

Risk factors in the pregnancy of patients with systemic lupus erythematosus: association of hypocomplementaemia with poor prognosis

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Abstract

Fetal wastage is still high in the pregnancies of patients with systemic lupus erythematosus (SLE). We examined retrospectively the cases of 38 patients with inactive SLE in whom pregnancy was either desired or had already been obtained. The prevalence of antiphospholipid antibodies in the group with fetal loss was high. The antibodies were, however, also detected in five of 14 patients who had had a live birth. It was noted that low levels of serum complement activity (CH50 < 25 U/ml) occurred in five of six patients with fetal loss, but in only two of 22 with a live birth. Serial studies also confirmed a close association between decreased serum complement activity and poor fetal prognosis in lupus pregnancy. Treatment with increased doses of prednisolone may help to achieve successful live births. Thus hypocomplementaemia may be associated with a worse prognosis for the fetus in the pregnancies of some patients with SLE in remission.

The natural history of pregnancy in patients with systemic lupus erythematosus (SLE) is variable. Fetal wastage is still high in these patients.¹⁻³ This may be due to the exacerbation of the disease with a subsequent change in fetomaternal interaction during the pregnancy. Fetal loss occurs often even in the pregnancies of patients whose disease is well controlled, in whom the abortion may be associated with the presence of anticoagulant or anticardiolipin antibodies.^{4,5} The administration of relatively high doses of corticosteroid in combination with aspirin brought about a successful outcome of pregnancy in these patients.^{6,7} Thus some autoantibodies may have a pathophysiological role in the mechanism of fetal wastage.⁸ Patients with habitual abortions, however, may lack anticoagulant activity or anticardiolipin antibodies, and a live birth may occur even in patients showing positive tests for antiphospholipid antibodies. Therefore, it is clinically important to study the factors that influence the prognosis of pregnancies in patients with well controlled SLE. In this paper we suggest that hypocomplementaemia may be an important indicator of a poor prognosis for the fetus in lupus pregnancy.

Patients and methods

PATIENTS

Since 1981 we have seen 38 women, all fulfilling the 1982 American Rheumatism Association

revised criteria for the diagnosis of SLE, who wanted children. Their average age was 27 years (range 22-37) and all were in an inactive stage of the disease⁹⁻¹⁴ before the studied pregnancy began. The infertile patients also had inactive disease during the study.

OUTCOME OF PREGNANCY

Pregnancy outcomes were classified into three groups: live birth, fetal death, and elective abortion. Fetal death was defined as: (a) miscarriage before 23 weeks' gestation; (b) still birth at or after 23 weeks. No infants had neonatal complications, such as infection, non-febrile seizures, neonatal lupus, congenital heart block, or any apparent deformity.

SEROLOGY AND OTHER CLINICAL INVESTIGATIONS

Clinical data were checked retrospectively for patients who had achieved pregnancy, from the time just before conception took place, and for patients who had not yet conceived. The following data were evaluated: doses of prednisolone, urine analysis (urinary protein and cellular casts), erythrocyte sedimentation rates, peripheral blood white blood cells, red blood cells, platelets, autoantibodies, coagulation studies, and serum complement activities measured as CH50.

Full immunological testing was performed, including total immunoglobulin estimations, determination of antinuclear antibodies, antibodies to double stranded (ds) DNA, antibodies to Sm, RNP, SS-A, SS-B, rheumatoid factors, and Coombs' test. Antibodies to dsDNA were measured by radioimmunoassay using a modified Farr assay.¹⁵ Antibodies to phospholipids were determined by modified enzyme linked immunosorbent assay (ELISA) according to the method of Harris *et al.*¹⁶ Briefly, the test serum samples, at a 1:100 dilution, were added to flat bottomed microtitre plates (Costar) precoated with cardiolipin micelles, phosphatidic acid, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, or phosphatidylethanolamine (Seikagaku Kogyo, Tokyo, Japan). After incubation the plates were washed, and peroxidase conjugated, antihuman IgG or IgM was added. After an appropriate incubation and a final wash, *o*-phenylenediamine with a suitable substrate was added. The optical density of the individual wells was read at 492 nm with an MR 600 plate reader (Dynatech, Alexandria, VA, USA). Values at least two standard deviations above the mean of normal control values were considered positive.

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The partial thromboplastin time was assessed in our laboratory. The presence of lupus anticoagulant was determined by the kaolin activated, partial prothrombin time and the cross mixing test.⁸ Lupus anticoagulant was considered present when the prolonged kaolin partial prothrombin time was not corrected by the addition of normal plasma.

