Letters to the Editors

Mothers' antiphospholipid antibodies during pregnancy and the relation to offspring outcome

Sirs,

The outcome of pregnancy in mothers with APS has been shown to be marked by prematurity, small-for-gestational age and neonates complications, even in pregnancies treated by the conventional APS treatment (1-2). The impact of the type of the mother's antiphospholipid antibodies and of the antibodies evolution during pregnancy is poorly understood. In the present study we aimed to describe the mother's antiphospholipid antibodies (APL) evolution during pregnancy and to correlate it to the neonates' complications. A prospective multicenter registry of children born to mothers with APS was initiated in 2003 by the European forum of Antiphospholipid antibodies until 2010. All consecutive newborns were included from women with thrombotic and/or obstetrical APS according to the Sapporo criteria. In the European multicentre cohort of 133 mothers with APS, APL were regularly evaluated during pregnancy (1). The cut-off values for the medium titre (99^{th} percentile) were 20 UGPL for IgG and 20 UMPL for IgM ACL as well as 15 U/ml for the IgG and IgM anti-β_2GPI antibodies. Neonates' complications were defined as the presence of 1 of the following features: <37 week term, birth weight <2500 g, height or cranial perimeter being $<10^{th}$ percentile, Apgar <8 or neonatal complications. The factors analysed to predict the neonate's complications in multivariate analysis included the mother's APS characteristics, associated SLE, type and number of aPL, treatments during pregnancy, Doppler data and term.

One hundred and thirty three women with APS were included and their 134 children (Supplementary Table I). Sixteen percent of neonates had a preterm birth (<37 weeks; n=22), and 14% weighed <2500 g at birth (n=19) (1). APL levels remained stable during pregnancy, although anticardiolipin IgG levels tended to decrease (Supplementary Table II, Fig. 1). APL levels were similar in mothers with neonates' complications and those without complications (Supplementary Table III, Fig. 2). Nevertheless, whereas anticardiolipin IgG levels decreased during pregnancy in mothers without neonates' complications, they tended to an opposite evolution and increased from the beginning to the delivery in mothers with neonates' complications. In multivariate analysis only the presence of lupus anticoagulant during pregnancy was associated with neonatal complications with OR 3.9 [1.2; 12.4].

Several factors have been previously established to be associated with poor APS obstetrical outcome and related neonates complications, such as the history of pregnancy morbidity and thrombosis, associated SLE, LA and APL triple positivity (2-5). The presence of LA could be also associated with poor obstetrical outcome, whereas the isolated APL are associated with better obstetrical outcome as previously reported (1-2, 5). The anticardiolipin IgG antibodies remain the most frequent APL in obstetrical APS, as represented in our study (1, 2, 6). Previously, only one report of 10 patients with at least 2 spontaneous abortions with anticardiolipins without LA demonstrated the decrease of APL during pregnancy with favorable outcome (7). As far as we know, this is the first report to describe the APL levels evolution during pregnancy and to analyse the impact of the APL evolution during pregnancy, as well on the neonate's outcome in a large multicentre cohort of prospective pregnancies. Physiological blood volume expansion may explain the tendency to decrease of APL concentrations during the course of pregnancy without complication and the concentrations of IgG, IgA, and IgM decrease significantly in the second and third trimesters (8, 10). On the other hand, the increase of APL concentrations in complicated pregnancies probably reflects the increase production of APL antibodies and the defective placentation (11). Because of predominant isolated APL in our study these data could suggest that the monitoring of APL titres during pregnancy in low-risk APS mothers could be predictive of obstetrical outcome. The value of APL monitoring during pregnancy remains to be determined in patients with high risk pregnancy (thrombosis, associated SLE, LA and triple positivity).

