Pregnancy Outcomes in Systemic Lupus Erythematosus with and without Previous Nephritis

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ABSTRACT. ***Objective.*** To compare rates and predictors of pregnancy complications in mothers with systemic lupus erythematosus (SLE) with and without previous nephritis (PN).

Methods. Retrospective analysis of 107 pregnancies in 83 women with SLE diagnosed prepregnancy.

Results. Mothers with PN had higher rates of preterm delivery (< 37/40, 30% vs 11%, p = 0.029) than those without PN. Women with PN had earlier onset of preeclampsia [median 34.5 weeks (IQR 32-37) vs 37.5 weeks (IQR 35-38, p = 0.047)] that was more frequently complicated by preterm delivery (p = 0.02). Risk factors for preeclampsia in women with PN include 10–13 weeks' gestation diastolic blood pressure > 80 mmHg and proteinuria, and prepregnancy estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m^2. In women with PN, midtrimester uterine-artery-Doppler notching had low negative predictive value (47%). After 39 months followup, eGFR was stable in women with or without PN.

Conclusion. In SLE, preterm deliveries are more frequent and preeclampsia occurs earlier in women with PN, but longterm eGFR is preserved. (First Release June 1 2011; J Rheumatol 2011;38:1906–13; doi:10.3899/jrheum.100997)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCY LUPUS NEPHRITIS
PRETERM DELIVERY PREECLAMPSIA

Several studies report that women with systemic lupus erythematosus (SLE) and previous nephritis (PN) have worse pregnancy outcomes than the general population, with increased rates of preeclampsia, fetal loss, preterm delivery, fetal growth restriction (FGR), and infants small for gestational age (SGA)[1,2,3,4]. Women included in these reports frequently had active disease at conception, associated with higher rates of pregnancy complications[2,5,6,7]. Improvements in immunosuppression have reduced mortality and preserved renal function for patients with PN[8,9,10]. Prepregnancy counseling enables women to commence pregnancies with quiescent disease. However, few studies have included pregnancies with predominantly inactive disease using modern management; the majority incorporate up to 30 years of single-center retrospective data[2,5,6,7,11].

Pregnancy-associated decline in renal function is well recognized with more severe renal impairment (Cr > 250 µmol/l) regardless of etiology, but pregnancy with preserved renal function (Cr < 125 µmol/l) does not usually cause irreversible renal damage[12]. In a recent review, women with PN had more obstetric complications than women with similar renal impairment[13]. The longest assessment of nephrological complications in mothers with PN due to SLE concluded after only 1 year of followup and did not compare women with SLE without PN[14].

Our purpose was 3-fold: to compare pregnancy outcomes in women with SLE with and without PN; to identify predictors of poor pregnancy outcomes; to examine the effects of pregnancy on longterm renal function.

MATERIALS AND METHODS

Antenatal clinic lists at St. Thomas' Hospital (January 2000-October 2008) were reviewed for women with SLE. Women were excluded if SLE was diagnosed during the current pregnancy or they delivered elsewhere. Women received local obstetric care if they were well, near term, or lived too far from St. Thomas'. All patients fulfilled the American College of Rheumatology criteria for SLE (1997)[15]. Histological features of renal disease were assessed by the 1995 World Health Organization (WHO) classification[16], because most renal biopsies were performed before recent classification changes[17].

Glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (using creatinine, age, sex, and race, prepregnancy and postpregnancy[18]). Proteinuria at 10–13 weeks' gestation was defined by standard urinalysis of ≥ 1+, protein:creatinine ratio > 30 mg/µmol or total protein excretion > 300 mg/24 hours.

Active SLE was defined by the presence of arthritis, malar rash, vasculitis, oral or nasal ulcers, serositis, neurological manifestations, leukopenia, thrombocytopenia not associated with antiphospholipid antibodies (aPL), or Coombs-positive autoimmune hemolytic anemia. Any extrarenal disease manifestation requiring a change in treatment up to 6 months postpartum was considered a flare[19]. Renal flare was defined as the development of urine protein > 500 mg/24 h (in the absence of preeclampsia), or worsening proteinuria (defined as an increase by 2 g/24 h if baseline proteinuria was < 3 g/24 h or doubling of proteinuria in women previously with nephrotic-range proteinuria[2]), urinary casts, dysmorphic hematuria, reduced levels of C3 and/or C4, or a rise in serum creatinine of > 30%.

