involved as discussed earlier (Systemic Lupus Erythematosus) (Lambert, 2010). Artlett and coworkers (1998) demonstrated Y-chromosomal DNA in almost half of women with systemic sclerosis compared with only 4 percent of controls. Rak and colleagues (2009b) identified male microchimerism in peripheral blood mononuclear cells more frequently in women with limited versus diffuse scleroderma—20 versus 5 percent.

Clinical Course

The hallmark is overproduction of normal collagen. In the more benign form—*limited cutaneous systemic sclerosis*—progression is slow. With *diffuse cutaneous systemic sclerosis*, skin thickening progresses rapidly, and skin fibrosis is followed by gastrointestinal tract fibrosis, especially the distal esophagus (Varga, 2015). Pulmonary interstitial fibrosis along with vascular changes may cause pulmonary hypertension, which develops in 15 percent of patients. Antinuclear antibodies are found in 95 percent of patients, and immunoincompetence often develops.

Raynaud phenomenon, which includes cold-induced episodic digital ischemia, is seen in 95 percent of patients, and there may also be swelling of the distal extremities and face. Half of patients have symptoms from esophageal involvement, especially fullness and epigastric burning pain. Pulmonary involvement is frequent and causes dyspnea. The 10-year cumulative survival rate is 70 percent in those with pulmonary fibrosis, and pulmonary arterial hypertension is the main cause of death (Joven, 2010; Varga, 2015). Women with limited cutaneous disease such as the *CREST syndrome*—*calcinosis*, *Raynaud phenomenon*, *esophageal involvement*, *sclerodactyly*, and *telangiectasia*—have milder disease.

Overlap syndrome refers to systemic sclerosis with features of other connective tissue disorders. *Mixed connective tissue disease* is a term used for the syndrome involving features of SLE, systemic sclerosis, polymyositis, rheumatoid arthritis, and high titers of anti-ribonucleoprotein (RNP) antibodies

(see [Table 59-1](#)). The disorder is also termed *undifferentiated connective tissue disease* ([Spinillo, 2008](#)).

Although systemic sclerosis is incurable, treatment directed at end-organ involvement can sometimes relieve symptoms and improve function. Renal involvement and hypertension are often comorbid. At times, ACE inhibitors may be required for blood pressure control despite their known teratogenicity. *Scleroderma renal crisis* develops in up to a fourth of these patients and is characterized by obliterative vasculopathy of the renal cortical arteries. This leads to renal failure and malignant hypertension. Interstitial restrictive lung disease is common and frequently becomes life threatening. Associated pulmonary hypertension is treated with [bosentan](#) or [sildenafil](#) ([Chap. 49, Pulmonary Hypertension](#)).

Pregnancy and Systemic Sclerosis

The prevalence of scleroderma in pregnancy approximates 1 in 22,000 pregnancies ([Chakravarty, 2008](#)). These women usually have stable disease during gestation if their baseline function is good. As perhaps expected, dysphagia and reflux esophagitis are aggravated by pregnancy ([Steen, 1999](#)). Dysphagia results from loss of esophageal motility due to neuromuscular dysfunction. A decrease in amplitude or disappearance of peristaltic waves in the lower two thirds of the esophagus is seen using manometry. Symptomatic treatment for reflux is described in [Chapter 54 \(Gastroesophageal Reflux Disease\)](#).

Women with renal insufficiency and malignant hypertension have a higher incidence of superimposed preeclampsia. With rapidly worsening renal or cardiac disease, pregnancy termination should be considered. As discussed, renal crisis is life threatening and is treated with ACE inhibitors, but it does not improve with delivery ([Gayed, 2007](#)). Pulmonary hypertension usually contraindicates pregnancy.

Vaginal delivery may be anticipated, unless the soft tissue thickening wrought by scleroderma produces dystocia requiring cesarean delivery. Tracheal intubation for general anesthesia has special concerns because of limited ability of these women to open their mouths widely ([Sobanski, 2016](#)). Because of esophageal dysfunction, aspiration is also more likely, and epidural analgesia is preferable. Warming the delivery room and intravenous fluids, extra blankets, and socks and gloves are recommended to improve impaired circulation from Raynaud phenomenon. If corticosteroids were used frequently, stress doses of [hydrocortisone](#) are recommended ([Sobanski, 2016](#)).

