

The Effect of Lupus Nephritis on Pregnancy Outcome and Fetal and Maternal Complications

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ABSTRACT. Objective. To evaluate the effect of lupus nephritis on pregnancy with respect to fetal outcome, maternal complications, and lupus activity.

Methods. All pregnancies seen between 1970 and 2003 in the Lupus Clinic were evaluated for the 3 outcomes. Renal disease was defined as the presence of nephrotic syndrome, dialysis, renal transplant, serum creatinine > 120 mmol/l, proteinuria, sterile hematuria and pyuria, or the presence of casts. Fetal complications were evaluated in pregnancies resulting in either live births or stillbirths. Generalized estimating equations were used to test for differences in outcomes between pregnancies with and without the presence of active renal disease. Repeated measures adjustments were made in the model for multiple pregnancies in the same mother.

Results. There were 193 pregnancies in 104 women. Of these, 81 occurred in the presence of active renal disease during the study period, defined as 6 months prior to conception until the date of pregnancy outcome. One hundred twelve pregnancies were defined as nonrenal. No statistical difference was found in pregnancy outcome. Fetal complications were not different between the 2 groups with the exception of low birth weight and congenital malformations, which were observed more frequently in the renal group. Pregnancy-induced hypertension was more frequent in pregnancies with renal disease. Lupus flares were also more likely to occur in pregnancies with renal disease compared to those without.

Conclusion. Lupus nephritis in pregnancy does not lead to worsened pregnancy or fetal outcomes. Active renal disease, however, is associated with pregnancy-induced hypertension, as well as a flare of lupus activity during pregnancy. (First Release March 15 2010; J Rheumatol 2010;37:754–8; doi:10.3899/jrheum.090872)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
LUPUS NEPHRITIS

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Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease that most commonly affects women in their reproductive years¹. While fertility does not appear to be an issue for women with SLE, there is increased fetal loss and impairment of fetal development². We have previously shown that disease activity at conception is associated with flares of lupus during pregnancy³.

Renal disease is a major manifestation in patients with SLE and is an important factor in morbidity and mortality¹. The relationship between renal disease and pregnancy in SLE has been investigated and conflicting results have been

reported^{4–8}. We have found that maternal renal disease was a strong predictor of adverse fetal outcome⁴. In a previous study we investigated the effect of pregnancy on lupus nephritis and found that during pregnancy, change in renal disease activity and deterioration in renal function are similar to those changes that occur in nonpregnant patients with lupus nephritis⁹. We investigated the effect of lupus nephritis at the onset or during pregnancy on the outcome of the pregnancy, fetal complications, maternal complications, and lupus activity.

MATERIALS AND METHODS

At the University of Toronto Lupus Clinic we prospectively followed patients with SLE at 2–6 month intervals, according to a standard protocol documenting clinical and laboratory features of the disease.

Patient selection. All pregnancies that occurred after entry and during followup between 1970 and 2003 were included in this study. Patients had at least 1 visit in the study period (6 months prior through end of pregnancy) and known pregnancy outcome. Patients were categorized into those with renal disease at some point in the study period and those with no evidence of renal disease in the study period. We categorized those without renal disease in the study period into those who never had renal disease and those who had had renal disease in the past that had completely resolved prior to the study period with no residual damage.

The definition of renal disease was the presence of nephrotic syndrome, dialysis, renal transplant, proteinuria (> 500 mg per 24 h), hematuria,

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pyuria, casts (red blood cells or granular casts), or a serum creatinine level > 120 mmol/l in the 6 months prior to pregnancy until pregnancy outcome. Active renal disease was defined by the presence of hematuria, pyuria (other causes ruled out), casts, and proteinuria.

The definition of disease activity was the SLE Disease Activity Index 2000 (SLEDAI-2K), a valid measure of disease activity¹⁰. All variables necessary to score the SLEDAI-2K are included in the standard assessment protocol. Disease activity over time was measured by the adjusted mean SLEDAI-2K, a validated measure¹¹. Adjusted mean SLEDAI-2K was calculated for both renal and nonrenal pregnancies over the study period (6 months prior to conception until pregnancy outcome).

