

Preterm Deliveries in Women with Systemic Lupus Erythematosus

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ABSTRACT. Objective. To compare the clinical, laboratory, and demographic variables of women in our clinic with systemic lupus erythematosus (SLE) who have had a pregnancy resulting in a live birth and identify any correlations with either term or preterm delivery.

Methods. Pregnancies in women with SLE from 1999 to 2001 were retrospectively reviewed. We recorded demographic data, disease activity (SLE Disease Activity Index, SLEDAI), obstetric history, prednisone dosage, other medications taken during pregnancy, history of renal disease, and autoantibody status [including antinuclear antibody, anti-DNA, anticardiolipin IgG (aCL), and lupus anticoagulant (LAC)]. Preterm delivery was defined as gestational age at delivery < 37 weeks. We performed a literature survey using PubMed and the key words SLE, pregnancy, and outcome.

Results. Of the 72 pregnancies, 28 (38.9%) resulted in preterm deliveries. There were no significant differences in any demographic or disease variables measured comparing term versus preterm delivery groups. More women in the preterm group were taking ≥ 10 mg/day prednisone during their pregnancy (50.0% vs 22.2%; $p = 0.028$), and the mean dose was significantly higher than the term group taking ≥ 10 mg/day (24.8 vs 16.7 mg/day; $p = 0.047$). There was a higher prevalence of women with aCL IgG in the preterm group ($p = 0.023$). The mean weeks gestation was shorter for women positive for aCL IgG compared to the group negative for aCL (34.9 ± 4.4 vs 37.5 ± 3.2 weeks, respectively; $p = 0.032$). There was no difference in second trimester disease activity between the term and preterm groups (33.3% and 36.4% of each group had a SLEDAI of 0). However, significantly more women in the term group received no medication during their pregnancies compared to women in the preterm group (20.0% vs 0.0%; $p = 0.031$).

Conclusion. The rates of preterm deliveries, premature rupture of membranes, intrauterine growth restriction, and aPL in SLE pregnancies vary considerably in published reports, most of which are retrospective analyses. Our rates closely approximate the median values for all measures. We found preterm deliveries to be associated with disease activity (as determined by the use of any medication throughout pregnancy vs no medication, and prednisone dose ≥ 10 mg/day) and the presence of aCL IgG but not LAC. Our results suggest that inactive disease rather than controlled disease at the onset of pregnancy may be the determining factor in extending SLE pregnancies to full term, thereby decreasing maternal and fetal morbidity. (J Rheumatol 2003;30:2127–32)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
PRETERM DELIVERY

PREDNISONE
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The causes of preterm delivery (< 37 weeks' gestation) include premature rupture of membranes (PROM), preeclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and preterm labor. The incidence of preterm labor and delivery in women with systemic lupus erythematosus (SLE) varies between 19% and 49% in pregnancies occurring after a diagnosis of SLE compared to the expected rate of 7% for the general popula-

tion¹⁻⁵. In a large retrospective review of data over a 2 year period, Yasmeen, *et al*⁶ found 21.0% of pregnant women with SLE had preterm deliveries (116/555) compared to 4.2% of controls (2520/60,000). This increased frequency of preterm deliveries in SLE has been variously attributed to the following: increased disease activity (monitored by clinical index, serum C3 concentration at first visit, or prednisone dose), a history of renal disease, PROM, hypertension (requiring antihypertensive treatment or elevation of second trimester diastolic blood pressure), preeclampsia, and the presence of antiphospholipid antibodies (aPL)⁷⁻²¹.

Any attempt to consolidate published results on SLE pregnancies from different centers is frustrated by incomplete or incompatible reporting methodologies, and it is difficult to formulate a consensus regarding frequencies of events and causal relationships when centers apparently have quite discrepant experiences. The highly variable rate

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of preterm delivery in the literature has been quite rightly attributed to differences in patient demographics and subjectively defined clinical and laboratory measures.

We have not previously reported preterm delivery rates in our clinic. In addition to assessing recent pregnancy outcomes in our patients with SLE, we reviewed the pertinent literature and placed our findings in the context of similar reports.

MATERIALS AND METHODS

Patients. We retrospectively reviewed pregnancy outcomes in our clinic for the period 1999–2001 in patients who fulfilled the American College of Rheumatology criteria for the classification of SLE²². Preterm delivery was defined as gestational age at delivery of < 37 weeks.

