18 Rheumatologic diseases and antiphospholipid syndrome

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Rheumatic diseases and associated autoimmune phenomena occur frequently in women of childbearing age (1). Many of these disorders occur in women who are pregnant or desire to become so. In pregnancy, complications arising from coexisting autoimmune diseases may be minor (e.g., exacerbations of low back pain in women with HLA-B27-related spondyloarthropathy syndromes) or life-threatening [e.g., progressive glomerulonephropathy, in patients with flare of renal involvement from systemic lupus erythematosus (SLE) or systemic sclerosis (SSc), or serious pregnancy-related thromboembolic events in patients with antiphospholipid (aPL) syndromes (APS)] (2–4).

GENERAL CONSIDERATIONS

Strategies for managing certain of these patients are controversial. Although all pregnancies in women with diffuse connective tissue disorders (CTDs), e.g., SLE or SSc, should be considered high risk, little effect from pregnancy may occur in such patients with remitted or mild disease. The obstetrician and internist/rheumatologist team should construct a well-planned assessment and management strategy in anticipation of pregnancy in the setting of autoimmunity. The plan should be aimed at

1. surveillance for disease activity,
2. provision of fully adequate therapy for maternal disease, and
3. assessment of fetal growth and well-being.

Diligent search for indications of maternal or fetal compromise is required, if prompt and effective therapy is to be provided.

Management decisions should consider both the effects of pregnancy on maternal disease and the effects of the disease on the developing fetus. Active management of the pregnancy might include

1. monitored progression to delivery (5),
2. interruption by early delivery and immediate specialized neonatal care (6), or
3. therapeutic abortion, if maternal survival is jeopardized.

The optimal goal is to attain a healthy term outcome for both mother and baby.

EFFECTS OF ANTIRHEUMATIC MEDICATIONS ON THE FETUS AND PREGNANCY

Ethical considerations mandate that most of the information that is used to assess the relative risk of maternal use of a drug on the viability of a pregnancy and/or fetus is based on developmental toxicity and reproductive studies done in animal models. The results of such studies may contribute

significantly to placing a drug in U.S. Food and Drug Administration Pregnancy Category A, B, C, D, or X. Such classification exists despite the fact that extrapolating data derived from teratogenicity studies done in animals to the human situation frequently requires assumptions that may not, in certain cases, be entirely valid. “Hard” human pregnancy safety data are available for only approximately 20% of the drugs currently marketed in the United States (7). With these limitations in mind, this section will provide a summary of our current understanding of the risks associated with the use of the more common antirheumatic drugs (i.e., anti-inflammatory agents, corticosteroids, small molecules, and biologics) in the setting of pregnancy.

Nonsteroidal Anti-inflammatory Agents (reviewed in ref. (8))

Nonsteroidal anti-inflammatory agents (NSAIDs), such as celecoxib, diclofenac, and ketorolac, are FDA category C drugs. This category derives from animal reproduction studies in which an adverse effect was shown on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks. However, all other NSAIDs, including ibuprofen, are category B drugs. For these drugs, animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. The D category drugs have shown positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. However, potential benefits may warrant the use of the drug in pregnant women despite potential risks.

Results from a number of studies have indicated that NSAIDs may, although rarely, be associated with congenital malformations (9,10) and, possibly, increase the risk of spontaneous abortions (11,12). These untoward effects discourage the use of NSAIDs during the third trimester and just prior to delivery (10). Whether maternal use of selective cyclooxygenase (COX) inhibitors such as celecoxib reduces the potential risk of congenital defects in the fetus compared with NSAIDs that target both COX-1 and COX-2 is currently unclear.

Glucocorticoids

Fetal regulation of glucocorticoid exposure is achieved by the placental glucocorticoid “barrier,” which involves glucocorticoid inactivation within the labyrinth zone by 11-beta-hydroxysteroid dehydrogenase 2 (11beta-HSD2) (13). Data from Murphy et al. (14) indicate that placental 11beta-HSD2 also has the capacity to metabolize a number of synthetic corticosteroids, including beclomethasone dipropionate, betamethasone, dexamethasone, and prednisolone, but not others, such as budesonide and fluticasone propionate. In a

series of 34 pregnancies in 30 women, prednisolone use was associated with increased placental insufficiency, fetal distress, and/or stillbirths (15). Overall, however, the available data suggest that the risk associated with prenatal exposure to corticosteroids, although real, is relatively small.

Small Molecules (Slow-Acting Antirheumatic Drugs; Disease-Modifying Agents)

Among the commonly used slow-acting antirheumatic drugs (SAARDs), or small molecules, methotrexate and leflunomide have been classified as FDA pregnancy category X drugs. Animal or human studies of these drugs have demonstrated fetal abnormalities and/or investigational or marketing data have indicated human fetal risk. The risk involved in use of these drugs in pregnancy clearly outweighs the potential benefits.

Methotrexate is considered the “anchor” drug in the treatment of rheumatoid arthritis (RA). It is an abortifacient (16) that may induce a pattern of congenital abnormalities, referred to as the fetal aminopterin/methotrexate syndrome (17). This condition consists of growth retardation, and craniofacial, limb, and neurologic developmental anomalies, which may be dose dependent. In planning conception, it is important to realize that it takes approximately 20 weeks for cell-associated methotrexate to become undetectable (18). In contrast to methotrexate, there are minimal data on the effects of leflunomide on human pregnancy, and the FDA’s pregnancy category X classification of this small molecule is largely based on the drug’s known inhibitory effects on transcription and translation (19) and its demonstrated teratogenicity and embryotoxicity in animal reproductive studies. Woman who become pregnant while undergoing treatment with leflunomide are advised to reduce fetal exposure to the drug by undergoing cholestyramine elimination procedure. In a study of 64 pregnant women with RA who were treated with leflunomide during pregnancy (61 of whom received cholestyramine), no increase in adverse pregnancy outcomes was found relative to 108 pregnant women with RA not treated with leflunomide and 78 healthy pregnant women (20).

