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Outcome of lupus pregnancy: a controlled study

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Abstract

Objective. The reciprocal relationship between systemic lupus erythematosus (SLE) and pregnancy was investigated in a controlled study.

Method. The outcome of 47 pregnant SLE patients with 59 pregnancies was compared with that of 57 healthy control women and 59 pregnancies. The results were also compared with those of 59 non-pregnant control SLE patients.

Results. All pregnant SLE patients but one were in remission at the onset of pregnancy and were being treated with low doses of prednisone ($\leq$10 mg/day, 26 patients), hydroxychloroquine (200 mg/day, eight patients) or azathioprine (100 mg/day, one patient). Sixty-one per cent of SLE pregnancies were delivered at term and 5% had premature deliveries. The rates of spontaneous abortion and total fetal loss were significantly higher in the mothers with SLE than in the control population ($P < 0.001$ and $P < 0.01$ respectively). None of the 39 neonates from SLE mothers had neonatal lupus, anti-Ro(SSA) or anti-La(SSB) antibodies. Eight out of 59 pregnancies of SLE mothers (13.5%) were characterized by disease exacerbation. Arthralgias or arthritis, fever and skin lesions were observed more frequently in the mothers with SLE than in the non-pregnant group ($P < 0.001$). Renal involvement was found in three SLE patients during pregnancy and in three after delivery.

Conclusions. Pregnant women with SLE are at high risk of fetal loss and spontaneous abortion. Pregnancy does not cause life-threatening manifestations of the disease. Thus, for a better outcome of lupus pregnancy, it is essential to control disease activity and to achieve clinical remission.

KEY WORDS: Systemic lupus erythematosus, Pregnancy, Outcome, Spontaneous abortion, Fetal loss, Neonatal lupus, Ro(SSA) antibodies, La(SSB) antibodies, Anticardiolipins.

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease of unknown cause, characterized by the production of multiple autoantibodies. It affects predominantly young women, whose fertility rate remains unaffected [1]. Patients with SLE frequently become pregnant. However, there seems to be little consensus about the effects of SLE on pregnancy and the influence of pregnancy on SLE. Early studies report an increased fetal and maternal risk [2, 3] but recent prospective studies do not indicate such a relationship [4, 5]. A variety of factors, such as disease activity, renal involvement, a history of fetal loss [6], antiphospholipid antibodies [7], lymphotoxic antibodies [8] and possibly antibodies to Ro(SSA) [9, 10], have been implicated in the pathogenesis of adverse pregnancy outcome in SLE patients. However, the precise mechanism remains unknown. The literature is controversial regarding the frequency of lupus flares during pregnancy and the organ systems in which flares occur [4, 11–14].

In this study we investigated pregnancy outcome in SLE patients compared with healthy pregnant controls. We also analysed the effects of clinical and serological variables of SLE on pregnancy outcome and neonatal morbidity and the effects of pregnancy on the activity of disease.

Patients and methods

From 1982 until December 1997 we followed the course of 352 SLE patients and the relationship between pregnancy and SLE in a controlled study. All patients fulfilled the American College of Rheumatology criteria for SLE [15].

Young women who wished to become pregnant were fully informed about possible fetal complications during pregnancy and the possible effects of pregnancy on SLE activity. Candidate pregnant patients were monitored carefully for disease activity and drug complications during the course of disease. The following laboratory

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tests were performed on all patients during the study: complete blood count and white blood count differential; erythrocyte sedimentation rate, serum glucose, urea, creatinine, uric acid and urinalysis. In addition, levels of antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA) antibodies, anti-Ro(SSA), anti-La(SSB), anticardiolipin (aCL) antibodies and complement C_3 and C_4 were also determined.

A total of 47 pregnant SLE patients (mean age 24.3 ± 2.5 yr; for women with more than one pregnancy, their age at each pregnancy was included in the calculation) were investigated. Pregnant SLE patients were followed for at least 12 months before pregnancy and 6 months after delivery. All patients but one (who had active lupus nephritis) were in remission at the onset of pregnancy. Twenty-six patients were treated with low doses of prednisone (≤ 10 mg/day), eight patients with hydroxychloroquine (200 mg/day) and one patient with azathioprine (100 mg/day). Exacerbation or flare of disease was treated with prednisone (≤ 60 mg/day). Renal flares after delivery were treated with i.v. cyclophosphamide pulse therapy (Table 1).

