Pregnancy and the rheumatic diseases

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Rheumatic diseases occur frequently in women of childbearing age1. Many of these disorders occur in women who are pregnant or desire to become so. Collectively, problems of pregnancy are common and varied among these disorders. They may range from minor exacerbations of low back pain in women with HLA-B27 related spondyloarthropathy to life-threatening, progressive glomerulonephritis in patients with either systemic lupus erythematosus (SLE) or systemic sclerosis (SSc) who have active renal involvement or patients with serious postpartum thromboembolic events associated with antiphospholipid syndromes.

Management strategies for some of these patients are controversial. In general, pregnancy in the connective tissue disorder (CTD's) should be considered high risk, although little if any effect may occur in patients with remitted or mild disease. Nevertheless, the obstetrician and internist or rheumatologist should construct a well-planned assessment and management strategy. It should anticipate pregnancy or be initiated at its earliest stage. It should be aimed at: 1. surveillance for disease activity; 2. providing adequate therapy for maternal disease; and 3. careful, ongoing assessment of fetal growth and well-being. Careful search for indications of maternal or fetal compromise is required if prompt and effective therapy are to be provided. Management decisions should consider both effects of the pregnancy on maternal disease and of the disease on the developing fetus. More aggressive therapy might be needed for the mother's disease, being mindful of possible effects on the fetus. Active management of the pregnancy might include: 1. interruption by early delivery and immediate specialized neonatal care; 2. monitored progression to term, or 3. even therapeutic maternal survival is jeopardized, as may be appropriate2,3. The

goals to attain a healthy term outcome for both mother and baby. Space limitation allows only an outline of counseling and management issues of pregnancy and the rheumatic disorders which may be more commonly encountered. Other general references should be consulted for further information2-8. More recent literature should be consulted for technological advances over the past decade, e.g., introduction of electronic fetal heartbeat monitoring and ultrasound surveillance of antenatal status, in the care of severely premature infants in specialized critical care nurseries.

Rheumatoid Arthritis (RA) and Pregnancy

Course of RA in Pregnancy

For unexplained reasons, a high proportion (circa 75%) of RA patients substantially improve or remit during pregnancy, starting after the first month or two, and exacerbate within several months after termination (by natural or elective means) with resumption to their pre-partum status8,9. The postpartum continuance of the phenomenon may be related somewhat to the duration of breast feeding and to postponement of the menstrual return5. About a quarter of patients do not improve or can worsen during the course of pregnancy8, especially in early stages. Similar patterns of improvement or non-improvement tend to recur with subsequent pregnancies8,11, for equally unknown reasons. An increased incidence of onset of RA, within 6-12 months13 post-partum, has been reported.

Theories of Pregnancy affecting RA

Multiple hypotheses have been advanced to explain gestational improvement in RA11,14-16. Generalized theories of pregnancy-induced immunosuppression11 do not explain why gestation might dramatically improve RA8-11, by not ankylosing spondylitis17, as an example of another rheu-
matic disease. Uniform or marked depression of humoral immunity is not evident during pregnancy11. However, cell-mediated immunity is depressed, both in the fetoplacental unit and more generally in the mother11, as indicated by increased susceptibility, recurrence and virulence of certain infections18. Such depression may be due to decreased levels of T-helper cells19, suppression of polymorphonuclear (PMN) and macrophage function20, 21, immunosuppressive mediators21 or an interaction of these and other complex mechanisms.

Pregnancy-associated alpha 2-glycoprotein (PAG), synthesized by mononuclear leukocytes in the maternal decidua, was reported to be inversely correlated with an index of RA activity during pregnancy, in one study22, but not confirmed, in another study23. Elevated free cortisol levels15 and reproductive steroid hormone mechanisms16 have also been suggested as ameliorating RA. However, oral contraceptive usage, as an example of combined estrogenic-progestogenic hormone administration, does not seem to affect risk of developing RA24. Interestingly, maternal-fetal disparities for HLA-DQ antigens occurred significantly (p<0.001) more frequently in pregnancies in which RA remitted or improved (21 (81%) of 26) compared to pregnancies in which RA remained active (1 (10%) of 10)25. However, the basis for such effect is unknown, be it immunological, metabolic or other mechanisms.

Fetal Outcome in RA Patients

Increased fetal morbidity or mortality is not generally observed in RA11. However, few data are available on women with severe disease, especially those with systemic manifestations. Fetal complications may occur in such pregnancies, due to either the patient’s status or their pharmacological therapy for RA8,11,14.

Effects of RA on the Gravida

RA presumably does not influence biological fertility or the potential for childbearing26. Women with RA have been reported to have lessened sexual desire and a substantial reduction of coital frequency after onset of disease27. Subfertility, both before and after development of RA28, may be related to such sexual behavior patterns, possibly from suspected lowered androgenicity29.

Effects of Pregnancy on Risk of RA

A question has also been raised as to whether or not pregnancy is a risk factor for developing RA30. An association has been found between RA and multiparity, particularly among women having greater than four children11. Multiparity may be associated with more severe RA8. Interestingly, maternal serum DHAS decreases significantly after a first pregnancy and the duration of the effect is at least 150 months after delivery32. This longterm hormonal effect of pregnancy may affect the risk of subsequently developing RA.

