Pregnancy Outcome in Thai Patients with Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies to cellular antigens resulting in multiple organ system inflammation. The disease usually affects women of childbearing age. Studies during the 1950s in women with SLE suggested that pregnancy could be hazardous to both mother and fetus. Pregnancy in patients with SLE could exacerbate the disease in 50-75% of cases, and it was recommended that pregnancy in these patients be avoided or terminated.[1,2] With improvement in the understanding of pathophysiology, better laboratory tests that lead to early diagnosis, increased experience in the use of corticosteroids and immunosuppressive drugs and better obstetric monitoring have greatly improved the outcome of pregnant lupus.

The effect of pregnancy on SLE and the fetal outcome of pregnant lupus have been well described in textbooks about lupus.[3,4]

SUMMARY The outcome of 48 pregnancies from 42 patients with systemic lupus erythematosus was studied. Their mean age and the duration of the disease were 28.47 and 4.42 years, respectively. The conception occurred when the disease was inactive or quiescent in 45 and active in 3. Four pregnancies were terminated by criminal abortion. Flares occurred in 16 pregnancies. The kidney and mucocutaneous system were the 2 organs that flared most commonly. The fetal outcomes were term delivery in 18 (40.90%), prematurity in 17 (38.64%), spontaneous abortion in 6 (13.64%) and still birth in 3 (6.82%). There was no statistical difference in pregnancy loss and successful delivery between pregnant patients with and without flares. Concerning 35 successful live births, those pregnancies without flares had significantly more full term deliveries ($p < 0.02$), higher gestational age ($p < 0.002$) and more birth weight ($p < 0.001$) than those with flares. Small for gestational age was seen in 20%. Pregnancy with active renal disease had a poor fetal outcome. There were no cases of congenital anomalies or neonatal lupus. Maternal complications were more common in patients with flares.

Most of the studies were from western countries. Studies from Southeast Asia, including Thailand, are limited.[5-7] This study reports a 7-year experience of the outcome of pregnancy in SLE patients, as seen in a university hospital.

MATERIALS AND METHODS

A retrospective review chart was completed for all pregnant SLE patients who were seen at the Division of Rheumatology and the Division of Allergy and Clinical Immunology, Department of Medicine, Chiang Mai University from January 1991 to July 1998. All patients fulfilled the revised criteria of the American Col-

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lege of Rheumatology (ACR) for the diagnosis of SLE.[8] It was routine practice that pregnancy in these patients was planned, and the disease was inactive or under-control for a minimum period of 6 months. All patients were seen by their physicians and they attended the antenatal care clinic regularly during their pregnancy and postpartum period. General symptoms and physical findings, particularly in those organs involved with SLE, were recorded. Laboratory investigations including complete blood counts, erythrocyte sedimentation rate and urine analyses, were carried out at every visit. Additional laboratory tests, e.g. serum complement levels, serum uric acid, biochemical profiles and a 24-hour urine protein determination were done if clinically indicated. A serological test for syphilis (VDRL) was carried out in all patients. Anticardiolipin (aCL) antibodies were not tested as they were not routinely available at our hospital. The dosage of the medication used in the treatment was also recorded.

The MEX-SLEDAI score was used to determine the clinical activity of SLE.[9] Patients were considered to have disease "flare" if they 1) had an increased MEX-SLEDAI score of more than 1 during the pregnancy or post-partum period, 2) had increasing symptoms or signs in the organs involved, 3) required more dosage of corticosteroids, and 4) were being considered by their physicians.

Obstetric terminology was used as follows. Spontaneous abortion referred to the spontaneous termination of pregnancy occurring at less than 20 weeks' gestation. Illegal or criminal abortion referred to abortion performed against medi-

cal advice. Fetal death or stillbirth was diagnosed if the spontaneous termination of a pregnancy occurred after 20 weeks' gestation. Prematurity or premature birth was considered as a spontaneous or induced termination of pregnancy with a live birth being between 21-37 weeks' gestation. Term delivery was defined as a spontaneous or induced termination of pregnancy with a live birth being between 37-40 weeks' gestation. Neonatal death was defined as death within 7 days of birth. Puerperium or post-partum period was a duration of 8 weeks after delivery or pregnancy loss. Premature rupture of the membrane referred to the spontaneous rupture of the amnion sac before the onset of labor pain, regardless of gestational age. Small for gestational age referred to a birth weight below the 10th percentile when compared with the same normal gestational age. Hypertension was defined as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg. Pregnancy induced hypertension (PIH) or pre-eclampsia referred to an abrupt onset of hypertension and proteinuria after 24 weeks' gestation, with or without edema, and in the absence of urinary tract infection. Eclampsia referred to PIH associated with convulsion. Pregnancy loss was the sum of spontaneous abortion and fetal death. Successful delivery referred to a delivery with live birth.

