Scientific papers

Fetal loss treatment in patients with antiphospholipid antibodies

J ORDI,¹ J BARQUINERO,¹ M VILARDELL,¹ R JORDANA,¹
C TOLOSA,¹ A SELVA,¹ AND E GENOVER²

From the Departments of ¹International Medicine and ²Obstetrics, General Hospital 'Valle Hebrón', Barcelona, Spain

SUMMARY A group of seven young women with antiphospholipid antibodies, histories of recurrent fetal loss, and no live births is reported. Two patients had systemic lupus erythematosus, and the other five fulfilled criteria for the primary antiphospholipid syndrome. A false Venereal Disease Research Laboratory (VDRL) test was present in four of the patients, three had a previous episode of arterial or venous thrombosis, or both, and two had thrombocytopenia. Prednisone and acetylsalicylic acid were given, and monthly controls of lupus anticoagulant activity were carried out. The dose of acetylsalicylic acid was fixed while the dose of steroids was adjusted according to the degree of lupus anticoagulant activity. A fetal survival was obtained in 7/9 (78%) of the pregnancies. Three of the newborn infants had transitory lupus anticoagulant activity. A search for antiphospholipid antibodies should be carried out in patients with otherwise unexplained fetal losses, falsely positive VDRL tests, thrombosis, or thrombocytopenia as the treatment of such patients with prednisone and acetylsalicylic acid is highly effective.

The so-called lupus anticoagulant is an antibody (IgG or IgM) that prolongs phospholipid dependent coagulation tests by binding to epitopes on the phospholipid portion of prothrombinase.¹

The lupus anticoagulant is characteristically found in patients with systemic lupus erythematosus but has also been observed in patients with other diseases, especially in those with the primary antiphospholipid syndrome,² and in apparently normal people.³ Despite in vitro prolongation of the partial thromboplastin time by lupus anticoagulant, its presence, paradoxically, has been associated with increased tendency towards thromboembolic events and not with an increased bleeding tendency.⁴⁻⁵ In women the presence of this antibody has recently emerged as an important marker for recurrent first trimester spontaneous miscarriages as well as for second and early third trimester fetal death.⁶⁻⁸ Treatment with prednisone and acetylsalicylic acid has been advocated as a means of improving pregnancy outcome in these patients.⁶⁻⁷ Treatment

with acetylsalicylic acid alone has recently been suggested to be effective in pregnant patients with systemic lupus erythematosus and previous fetal losses.⁹ This report describes our experience with steroids and acetylsalicylic acid and the maternal and fetal complications encountered in the care of seven pregnant patients with the lupus anticoagulant.

Patients and methods

COAGULATION ASSAYS

We suspected the presence of lupus anticoagulant when a prolonged activated partial thromboplastin time (APTT) could not be corrected by addition of normal plasma (APTT > 10 seconds of the 1:1 mixture of the patient and control plasmas) and there was a normal or prolonged prothrombin time. Lupus anticoagulant was confirmed by a diluted tissue thromboplastin time and by a blood thromboplastin time performed by the Schleider method.²

LABORATORY TESTS

The following investigations were made: basic blood variables, platelet count, antinuclear antibodies by immunofluorescence using mouse liver as substrate.

Accepted for publication 24 January 1989.

Correspondence to Dr J Ordi, Rda. General Mitre 240; 2. 1. 08006 Barcelona, Spain.

Table 1 Previous obstetric and thrombotic histories of seven women with the lupus anticoagulant

Patient No	Disease	Spontaneous abortions before 12 weeks (n)	Fetal deaths after 13 weeks (n)	Thrombosis	
				Arterial	Venous
1	SLE*	3	2	—	—
2	PAS*	1	1	PTE*	Femoropopliteal
3	SLE	—	2	—	—
4	PAS	2	1	—	Ileofemoral
5	PAS	2	3	—	—
6	PAS	—	1	—	Femoropopliteal
7	PAS	0	0	—	—

*SLE=systemic lupus erythematosus; PAS=primary antiphospholipid syndrome; PTE=pulmonary thromboembolism.

and anti-Ro antibodies by immunoelectrophoresis using human spleen of a group O subject as substrate. The presence or absence of anti-DNA antibodies was indicated by radioimmunoanalysis. Serum complement components C3, C4, and C3PA were measured by nephelometry and rheumatoid factor by the Waaler-Rose method and the Venereal Disease Research Laboratory (VDRL) test. From 1986 onwards the anticardiolipin antibodies were measured by an internationally standardised enzyme linked immunosorbent assay (ELISA).¹⁰