Familial Predisposition and Counseling

Genetic factors probably contribute the strongest risk to developing RA13, particularly when a parent has developed crippling disease early in adult life. However, actual chances of developing RA are rather low with only one parent affected, possibly circa 10-20 percent. This risk is lower than might occur in a strictly autosomal dominant condition with full penetrance. Susceptibilities would be increased in the presence of certain HLA-DR4 or -DR1 antigenic specificities, which are significantly associated with RA13. However, such testing is not recommended for counseling on such issues.

Effects of Anti-Rheumatic Medications on the Fetus and Pregnancy

A major concern is women with RA who may wish to become pregnant or who present during gestation is the potential effects of antirheumatic medications on the fetus and outcome of pregnancy6, 14, 24. When disease activity is mild, stopping all systemic medication, including salicylates and nosteroidal anti-inflammatory drugs (NSAIDs) is optimal, but not always practical. When needed, anti-inflammatory agents should be administered in the lowest possible dose8. Local intra-articular depocorticosteroids for actively inflamed joints or use of simple analgesics, e.g., acetaminophen, may be employed, if necessary. Most mild cases are expected to improve during the course of pregnancy. For those who do not improve or who may worsen, appropriate pharmacological intervention needs to be given, based upon considerations of risks and benefits8, 14, 24.

Salicylates and NSAIDs: Aspirin crosses the placenta and can reach significant concentrations in the fetus when used in antiinflammatory dosage31. However, low doses, e.g., 60-80 mg of aspirin daily, administered in the third trimester of pregnancy, is thought to selectively inhibit maternal platelet cyclo-oxygenase without affecting neonatal platelet aggregation or pulmonary circulation32. Low dose aspirin significantly decreased production of thromboxane, but not prostacyclin, in human placental arteries studied in vitro36.

Whether or not first trimester use of aspirin can cause fetal malformations in humans is controversial33-35. A recent large scale case control study suggests no association with an increased risk of cardiac defects46. Because of aspirin’s potential effects on prolonging labor, enhancing maternal and fetal bleeding tendencies, premature closure of the ductus and other effects34, 39, its risks may outweigh benefits in the third trimester. FDA has issued a warning label to this effect41. Similar general impressions prevail with regard to NSAIDs in pregnancy11, 34, 39. Aspirin use may be preferred to NSAIDs for essential antiinflammatory therapy in pregnancy because of the greater experience with this drug37, 39. During lactation, NSAIDs with short elimination half-lives and inactive metabolites, e.g., ibuprofen, are advisable rather than salicylates or indomethacin.

Glucocorticoids: The placental enzyme, 11β-hydro-steroiddehydrogenase, inactivates cortisol and certain other
corticosteroids, allowing relative protection of the fetus\textsuperscript{42}. However, dexamethasone is not effectively inactivated by this enzyme and should be avoided for treatment of RA in the pregnant woman. Other glucocorticosteroids, e.g., prednisone, especially in low oral dosage, or intra-articularly appear to be safe for both the mother and fetus in pregnancy\textsuperscript{14, 39}, without increased malformations\textsuperscript{1}.

**Slow Acting Anti-Rheumatic Drugs (SAARDs):** Antimalarial drugs, e.g., chloroquine phosphate or hydroxychloroquine sulfate, cross the placental barrier and deposit in fetal tissue, e.g., the uveal tract\textsuperscript{39, 43}. Early intrauterine exposure to these agents may not necessarily result in congenital abnormalities or clinical visual loss\textsuperscript{44}. However, nerve deafness has been reported in children exposed to chloroquine phosphate during pregnancy\textsuperscript{45}. 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 penicillamine treatment during pregnancy\textsuperscript{46, 47}. In RA, discontinuation of this drug is recommended prior to conception and during pregnancy\textsuperscript{39, 48}.

Gold therapy, either oral or intramuscular, has not been well studied in humans\textsuperscript{8, 39, 49} and it is not known if an increased risk of teratogenicity might exist. However, it is generally not recommended to initiate or continue gold therapy for RA during pregnancy\textsuperscript{39}.

**Cytotoxic Agents:** Congenital abnormalities\textsuperscript{7, 8, 39, 42} or malformations\textsuperscript{5} may occur with cytotoxic agents sometimes used to treat RA, i.e., azathioprine, and its active metabolite, 6-mercaptopurine, methotrexate, cyclophosphamide or chlorambucil. Avoidance and discontinuation of these drugs prior to conception and during pregnancy is recommended, especially in the first trimester. Exposure to cytotoxic drugs with or without evidence of congenital malformation during pregnancy raises the issue of therapeutic termination.