Results

FERTILITY AND OUTCOME OF PREGNANCY IN LUPUS PATIENTS

Of 38 patients, 30 had 33 pregnancies and the remaining eight were infertile despite wishing to conceive. Of the 33 pregnancies, five had elective abortions for social reasons. Live births were achieved in 22 pregnancies, whereas six pregnancies resulted in fetal death.

RELATIONS BETWEEN LABORATORY FINDINGS BEFORE PREGNANCY AND PROGNOSIS OF THE FETUS

The patients were divided into four groups according to the ability to conceive and the fetal prognosis: infertility, fetal death, elective abortion, and live birth. Each group was retrospectively compared for their clinical and laboratory data before pregnancy to discover what factors might be associated with the

outcome of pregnancy in lupus patients (table 1). There were no significant differences in erythrocyte sedimentation rate, complete blood counts, liver function, serum creatinine, or anti-nuclear antibody titre between the groups (data not shown).

Table 2 shows clinical profiles of patients who were infertile or had had a fetal death. There were no typical clinical manifestations of SLE, such as skin rash, arthritis, stomatitis, serositis, or ankle oedema in any patients at the time of the study. The only exception was Raynaud's phenomenon, which was found in three cases. Urinary protein was positive in two cases, but the urine analysis showed no haematuria or cellular casts in their sediments. No serum samples showed significantly raised antibody titres to dsDNA. It was noted that three out of four pregnancies in three patients with positive lupus anticoagulant resulted in fetal death. Antiphospholipid antibodies were 80% positive in the group with fetal death (fig 1, table 1). Another remarkable finding was hypocomplementaemia in patients with infertility or with fetal loss. Six of eight infertile patients showed significantly decreased CH50 levels in their serum samples, which have persisted to the present. As shown in fig 2 the incidence of pregnancy in lupus patients showing low levels of serum complement activity (CH50 < 25 U/ml) was lower than for those with normal levels

Table 1 Correlation between laboratory findings and prognosis of pregnancy in patients with systemic lupus erythematosus. Results are shown as number of positive cases/total number of cases (except for prednisolone dose)

Laboratory data	Infertile	Outcome of pregnancy		
		Fetal death	Elective abortion	Live birth
Active disease*	0/8 [†]	0/6	0/5	0/22
Mean doses of prednisolone (mg/day)	9.2	10.5	8.8	8.8
Urinary protein present	2/7	0/5	1/4	0/21
Antibodies to dsDNA	0/7	0/6	0/3	0/21
Lupus anticoagulant	0/7	3/6	0/2	1/14
Antiphospholipid Ab [†]	4/8	4/6	0/3	5/14
Hypocomplementaemia (CH50 < 25 U/ml)	6/8	5/6	1/5	2/21

*Lupus activity was determined by previously described criteria.⁹⁻¹⁴

[†]Positive tests for antibodies to cardiolipin, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, or phosphatidylethanolamine.

Table 2 Clinical profiles of patients with clinically inactive systemic lupus erythematosus⁵⁻¹⁴ at the time studied

Case No	Age (years)	Clinical signs	Urinary protein (g/day)	CH50* (U/ml)	C3* (mg/l)	C4* (mg/l)	Antibodies to dsDNA (U)	Lupus anti-coagulant	Anti-phospholipid antibodies	Prognosis
1	37	—	0	37.0	750	220	1	(-)	(-)	Infertile
2	28	Raynaud's phenomenon	1.0	24.6	430	100	12	(-)	(+)	Infertile
3	30	—	0	23.4	430	126	0	(-)	(-)	Infertile
4	30	—	Trace	22.8	440	150	0	(-)	(-)	Infertile
5	27	Raynaud's phenomenon	Trace	16.7	460	126	2	(-)	(-)	Infertile
6	37	—	0	16.4	440	20	1	(-)	(+)	Infertile
7	26	—	1.0	14.9	440	50	10	(-)	(+)	Infertile
8	25	—	0	29.8	720	310	0	(-)	(+)	Infertile
9	27	Raynaud's phenomenon	0	29.6	770	110	2	(+)	(+)	Miscarriage at 16 weeks
10	30	—	0	24.5	—	—	3	(-)	(-)	Miscarriage at 11 weeks
11	24	—	0	19.9	770	—	4	(+)	(+)	Miscarriage at 10 weeks
12	25	—	0	19.8	700	190	4	(+)	(+)	Miscarriage at 6 weeks
13	31	—	0	21.5	670	50	5	(-)	(-)	Miscarriage at 13 weeks
14	25	—	Trace	24.0	420	100	0	(-)	(+)	Miscarriage at 12 weeks

*Normal range: CH50 30-50 U/ml, C3 500-1000 mg/l, C4 150-400 mg/l.

