

Outcome of pregnancy in patients with autoimmune rheumatic disease before the disease onset

A SIAMOPOULOU-MAVRIDOU, M N MANOUSSAKIS, A K MAVRIDIS, AND H M MOUTSOPOULOS

From the Department of Medicine, Medical School, University of Ioannina, 453 32 Ioannina, Greece

SUMMARY The outcomes of 419 pregnancies of 154 unselected patients with various autoimmune diseases, including 390 pregnancies before the disease onset, were studied retrospectively. The patients comprised 40 with systemic lupus erythematosus (SLE), 72 with rheumatoid arthritis, 21 with primary Sjögren's syndrome (1°SS), 14 with progressive systemic sclerosis (PSS), and seven with mixed connective tissue disease. The histories of 267 pregnancies of 99 healthy, age matched women served as controls. Our data indicate that compared with healthy controls autoimmune patients do not experience a higher incidence of fetal loss. The incidence of fetal loss before disease onset in the various groups of autoimmune patients (as well as after disease onset in patients with SLE and RA) was not significantly different from that of controls. Spontaneous abortions in patients with 1°SS and PSS before disease onset occurred significantly more frequently ($p < 0.05$) than in controls. Nevertheless, it should be noted that this was not the case when the incidence per woman was considered. On the other hand, patients with SLE, both before and after disease onset, experienced a higher incidence of premature deliveries ($p < 0.05$). Finally, the analysis of autoantibody profiles, including antibodies to nuclear antigens, Ro(SSA) cellular antigen, to double stranded DNA, and to cardiolipin, could not demonstrate any association of autoantibodies with any particular pregnancy outcome.

Key words: fetal loss, autoantibodies, anticardiolipin antibodies.

Autoimmune rheumatic diseases (ARD) are known to occur predominantly in women. Fertility in patients with ARD does not seem to be impaired,¹ therefore pregnancy in these individuals is frequently of clinical relevance.

Several studies have shown that spontaneous abortion and premature deliveries are frequently encountered in the pregnancies of women with systemic lupus erythematosus (SLE).¹⁻³ Pregnancy in SLE has been extensively studied owing to the fact that this disease affects primarily women of childbearing age. In contrast, data on pregnancy outcome in certain other autoimmune diseases, such as primary Sjögren's syndrome (1°SS) or progressive systemic sclerosis (PSS), are as yet inadequate, presumably because these entities mainly occur in women during the fourth or the fifth decade of

life.^{4,5} Furthermore, there is some controversy between previously published studies regarding whether patients with SLE already present a higher incidence of complicated pregnancies before the disease onset.^{3,6}

The increased incidence of fetal loss in patients with SLE has been attributed to the presence of placental vasculitis and infarctions. Further, maternal autoantibody responses, including immune complex deposition and the cross reaction of lymphocytotoxic antibodies with trophoblast, have been incriminated.⁷ The recently presented association between the presence of anticardiolipin (anti-CL) antibodies and habitual abortions in patients with SLE is currently receiving considerable attention. Antibodies reacting with cardiolipin and other anionic phospholipids have also been associated with the presence of vascular thrombosis in patients with SLE and SLE-like disease.⁸ Such anti-CL associated thrombotic events are believed to cause placental infarctions and subsequent fetal loss in these patients.⁸

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Correspondence to Dr A Siamopoulou-Mavridou, Department of Medicine, Medical School, University of Ioannina, 453 32 Ioannina, Greece.

The main purpose of this study was to investigate whether patients with autoimmune diseases suffer from an increased incidence of complicated pregnancies before the development of clinical manifestations. For this purpose, the histories of pregnancies both before and after the disease onset of a fairly large number of unselected patients with various autoimmune diseases were retrospectively studied. Further, we evaluated the autoantibody profiles of these patients, including anti-CL antibodies, with respect to the outcome of their pregnancies.

