be relevant in patients with SLE. These include the known proapoptotic (antiendothelial cell antibodies, anti-dsDNA antibodies, lupus anticoagulant, inflammatory mediators, neutrophil proteases) and antiapoptotic (glucocorticoids, cyclosporine A) agents. One approach could involve exposure of endothelial cells in vitro to serum from patients with SLE, neutralization of known proapoptotic factors to gain an impression of their relative importance in SLE, and testing of available antiapoptotic stimuli as agents that may be useful for subsequent clinical trials. This may permit a rational advance toward therapies that will improve the prognosis in patients with SLE.

—Tihomir Štefanec
Memorial Hospital of Rhode Island


**CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS**

**Improving pregnancy outcome in women with thrombophilia**

Pregnancy is an acquired hypercoagulable state due to an increase in procoagulants, a decrease in natural anticoagulants, and impaired fibrinolysis. While this setting may prevent bleeding, the likelihood for gestational vascular complications is increased.

Recurrent fetal loss (RFL) affects 1% to 3% of women at the reproductive age and poses a significant economic and psychologic burden. RFL has long been known to be associated with acquired thrombophilic states such as antiphospholipid syndrome. Data emerging over the past 8 years suggest that hereditary thrombophilia is a major cause of RFL.

Gestational outcome in women with thrombophilia and previous RFL is poor, with an estimated live birth rate of only 20% to 50%. Heparin derivatives do not cross the placenta and are safe for women and fetus. Small-scale studies have suggested that antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) significantly improves gestational outcome.

However, in the absence of placebo-controlled trials, the optimal dose of LMWH and the role of low-dose aspirin (LDA) in this setting remained to be determined.

In a previous study, Gris et al have demonstrated that enoxaparin improves gestational outcome in women with aspirin-resistant antiphospholipid syndrome.

In this issue of Blood, Gris and colleagues present the results of an elegant study comparing 40 mg/day enoxaparin to LDA in women with thrombophilia and 1 or 2 previous pregnancy losses after 10 weeks of gestation. The results clearly show the superiority of 40 mg/day enoxaparin compared with LDA in the whole group of 160 thrombophilic women as well as in subgroups of women with the specific thrombophilic defects of factor V Leiden, factor II G20210A, and protein S deficiency. In addition, Gris et al demonstrated that the presence of antibodies to protein Z and protein Z deficiency negatively affected gestational outcome. This is in accordance with previous observations that multiple hereditary or acquired thrombophilic defects further increase the risk for fetal loss.

The optimal prophylactic dose of enoxaparin in women with thrombophilia and previous RFL as well as its impact on gestational outcome were evaluated by the LIVE-ENOX trial, which has recently been completed.

These are important times for women with RFL, as the role of thrombophilia is unveiled and a successful prophylaxis can be applied. The time has come to rigorously assess the role of antithrombotic prophylaxis in women with unexplained RFL, without thrombophilia, and in those with thrombophilia and placental vascular complications such as early onset pre-eclampsia, severe intrauterine growth restriction, and placental abruption.

—Benjamin Brenner
Israel Institute of Technology, Haifa


**GENE THERAPY**

**Lentiviral vector for hemophilia gene therapy**

For the past decade, gene therapy for hemophilia, the X-linked bleeding disorder caused by mutations in the factor VIII (F8) in hemophilia A or factor IX gene (F9 in hemophilia B), has been at the center of the efforts of many gene transfer laboratories. Several clinical trials have been carried out or are under way, and sustained, nearly curative correction of canine hemophilia A and B have been reported using viral vectors. However, clear clinical success has not yet been achieved, and continuous development of novel gene transfer vectors and an improved understanding of existing vector systems is prudent.

Just a few years ago, lentiviral vectors were developed, and they have since emerged as powerful tools for gene transfer to dividing and nondividing target cells. In particular, transduction of hematopoietic stem cells in murine models of β-thalassemia and sickle cell disease was achieved with spectacular efficiencies. The latest generation of vectors are devoid of genes from the HIV parent virus and are produced using protocols with minimal potential for accidental generation of wild-type HIV through recombination.
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