Clinical variables. Age, disease duration at time of pregnancy, and age of disease onset were obtained from patient charts. Disease activity was determined in the second trimester using the SLE Disease Activity Index (SLEDAI)²³. Obstetrical history included number of pregnancies, live births, spontaneous abortions, stillbirths, and therapeutic abortions. A history of renal disease was determined based on proteinuria > 0.5 g/24 h prior to the pregnancy and biopsy results when available. Prednisone dosage in the second trimester was recorded in addition to any other medications taken during the pregnancy.

Laboratory variables. Our serological analysis included antinuclear antibodies (ANA titer \geq 1/80, using a HEp-2 substrate), anti-double stranded DNA antibodies (anti-dsDNA by ELISA), anticardiolipin IgG (aCL IgG; Quantalite Kit, Inova, Intermedico, Markham, ON, Canada), the lupus anticoagulant (LAC) measured in plasma by a panel of coagulation tests (Russell's viper venom time, lupus sensitive partial thromboplastin time, kaolin cephalin clotting time, and a dilute prothrombin time confirmed by 1:1 and 4:1 repeat testing with normal plasma), and a routine activated partial thromboplastin time (aPTT).

Statistical analysis. Data were analyzed using the Sigma Stat programme 9 (Version 2.0, SPSS, Chicago, IL, USA). Student's *t* test and the Mann-Whitney rank-sum test (for data not normally distributed) were used to compare group means or medians, and 95% confidence intervals (CI) were also calculated. Population prevalences were compared using the *z* test. A *p* value < 0.05 was considered significant.

Literature review. Using the PubMed database (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) we entered the search words SLE, pregnancy, and outcome and accessed the titles and abstracts from 1992 to 2002. From those, we identified original studies of lupus pregnancies and obtained full articles for those reporting similar clinical outcome criteria for comparison purposes. We attempted to extract from each report the following data: number of live births, rates of preterm deliveries, PROM, intrauterine growth restriction (IUGR), aCL and/or LAC positivity, and conclusions regarding factors that might contribute to preterm deliveries including prednisone usage or dosage, disease activity, and aPL positivity.

RESULTS

Demographic and clinical variables. There were 88 pregnancies in women with SLE in our clinic between 1999 and 2001, 73 of which resulted in a live birth (82.9%). Of the 73 pregnancies, there were 28 (38.4%) preterm deliveries (< 37 weeks). There were no statistically significant differences between the mean ages, disease durations, ages at disease onset, second trimester SLEDAI, or histories of renal disease in the preterm and term delivery groups (Table 1).

Laboratory variables. There was a statistically significant

difference in the frequency of aCL IgG-positive patients in the preterm delivery group compared to the term delivery group (55.5% vs 19.4%, respectively; *p* = 0.023). There were no significant differences with any other autoantibodies measured (Table 1).

Obstetric histories. There were no differences between the obstetrical histories of either the term or preterm delivery groups (Table 2). There were no significant differences in the obstetrical histories of women who spontaneously went into labor or who required medical intervention in the labor and delivery process regardless of the gestational age (data not shown).

Medications in pregnancy. Significantly more women in the preterm delivery group were taking \geq 10 mg/day prednisone compared to the term delivery group (50.0% vs 22.2%; *p* = 0.028; Table 3). The mean dose in the preterm group receiving \geq 10 mg/day was higher than the mean in the comparable term delivery group (28.8 vs 16.6 mg/day; *p* = 0.047). There were no other significant differences in the frequencies of medications used by the 2 groups.

There were no women in the preterm delivery group who received no medication at all throughout the pregnancy, compared to 9/45 women in the term delivery group (0.0 vs 20.0%, respectively; *p* = 0.031), despite the lack of significant difference in second trimester disease activity as measured by SLEDAI (Table 1).

Labour and delivery. Fifty women went into labor spontaneously: 44 eventually delivered vaginally and 6 had Cesarean sections (C-sections) due to nonprogressing labor (Table 4). Of those, 33/50 (66.0%) delivered at or beyond 37 weeks' gestation and 17/50 (34.0%) delivered preterm. There was a trend to increased prevalence of aCL IgG in the spontaneous preterm delivery group compared to the spontaneous term delivery group (58.3% vs 24.0%; *p* = 0.093, data not shown), but because of small sample size, this did not reach significance. There were no statistically significant differences in number of women in each group receiving prednisone, prednisone dosage, or taking no medication at all throughout the pregnancy.

Twenty-three women required medical intervention (induction and/or C-section) in their deliveries (Table 4). Analyzing demographic, clinical, and laboratory results for spontaneous versus induced deliveries, we found no significant differences between the 2 groups (data not shown).