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Antiphospholipid syndrome (APS) was defined according to the Sapporo criteria[20] because the study period started before more recent guidelines were published[20]. Women with both thrombotic and obstetric APS were classified and managed according to the thrombotic protocol (Table 1) to achieve appropriate anticoagulation to prevent recurrent thromboses.

Obstetric definitions were miscarriage: spontaneous fetal loss < 20 weeks' gestation; intrauterine death: spontaneous death of fetus > 20 weeks' gestation; preterm birth: live birth between 21 and 36+6 weeks; SGA: birth weight < 10th centile according to customized charts (available from: www.gestation.net/birthweight_centiles/centile_online.htm).

Preeclampsia was diagnosed according to International Society of Study of Hypertension in Pregnancy guidelines[21]. For women with preexisting hypertension or proteinuria, preeclampsia was diagnosed after identification of additional clinical or biochemical markers.

All women were managed by a multidisciplinary team, including maternal-fetal-medicine obstetrician, hematologist, rheumatologist, obstetric physician, specialist midwives, and nephrologists. Women were seen for prepregnancy counseling and advised to conceive after their SLE had been in remission, or at least stable, for at least 6 months. Those receiving mycophenolate mofetil requiring ongoing immunosuppression were transferred to azathioprine.

Second trimester uterine artery Doppler waveform analysis was performed at 20 weeks anomaly scan (and repeated at 24 weeks if abnormal – defined as bilateral notching). Low molecular weight heparin was used in aPL patients according to local protocol (Table 1).

Statistical analysis was performed using SPSS V17. Logistic regression analysis with generalized link function to correct pregnancy outcomes for > 1 pregnancy in the same woman was performed with corrections for age and ethnicity. Chi-squared, 2-sided Fisher's exact test and the Mann-Whitney U test were used for nonparametric data and the paired Student t-tests were used for parametric data. Logistic regression assessed the predictive value of each demographic variable on binary outcomes. Differences were considered to be significant if $p < 0.05$. Terminations and miscarriages were excluded from final analysis because of incomplete data collection.

RESULTS

Over 8 years, 86 women with SLE had 110 pregnancies. Three were excluded (2 miscarried at 13 and 18.5 weeks' gestation, and 1 had twins), leaving 83 women with 107 pregnancies. Clinical details are summarized in Table 2.

Women with PN predominantly had WHO Class III or IV renal disease (26/43, 60%) and had higher prepregnancy creatinine and lower eGFR than women without PN (Table 2). They were more likely to have received cyclophosphamide or mycophenolate mofetil prior to pregnancy; were more frequently taking low-dose aspirin, prednisolone or azathioprine; more commonly had proteinuria and hematuria at booking. Median systolic and diastolic booking blood pressures (BP) were higher in women with PN.

Maternal outcome. Outcomes are shown in Table 3. Preeclampsia was diagnosed in 11 women with preexisting proteinuria [2 women developed raised liver enzymes, 1 had headache and visual disturbance associated with uncontrolled hypertension that resolved after delivery, and 9 women had sudden onset, substantial increases in serum creatinine, proteinuria, and hypertension requiring at least 2 antihypertensive agents, with no immunological changes consistent with lupus nephritis (LN), which resolved after delivery]. Preeclampsia onset occurred at significantly earlier gestations in women with PN than without. Disease flare occurred in 39 pregnancies (36%) and twice postpartum (5%). Renal flare was reported in 7 women, including a renal biopsy diagnosed flare in 1 postpartum woman with no previous renal involvement. Treatment of increased disease activity is shown in Table 3. Significantly fewer women without PN received immunosuppression during pregnancy ($p = 0.002$).

One woman with secondary APS developed a pulmonary embolus at 36 weeks' gestation. Enoxaparin was increased from 40 mg bd to treatment dose (60 mg bd). One out of 5 women without PN and proteinuria at booking had ongoing proteinuria during pregnancy and developed preeclampsia at 39 weeks' gestation; no features of LN developed postpartum after 25 months of followup.

