# Antinuclear antibody testing in obstetric patients

**I E Afman, H S Cronjé, G Joubert, P N Badenhorst, M G Schoon**

*Objectives.* To assess possible associations between the presence of antinuclear antibodies (ANAs) and pregnancy outcome in order to determine the significance of this test in obstetric practice.

*Methods.* A case-control study was performed on 408 patients admitted to an obstetric high care unit and on whom ANA testing was consecutively performed. The study group consisted of 46 patients who tested positive for ANAs and a control group of 92 patients who tested negative for ANAs. In addition to demographic data, indications for admission and pregnancy outcome were compared between the two groups.

*Results.* Of the 46 patients with a positive ANA result, 28 had an antinuclear pattern, 13 an anticytoplasmic pattern and 5 an antinuclear and an anticytoplasmic pattern. No significant differences were observed between the two groups (ANA-positive and negative) with regard to demographic data, indication for admission, clinical and laboratory data, and pregnancy outcome. The patients were also tested for anticardiolipin antibodies, and significantly more patients with severe pre-eclampsia tested positive (24% versus 4.7%, $p = 0.01$). No difference in HIV status and presence of autoantibodies was found between the two groups.

*Conclusion.* The presence of ANAs was not associated with adverse pregnancy outcome. Therefore routine patient testing for ANAs in an obstetric high-care unit is not recommended.

*S Afr Med J* 2003; **93**: 932-937.

Autoimmune disorders during pregnancy are an established cause of complications and mortality.[1,2] Women without an autoimmune disorder history, but with complications during pregnancy, have a raised number of autoantibodies.[3,4] This may be due to exacerbation of an undiagnosed autoimmune disorder or an unknown maternal immune reaction. It is not known whether the occurrence of autoantibodies, which is usually transient and limited to pregnancy and the immediate postpartum period, is predictive of future immunological disease.[5]

Some studies have found that antinuclear antibodies (ANAs) occur more often in patients with pre-eclampsia, intrauterine growth retardation, fetal death and placental abruption.[6-8] Other studies, however, have not confirmed these results.[9-11] Therefore, there is no consensus on the role of ANAs during pregnancy. If the exact role of this disorder could be established, it is possible that ANA determination may serve as a prognostic factor for pregnancy outcome, and possibly also influence therapy.

*Department of Obstetrics and Gynaecology, University of the Free State, Bloemfontein*

**I E Afman,** Medical Student (Current address: Department of Obstetrics and Gynaecology, University of Groningen, The Netherlands)
**H S Cronjé,** MMed (O&G), FCOG (SA), MD
**M G Schoon,** MMed (O&G), PhD

*Department of Biostatistics, University of the Free State, Bloemfontein*

**G Joubert,** MSc

*Department of Haematology and Cell Biology, University of the Free State, Bloemfontein*

**P N Badenhorst,** MMed (Haematol), PhD

## Patients and methods

### Patients

Sera from 408 consecutive pregnant patients admitted from January 2001 to November 2001 at the high-risk obstetric unit (HROU), Universitas Hospital, Bloemfontein, were tested for the presence of ANAs. The patients were all admitted with complications during pregnancy, including hypertensive disorders, cardiac disease, diabetes mellitus and fetal complications. Forty-six patients with a positive ANA determination (11% of the total group) served as the study group. The first 2 eligible patients with a negative ANA test before and after a patient with a positive result were selected as controls, and 92 control patients were included in the study. In order to be included delivery must have taken place at the Universitas Hospital and the ANA determination must have been performed during pregnancy or within 48 hours after delivery. Patients admitted postpartum were excluded. Demographic data, obstetric history, reason for admission, clinical and laboratory data and pregnancy outcome were compared in the two groups. In case of a positive ANA test the titre and pattern of the antibodies were determined, either antinuclear or anticytoplasmic. In addition, anticardiolipin (ACL) antibodies and HIV status were determined for all the patients. Pregnancy outcome was determined and compared between the two groups. A standard enquiry form was used to collect data from all the patients' records. The Ethics Committee of the Faculty of Health Sciences, University of the Free State approved the study.

### Definitions

Complications in pregnancy outcome were defined as relevant complications during pregnancy subsequent to admission. If the reason for admission remained relevant or caused complications during the course of the pregnancy it was also considered a complication in pregnancy outcome.

Gestational age at time of ANA determination and delivery was determined by dates of last normal menses. In case this determination differed from ultrasound dating by more than 1 - 3 weeks in the first, second or third trimester respectively, the ultrasonographic dating was used to determine the gestational age.