Outcome measures. Outcomes were defined as stillbirth: death of fetus in utero past 20 weeks' gestation; spontaneous abortion: loss of pregnancy in < 20 weeks' gestation; therapeutic abortion: voluntary termination of pregnancy; and perinatal death: neonate death within 7 days of birth.

A lupus flare was defined as an increase ≥ 4 in SLEDAI-2K from the SLEDAI-2K measured 6 months prior to pregnancy. This measure has been found to accurately describe flare in patients with SLE¹². Fetal complications measured were low birth weight (< 10th percentile for sex and gestational age¹³), perinatal death, congenital malformations (derived from medical records), neonatal lupus, newborn fever/sepsis, or fetal distress. Maternal complications were preeclampsia, gestational hypertension, hemorrhage, gestational diabetes, maternal infection, vascular complications, or surgical complications.

Statistical analysis. Multiple pregnancies from a single patient were included in the study. The total number of pregnancies included per patient varied from 1 to 6. Comparisons of characteristics between pregnancies in the presence or absence of renal disease were done through generalized estimating equations (GEE). Adjustments for repeated measures on the mother were made for all comparisons with the assumption of autoregressive structure of the correlation matrix.

Evaluating the difference in pregnancy outcome, adjustments were also made in the GEE model for medication used in the study period (specifically, steroids, antimalarials, or immunosuppressives).

Looking at fetal and maternal complications as well as flare, the adjustments for medication use were made where the sample size was large enough. Otherwise, only the repeated measures adjustment was made.

RESULTS

Between 1970 and 2003, there were 213 pregnancies recorded. Twenty occurred prior to entry into the clinic or in a period of prolonged absence from the clinic. The basis for our study was 193 pregnancies in 104 women seen in the University of Toronto Lupus Clinic. Eighty-one pregnancies were categorized as renal and 112 as nonrenal. Of the latter, 49 had no renal disease ever and 63 had some renal disease in the past. The demographic data for all pregnancies as well as renal and nonrenal pregnancies are shown in Table 1.

Renal pregnancies were associated with a lower age at pregnancy, a higher SLEDAI-2K at presentation to the clinic as well as before the pregnancy, and a higher adjusted mean SLEDAI-2K during pregnancy. Once the renal component of SLEDAI-2K was removed, however, the difference was not statistically significant. Medications taken ever, before, and during pregnancy are shown in Table 2.

Outcome of pregnancy. Overall, of the 193 pregnancies, 114 resulted in live births (Table 3). Pregnancies associated with renal disease had the same frequency of live births as those without renal disease (59.8% vs 58.0%, respectively; $p = 0.96$). The weeks of gestation in the nonrenal and renal

patients were the same (37.7 ± 2.9 and 36.8 ± 3.2 weeks, respectively; $p = 0.77$). There were 6 stillbirths, 3 in each group (2.7% in the nonrenal and 3.7% the renal group). Forty-two pregnancies resulted in spontaneous abortions, 24 (21.4%) in the nonrenal pregnancies and 18 (22.2%) in the renal pregnancies. Eighteen (16.1%) of the nonrenal pregnancies and 13 (16.1%) of the renal pregnancies ended in therapeutic abortions. The results were the same when the nonrenal patients were categorized as never renal or previous renal.

Fetal complications. Of the 120 pregnancies resulting in deliveries, 6 were stillbirths. Therefore fetal complications were assessed in 114 live births, 67 nonrenal and 47 renal (Table 4). Low birth weight is defined as below the 10th percentile for sex and gestational age. Overall there was a 30% frequency of low birth weight in the lupus pregnancies. Low birth weight was significantly more frequent among renal patients compared with nonrenal patients (46% vs 20%, respectively; $p = 0.01$). The mean birth weights were 2574 ± 788 g in the renal group and 3026 ± 677 g in the nonrenal group ($p = 0.001$), even though the gestational weeks were similar. There were no differences in perinatal deaths, neonatal lupus, fever/sepsis, and fetal distress between the 2 groups (each obtained from medical records; Table 4). Congenital malformations occurred in 3 infants in the renal group and included 1 infant with cleft lip, 1 with cleft lip/palate, facial palsy, and visual/hearing impairment, and 1 with bilateral 2nd and 3rd toe syndactyly. The mothers of the 2 infants with cleft lip and cleft lip/palate were taking glucocorticosteroids during pregnancy, while the mother of the infant with the syndactyly was not taking glucocorticosteroids during pregnancy. None of these women took anti-malarials or immunosuppressives during pregnancy. The results were the same when the nonrenal patients were categorized as never renal or previous renal.