### Ankylosing Spondylitis (AS) and Pregnancy

Ankylosing spondylitis manifests mainly during early adulthood in both sexes\textsuperscript{50}. Prevalence among carefully-surveyed Scandinavian women may be as high as 0.3 percent\textsuperscript{51}. The condition is believed to be milder in women than men\textsuperscript{52–54}, at least radiographically\textsuperscript{55}. Ankylosing spondylitis during pregnancy usually presents as low back or sacroiliac area pain. However, anterior uveitis, cervical spine, symphysis pubis or peripheral arthritis manifestations may be present\textsuperscript{55–58}. Available data suggest that AS does not adversely affect pregnancy\textsuperscript{17, 58, 59}, but, mechanical hindrance to normal delivery may occur in women with advanced disease\textsuperscript{58}. Fertility does not seem to be adversely affected by AS\textsuperscript{17, 56, 59}.

**Course of AS during Pregnancy**

In contrast to experience with RA, pregnancy does not generally improve manifestations of AS\textsuperscript{11, 17, 58}. In a prospective study of 27 pregnancies in 22 women with milder AS, i.e., women who had radiographic sacroiliitis but without ankylosis or spinal deformity, only 6 AS patients improved during pregnancy\textsuperscript{59}. Interestingly, all six who improved had AS associated with ulcerative colitis or psoriasis\textsuperscript{11–50}. The remaining 16 patients with “primary” AS had persisting symptoms and required NSAIDs through pregnancy\textsuperscript{55}. Temporary post-partum flare of AS may occur during the first 6 months after delivery in about 50 percent of cases\textsuperscript{17, 56, 57}, but with no substantial change in the overall course of disease.

### Management of Women with AS

Aggravation of spinal symptoms or flare of peripheral arthritis during pregnancy may require additional rest or physical therapy\textsuperscript{56, 59} as well as use of NSAIDs\textsuperscript{56} for relief of pain and stiffness or to improve nocturnal comfort. The lowest possible effective dose is advised for limited periods of time, up until the last 4 weeks of pregnancy\textsuperscript{56}. During such time, the minor analgesics may be used with safety\textsuperscript{60}, when effective.

### Systemic Lupus Erythematosus (SLE) and Pregnancy

Systemic lupus erythematosus is a disease which predominantly affects younger adult women, especially non-caucasians\textsuperscript{1} and frequently occurs during pregnancy\textsuperscript{61–65}. Fertility is not known to be impaired in most women with SLE\textsuperscript{61, 64}, excepting those with more severe renal disease\textsuperscript{62} or exposed to Cytoxan or chlorambucil therapy\textsuperscript{64}. In contrast to RA, fetal loss and prematurity tend to be increased\textsuperscript{61–65}. In SLE pregnancies, the fetus, not the parturient, has the greater risk of adverse outcome\textsuperscript{5}. Maternal mortality decreased from 17% in studies reported between 1950-1959, mainly before glucocorticoids were aggressively used, to 7.7% in reports from 1960-1969 and to 1.1% in 1970-1980 publications\textsuperscript{64}. Specialized knowledge and technologies are necessary for evaluating fetal health and should be utilized aggressively in managing the pregnant woman with lupus.

**Course of SLE in Pregnancy**

Few data are available in the modern literature on the untreated course of SLE in pregnancy. In contrast to RA, earlier studies indicated that pregnancy could exacerbate disease in up to one-third to one-half of patients or higher\textsuperscript{61–65}. However, more recent experience suggests that pregnancy may not cause adequately treated SLE to worsen\textsuperscript{65–7}. The activity of SLE at onset of gestation is clearly associated with its subsequent course\textsuperscript{61–4}.

Adequate therapy is essential to improved maternal and perinatal outcome\textsuperscript{5, 64, 65}. In the inactive or well-controlled patient, the frequency of flares may not be greater during pregnancy than in the non-pregnant state. Flares occurred in 13 to 25 percent of 80 pregnant SLE patients, depending upon the strictness of definition, as recently reported from...
New York City64. With inactive SLE at onset of gestation, flares tend to be mild and occur about equally in each trimester and postpartum8. With active SLE, flares occur more frequently, particularly in the third trimester, postpartum and following elective pregnancy termination. Clinically, mucocutaneous involvement, synovitis or hematological abnormalities are most commonly seen. However, nephritis and CNS deficits can also occur and can be more serious for both mother and fetus. The severity of flares during pregnancy does not seem different from those in the general lupus patient population and the diagnosis for maternal survival is excellent64.

In a large prospective study of 102 SLE pregnancies reported from Mexico City64, 51 (50 percent) showed activity at some time during gestation: mainly in the first trimester. Six (10.3 percent) of 58 patients with known, but inactive kidney disease had exacerbation of their renal involvement. The most frequent CNS manifestation was headache. Disease activity required between 15 and 45 mg prednisone for control in the majority of patients, but up to 60 mg was used in the setting of renal manifestations. In contrast, case-control experience reported from New York City65, 67 did not demonstrate more than an expected frequency of exacerbation of lupus during or after pregnancy. No evidence was found that pregnancy alters the long-term course of pre-existing SLE, especially when disease is maintained inactive throughout gestation.