Statistical analysis

The Epi Info version 6.0 statistical program was used to determine the statistical analysis. Proportional data were compared with the Chi-square test. Student's t tests were applied in comparisons of continuous variables. A p-value

of less than 0.05 was considered to have statistical significance.

RESULTS

Forty-eight pregnancies were identified in 42 lupus patients. Nineteen women were nulliparous and 23 multiparous. None was pregnant with twins. None had a history of recurrent abortions or recurrent arterial or venous thrombosis that suggested the presence of antiphospholipid antibodies, nor had they positive VDRL tests. Demographics of the patients studied are shown in Table 1. Their mean age and the duration of the disease were 28.47 and 4.42 years, respectively. Thirty pregnancies occurred in patients taking prednisolone at 10 mg/day or less (mean 5.88 ± 3.17 mg/day), and 4 were taking prednisolone at more than 10 mg/day (mean 22.5 ± 6.5 mg/day). Three patients were taking cyclophosphamide at an average dosage of 41.66 ± 14.33 mg/day and 12 patients were taking chloroquine at an average dosage of 166.67 ± 61.55 mg/day. Fourteen patients were free of therapy. Chloroquine and cyclophosphamide were discontinued when conception occurred.

In 45 pregnancies, conception occurred in patients where the disease was inactive or quiescent (MEX-SLEDAI score = 0). Four of these pregnancies were terminated against medical advice by criminal abortion during their first trimester. Two of these 4 patients had disease flares; one had a renal flare (MEX-SLEDAI score = 6) and the other had a flare of the mucocutaneous and articular systems (MEX-SLEDAI score = 4). Of the remaining 41 pregnancies with inactive disease at conception,

Table 1. Characteristics of the patients studied

Patients' characteristics	No. (%)
No. of patients	42
No. of pregnancies	48
Mean ± SD age, yr.	28.47 ± 5.29
Mean ± SD duration of disease, yr.	4.42 ± 3.71
Major SLE manifestations before conception	
Mucocutaneous	33 (78.57)
Articular	29 (69.05)
Renal	24 (57.14)
Hematologic	11 (26.19)
Neuropsychiatric	3 (7.14)
Serositis	3 (7.14)
Previous obstetric history	36
Illegal abortion	5 (13.89)
Spontaneous abortion	8 (22.22)
Live birth	23 (63.89)
Drug used at the time of conception	
No medication	14 (29.16)
Prednisolone ≤10 mg/d	30 (62.50)
Prednisolone >10 mg/d	4 (8.33)
NSAIDs	12 (25.00)
Chloroquine	12 (25.00)
Cyclophosphamide	3 (6.25)

13 had disease flares (mean MEX-SLEDAI score = 8.23 ± 3.77). In 3 pregnancies, conception occurred when the disease was active (mean MEX-SLEDAI score = 9.33 ± 3.05), and a flare occurred in one (MEX-SLEDAI score increased from 6 to 12) (Figure 1). These 16 flares occurred during the first, second and third trimester in 8, 5 and 3 cases, respectively. No flares occurred during the post-partum period. The kidney and mucocutaneous system were the 2 organs that flared most commonly (Table 2). However, flares were usually mild and could be controlled by a modest increase in the dosage of corticosteroids.

The outcome of 41 pregnancies where the disease was inactive at the time of conception was successful delivery in 35 (term delivery in 18 and prematurity in

Pregnant SLE (n = 48)

Active disease (n = 3)

Flare (n = 1)

Pregnancy loss

Stillbirth 1

No flare (n = 2)

Pregnancy loss

Stillbirth 1

Spontaneous abortion 1

Pregnancy loss (n = 3)

Stillbirth 1

Spontaneous abortion 2

Successful pregnancy

(n = 10)

Term baby 3

Preterm baby 8

Inactive disease (n = 45)

Flare (n = 13)

Pregnancy loss (n = 3)