The antimalarial, hydroxychloroquine, a pregnancy category C drug, has not been associated with growth or developmental abnormalities. However, it has known potential untoward effects of retinal or ototoxicity following maternal exposure to the drug in the first trimester for the treatment of a variety of connective tissue diseases (21,22). In a randomized, controlled trial of nonpregnant lupus patients, discontinuation of hydroxychloroquine doubled the risk of an SLE flare within the subsequent 6 months (23). Taken together, the data suggest that hydroxychloroquine use in pregnant patients with connective tissue diseases is relatively safe, although not without risk. It may be prudent to continue such therapy in some SLE patients who unexpectedly become pregnant.

D-penicillamine traverses the placental barrier and can probably decrease molecular cross-linking of collagen in the fetus. Two reports describe congenital cutis laxa and associated connective tissue birth defects, probably due to D-penicillamine treatment during pregnancy (24,25). Discontinuation of

this drug is recommended prior to conception as well as during pregnancy and lactation (26,27).

Sulfasalazine is FDA approved for the treatment of RA. Isolated case reports of fetal malformations exist in the setting of maternal sulfasalazine use (28). However, a population-based case-control study (29) together with two observational studies (30,31) revealed no evidence of teratogenicity in the offspring of pregnant women with inflammatory bowel disease who had been treated with sulfasalazine. Similarly, no increase in the rate of birth defects compared with the general population was found in two more recent studies when sulfasalazine was used during pregnancy (29,32). Accordingly, sulfasalazine enjoys an FDA pregnancy category B classification. If used in a pregnant patient with an autoimmune disease (e.g., RA), it should be administered with folic acid supplementation, since this drug impairs folate absorption and metabolism (29,32).

Immunosuppressive Agents

Chlorambucil and cyclophosphamide are FDA pregnancy category D drugs. They should be discontinued during pregnancy and lactation based on their teratogenic potential (33,34). Mycophenolate mofetil is used in the treatment of lupus and in refractory RA. Although initially given pregnancy category C status, use of this drug has been associated with recurrent pregnancy loss and congenital malformations and it is now classified as a category D drug (available from: <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm093675.pdf>). Cyclosporin A is FDA approved for the treatment of RA and is used as an immunosuppressive agent in a variety of other autoimmune diseases as well. Based on the transplantation literature, the observed rate of birth defects and neonatal deaths after cyclosporine A treatment in doses of 2.5 to 5 mg/kg/day during pregnancy does not exceed that seen in the general population (35,36).

Azathioprine was not infrequently employed in the treatment of refractory RA prior to the widespread use of biologics. Azathioprine is currently used in the treatment of pregnant patients with active SLE, where toxicity concerns for the fetus obviate the use of cyclophosphamide. Solid evidence linking congenital abnormalities to azathioprine and its more active metabolite, 6-mercaptopurine (6-MP), does not exist (16,37,38). In this connection, a recent study showed no increase in the rate of birth defects in 160 children of women who were exposed to azathioprine in doses of 50 to 100 mg/day (39). This notwithstanding, it is prudent to discontinue the use of azathioprine, 6-MP, or cyclosporine A prior to conception and to avoid the use of these drugs during pregnancy, if possible, especially in the first trimester and during lactation (16,37,38).

Biologics

Inhibitors of tumor necrosis factor- α (TNF- α) have become a mainstay in the treatment of aggressive and refractory RA. Over 300 women have been exposed to the anti-TNF- α agents, infliximab, etanercept, and adalimumab during pregnancy, most during the first trimester (40). Approximately 10% of such women were treated with TNF- α inhibitors throughout pregnancy. Overall, the numbers are

too small to draw definitive conclusions. Two prospective controlled studies have shown comparable rates of malformation and miscarriage rates in women treated or not with anti-TNF- α agents (41). However, the monoclonal anti-TNF- α agents (infliximab, adalimumab) do cross the placenta and achieve significant plasma level in cord blood (42), and the role of TNF- α in embryogenesis remains incompletely understood. As of 2005, 61 congenital anomalies in 41 children born to mothers taking TNF- α inhibitors have been reported to the FDA (43). The data provided by the FDA do not permit drawing a conclusion of the actual rate of birth defects with the use of such agents, but tend to argue against the use of TNF- α inhibitors in pregnancy.

Rituximab is a monoclonal antibody, which is directed against a receptor expressed on a broad lineage of B cells that is FDA approved for the treatment of RA. Anecdotal reports indicated that rituximab can suppress neonatal B cell development and the manufacturer recommends the drug be discontinued 12 months before pregnancy (44).

Bisphosphonates

Bisphosphonates are frequently used to prevent glucocorticoid-induced osteoporosis in a number of autoimmune diseases. In a small study ($n=21$), exposure to these drugs during the first trimester did not increase the risk of abortion, birth defects, or growth retardation relative to controls (45). This notwithstanding, bisphosphonates have a half-life of approximately 10 years (in bone), may be mobilized during pregnancy, and have been shown in experimental studies to cross the placenta and accumulate in the fetus. Given the limited amount of data available on this class of drugs, use of bisphosphonates in pregnancy is not advised.