Miscarriage was defined as fetal birth weight below 500 g, and neonatal death as death in the first 28 days of life.

Intrauterine growth restriction (IUGR) was defined as a gestational age-controlled birth weight below the 10th percentile.

Preterm labour was diagnosed if spontaneous labour occurred before 37 weeks of gestation, with a fetal birth weight of 500 g or more. Preterm rupture of membranes (PROM) was defined as spontaneous rupture of membranes before the onset of labour when this occurred before a gestational age of 37 weeks and the birth weight was at least 500 g. Oligohydramnios was defined as an amniotic fluid index less than 5 on sonar, and poor obstetric history was defined as repetitive reproductive failure.

Hypertensive disorders were defined as a systolic blood pressure (SBP) of 140 mmHg or more or a diastolic blood pressure (DBP) of 90 mmHg or more. Gestational hypertension was defined as a rise in BP as described above without proteinuria. Pre-eclampsia was diagnosed in case of a SBP of 140 mmHg or more or a DBP of 90 mmHg or more in combination with proteinuria of at least 0.3 g/24 h. The presence of one or more of the following signs or symptoms indicated that the pre-eclampsia was severe: SBP 160 mmHg or DBP 110 mmHg or more, proteinuria of at least 5 g/24 h or 3+ or more with the dipstick method, oliguria (urinary volume of < 400 ml/24 h), cerebral or visual disturbances, cyanosis or pulmonary oedema. The diagnosis of chronic hypertension was based on a history of hypertension before pregnancy or before 20 weeks' gestation. Superimposed pre-eclampsia was diagnosed as a combination of chronic hypertension and pre-eclampsia.

Cardiac failure was diagnosed in cases of clinical pulmonary oedema and respiratory failure if patients had to be ventilated. Thromboembolism included deep-vein thrombosis (DVT), pulmonary embolism and sinus cavernosus thrombosis diagnosed with radiological confirmation.

### Laboratory measurements

Proteinuria was quantified by 24-hour urine collection or with a semiquantitative assessment using a standard dipstick method. Liver and renal function parameters were determined using a standard hospital autoanalyser. Liver enzyme abnormalities were defined as alanine aminotransferase (ALAT) ≥ 75 IU/l. Haemolysis was defined as lactate dehydrogenase (LDH) ≥ 600 IU/l in combination with anaemia with red cell fragments. Total platelet concentrations were established using a Technicon H1 blood cell analyser. Thrombocytopenia was defined as platelet count < 150 x $10^9$/l. Coagulopathy was diagnosed when the whole-blood clotting time was ≥ 8 minutes.

The Enzygnost HIV Integral test (Dade Behring, Marburg) and the Vironostika HIV Uniform II Ag/Ab test (Organon Teknika, Boxtel) were used in a parallel test to determine HIV status. In order to test positive both test results had to be positive. If the test results differed a new parallel test was performed on a new sample. The CD4+ cell counts were determined by flow cytometry using the MultiTEST CD3 FITC/CD8 PE CD45 PerCP/CD4 APC reagent (Becton Dickinson, San Jose).

The QUANTA Lite (INOVA Diagnostics, San Diego) was used for immunological studies. ANAs were assayed by indirect immunofluorescence on smears of HEp-2 cells. The different dilutions were incubated with phosphate-buffered saline solution for 30 minutes at room temperature. Fluorescein-conjugated goat monovalent antiserum against human immunoglobulin G (IgG) was the second antibody. The results were given in serum dilutions. The threshold for positive was established at 1:40, and any positive serum was then titrated by successive dilutions until extinction of fluorescence. If the test was positive the pattern was determined. In case of a cytoplasmic pattern the threshold for positive was established at 1:10.

IgG and IgM ACL antibodies were quantified in serum using an enzyme-linked immunosorbent assay (ELISA). The upper limit of normal was set more than 5 standard deviations (SDs) above mean at 15 GPL or 12.5 MPL. Values ranging from 15 to 25 GPL or 12.5 to 25 MPL were considered intermediate. Values above 25 GPL or MPL were considered positive. If the value of IgG or IgM or both was indeterminate the ACL test was considered indeterminate. When both values were negative the test was considered negative.

### Statistical analysis

Results are given as median values with quartiles or as *N* (%). To test for statistical associations between categorical variables the chi-squared test was used. However, in case of an expected cell size < 5 the Fisher's exact test was used instead of the chi-squared test. Numerical variables were compared using the Mann-Whitney test. A *p*-value < 0.05 was considered statistically significant and 95% confidence intervals (CIs) were calculated for differences in medians and percentages.

