INCREASED RATE OF LUPUS FLARE DURING PREGNANCY AND THE PUERPERIUM: A PROSPECTIVE STUDY OF 78 PREGNANCIES

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SUMMARY

The objective was to determine whether the frequency of flare in systemic lupus erythematosus (SLE) patients is increased during pregnancy and the puerperium. Seventy-eight pregnancies in 68 SLE patients attending the lupus pregnancy clinic, at St Thomas' Hospital, during the last 5 yr were included. The pregnancy period and 8 weeks post-delivery were considered. This group was compared with a control group of 50 consecutive, non-pregnant, age-matched SLE patients attending our weekly lupus clinic. Additionally, 43 of the pregnant patients carried on attending the lupus clinic for the year after puerperium, and their course was compared with themselves during pregnancy. SLE activity was assessed using the Lupus Activity Index (LAI) score. An increase $\geqslant 0.26$ in the score was considered as a flare of the disease. Pregnancy and control groups were homogeneous for age, race, disease duration and distribution of autoantibodies. Sixty-five per cent of the patients flared during pregnancy and/or the puerperium and 42% flared in the control group ($P = 0.015$).The rates of flare per patient/month were 0.082 ± 0.004 for the pregnancy group and 0.039 ± 0.003 for the control group ($P < 0.001$). The 43 patients whose course was controlled after the puerperium flared more frequently during pregnancy than thereafter (McNemar test, $P = 0.003$). The rates of flare per patient/month were 0.093 ± 0.006 during pregnancy and the puerperium, and 0.049 ± 0.004 after the puerperium ($P = 0.0015$). Kidney and central nervous system involvement was not different between the pregnancy and control groups. In terms of frequency of flares, there was no difference in any of the groups between patients taking and not taking steroids. We conclude that SLE tends to flare during pregnancy. Flares are maximal during the second and third trimester and the puerperium. Flares are not more severe than in non-pregnant patients, and most of the flares can be managed conservatively. Prednisolone does not prevent flares.

KEY WORDS: Lupus severity, Activity index, Antibodies, Nephritis, Steroids.

IN recent years, pregnancy has become an important management focus in systemic lupus erythematosus (SLE) patients. The fertility rate in SLE women is normal [1], improvement in patients' care has provided longer periods of remission and a better quality of life, and the advent of combined obstetric–medical clinics has ameliorated the course and outcome of pregnancy.

Clearly, the relationships between SLE and pregnancy are complex, and increasing evidence points to an important role of sex hormones in immunity. Increased prolactin levels have been demonstrated in mice and humans during SLE flares [2–4]. Changes in sex hormone levels during pregnancy and the puerperium are more apparent than in any other period of life.

During the last 5 yr, we have prospectively followed a large number of patients with SLE, primary antiphospholipid syndrome and other autoimmune conditions, who have attended our lupus pregnancy clinic at St Thomas' Hospital. In order to assess the interaction of pregnancy and lupus, we have studied 78 pregnancies in SLE patients. We include in our data our experience of lupus in the puerperium.

PATIENTS AND METHODS

Study group

Sixty-eight SLE patients (78 pregnancies) attending the lupus pregnancy clinic were included in this study.

All patients fulfilled at least four of the 1982 American College of Rheumatolgy criteria for the classification of SLE [5]. The patients were referred either from our weekly lupus clinic or from other UK medical centres. Twenty-three of these patients were followed for at least 1 yr prior to conception in our lupus clinic.

Lupus pregnancy clinic protocol

All patients were attended by an interdisciplinary team, including a rheumatologist, an obstetrician and a haematologist when needed. Patients were first booked in the first trimester of pregnancy. On booking, a complete medical history and physical examination were done, and the following tests were performed: complete blood cell count (CBC) with erythrocyte sedimentation rate (ESR); blood urea, creatinine, fasting glucose, sodium and potassium levels; antinuclear antibodies (ANA) by indirect immunofluorescence on mouse liver and Hep-2 cells; anti-native DNA antibodies (anti-dsDNA) by radioimmunoassay; anti-extractable nuclear antigen antibodies (anti-ENA) by counter-immunoelectrophoresis, using rabbit kidney and human spleen as substrates; C3 and C4 levels by radial immunodiffusion; lupus anticoagulant (LA) by activated partial thromboplastin time (APTT), and dilute Russell viper venom time (dRVVT); anticardiolipin antibodies (aCL), IgG and IgM, by enzyme-linked immunosorbent assay; urinalysis; and obstetrical ultrasonography. Patients were seen every 4 weeks until the 13th week, every 2 weeks until the 32nd week, and weekly thereafter. Multi-stix test for proteinuria was carried out on