Spontaneous abortion 3

No flare (n = 28)

Successful pregnancy (n = 25)

Term baby 16

Preterm baby 9

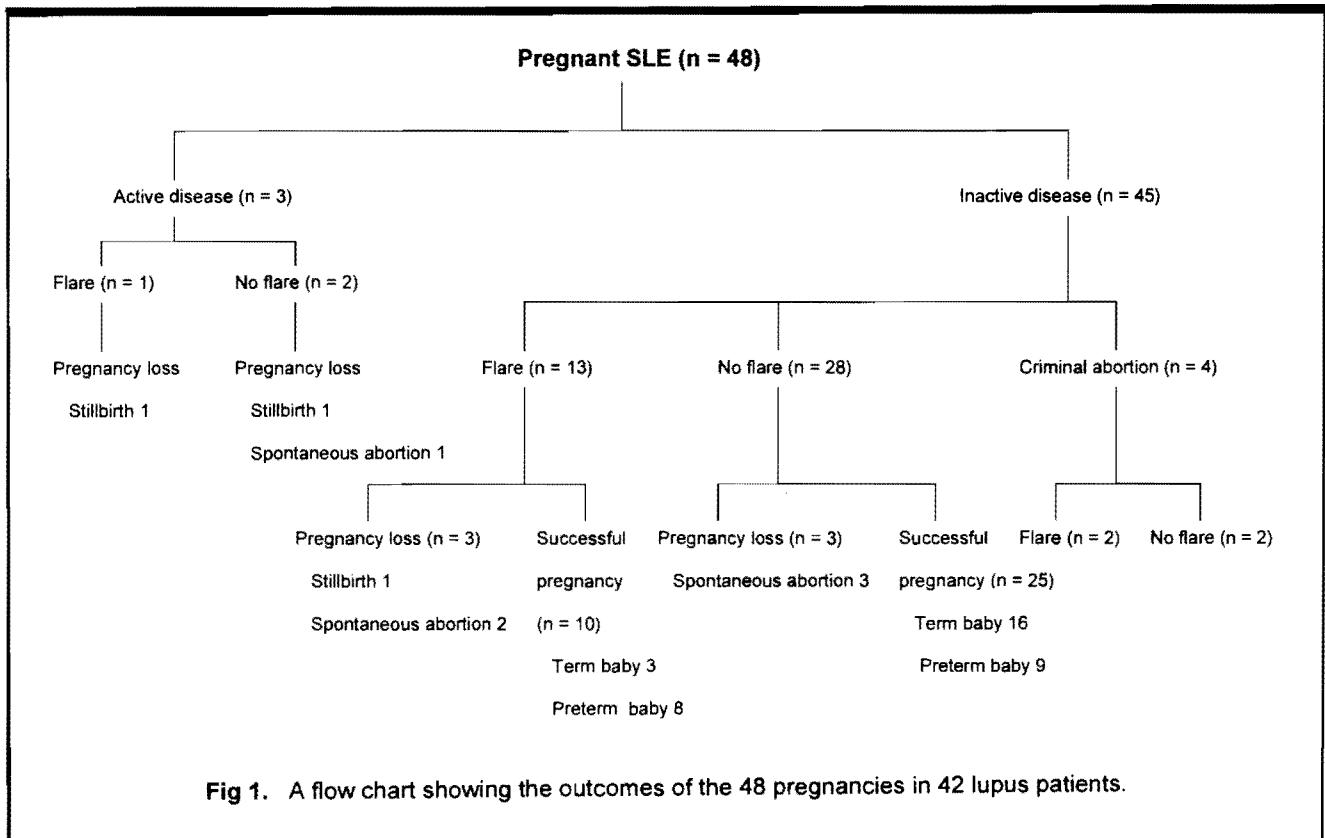Criminal abortion (n = 4)

Flare (n = 2)

No flare (n = 2)

Fig 1. A flow chart showing the outcomes of the 48 pregnancies in 42 lupus patients.

