IVF in the Medically Complicated Patient

Second Edition

A Guide to Management

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Contents

The Patient with Autoimmune Disease

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CONTENTS

KEY WORDS: *systemic lupus erythematosus, antiphospholipid syndrome, ovarian stimulation, infertility, IVF, pregnancy*

Background

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease characterized by the production of autoantibodies and the presence of clinical manifestations affecting multiple organs.[1] SLE is a chronic disorder with an unpredictable course, alternating between periods of flares with remissions. The prevalence ranges from 20 to 150 cases per 100,000 persons and appears to be increasing due to better diagnosis and survival. The disease occurs nine times more often in women than in men, especially in women of childbearing age, and tends to be more severe among the black population. Due to earlier diagnosis and advances in treatments, the current life expectancy of such patients has improved to approximately 80% at 15 years. Even with these advances, however, one-third of SLE-related deaths in the United States occur in patients younger than 45 years due to active disease, cardiovascular complications, or infections secondary to immunosuppressive treatment.

SLE etiology is not fully known, but a strong genetic component has been shown

TABLE 4.1

Classification Clinical and Laboratory Criteria for SLE

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Pleuritis or pericarditis
7. Renal disorder
8. Neurologic disorder
9. Hematologic disorder
10. Immunologic disorder
11. Antinuclear antibodies

Source: Adapted from Bellver J, Pellicer A. *Fertil Steril* 2009 Dec;92(6):1803–10.

Note: Four of the 11 criteria are needed for the formal diagnosis.

Genes of the major histocompatibility complex (MHC), particularly HLA-A1, B8, and DR3, have been linked to SLE, as well as certain single-nucleotide polymorphisms (SNPs) that are associated with its clinical manifestations.[2]

Ninety percent of patients affected with SLE are women, and in genetically manipulated mice the presence of two X chromosomes increases the severity of the disorder, demonstrating the strong link between SLE and gender.[2] Environmental factors, such as smoking and exposure to ultraviolet radiation, have also been associated with SLE, as well as drugs such as procainamide, hydralazine and quinidine. Epstein–Barr virus (EBV) infection may also trigger lupus, as suggested by higher viral load in patients with SLE than in controls, as well as the inability of CD8+ T cells to control EBV-infected B cells. Genetic, epigenetic, environmental, and hormonal factors contribute to the expression of inflammation and damage to vital organs and tissues, especially joints, kidneys, skin, liver, and vessel walls, with varying degrees of severity, ranging from dermatologic and musculoskeletal symptoms to anemia, serositis, nephritis, and neuropsychiatric disorders.

Due to the clinical heterogeneity of the disease, 11 clinical or laboratory criteria have been established by the American College of Rheumatology, with a minimum of 4 criteria required for the correct diagnosis of SLE (95% specificity and 85% sensitivity) (Table 4.1).

Treatment of the disease includes nonsteroidal anti-inflammatory medications, antimalarial agents, glucocorticoids and immunosuppressive/cytotoxic drugs, such as hydroxychloroquine, azathioprine, methotrexate and cyclophosphamide.

respectively, with the risk of thrombosis ranging from 0.5–30%. Catastrophic APS is rare and presents high mortality due to multiorgan failure. Although several pathogenic mechanisms explaining how aPLs cause thrombosis have been proposed, the relationship between aPLs and the wide variety of clinical findings – ranging from normal pregnancies to thromboembolism or obstetric complications – remains unclear.[4]

The revised classification criteria for APS (2006) include specific autoantibodies as a needed component of the diagnosis. The persistence of more than 12 weeks of high titers of anti–β2-glycoprotein I (ab2GP1), or immunoglobulin (Ig) M and/or IgG anticardiolipin antibodies (ACAs) or lupus anticoagulant (LAC), is required. A diagnosis of APS is made if at least one of these clinical criteria and one of the laboratory criteria are met. The clinical criteria include vascular thrombosis and pregnancy morbidity, defined as recurrent early miscarriage, fetal death, preterm delivery (< 34 weeks) caused by placental insufficiency or preeclampsia, and small size for gestational age (birth weight < 5th percentile). Even if aPLs are closely related to pregnancy complications, no consensus exists regarding which specific autoantibodies are more predictive of adverse obstetric outcome. Indeed, some retrospective studies have suggested that the simultaneous presence of LAC, ACAs, and ab2GP1 is the best predictor of at-risk patients; SLE or recurrent pregnancy loss (RPL) have been suggested by other investigators to have predictive power; and a recent prospective, multicenter study has shown that LAC is the only component of triple positivity that is strictly predictive.[5]

Impact of SLE and APS on IVF and Pregnancy

Fertility seems to be normal in women with SLE, except in cases of severe disease and ovarian failure secondary to cyclophosphamide (CTX) therapy, which is reported in up to 70% of patients. In this regard, ovarian or oocyte cryopreservation before receiving alkylating agents employed in SLE should be recommended to preserve future fertility.