## Results

The study group comprised 46 ANA-positive patients and the control group 92 ANA-negative patients. No patients had a history of autoimmune disease.

The study group included 28 patients with an antinuclear pattern, 13 with an anticytoplasmic pattern and 5 with an antinuclear and an anticytoplasmic pattern (Table I). Four patients had two different antinuclear patterns. With regard to antinuclear patterns, a speckled pattern was found in 20 patients (60.6%), a nucleolar pattern in 8 (24.2%), and a homogeneous pattern in 7 (21.2%). Scl70 and lysosomal antibodies were found in 1 patient (3.0%). With regard to anticytoplasmic patterns, all patients had a smooth muscle pattern and 1 patient had two patterns (smooth muscle and parietal cell).

Demographic, reproductive and clinical data, as well as reasons for admission, are described in Table II. Age, gravidity, obstetric history and gestational age at ANA determination and at delivery did not differ significantly between the study and control groups. Primigravidas were equally distributed between the study and control groups. No significant differences between the two groups were found for presence of chronic hypertension or for BP level on admission. BP levels were, however, slightly higher in the control group (statistically not significant).

The main reasons for admission were hypertensive disorders, cardiac disease, preterm labour, PROM, congenital malformations and poor obstetric history. There was no statistical difference between the two groups. Drugs known to induce ANAs, namely methyldopa and hydralazine, were equally distributed between the study and control groups (43.5% and 42.4% respectively).

**Table I. Titre and pattern in case of a positive ANA determination**

| | Antinuclear (*N* = 33) | | Anticytoplasmic (*N* = 18) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Titre | | | | |
| 1:20 | - | - | 5 | 27.8 |
| 1:40 | 16 | 48.5 | 6 | 33.3 |
| 1:80 | 12 | 36.4 | 3 | 16.7 |
| ≥ 1:160 | 5 | 15.1 | 4 | 22.2 |
| Pattern* | | | | |
| Speckled | 20 | 60.6 | | |
| Homogeneous | 7 | 21.2 | | |
| Nucleolar | 8 | 24.2 | | |
| Scl70 | 1 | 3.0 | | |
| Lysosomal | 1 | 3.0 | | |
| Centromere | 0 | 0.0 | | |
| Mitotic spindle | 0 | 0.0 | | |
| PCNA | 0 | 0.0 | | |
| Nuclear membrane | 0 | 0.0 | | |
| Smooth muscle | | | 18 | 100.0 |
| Parietal cell | | | 1 | 5.6 |

*Four patients had two different antinuclear patterns, 1 patient had two different anticytoplasmic patterns and 5 patients had an antinuclear as well as an anticytoplasmic pattern.
PCNA = proliferating cell nuclear antigen.

Both groups were tested for ACL antibodies. Significantly more negative ACL tests were found in the control group than in the study group (54.4% versus 34.9%, $p = 0.03$).

**Table II. Demographic, reproductive and clinical data according to ANA determination. Data are presented as median (quartiles)**

| | ANA determination | | | |
|---|---|---|---|---|
| | Positive (*N* = 46)* (study group) | Negative (*N* = 92)* (control group) | *p*-value | 95% CI for differences |
| Mean age (yrs) | 26.5 | 28.5 | 0.80 | -2, 3 |
| Obstetric indices | | | | |
| Mean gravidity | 2.5 | 2.5 | 0.95 | -1, 1 |
| Primigravida (%) | 2.83 | 26.1 | 0.79 | -13.1, 18.2 |
| Reproductive failure (%)† | 36.4 | 41.2 | 0.64 | -19.4, 11.8 |
| Hypertension during pregnancy (%)‡ | 34.6 | 37.3 | 0.81 | -18.0, 10.7 |
| GA at ANA determination (weeks) | 30 (26.0 - 35.0) | 30 (27.0 - 32.5) | 0.75 | -3, 2 |
| GA at delivery (weeks) | 32 (28.0 - 38.0) | 32 (30.0 - 36.0) | 0.89 | -2, 2 |
| Clinical indices | | | | |
| Chronic hypertension (%) | 8.7 | 10.9 | 0.77 | -11.8, 9.2 |
| Mean systolic blood pressure | 138.0 | 150.0 | 0.07 | 0, 2 |
| Mean diastolic blood pressure | 80.0 | 84.0 | 0.37 | -4, 10 |
| Main reasons for admission | | | | |
| Hypertensive disorder (%) | 50.0 | 58.7 | 0.33 | -25.9, 8.8 |
| Cardiac disease (%) | 10.9 | 9.8 | 1.00 | -9.1, 12.8 |
| Preterm labour (%) | 8.7 | 5.4 | 0.48 | -5.6, 13.6 |
| PROM (%) | 2.2 | 4.4 | 0.66 | -7.8, 5.4 |
| Congenital malformations (%) | 4.4 | 3.3 | 1.00 | -5.5, 9.4 |
| Poor obstetric history (%) | 6.5 | 8.7 | 0.75 | 10.7, 8.2 |