Fetal Outcome in SLE Patients

Reported Frequencies: Fetal outcome in SLE patients has been difficult to study due to the marked heterogeneity among patients8, 61-69. However, some observations have been repeatedly made. SLE patients have a significantly higher prevalence of spontaneous abortions and stillborns, ranging from 22% to 41%7, 61-69, than normal women in the general population, estimated at 10%. In a retrospective review of reported fetal wastage over the decades from 1950 to 19808, the level had remained consistent at 27 to 28 percent. However, like maternal mortality, perinatal deaths decreased significantly from 5.4% in 1950-1959 reports to essentially none in 1970-1980 reports8. Adverse outcome may be anticipated in patients with new onset SLE during pregnancy or postpartum and those having active disease or nephritis7. 62, 74. It is not known if steroid therapy during pregnancy affects fetal wastage60. 64-69, except perhaps for decreasing perinatal deaths8.

Correlated factors: As described under antiphospholipid antibody (aPL) syndromes (vide infra), excess early pregnancy losses are associated with persistently positive IgG anticardiolipin antibody (aCL)70, despite such patients having overall milder disease activity71. Although not specific, a decidual vasculopathy with necrotizing inflammatory lesions was described in 5 of 11 placentas from lupus patients72. Also, placental size was reported to be reduced in SLE patients compared to both healthy and diabetic controls73. Most later pregnancy losses may be attributable to the pathophysiologic changes associated with the disease, expressed by placental dysfunction72,73. Thus, placental changes throughout gestation may contribute significantly to fetal compromise in SLE.

In the Mexico City of 102 pregnancies64, active and inactive SLE patients had similar abortion rates. Prematurity occurred in 58.8% of deliveries and was more frequent in patients with clinically active disease. Among term deliveries in SLE patients, a significant excess of small for gestational age infants occurred and those with features of symmetric and asymmetric intrauterine growth retardation (IUGR). High Cesarean section rates may be experienced in SLE pregnancies, with the excess number attributable to fetal distress, possibly due to IUGR.

Neonatal Lupus Syndrome and Congenital Heart Block

Neonatal Lupus Syndrome: Clinical evidence of neonatal SLE or congenital malformations75-77, associated with transplacental passage of maternal antibodies, occur rarely in SLE, estimated at less than 1% (7.62) to 3%77. However, interestingly, most infants with this syndrome are born to asymptomatic mothers who often develop a lupus-like disorder at a later time76. Neonatal lupus was estimated to occur in 25-32% of SLE pregnancies with Ro antibodies, but fewer than 3% of such pregnancies resulted in a life-threatening outcome77.

Congenital Heart Block: This manifestation is more problematic than the other transient abnormalities in the neonatal lupus syndrome. It is associated with other cardiac abnormalities and maternal anti-Ro (SSA) antibody75-77. Congenital complete heart block (CCHB) is a rare, potentially fatal complication of the neonatal lupus syndrome. Should heart block be detected on antepartum fetal heartbeat testing, a fetal echocardiogram should be obtained for detection of other cardiac anomalies which may occur in 20% of these infants.

Management of Women with SLE

Careful Monitoring: A team approach and individualized management is optimal. Specific maternal studies should be obtained immediately on diagnosis of pregnancy in SLE patients. These include CBC, 24-hour urine collection for protein and creatinine clearance, microscopic urinalysis, serum chemistry, including BUN and uric acid, C3, C4, antibody studies, including anti-dsDNA, IgG anti-cardiolipin (ACL), lupus anticoagulant, anti-SSA (Ro) and anti-SSB(LA). The CBC, urinalysis, serum chemistry, C3 and dsDNA should be repeated at approximately 4 to 6 week intervals, as appropriate, during pregnancy and for 3 months postpartum. A team approach is employed as well as serial measurement of laboratory indicators of disease activity in order to distinguish new onset or exacerbations of kidney (or other vital organ) involvement versus development of superimposed preeclampsia as early as possible and to manage them appropriately.

Steroid Administration: Corticosteroid treatment with prednisone is the mainstay in patients with active SLE64-69.
For best outcome, the disease should be maintained as inactive as possible during pregnancy with an adequate dose of prednisone and close monitoring. In experience from Mexico City, at least 10 mg prednisone daily was administered to all pregnant SLE patients throughout gestation and up to 8 weeks post-partum. Dosage was increased, if the disease was considered active. Such practice was believed to have lowered maternal morbidity, from that of an earlier series. However, prophylactic use of glucocorticosteroids is not universally recommended.

Fetal complications from prednisone or prednisolone is not a major issue when used to control disease flares. Fetal concentrations of methylprednisolone were found to be only 10 percent of maternal blood levels, due to placental steroid metabolism. In contrast, fetal and maternal concentrations of dexamethasone are equal. Insignificant levels of steroid metabolites are found in the fetal circulation. Rarely does adrenal hypoplasia of the infant occur following prolonged, high dose prednisone use during gestation.

Additional considerations relevant to steroid administration in pregnant patients include measures designed to decrease gastrointestinal consequences and screening for gestational diabetes, which should be initiated earlier and followed later than for normal patients. Patients taking prednisone should have additional parenteral hydrocortisone or methylprednisolone administered for labor and delivery. Parenteral administration should continue in the recovering Cesarean section patient until oral medication can be taken.