DRUGS DURING LACTATION (REVIEWED IN REF. (38))

Effects of NSAIDs on the infant are largely unknown. Aspirin is generally considered safe for nursing mothers. However, the American Academy of Pediatrics recommends that aspirin should be used cautiously by the mother during lactation because of potential adverse effects in the nursing infant (38). The SAARDs, particularly cytotoxic agents, biologics, and bisphosphonates, are not recommended during lactation (16,38,46).

RA AND PREGNANCY

Clinical Profile of RA

RA is a chronic systemic disease characterized by inflammatory changes in the synovial membranes that primarily affect small joints of the extremities in a symmetrical fashion (47). The untreated pathologic process often extends beyond the synovial tissue and can erode adjacent joint cartilage and bone, leading to deformities and disability. The underlying mechanisms preceding symptomatic onset that predispose to this disease are unknown (48), although inflammatory pathways predominate in the clinical phase. Women are affected about three times as often as men or to an even greater preponderance during childbearing ages. This sex predisposition and increasing incidence with age in adults are important clues to predisposing mechanisms (48).

Course of RA in Pregnancy

The course of this disease often improves during pregnancy, usually beginning in the first trimester, although a full remission occurs only in the minority of patients (49,50). About a quarter of patients do not improve or can worsen during the course of pregnancy. Clinically, the features of pain, objective swelling, and systemic inflammatory markers tend to diminish. Aggravating or stressor factors can increase both symptoms and objective manifestations of RA in pregnancy, as with other patients. The ameliorating influence usually diminishes within weeks following delivery and the course may even rebound, unless actively treated (49,50).

Theories of Pregnancy—Amelioration of RA

Multiple hypotheses have been advanced to explain gestational improvement in RA, as recently reviewed (49,50). Interactions in the core hormonal, immunologic, and microvascular endothelial (MVE) systems are believed to be important determinants of RA (51). These alterations may be favorably influenced during pregnancy, but reverse postpartum (52). The glucocorticoid and reproductive hormone physiology of normal pregnancy and postpartum have been described (53). However, their influences upon the neuroendocrine immune (NEI) and MVE systems have been less well documented (47). During pregnancy, the placenta produces increasing amounts of corticotrophin-releasing hormone (CRH) (54,55). A state of *physiologic* hypercortisolism with increased production and secretion of cortisol thereby results during pregnancy from placental CRH-induced hypothalamic–pituitary–adrenal (HPA) activation (53–55). The placental CRH induces HPA stimulation and also causes adrenal gland hypertrophy during pregnancy (55).

Generalized immunosuppression is not evident during pregnancy, as recently reviewed (49,50). However, the increased adrenal and ovarian hormones produced during pregnancy are believed to suppress T helper type 1 (Th1) activity, which is a pathway implicated in the pathogenesis of RA (56,57). Moreover, concentrations of estradiol (E2), as found during pregnancy, promoted proliferation of T regulatory (Treg) cells exposed to an activating stimulus (58).

The above NEI interactions favor a shift from Th1 to Th2 immunity during pregnancy that is believed to have a salutary effect on RA activity (49,50). However, recent research has called greater attention to the roles of natural killer (NK) and NK-T cells in local immune responses of pregnancy and in the production of pro-inflammatory cytokines (49,50,59). Insufficient studies have been performed of cytokine levels during normal pregnancy or in those with RA. Critical sequential (repeated) multivariate analytic techniques are needed to uncover independent predictors of inflammatory mediators and clinical features of RA activity status during pregnancy (49).

In normal pregnancies, syncytiotrophoblast microvilli, fetal cells, and cell-free fetal nucleic acids are found circulating in maternal blood and in even significantly higher levels in pre-eclamptic states (60,61). These microparticles are scavenged by antigen-presenting cells and are believed to influence cytokine production (59). Serum levels of fetal DNA correlated with arthritis improvement during pregnancy in one study (62). Microchimerism, that is, two genetically distinct and

separately derived populations of cells, can occur during pregnancy from placental release of fetal cells into the maternal circulation. Incompatibility of HLA-class II antigens between mother and fetus is suspected to influence the maternal course of RA (63). This area of HLA antigens, maternal-fetal incompatibility, and microchimerism were recently reviewed (49,50).

RA and Fertility, and Fetal Outcome in Patients

Biologic fertility is not believed to be diminished in RA, but data are few. Before the onset of RA, the length of time of unprotected intercourse until first pregnancy (fecundity) was reported to be longer in one study (64), but not in a more recent investigation (65). Fertility following the onset of RA may be influenced by lessened sexual desire in active disease, but firm data are lacking. Fetal outcome of RA patients is believed to be comparable with healthy controls (66).

Effects of Pregnancy on Risk of Developing RA

The timing of pregnancy history was studied in relation to RA onset compared with age-matched normal control women (67). The risk of developing RA was about 30% of expected incidence during the pregnancy period, but was about fivefold greater during the first 3 months postpartum. These data mirror the previously described suppression of disease activity during pregnancy and postpartum flare in women with RA. The postpartum flare was suspected to be explained by breast-feeding during that period (68), but the risk ratio of developing RA while breast-feeding for 3 months or less was not excessive in another study (69).