Maternal complications. Pregnancies with renal disease had more pregnancy-induced hypertension than pregnancies without renal disease (Table 5). There was no difference in the occurrence of preeclampsia, hemorrhage, gestational diabetes, infection, or vascular or surgical complications in the 2 groups (Table 5). There were no maternal deaths. The results were the same when the nonrenal patients were categorized as never renal or previous renal.

Lupus flares occurred significantly more frequently in pregnancies with renal disease. Using the SLEDAI-2K with renal descriptors, 37 (45.7%) pregnancies with renal disease flared compared to 15 (13.4%) pregnancies without renal disease ($p \leq 0.0001$). When the renal descriptors were removed from the SLEDAI-2K score, 24 (39.6%) pregnancies with renal disease had a flare compared to 15 (13.4%) pregnancies without renal disease ($p = 0.01$).

Renal disease was present in the 6 months before pregnancy in 47 of the 81 renal pregnancies. Of these 47, 45 had active renal disease. Of those, 16 (35.6%) were associated

Table 1. Demographic data for patient population. Eighty of the 81 patients with renal disease had evidence of active renal disease during the study interval. P value was obtained from GEE model, adjusting for repeated measures (using autoregressive correlation structure) for multiple pregnancies in the same mother. Hypertension was defined as systolic > 140 mm Hg, diastolic > 90 mm Hg, or taking antihypertensive medications.

Characteristic	All Pregnancies, N = 193	Nonrenal, N = 112	Renal, N = 81	p
Age at diagnosis, yrs	22.2 ± 5.0	22.7 ± 5.4	21.5 ± 4.4	0.01
Age at pregnancy, yrs	29.8 ± 4.7	30.8 ± 4.5	28.3 ± 4.7	0.002
Disease duration at pregnancy, yrs	7.6 ± 5.4	8.1 ± 5.6	6.9 ± 5.1	0.27
SLEDAI-2K at presentation	8.8 ± 5.9	7.3 ± 5.2	10.9 ± 6.2	0.08
SLEDAI-2K pre-pregnancy	4.2 ± 3.8	3.5 ± 3.5	5.2 ± 4.0	0.008
AMS during study period	4.6 ± 3.4	3.2 ± 2.2	6.5 ± 3.9	< 0.0001
SLEDAI-2K (excluding renal) pre-pregnancy	3.3 ± 3.2	3.5 ± 3.5	3.0 ± 2.8	0.23
AMS (excluding renal) during study period	3.5 ± 2.6	3.2 ± 2.2	3.9 ± 2.9	0.20
Hypertension, n (%)	35 (18.1)	13 (11.6)	22 (27.2)	0.18
Diabetes, n (%)	7 (3.7)	6 (5.4)	1 (1.3)	0.17
Antiphospholipid antibody, n (%)	92 (51.7)	57 (54.8)	35 (47.3)	0.59

GEE: generalized estimating equations; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; AMS: adjusted mean SLEDAI-2K.

Table 2. Medications in the 6 months prior to pregnancy and during pregnancy. P values are obtained from generalized estimating equations model, adjusting for repeated measures (using autoregressive correlation structure) for multiple pregnancies in the same mother.