Patients and methods

The histories of 419 pregnancies in 154 consecutive unselected Greek married women with various autoimmune rheumatic diseases were retrospectively evaluated. Patients in this study included 72 women with classical rheumatoid arthritis (RA),¹⁰ 40 with SLE,¹⁰ 21 with 1°SS,⁴ 14 with PSS,⁵ and seven with mixed connective tissue disease (MCTD).³ Patients were specifically interviewed for the number of pregnancies, full terms, premature deliveries (spontaneous termination of gestation between the 21st and 37th week), stillbirths (intra-uterine fetal death after 21st week of gestation and before birth), and spontaneous abortions (interruption of pregnancy before 20 weeks of gestation). In addition, fetal loss (sum of spontaneous abortions and stillbirths) and fertility rate (average number of pregnancies per individual) were estimated.³ Control material consisted of the histories of 267 pregnancies of 98 healthy Greek women visiting the outpatient gynaecological clinic routinely, matched for age and for socioeconomic and marital status with the patients studied. In addition, serum samples from these healthy individuals were used as controls in serological studies. We also retrospectively evaluated the autoantibody profile of patients during their first assessment in our clinic, at a time ranging from 0 to 12 years after their disease onset (mean (SD) for SLE 2.5 (2.0) years, RA 3.1 (3.0) years, 1°SS 3.8 (3.5) years, PSS 3.2 (2.9) years, and MCTD 1.3 (0.8) years after disease onset). Autoantibody profiles consisted of antibodies to nuclear antigens (ANAs, detected by indirect immunofluorescence using HEp₂ epithelial cells as substrate, positive ANA titre 1/80), antibodies to Ro(SSA) cellular antigen (by counterimmunoelectrophoresis and double immunodiffusion using human spleen and calf thymus extracts), as well as of IgG antibodies to double stranded DNA (anti-dsDNA) and IgG and IgM antibodies to cardiolipin (anti-CL) by isotype specific, enzyme linked immunosorbent assays (ELISAs), as previously described.^{11 12}

Results in anti-dsDNA and anti-CL assays were expressed as a binding index (BI), as previously.¹³ A binding index of 100 (BI=100) was defined as the cut off point for positivity (four standard deviations above the mean of a large number of healthy blood donors previously examined). The presence of the above autoantibodies was also examined in the serum samples from the 98 healthy women (controls).

STATISTICAL ANALYSIS

Data were analysed by χ^2 test with Yates's correction and Student's *t* test, where applicable.

Results

No differences were observed between the fertility rates of the healthy control group (2.7) and the various groups of patients studied (ranging from 2.5 to 3.0).

In the various groups of patients 390 out of the 419 pregnancies had ended before the disease onset (Tables 1, 2). The time between the above pregnancies and the disease onset ranged between 1 and 45 years, and no differences were observed in this between the various groups of patients. Twenty nine additional pregnancies (Table 1) occurred—14 in 12 patients with SLE and 15 in 10 patients with RA—after the onset of the disease (two months up to four years). Tables 1 and 2 show the incidences of the various outcomes of pregnancies in patients and controls.

Recurrent (more than one, ranging from two to four) spontaneous abortions occurred in 18 patients with ARD (two with SLE, nine with RA, three each with 1°SS and PSS, and one with MCTD) and three healthy women, while recurrent stillbirths occurred in four patients with ARD (two with SLE and one each with RA and 1°SS).

A comparison of the pregnancy outcome in the various patients groups before the development of the disease and in the controls did not show any remarkable differences (Tables 1 and 2). The incidence of fetal loss was found to be similar in all groups examined. Patients with 1°SS and PSS had a higher incidence of spontaneous abortions (per pregnancy) than controls ($p<0.05$) (Table 2). On the other hand, prematurity was significantly more frequent in patients with SLE than in controls (per pregnancy, as well as per woman, $p<0.05$). Stillbirths in pregnancies of patients with SLE were significantly more frequent after than before disease onset ($p<0.05$) (Table 1). Further, although the difference was not statistically significant, the incidence of prematurity increased in patients with SLE after disease onset.

Table 1 Outcome of pregnancy before and after the clinical onset of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)

| | SLE (n=40) | | RA (n=72) | | Control (n=98) |
|---------------------------------|-----------------|----------------|-----------------|----------------|-----------------|
| | Before (n=38) | After (n=12) | Before (n=69) | After (n=10) | |
| Mean age† (SD) (range) | 43 (13) (25-75) | 26 (8) (19-40) | 43 (12) (19-69) | 23 (5) (19-38) | 41 (11) (20-70) |
| No of pregnancies | 81 | 14 | 191 | 15 | 267 |
| No of full terms‡ (%) | 69 (85) | 11 (79) | 155 (81) | 11 (73) | 226 (85) |
| No of premature births (%) | 4 (5)* | 1 (7)* | 2 (1) | 0 (0) | 2 (1) |
| No of spontaneous abortions (%) | 7 (9) | 0 (0) | 30 (16) | 4 (27) | 31 (12) |
| No of stillbirths (%) | 1 (1) | 2 (14)** | 4 (2) | 0 (0) | 8 (3) |
| No of fetal losses (%) | 8 (10) | 2 (14) | 34 (18) | 4 (27) | 39 (15) |

*p<0.05 compared with control; **p<0.05 compared with data from patients with SLE before disease onset.

†Mean age (years) at disease onset.