Despite lack of good data addressing this issue, SLE patients on steroids, particularly 30 mg or greater, or having active disease should probably refrain from breast feeding. Breast feeding is a catabolic maternal state and may predispose to postpartum exacerbation of disease. Also, potential exists for active steroids to be secreted in breast milk.

Renal Considerations: Because renal involvement is a common, potentially life-threatening manifestation of SLE, particular attention must be paid to managing such activity in pregnant women. Among 102 pregnancies reported in the Mexico City study, renal disease first develop during gestation in 3 (6.8%) of the 44 in which kidney disease was not previously present and exacerbated in 6 (10.3%) of the 58 pregnancies in which kidney disease was previously known. Exacerbations develop after 2 to 5 years inactivity of renal involvement. All 9 episodes of either onset or exacerbation of kidney disease in pregnancy were controlled with prednisone therapy within several months. No patient received cytotoxic drugs during gestation in this series, although such therapy may rarely be required with severe renal flares which fail to respond to high dose prednisone.

Fetal outcome overall did not differ significantly among patients with or without nephropathy in the Mexico City study. However, abortions were somewhat higher among those with (20.6%) than without (11.3%) renal involvement. As in most studies, the outcome of pregnancy seemed to be determined more by the activity or inactivity of disease in general than renal involvement per se.

Preeclampsia or lupus flare?: A serious challenge is differentiating preeclampsia from renal, cerebral and circulatory abnormalities encountered during a lupus flare. The former complication requires aggressive management of fluid volume and hypertension, without excessive glucocorticosteroids, whereas the mainstay of therapy for active lupus is sufficient prednisone therapy plus supportive management. Certain changes that reflect SLE activity rather than pregnancy include, synovitis, fever, pleuritis, lymphadenopathy and decreasing serum complement combined with increasing anti-dsDNA. These features need to be carefully monitored in order to treat an early or impending disease flare. Increasing dsDNA antibody titters combined with decreasing C3 levels can presage a disease flare, although decreases in complement alone may not be discriminatory.

Microscopic urine findings of significant hematuria and cellular casts as well as clinical findings of extrarenal disease can help distinguish a lupus flare from development of preeclampsia. Proteinuria, low serum complement and thrombocytopenia may occur in preeclampsia. Lupus cerebritis may require anticonvulsant therapy as part of the aggressive management. Phenobarbital is safest during the first trimester and phenytoin may be used thereafter.

Course of SLE: During pregnancy, the course is not different compared with the nonpregnant state. Management remains the same, except for with holding certain cytotoxic agents, unless administration of high dose glucocorticoids is not sufficient to control active nephritis.

Then, the addition of cytotoxic drugs is usually considered after the first trimester. Whenever possible, cytotoxic drugs should be avoided in pregnant patients. However, when informed risk versus benefit warrants use, e.g., in transplant and active SLE patients, normal pregnancies have resulted with concomitant azathioprine administration; the drug being degraded to some degree by the placenta.

Treatment of acute hypertension associated with lupus is similar to that of preeclampsia and may be accomplished with a number of agents. Systemic pressures of 140 to 160 mm Hg systolic and 90-104 mm Hg diastolic are recommended in order to maintain adequate uteroplacental perfusion.

Fetal Surveillance: Because of the high incidence of fetal wastage, early and continuing fetal surveillance is mandatory. The presence of high titer IgG aCL appears to be the most important risk marker for midtrimester pregnancy loss (vide infra), whereas active lupus is the most important risk factor for preterm birth, both possibly occurring through placental abnormalities. Ultrasound studies should include first trimester confirmation of menstrual dates, serial fetal growth measurements, including growth-adjusted sonographic age, and a mid-gestation study for detection of cardiac anomalies. Should IUGR be detected, appropriate therapy should be begun.
surveillance should be initiated. Fetal heart rate monitoring is recommended, starting at 28 weeks, with follow-up of abnormalities by contraction stress test or biophysical profile. Findings of IUGR, decreasing amniotic fluid and abnormal fetal heart rate patterns may be particularly ominous. Rarely has a bad outcome been associated with a fetal weight >2500 g.

Route and timing of delivery should be based on results of fetal studies. The need for neonatologist attendance should be determined by both maternal and fetal status prior to labor. If necessary, transport may be arranged to a facility where labor may be induced and where a nursery is equipped for care of complicated premature infants.

Antiphospholipid Antibody (aPL) Syndromes

Associations have been found between serum antibodies to anionic or negatively charged phospholipids and a variety of clinical manifestations, e.g., recurrent, usually mid-trimester spontaneous abortions (with placentae infarctions), "autoimmune" thrombocytopenia, arterial and deep venous thromboses, as well as livido reticularis, among others. The spectrum of aPL antibodies (which may vary in titer over the course of follow-up) can be assayed by various tests, e.g., the lupus anticoagulant (LAC), the VDRL indicator for a biologically false positive reaction to syphilis, i.e., the "reagin," and the more popular anticardiolipin (aCL) tests. The exact relationship between these complex antibody systems is controversial. These clinical-immunological associations are referred to as the "antiphospholipid antibody (aPL) syndromes." They may be found in otherwise healthy persons, without previously recognized clinical abnormalities, and are then designated as the "primary" aPL syndrome, or in persons with one or another rheumatic disorder, e.g., SLE, occurring as "secondary" manifestations.