17) with a pregnancy loss in 6 (spontaneous abortion in 5 and still-birth in 1). In all 3 pregnancies where the disease was active at the time of conception resulted in fetal losses (spontaneous abortion in 1 and stillbirth in 2). Details of the fetal outcome of patients studied in relation to disease flares during pregnancy are shown in Table 3. There was no statistically significant difference in pregnancy loss or successful pregnancy between pregnant SLE patients who had flares and those who had not. Concerning successful pregnancy, patients without flares had significantly more full term babies ($p <$ 0.02). mean gestational age ($p <$

0.002) and birth weight ($p < 0.001$) than those with flares. Neonatal death occurred in 2 premature babies. One of these 2 infants was delivered from the flare group at 27 weeks' gestation weighing 900 g, while the other was born from the non-flare group at 26 weeks' gestation weighing 920 g. There was no statistical difference between the number of babies with a small for gestational age born to a mother with flares and to those without. No case of neonatal lupus syndrome or congenital anomalies was identified.

The fetal outcome of 13 pregnancies with active renal dis-

ease (11 with renal flares during pregnancy and 2 with active renal disease at the time of conception) was poor. The fetal outcome was term baby in 1, prematurity in 7 and pregnancy loss in 5 (spontaneous abortion in 2 and stillbirth in 3). Seven of these 13 pregnancies had hypertension, one of whom already had hypertension before becoming pregnant. The fetal outcome in these 7 pregnancies was prematurity in 4 and still-birth in 3. The hypertension seen in these patients was due to active disease, as all patients had active nephritis and low complement levels. Proteinuria and hypertension persisted after the delivery or termination of the pregnancy. One pregnant patient had central nervous system lupus with seizures and vaginal bleeding at 27 weeks' gestation. The pregnancy was terminated and resulted in a live birth baby weighing 1,250 g.

Maternal obstetric complications are shown in Table 4. There was a trend of more maternal complications in patients with flares, but this did not show a statistically significant difference

Table 2. Organ flares in 48 pregnancies

Organ system	No. (%)
Renal	12 (25.00)
Mucocutaneous	11 (22.91)
Articular	4 (8.33)
Serositis	2 (4.17)
Hematologic	2 (4.17)
Neuropsychiatric	1 (2.08)
Others: fever, fatigue	1 (2.08)

Table 3. Fetal outcomes in 44 pregnancies with regard to flare and non-flare*

	Total (n = 44)	Flare (n = 14)	Non-flare (n = 30)	p value
Pregnancy loss	9	4	5	NS
Spontaneous abortion	6	2	4	NS
Still birth	3	2	1	NS
Successful pregnancy	35	10	25	NS
Prematurity	17	8	9	0.02
Term delivery	18	2	16	0.02
Mean gestational age, wk	35.74 ± 3.51	33.00 ± 3.68	36.84 ± 2.82	0.002
Mean birth weight, g	2,250.88 ± 642.42	1,711.11 ± 498.03	3,445.20 ± 579.82	0.001
Small for gestational age	9	3	6	NS

* Excluding cases of criminal abortion; p value between the flare and non-flare groups

Table 4. Maternal obstetric complications*

	Total (n = 44)	Flare (n = 14)	Non-flare (n = 30)
No complications	28	5	23
Complications	13	6	7
Premature rupture of the membrane	4	2	2
Oligohydramnios	3	1	2
Ante-partum hemorrhage	2	1	1
Post-partum hemorrhage	3	1	2
Post-partum endometritis	1	1	0

* Excluding cases of criminal abortion

($p = 0.07$). There was no maternal death in this study.

DISCUSSION

Pregnancy in patients with SLE is a field of interest in rheumatology. The effect of pregnancy on disease activity and fetal outcome are the most common subjects of studies. The activity of lupus during pregnancy is difficult to assess because many clinical features such as joint pain, cutaneous erythema and an increase in the erythrocyte sedimentation rate can be seen in normal pregnant women.

Most studies of lupus pregnancy between 1950-1980 were uncontrolled and retrospective. After the mid 1980s, many prospective studies have been carried out in pregnant patients with SLE and an incidence of flare of 13-63% has been found.[10-15] Flares can occur at any trimester and post-partum period. This great variation in incidence might have been related to the severity in patients, selection of controls and the criteria used to determine the flare or activity of the disease. Although many of these studies have shown that the flare

rate during pregnancy is higher compared to the non-pregnant lupus controls,[11,12] others could not confirm this finding.[10,13,16,17] Prophylactic use of corticosteroids has shown to be unable to prevent flares.[10]