PATIENTS

With the above mentioned methods we diagnosed 56 patients with lupus anticoagulant prospectively in the period between 1981 and 1986. In each case a clinical history was taken with emphasis on obstetric and thrombotic data. Seven patients were fertile and had histories of obstetric problems with no live births. Only one patient had had no previous pregnancy, and we decided to include her as she became pregnant while receiving treatment for autoimmune thrombocytopenic purpura. Two patients fulfilled the American Rheumatism Association criteria for systemic lupus erythematosus,¹¹

and the other five fulfilled criteria for the recently described primary antiphospholipid syndrome.² These patients had had 18 fetal losses, with eight miscarriages (before the third month of pregnancy) and 10 dead fetuses (after the third month). In three patients there was a history of arterial or venous thrombosis (Table 1). Laboratory data showed thrombocytopenia in two patients, negative anti-Ro in all, positive anticardiolipin antibodies in five of seven patients, with a titre >15 GPL (IgG anticardiolipin units, normal value <5) or >6 MPL (IgM anticardiolipin units, normal value <3.2), or both, in three of the five, antinuclear antibodies positive in five patients, anti-DNA antibodies positive only in the patients with systemic lupus erythematosus, and a falsely positive VDRL test in four of seven patients (Table 2).

TREATMENT AND CONTROLS DURING THE PREGNANCY

A pregnancy test was carried out at the 10th day after the expected onset of the menses. If positive, the patient received a daily dose of 50 mg of acetylsalicylic acid and 20 mg of prednisone. From that moment monthly check-ups were carried out, including clinical data, obstetric review, sonography, and determination of lupus anticoagulant concentration. Lupus anticoagulant activity was measured by the 1:1 APTT patient/control ratio; an attempt was made to obtain a ratio ≥ 1.2 . When lupus anticoagulant was detected we increased the daily dose of prednisone by 10 mg each month, but whenever lupus anticoagulant activity was undetectable in two consecutive measurements the dose was reduced by 5 mg a day. The dose of acetylsalicylic acid was not modified. Patient No 1 started treatment in both pregnancies after some delay (between the 8th and 12th week) owing to her poor compliance. The plasma samples for lupus anticoagulant determinations were stored at -30°C and were later used for analysis of anticardiolipin antibodies. The protocol also included guidelines for pathological review of

Table 2 Immunological profiles of the patients

Patient No	ANA*	Ro	DNA	VDRL* test	ACA*†		Platelets
					IgG	IgM	
1	+	-	+	+	++	-	Normal
2	+	-	-	-	+	-	Normal
3	-	-	+	+	-	+	Normal
4	+	-	-	+	+++	-	↓
5	+	-	-	-	++	-	Normal
6	-	-	-	+	-	-	Normal
7	+	-	-	-	-	-	↓

*ANA=antinuclear antibodies; VDRL=Venereal Disease Research Laboratory; ACA=anticardiolipin antibodies.

†-=negative; +=low positive (<15 GPL or <6 MPL); ++=moderately positive (15-80 GPL or 6-50 MPL); +++=high positive (>80 or >50 MPL).

the placentas as well as a screening study of the coagulation to assess the possibility of transmission of the immunoglobulin with lupus anticoagulant activity from mother to fetus.

Results

COAGULATION ASSAYS

The APTTs returned to normal at different rates. In patients 3 and 6 normalisation took place after a month of treatment. In patients 2, 4, and 5 the APTT became normal after two months with doses of prednisone of 30 mg a day. In patient 7 we were unable to normalise the APTT despite a daily prednisone dose of 60 mg. In patients 3 and 6 we were unable to reduce the dose of prednisone to 10 mg a day, and in patients 2, 4, and 6 20–30 mg a day of prednisone were required. In patient No 1 we started the treatment at the 8th and 12th week of each of her two pregnancies. During her first pregnancy we followed the usual protocol, but in the second pregnancy we started with a dose of 40 mg a day of prednisone and the APTT was not normal by the time the fetus died. Anticardiolipin antibody concentrations decreased in all five patients, being positive at concentrations below 15 GPL or 6 MPL, but not disappearing completely.

FETAL SURVIVAL

Seven of nine pregnancies ended with normal live births. Both failures occurred in patient No 1, at the 14th and 16th week of pregnancy, and were accompanied by vaginal haemorrhage; the fetal death was recorded by ultrasonography. In both instances there was complete vaginal expulsion and the fetuses appeared macroscopically normal. The placentas were of normal height and appearance, and histologically there were vascular thrombotic lesions and infarctions in the two specimens from

patient No 1. The APTT had not returned to normal by the time of these obstetric complications.