ANKYLOSING SPONDYLITIS AND PREGNANCY

Clinical Profile of AS

Ankylosing spondylitis (AS) mainly affects the spine and sacroiliac joints (SIJs) and also those of the girdles as well as *lower* extremities to a lesser degree (70). A striking (circa 80-fold) association occurs with the genetic factor HLA-B27 and familial aggregation is strong. The typical spinal and peripheral lesions are localized at attachments of ligaments, tendons, or joint capsules to bone, that is, enthesopathy sites. The SIJ lesions in AS are also unique, characterized by joint space narrowing, erosions, bony bridging, and late-stage intra-articular bony fusion. Underlying disease mechanisms remain obscure, but the enthesopathy feature and SIJ pathology suggest that biomechanical stresses could predispose to onset and also activate inflammatory pathways in its physiopathogenesis (70). Unlike RA, AS occurs in opposite male to female preponderance (circa 2–3M:1F), and has disease onset mainly during adolescence or early adulthood (70).

In early disease, pain and stiffness of the spine and other affected areas are the typical symptoms. In later disease, symptomatology is accompanied by restricted motion or spinal deformities and arthritis of the hips or other lower extremity joints. Disease course tends to be less progressive in women than men, and fertility is not adversely affected.

Course of AS in Pregnancy and Outcomes

Pregnancy does not improve manifestations of primary AS, that is, without associated ulcerative colitis or psoriasis (71–73). However, postpartum flares can occur during the

first 3 months after delivery up to about 90% of the AS pregnancies (73). Nevertheless, no substantial change was observed in the overall course of disease (71,72). Rather, the chronic low back, sacroiliac area, or other pain sites were aggravated during a flare. Available data indicate that AS does not adversely affect pregnancy (71,72). Worsening of symptoms in AS patients during pregnancy or postpartum may require additional rest or physical measures, for example, non-straining and stretching activities, hot showers or baths, and avoidance of impacts or undue fatigue. Lowest effective dosages of anti-inflammatory medication are advisable for limited time periods, until discontinuation in the last month of pregnancy (72).

POLYMYOSITIS DERMATOMYOSITIS AND PREGNANCY **Clinical Profile of PM-DM**

Polymyositis (PM) and dermatomyositis (DM) are acquired degenerative and inflammatory myopathies of striated muscles that belong to a spectrum of CTDs (74,75). Proximal, rather than distal, muscle weakness is the typical early feature, with skin involvement of the face, neck, and extensor articular surfaces occurring in dermatomyositis. The onset of these disorders is bimodal in age, with peaks occurring in the juvenile and middle ages. Associated malignancy occurs in a minority of adults, particularly in those older than 40 years, circa 10% to 15%.

Active PM-DM is rarely seen in association with pregnancy (76,77), due to the low incidence of this disease in childbearing ages, less than one-tenth of SLE. However, a greater number of remitted patients with prior history of juvenile-onset PM-DM may present in pregnancy or for prepregnancy counseling (76,77). Only rarely does PM-DM first develop during pregnancy. Overall, the prognosis for the mother is good (78), and the chances of fetal loss reflect the level of maternal disease (76,77). The pregnancy with PM-DM should be considered high risk for both the mother and the baby, with monitoring of disease activity in the mother and of the growth and well-being of the fetus (79).

Onset of PM-DM in Pregnancy

As stated, onset of PM-DM during pregnancy is rare, but has the poorest prognosis for the fetus (77,78,80,81). Increasing corticosteroid dosage is a standard treatment for active dermatomyositis in pregnancy, but can have deleterious maternal effects. Intravenous immunoglobulin monotherapy was successful for the outcome of mother and infant in managing a primigravida who presented with dermatomyositis in the first trimester of pregnancy (81).

PM-DM Antedating Pregnancy

A preceding history of PM-DM occurs more frequently than new disease in pregnant patients, due to the juvenile onset of this disease (78,80). One study (78) reported 10 pregnancies in 6 juvenile-onset PM-DM women. The six pregnancies without exacerbation of PM-DM resulted in term births, whereas the four pregnancies with exacerbations were associated with two abortions. Although the disease is often controlled before the onset of pregnancy, management of such patients is guided by the activity of the PM-DM. The dosage of corticosteroids should be sufficient to control disease, since exacerbation may increase fetal loss or prematurity (77,78). No neonatal effects

of PM-DM were reported in one study of surviving children nor have placental abnormalities been reported (78)).

SSC AND PREGNANCY

Clinical Profile of Systemic Sclerosis

SSc or scleroderma is an uncommon multisystem CTD that encompasses a broad spectrum of clinical entities (82). The spectrum of skin involvement ranges from the most limited form of tightening and hardening that affects only the fingers (sclerodactyly) to a diffuse form that affects proximal extremities and the trunk. Raynaud's phenomenon, or the discoloration of skin on exposure to cold or increased emotion, occurs typically before or during the earliest skin manifestations of scleroderma. An example of a limited form of SSc is the CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias).

The systemic manifestations are also broad and depend upon the degree of the three main pathologic features of this disease: (i) increased deposition of collagen in tissues, which contributes to the skin hardening; (ii) microvascular damage and dysfunction, which contribute to skin atrophy and ischemia of parenchymal tissues of the gastrointestinal tract and circulatory organs (heart, lungs, and kidneys); and (iii) immune activation leading to multiple autoantibodies (83,84). A number of other scleroderma-like fibrosing conditions can also present with clinically hard skin and tissue fibrosis, which should be differentiated from SSc (85). Such conditions and subsets of SSc can be differentiated by their clinical features and occurrence of specific autoantibodies (83,84).

