Editorial

Improving Management of Pregnancy in Antiphospholipid Antibody-Positive Women

Pregnancy is a "risky business" for antiphospholipid antibody (aPL)-positive women, bringing increased occurrence of both adverse pregnancy outcome and thrombosis. One or more of the manifestations of aPL — early abortion, fetal death, and fetal growth restriction — occur in as many as 20% of women carrying the lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL)[1], whereas the true prevalence of maternal thrombosis during pregnancy and the postpartum period remains unknown. Guidelines for prevention of obstetric events have been developed[2,3] based on results of a number of clinical trials dealing with aPL-positive women with recurrent abortion (as reviewed[4]); however, no real consensus exists on the best way to treat these women to increase their rate of successful pregnancy. Clinical trials of prevention and treatment of thrombosis in pregnant and postpartum women are lacking, and no specific guideline is available.

There are several reasons for these uncertainties.

1. CLINICAL HETEROGENEITY

Patients may have systemic lupus erythematosus (SLE) or other (autoimmune) diseases or they may be asymptomatic. Patients' pregnancy history may be very variable, ranging from women pregnant for the first time to those in whom all obstetric events have been adverse ones. Also patients' thrombotic history may vary considerably. Each factor influences the decision on how to treat aPL-positive patients during pregnancy and multiplies the possible scenarios in clinical trials.

2. PHYSICIAN HETEROGENEITY

The clinical heterogeneity of patients is mirrored by the many specialties of involved physicians, including hematology, rheumatology, obstetrics, neurology, cardiology, and nephrology, a list that is far from complete. The question, therefore, is whether these different clinical backgrounds influence the choice of treatment for an individual patient.

3. LABORATORY HETEROGENEITY

The updated laboratory criteria for definite antiphospholipid syndrome (APS) require the presence, alone or in various combinations, of LAC, IgG/IgM aCL, and anti-$ß_2$-glycoprotein I antibodies (anti-$ß_2$-GPI)[5]. Most clinical trials of prevention of recurrent abortion were performed in the 1990s, when anti-$ß_2$-GPI was not a criterion of APS. Thus, the best treatment of patients carrying anti-$ß_2$-GPI may only be inferred from studies on LAC and/or aCL-positive patients. IgG and IgM isotypes are considered equally important as laboratory criteria of APS, although 2 systematic reviews showed the G rather than the M isotype to be a risk factor for thrombosis for both aCL and anti-$ß_2$-GPI[6,7].

The antibody titer is another important issue. The updated criteria require the ELISA titer to be above an established cutoff[5]. However, the individual patient may have a low antibody titer: should this patient be dealt with similarly or differently from patients with high aPL titers? Antibody presence and titer may change over time: should a patient be treated differently if she turns out aPL-negative during pregnancy? Another unsolved issue deals with the clinical significance of single versus multiple aPL positivities. In other words, no solid information is available for the risk of obstetric and thrombotic events in patients with either a single or multiple aPL antibodies.

An emerging concept is that the greater the number of positive aPL, the higher the risk of thrombosis[8,9]. Again, no information is available regarding pregnancy outcome according to number of positive assays. Standardization of LAC, aCL, and anti-$ß_2$-GPI measurement is far from optimal, so that the definition of positive versus negative LAC and the quantification of aCL and anti-$ß_2$-GPI may vary considerably in different laboratories.

Finally, antibodies other than LAC, aCL, and anti-$ß_2$-GPI have been described, whose pathogenic role in pregnancy still has to be established. Among them, there are antibodies to prothrombin, annexin AV, and protein S[10].

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Should these antibodies be investigated in women with poor obstetric history and/or thrombosis during pregnancy? Should their presence influence the treatment choice? Again, no answer to these questions.

FIRST STEP TO IMPROVING MANAGEMENT

In their article in this issue of *The Journal*, Spitzer and coworkers tackle some of the issues highlighted above[11]. Their survey focused on postpartum management of thrombotic risk of aPL-positive women, a scenario that has not been the object of clinical trials and that poses critical therapeutic choices to physicians. The authors developed 6 "real-life" cases that range from an APS patient with pregnancy loss treated with aspirin to an aPL-negative woman with previous deep vein thrombosis related to oral contraceptive use. Antibody specificity, titers, and isotypes varied among the different cases, as well as the patients' thrombotic and obstetric history. Some patients had either primary or secondary APS.