All other pregnancies ended between the 32nd and 36th week with normal deliveries and with fetal weights ranging from 2500 to 3500 g. We could only study the placentas of three of them (Nos 5, 6, 7) which were normal. Apgar scores were normal, and no malformations or complications were seen in the newborns. Determinations of APTT and DTT were performed in three infants and were consistent with the presence of a circulating anticoagulant. Further examinations carried out at six months were normal.

The prednisone treatment produced Cushingoid features in these patients, except in patient No 7 who, paradoxically, was receiving the largest dose of steroids. Steroids were progressively tapered in the postpartum period while acetylsalicylic acid was discontinued abruptly. In patient No 6 the lupus anticoagulant could not be detected by the usual coagulation tests in the controls performed after the puerperium. Thrombotic complications in the postpartum period were not observed, which contrasted with the experience of several patients in previous pregnancies (Table 3).

Discussion

The presence of the lupus anticoagulant in women with or without systemic lupus erythematosus has been reported to be associated with a high incidence of first trimester spontaneous miscarriages and second and third trimester fetal deaths.^{6 7 8 11–22} Measurement of anticardiolipin antibodies, alone or in conjunction with lupus anticoagulant determinations, has proved to be a good predictor of fetal distress or fetal death.¹³ Currently, lupus anticoagulant and anticardiolipin antibodies are considered good markers of obstetric complications. Most patients with the lupus anticoagulant also have anticardiolipin antibodies, but some are only positive for one of the two antibodies.^{23 24} Both types of antiphospholipid antibody are useful as predictors of obstetric complications, though anticardiolipin antibodies seem to be more sensitive and easier to measure.^{13 19 20 25} In this series two patients were positive for lupus anticoagulant and negative for anticardiolipin antibodies.

It seems likely that the anticardiolipin antibody and lupus anticoagulant tests will become a routine screening procedure in evaluating women with history of obstetric complications. The mechanism of fetal loss in patients with antiphospholipid antibodies is unknown, but it has been thought to be similar to the mechanism implicated in the vascular thrombosis related to these antibodies. Currently, it is suggested that the endothelial cell itself, or

Table 3 *Obstetric aspects after treatment with prednisone and acetylsalicylic acid (only three newborn infants were studied)*

Patient No	Pregnancies (n)	Liveborn infants (n)	Weeks of gestation	Maternal problems	Fetal LA* search
1	2	0	12–16	—	Not done
2	1	1	32	Cushingoid	Not done
3	1	1	32	Cushingoid	Not done
4	1	1	32	Cushingoid	Not done
5	1	1	36	Cushingoid	LA
6	2	2	32–36	Cushingoid	LA
7	1	1	32	—	LA

*LA=lupus anticoagulant.

Ann Rheum Dis: first published as 10.1136/ard.48.10.728 on 1 October 1989. Downloaded from <http://ard.bmj.com/> on April 26, 2023 by guest. Protected by copyright.

membrane linked molecule, is the target antigen. Decreased prostacyclin production,¹⁴ anti-endothelial cell thrombomodulin activity²⁶ and inhibition of protein C activation,^{27 28} inhibition of the release of venous plasminogen activator (an endothelial cell product),²⁹ and inhibition of pre-kallikrein activity³⁰ have all been suggested to affect the presence of antiphospholipid antibodies, leading to thrombosis. The most common pathological findings have been decidual and placental vascular thrombosis and placental infarction.^{6 14 16} Thrombosis of placental vessels has not been found uniformly however, and placental infarction was said not to be extensive enough to account for fetal loss.¹³ We observed histopathological abnormalities in both placentas of the patient with two fetal losses despite prophylactic treatment. We believe that these patients with anticardiolipin antibodies had a hypercoagulable state as shown by the episodes of arterial or venous thrombosis in three of our seven patients. Likewise, we feel that this antiphospholipid antibody of the IgG type could be passively transmitted from mother to fetus, producing direct effects on the fetus. Coagulation abnormalities compatible with lupus anticoagulant were shown in all three newborn infants examined. This aspect has not been previously studied. Thus we recommend examination of the dead fetuses and placentas of such cases, as well as performance of coagulation tests on the newborns.