Effect of Pregnancy on SSc

Pregnancy in SSc may be uneventful, with good outcomes in mother and fetus (86). Those women who have diffuse scleroderma could be at higher risk for developing cardiopulmonary or renal problems for which they should be carefully monitored. In one study of 59 women with SSc who had 91 pregnancies (87), miscarriage was increased only in those with long-standing diffuse scleroderma. Three cases of renal crisis during pregnancy occurred in that subset. Preterm births occurred in almost one-third (29%) of pregnancies, and all but one of the infants survived.

Effect of SSc on Pregnancy and Fertility

In a case-control study of women with self-reported scleroderma, spontaneous abortion was twice as high in the cases than controls (88). Pregnancy loss was also high (44%) in another series of 28 SSc patients, even though the majority (78%) of the 81 gestations had occurred before clinical disease onset (89). In another case-control study of 46 women with SSc, the odds ratio of pregnancy (abortive or completed) was lower than that in controls (90), suggesting lower fertility. In another study of 100 consecutive women with SSc (91), those with limited disease had significantly more children than those with diffuse disease, again suggesting subfertility in the latter group.

SLE AND PREGNANCY

Clinical Profile of SLE

SLE, or lupus, is distinguished from other diffuse CTD by its characteristic multiple organ system and serologic abnormal-

ities (1,4,92). Erythematous malar rash, discoid skin lesions, photosensitivity, and painless oral or nasopharyngeal ulcers are characteristic mucocutaneous features. The arthritis of SLE is non-erosive, but may show deformities, such as ulnar deviation of the fingers. Pleuritis, pericarditis, and abnormalities in renal (proteinuria or cellular casts), neurologic (seizures or psychosis), and hematologic (hemolytic anemia, leukopenia, or thrombopenia) function are also clinically typical of SLE and contribute to its classification criteria (92).

Lupus predominantly affects younger adult women, having a F:M sex ratio in the child-bearing ages of approximately 8:1. The disease is more common in non-Caucasians (1). The clinical presentation, degree of severity, and course of disease are all highly variable (4).

Diagnosis depends upon characteristic clinical manifestations together with confirmation by typical laboratory abnormalities (1-4,93). The antinuclear antibody (ANA) test is positive in essentially all SLE patients. However, it also occurs frequently in other CTD. The ANA has greater diagnostic import when either absent (tending to exclude SLE) or when present in high titers, especially with homogeneous or peripheral-staining nuclear patterns (typical of SLE). An isolated low-titer ANA lacks association with SLE or adverse pregnancy outcome, compared with high-titer ANA or the more specific antibodies that correlate with this disorder. The specific and confirmatory immunologic abnormalities of SLE include anti-native (double-stranded) DNA (nDNA) or anti-Smith (Sm) antibody. Positive lupus erythematosus (LE) cell preparation, a test that is rarely performed today, or chronic (at least 6 months) biologic false-positive test for syphilis supports, but does not confirm the diagnosis, since these serologic findings are typical but are not specific for SLE (1).

Course of SLE in Pregnancy

The outcome for pregnant women with SLE has substantially improved over the last four decades as evidenced by the decline in fetal loss from 40% in 1960 to 1965 to 17% in 2000 to 2003 (94). However, pregnancy in women with lupus can still be associated with significant maternal and fetal complications. A recent study reported that the incidence of spontaneous abortion, stillbirth, intrauterine growth retardation (IUGR), and prematurity are increased at least twofold among SLE patients compared with the normal population (95). Following the diagnosis of SLE, a greater than fourfold increase was observed in pregnancy loss compared with an individual's reproductive history before the diagnosis of lupus was made (96). Similarly, a cross-sectional analysis of adverse outcomes in 1029 pregnancies of Afro-Caribbean women in Trinidad found that SLE pregnancies were more than twice as likely to end in fetal death than non-SLE pregnancies (97). In a study of 16.7 million pregnancies, which included 13,555 lupus patients, an increased maternal mortality of more than 20-fold, 325 per 100,000 live births, was observed in SLE patients (98). The latter rate is lower than that reported in the Hopkins Cohort Study (1130 maternal deaths per 100,000 live births) (99).

There is general agreement that increased lupus activity at the time of conception increases the likelihood of a flare during gestation (99-102). Hence the recommendation: pregnancy

should be planned when SLE is in remission. In support of this recommendation, a number of reports indicate that pregnancy may not increase the risk of lupus flares in the inactive or well-controlled patient (94,98,99) and that frequency of flares may not be greater in the well-controlled lupus patient in pregnant state than in the nonpregnant state (4,93,103–105).

Exacerbation of disease has been reported in up to 50% of SLE pregnancies. In a recent case-control study, flares were observed in 18% of SLE pregnancies (106), a rate that agrees favorably with another recently published report in Argentina (107). Apart from glomerulonephritis and, less commonly, neuropsychiatric SLE, flares during pregnancy and in the postpartum period are generally mild or moderate, with a predominance of cutaneous, articular, and minor hematologic manifestations (98,100,107). Of the 309 pregnancies cited in the review by Moroni and Ponticelli (102), only 12% of SLE flares were associated with renal insufficiency. Active lupus nephritis was found to result in greater fetal loss compared with pregnancies in women without lupus nephritis and in more frequent preterm delivery in the study by Wagner et al. (108). By contrast, active renal disease had no effect on pregnancy outcome (save for low birth rate) in the study by Gladman et al. (109).