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every visit and, when positive (2+ or more), a microscopic examination for casts was performed, and a 24 h urine sample was collected for proteinuria and creatinine clearance. Blood pressure was measured on every visit. CBC, ESR, biochemical profile, ANA, anti-dsDNA, C3 and C4 were determined at least once monthly, and whenever considered necessary. Doppler studies of the uterine and umbilical vessels' flow were performed regularly from the 16th week onwards. Fetal growth was determined by abdominal palpation and echography, and the fetus was monitored by cardiotocography from the 24th week onwards. Every patient, whatever the outcome of the pregnancy (successful delivery or miscarriage), was followed up at the lupus pregnancy clinic during 8 weeks postpartum or post-abortion.

Disease activity

In order to rule out any observational bias, the Lupus Activity Index (LAI) score [6] was determined for each patient at least for every other visit. According to the study by Petri et al. [6], SLE flare was defined as an increase of ≥0.26 or more from the minimum score during the follow-up. Continuously increasing activity was considered as one flare only. To be diagnosed as having two or more flares, the patient should have had a decrease in activity between two high-scored periods. SLE renal involvement was defined as the association of proteinuria >0.5 g/l with either granular, red or white cell casts in the urinary sediment and/or favourable response to prednisolone increase, with or without hypertension. Additionally, low C3 or C4 levels, increased anti-dsDNA levels or signs of extra-renal activity were also considered suggestive of renal flare, and justified a therapeutic trial with steroids. Any other condition accounting for proteinuria and hypertension, and not fulfilling the latter criteria, was considered as pre-eclampsia. Central nervous system (CNS) involvement was considered in the presence of seizures, neurological focalty or psychosis in the absence of any other aetiological condition. Focal neurological events, thrombocytopenia or thrombosis in the presence of antiphospholipid antibodies (aCL and/or LA) were not considered as lupus activity. Migraine and Raynaud's phenomenon were not considered criteria for SLE activity. Lupus activity at conception was not considered as a flare. Once the disease was controlled, any further increase in activity was considered as a flare. The attending physicians remained unchanged during the period of study.

Therapeutic protocol

Pre-conceptual treatment was kept unchanged as much as possible. Cyclophosphamide was discontinued in every case at least 6 months before conception and switched to azathioprine. Hydroxychloroquine was maintained in all but two patients. Prednisolone dosage was not modified during pregnancy unless needed in order to control disease activity. No prophylactic steroids were given to any patient during pregnancy or the puerperium. SLE flares were treated according to the

attending physicians' best judgement, with naproxen, hydroxychloroquine, prednisolone or azathioprine. Patients with the antiphospholipid syndrome were treated with aspirin, 75 mg/day. Subcutaneous heparin was added in patients with a history of previous thrombosis. Both were maintained for 8 weeks after delivery.

Definition of trimesters of pregnancy

The first trimester was considered from conception until the 13th week; second trimester, from the 14th until the 27th week; third trimester, from the 28th week until delivery; puerperium, 8 weeks post-delivery or post-abortion [7].

Control groups

The control group consisted of 50 consecutive, race- and age-matched non-pregnant patients, attending our weekly lupus clinic. Additionally, 43 of the pregnant patients carried on attending the lupus clinic for the year after puerperium, and its course was compared with themselves during pregnancy. For these two groups, the last year of follow-up and the year after puerperium, respectively, were considered. Non-pregnant patients were followed at the lupus clinic on a quarterly basis, unless the attending clinician modified this schedule according to disease activity (i.e. patients with active disease were seen more frequently). Disease activity was measured using the LAI score, in the same way as in pregnant patients [6].

Statistical analysis

Proportions were compared using the χ^2 test. Means were compared using either Student's t-test or the Mann–Whitney U-test. The 43 patients who were followed up 1 yr after pregnancy were compared with themselves during pregnancy using the McNemar and paired Student's t-tests. Multiple regression analyses were performed to investigate any confounding associated with the treatment variables.