It is generally accepted that if the disease is well controlled at conception or there is a mild flare of the disease during pregnancy, a good fetal outcome could be expected. In contrast, if there is moderate or severe renal disease or hypertension, at the time of conception or during pregnancy, then the fetal outcome is less favorable.[15,18-24] The fetal outcome has been reported to be related to the outcome of a previous pregnancy,[25] the presence of aCL antibodies,[21,26-31] the long duration of SLE and the use of immunosuppressive drugs by mothers during pregnancy.[21,32]

An incidence of flares of 33.33% was found in this study, despite 93.75% of the patients having inactive or quiescent conditions at the time of conception. This incidence was similar to those that have been previously des-

cribed.[10-14,33] No cases of post-partum flares were found that differed from others in which a majority occurred in the first half of pregnancy and post-partum period.[10,11,18] Without a control group, it was not known whether the incidence of flare was higher than that of non-pregnant lupus. Almost half of the flares in patients in this study involved the kidney and mucocutaneous system. However, these flares were usually mild, did not require hospital admission, and responded well to a modest increase in the dosage of corticosteroids. In this study we found no cases of PIH. Although 7 of our patients had active nephritis and hypertension during pregnancy, the proteinuria responded to the increased dosage of corticosteroids, and in many of them the hypertension and proteinuria persisted after delivery. Moreover, all of these patients had low complement levels and none had hyperuricemia. This situation made the diagnosis of PIH in our patients unlikely.

It is sometimes difficult to differentiate PIH from active lupus nephritis in a pregnant lupus patient because proteinuria, hyperten-

sion, edema and thrombocytopenia can be seen in both conditions. In a "normal" pregnancy, PIH usually occurs during the second and third trimester in primigravida, with normal complement levels and an elevation of serum uric acid. Hypertension and proteinuria are usually resolved after pregnancy. This is in contrast to active lupus nephritis, in which proteinuria usually responds to corticosteroids. However, cases of lupus nephritis, which did not respond to corticosteroids but did improve spontaneously over several months post-partum, have been described as a variant of PIH.[16] The low level of complement components has been reported to be associated with a flare of SLE.[11,33,34] However, low complement levels could not be used sometimes to distinguish SLE with active disease from preeclampsia.[34,35] Therefore, frequent assessment of pregnant lupus patients, especially those with nephritis, is recommended.

Excluding cases of criminal abortion, we found an incidence of pregnancy loss of 20.45%, in which 13.63% was due to spontaneous abortion. This incidence of fetal loss was similar to the 13-35% reported previously.[5,10,13-15,23,36-38] The incidence of fetal loss in lupus patients was higher than that in the general population. Our patients who had active renal disease during pregnancy, either with or without hypertension, had a fetal loss incidence of 38%. This result agreed with previous reports that the presence of active nephritis and hypertension during pregnancy were associated with a poor obstetric outcome and a high incidence of fetal loss and prematurity.[19-24,30] As the aCL antibody assay was not performed in our patients, it was not

known whether the high incidence of pregnancy loss was related to the presence of aCL antibodies. However, none of the patients had a history that suggested a presence of antiphospholipid antibodies.

Eighty percent of our lupus pregnancies had successful deliveries. We found an incidence of prematurity of 38.63%, which was similar to the 12-57% reported previously.[14,15,22,29,31,33,36-38] The prematurity rate in this series was high despite the fact that a majority of the patients had conceived when the disease was inactive or quiescent. However, no correlation between prematurity and the flare of the disease could be found. The causes of prematurity in lupus patients could have been multifactorial, including maternal lupus activity, maternal hypertension and renal disease, concurrent use of corticosteroids and the presence of antiphospholipid antibodies.[4] Twenty percent of our live birth babies was small for gestational age. Low birth weight and small for gestational age babies born from pregnant lupus patients were not uncommon.[20,29,33,39] The small for gestational age babies could have been related to intrauterine growth retardation secondary to placenta insufficiency, which was supported by the presence of placental thrombosis in association with aCL.[40-43]

In this study, there was no statistical difference in pregnancy loss and live birth between pregnant patients with flares and those without, but patients without flares had significantly more term babies, higher gestational age and greater birth weight. Maternal obstetric complications were seen as more common in patients with flares, but

these were generally mild and manageable. No maternal death was found.

It was concluded from this study that flares in pregnant SLE were common, even though the disease was inactive at the time of conception. However, flares were usually mild and responded well to medical treatment. Patients without flares had more full term, mean gestational age and mean birth weight babies. The presence of active renal disease or hypertension was associated with a poor fetal outcome.

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