Even though some retrospective studies have in the past suggested a relationship between antiphospholipid antibodies, infertility and poor assisted reproductive technique (ART) outcome, more recent studies, including from our own group, have not detected a higher prevalence of lupus anticoagulant or ACAs in infertile women compared to fertile egg donors. Indeed, neither the routine screening in the infertile population nor the anticoagulant therapy in the presence of antiphospholipid antibodies appears justified since such antibodies do not seem to affect ART outcome.

Pregnancy represents a dangerous period in which the rates of obstetrical complications are high, particularly the unexplained death of normal fetuses and recurrent spontaneous abortions prior to the 10th week of gestation, and the premature birth

TABLE 4.2

Clinical Situations in which Ovarian Stimulation Should Be Discouraged in Women with SLE

Acute flare (and the following 6–12 months)
Pulmonary hypertension or arterial hypertension
Valvulopathy or heart disease
Previous thromboembolism
Severe renal disease
Antiphospholipid syndrome and anti-Ro/anti-La antibodies

Source: Adapted from Bellver J, Pellicer A. *Fertil Steril* 2009 Dec;92(6):1803–10.

less than 6–12 months, arterial and pulmonary hypertension, renal involvement, and antiphospholipid or anti-Ro/anti-La antibodies (Table 4.2).

Impact of IVF and Pregnancy on SLE and APS

Women with SLE and APS undergoing controlled ovarian hyperstimulation (COH) and IVF are at increased risk of hormone-associated flare and venous and arterial thromboembolism due to the hypercoagulable state induced by high serum estradiol (E2) concentrations, as well as enhanced risk of maternal and fetal complications. A planned and short COH with administration of prophylactic therapy, during a remission phase of the disease, especially with corticosteroids and anticoagulants, increases the safety of the procedure and reduces the risk of these complications. Pregnancy may aggravate SLE in several ways, for instance, by increasing the likelihood of a flare, which occurs in late pregnancy or puerperium in 46.6% of cases; deteriorating renal function, especially in patients with hypertension, heavy proteinuria, or high serum creatinine concentration; and increasing the risk of maternal thrombosis, especially in the puerperium and when antiphospholipid antibodies are present.

Preparing the Patient for IVF

IVF physicians should be aware of the relationship between immunologic alterations and reproductive outcomes and therefore recommend thrombophilia screening, immunologic tests and genetic study to patients in the presence of RPL, chemical pregnancy losses, or two or three failed IVF cycles. According to the first recent world survey, the most ordered immunologic tests for RPL and repeated implantation failures (RIF) are ACAs, LAC, thyroid peroxidase antibody, and antinuclear antibody, as opposed to the less-frequently investigated NK assay, human leukocyte antigen study, Th1/Th2 study or immunophenotype assay.[6]

Women with antiphospholipid antibodies and no history of thrombosis should be treated with heparin from the beginning of the luteal phase after embryo transfer, when the risk of thrombosis is increased, and not prior to ovum retrieval. In contrast, women with antiphospholipid antibodies who have a history of thrombosis should be switched from oral anticoagulant therapy to heparin from the beginning of the ovarian stimulation. In both cases, heparin should be stopped 12–24 hours prior to ovum retrieval to reduce bleeding complications, re-started 6–12 hours later, and then maintained until the day of the pregnancy test and continued in case of pregnancy. To avoid bleeding, low-dose aspirin should be considered and interrupted 5 to 7 days before oocyte retrieval. In women with only SLE and not APS, anticoagulation is not recommended, but corticosteroids and immunosuppressants should be employed to reduce lupus flares, especially when gonadotropins are given.[8]

Management in Early Pregnancy

Pregnancy in patients with SLE/APS leads to an increased risk of maternal and fetal complications which require close monitoring with the involvement of experienced specialists. Despite the advances made in the management of these pregnancies, however, adverse outcomes, including preeclampsia, pregnancy loss, intrauterine growth restriction (IUGR), and prematurity, still remain frequent as well as placental ischemia due to poor vascularization and impairment of early placenta.

In order to prevent or promptly recognize these complications in early pregnancy, clinical and laboratory biomarkers have been investigated, but the current evidence has shown LAC to be the strongest factor predicting adverse pregnancy outcomes, especially thrombosis, in these women.[9,10] Therefore, because of this increased rate of complications, early pregnancy must be strictly followed up, with strong consideration of the fact that some immunosuppressants, such as cyclophosphamide, mycophenolate mofetil, metothrexate and leflunomide, are contraindicated in pregnancy and lactation due to their teratogenicity.

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