SLE was considered to be active if two or more of the following were present: (i) acute synovitis detected on physical examination; (ii) pleurisy or pericarditis with electrocardiographic, echocardiographic and/or radiological changes; (iii) psychiatric or central nervous system (CNS) manifestations; (iv) thrombocytopenia $< 90\,000/mm^3$, leucopenia $< 4000/mm^3$ or Coombs' positive haemolytic anaemia; (v) active skin or mucous membrane lesions; (vi) fever without infection; and (vii) active renal disease with abnormal urinalysis and/or proteinuria and low serum complement levels. Exacerbation or flare of disease was defined by the onset of new signs of disease in a previously normal organ system.

We used two control groups. We first compared pregnant SLE patients with 59 non-pregnant SLE women (mean age 31.9 ± 7.7 yr). The two SLE groups were selected in terms of matching for parameters other than disease duration and activity. Non-pregnant SLE patients were followed for disease manifestations for exactly the same period of time as the SLE pregnant patients, and only the prospective follow-up manifestations were compared with those of pregnant SLE patients. The pregnant SLE patients were also compared with 57 healthy pregnant women (mean age 27.2 ± 6.2 yr). All of the women received medical care in the obstetrics and gynaecology clinic of our hospital during the period 1982–1997. For each pregnant SLE woman, one age-matched, healthy pregnant subject was selected. All healthy pregnant women were followed up during pregnancy and for 6 months after delivery, with the same frequency of evaluation as pregnant SLE patients. For the purpose of classification we defined 'therapeutic abortion' as a termination of pregnancy induced after medical consultation, 'elective abortion' as a termination of pregnancy requested by the patients for social reasons, 'spontaneous abortion' as the spontaneous loss of a fetus before the end of the 21st week of gestation, 'prematurity' as the spontaneous termination of gestation between the 21st and 37th weeks, 'at term' as delivery between weeks 38 and 40, 'stillbirth' as intrauterine fetal death after week 21, 'total fetal loss' as the sum of abortion (spontaneous and therapeutic) and stillbirth, and 'low birth weight' as birth weight < 2500 g.

Results

There were a total of 59 pregnancies from 47 SLE patients. Thirty-five of these had one pregnancy and 12 had two pregnancies. Eight of the 59 pregnancies were characterized as having lupus flare-up.

Effects of SLE on pregnancy

Measures of pregnancy outcome were compared between 47 SLE patients and 57 healthy controls (Fig. 1). Of the 59 pregnancies in SLE patients, 36 (61%) were normal full-term deliveries, with an almost similar number in the control group (76%). There were no statistical differences between the two groups in frequencies of premature delivery, stillbirth and low birth weight. However, therapeutic abortions, spontan-

TABLE 1. Therapy of systemic lupus erythematosus patients. No patient was given a dose higher than those mentioned in the table

Pregnant SLE patients			Non-pregnant SLE patients		
Therapy	Dose (mg/day)	*n*	Therapy	Dose (mg/day)	*n*
Before pregnancy					
Prednisone	≤ 20	36	Prednisone	≤ 20	40
Hydroxychloroquine	200	15	Hydroxychloroquine	200	16
Azathioprine	100	3	Azathioprine	100	1
Cyclophosphamide	i.v. pulse therapy	1	Methotrexate	≤ 10 (mg/week)	5
			Cyclophosphamide	i.v. pulse therapy	7
During pregnancy					
Prednisone	≤ 10	26			
Hydroxychloroquine	200	8			
Azathioprine	100	1			
Flares during pregnancy					
Prednisone	≤ 60	8			
Flares after delivery					
Cyclophosphamide	i.v. pulse therapy	6			