RESULTS

Demographic data

Seventy-eight pregnancies were studied in 68 patients. The demographic data of the study and control group are shown in Table I. The two groups were homogeneous for age, race, disease duration, and distribution of Ro, La, Sm and RNP antibodies, IgG aCL and IgM aCL (moderate or high titres) and LA at the first visit of the follow-up. The treatment at the first visit of the follow-up is shown in Table II. More patients in the control group were on hydroxychloroquine than in the pregnancy group (48% vs 18%, $P < 0.001$). Pregnancy and control groups were not different for prednisolone and azathioprine treatment.

Follow-up

The pregnancy group was followed for 9.47 ± 2 months and the control group for 11.7 ± 0.78 months. The mean duration of the pregnancies was 31.8 ± 8.8 weeks (range 6–40). Seven pregnancies ended before the 14th week and 15 before the 27th week.

Pregnancy vs control SLE flare

Fifty-one patients (65%) flared during pregnancy and/or the puerperium. Twenty-one patients (42%) flared in the control group during the follow-up.

TABLE I
Demographic data (*n* = number of patients)

	Pregnancy (*n* = 78)	Control (*n* = 50)	*P*
Age (yr) (mean ± s.d.)	31.2 ± 5.3	33 ± 7.8	0.12
White race *n* (%)	59/78 (75%)	38/50 (76%)	0.99
Disease duration (yr) (mean ± s.d.)	6.9 ± 5.4	7 ± 5.6	0.81
Ro antibodies *n* (%)	36/78 (46%)	19/50 (38%)	0.46
La antibodies *n* (%)	19/78 (24%)	6/50 (12%)	0.13
Sm antibodies *n* (%)	6/78 (7.7%)	8/50 (16%)	0.24
RNP antibodies *n* (%)	13/78 (17%)	12/50 (24%)	0.42
IgG aCL *n* (%)	33/78 (42%)	18/50 (36%)	0.59
IgM aCL *n* (%)	6/78 (7.7%)	8/50 (16%)	0.24
LA *n* (%)	29/78 (39%)	10/50 (20%)	0.062

TABLE II
Treatment at the first visit of the follow-up (*n* = number of patients)

	Pregnancy (*n* = 78)	Control (*n* = 50)
Prednisolone (% of patients)	62	64
Prednisolone dose (mg/day) (mean + s.d.)	7 ± 7.4	5.1 ± 5.6
Immunosuppressors (% of patients)	19	30
Hydroxychloroquine (% of patients)	18*	48

*$P < 0.001$.

TABLE III
Rates of flare of the pregnancy and control groups (*n* = number of patients at risk)

	Pregnancy		Control (*n* = 50)
Flare	First (*n* = 68)	All (*n* = 78)	
% of patients	66*	65*	42
per patient/month (mean ± s.d.)	0.084 ± 0.004†	0.082 ± 0.004†	0.039 ± 0.003

*$P = 0.015$.
†$P < 0.001$.

This difference was significant (χ^2, $P = 0.015$). When considering the 68 first pregnancies only, 45 patients (66%) flared, and the difference with the control group was also significant (χ^2, $P = 0.015$).

The rates of flare per patient/month were 0.082 ± 0.004 for the pregnancy group and 0.0399 ± 0.0036 for the control group. This difference was significant (Mann–Whitney U-test, $P < 0.001$). When considering the 68 first pregnancies only, the rate of flare was 0.084 ± 0.004, and the difference with the control group still significant (Mann–Whitney U-test, $P < 0.001$). Flare rates are shown in Table III.

Pregnancy vs post-pregnancy SLE flare

Forty-three patients were followed up in the lupus clinic during the year after the puerperium. The mean follow-up after the puerperium was 10.7 ± 1.8 months.

Seventeen of these patients flared during pregnancy and/or the puerperium, but not the year thereafter, 17 flared during pregnancy and/or the puerperium and also the year thereafter, three flared only during the year after puerperium and six did not flare during either period. Comparing these figures, flare during pregnancy was significantly more frequent for this group (McNemar test, $P = 0.003$).

The rates of flare per patient/month were 0.093 ± 0.006 during pregnancy and the puerperium, and 0.049 ± 0.0044 during the year after puerperium. This difference was significant (paired *t*-test, $P = 0.0015$).