Complications in pregnancy. Table 4 describes the frequency and distribution of complications requiring delivery intervention. Significantly more women in the preterm delivery group were either induced or had a C-section due to high blood pressure, the HELLP syndrome, fetal distress, preeclampsia, proteinuria, IUGR, and decreased amniotic fluid volume combined than in the term delivery group (10/28 vs 5/45; *p* = 0.023, 95% CI –0.441 to –0.0592, power with α = 0.05: 0.617), although there were

Table 1. Demographic, laboratory, and clinical variables.

Variable, Mean \pm SD	Preterm Deliveries, n = 28	Term Deliveries, n = 45	p
Age, yrs (range)	30.6 \pm 4.0 (22–39)	31.2 \pm 3.9 (23–39)	0.536
Disease duration, yrs (range)	8.3 \pm 5.6 (1–21)	7.1 \pm 5.4 (1–21)	0.354
Age at disease onset (range)	22.2 \pm 5.8 (11–32)	24.0 \pm 5.6 (12–36)	0.226
2nd trimester SLEDAI (range)	3.1 \pm 3.1 (0–12)	2.3 \pm 2.8 (0–12)	0.192
History of renal disease (%)	9 (32.1)	13 (28.9)	0.978
Receiving prednisone (%)	19 (67.9)	24 (53.3)	0.329
ANA (%)	24/25 (96.0)	34/39 (87.2)	0.481
Anti-dsDNA (%)	15/22 (68.2)	21/34 (61.8)	0.904
aCL IgG* (%)	10/18 (55.5)	6/31 (19.4)	0.023
LAC (%)	5/16 (31.3)	11/24 (45.8)	0.557
PTT** (%)	6/25 (24.0)	7/40 (17.5)	0.750

* aCL \geq 15 GPL. **PTT > 37 s.

Table 2. Comparison of reproductive histories of women with term or preterm deliveries. There were no significant differences between the 2 groups for any variable.

Variable	Preterm Deliveries, n = 28	Term Deliveries, n = 45
Previous pregnancies, mean \pm SD	1.8 \pm 0.9	2.3 \pm 1.3
1 spontaneous abortion (%)	4 (14.3)	11 (24.4)
\geq 2 spontaneous abortions (%)	1 (3.6)	4 (8.9)
\geq 1 stillbirth (%)	3 (12.5)	4 (8.9)
No history of adverse obstetrical outcome (%)	15 (53.6)	23 (51.1)

Table 3. Specific medications used throughout 72 pregnancies of women with SLE. Many women received a combination of therapies.

Medication during Pregnancy	Term Deliveries, n = 45 (%)	Preterm Deliveries, n = 28 (%)	p
Prednisone	24 (53.3)	19 (67.9)	NS
Prednisone dose > 10 mg/day	10 (22.2)	14 (50.0)	0.028
Azathioprine	3 (6.7)	5 (17.9)	NS
Hydroxychloroquine/chloroquine	10 (22.2)	4 (14.3)	NS
Dexamethasone	1 (2.2)	1 (3.6)	NS
LMW heparin	8 (17.7)	5 (17.9)	NS
Aspirin	25 (55.5)	16 (57.1)	NS
IV gamma globulin	1 (2.2)	0 (0)	NS
Aspirin only	4 (8.8)	3 (10.7)	NS
No therapy	9 (20.0)	0 (0.0)	0.031

LMW: low molecular weight.

no significant differences in the frequencies of each individual complication between the term and preterm groups.

Literature review. Using the search words SLE, pregnancy, and outcome, the PubMed database identified 180 publications from 1992 to 2002. From the abstracts, we selected 27 publications and obtained full texts for each. We then selected only observational studies (retrospective or prospective) with adequate sample size that reported outcome data, and measured the same variables for comparison (Table 5).

With a median sample size of 67 and a total of 638 pregnancies, 10 studies including our own found a median of 33.4% (range 7.8%–63.2%) of SLE pregnancies resulted in preterm deliveries. Rates of PROM and IUGR ranged from

5.6% to 37.9% and 2% to 39.5%, respectively, although the medians for both were quite low: 7.5% and 9.4%, respectively. The prevalence of aPL in the different samples ranged from 13.5% to 51.7%, median 32.6%. The median live-birth rate for SLE pregnancies in 10 studies over the last 10 years is 80.9% (mean \pm SD 80.1 \pm 8.1). Our results closely match the median values for all variables (Table 5).

There was no consensus regarding the influence of disease activity, prednisone usage, or aPL positivity on the incidence of prematurity in SLE pregnancies.