A. MEKINIAN[1], L. CARBILLON[2], P. NICAISE-ROLAND[3], H. ROUSSEAU[4], E. LACHASSINNE[5], M. MOTTA[6], E. VICAUT[4], C. BOINOT[7], T. AVCIN[8], S. DE CAROLIS[9], P. ROVERE-QUERINI[10], M. LAMBERT[11], S. DERENNE[12], O. POURRAT[7], S. CHOLLET-MARTIN[3], R. BIASINI-REBAIOLI[6], R. ROVELLI[10], A. LOJACONO[6], A. AMBROZIC[8], A. BENBARA[2], F. PIERRE[7], F. ALLEGRI[6], M. NUZZO[6], P.Y. HATRON[11], A. TINCANI[6], M.H. AUROUSSEAU[13], M.C. BOFFA[13], O. FAIN[1]

[1]Service de Médecine Interne, and [2]Service de Gynécologie- Obstétrique, Université Paris 13, AP-HP, Hôpital Jean Verdier, Bondy, France; [3]Unité Fonctionnelles d'Immunologie "Autoimmunité et Hypersensibilités", AP-HP, Hôpital Bichat-Claude Bernard, Paris, France; [4]Service d'Epidémiologie et Biostatistiques, Hôpital Lariboisière, AP-HP, Hôpitaux de Paris, Université Paris 7, Paris, France; [5]Service de Néonatologie et Pédiatrie, Université Paris 13, AP-HP, Hôpital Jean Verdier, Bondy, France; [6]Rheumatology, Obstetrics, Neonatology and Neonatal Intensive Care Unit, Spedali Civili, University of Brescia, Brescia, Italy; [7]Service d'Hématologie Biologique, Médecine Interne, Gynécologie-Obstétrique, Néonatologie, CHU Poitiers, Poitiers, France; [8]Paediatrics, Rheumatology, Gynecology-Obstetrics, University Chidren's Hospital Ljubljana, University Medical Centre, Ljubljana, Slovenia; [9]Rheumatology, Obstetrics and Gynecology, Paediatrics, Catholic University, Rome, Italy; [10]Rheumatology, Obstetrics, and Neonatology, San Rafaele Scientific Institute, Milano, Italy; [11]Service de Médecine Interne, Université Lille 2, Hôpital Claude Huriez, Lille, France; [12]Service d'Hématologie Biologique, CHU Nantes, Nantes, France; [13]Service d'Hématologie Biologique, Université Paris 13, AP-HP, Hôpital Jean Verdier, Bondy, France.

Address correspondence and reprint requests to: Arsène Mekinian, Service de Médecine Interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140 Bondy, France.
E-mail: arsene.mekinian@jvr.aphp.fr

Competing interests: none declared.

References

1. MEKINIAN A, LACHASSINNE E, NICAISE-ROLAND P *et al*.: European registry of babies born to mothers with antiphospholipid syndrome. *Ann Rheum Dis* 2013 Feb; 72: 217-22.
2. RUFFATTI A, TONELLO M, CAVAZZANA A *et al*.: Laboratory classification categories and pregnancy outcome in patients with primary antiphospholipid syndrome prescribed antithrombotic therapy. *Thromb Res* 2009; 123: 482-7.
3. BOFFA MC, AUROUSSEAU MH, LACHASSINNE E *et al*.: European register of babies born to mothers with antiphospholipid syndrome. *Lupus* 2004; 13: 713-7.
4. RUFFATTI A, CALLIGARO A, HOXHA A *et al*.: Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. *Arthritis Care Res* 2010; 62: 302-7.
5. LOCKSHIN MD, KIM M, LASKIN CA *et al*.: Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum* 2012; 64: 2311-8.
6. RUFFATTI A, SCAPINELLO MP, TONETTO S *et al*.: Trends in immunoglobulin G anticardiolipin antibodies in ten successful heparin-treated pregnancies. *Rheumatol Int* 1996; 16: 15-8.
7. RUFFATTI A, TONELLO M, VISENTIN MS *et al*.: Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. *Rheumatology* 2011; 50: 1684-9.
8. CARBILLON L, UZAN M, UZAN S: Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. *Obstet Gynecol Surv* 2000; 55: 574-81.
9. AMINO N, TANIZAWA O, MIYAI K *et al*.: Changes of serum immunoglobulins IgG, IgA, IgM, and IgE during pregnancy. *Obstet Gynecol* 1978; 52: 415-20.
10. YASUHARA M, TAMAKI H, IYAMA S, YAMAGUCHI Y, TACHI J, AMINO N: Reciprocal changes in serum levels of immunoglobulins (IgG, IgA, IgM) and complements (C3, C4) in normal pregnancy and after delivery. *J Clin Lab Immunol* 1992; 38: 137-41.
11. CARBILLON L, CHALLIER JC, ALOUINI S *et al*.: Uteroplacental circulation development: Doppler assessment and clinical importance. *Placenta* 2001; 22: 795-9.