Jane Salmon, MD, and her team rewrote the knowledge banks about pregnancy loss in women with lupus and antiphospholipid syndrome. And as she heads the ten-year, multi-center, 700-patient PROMISSE Study that grew from her lab’s ground-breaking work, she intends to change even more.

The Discovery That Changed It All

Before 2001, thrombosis was widely assumed to be causing miscarriages in women with lupus and antiphospholipid antibodies. So, preventing thrombosis was standard procedure. Yet, anticoagulation treatment throughout pregnancy was not just risky and unreliable, it did not consistently result in more successful pregnancies.

Then Dr. Salmon and her team discovered why: thrombosis, in and of itself, was not responsible for pregnancy loss. The real culprit was the complement system. The complement system is a cascade of immune system responses that is supposed to help protect the body against invaders. The complement system also helps clean up and remove complexes the immune system creates in its fight.
In an experimental mouse model resembling pregnant women with lupus and antiphospholipid antibodies, the team found that the complement system was causing inflammation and damage to the placenta and developing fetus. Complement activation led to placental dysfunction and growth factor imbalance like that seen in preeclampsia, and other pregnancy complications. (Scientific details on last page, click here)

Since their initial paradigm-shifting research, Dr. Salmon and her team have demonstrated that inhibiting the inflammatory cascade triggered by the complement system prevents fetal loss, fetal growth restriction, and features of preeclampsia in experimental models.

**Real Help for Women Now**

Starting with the large lupus registries at the Mary Kirkland Center for Lupus Research, and expanding to the nationwide PROMISSE Study, the rich banks of information have already yielded results. Timing conception and monitoring known risk factors with blood tests early in pregnancy have been shown to improve outcomes. (See sidebar to right)

“In the PROMISSE Study”, Dr. Salmon notes, “We are prospectively collecting data and assessing activity of inflammatory and immune pathways throughout each patient’s pregnancy.” Over 590 patients have already been enrolled. With such a large, carefully-studied patient population, the PROMISSE Study is well poised to achieve its ultimate goal: uncover therapeutic targets and establish treatment strategies that will help women with lupus and antiphospholipid antibodies deliver healthy babies.

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**Preventing Pregnancy Loss Now**

**Conceiving Without Flares Helps**

Investigators found timing conception mattered. Women who conceived while their lupus was stable and inactive had better outcomes.

Conception during low SLE activity resulted in fewer flares for the mother during pregnancy and, most importantly, more full-term pregnancies resulting in delivery of healthy babies.

**Lupus Anticoagulant Monitoring**

The presence of lupus anticoagulant, a specific subset of antiphospholipid autoantibodies, is highly associated with poor pregnancy outcome. Women testing positive for the autoantibodies can be very closely monitored for complications.

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"The PROMISSE study is the type of research that will lead to a new textbook that will rewrite the rules about lupus pregnancy"

– Michael Lockshin, MD  
Attending Physician; 
Director, Barbara Volcker Center for Women & Rheumatic Disease; 
Co-Director, Mary Kirkland Center for Lupus Research & Care
Studies in humans and mice have shown that the balance of circulating angiogenic and antiangiogenic factors may predict preeclampsia in patients with lupus as well as in healthy pregnant women. Pregnancy does not abrogate the IFN signature in lupus patients. Preeclampsia (which is more frequent in SLE), in and of itself, is not associated with increase in type I IFN. Elevated type I IFN signature may help distinguish SLE flare from PE in pregnant patients.

Next steps: Identification of complement components and downstream effectors that trigger damage to the maternal-fetal unit that are associated with antiphospholipid antibodies and lupus will provide the basis for new clinical trials of therapies to improve pregnancy outcomes and reduce pregnancy complications in these women and, potentially, also for women without an underlying autoimmune disease.

Increased complement activation causes and/or perpetuates placental inflammation during pregnancy.

Experiments inhibiting the complement cascade in in vivo mouse models can block fetal loss and growth restriction associated with antiphospholipid antibodies.

Complement activation leads to elevated levels of circulating anti-angiogenic factors and complement inhibition prevents increased levels of antiangiogenic factors, placental dysfunction, and fetal growth restriction in a mouse model of antiphospholipid syndrome.

Complement component C5, and particularly its cleavage product C5a, act as key mediators of fetal loss.

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