GA = gestational age; PROM = pre-term rupture of membranes.
*The interquartile range or percentage is given in brackets.
†Reproductive failure = the occurrence of a miscarriage, fetal loss, ectopic pregnancy or neonatal death in the obstetric history (excluding primigravida).
‡Hypertension during pregnancy = hypertension during pregnancy in the obstetric history (excluding primigravida).

Although not significant, more positive ACL tests were found in the study group than in the control group (27.9% v. 14.4%, $p = 0.06$). There was no difference between the study and control groups for positive IgG ACL measurements (14.0% v. 8.9%, $p = 0.38$) and IgM ACL measurements (16.3% v. 8.8%, $p = 0.24$). Furthermore, HIV status and CD4+ count were not statistically different between the two groups.

Comparison of maternal pregnancy outcome between the study and control groups is given in Table III. There was no significant difference between the two groups for complications such as severe pre-eclampsia, the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), eclampsia, thromboembolism, respiratory complications, renal failure and coagulopathy. There was 1 maternal death in the study group and 2 in the control group ($p = 1.00$).

Fetal outcome was compared between the 51 newborns from the study group and the 95 newborns in the control group (Table IV). There were 5 twins in the study group and 3 in the control group. No significant differences were found in the number of miscarriages, fetal losses and complications after birth between the two groups. The presence of major complications, including neonatal death, did not differ significantly between the newborns in the study and control groups.

There were no significant differences in admission to the intensive care unit between the two groups ($N = 17$, 41.5% v. $N = 38$, 50.0%), $p = 0.38$). Newborns in the study group had a slightly higher birth weight than newborns in the control group (1 765.0 g v. 1 502.5 g), but this was not statistically significant ($p = 0.26$). There was no significant difference in the study and control groups for the presence of IUGR (14.9% v. 17.8%, $p = 0.67$), preterm labour (15.2% v. 12%, $p = 0.59$), PROM (8.7% v. 9.8%, $p = 1.00$) and oligohydramnios (15.2% v. 18.2%, $p = 0.63$).

Pregnancy outcome was compared for the ACL-positive and negative patients. The ACL-positive patients experienced more complications, but this was not statistically significant. Severe pre-eclampsia, however, occurred significantly more often in the

**Table III. Maternal outcome in relation to ANA determination (median)**

| | ANA determination | | | |
|---|---|---|---|---|
| | Positive (%) ($N = 46$) (study group) | Negative (%) ($N = 92$) (control group) | *p*-value | 95% CI for differences |
| Discharge without complications | 52.2 | 55.4 | 0.72 | -20.6, 14.1 |
| Discharge with complications | 47.8 | 44.5 | 0.72 | -14.1, 20.6 |
| Hypertensive disorders | 30.4 | 33.7 | 0.70 | -19.0, 13.4 |
| Severe pre-eclampsia | 6.5 | 8.7 | 0.75 | -10.7, 8.2 |
| Thromboembolism | 2.2 | 1.1 | 1.00 | -3.6, 7.6 |
| Eclampsia | 10.9 | 9.8 | 1.00 | -9.1, 12.8 |
| Pleural effusion | 6.5 | 5.4 | 1.00 | -6.9, 10.8 |
| Respiratory failure | 2.2 | 1.1 | 1.00 | -3.6, 7.6 |
| Cardiac failure | 6.5 | 6.5 | 1.00 | -8.2, 9.9 |
| Creatinine > 200 µmol/l | 0.0 | 7.6 | 0.10 | -12.7, -0.3 |
| Liver enzyme abnormalities | 4.4 | 9.8 | 0.36 | -13.2, 4.4 |
| Thrombocytopenia | 15.2 | 19.6 | 0.53 | -16.7, 9.6 |
| Haemolysis | 8.7 | 15.2 | 0.20 | -16.7, 5.5 |
| Placental abruption | 8.7 | 7.6 | 1.00 | -8.1, 11.9 |
| Coagulopathy | 2.2 | 4.4 | 0.66 | -7.8, 5.4 |
| Death | 2.2 | 2.2 | 1.00 | -5.0, 6.9 |