Medication	Nonrenal, n (%)	Renal, n (%)	p
Ever prior to the study period			
n	112	81	
Antihypertensive	9 (13.4)	10 (33.3)	0.002
Steroids	76 (67.9)	61 (75.3)	0.53
Antimalarials	58 (51.8)	30 (37.0)	0.93
Immunosuppressives	19 (17.0)	22 (27.2)	0.11
In the 6 months pre-pregnancy			
n	92	69	
Antihypertensive	5 (9.4)	8 (28.6)	0.002
Steroids	50 (54.4)	48 (69.6)	0.07
Antimalarials	34 (37.0)	17 (24.6)	0.85
Immunosuppressives	7 (7.6)	13 (18.8)	0.04
During pregnancy			
n	92	72	
Antihypertensive	4 (7.4)	7 (22.6)	0.02
Steroids	59 (64.1)	53 (73.6)	0.43
Antimalarials	27 (29.4)	19 (26.4)	0.95
Immunosuppressives	1 (1.1)	9 (12.5)	0.02
Ever in study period			
n	112	81	
Antihypertensive	7 (10.3)	9 (27.3)	0.001
Steroids	66 (58.9)	61 (75.3)	0.18
Antimalarials	41 (36.6)	22 (27.2)	0.72
Immunosuppressives	7 (6.3)	14 (17.3)	0.03

with lupus flare, compared to 15 pregnancies (13.4%) without renal disease ($p = 0.02$). When the renal descriptors were removed from the SLEDAI-2K, 14 (31.1%) had had flare compared to 15 (13.4%) nonrenal patients ($p = 0.04$).

DISCUSSION

We reported on 193 pregnancies in 104 women with SLE. Pregnancies were divided into those with and without renal

disease. Eighty-one women had evidence of renal disease, 80 of whom had active renal disease occurring in the 6 months prior to pregnancy through the end of the pregnancy. These pregnancies were compared with 112 pregnancies without evidence of renal disease. Pregnancy outcome was not different between these 2 groups.

Previous studies of the effect of lupus nephritis on pregnancy included small numbers of patients and pregnancies. Soubassi, *et al*⁵ reported a 25% fetal loss in 24 pregnancies in 22 patients with lupus nephritis. Rahman, *et al*⁶ documented fetal loss in 38% of 55 pregnancies in 24 patients with lupus nephritis, while Carmona, *et al*⁷ found fetal loss, excluding therapeutic abortion, in 17% of study patients with lupus nephritis. In our study, fetal loss of 30% was noted, excluding therapeutic abortions. The frequency of live births in pregnancies with lupus nephritis in our study was 69%, and was not different from lupus pregnancies not associated with lupus nephritis (71%). Carmona, *et al*⁷ compared 42 pregnancies in 35 patients with World Health Organization (WHO) class 3 or 4 lupus nephritis with 12 pregnancies in 10 patients with WHO class 2 or 5 as well as 54 pregnant women with SLE without nephritis, matched by age and parity to the patients with class 3 and 4 lupus nephritis. Pregnancy outcome in terms of live births was greater than 70%, similar in the 3 groups and similar to our study.

We found that overall there was a higher frequency than expected of low birth weight. Moreover, infants born to patients with renal disease were smaller than those born to patients without renal disease. This was so even though the gestational ages were similar. We found 3 infants with congenital malformations (Table 4), all in the renal group. Although this finding is significant, the numbers are small and will have to be confirmed in other studies. An increased risk for the development of cleft lip/palate in babies born to

Table 3. Outcomes of pregnancy. Comparing live birth rates to stillbirths and spontaneous abortions using GEE and adjusting for medication use during pregnancy, as well as repeated measures for multiple pregnancies in the same mother. P = 0.96.

Status	Live Births, n (%)	Stillbirths, n (%)	Spontaneous Abortions, n (%)	Therapeutic Abortions, n (%)	Total
Nonrenal pregnancies	67 (59.8)	3 (2.7)	24 (21.4)	18 (16.1)	112
Renal pregnancies	47 (58.0)	3 (3.7)	18 (22.2)	13 (16.1)	81
Total	114	6	42	31	193

GEE: generalized estimating equations.

Table 4. Fetal complications (including only live births). P values are obtained from generalized estimating equations model, adjusting for repeated measures (using autoregressive correlation structure) for multiple pregnancies in the same mother.