Distribution of pregnancy flares

The total number of flares during pregnancy and the puerperium was 63. Two flares (3%) happened during the first trimester, 30 (48%) during the second, nine (14%) during the third and 22 (35%) during the puerperium (Table IV).

The rates of flare per patient/month were 0.0082 ± 0.051 for the first trimester, 0.153 ± 0.22 for the second trimester, 0.074 ± 0.218 for the third trimester and 0.148 ± 0.237 for the puerperium (Table IV).

Disease activity at conception and hydroxychloroquine withdrawal

Only five patients presented with signs of disease activity at conception. Four of them flared again during pregnancy, after the initial activity was controlled. The remaining patients entered the study in remission.

One of the two patients who were withdrawn from hydroxychloroquine flared during pregnancy (second trimester flare).

Severity of flares

The severity of the flares was defined according to deep organ involvement (renal, CNS, haematological

TABLE IV
Flare per trimester of pregnancy (*n* = number of patients at risk)

Flare	1st trimester (*n* = 78)	2nd trimester (*n* = 71)	3rd trimester (*n* = 63)	Puerperium (*n* = 78)
% of flares	3	48	14	35
per patient/month (mean ± s.d.)	0.0082 ± 0.051	0.153 ± 0.22	0.074 ± 0.21	0.148 ± 0.23

or pulmonary) and requirement for prednisolone and/or immunosuppressive drugs. For none of these parameters were flares during pregnancy more severe than flares in control patients (data not shown).

Nature of pregnancy flares

We observed 12 renal flares during pregnancy. Seven happened during the second trimester and five during the puerperium. Six were confirmed by postnatal renal biopsy, and six were diagnosed according to clinical data and response to steroids and/or immunosuppressive drugs. Only two of these patients had a diagnosis of nephritis previous to pregnancy. Three patients presented with CNS involvement: two in the postnatal period and one in the third trimester. Of the remaining 48 flares observed, two were serositis (pleural effusion) and 46 musculoskeletal and/or cutaneous flares. Thirty-three of these 48 flares required the addition of prednisolone and/or azathioprine.

We did not observe any episode of haemolytic anaemia, thrombocytopenia not related to antiphospholipid syndrome or pneumonitis.

Activity before conception

Twenty-three of our patients were followed at our lupus clinic for 1 yr before conception. We have not included this period in the general analysis. Eight out of 9 patients (88%) who flared during the year prior to conception flared again during pregnancy.

Treatment and flare

The proportions of flares in patients taking and not taking steroids were not significantly different considering any of the groups (Table V). We also analysed in a multiple regression curve the influence of pregnancy, treatment with prednisolone, hydroxychloroquine, azathioprine and the mean dose of prednisolone at the first visit of the follow-up on the development of flare. Only pregnancy showed a positive influence on the development of flare ($P = 0.001$). All the P values are shown in Table VI. The results remained unchanged considering the 68 first pregnancies only (data not shown).

TABLE V
Prednisolone treatment and flare

Group	Flare on prednisolone	Flare off prednisolone	P
Pregnancy	34/49 (69%)	17/29 (58%)	0.47
Control	16/32 (50%)	5/18 (28%)	0.21
Post-pregnancy	19/37 (51%)	1/6 (16%)	0.25

TABLE VI
Multiple regression analysis for flare-related variables

Variable	P
Pregnancy	0.001
Prednisolone treatment	0.740
Prednisolone dosage	0.086
Hydroxychloroquine treatment	0.084
Immunosuppressive treatment	0.376

DISCUSSION

Although the outcome of lupus pregnancy has improved dramatically in recent years, figures on maternal and fetal morbidity still vary widely. Among the different factors which account for the discordant results are ethnicity and economic level of the studied population, reasons for patient referral, SLE activity on entering the study and the absence of consensus to define a 'lupus flare' [8–11].