The relationship of the various clinical manifestations to the different in vitro antibody assay systems is complex and incompletely understood. Assays vary in sensitivity and specificity with regard to different clinical manifestations. Also, titers may vary with activity of disease (e.g., SLE) or over the course of pregnancy. Clinical correlations are influenced by the specific testing system, the degree of titer elevation (compared to the normal range), and immunoglobulin type of the antibody. Furthermore, the antigenic epitope specificities of the various antibodies are incompletely defined. However, some guidelines for standardization of the aCL test have been provided.

Lupus Anticoagulant (LAC) — A Mismomer

The LAC behaves as an anticoagulant in vitro by virtue of its inhibition of procoagulant phospholipid-containing factors. However, in vivo, it is paradoxically associated with predisposition to thrombosis, for unknown reasons. Membranes of circulating or vascular endothelial cells may be perturbed in such aPL syndromes possibly contributing to the antibody formation. Thus, the LAC might result, to some extent, from an immunological reaction to damaged membranes, e.g., those found in platelets, abnormal placentae, abnormal blood flow, or other endothelial cell damage. Under such circumstance, it would be a marker for risk to thrombosis or fetal loss, e.g., that due to placental insufficiency, rather than a primary pathogenetic factor which needs to be treated specifically. If the antibody does contribute primarily to clinical manifestations, its mechanisms are not known. aPL’s have not been described in situ in affected placentas. Further investigation is needed in order to develop rational therapy.

Antiphospholipid Antibodies (aPL’s) and Fetal Wastage

One recent literature review concluded that the available data support an association between aPL’s and history of fetal loss in women with SLE (circa 60%), but are inconclusive in women without SLE (circa 4 to 13%), 92. Antiphospholipid antibodies have been detected in a small minority (<15%) of otherwise healthy women with a history of unexplained recurrent abortion, but inclusion of these tests is justified in work-up of such patients. Frequencies are even lower (5%) in a consecutive sample of healthy pregnant women and no significant correlation was found with fetal or maternal complications. Moderate to high levels of aCL of the IgG isotype correlate best with fetal wastage and no significant correlation was found with fetal or maternal complications. However, women who develop such antibody titers may have primary risk factors for increased fetal wastage, e.g., clinically active lupus or possibly small, infarcted inadequate placentae.

Antiphospholipid Antibodies (aPL’s) and Spectrum of Fetal-Maternal Complications

It is difficult to interpret the specific inter-relationships of aPL’s to fetal wastage or even of the high-titered IgG aCL, as well as the considerable variety of complications described for the fetus and mother. Such findings must be interpreted within the clinical setting of the individual pregnancy as well as the past obstetrical history.

Complicated pregnancies associated with aPL’s should be managed by high-risk obstetrical specialists in facilities equipped to provide fetal monitoring and full care of both premature infants and their mothers at increased risks. Certainly, lupus activity must be treated appropriately, as indicated above, and second-trimester fetal monitoring with early delivery may be useful.

Treatment of Recurrent Abortion and Antiphospholipid Antibodies (aPLA’s)

In the absence of controlled trials, it is difficult to know how best to manage pregnant women with recurrent abortion and aPL’s. Prednisone suppression of maternal LAC has been suggested as one method to promote fetal survival, but convincing data are not available. Others have found that full-dose anticoagulation with heparin can prevent fetal wastage in most women with aCL and LAC who have had recurrent losses or previous abnormal outcomes. However, successful pregnancy occurs in SLE with untreated...
Chronic gamma globulin therapy has been the usual finding. One must consider the possible deleterious effects of high-dose prednisone on fluid retention and hypertensive aspects during pregnancy. Thus, high-dose prednisone may be a “two-edged” sword, especially if administered in the lupus patient with predisposition to preeclampsia.

Polymyositis-dermatomyositis (PM-DM) and Pregnancy

Polymyositis (PM) and dermatomyositis (DM) are acquired degenerative and inflammatory diseases of striated muscles which belong to the spectrum of connective tissue disorders. Clinically, PM and DM are similar, especially in adults, and can be included within the rubric, polymyositis, which clinically does not have the evident skin involvement. These disorders may occur at all ages, with peaks in the juvenile and later middle years.

Because of the low incidence of PM-DM, i.e., about one-tenth of SLE over all ages, and its relative paucity in younger adults, the active condition is rarely seen in association with pregnancy. However, some patients with a history of prior juvenile-onset PM-DM, now in remission, may present for prepregnancy counseling or already be pregnant. Less commonly seen are patients with either prior adult-onset PM-DM who have become pregnant or those few who develop polymyositis during pregnancy. Overall, the prognosis is good for the mother, but fetal risk of morbidity and mortality is significant. The pregnancy should be considered high-risk, with careful monitoring of the mother for disease activity and the fetus for growth and well-being.