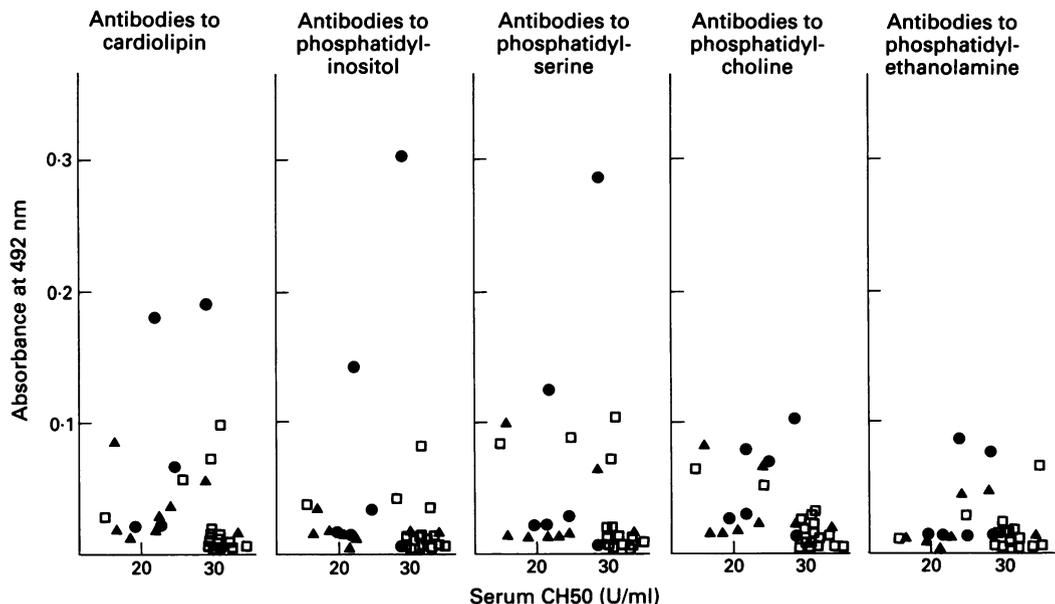


Figure 1 Antiphospholipid antibodies and serum CH50 values in each group. Antibody activity to cardiolipin, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, or phosphatidylethanolamine was determined by ELISA as described in 'Materials and methods'. Data for CH50 values and antiphospholipid activity were obtained from serum samples taken before conception in all pregnant patients or taken from infertile patients. \blacktriangle = infertile group; \bullet = fetal death group; \square = live birth group.

($p < 0.01$). Of interest was that hypocomplementaemia ($CH50 < 25$ U/ml) occurred in most patients in the group with fetal death. Figure 2 also shows that low complement levels are associated with a low incidence of live births when compared with normal levels ($p < 0.01$).

SERIAL STUDIES

Serial studies were performed to determine whether the level of serum complement activity determined before pregnancy can be linked to fetal prognosis. Some cases are shown below.

Patient No 13 (see table 2)

Figure 3 shows the clinical course of this

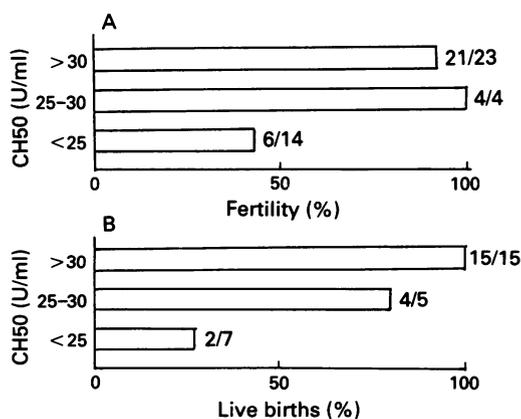


Figure 2 Correlation between serum CH50 values and (A) fertility or (B) outcome of pregnancy. The percentage frequency of fertility (A) was expressed as (number of pregnant patients/total number of patients) $\times 100$ and the percentage frequency of live birth (B) as (numbers of live births/(number of live births + number of fetal deaths)) $\times 100$. The numbers at the end of the blocks show the number of positive cases/total cases.