DISCUSSION

In any discussion of preterm deliveries, it is essential to differentiate between those resulting from spontaneous

Table 4. Delivery data for all patients. There was no statistically significant difference in the proportion of women delivering spontaneously in either the term or preterm delivery groups. However, significantly more women in the preterm delivery group were either induced or had a C-section due to high blood pressure, HELLP syndrome, fetal distress, preeclampsia, proteinuria, IUGR, and decreased amniotic fluid than in the term delivery group (10/28 vs 5/45; $p = 0.026$, 95% CI 0.0554 to 0.437, power with $\alpha = 0.05$: 0.602).

Labor and Delivery	Total n = 73 (%)	Preterm Deliveries, n = 28 (%)	Term Deliveries, n = 45 (%)
Spontaneous onset of labor	50 (68.5)	17 (60.7)	33 (73.3)
Normal vaginal delivery	44 (60.3)	15 (53.6)	29 (64.4)
C-section (nonprogressing labor)	6 (8.2)	2 (7.1)	4 (8.9)
Prelabor intervention: C-section	14 (19.2)	8 (28.6)	6 (13.3)
Breech presentation	3 (4.1)	1 (3.6)	2 (4.4)
High blood pressure	2 (2.7)	2 (7.1)	0
HELLP	1 (1.4)	1 (3.6)	0
Preeclampsia	2 (2.7)	1 (3.6)	1 (2.2)
IUGR	2 (2.7)	2 (7.1)	0
Fetal distress	2 (2.7)	1 (3.6)	1 (2.2)
Low-lying placenta	1 (1.4)	0	1 (2.2)
Repeat	1 (1.4)	0	1 (2.2)
Prelabor intervention: induction	9 (12.3)	3 (10.7)	6 (13.3)
Decreased amniotic fluid volume	4 (5.5)	2 (7.1)	2 (4.4)
Proteinuria	2 (2.7)	1 (3.6)	1 (2.2)
Miscellaneous*	3 (4.1)	0	3 (6.7)

* Includes post-term inductions.

Table 5 . Comparison of results from different studies of SLE pregnancies. Total pregnancies do not include those electively terminated.

Study	Total Pregnancies, n (Live Birth Rate, %)	Index Pregnancies, n	Preterm Deliveries, n (%)	PROM, n (%)	IUGR, n (%)	+ aPL* (%)	Concluded that Prematurity Correlates With		
							Disease Activity	Prednisone Use	aPL
Le Thi Huong ¹²	94 (80.9)	76	48 (63.2)	ND	30 (39.5)	10/74 (13.5)	Yes	Yes	No
Lima ¹⁴	108 (82.4)	89	38 (42.3)	5** (5.6)	30 (33.7)	25/73 (34.2)	No	No	No
Johnson ¹⁹	NA***	58	27 (46.6)	22 (37.9)	ND	ND	No	No	No
Le Thi Huong ¹⁸	60 (80.0)	48	29 (60.4)	ND	1 (2.0)	Not Clear	No	No	Yes
Rahman ¹⁶	121 (71.1)	86	21 (24.4)	ND	6 (7.0)	15/29 (51.7)	No	No	No
Carmona ¹³	57 (93.0)	53	11 (20.8)	4 (7.5)	5 (9.4)	16 (30.2)	No	No	No
Kobayashi ¹⁷	74 (89.2)	66	11 (16.7)	8 (12.1)	14 (21.2)	12/33 (36.7)	Yes	Yes	No
Georgiou ¹⁵	56 (69.6)	39	3 (7.8)	ND	2 (5.1)	7 (17.9)	Yes	ND	No
Cortez-Hernandez ¹¹	95 (71.6)	68	19 (27.9)	ND	21 (31.0)	22/68 (32.4)	Yes	Yes	Yes
Present study	88 (83.0)	73	28 (38.4)	5 (6.8)	2 (2.7)	16/49 (32.7)	Yes	Yes	Yes
Median (min–max)	88 (80.9)	67 (39–89)	33.4% (7.8–63.2)	7.5% (5.6–37.9)	9.4% (2–39.5)	32.6% (13.5–51.7)	5/10 Yes	4/9 Yes	3/10 Yes

* Anticardiolipin IgG and/or IgM and/or LAC. ** The authors reported both 5.6% in the results section and 11% in the discussion section. *** Only reported data for women with gestations > 23 weeks. ND: not done or not discussed.

onset of labor before 37 weeks and those that are the result of a clinical condition, either maternal or fetal, necessitating medical intervention. In our sample of women with SLE, 34.0% (17/50) went into labor before 37 weeks' gestation spontaneously, not a significantly different proportion than the proportion in the whole sample including both spontaneous and induced deliveries (38.4%, 28/73; $p = 0.759$; Table 4).