‡Newborns, small for gestational age, were one found in SLE and the RA groups.

Table 2 Outcome of pregnancy before the clinical onset of primary Sjögren's syndrome (I°SS), progressive systemic sclerosis (PSS), and mixed connective tissue disease (MCTD)

| | I°SS (n=21) | PSS (n=14) | MCTD (n=7) | Controls (n=98) |
|---------------------------------|----------------|-----------------|-----------------|-----------------|
| Mean age† (SD) (range) | 48 (9) (35-69) | 45 (11) (30-73) | 38 (12) (23-60) | 41 (13) (20-70) |
| No of pregnancies | 63 | 36 | 19 | 267 |
| No of full terms (%) | 48 (76) | 28 (78) | 16 (84) | 226 (85) |
| No of premature births (%) | 0 (0) | 0 (0) | 0 (0) | 2 (1) |
| No of spontaneous abortions (%) | 13 (21)* | 8 (22)* | 3 (16) | 31 (12) |
| No of stillbirths (%) | 2 (3) | 0 (0) | 0 (0) | 8 (3) |
| No of fetal losses (%) | 15 (24) | 8 (22) | 3 (16) | 39 (15) |

*p<0.05 compared with control.

†Mean age (years) at disease onset.

When data for patients with RA before and after disease onset were compared, an increase (not statistically significant) in the incidence of spontaneous abortions was noted (Table 1).

Most patients studied were serologically hyper-reactive, as exemplified by the incidence of positive ANA tests (in 70% of patients, mean positive ANA titre 1/905), anti-Ro(SSA) antibodies (in 25% of patients), IgG anti-CL (in 10%, mean positive BI=235), and IgM anti-CL (in 5%, mean positive BI=343). Finally, more than half (55%) of the patients with SLE had anti-dsDNA antibodies (mean positive BI=413) (Table 3). In the healthy control population positive ANA tests were evident in three women (titre 1/320), while IgG anti-CL were found in another three (with BI=143, 197, and 111 respectively) and IgM anti-CL in one (BI=132) (Table 3). We could not show any association between the outcome of pregnancy and the presence

of any particular autoantibody under consideration. This was still the case when data from women older than 40 years at the time of serum collection were omitted, in an attempt to exclude the possibility of age induced autoantibodies¹³ (data not shown). The occurrence of autoantibodies before the disease onset could not be verified, however. Therefore, we further examined the correlation of autoantibody profiles with the outcome of pregnancies in the 14 patients with SLE and the 10 patients with RA with pregnancies after the disease onset (14 and 15 pregnancies respectively), where serum samples before gestation were available. Antibodies could still not be associated with any of the various pregnancy outcomes (Table 4). Six pregnancies ended with fetal loss; anti-Ro(SSA) and anti-dsDNA antibodies were present in two of them, while anti-CL antibodies were detected in one. In addition, a premature delivery was experienced by

Table 3 Autoantibody profile of patients and controls

| Serological parameters | SLE (n=40) | RA (n=72) | 1°SS (n=21) | PSS (n=14) | MCTD (n=7) | Controls (n=98) |
|------------------------|------------|-----------|-------------|------------|------------|-----------------|
| ANA | 35 (88)* | 35 (49) | 17 (81) | 14 (100) | 6 (86) | 3 (3) |
| Anti-Ro(SSA) | 23 (58) | 7 (10) | 7 (33) | 1 (7) | 1 (14) | 0 (0) |
| IgG anti-dsDNA | 22 (55) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| IgG anti-CL | 10 (25) | 4 (6) | 1 (5) | 0 (0) | 0 (0) | 3 (3) |
| IgM anti-CL | 4 (10) | 1 (1) | 2 (10) | 0 (0) | 1 (14) | 1 (1) |

*Values are No (%).

SLE=systemic lupus erythematosus; RA=rheumatoid arthritis; 1°SS=primary Sjögren's syndrome; PSS=progressive systemic sclerosis; MCTD=mixed connective tissue disease; ANA=antinuclear antibody; anti-CL=anticardiolipin.