**Table IV. Fetal outcome in relation to ANA determination of the mother**

| | ANA determination | | | |
|---|---|---|---|---|
| | Positive (%) ($N = 51$) (study group) | Negative (%) ($N = 95$) (control group) | *p*-value | 95% CI for differences |
| Miscarriage | 5.9 | 2.1 | 0.34 | -3.0, 11.9 |
| Fetal loss | 13.7 | 20.0 | 0.22 | -17.9, 6.9 |
| Neonatal death | 2.0 | 1.1 | 1.00 | -3.5, 6.8 |
| Discharge without complications | 47.1 | 40.0 | 0.41 | -9.7, 23.6 |
| Discharge with complications | 31.4 | 36.8 | 0.58 | -20.2, 11.8 |

ACL-positive than the ACL-negative patients (24.0% v. 4.7%, $p$ = 0.01). There was a tendency to more thrombocytopenia among ACL-positive than ACL-negative patients, but this was also not statistically significant (28.0% v. 14.1%, $p$ = 0.14).

No significant differences were found when comparing HIV-positive and negative patients. Three maternal deaths (3.2%) occurred in the HIV-negative group and none in the positive group ($p$ = 0.57). A low platelet count was present in 9 HIV-positive patients (26.5%) compared with 9 HIV-negative patients (15.0%, $p$ = 0.13).

## Discussion

No consensus exists on the association between autoantibodies and complications during pregnancy or a poor pregnancy outcome. Several authors have described a positive association between ANAs and adverse pregnancy outcome, while others could not confirm such an association. Iijima *et al*.[7] observed that a significantly higher rate of spontaneous abortion was observed in ANA-positive subjects. However, they found that ANAs did not affect the rates of preterm delivery, stillbirth, pregnancy-induced hypertension, malformation, or gender ratio. Kiuttu *et al*.[6] demonstrated a raised number of stillbirths in ANA-positive women. An association between the presence of ANAs and pre-eclampsia was found by Matthiesen *et al*.[8] However, in the study by Patton *et al*.[11] the presence of autoantibodies in subjects without a documented autoimmune disease did not appear to have an adverse effect on maternal or fetal well-being. Similar results were reported by El-Roeiy *et al*.[10] They suggested that autoantibody abnormalities (phospholipids, histones, polynucleotides) after 16 weeks' gestation and at low titres may have no major adverse effects of pregnancy outcome and may not require treatment. Incerpi *et al*.[9] found no relationship between explained or unexplained fetal death and a positive ANA determination and no significant association between ANA titres or patterns and fetal outcome.

The purpose of this study was to compare the pregnancy outcome of obstetric patients with a positive ANA determination with that of patients with a negative test, and to determine if the presence of ANA was related to adverse pregnancy outcome. Comparison of the study and control group was justified because the demographic data, obstetric history and reasons for admission did not differ significantly between the two groups. In this study, no association was found between the presence of ANA and adverse pregnancy outcome. This finding suggests that ANAs were not responsible for complications during pregnancy in patients without a documented autoimmune disease. This applies especially to hypertensive disorders, including pre-eclampsia. Contrary to our expectations a tendency was observed to more HELLP syndrome and renal insufficiency in the ANA-negative group, although this was not statistically significant (Table III). This finding correlated with slightly higher median BP in this group (Table II).

This study population consisted of women with extremely complicated pregnancies who were referred to a tertiary referral centre. As this was the only tertiary referral centre for a large area in central South Africa, it is unlikely that patients with similar complications had been referred to another centre. Nevertheless, since these patients were highly selected, they do not represent the obstetric population as a whole and a selection bias was possible. The limited data in some of the categories could have introduced a beta error and the results have to be interpreted against this background. The only reassuring factor was the similarity in demographic data between the study and control groups.

The control group often tested negative for ACL, with the study group more positive, although the difference was not statistically significant. An explanation for this observation could be that stimulation of the immune system caused elevation of different autoantibodies. Some studies have suggested that autoantibodies occurred more often in HIV-infected patients, possibly because of B-cell stimulation. [12,13] However this was not confirmed in the present study.