Maternal and fetal outcomes correlate with underlying disease severity. In a review of 214 gravidas with systemic sclerosis, 45 percent had diffuse disease. Major complications included renal crisis in three and greater rates of preterm birth ([Steen, 1989, 1999](#)). [Chung and coworkers \(2006\)](#) also reported elevated rates of preterm delivery, fetal-growth restriction, and perinatal mortality. A multicenter study of 109 pregnancies from 25 centers reported higher rates of preterm delivery, fetal-growth restriction, and very-low-birthweight newborns ([Taraborelli, 2012](#)). These are likely related to placental abnormalities that include decidual vasculopathy, acute atherosclerosis, and infarcts ([Sobanski, 2016](#)).

Scleroderma may be associated with subfertility ([Bernatsky, 2008; Lambe, 2004](#)). For women who do not choose pregnancy, several reversible contraceptive methods are acceptable. However, hormonal agents, especially combination oral contraceptives, probably should not be used, especially in women with pulmonary, cardiac, or renal involvement. Due to the often unrelenting progression of systemic sclerosis, permanent sterilization is also considered.

VASCULITIS SYNDROMES

Inflammation and damage to blood vessels may be primary or caused by another disease. Immune-complex deposition is presumed to underlie most cases ([Langford, 2015](#)). Primary types include polyarteritis nodosa, temporal or giant-cell arteritis, Takayasu arteritis, Henoch-Schönlein purpura, Behçet syndrome, and cutaneous or hypersensitivity arteritis ([Goodman, 2014](#)). Small vessel vasculitides such as *granulomatosis with polyangiitis* and *eosinophilic granulomatosis with polyangiitis* have antibodies directed against proteins in the cytoplasmic granules of leukocytes—*antineutrophil cytoplasmic antibodies*—ANCA ([Pagnoux, 2016](#)).

Polyarteritis Nodosa

This necrotizing vasculitis of small and medium-sized arteries is characterized clinically by myalgia, neuropathy, gastrointestinal disorders, hypertension, and renal disease ([Goodman, 2014](#)). Of cases, approximately a third is associated with hepatitis B antigenemia ([Langford, 2015](#)). Symptoms are nonspecific, and fever, weight loss, and malaise are present in more than half of cases. Diagnosis is made by biopsy, and treatment consists of high-dose [prednisone](#) plus [cyclophosphamide](#). Vasculitis due to hepatitis B antigenemia responds to antivirals, glucocorticosteroids, and plasma exchange ([Chap. 55, Chronic Viral Hepatitis](#)).

Only a few reports describe polyarteritis nodosa associated with pregnancy. Of 12 affected gravidas, polyarteritis first manifested during pregnancy in seven, and it was rapidly fatal by 6 weeks postpartum (Owen, 1989). The diagnosis was not made until autopsy in six of the seven women. Four women continued pregnancy, which resulted in one stillborn and three successful outcomes.

Granulomatosis with Polyangiitis

Formerly Wegener granulomatosis, this is a small-vessel necrotizing granulomatous vasculitis affecting the upper and lower respiratory tract and kidney (Pagnoux, 2016). Disease frequently includes sinusitis and nasal disease—90 percent; pulmonary infiltrates, cavities, or nodules—85 percent; glomerulonephritis—75 percent; and musculoskeletal lesions—65 percent (Sneller, 1995). At least 90 percent have polyangiitis (Langford, 2015). It is uncommon and usually encountered after age 50. Koukoura and associates (2008) reviewed 36 cases in association with pregnancy and found a higher preterm birth rate. In another report, a second woman had disease-related pneumonitis, but pregnancy did not appear to affect disease activity (Pagnoux, 2011). Because subglottic stenosis is found in up to a fourth of patients, the anesthesia team is ideally consulted antepartum (Engel, 2011).

Corticosteroids are standard treatment, but azathioprine, cyclosporine, and IVIG therapy may also be used. For severe disease in the late second or third trimester, cyclophosphamide in combination with prednisolone seems acceptable.

Takayasu Arteritis

Also called *pulseless disease*, this is a chronic inflammatory arteritis affecting large vessels (Goodman, 2014). Unlike *temporal arteritis*, which develops almost exclusively after age 55, the onset of Takayasu arteritis is almost always before age 40. It is associated with abnormal angiography of the upper aorta and its main branches and with upper extremity vascular impairment. Death usually results from congestive heart failure or cerebrovascular events. Computed tomography or magnetic resonance angiography can detect this disorder before the development of severe vascular compromise. Takayasu arteritis may respond symptomatically to corticosteroid therapy, however, it is not curative. Surgical bypass or angioplasty improves survival rates.

