Letters to the Editors

Changes of flow mediated dilation in pregnant patients with systemic autoimmune diseases

Sirs,

Pregnancy in connective tissue diseases can be at high risk for maternal and foetal complications including pre-eclampsia (1-6). Hypertension, anti-phospholipid antibodies and kidney involvement have been identified as the main risk factors for its development (7-10).

Pre-eclampsia is actually considered an endothelial disease, since endothelial injury and altered vascular reactivity key mechanism are involved in its pathogenesis. Previous reports with the non-invasive evaluation of endothelial function by the flow-mediated dilation of the brachial artery (FMD), which assesses endothelial response to a reactive hyperaemia (11), suggested prognostic significance of endothelial dysfunction (reduced FMD) for future pre-eclampsia development in high-risk patients (12, 13).

The purpose of this study was to prospectively evaluate the variation in FMD during the course of pregnancy in patients with systemic autoimmune diseases in order to investigate whether changes in endothelium-dependent vasodilation could predict the future occurrence of pre-eclampsia in these patients.

A cohort of 33 pregnant women with systemic autoimmune diseases (6 undifferentiated connective tissue diseases, 6 primary anti-phospholipid syndrome, 15 systemic lupus erythematosus, 5 Sjögren's syndrome, 1 systemic vasculitis) was recruited during the first half of gestation from the pregnancy clinic of the Rheumatology Unit, University of Pisa, and compared to 22 pregnant healthy volunteers. The prospective cohort was followed until delivery and data regarding eventual maternal and newborn complications were collected.

FMD was assessed as percentage change of diameter of the brachial artery following forearm reactive hyperaemia, as percentage increase in flow (11). Two FMD determinations were performed in each patient during the first and second pregnancy trimester.

The mean age at pregnancy onset was 31.7±4.5 years and the mean disease duration of 8.5 years (±4.5). No traditional cardiovascular risk factors were present in the patient groups with the exception of smoking habit that was referred by 5 patients. Seven patients were drug-free at our evaluations, 7 were treated with medium-low doses of glucocorticoids, 6 with hydroxychloroquine while 4 were treated with immunosuppressants. In 16 pregnancies low dose aspirin and in 14 low molecular weight heparins were added. At pregnancy onset, the disease was inactive in all patients. The mean pregnancy duration was 37.2 weeks. The mean body weight of the newborns was 2890g ± 800g. During pregnancy, 4 patients had a flare of disease activity. Obstetric complications were observed in 6 pregnancies: one intra uterine death, four cases of pre-eclampsia, two small for gestational age newborns.

No statistically significant differences have been observed in FMD between patients and controls (patients: 10.6±4.6% *vs*. healthy volunteers: 10.0±3.9%). As expected, according to the physiological increase in endothelial function occurring during pregnancy, we observed an increase in FMD between the first and second trimester in both groups (patients: 12.6±4.6% *vs*. healthy volunteers: 10.9±4.2%), without changes in reactive hyperaemia.

At the first trimester patients who developed pre-eclampsia tended to have lower FMD with respect to the patients that did not (9.1±1.2% *vs*. healthy volunteers: 11.0±4.9%), although no statistically significant differences were observed. A progressive increase in FMD was observed in both groups at the second trimester (pre-eclampsia: 12.5±4.8% *vs*. no-eclampsia: 13.5±2.2%). However, the stimulus for FMD was significantly higher in patients developing pre-eclampsia (pre-eclampsia: 986±725% *vs*. no-eclampsia: 406±335%).

This is the first preliminary description of a prospective study of the endothelial function in pregnant patients with systemic autoimmune disease aimed at assessing whether changes in FMD could have a predictive value for the development of pre-eclampsia in these patients.

Despite the relative low sample size and incidence of events observed, our preliminary findings suggest that assessment of FMD together with reactive hyperaemia might offer useful information along with disease-related factors (disease diagnosis, severity, duration and concomitant treatments) in predicting maternal and foetal complications in patients with systemic autoimmune diseases. Studies on more homogeneous and larger cohorts are ongoing.

C. Tani[1]
R.M. Bruno[2]
F. Strigini[3]
L. Carli[1]
M. Bernardini[2]
R. Talarico[1]
C. Baldini[1]
L. Ghiadoni[2]
M. Mosca[1]

[1]Rheumatology Unit, [2]Hypertension Unit, Department of Internal Medicine; [3]Division of Obstetrics and Gynaecology, Department of Reproductive Medicine and Child Development, University of Pisa, Italy.

Address correspondence to:
Prof. Marta Mosca, Rheumatology Unit, University of Pisa, Via Roma 67, 56126 Pisa, Italy.
E-mail: marta.mosca@med.unipi.it

Competing interests: none declared.

References

1. SMYTH A, OLIVEIRA GH, LAHR BD, BAILEY KR, NORBY SM, GAROVIC VD: A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060-8.
2. AGMON-LEVIN N, MOSCA M, PETRI M, SHOENFELD Y: Systemic lupus erythematosusonedisease or many? *Autoimmun Rev* 2012; 11: 593-5.
3. MOSCA M, NERI R, BOMBARDIERI S: Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. *Clin Exp Rheumatol* 1999; 17: 615-20.
4. MOSCA M, TANI C, CARLI L, BOMBARDIERI S. Undifferentiated CTD: a wide spectrum of autoimmune diseases. *Best Pract Res Clin Rheumatol* 2012; 26: 73-7.
5. MOSCA M, TANI C, TALARICO R, BOMBARDIERI S: Undifferentiated connective tissue disease (UCTD): simplified systemic autoimmune diseases. *Autoimmun Rev* 2011; 10: 256-8.
6. MOSCA M, TANI C, NERI R, BALDINI C, BOMBARDIERI S: Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev* 2006; 6: 1-4.
7. REGGIA R, ZIGLIOLI T, ANDREOLI L *et al*.: Primary anti-phospholipid syndrome: any role for serum complement levels in predicting pregnancy complications? *Rheumatology* (Oxford) 2012; 51: 2186-90
8. RUFFATTI A, TONELLO M, VISENTIN MS *et al*.: Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicenter, case-control study. *Rheumatology* 2011; 50: 1684-9.
9. TARABORELLI M, RAMONI V, BRUCATO A *et al*.: Brief report: successful pregnancies but a higher risk of preterm births in patients with systemic sclerosis: an Italian multicenter study. *Arthritis Rheum* 2012; 64: 1970-7.
10. MOSCA M, NERI R, STRIGINI F *et al*.: Pregnancy outcome in patients with undifferentiated connective tissue disease: a preliminary study on 25 pregnancies. *Lupus* 2002; 11: 304-7.
11. GHIADONI L, MOSCA M, TANI C, VIRDIS A, TADDEI S, BOMBARDIERI S: Clinical and methodological aspects of endothelial function in patients with systemic autoimmune diseases. *Clin Exp Rheumatol* 2008; 26: 680-7.
12. TAKASE B, GOTO T, HAMABE A *et al*.: Flow-mediated dilation in brachial artery in the second half of pregnancy and prediction of pre-eclampsia. *J Hum Hypertens* 2003; 17: 697-704.
13. BRANDÃO AH, PEREIRA LM, GONÇALVES AC, REIS ZS, LEITE HV, CABRAL AC: Comparative study of endothelial function and uterine artery doppler velocimetry between pregnant women with or without preeclampsia development. *J Pregnancy* 2012; 2012: 909315.