When comparing the pregnancy outcome of the ACL-positive and negative patients, twice as many ACL-positive patients presented with severe pre-eclampsia ($p$ = 0.01). This finding was consistent with previous reports by Kilpatrick[14] and Branch *et al*.[15] ACL antibodies have been associated with a predisposition to arterial and venous thrombosis. It is possible that these autoantibodies account for some of the placental damage seen in hypertensive disorders.[4,16] It was remarkable that reproductive failure in the obstetric history did not differ significantly between the ACL-positive and negative patients, since ACL antibodies are known to cause reproductive failure.[17,18] These results must, however, be used with caution, because there was a large intra-patient variation on test results over time.[19]

This study could not confirm an association between ANA and an adverse pregnancy outcome. Unless the patient presents with a history or symptoms suggesting an autoimmune disease, ANA testing is unlikely to contribute towards the diagnosis or management of the patient.

We acknowledge the valuable input of Cornel van Rooyen (biostatistician), Lucas Kapsenberg (research assistant), and Ina Venter, who prepared the manuscript.

**References**

1. Varner MW. Autoimmune disorders and pregnancy. *Semin Perinatol* 1991; **15:** 238-250.
2. Yasmeen S, Wilkins EE, Field NT, Sheikh RA, Gilbert WM. Pregnancy outcomes in women with systemic lupus erythematosus. *J Matern Fetal Med* 2001; **10:** 91-96.
3. Weitgasser R, Spitzer D, Karting I, Zajc M, Staudach A, Sandhofer F. Association of HELLP syndrome with autoimmune antibodies and glucose intolerance. *Diabetes Care* 2000; **23:** 786-790.
4. El-Roeiy A, Myers SA, Gleicher N. The relationship between autoantibodies and intrauterine growth retardation in hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1991; **164:** 1253-1261.
5. Gleicher N. Pregnancy and autoimmunity. *Acta Haematol* 1986; **76:** 68-77.
6. Kiuttu J, Hartikainen AL, Makitalo R, Ruuska P. The outcome of pregnancy in antinuclear antibody-positive women. *Gynecol Obstet Invest* 1994; **37:** 160-163.

7. Iijima T, Tada H, Hidaka Y, Mitsuda N, Murata Y, Amino N. Effects of autoantibodies on the course of pregnancy and fetal growth. *Obstet Gynecol* 1997; **90:** 364-369.
8. Matthiesen LS, Berg G, Ernerudh J, Skogh T. A prospective study on the occurrence of autoantibodies in low-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1999; **83:** 21-26.
9. Incerpi MH, Banks EH, Goodwein SN, Samadi R, Goodwin TM. Significance of antinuclear antibody testing in unexplained second and third trimester fetal deaths. *J Matern Fetal Med* 1998; **7:** 61-64.
10. El-Roeiy A, Myers SA, Gleicher N. The prevalence of autoantibodies and lupus anticoagulant in healthy pregnant women. *Obstet Gynecol* 1990; **75:** 390-396.
11. Patton PE, Coulam CB, Bergstralh E. The prevalence of autoantibodies in pregnant and nonpregnant women. *Am J Obstet Gynecol* 1987; **157:** 1345-1350.
12. Kopelman RG, Zolla-Pazner S. Association of human immunodeficiency virus infection and autoimmune phenomena. *Am J Med* 1988; **84:** 82-88.
13. Massabki PS, Accetturi C, Nishie IA, da Silva NP, Sato EI, Andrade LE. Clinical implications of autoantibodies in HIV infection. *AIDS* 1997; **11:** 1845-1850.
14. Kilpatrick DC. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations (comment). *Br J Obstet Gynaecol* 1994; **101:** 739-740.
15. Branch DW, Andres R, Digre KB, Rote NS, Scott JR. The association of antiphospholipid antibodies with severe preeclampsia. *Obstet Gynecol* 1989; **73:** 541-545.
16. Ikematsu W, Luan FL, La Rosa L, *et al*. Human anticardiolipin monoclonal autoantibodies cause placental necrosis and fetal loss in BALB/c mice. *Arthritis Rheum* 1998; **41:** 1026-1039.
17. Lynch A, Marlar R, Murphy J, *et al*. Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study. *Ann Intern Med* 1994; **120:** 470-475.
18. Faussett MB, Branch DW. Autoimmunity and pregnancy loss. *Semin Reprod Med* 2000; **18:** 379-392.
19. Topping J, Quenby S, Farquharson R, Malia R, Greaves M. Marked variation in antiphospholipid antibodies during pregnancy: relationships to pregnancy outcome. *Hum Reprod* 1999; **14:** 224-228.


*Accepted 24 July 2003.*