A high rate of adverse fetal events can occur in pregnant woman with lupus independent of the presence of lupus nephritis (2–4,110,111). Published data have identified several risk factors for poor pregnancy outcomes, including the presence of hypertension, the presence of lupus nephritis, the presence and degree of proteinuria (112,113), and the presence of high-titer aPL antibodies. Most American physicians do not believe that routine “prophylactic” steroid therapy to suppress disease activity during pregnancy reduces risk for maternal flare or decreases fetal wastage, unless needed to control intercurrent disease flare.

Decidual vasculopathy with necrotizing inflammatory lesions and “acute atherosclerosis” occurs in placentas from lupus patients (114,115) as well as in those with the aPL syndrome (115,116), irrespective of whether the pregnancies resulted in fetal deaths (115) or in live-born SGA infants (117). Placental size is reduced in SLE patients compared with both healthy and diabetic controls (118). Most later pregnancy losses may be attributable to placental dysfunction (114–116,118).

NEONATAL LUPUS SYNDROME AND CONGENITAL HEART BLOCK

Neonatal lupus is characterized by transient hematologic and cutaneous disorders and permanent incomplete or complete congenital heart block (CCHB). It occurs in less than 1% of the offspring of SLE patients (3,4,119–123) and only in pregnancies associated with maternal antibodies to SSA (i.e., Sjögren’s syndrome A/Ro) or SSB/La (124). These auto-antibodies are present in 25% to 32% of pregnant SLE patients (122). In one prospective study of sequential pregnancies, none of 38 infants of lupus mothers with anti-SSA (Ro) antibody had children with heart block (122). In another prospective study of 100 women with anti-Ro/SSA antibodies, 2 had infants who developed CCHB in utero. Among the 53 lupus mothers who harbored such antibodies, no case of CCHB occurred (125). Thus, most infants with this syndrome are born of asymptomatic mothers with such

antibodies who rarely develop a lupus-like disorder later in life (121,124,126).

CCHB

Substantial morbidity and mortality are associated with CCHB (123). This rare, potentially fatal complication (120,122,124,126,127) is more problematic than the non-cardiac transient abnormalities in the neonatal lupus syndrome. The CCHB is associated with myocarditis and with simultaneously present maternal anti-Ro (SSA) and anti-La (SSB) antibodies (120–122,124,126,127). If cardiac conduction defects are detected by antepartum fetal heart rate monitoring, a fetal echocardiogram should be obtained for detection of other cardiac anomalies (120–122,128). Appropriate fetal monitoring and management procedures should be employed (128).

Effects of SLE on Fertility

There are insufficient data to support a deleterious effect of SLE on fertility (129–132). Generally, fertility is not considered to be impaired in women with SLE (127,133) except in those with severe renal disease (i.e., creatinine clearance <50 ml/min) (3,119) or those exposed to cyclophosphamide or chlorambucil.

MANAGEMENT OF PREGNANT WOMEN WITH SLE

Initial Assessment and Monitoring

Management of pregnant women with SLE should be a collaborative effort between the obstetrician and the rheumatologist. The initial intake should consist of a careful history, including duration of lupus, an assessment of the patient’s current disease activity, the patient’s past obstetric history, and the timing of past pregnancies with regard to onset of lupus. If the patient is in remission, the duration of remission should be noted. Physical examination should include blood pressure measurement, cardiovascular assessment, and accurate pregnancy dating with confirmation by early obstetrical sonogram. Laboratory testing is suggested to include a complete blood count with quantitative assessment of platelets; serum creatinine (and measurement of creatinine clearance if indicated); complement 3 (C3), C4, and total complement levels; the presence of anti-dsDNA, anticardiolipin antibodies (aCLs), lupus anticoagulant (LAC), anti-SSA (Ro), and anti-SSB (La) (96). In pregnancy, baseline values of C3 and C4 are higher secondary to the permissive effect of estrogen on complement synthesis. Thus, normal levels of C3 and/or C4 do not necessarily mean that a pregnant SLE patient’s disease is quiescent.

Monitoring During Pregnancies

The complete blood count, creatinine, serum complements, anti-dsDNA, and urine with microscopic analysis should be repeated at 1- to 2-month intervals, as appropriate, during pregnancy and for 3 months postpartum (112). Beginning at 20 weeks of gestation, obstetrical visits are increased to every 2 weeks, because pre-eclampsia may occur at this point. At 28 weeks, visits should be weekly (96). aCL Should be repeated if initially negative, each trimester. The other laboratory parameter to indicate lupus flares are increases in erythrocyte sedimentation rate, lower hemoglobin, and increased activity

indices such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), European Consensus Lupus Activity Measure (ECLAM), and Lupus Activity Index (LAI). The SLEDAI and LAI have been validated as indicators of flares in pregnant SLE patients with a sensitivity of 93% and a specificity of 98% (134). Clinical and laboratory measures of disease activity are used to distinguish kidney involvement in lupus from superimposed pre-eclampsia. Early detection and aggressive management of lupus activity is the approach recommended by most rheumatologists, although determination of lupus activity during the pregnancy may be challenging (96,101,112).

Fetal Surveillance

Surveillance for fetal growth can be conducted by serial obstetrical sonography (96,135–138). This is especially important in patients with chronic hypertension in whom pre-eclampsia has developed, and in SLE mothers with aPL antibodies and a history of prior unexplained pregnancy losses (139,140). Interestingly, although spontaneous abortions were somewhat higher among those with (20.6%) than without (11.3%) renal involvement, the presence of nephropathy did not significantly alter fetal outcome overall among patients in the Mexico City study (110).