Complication	Nonrenal Pregnancies, n = 67 (%)	Renal Pregnancies, n = 47 (%)	p
Low birth weight	13 (20.3)	18 (46.2)	0.01
Perinatal death	2 (3.0)	1 (2.1)	0.87
Congenital malformations	0 (0)	3 (6.4)*	0.05**
Neonatal lupus	3 (4.5)	1 (2.1)	0.57
Fever/sepsis	1 (1.5)	0 (0)	1.00**
Fetal distress	3 (4.5)	1 (2.1)	0.51
Births with complications	21 (31.3)	21 (46.7)	0.15

* One infant with cleft lip, 1 infant with cleft lip/palate, facial palsy, and visual/hearing impairment, and 1 infant with bilateral 2nd and 3rd toe syndactyly. ** Regression not possible due to "0" in one of the group. Fisher's exact test.

Table 5. Maternal complications (all pregnancies). P values are obtained from generalized estimating equations model, adjusting for repeated measures (using autoregressive correlation structure) for multiple pregnancies in the same mother.

Complication	Nonrenal Pregnancies, n (%)	Renal Pregnancies, n (%)	p
Preeclampsia	1 (1.2)	4 (6.4)	0.13
Pregnancy-induced hypertension	1 (1.2)	6 (9.5)	0.05
Hemorrhage	1 (1.2)	2 (3.2)	0.47
Gestational diabetes	3 (3.7)	1 (1.6)	0.46
Infection	4 (4.9)	2 (3.2)	0.59
Vascular complications	2 (2.5)	1 (1.6)	0.72
Surgical complications	2 (2.5)	0 (0)	0.50*
Pregnancies with complications	14 (17.3)	14 (22.2)	0.83

* Regression not possible due to "0" in one of the group. Fisher's exact test.

mothers who had taken corticosteroids during pregnancy has been reported¹⁴. In our study, the children born with cleft lip or cleft lip/palate were born to mothers on glucocorticosteroid therapy. Soubassi, *et al*⁵ reported on 2 infants with congenital heart block but no other congenital abnormalities or neonatal lupus. Rahman, *et al*⁶ reported 1 neonatal death in a premature baby born to a mother with active

renal disease. They do not report on congenital abnormalities. Carmona, *et al*⁷ reported no newborns with neonatal lupus and did not comment on any congenital abnormalities.

Most maternal complications occurred with the same frequency in pregnancies with and without renal disease in our study. However, the frequency of pregnancy-induced hypertension was significantly higher in pregnancies with renal disease. Soubassi, *et al*⁵ reported on a number of maternal complications including 42% with hypertension and 25% with preeclampsia, but there was no comparison group. These numbers are higher than the numbers shown in our study. Two maternal deaths were reported in 24 patients by Rahman, *et al*⁶. Carmona, *et al*⁷ found hypertension and preeclampsia to occur more frequently in patients with class 3 and 4 lupus nephritis (37.1%) than in those with no disease (11.6%) or class 2 and 5 disease (11.1%). The frequency of these complications was higher among their patients than ours, but it is not clear from the report whether these were any hypertensive patients or whether this was specifically pregnancy-induced hypertension. Carmona, *et al*⁷ did not comment on maternal deaths.

We found that pregnancies with active lupus nephritis were associated with a higher frequency of flares of lupus. This is similar to our findings in unselected lupus pregnancies, where active disease at onset of pregnancy predicted subsequent flares³. Similar to our study, Rahman, *et al*⁶ concluded that inactive lupus nephritis and normal renal function at conception were the only predictors of a favorable maternal outcome of pregnancy. They recommended that it would be essential to control disease activity prior to pregnancy. Moroni, *et al*⁸ found no increase in flares in patients with lupus nephritis during pregnancy compared to prepregnancy and postpregnancy rates. Similarly, Carmona, *et al*⁷ showed that lupus flare and renal flare rates during pregnancy and the puerperium were similar in patients with and without lupus nephritis.

Lupus nephritis at the onset or during pregnancy does not affect pregnancy outcome and fetal complications. Active lupus nephritis is associated with pregnancy-induced hypertension and with flares of lupus disease activity in pregnancy. Thus, although pregnancy is not contraindicated in patients with lupus nephritis, these patients should be monitored carefully for pregnancy-induced hypertension, and

lupus disease activity should be controlled before and during pregnancy in order to optimize maternal outcomes.

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