We found 38.4% of deliveries were preterm in our sample of 73 SLE pregnancies. They were associated with disease activity as determined by either prednisone dose or

no medication at all, and aCL IgG positivity. However, after controlling for spontaneous versus induced onset of labor, these differences disappeared other than a trend toward increased prevalence of aCL IgG in the preterm group. There were no differences in the demographic or obstetrical histories of our patients to indicate any associations with preterm delivery.

The increased incidence of preterm deliveries in SLE compared to the general population is well described, and a number of factors have been reported in association with the increase including hypertension, active disease at pregnancy

outset, decreased serum C3, prednisone treatment, and aCL^{7,9,10}. However, there is no consensus regarding these factors (Table 5). Johnson, *et al*¹⁹ and Lima, *et al*¹⁴ did not find disease activity, prednisone use, or serologic studies predictive of preterm delivery. In contrast, in a review of 9 years' experience at the Hopkins Lupus Pregnancy Center, Petri reported that disease activity, measured by either disease activity indices or laboratory markers, was predictive of preterm deliveries in SLE patients²⁰.

Lockwood, *et al*²⁴ reported an association between anti-cardiolipin antibodies and preterm delivery in a general obstetric population. Anticardiolipin antibodies were associated with an increased incidence of preterm deliveries in a report by Ramsey-Goldman, *et al*⁸. However, in that study, preterm delivery was defined as before 38 weeks' vs 37 weeks' gestation, and pregnancies were stratified by timing before and after diagnosis of SLE and by number of pregnancies, before the increase became significant. Cortes-Hernandez, *et al*¹¹ also noted a significant association of preterm delivery with aPL positivity, using multiple logistic regression. Others have not found an association with aPL^{14,20}. Although aCL were found twice as frequently in the preterm delivery group, there did not appear to be a coincident occurrence of IUGR or placental abnormalities that are characteristic of the aPL syndrome. Interestingly, there was no increase in the frequency of LAC in the preterm group. There was no distinguishing autoantibody profile, other than the increased aCL, associated with preterm delivery.

In a randomized controlled trial, we found a significant increase in preterm delivery but not PROM or IUGR in a group of women with recurrent pregnancy loss and circulating autoantibodies (but not SLE) treated with prednisone and acetylsalicylic acid, suggesting that prednisone itself may have a significant effect on the incidence of preterm delivery²⁵. We did not find an increased number of women using prednisone in the preterm delivery group in this study of SLE pregnancies, but we did find a significantly higher number of women in the preterm delivery group taking ≥ 10 mg/day. This was not a reflection of increased disease activity during the pregnancy as measured by the second trimester SLEDAI, as we found no association between disease duration or activity with preterm delivery. The higher frequency was more likely due to a higher antenatal dose maintained throughout the pregnancy, reflecting a situation in which the patients had stable but not inactive disease at onset of pregnancy. There are a number of investigators whose experience differs from ours, although others have also observed this association between prednisone dose and preterm delivery^{11,12,20}.

An increase in the frequency of renal disease in SLE patients with preterm deliveries has been reported¹³, but we did not observe this in our sample.

Our study has some limitations and our results should be

interpreted within the context of those limitations. Because the study was retrospective, we have incomplete laboratory results (Table 1) and the sample sizes for each antibody measured are variable, resulting in inadequate or reduced confidence in our statistical analysis. In addition, the SLEDAI is validated for prospective studies and may be limited when applied retrospectively²⁶. For example, 20% of women in the term delivery group were medication-free during their pregnancies compared to none of the women with preterm deliveries, although there was no significant difference in the mean disease activity levels between the 2 groups as determined by our chart review. Intuitively, one would expect to find higher levels of disease activity in conjunction with higher doses of prednisone, and we did not find this to be the case. Whether the timing of the SLEDAI assessment would alter this result is not known.

With regard to the literature review, it was challenging to extract the necessary values from many of the reports, and in several cases we had to estimate rates and prevalences from raw data scattered throughout the results and discussion sections. In addition, there are no standardized criteria for classifying patients, symptoms, and laboratory values. There is continuing controversy regarding assay methodology and titer interpretation of aCL levels, and reporting of aPL positivity may not specifically provide aCL or LAC results separately. This makes comparisons all the more difficult and unreliable. Our attempt to compare specific outcomes and frequencies of preterm deliveries, PROM, IUGR, and aPL positivities in SLE pregnancies in different reports highlighted the difficulty of developing a consensus in the absence of standardized documentation.

On a more positive note, and in conclusion, it should be reiterated that 73 of 88 pregnancies among our patients with SLE over a 2 year period resulted in a live birth (83%) regardless of disease status and therapy. In our experience, and in that of many other investigators, closely monitored SLE pregnancies have a good prognosis for both mother and neonate.

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