Table 4 Correlation of the presence of antibodies to Ro(SSA), dsDNA, and cardiolipin (CL) with the incidence of complicated pregnancies in patients after the disease onset

| | SLE (14 pregnancies/12 patients) | | RA (15 pregnancies/10 patients) | | Total (29 pregnancies/22 patients) | |
|-------------------------|----------------------------------|----------------------|---------------------------------|----------------------|------------------------------------|----------------------|
| | Complicated (n=3) | Uncomplicated (n=11) | Complicated (n=4) | Uncomplicated (n=11) | Complicated (n=7) | Uncomplicated (n=22) |
| Anti-Ro ⁺ | 3 | 6 | 0 | 2 | 3 | 8 |
| Anti-Ro ⁻ | 0 | 5 | 4 | 9 | 4 | 14 |
| Anti-dsDNA ⁺ | 3 | 5 | 0 | 0 | 3 | 5 |
| Anti-dsDNA ⁻ | 0 | 6 | 4 | 11 | 4 | 17 |
| Anti-CL ⁺ | 1 | 4 | 1 | 1 | 2 | 5 |
| Anti-CL ⁻ | 2 | 7 | 3 | 10 | 5 | 17 |

mother with anti-Ro(SSA), anti-dsDNA, and anti-CL antibodies. In the pregnancies of the patients with SLE the presence of anti-Ro(SSA) or anti-dsDNA antibodies was highly sensitive (100%) but quite unspecific (specificity 45.5% and 54.5% respectively) in predicting pregnancy complication—that is, premature deliveries and fetal losses). On the other hand, in these patients the presence of anti-CL antibodies was not a sensitive index of pregnancy complication (sensitivity 33.3%) (Table 4). Of the four healthy controls with anti-CL antibodies (Table 2), a woman (aged 27) with IgM anti-CL had a history of one premature delivery and one spontaneous abortion. In addition, no autoantibody was found in two other women with multiple spontaneous abortions but also with full term deliveries.

Discussion

Pregnancy in autoimmune patients is a frequent clinical situation in the specialties of both obstetrics and rheumatology. The outcome of pregnancy can be affected by the presence of the autoimmune disease and vice versa. Therefore the interaction of these processes may be important for the health of both the mother and fetus.⁷

In comparison with healthy controls, women with SLE and MCTD were previously shown to have an increased incidence of total fetal loss—that is, the sum of fetal losses and therapeutic abortions—even before the clinical onset of their disease.³ Further, it has been suggested that the incidence of complicated pregnancies in these individuals increased after the development of clinical manifestations.³⁻⁶

In the present report we retrospectively evaluated the histories of a fairly large number of pregnancies of several unselected patients with ARD, including pregnancies before and after the disease onset. Our data indicate that compared with healthy controls women with ARD did not experience more frequently complicated pregnancies in general, or fetal loss in particular, either before or after the disease onset. As also previously described,²⁻⁶ however, prematurity (per pregnancy as well as per woman) was consistently more prevalent in our patients with SLE, both before and after their disease onset ($p<0.05$), than in healthy controls. In addition, the incidence of stillbirths among pregnancies of patients with SLE increased significantly ($p<0.05$) after the disease onset, a fact also previously reported.³⁻⁶ It is noteworthy that, compared with data from some previous studies, complicated pregnancies in our patients with SLE were not as

common. Previous reports on pregnancy outcome in SLE as well as in healthy women have indicated considerable variation in the prevalence of fetal loss, spontaneous abortions, stillbirths, and premature deliveries.^{3 6 7 14 15} Reasons which may account for these discrepancies include differences in patients and healthy control populations as well as in the severity and activity of the disease in the pregnant women examined.

In contrast with SLE, the course of pregnancy in patients with established diagnosis of RA or PSS is reported not to carry any particular fetal risk due to the presence of the disease.^{16 17} To our knowledge there are no data available on the pregnancy outcome in patients with RA or with 1°SS before the clinical appearance of their disease, while previously studied pregnancies before PSS did not show any remarkable incidence of complication.¹⁷ In this study it is shown that the incidence of spontaneous abortions (per pregnancy but not per women) in patients with PSS or 1°SS several years before their disease onset was significantly higher than in controls. We do not have a ready explanation for this observation, but it should be noted that these observed differences were of borderline statistical significance. Nevertheless, further studies are needed to clarify the issue.

The outcomes of the limited number of pregnancies before MCTD did not show any remarkable differences compared with controls. A previous study found that total fetal loss—that is, the sum of fetal losses and therapeutic abortions—was significantly higher in patients before MCTD.³ In that study, however, the incidence of fetal loss (termed fetal wastage) in patients before MCTD (16% of pregnancies) did not differ from that of controls.