A number of physicians from different specialties were asked whether they would recommend postpartum antithrombotic therapy in each scenario and, if so, to choose from a list of treatment options. Responding physicians (in decreasing order of prevalence) were obstetricians, rheumatologists, hematologists/internists, and gynecologists, who either treated patients similar to those in our survey or referred them to other specialists.

A first interesting finding from the survey was that rheumatologists — irrespective of the clinical scenario — were the least prone to administer antithrombotic therapy, while in all but one case, hematologists/internists were the most inclined to order this treatment. A second interesting finding was that no case was met with complete agreement with respect to the treatment choice. The highest degree of consensus regarded case number 1 (APS patients with recurrent pregnancy loss treated with aspirin during pregnancy), for which about 70% of physicians did not suggest treatment during the postpartum period. Nevertheless, about 20% of physicians proposed postpartum prophylactic heparin for the same hypothetical patient. More diversified treatment proposals were given in the other cases.

These findings highlight the lack of consensus among tertiary care-based practitioners, who appear to have different perceptions of the thrombotic risk of aPL-positive women in the postpartum period. Prophylactic heparin was the most commonly chosen treatment, each other therapeutic possibility (aspirin alone or in combination with heparin at prophylactic or therapeutic dosage, or heparin alone at therapeutic dosage) being the choice of less than 10% of the interviewed physicians. This suggests that there is good but not complete transferability into daily practice of results of clinical trials, most of which propose low molecular weight heparin at prophylactic dosage for aPL-positive women with recurrent pregnancy loss to increase their live birth rate.

The results of Spitzer, *et al*'s survey also suggest the need to improve harmonization of treatment by means of well designed trials. Ideally, these studies should enroll patients before conception and follow them until the end of the postpartum period. The main aims of such studies should take the following into account during pregnancy and post partum: live birth rate, maternal and neonatal morbidity, and conception rate and incidence of maternal thrombosis. Efforts should also be made to stratify patients according to the type, number, and titer of aPL antibodies.

This survey represents the first step towards improvement of the management of aPL-positive women at a potentially critical time of their life.

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REFERENCES

1. Lynch A, Marlar R, Murphy J, et al. Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study. Ann Intern Med 1994;120:470-5.
2. Nelson-Piercy C, on behalf of the Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis during pregnancy, labour and after vaginal delivery. Guideline 37. Internet. Available at: www.rcog.org.uk/resources/Public/pdf/Thromboprophylaxis_no037.pdf. Accessed October 10, 2006.
3. American College of Obstetricians and Gynecologists Educational Bulletin 1998;244:151-60.
4. Porter TF, Silver RM, Branch DW. Obstetric antiphospholipid syndrome. In: Khamashta MA, editor. Hughes syndrome. Antiphospholipid syndrome. 2nd ed. London: Springer; 2006:181-95.
5. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295-306.
6. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors of thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003;101:1827-32.
7. Galli M, Luciani D, Bertolini G, Barbui T. Anti-ß2-glycoprotein I, antiprothrombin antibodies and the risk of thrombosis in the antiphospholipid syndrome. Blood 2003;102:2717-23.
8. de Laat BH, Derksen RHWM, Ubanus RT, et al. Beta 2-GPI-dependent lupus anticoagulant activity highly correlates with thrombosis in the antiphospholipid syndrome. Blood 2004;104:3598-602.
9. Pengo V, Biasiolo A, Pegoraro C, et al. Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost 2005;93:1147-52.
10. Galli M, Barbui T. Antiphospholipid syndrome: definition and treatment. Semin Thromb Hemost 2003;29:195-204.
11. Spitzer K, Murphy K, Crowther M, Clark C, Laskin C. Postpartum management of women at increased risk of thrombosis — results of a Canadian pilot survey. J Rheumatol 2006;33:2222-6.