In 1984, Lockshin et al. [12], in a prospective study of 33 pregnancies, concluded that SLE does not flare during pregnancy. In 1989 [13], the same author published a large series of 80 pregnancies, reaching the same conclusion. Mintz et al., in 1986 [14], published a large prospective series of 102 pregnancies in 75 patients, and found a high rate of flare during pregnancy: 0.06 flares per patient/month. However, this was not found to be significant compared with the 0.04 flares per patient/month for the control group. More recently, in 1993, Urowitz et al. [15] also reported a high percentage of flares (70%) in 61 pregnant patients (those who aborted were excluded). However, even more patients flared in the control group (80%). Two recent studies by Tincani et al. [16] and Derksen et al. [17] also concluded that lupus flares were not more common during pregnancy, although the rate of flare was as high as 0.07 per patient/month in Tincani's study. Petri et al., in 1991 [18], reported a high flare rate during pregnancy (1.6337 flares per patient/year)—significantly higher than in post-pregnant or control patients (0.6392 and 0.6518, respectively). Nossent et al., in 1990 [19], in a group of 39 pregnancies, found that 74% of the patients flared. Wong et al., in 1991 [20], reported a flare rate of 0.08 per patient/month in 29 pregnancies, higher than in the control group (0.04 flares per patient/month). Finally, Le Thi Huong et al., in 1994 [21], in a prospective, multicentre study of 117 pregnancies, found SLE activity in 60% of their pregnant patients, although 27% of the patients were active at conception. They concluded that lupus activity is increased during pregnancy.

Each of these studies has provided valuable information concerning the course of SLE during pregnancy. However, many of them were not designed to exclusively assess the effect of pregnancy on SLE, but to globally study the outcome of lupus pregnancies [14, 16, 17, 19–21]. Additional confusion was provided by the use of non-matched control groups [14, 18, 20], or even the absence of any [13, 16, 17, 19, 21], and the inclusion of criteria for SLE activity such as Raynaud's phenomenon and migraine [14, 15], which may actually improve during pregnancy [22] and bias the comparison with the control group. Additionally, the high rate of abortion in some studies, up to 24% [12, 17], could have also underestimated the frequency of pregnancy flares. Two recent editorials from Lockshin [8, 9] addressed these issues, and provided guidelines for further studies [9].

This study fulfils most of these guidelines: it is prospective; every patient was seen on every visit by a co-ordinated team of obstetricians, rheumatologists and

haematologists; all of our patients were classified as having SLE prior to the studied pregnancies, which rules out the bias of those patients diagnosed during pregnancy (100% flare rate for them); our study and control groups were homogeneous for age, race, disease duration, and presence of Ro, La, Sm, RNP, aCL and LA at the first visit of the follow-up; the same diagnostic and therapeutic protocol was applied to every patient; and, finally, the same definition of flare was stated for all groups, excluding confusing features such as thrombocytopenia and stroke in antiphospholipid-positive patients, Raynaud's or migraine. Patients who conceived whilst the disease was active and those who stopped hydroxychloroquine during pregnancy were a minority in this study (five and two patients, respectively). The control group and the 43 post-pregnant patients seem validated by the fact that their rates of flare per patient/month (0.039 and 0.049, respectively) were in the range of the control populations of previous, large studies [14, 18, 20].

We have found that, considering pregnancy and the puerperium as a whole, SLE flares are much more frequent than in non-pregnant patients, either considering the first or subsequent pregnancies per patient. Previous studies have suggested that the last two trimesters and the puerperium are the most likely for lupus flares [23]. In this study, 97% of the patients who flared did so during the second trimester, third trimester or puerperium (Table IV).

Although only a small number of patients were followed before conception, in our experience, SLE activity during the year prior to conception pointed to a high risk of flaring during pregnancy. This supports previous observations [15].

Neither the direct comparison group by group nor the multiple regression analysis could disclose any beneficial effect of prednisolone in decreasing the number of flares. Two previous studies have suggested that flares during the puerperium are absent in patients treated prophylactically with prednisone during pregnancy [16, 20]. However, other studies showed high rates of puerperal flare using a similar therapeutic protocol [14, 24]. Additionally, it has been shown that many patients treated with prednisone during pregnancy developed significant side-effects [25]. Accordingly, we agree with Lockshin [9] that prophylactic steroids should not be used during pregnancy.

CONCLUSIONS

We conclude that pregnancy statistically increases SLE activity. This is maximal during the second trimester and carries on until the end of the puerperium. Serious visceral involvement, however, is rare and most of the flares can be managed conservatively. Pregnancy should best be avoided, if possible, during an active phase of the disease. Prednisolone does not prevent SLE flares during pregnancy.

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