In those patients at risk for fetal congenital heart block associated with anti-SSA (Ro) and anti-SSB (La) antibodies, additional testing is required (127). This fetal condition occurs after 16 weeks of gestation. Screening by m-mode echocardiography should be started at 16 weeks and should continue weekly until delivery (127).

Treatment

(See also Effects of Antirheumatic Medications on the Fetus and Pregnancy above). The reader is referred to a number of recent reviews for a discussion of treatment of SLE in pregnancy (96,101,102).

Route and Timing of Delivery

For SLE patients, route and timing of delivery should be based upon results of fetal studies with attention to the maternal condition, especially renal and blood pressure status. The need for neonatologist attendance should be determined prior to labor by both maternal and fetal statuses. If necessary, transport should be arranged to a facility equipped for care of complicated premature infants.

APS

Definition of APS

Antibodies to anionic (negatively charged) phospholipids or phospholipid-binding proteins (aPL antibodies) are associated with recurrent, usually mid-trimester, spontaneous abortions, autoimmune thrombocytopenia, arterial and deep venous thromboses, and livedo reticularis (141–145). The definition of recurrent miscarriage has varied in the literature, with implications as to prognosis of the untreated pregnancy. The standard obstetrical definition is three or more consecutive losses. However, the definition used for most rheumatologic patients has been two or more losses (sometimes even one). Incidence of pregnancy loss increases with greater number of

preceding miscarriages, which has implications in evaluating efficacy of one or another therapeutic approach.

aPL Antibodies and Laboratory Tests for Measuring aPL Antibodies

The aPL antibodies are heterogeneous, polyclonal and may vary in titer over the course of follow-up. LACs are aPL antibodies that block phospholipid surfaces and reduce the coagulant potential of plasma, thereby prolonging the clotting time in coagulation tests based on the activated partial thromboplastin time (146). The presence of LAC is determined functionally by (i) a failure to correct the prolonged clotting time after mixing with normal platelet-free plasma and (ii) the dilute Russell's viper venom time (147). aCL Are IgG, IgM, or IgA antibodies that bind to the phospholipid cardiolipin. They do not prolong functional assessments of clotting (i.e., coagulation assays). Detection of aCL is done using an enzyme-linked immunosorbent assay (148). It is generally believed that aCL antibodies are significant only when present in the context of a thrombotic event and that anti-IgG antibodies carry greater pathogenetic significance than do those of the IgM isotype (149). The aCL antibodies are sensitive, being present in ~80% of patients with APS, but not as specific as that of LAC and have been reported in numerous infectious diseases (150–153). False-positive tests for syphilis occur with increased frequency in individuals with LAC and aCL activities using a variety of tests (e.g., the rapid plasma reagin and Venereal Disease Research Laboratories tests). These tests are not reliable indicators of clinically important outcomes. In patients with false-positive syphilis tests secondary to aPL antibodies, the fluorescent treponema antibody test remains negative (154).

Beta-2-glycoprotein I (beta2GPI) (155) is a naturally occurring anticoagulant and potential antigenic target for some aPL antibodies that are detected by solid-phase assay (156). It is thought that aPL-associated thrombosis occurs when anti-beta2GPI antibodies bind and promote dimerization of beta2GPI, which increases binding affinity for phospholipids and induces activation of complement, platelets, endothelial cells, and monocytes (157). The revised Sapporo criteria (158) for diagnosing APS (159) include the presence of LAC, or IgG or IgM aCL, or anti-beta2GPI antibodies (measured on two occasions 12 weeks apart) together with vascular thrombosis or pregnancy morbidity.

Primary and Secondary APS

aPL Antibodies without clinical symptoms may be found in otherwise healthy persons (144). Those with symptoms who do not have SLE or previously recognized clinical disorders are designated as having a "primary" APS (160). Persons with SLE or other rheumatic disorders (143–145,161,162) are designated as having "secondary" APS. Close to 50% of patients who have APS also have SLE; however, less than 10% of SLE patients have an APS (163). In lupus, APS seems to correlate with increased fetal loss (115,139,140,164) and appears to be part of the disease, rather than a separate, associated condition (162). That said, there may be a negative correlation of aPL antibodies with active lupus (115), nephrotic syndrome, and certain cutaneous forms of lupus (162). Secondary and primary APS patients have similar overall clinical and

laboratory profiles (165), although lupus patients with APS have more hemolytic anemia, endocardial valve disease, neutropenia, and lower C4 levels (165). In pregnancy, lupus disease activity and associated APS, when present, behave independently. A patient with remitted lupus and secondary aPL syndrome behaves like one with primary APS. A patient with active lupus and APS develops complications of, and needs treatment for, both diseases.

Do aPL Antibodies Predispose to Fetal Wastage?

A literature review concluded that there was an association between the prevalence of aPL antibodies in women with SLE and history of fetal loss (60%), but remained inconclusive about the relationship between aPL antibodies and miscarriages in women without SLE (4–13% losses) (144). Most studies, however, do find an association between high-level aPL antibodies and repeated, but not first, fetal loss (4,139,140,161,164,166). In one study, aCL titers remained high in aborting patients (167), which is not uncommon (142,164,168). aPL Antibodies have been detected in 5% to 15% of otherwise healthy women with a history of unexplained recurrent abortions (144).

Frequencies of aCL antibodies are low (<5%) in consecutive samples of healthy pregnant women without prior pregnancy losses, and there is no significant correlation with fetal or maternal complications (169). Moderate to high levels of aCL antibodies, of the IgG isotype, do correlate with fetal wastage, in referral, high-risk (142,164) and general obstetric (168,170) populations.