Onset of PM-DM during Pregnancy

Onset of PM-DM during pregnancy is associated with the poorest prognosis for the fetus. The eight reported cases reviewed mainly occurred in the pre-monitoring era of obstetrics and may not represent modern expectations. Fetal outcome has been variable and may not be related to steroid use. Active PM-DM seems to improve following delivery.

The Initial U.S. report of DM developing during pregnancy was a 33-year old primigravida who presented with rheumatic complaints in the first trimester. Because of a past history of pulmonary tuberculosis, she was managed without systemic corticosteroids, until after labor was induced in the 39th gestational week. A live infant weighing 2570g was delivered, but the child survived only 24 hours. The mother’s clinical findings of dermatomyositis remained otherwise unchanged after delivery. Prednisone therapy (40 mg/day) was instituted two months postpartum with favorable results.

The second case of polymyositis developing during pregnancy also presented in the first trimester. This 25-year old gravida 3 had more profound muscle weakness. She was initially treated with 60 mg prednisone daily, later increasing to 160 mg daily during the third trimester, in order to control severe muscle weakness. A stillbirth occurred at home during the eighth gestational month and the mother experienced dramatic improvement of her myositis within two days following delivery.

Another case involved a 26-year old gravida 7 who developed generalized muscle weakness in the first trimester of pregnancy. She was not admitted until 36 weeks of gestation when the diagnosis of polymyositis was confirmed. Spontaneous labor was induced by artificial rupture of membranes and a healthy baby was delivered, unlike the previous reports. Steroid therapy was withheld because of a prompt clinical improvement during the immediate postpartum period.

The above-described vignettes of new onset PM-DM during pregnancy indicate the variety of reported fetal outcomes under different therapy. Of the total eight such cases reviewed, all but one had onset of PM-DM in the first trimester. No normal, term spontaneous delivery occurred in this group of pregnancies. Only four of the nine neonates survived. One 35-year old mother at gestation, the oldest in the series, succumbed, at 6 week’s postpartum of an acute, pregnancy-induced hypertensive exacerbation, at a time of steroid withdrawal.

PM-DM Antedating Pregnancy

Pregnancy in patients with a preceding history of PM-DM has been reviewed and summarized, both in total and stratified according to childhood versus adult onset. The advantage of stratified analysis is that it segregates the juvenile onset patients who are more likely to have been in remission from polymyositis and for longer intervals prior to gestation, and have a better outcome.

Pregnancy in Juvenile Onset PM-DM: Five juvenile-onset PM-DM women with 10 pregnancies have been reviewed. All conceived during a period of remission of some months to 4 years duration. Exacerbation of PM-DM occurred in 4 pregnancies, 2 of which were post-abortion (1 spontaneous, 1 elective). The other 2 pregnancies resulted in live births. All 6 pregnancies without exacerbation of PM-DM resulted in live, term births.

Pregnancy in Adult Onset PM-DM: A total of 5 adult-onset PM-DM cases with 8 pregnancies were reviewed. Two patients conceived with active disease and both delivered at term. Six conceptions occurred during a time of inactive disease and only one resulted in an exacerbation in the third trimester. One neonatal death secondary to extreme prematurity and two spontaneous abortions occurred in these 6 pregnancies.

These experiences suggest that pregnancy outcome is worse in patients with active, adult-onset PM-DM and more...
favorable in remitted juvenile-onset disease which does not exacerbate during gestation. No neonatal effects of PM-DM have been reported in surviving children nor have placental abnormalities been reported.  

Management of Pregnancy in PM-DM

Planning for pregnancy during a period of inactive disease is desirable. During pregnancy, close monitoring both for disease flares and fetal wellbeing are indicated, extending into the postpartum period. When PM-DM is first diagnosed during pregnancy, patients should have early sonographic confirmation of menstrual dates, serial growth studies and early institution of electronic fetal heart rate monitoring.

Only one postpartum maternal death was reported in gestational PM-DM. Prednisone therapy is recommended for disease activity in the same doses sufficient for control as in non-pregnant patients. Cytotoxic agents are not recommended, particularly in the first trimester. However, when the disease is unresponsive to corticosteroids, more aggressive therapy may be considered, especially in gestational PM-DM, which is associated with high fetal mortality. Experimental therapy in such circumstances may necessitate intravenous immunoglobulins, plasmapheresis and even azathioprine.

Systemic Sclerosis (scleroderma) and Pregnancy

Systemic sclerosis (SSc) or scleroderma is a rare, multisystem CTD with prominent vascular changes which affects women more frequently than men, especially during the reproductive ages. Its incidence increases with age and overall is about one-fifth of SLE and twice that of PM-DM, making pregnancy in SSc uncommon. Severity of SSc varies considerably, from involvement of only the digital or distal extremity skin (i.e., the CREST variant) to widespread skin and vital organ involvement, i.e., diffuse scleroderma. Advanced cases may have important cardiorespiratory and renal sequelae as well as significant impairment of fertility and fetal outcome.