Another study with similar good results was carried out by Branch *et al.*⁷ With our treatment, which contains some minor modifications, we obtained a 78% (7/9) fetal survival. The correct dose of acetylsalicylic acid is not known, but it seems that lower doses than those used by Branch *et al* can inhibit platelet aggregation. Thus we used a lower dose of 50 mg a day.^{31 32} It is difficult to select an initial dose of prednisone, but we decided to use initially a daily dose of 20 mg, instead of the 40 mg recommended by other authors.^{6 7} In our experience most fetal losses take place after the eighth week of pregnancy, and during this period a dose of 20 mg a day is sufficient to suppress or decrease the activity of the lupus anticoagulant. In the patient with fetal losses failure of the treatment might be attributed to the delay in starting treatment. Nevertheless, other workers have obtained good fetal survival in such circumstances.^{8 17} Like other workers we do not have a satisfactory explanation for the therapeutic failure of these cases.

Treatment with steroids produced Cushingoid features except in the mother taking the highest dose. Other workers have observed other side effects, such as acne, mycobacterial infections, and adrenal insufficiency.^{6 7}

After discontinuation of treatment in the post-

partum period the activity of the lupus anticoagulant reappeared in all but one patient.

In view of the expected side effects of steroids several groups of investigators have initiated trials to determine the treatment best able to ensure successful pregnancy outcome with the least risk for women and their fetuses. Successful pregnancies have been reported in cases in which the mothers were given heparin,^{6 33} but two fetal deaths occurred despite the anticoagulation treatment.⁷ Successful pregnancies after treatment with prednisone and azathioprine,^{7 34} acetylsalicylic acid without prednisone,³⁵ and gammaglobulin³⁶ have been reported. Treatment with acetylsalicylic acid, dipyridamole, and anticoagulants must be evaluated. An international, randomised, prospective, controlled trial (the Kingston Antiphospholipid Syndrome) is to be started in these patients to evaluate the different treatments.³⁷

We thank P Montero for excellent technical assistance. This work was supported by a grant from the Fondo de Investigaciones, Sanitarias de la Seguridad Social (FISS).

References

- 1 Thiagarajan P, Shapiro S S, De Marco L. Monoclonal immunoglobulin M coagulation inhibitor with phospholipid specificity: mechanism of a lupus anticoagulant. *J Clin Invest* 1980; **66**: 397-405.
- 2 Harris E N. Syndrome of the black swan. *Br J Rheumatol* 1987; **26**: 324-6.
- 3 Gastineau D A, Kazmier J F, Nichols W L, Bowie E J W. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. *Am J Hematol* 1985; **19**: 265-75.
- 4 Elias M, Eldor A. Thromboembolism in patients with the lupus-type anticoagulant. *Arch Intern Med* 1984; **144**: 510-5.
- 5 Glueck H I, Kant K S, Weiss M A, Pollak V E, Miller M A, Coots M. Thrombosis in systemic lupus erythematosus. Relation to the presence of circulating anticoagulants. *Arch Intern Med* 1985; **145**: 1389-95.
- 6 Lubbe W F, Butler W S, Palmer S J, Liggins G C. Lupus anticoagulant in pregnancy. *Br J Obstet Gynaecol* 1984; **91**: 357-63.
- 7 Branch D W, Scott J R, Kochenour N K, Hershgold E. Obstetric complications associated with the lupus anticoagulant. *N Engl J Med* 1985; **313**: 1322-6.
- 8 Ordi-Ros J, Vilardell Tarres M, Vila Baucells M, Mairé J J, Solano J T. Prednisone and maternal lupus anticoagulant. *Lancet* 1983; **ii**: 576-7.
- 9 Elder M G, de Swiet M, Robertson A, Elder M A, Flloyd E, Hawkins D F. Low-dose aspirin in pregnancy. *Lancet* 1988; **i**: 410.
- 10 Loizou S, McCrea J D, Rudge A C, Reynolds R, Boyle C C, Harris E N. Measurement of anticardiolipin antibodies by an enzyme-linked immunosorbent assay (ELISA): standardization and quantitation of results. *Clin Exp Immunol* 1985; **62**: 738-45.
- 11 Tan E M, Cohen A S, Fries J F, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.
- 12 Boey M L, Colaço C B, Gharavi A E, Elkin K B, Loizou S, Hughes G R V. Thrombosis in systemic lupus erythematosus: striking association with the presence of circulating lupus anticoagulant. *Br Med J* 1983; **287**: 1021-3.