patient. In 1981 she had typical SLE, showing facial erythema and arthralgia. Laboratory findings also showed abnormal liver functions, leucocytopenia (white blood cell count $2.5 \times 10^9/l$), positive LE cells, and high titres of antibodies to dsDNA. Histological examination of a liver biopsy specimen showed lupoid hepatitis. She was in remission and her serum CH50 value was 27.1 U/ml when she first became pregnant in March 1983. The pregnancy went successfully and she delivered a live infant at term. She was still clinically well and no antibodies to dsDNA were detected. Her serum CH50, however, dropped to 19.7 U/ml before her second pregnancy in spring 1988, and fetal death occurred at the first trimester. She again became pregnant in November 1988, when her CH50 level was 25.0 U/ml. Increased doses of prednisolone (20 mg/day) normalised her serum complement level and she had a trouble free delivery of a healthy boy in August 1989.

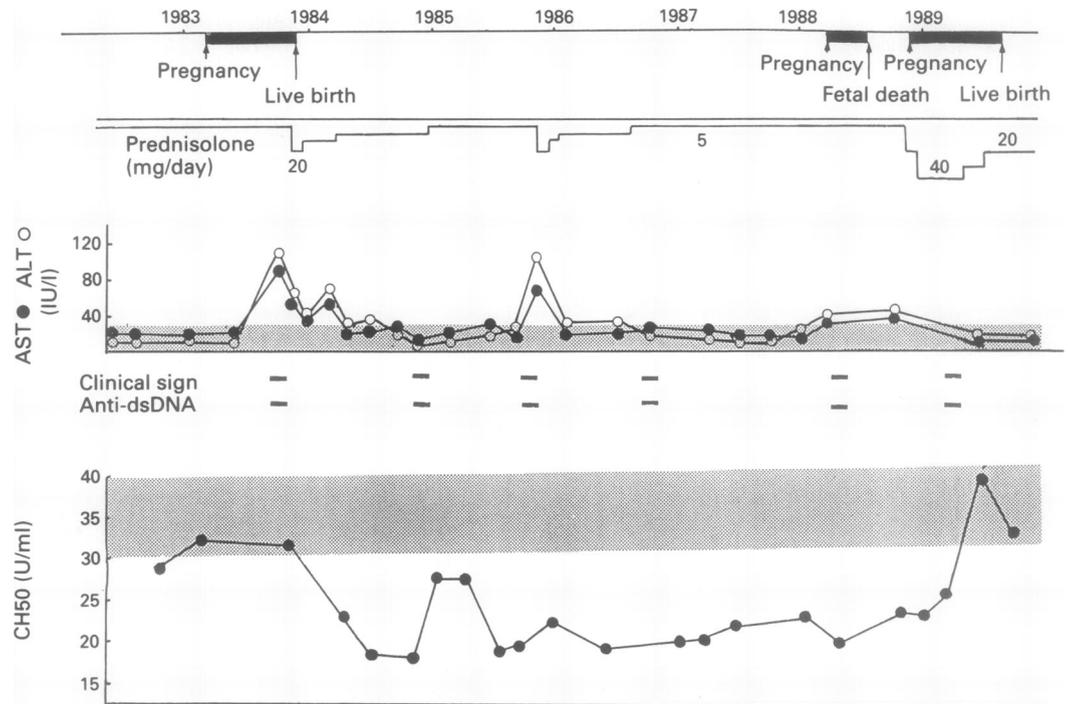
Patient No 10 (see table 2)

After the onset of SLE with acute episodes characterised by butterfly rash, alopecia, and arthralgia in 1981 this patient was treated with prednisolone until the disease went into remission. Since then she has had three pregnancies. Serum CH50 values were normal before the first and the third pregnancies, both of which were successful. The level of her serum CH50 was 24.5 U/ml just before the second pregnancy, which resulted in fetal death at the 11th week.

Patient No 15

This patient had facial erythema, arthralgia, and Raynaud's phenomenon in 1982. Laboratory examination also showed positive antinuclear

Figure 3 Clinical course of patient No 13. AST=aspartate transaminase; ALT=alanine transaminase.



antibodies, raised antibody titres to dsDNA, thrombocytopenia, and positive urinary protein at that time. All findings except hypocomplementaemia returned to normal after treatment. She became pregnant in June 1986, when her serum CH50 was 11.0 U/ml. Serum complement activity was still low until the third trimester, when rash, thrombocytopenia ($47 \times 10^9/l$), and proteinuria (1.2 g/day) occurred. Doses of prednisolone up to 40 mg/day were given and a liveborn infant was delivered by caesarian section.