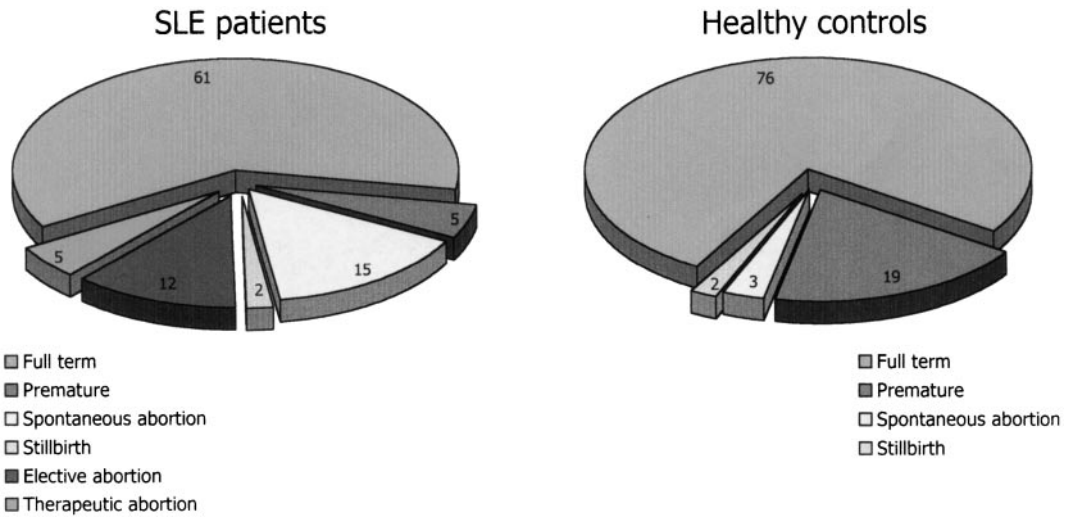

FIG. 1. Pregnancy outcome of lupus patients (%).

eous abortions and total fetal loss were observed significantly more frequently in SLE patients (Fig. 1). More specifically, 61% of SLE pregnant women and 76% of the healthy group achieved full-term deliveries. The remaining 24% of the healthy women had a premature delivery (19%) and only a small percentage had a spontaneous abortion (3%) or stillbirth (2%), giving a total fetal loss of 5%. On the other hand, the total fetal loss of SLE patients was 22% ($P < 0.001$). This was due to the high frequency of spontaneous abortion (15%) and to therapeutic abortions (5%) and stillbirths (2%). The elective abortions (12%), which were carried out for social reasons, were not included in the count of total fetal loss (Fig. 1).

Pregnancy outcome was also examined in active SLE patients. There were eight patients with active disease. The only parameter of SLE activity that affected pregnancy outcome adversely was lupus nephritis. Six of the eight patients with active SLE had lupus nephritis. More specifically, one had active lupus nephritis at conception, two developed lupus nephritis during pregnancy and three after delivery. The outcome of these patients is shown in Table 2.

There was only one full-term delivery among the eight pregnancies (12.5%) in patients with active SLE, while in the group with non-active SLE there were 35 (69%) and in the healthy pregnant group there were 45 (76%). In addition, there were three therapeutic abortions, two spontaneous abortions and one stillbirth, giving a total of 6 (75%) fetal deaths in the patients with active SLE. These figures are significantly higher ($P < 0.001$) than those for the two control groups (Table 2). Therapeutic abortions, which were responsible for half of the total fetal loss in active SLE patients, were done in order to prevent further disease exacerbation and to treat the patients appropriately after the interruption of pregnancy.

We also analysed the outcome of pregnancy according to the presence of autoantibodies (Table 3). In the group of pregnant patients with SLE, 28 had anti-dsDNA antibodies, 17 had anti-Ro(SSA) antibodies, four had anti-La(SSB) and 10 had aCL antibodies. There were no differences in the outcome of pregnancy with respect to the presence or absence of these autoantibodies. None of the 39 neonates from SLE mothers had neonatal lupus (complete heart block, thrombocytopenia or skin lesions) or antibodies to Ro(SSA) or La(SSB). Increased titres of ANA were found in one neonate and decreased levels of C_3 or C_4 in two neonates. Low birth weight was observed in two premature neonates (one

TABLE 2. Outcome of pregnancy in active systemic lupus patients

	Pregnant patients with active SLE ($n = 8$)		Pregnant patients with non-active SLE ($n = 39$)		Healthy pregnant women ($n = 57$)	
	n	%	*n*	%	*n*	%
Total pregnancies	8		51		59	
Term deliveries	1	12.5	35	69*	45	76*
Premature deliveries	1	12.5	2	4	8	19
Therapeutic abortions	3	37.5	–	–	–	–
Spontaneous abortions	2	25	7	14	2	3
Stillbirth	1	12.5	–	–	1	2
Total fetal loss	6	75	7	14	3	5

*$P < 0.01$; **$P < 0.001$.

Table 3. Association of maternal autoantibodies with pregnancy outcome

Pregnancy outcome	Number of pregnancies	dsDNA	Ro(SSA)	La(SSB)	aCL
Total pregnancies	59	28	17	4	10
Term deliveries	36	23	13	1	6
Premature deliveries	3	1	0		1
Therapeutic abortions	3	1	1	1	0
Spontaneous abortions	9	2	2	1	2
Stillbirth	1	1	1	1	1

from a mother with active disease and the other from an inactive patient). There was one intrauterine fetal death in a neonate from a mother with active nephritis who was positive for dsDNA, Ro(SSA), La(SSB) and aCL antibodies at conception.