Comorbid severe renovascular hypertension, cardiac involvement, or pulmonary hypertension worsen pregnancy prognosis (Singh, 2015). Hypertension is relatively common and should be carefully controlled. Blood pressure is most accurately measured in the lower extremity. Overall, the prognosis for pregnancy is good (Johnston, 2002). A study of 58 women with Takayasu arteritis found an elevated risk of pregnancy-related hypertension and preeclampsia but overall favorable maternal and fetal outcomes (Gudbrandsson, 2017). A study of 52 patients comparing obstetrical outcomes before and after diagnosis reported higher rates of obstetrical complications after diagnosis. These included preeclampsia, preterm birth, and fetal-growth restriction or death (Comarmond, 2015). Involvement of the abdominal aorta portends worse perinatal outcome (Sharma, 2000). Vaginal delivery is preferred, and epidural analgesia has been advocated for labor and delivery.

Other Vasculitides

Henoch-Schönlein purpura is uncommon after childhood. Tayabali and associates (2012) reviewed 20 pregnancies complicated by this vasculitis and described cutaneous lesions in three fourths. Approximately half had arthralgias. For *Behçet disease*, Gungor and colleagues (2014) described 298 pregnancies in 94 women and found higher miscarriage rates and smaller babies compared with healthy controls. Formerly *Churg-Strauss vasculitis*, eosinophilic granulomatosis with polyangiitis is rare in pregnancy (Jennette, 2013). Hot and associates (2007) described a pregnant woman who responded to IVIG therapy. Corradi and associates (2009) described an affected 35-year-old woman at term whose necrotizing vasculitis involved the heart, and she subsequently underwent cardiac transplantation. Edwards (2015) described one woman who developed postpartum relapses of this vasculitis in each of two pregnancies.

INFLAMMATORY MYOPATHIES

These are acquired and potentially treatable causes of skeletal muscle weakness with a prevalence of 1 in 100,000 persons (Dalakas, 2012). There are three major groups: polymyositis, dermatomyositis, and inclusion-body myositis, which all present with progressive asymmetrical muscle weakness. They have a variable association with connective tissue diseases, malignancy, drugs, systemic autoimmune disease such as Crohn disease, and viral, bacterial, and parasitic infections.

Polymyositis is a subacute inflammatory myopathy that is frequently associated with one of the autoimmune connective tissue disorders.

Dermatomyositis manifests as a characteristic rash accompanying or preceding weakness. Laboratory findings include elevated muscle enzyme levels in serum and an abnormal electromyogram. Confirmation is by biopsy, which shows perivascular and perimysial inflammatory infiltrates, vasculitis, and muscle fiber degeneration. It usually develops alone but can overlap with systemic sclerosis or mixed connective tissue disease.

Prevailing theories suggest that the syndromes are caused by viral infections, autoimmune disorders, or both. *Importantly, approximately 15 percent of adults who develop dermatomyositis have an associated malignant tumor.* The timing of myositis and tumor appearance may be separated by several years. The most common sites of associated cancer are breast, lung, stomach, and ovary. The disease usually responds to high-dose corticosteroid therapy, immunosuppressive drugs such as [azathioprine](#) or [methotrexate](#), or IVIG ([Dalakas, 2012](#); [Linardaki, 2011](#)).

Experiences in pregnancy are garnered mostly from case series and reviews. [Chen and colleagues \(2015\)](#) found 17 women with polymyositis/dermatomyositis in an Australian population-based cohort of births. These women had higher rates of hypertension (23 percent), antepartum hemorrhage (11 percent), cesarean delivery (88 percent), and preterm birth (35 percent). Another series of 60 women with dermatomyositis and 38 with polymyositis found that in 80 percent, pregnancy had no adverse effect on their disease. Similar results have been reported by others ([Missumi, 2015](#); [Pinal-Fernandez, 2014](#)). [Rosenzweig and colleagues \(1989\)](#) reviewed 24 pregnancy outcomes in 18 women with primary disease. Of these, a fourth had an exacerbation in the second or third trimester. In 12 in whom disease became manifest first during pregnancy, half of the eight pregnancies resulted in perinatal death, and one woman died postpartum. From their review, [Doria and associates \(2004\)](#) concluded that pregnancy outcome was related to dermatomyositis activity and that new-onset disease was particularly aggressive.

HEREDITARY CONNECTIVE TISSUE DISORDERS

Numerous inherited mutations involve genes that encode for structural proteins of bone, skin, cartilage, blood vessels, and basement membranes. Although connective tissues contain many complex macromolecules such as elastin and more than 30 proteoglycans, the most common constituents are fibrillar [collagen](#) types I, II, and III. Various mutations, some recessively and some dominantly inherited, result in clinical syndromes that include Marfan and Ehlers-Danlos syndromes, osteogenesis imperfecta, chondrodysplasias, and epidermolysis bulla. Of concern during pregnancy is the predilection for these disorders to result in aortic aneurysms ([Schoenhoff, 2013](#)).