Discussion

Patients with SLE have an increased incidence of fetal wastage.¹⁻³ The precise pathophysiological mechanisms for the increased fetal loss remain unclear. Recent data have shown that the incidence of lupus anticoagulant and antiphospholipid antibodies might be associated with a poor prognosis for pregnancy.⁴⁻⁶ One study of 11 lupus patients showed that fetal or neonatal death occurred in four cases, in all of which lupus anticoagulant activity was present in the serum samples, and in one anticardiolipin antibody activity was noted.⁴ In another study lupus anticoagulant was positive for six of 12 patients with SLE, which resulted in fetal loss, and anticardiolipin antibodies were present in 75% of cases with unsatisfactory fetal development.⁵

Our data also showed that most patients with fetal loss were positive for lupus anticoagulant activity or for antiphospholipid antibody activity. Thus these data indicate that antiphospholipid antibodies or lupus anticoagulant may play a part in the pathogenesis of an impaired fetomaternal interaction, and that detection of these antibodies may be useful for predicting the prognosis of pregnancy, especially in cases of repeated abortion. Fetal loss, however, often occurs in pregnant patients with SLE with no

lupus anticoagulant or anticardiolipin antibodies^{5,6} (table 2) and, conversely, anticoagulant or antiphospholipid antibodies were detected in patients with a live birth^{17,18} (table 1). Therefore, it is clinically important to find other markers associated with prognosis for the fetus in lupus pregnancies.

We have shown in this paper the close association of hypocomplementaemia with a poor prognosis for the fetus. Similar results have been obtained previously for the outcome of lupus pregnancies.^{19,20} Low C3 and C4 concentrations were found in four pregnancies, all of which resulted in spontaneous abortion.¹⁹ The report, however, included clinically active patients, who would be expected to have a poor fetomaternal interaction. Furthermore, the authors emphasised the clinical importance of monitoring C3 and C4 activity during pregnancy. Our intention, however, was to assess the relation between the fetal prognosis and laboratory findings before pregnancy of lupus patients in remission. Some of our patients showed low complement activity in their serum samples. As hypocomplementaemia is one of the clinical markers indicating lupus activity it is possible that these patients were not in remission at the studied time.⁹⁻¹³ None of these patients, however, had either apparent clinical manifestations or laboratory findings associated with an exacerbation of the disease. Thus these patients were regarded as inactive by each of six different previously reported criteria.^{9-14,21}

Hypocomplementaemia occurred in six of eight cases with infertility and in five of six pregnancies with fetal loss, whereas only two of 22 successful pregnancies showed low levels of CH50 activity before and during the conception. Patient No 15 with hypocomplementaemia had a live birth. She, however, had an episode of thrombocytopenia in the third trimester of pregnancy. Serial studies in patients Nos 10 and 13 showed that treatment with increased doses

of prednisolone brought about not only normalisation of serum complement activity but also a successful live birth. Thus serum complement activity may be closely associated with fetal prognosis in lupus pregnancy, and measurement of serum complement activity before pregnancy may be useful as a predictor of lupus pregnancy.

We do not yet know the mechanism by which hypocomplementaemia in pregnancy is produced. Low complementaemia might be attributed to a decreased production of complement factors. This is unlikely, however, because severe dysfunction in the liver or macrophages responsible for complement synthesis did not occur in the patients presented here. We prefer the hypothesis that low serum complement activity might reflect an activation of some immunological factors or an increased formation of immune complexes, which might evoke an immunological disorder, thus impairing the fetomaternal interaction in pregnancy. This is interesting in the light of the antiphospholipid syndrome.²²⁻²⁴ This newly proposed entity is characterised by thrombosis and recurrent abortion, and in most cases thrombocytopenia, positive lupus anticoagulant, and a raised anticardiolipin antibody titre were present. Antinuclear antibodies and other serological findings of autoimmunity are commonly detected in such patients. Some patients may fulfil the American Rheumatism Association criteria for the diagnosis of SLE and constitute a subgroup of SLE, characterised by the symptoms mentioned together with recurrent abortions.

Antiphospholipid antibodies, however, often occurred in patients with a live birth. This may be attributed to the heterogeneity of antiphospholipid antibodies, so that some antiphospholipid antibodies, such as those with complement fixing ability, may cause abortions in these patients, but others not (Sibata, unpublished data).