Influence of pregnancy on SLE

To find out whether the clinical course of SLE is affected by pregnancy, we compared the clinical manifestations and immunological profile between pregnant SLE patients and non-pregnant SLE patients (Table 4). Arthralgias or arthritis, fever, skin lesions and high titres of ANA were observed significantly more frequently ($P < 0.001$) in the pregnant SLE group. The rate of serositis was also increased in pregnant SLE patients, while there was no statistical difference in the frequency of CNS involvement, thrombocytopenia or leucopenia, nephritis and autoantibody profile between the pregnant and non-pregnant group. Among the women with SLE, exacerbation of the SLE occurred in eight of the 59 pregnant women (13.5%) compared with 13 (22%) of the non-pregnant women (Table 5). Although fever and serositis were observed more frequently in pregnant patients during disease flares, there was no statistically significant difference regarding these manifestations between the two groups. The majority of the clinical features of SLE during pregnancy, such as arthralgias, arthritis, skin lesions, fever and nephritis, occurred during the first trimester (57% of patients). Thirteen per cent of lupus pregnant patients presented serositis, fever and haematological disorders during the second trimester. A similar percentage of patients (13%) developed clinical features related to SLE during the third trimester (CNS disease, arthralgias and fever). Nineteen per cent of patients manifested clinical features of SLE immediately after delivery (nephritis, skin lesions, fever). Nephritis flares were observed in three pregnant patients. One of these patients had a recent onset of SLE, 3 months before conception, without evidence of renal involvement. Therapeutic abortion was performed during the second month of pregnancy, because of impairment of renal function. Renal biopsy, performed at that time, showed diffuse proliferative glomerulonephritis. The second patient had inactive renal disease before pregnancy. Renal biopsy after the therapeutic abortion showed focal proliferative glomerulonephritis. Both patients were treated successfully with i.v. pulses of cyclophosphamide. The third patient had active renal disease at the time of conception, with diffuse glomerulonephritis. She decided to become pregnant despite our opposition. The outcome was an intrauterine fetal death as previously described. Although she was treated aggressively immediately after this event with i.v. pulses of cyclophosphamide, high doses of prednisone and plasmapheresis, she died. A further three patients developed nephritis immediately after delivery. Kidney biopsies showed focal proliferative glomerulonephritis in two patients and diffuse proliferative glomerulonephritis in the third. All three patients were treated successfully with i.v. pulses of cyclophosphamide.

Table 4. Clinical characteristics of SLE patients

	Pregnant ($n = 59$)		Non-pregnant ($n = 59$)	
	n	%	*n*	%
Arthralgias or arthritis	48	81*	11	19
Fever	28	47*	3	5
Skin lesions	55	93*	13	22
Nephritis	6	10	9	15
Serositis	5	8	2	3.5
CNS involvement	2	3.5	3	5
Haematological involvement	6	10	11	19

*$P < 0.001$.

Table 5. Clinical features of SLE patients with exacerbations of their disease

	Pregnant ($n = 8$)		Non-pregnant ($n = 13$)	
	n	%	*n*	%
Acute synovitis	0	0	1	8
Serositis	5	62.5	2	15
CNS involvement	2	25	3	23
Haematological involvement	3	37.5	4	31
Skin lesions	7	87.5	8	62
Fever	7	87.5	3	23
Nephritis	6	75	8	62

Discussion

Women with SLE have frequently been reported as having high-risk pregnancies due to an increased frequency of fetal loss, premature births, neonatal lupus and perinatal mortality [6, 16]. Several studies have found the frequency of fetal loss to vary between 11 and 24% [4, 12, 17–19]. These differences may be due

to many factors, such as patient selection, treatment and the availability and use of modern obstetric care and fetal monitoring. In our study the rates of total fetal loss (22%) and spontaneous abortion (15%) were in accordance with recent studies [4, 18, 20, 21]. These rates were significantly higher than those in healthy women. SLE activity, renal disease and antiphospholipid antibodies may play a causal role in the increased frequency of fetal loss in SLE. Many prospective studies, however, have shown that SLE activity does not affect fetal outcome adversely [12, 19, 20, 22–24]. In contrast, Mintz *et al.* [4] and Petri [6] found a significant correlation between SLE activity and prematurity. Despite the small number of patients with active disease in our study, we found that disease activity reduced the number of term deliveries and increased the total number of fetal losses.