Marfan Syndrome

This is an autosomal dominant connective tissue disorder that has a population prevalence of 1 in 3000 to 5000 ([Prockop, 2015](#)). Marfan syndrome affects both sexes equally. The syndrome is due to abnormal fibrillin—a constituent of elastin—caused by any of several different mutations in the *FBN1* gene ([Biggin, 2004](#)). Located on chromosome 15q21, the *FBN1* gene has a high mutation rate, and there are many mild, subclinical cases. A 50-percent risk of disease transmission to the offspring exists, however, the ability to predict disease severity in progeny is limited by the lack of distinct genotype-phenotype correlation and large clinical variability. Currently, preimplantation and prenatal diagnoses are limited to the 80 percent of cases in which the mutation in the *FBN1* gene is known ([Smok, 2014](#)).

In severe disease, there is degeneration of the elastic lamina in the media of the aorta. This weakness predisposes to aortic dilation or dissecting aneurysm, which appears more commonly during pregnancy ([Curry, 2014](#); [Roman, 2016](#)). Marfan syndrome complicating pregnancy is discussed in more detail in [Chapter 49, Diseases of the Aorta](#).

Ehlers-Danlos Syndrome

This disease is characterized by various connective tissue changes, including skin hyperelasticity. In the more severe types, rupture of any of several arteries can cause either stroke or bleeding. There are several disease types based on skin, joint, or other tissue involvement. Some are autosomal dominant, some recessive, and some X-linked ([Solomons, 2013](#)). Their aggregate prevalence approximates 1 in 5000 births ([Prockop, 2015](#)). Types I, II, and III are autosomally dominant, and each accounts for approximately 30 percent of cases. Type IV is uncommon but is known to predispose to preterm delivery, maternal great-vessel rupture, postpartum bleeding, and uterine rupture ([Pepin, 2000](#)). In most, the underlying molecular defect affects [collagen](#) or procollagen.

In general, women with Ehlers-Danlos syndrome reportedly have a higher frequency of preterm rupture of membranes, preterm delivery, and antepartum and postpartum hemorrhage ([Volkov, 2006](#)). That said, a recent cohort study of 314 women reported no greater risk of adverse pregnancy outcome, including preterm birth ([Sundelin, 2017](#)). Several cases of spontaneous uterine rupture have been described ([Rudd, 1983](#)). Tissue fragility

makes episiotomy repair and cesarean delivery difficult. [Hurst and colleagues \(2014\)](#) surveyed 1769 respondents of the Ehlers-Danlos National Foundation and found a preterm birth rate of 25 percent and infertility rate of 44 percent. A maternal and fetal death from spontaneous rupture of the right iliac artery has been reported ([Esaka, 2009](#)). [Bar-Yosef and associates \(2008\)](#) described a newborn with multiple congenital skull fractures and intracranial hemorrhage caused by Ehlers-Danlos type VIIC.

Osteogenesis Imperfecta

This disorder has a prevalence of 1 in 20,000 births for type I and 1 in 60,000 for type II. It is characterized by brittle bones and affected patients often have blue sclerae, hearing loss, multiple prior bone fractures, and dental abnormalities. There are up to 15 subtypes based on the causative gene and clinical picture, which ranges from mild to severe ([Van Dijk, 2010](#)). Genetic inheritance includes autosomal dominant, autosomal recessive, and sporadic patterns. Type I is the mildest form, and the typical mutation affects the *COL1A1* gene ([Sykes, 1990](#)). Type II is typically lethal in utero ([Prockop, 2015](#)).

Women with osteogenesis imperfecta, most commonly type I, may have successful pregnancies. That said, several risks in pregnancy include fractures, complications related to scoliosis with restrictive lung disease, micrognathia, brittle teeth, an unstable cervical spine, uterine rupture, and cephalopelvic disproportion. A retrospective cohort of 295 women with osteogenesis imperfecta found greater risks of antepartum hemorrhage, abruption, fetal-growth restriction, congenital malformations, and preterm birth ([Ruiter-Ligeti, 2016](#)). It is not unusual for affected women to enter pregnancy having had 20 to 30 prior fractures. Most require minimal treatment other than management of the fractures and consideration of bisphosphonates to decrease bone loss.

Depending on the type of osteogenesis imperfecta, the fetus may be affected and may also suffer fractures in utero or during delivery ([Chap. 10, Skeletal Abnormalities](#)). Prenatal diagnosis is available in many situations, if desired, and in utero stem cell therapy is being evaluated ([Couzin-Frankel, 2016](#)).

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