Taken together, these data indicate that low serum complement activity may be associated with a worse prognosis for the fetus in the pregnancy of patients with SLE who are regarded as inactive according to previously described criteria. Further studies are needed to establish the degree to which such findings are clinically reliable as predictors.

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- 1 Tozman E C S, Urowitz M B, Gladman D D. Systemic lupus erythematosus and pregnancy. *J Rheumatol* 1980; **7**: 624-32.
- 2 Fine L G, Barnett E V, Danovitch G M, et al. Systemic lupus erythematosus in pregnancy. *Ann Intern Med* 1981; **94**: 667-77.
- 3 Lockshin M D. Lupus pregnancy. *Clin Rheum Dis* 1985; **11**: 611-32.
- 4 Hanly J G, Gladman D D, Rose T H, Laskin C A, Urowitz M B. Lupus pregnancy. A prospective study of placental changes. *Arthritis Rheum* 1988; **31**: 358-66.
- 5 Lockshin M D, Qamar T, Druzin M L. Hazards of lupus pregnancy. *J Rheumatol* 1987; **14**: 214-7.
- 6 Derue G J, Englert H J, Harris E N, et al. Fetal loss in systemic lupus: association with anticardiolipin antibodies. *J Obstet Gynecol* 1985; **5**: 207-9.
- 7 Lubbe W F, Butler W S, Palmer S J, Liggins G C. Fetal survival after prednisolone suppression of maternal lupus-anticoagulant. *Lancet* 1983; **i**: 1361-3.
- 8 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.
- 9 Budman D R, Merchant E B, Steinberg A D, et al. Increased spontaneous activity of antibody-forming cells in the peripheral blood of patients with active SLE. *Arthritis Rheum* 1977; **20**: 829-33.
- 10 Morrow W J W, Isenberg D A, Parry H F, Snaith M L. C-reactive protein in sera from patients with systemic lupus erythematosus. *J Rheumatol* 1981; **8**: 599-604.
- 11 Smolen J S, Chused T M, Leiserson W M, Reeves J P, Alling D, Steinberg A D. Heterogeneity of immunoregulatory T-cell subsets in systemic lupus erythematosus. *Am J Med* 1982; **72**: 783-90.
- 12 Lockshin M D, Reinitz E, Druzin M L, Murrman M, Estes D. Lupus pregnancy: case-control study demonstrating absence of lupus exacerbation during or after pregnancy. *Am J Med* 1984; **77**: 893-8.
- 13 Ropes M W. *Systemic lupus erythematosus*. Cambridge, MA, USA: Harvard University Press, 1976.
- 14 Committee on prognosis studies in SLE. Prognosis studies in SLE: an activity index [abstract]. *Arthritis Rheum* 1986; **29** (suppl 4): s93.
- 15 Pincus T, Schur P H, Rose J A, Decker J L, Talal N. Measurement of serum DNA binding activity in lupus erythematosus. *N Engl J Med* 1969; **281**: 701-5.
- 16 Harris E N, Gharavi A E, Boey M L, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983; **ii**: 1211-4.
- 17 Petri M, Rheinschmidt M, Whiting-O'Keefe Q, Hellmann D, Corash L. The frequency of lupus anticoagulant in systemic lupus erythematosus. *Ann Intern Med* 1987; **106**: 524-31.
- 18 Fort J G, Cowchock F S, Abruzzo J L. Anticardiolipin antibodies in patients with rheumatic diseases. *Arthritis Rheum* 1987; **30**: 752-60.
- 19 Lawrence D D, Gary L L. Serum complement levels and perinatal outcome in pregnancies complicated by systemic lupus erythematosus. *Obstet Gynecol* 1984; **63**: 796-800.
- 20 Lockshin M D, Harpet P C, Druzin M L, et al. Lupus pregnancy: II. Unusual pattern of hypocomplementaemia and thrombocytopenia in the pregnant patient. *Arthritis Rheum* 1985; **28**: 58-66.
- 21 Liang M H, Socher S A, Larson M G, Schur P H. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1989; **32**: 1107-18.
- 22 Harris E N, Gharavi A E, Hughes G R V. Antiphospholipid antibodies. *Clin Rheum Dis* 1985; **11**: 591-609.
- 23 Hughes G E V, Harris E N, Gharavi A E. The anticardiolipin syndrome. *J Rheumatol* 1986; **13**: 486-9.
- 24 Unander A M, Norberg R, Hahn L, Årfors L. Anticardiolipin and complement in ninety-nine women with habitual abortion. *Am J Obstet Gynecol* 1987; **156**: 114-9.