Antibodies to beta2GPI-CL complex were significantly associated with fetal complications in a large cohort of apparently healthy pregnant women followed prospectively in Japan (171). It is not known whether women with positive titers have other primary risk factors for increased fetal wastage such as clinically inactive lupus (114–116,118,166).

Fetal Complications Reported with aPL Antibodies

APS is the most common association of recurrent miscarriage syndrome, a condition that affects more than 500,000 women in the United States annually (172,173). Recurrent fetal losses due to intrauterine death at any stage of pregnancy, but particularly in the second and third trimesters of gestation, and fetal growth restriction, are characteristic complications associated with aPL antibodies (168,170,174). Recurrent, late first-trimester fetal loss after detection of fetal heart activity has also been associated with aPL antibodies (175). No fetal pathology can explain the spontaneous abortions and stillbirths. Instead, the placentas invariably show scattered areas of infarction, intervillous thrombosis, and fibrin deposition (114–118,174).

Few published data are available on the aPL antibody status of live-born infants of mothers positive for these antibodies. Most infants in whom antibody can be detected are well, except for the effects of prematurity and IUGR, although reports are anecdotal.

Maternal Complications Reported with aPL Syndromes

Maternal complications of pregnancies associated with APS can be life-threatening or fatal (172,173) and include severe pre-eclampsia (176), arterial or venous thromboses (177,178),

pulmonary hypertension (179), and the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) (163). Although aPL antibodies are not present in the majority of individuals with pre-eclampsia (180), a systematic review indicates that positivity for aPL antibodies is a highly significant risk factor for the development of pre-eclampsia (181). Over half of women presenting with obstetrical problems in the setting of APS have not had a previously recognized autoimmune disease (166) although a minority go on to develop SLE. The majority experience thrombotic vascular complications of APS (165). There may also be an increased risk of cardiopulmonary complications associated with delivery (159,160,166,167) and an increased risk of stroke in the postpartum period (176).

Treatment of Pregnancy-Related Complications Associated with aPL Antibodies

Patients with aPL antibodies should have consultations with maternal-fetal specialists, either on a preconception basis or immediately following verification of pregnancy. Patients with prior complicated aPL-related gestations should be managed by a maternal-fetal medicine team familiar with the illness and skilled in critical care. Infants of such gestations should be delivered in facilities experienced in the care of premature small infants (500–1500 g birth weight). Careful monitoring of fetal growth and uteroplacental function (5), beginning as early as the second trimester, may detect impending fetal compromise and necessitate early delivery (6).

Anticoagulation plus Low-Dose Aspirin

In an earlier uncontrolled study, fetal wastage was prevented with heparin therapy in most women with aCL and LAC antibodies who had recurrent losses or previous abnormal outcomes (182). However, successful pregnancy has been observed in SLE patients with untreated LAC (183). Full-dose heparin plus low-dose aspirin was found to provide significantly better pregnancy outcome than low-dose aspirin alone in women who had at least three consecutive pregnancy losses, without causing increased complications (184). By contrast, ongoing studies (185) indicate that treatment of aPL antibody-associated pregnancy loss with lower dose heparin and aspirin is equivalent to full-dose anticoagulation (184). As recently pointed out (186), the optimal dose of heparin to maximize benefit and minimize harm is currently unknown.

Based on controlled clinical trials (184,185,187,188), aspirin (81 mg/day) plus heparin, either unfractionated heparin or low-molecular weight heparin, is the preferred treatment for repeated fetal losses associated with aPL antibodies (172). However, a Cochrane collaboration review on the therapy of miscarriage in women with aPL recommends aspirin (81 mg/day) and unfractionated heparin (186). Therapy with aspirin and heparin should be begun immediately postconception and should be taken throughout the pregnancy (172).

Prednisone Suppression of Maternal LAC

Initial reports in the 1980s (166) suggested that high-dose prednisone therapy (e.g., 40–60 mg/day, orally) promotes fetal survival in pregnancies of women with recurrent abortions associated with LAC; however, more recent experience argues against glucocorticoid prophylaxis (4,139,189) in favor of

anticoagulation therapy as noted above (184–188,190). Importantly, lupus patients will likely need to be treated with sufficient prednisone for suppression of disease activity in pregnancy. However, there is no compelling evidence to indicate that higher doses of steroids intended for immunosuppression of aPL antibodies per se are beneficial. Furthermore, since pre-eclampsia may be associated with the presence of LAC (176,191), the indication of fluid retention and hypertension argues against the use of high-dose prednisone (189,192). Finally, the use of high-dose prednisone increases the risk of long-term complications, especially osteonecrosis and osteoporosis.

Intravenous Gamma-globulin Therapy

Anecdotal reports comprising a small number of patients have suggested improved pregnancy outcomes with experimental gamma-globulin therapy (193,194) in patients with recurrent miscarriages due to APS. However, The Pregnancy Loss Study Group reported that gamma-globulin therapy had no beneficial effect in such patients in a double-blinded randomized trial (195). Also it has been shown that immunoglobulin therapy is inferior to aspirin plus heparin in the treatment of recurrent fetal loss associated with aPL antibodies (196).

Low-Dose Aspirin

Although mini-dose aspirin (e.g., 60–100 mg daily) has been recommended for treatment in pregnant women with primary APS and history of recurrent abortions (190), recent studies suggest that aspirin therapy in the absence of anticoagulation is not sufficient to prevent fetal loss in high-risk pregnancies (184).

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