Pregnancies in patients with active nephritis have a worse prognosis. While the rate of pregnancy loss in patients with mild renal disease is only 10%, in patients with moderate or active nephritis this number increases to 60% [6]. Our experience shows that, among three patients with renal flares during pregnancy, two had therapeutic abortions and one had an intrauterine fetal death. However, we found that the development of lupus nephritis in the puerperium did not adversely affect pregnancy outcome.

A large retrospective study of Greek SLE patients showed that 21.7% were positive for aCL antibodies [25]. In our study aCL antibodies were found in 17% of pregnant SLE patients. We found no association between aCL antibodies and fetal loss. In the past, reports have shown a positive correlation between antibodies to aCL and an increased fetal loss rate in both SLE and non-SLE patients [26, 27]. However, recent prospective and retrospective studies failed to find an association between antiphospholipid antibodies and fetal loss [6, 19, 20]. This discrepancy in the results may be due to the use of appropriate therapy (prednisone, aspirin and heparin) in patients with secondary antiphospholipid syndrome and a history of pregnancy loss, thus improving the outcome of future pregnancies.

The incidence of neonatal lupus in the offspring of mothers with anti-Ro(SSA) antibodies is estimated at 1.5–2% [28]. Watson *et al.* [29] found that pregnancy loss was strongly correlated with the presence of anti-Ro(SSA) antibodies only in the black subpopulation of SLE mothers. Moreover, recent studies have found no differences in the rates of fertility and adverse pregnancy outcome between anti-Ro(SSA)-positive and anti-Ro(SSA)-negative SLE patients [30, 31]. Our results, which are compatible with these studies, indicate that anti-Ro(SSA) antibodies have no influence on the pregnancy outcome in SLE patients. Buyon *et al.* [32] reported a statistically significant prevalence of anti-Ro(SSA) in mothers of children with heart disease or transient neonatal lupus. The existence of a qualitatively different population of anti-Ro(SSA) antibodies in SLE patients (not recognizing the 52 kDa polypeptide, which is responsible for neonatal lupus) is a possible explanation for the low rate of adverse pregnancy outcome in SLE patients with anti-Ro(SSA) antibodies.

Cutaneous or articular manifestations are the most common clinical findings of SLE during pregnancy [33]. In our study, arthralgias, arthritis, skin lesions and fever were the most prominent symptoms in pregnant SLE patients. However, we did not observe any acute synovitis in our SLE patients. All the above symptoms and signs are not related exclusively to SLE activity, since it is known that palmar erythema and bland synovial effusions also occur during pregnancy. Only a minority of patients, as shown by most of the prospective studies, suffer from severe complications of SLE, such as nephritis (10%), CNS complications (3.5%), serositis (8%) and haematological involvement (10%) [4, 13, 19, 20, 34].

Exacerbations of SLE during pregnancy occurred in 13.5% of our patients. Our findings are in agreement with previous studies evaluating the risk of exacerbation of SLE during pregnancy [12, 19]. Disease flares presented most commonly with fever, renal or skin involvement. Three recent retrospective studies [35–37] have shown that pregnancy did not adversely affect renal function in patients with a previous diagnosis of lupus nephritis when there were no clinical signs of SLE activity before conception. Accordingly, pregnancy should not be discouraged in women with SLE and inactive renal disease. Because of the small number of pregnant patients with lupus nephritis in our study, we were unable to draw any conclusion about the influence of pregnancy on lupus nephritis. However, in one patient with active nephritis before gestation we were unable to reverse the deterioration of renal function. We and others [21] have also observed exacerbations of lupus nephritis soon after delivery. A possible explanation could be that coagulation abnormalities related to pregnancy promote small thromboses which are superimposed on the pre-existent nephritis lesions. Another reason may be changes in the immune system, as the immune tolerance that accompanies pregnancy terminates abruptly after delivery [28]. In all series, including ours, disease flares are no more severe during pregnancy compared with those not related to pregnancy [4, 13, 19, 20, 34]. This may be due in part to the use of prednisone instead of antimalarial agents for the treatment of pregnant patients with SLE flares but not of control patients with mild SLE flares.

In summary, we found that pregnant women with SLE remain at high risk in terms of fetal loss and spontaneous abortions. SLE activity influences term delivery and total fetal loss. Pregnancy does not cause life-threatening manifestations of SLE, although fever, arthralgias or arthritis and skin lesions were observed more frequently during pregnancy. Nevertheless, in order to achieve a better outcome of lupus pregnancy it is essential to control disease activity. Close monitoring of the patients and their treatment, resulting in the remission of SLE before conception, will improve fetal survival and reduce lupus flare rates.

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