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Preventing antiphospholipid antibody-induced fetal loss: a new idea.

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Editorial

Women with antiphospholipid antibodies (aPL) lose pregnancies. The reason they do is unknown. Current hypotheses suggest that fetal loss is caused by placental vascular occlusion, which itself results from excess procoagulant activity (1), opposed placental anticoagulants (2), inhibited endothelial PGI_2 production (3), or coagulation-independent vasculopathy (4). Each hypothesis is based on descriptive data; none has been critically tested. The hypotheses justify therapies currently offered to women: heparin and aspirin, on the assumption that abnormal coagulation causes placental failure, or prednisone, on the assumptions that aPLs are harmful and can be suppressed (5). These treatments have had limited success.

There are animal models for the aPL syndrome (6, 7). Pregnant mice with aPL resorb fetuses, providing a surrogate for aPL-associated human fetal loss. But fetal resorption is not specific for aPL. CBA crossed with DBA/2 mice do not have aPL and also abort (8). Whether the mechanisms in aPL-induced and in CBA × DBA/2 aborting mice differ at the placental level is unknown.

In this issue of *The Journal* Fishman et al. abandon conventional hypotheses and introduce new ideas about aPL-induced fetal death (9). The authors build on data derived from the CBA × DBA/2 mice: these pregnant mice have low plasma IL-3, and treatment with IL-3 prevents their abortions (8, 10). Fishman et al. demonstrate that aPL mice, too, are IL-3 deficient and respond, spectacularly, to exogenous IL-3. Since control animals have giant fetuses and early deliveries, the likely mechanism is that IL-3 induces trophoblast growth ample enough to compensate for placental ischemic atrophy. Alternatively, because thrombocytopenia and the lupus anticoagulant returned to normal in treated animals, IL-3 might have an unrecognized primary effect on coagulation. Elsewhere the same investigators showed that both aspirin and low molecular weight heparin partially prevent fetal resorptions (11), and clinicians believe these drugs are effective in humans. Thus data support the hypothesis that hypercoagulation is an important element of murine aPL-induced fetal loss but do not prove that it is a primary cause. That IL-3 corrects it suggests that hypercoagulation is not primary.

The authors are tempted to recommend IL-3 treatment trials for humans, but there are three caveats. First, it is not possible to predict which women bearing aPL will have compromised pregnancies; certainly not all do. Second, placental dysfunction in an individual patient is not quantifiable. Hence the treating physician can neither calibrate the IL-3 dose nor accurately decide when or in whom to intervene. Finally, IL-3 is far more than a trophoblast growth factor and will certainly have other effects on the mother and her child.

By suggesting a cytokine/growth factor intervention, Fishman et al. free us of the stultifying notion that coagulation abnormalities are the primary abnormality and the only reasonable target for medical intervention. Investigators and clinicians now have new worlds to explore.

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References

1. Out, H. J., C. D. Kooijman, H. W. Bruinse, and R. H. Derksen. 1991. Histopathologic findings in placentae from patients with intrauterine fetal death and anti-phospholipid antibodies. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 41:179–186.

2. Sammaritano, L. R., A. E. Gharavi, C. Soberano, R. A. Levy, and M. D. Lockshin. 1992. Phospholipid binding of antiphospholipid antibodies and placental anticoagulant protein. *J. Clin. Immunol.* 12:27–35.

3. Rustin, M. H., H. A. Bull, S. J. Machin, D. A. Isenberg, M. L. Snaith, and P. M. Dowd. 1988. Effects of the lupus anticoagulant in patients with systemic lupus erythematosus on endothelial cell prostacyclin release and procoagulant activity. *J. Invest. Dermatol.* 90:744–748.

4. Lockshin, M. D., and C. H. Letendre. 1992. Antiphospholipid antibody-lupus anticoagulant workshop. *Arthritis Rheum.* 35:1234–1237.

5. Cowchock, F. S., E. A. Reece, D. Balaban, D. W. Branch, and L. Plouffe. 1992. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. *Am. J. Obstet. Gynecol.* 166:1318–1323.

6. Bakimer, R., P. Fishman, M. Blank, B. Sredni, M. Djaldetti, and Y. Shoenfeld. 1992. Induction of primary antiphospholipid syndrome in mice by immunization with a human monoclonal anticardiolipin antibody H3. *J. Clin. Invest.* 89:1558–1563.

7. Gharavi, A. E., L. R. Sammaritano, J. Wen, and K. B. Elkon. 1992. Induction of antiphospholipid autoantibodies by immunization with β_2 glycoprotein I (apolipoprotein H). *J. Clin. Invest.* 90:1105–1109.

8. Chaouat, G., E. Menu, D. A. Clark, M. Dy, M. Minkowski, and T. G. Wegmann. 1990. Control of fetal survival in CBA × DBA/2 mice by lymphokine therapy. *J. Reprod. Fertil.* 89:447–458.

9. Fishman, P., E. Falach-Vaknine, R. Zigelman, R. Bakimer, B. Sredni, M. Djaldetti, and Y. Shoenfeld. 1993. Prevention of fetal loss in experimental antiphospholipid syndrome by in vivo administration of recombinant interleukin-3. *J. Clin. Invest.* 91:1834–1837.

10. Fishman, P., R. Bakimer, M. Blank, D. Sredni, M. Djaldetti, and Y. Shoenfeld. 1992. The putative role of cytokines in the induction of primary anti-phospholipid syndrome in mice. *Clin. Exp. Immunol.* 90:266–270.

11. Y. Shoenfeld. 1992. Induction of experimental primary and secondary antiphospholipid syndromes in naive mice. *Am. J. Reprod. Immunol.* 28:219–221.

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