We could not show any association between the presence of autoantibodies under consideration, including anti-Ro(SSA), anti-dsDNA, and anti-CL antibodies, and any particular complication of pregnancy in the patients with ARD. In fact, a considerable percentage of pregnancies of anti-CL positive women (five out of seven) were completed as full term deliveries, suggesting limited, if any, predictive value of these autoantibodies for fetal risk. This finding, though in contrast with several reports,^{9 18} is in agreement with others.^{19 20} In fact, the present data confirm our previous observations in unselected patients with ARD where, using an anti-CL assay shown to be highly specific and reproducible (by extensive preliminary experiments), we failed to show any association between the incidence of multiple abortions and the presence, the levels, or the isotypes of anti-CL antibodies.¹² Apart from several methodological differences, which may account for the discrepancies

between studies,¹² multiple intrinsic or extrinsic factors, or both, including drug treatment and infections may be implicated in the miscarriages encountered in patients with ARD. Therefore, prospective studies are necessary to investigate further the prognostic significance of anti-CL antibodies for the outcome of pregnancy in unselected patients with SLE and other autoimmune diseases. In addition, the influence of genetic and environmental factors on the development of the anti-CL associated manifestations remains to be determined.

In conclusion, our data indicate that subclinical factors, which presumably may be present in patients with ARD before their disease onset, do not appear to influence significantly the outcome of pregnancies of these individuals.

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References

- 1 Fraga A, Mintz G, Orazco J, et al. Sterility and fertility rates, fetal wastage and maternal morbidity in systemic lupus erythematosus. *J Rheumatol* 1974; **1**: 293-8.
- 2 Mintz G, Niz J, Gutierrez G, et al. Prospective study of pregnancy in systemic lupus erythematosus. Results of a multidisciplinary approach. *J Rheumatol* 1986; **13**: 732-9.
- 3 Kaufman R L, Kitridou R C. Pregnancy in mixed connective tissue disease. Comparison with systemic lupus erythematosus. *J Rheumatol* 1982; **9**: 549-55.
- 4 Moutsopoulos H M, Webber B L, Vlagopoulos T P, et al. Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. *Am J Med* 1979; **66**: 733-6.
- 5 Masi A T, Rodnan G P, Medsger T A, et al. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; **23**: 581-90.
- 6 Gimovsky M L, Montoro M, Paul R H. Pregnancy outcome in women with systemic lupus erythematosus. *Obstet Gynecol* 1984; **63**: 686-92.
- 7 Fine G L. Systemic lupus erythematosus in pregnancy. *Ann Intern Med* 1981; **94**: 667-77.
- 8 Harris E N, Gharavi A E, Hughes G R V. Anti-phospholipid antibodies. *Clin Rheum Dis* 1985; **11**: 591-609.
- 9 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.
- 10 Kelley W N, Harris E D Jr, Ruddy S, Sledge C B, eds. *Textbook of rheumatology*. 2nd ed. Philadelphia: Saunders, 1985.
- 11 Tzioufas A G, Manoussakis M N, Drosos A A, Silis G, Gharavi A E, Moutsopoulos H M. Enzyme immunoassays for the detection of IgG and IgM anti-dsDNA antibodies: clinical significance and specificity. *Clin Exp Rheumatol* 1987; **5**: 247-53.
- 12 Manoussakis M N, Gharavi A E, Drosos A A, Kitridou R C, Moutsopoulos H M. Anti-cardiolipin antibodies in unselected autoimmune rheumatic disease patients. *Clin Immunol Immunopathol* 1987; **44**: 297-307.
- 13 Manoussakis M N, Tzioufas A G, Silis M P, Pange P J E, Goudevenos J, Moutsopoulos H M. High prevalence of anticardiolipin and other autoantibodies in a healthy elderly population. *Clin Exp Immunol* 1987; **69**: 557-65.

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- 14 Devoe L D, Taylor R L. Systemic lupus erythematosus in pregnancy. *Am J Obstet Gynecol* 1979; **135**: 473–9.
- 15 McCune A B, Weston W L, Lee L A. Maternal and fetal outcome in neonatal lupus erythematosus. *Ann Intern Med* 1987; **106**: 518–23.
- 16 Neely N T, Persellin R H. Activity of rheumatoid arthritis during pregnancy. *Tex Med* 1977; **73**: 59–63.
- 17 Ballou S P, Morley J J, Kushner I. Pregnancy and systemic sclerosis. *Arthritis Rheum* 1984; **27**: 295–8.
- 18 Derue G, Englert H, Harris E N, *et al.* Fetal loss in systemic lupus erythematosus. Association with anti-cardiolipin antibodies. *J Obstet Gynecol Neonatal Nurs* 1985; **5**: 207–9.
- 19 Stimmler M M, McGehee W G, Quismorio F P. A prospective study of anti-cardiolipin antibodies (ACA) in hospitalized SLE patients [Abstract]. *Arthritis Rheum* 1986; **29** (suppl): S44.
- 20 Petri M, Rheinschmidt M, Whiting-O’Keefe Q, *et al.* The frequency of lupus anticoagulant in systemic lupus erythematosus. *Ann Intern Med* 1987; **106**: 524–31.