Raynaud’s phenomenon, which is an almost universal manifestation of SSc in women, also occurs in a primary form without associated disease. The latter occurs not infrequently in pregnancy. No serious outcomes were noted in pregnancies which occurred after onset of primary Raynaud’s. However, premature births were more common than among controls. Mean weights of full-term babies were less than babies born to control mothers, findings similar to pregnancy outcomes in women with limited SSc.

Review of Case Reports

A recent review of case reports included 21 women with SSc who had 27 pregnancies, between the ages of 18 and 40 years (median 25 1/2 years). Duration of SSc at the time of pregnancy ranged from a few months to 10 years (median 3 1/2 years) and all but 4 patients had diffuse cutaneous sclerosis, suggesting a bias toward more advanced cases having been reported.

Effect of Pregnancy on SSc: Among the 21 patients reviewed, 9 (43%) deceased as a result of complications during pregnancy, 6 with preeclampsia. Among the 12 surviving mothers, 3 (25%) also experienced preeclampsia. Postpartum renal failure was the cause of death in 5 of the 6 mothers who succumbed in a setting of preeclampsia. All had biopsy-proven renal scleroderma. Among the 9 maternal deaths, all but one (89%) had progression of disease during pregnancy, compared with 4 (33%) who progressed among the 12 survivors. In contrast, regression of SSc occurred in only one patient during two pregnancies, but progression occurred in a third pregnancy.

Effect of SSc on Pregnancy: Twenty (74%) of the 27 pregnancies progressed to live-births, two (7.4%) were aborted and five (18.5%) resulted in perinatal deaths (one intrauterine death undelivered, one still-born and three early neonatal deaths). Perinatal death did not correlate with either preeclampsia or maternal death (or both combined); two occurred in 9 surviving mothers without eclampsia and three in the remaining 12 who either had preeclampsia or succumbed. Among the 9 preeclamptic pregnancies, two resulted in both maternal and perinatal deaths, four in maternal death alone and three in survival of mother and child.

Review of Reported Series

In contradistinction to individual case reports, review of available series yields a more favorable impression of the frequency of preeclampsia, as well as maternal and perinatal survival, although abortions were relatively more common. Among 101 pregnancies, most having occurred in patients with limited scleroderma involvement, 2 maternal deaths were noted and only 6 patients experienced preeclampsia. Similarly, only 5 (5%) pregnancies resulted in perinatal death. However, spontaneous abortions occurred in 24 (24%) of the pregnancies, a higher proportion than described in the case reports, i.e., 2 (7%) of the 27 pregnancies, suggesting selection bias in the case reports.

Onset of scleroderma occurred during 9 pregnancies. Among the remaining 92 pregnancies, SSc progressed in 30, regressed in 11, was stable in 34 and unspecified in 17. Again, progression was more common than regression.

Spontaneous Abortion in Case-Control Studies

In a retrospective study of 86 SSc patients and 86 healthy controls, spontaneous abortion occurred in 50 (16.7%) of the 299 case pregnancies compared with 32 (9.6%) of the 332 control pregnancies (P < 0.05). The rate was not analyzed before or after onset of scleroderma.

In a nationwide case-controlled, paired study conducted in Britain, using a postal questionnaire, the relative risk of abortion prior to a diagnosis of scleroderma (28.7%) was twice (2.1:1) that of the controls (17.4%), 95% confidence interval 1.1 - 4.5.
interval, 1.0-4.3). This result was supported by a small-sample, controlled study (14 SSc patients) from Bath, England

Case-Control Study of Pregnancy Outcome

No statistically significant increase was found in the rate of past miscarriages, fetal deaths, maternal morbidity or mortality among 48 women with a history of scleroderma and a concomitant pregnancy compared with neighborhood mortality among 48 women with scleroderma of past miscarriages, fetal deaths, maternal morbidity or maternal disease

Management of Pregnancy in Scleroderma

Pregnancy in women with significant pulmonary, cardiac or renal involvement from SSc is not medically advised. Should pregnancy result from a failure of contraception, therapeutic abortion should be offered[18,19]. As with SLE or PM-DM pregnancies, close monitoring of both the gravida and fetus is required in the scleroderma pregnancy. In patients with renal involvement, a scleroderma renal crisis (SRC) may be difficult to distinguish from preeclampsia. Plasma renin activity is likely to be elevated in SRC and normal or decreased in preeclampsia. Episodes occurring during the first half of a viable pregnancy are more likely due to SSc whereas preeclampsia is more likely to occur in later pregnancy. If complications arise, the option of prompt termination of pregnancy at any gestational age should be considered[20]. Special attention must be given to the possible fetal effects of medications which may be necessary to control maternal disease[18,20], especially D-Penicillamine[21,48] or cytotoxic agents[49].

Other Rheumatic Disorders

Space limitations do not permit comment on other rheumatic or autoimmune disorders, which may be reviewed in other references[4,6]. However, mention is made of lymphocytic adenohypophysitis, a nonneoplastic cause of pituitary enlargement and insufficiency occurring in pregnancy, in which early diagnosis and therapy may avert life-threatening complications[25].

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References

PREGNANCY AND THE RHEUMATIC DISEASES