- 13 Lockshin M D, Druzin M L, Goei S, *et al.* Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. *N Engl J Med* 1985; **313**: 152-6.
- 14 De Wolf F, Carreras L O, Moerman P, Vermeylen J, Van Assche A, Renaer M. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant. *Am J Obstet Gynecol* 1982; **142**: 829-34.
- 15 Firkin B G, Howard M A, Radford N. Possible relationship between lupus inhibitor and recurrent abortion in young women. *Lancet* 1980; **ii**: 366.
- 16 Nilsson I M, Astedt B, Hedner U, Berezin D. Intrauterine death and circulating anticoagulant ('antithromboplastin'). *Acta Med Scand* 1975; **197**: 153-9.
- 17 Farquharson R G, Pearson J F, John L. Lupus anticoagulant and pregnancy management. *Lancet* 1984; **iii**: 228-9.
- 18 Clauvel J P, Tchobrousky C, Danon F, Sultan Y, Intrator L, Brouet J C. Spontaneous recurrent fetal wastage and autoimmune abnormalities: a study of fourteen cases. *Clin Immunol Immunopathol* 1986; **39**: 523-30.
- 19 Derue G L, Englert H J, Harris E N, Hughes G R V. Fetal loss in systemic lupus: association with anticardiolipin antibodies. *J Obstet Gynecol* 1985; **2**: 207-9.
- 20 Harris E N, Chan J K W, Asherson R A, Aber V R, Gharavi A E, Hughes G R. Thrombosis, recurrent fetal loss, and thrombocytopenia. Predictive value of the anticardiolipin antibody test. *Arch Intern Med* 1986; **146**: 2153-6.
- 21 Gastineau D A, Kazmier F J, Nichols W Z, Bowie F J W. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. *Am J Hematol* 1985; **19**: 265-75.
- 22 Soulier R P, Boffa M C. Avertissements à répétition, thromboses et anticoagulant circulant antithromboplastine. *La Nouvelle Presse Medicale* 1980; **9**: 859-64.
- 23 Triplett D A, Brandt J T, Musgrave K A, Orr C A. The relationship between lupus anticoagulants and antibodies to phospholipid. *JAMA* 1988; **259**: 550-4.
- 24 Ordi J, Barquinero J, Montalbán J, Selva A, Vilardell M. Anticardiolipin antibodies in patients with lupus anticoagulants without systemic lupus erythematosus. *Clin Exp Rheumatol* (in press).
- 25 Lockwood C J, Reece E A, Romero R, Hobbins J C. Antiphospholipid antibody and pregnancy wastage. *Lancet* 1986; **ii**: 742-3.
- 26 Comp P C, DeBeault L E, Esmon N L, Esmon C T. Human thrombomodulin is inhibited by IgG from two patients with non-specific anticoagulants [Abstract]. *Blood* 1983; **62** (suppl 1): 299a.
- 27 Cariou R, Tobelem G, Soria C, Caen J. Inhibition of protein C activation by endothelial cells in the presence of the lupus anticoagulant. *Lancet* 1986; **i**: 1193-4.
- 28 Freyssinet J M, Gazenave J P. Lupus-like anticoagulants: modulation of the protein C pathway and thrombosis. *Thromb Haemost* 1986; **55**: 309-13.
- 29 Anglés-Cano E, Clauvel J P, Sultan Y. Predisposing factors to thrombosis in systemic lupus erythematosus: possible relation to endothelial cell damage. *J Lab Clin Med* 1979; **94**: 312-23.
- 30 Sanfelippo M J, Drayna C J. Prekallikrein inhibition associated with the lupus anticoagulant: mechanism of thrombosis. *Am J Clin Pathol* 1982; **77**: 275-9.
- 31 Sinzinger H, O'Grady J, Fitscha P, Kaliman J. Extremely-low-dose aspirin (one milligram per day) renders human platelets more sensitive to antiaggregation prostaglandins. *N Engl J Med* 1984; **311**: 1052.
- 32 Weksler B B, Pett S B, Alonso D, *et al.* Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients. *N Engl J Med* 1983; **308**: 800-5.
- 33 Gardlund B. The lupus inhibitor in thromboembolic disease and intrauterine death in the absence of systemic lupus. *Acta Med Scand* 1984; **215**: 293-8.
- 34 Gregorini G, Setti G, Remuzzi G. Recurrent abortion with lupus anticoagulant and pre-eclampsia: A common final pathway for two different diseases? Case report. *Br J Obstet Gynaecol* 1986; **93**: 194-6.
- 35 Tchobrousky C, Clauvel J P, Danon F, Sultan Y, Intrator L. Successful pregnancies in women with antiphospholipid antibodies without prednisone. *Clin Exp Rheumatol* (suppl 1) (in press).
- 36 Carreras L O, Pérez G N, Vega H R, Casavilla F. Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. *Lancet* 1988; **ii**: 393-4.
- 37 Harris E N. Third International Antiphospholipid Conference: barbecues, rum punches, and kops. *Ann Rheum Dis* 1988; **47**: 612-4.