Uterine artery Doppler. Results for uterine artery Doppler at 20-24 weeks' gestation were available for 98 pregnancies. Sensitivity, specificity, positive and negative predictive values for the ability of uterine artery Doppler to predict preeclampsia or SGA are shown in Table 3. Bilateral notches were noted in 9 out of 58 (16%) women without PN and were absent in all women with PN. Sensitivity for women with and without

Table 1. Protocol for treatment of antiphospholipid antibodies/antiphospholipid syndrome.

Clinical History	Anticoagulant Therapy
No thrombosis, miscarriage, or adverse pregnancy outcome	Start aspirin 75 mg preconception
Previous thrombosis	
Previous venous events	Start aspirin 75 mg and LMWH (enoxaparin 40 mg, dalteparin 5000 IU) as soon as pregnancy confirmed and increase LMWH to BD at 16 weeks
Previous arterial events	Start aspirin 75 mg and LMWH (enoxaparin 40 mg, dalteparin 5000 IU) twice daily as soon as pregnancy confirmed.
Recurrent miscarriage < 10 weeks	
No anticoagulation	Start aspirin 75 mg preconception
Miscarriage on aspirin alone	Add LMWH OD once pregnancy confirmed. Considered discontinuing LMWH at 20 weeks' gestation if uterine artery waveform normal
Late fetal loss, neonatal death or adverse outcome due to preeclampsia, FGR, or abruption	Start aspirin 75 mg preconception. Add LMWH OD once pregnancy confirmed and continue until term.

LMWH: low molecular weight heparin; FGR: fetal growth restriction.

Table 2. Demographics of women with SLE with and without lupus nephritis.

Characteristics	No Previous Lupus Nephritis	Previous Lupus Nephritis
No. pregnancies (no. women)	64 (52)	43 (31)
Maternal age, yrs, mean ± SD	32.5 ± 5.3	31.6 ± 5.2
Prepregnancy creatinine, µmol/l	n = 38	n = 33
Median (IQR)	63 (55–71)	69* (62–94)
Prepregnancy eGFR, ml/min/1.73m^2	n = 38	n = 33
Median (IQR)	115 (100–125)	99** (75–122)
Prepregnancy eGFR, ml/min/1.73m^2	n = 38	n = 33
< 90	8 (21%)	16 (48%)***
< 60	0	4 (12%)****
Body mass index, kg/m^2	n = 61	n = 41
Median (IQR)	22.5 (21–27)	22.0 (21–24)
Ethnicity, no. (%)		
White	33 (52)	25 (58)
Black	22 (34)	12 (30)
Asian	3 (5)	2 (5)
Other	6 (9)	4 (9)
Autoantibodies, n (%)		
Anti-Ro/SSA	22 (34)	13 (30)
aPL	33 (52)	19 (44)
APS, n (%)	12 (19)	10 (23)
Obstetric, late pregnancy loss	2 (3)	1 (2)
Thrombotic	10 (16)	9 (21)
Previous immunosuppression	n = 61	n = 41
Cyclophosphamide	4 (7%)	17 (41%)†
Mycophenolate mofetil	1 (2%)	7 (17%)††
Current medication, n (%)		
Aspirin	39 (62)	37 (86)$
LMWH	17 (27)	15 (35)
Prednisolone	34 (53)	37 (86)$$
Azathioprine	8 (13)	35 (81)Ω
Hydroxychloroquine	35 (55)	20 (47)
Nulliparous	39 (61%)	25 (58%)
Years since SLE diagnosed, median (IQR)	6 (4–10)	7 (4–13)
Active disease at booking	4 (6%)	4 (9%)
Proteinuria at booking, + or more	5/60 (8%)	19/40 (48%)¶
Hematuria at booking, + or more	4/60 (7%)	11/40 (28%)¶¶
Blood pressure at booking, mm/hg, median (IQR)		
Systolic	110 (100–120)	117 (107–130)‡
Diastolic	70 (60–75)‡	72 (68–80)‡‡

* p = 0.015, ** p = 0.051, *** p = 0.02, **** p = 0.04, † p < 0.01, †† p < 0.001, $ p = 0.008, $$ p < 0.0001, Ω p = 0.0001, ‡ p = 0.018, ‡‡ p = 0.025, ¶ p < 0.001, ¶¶ p = 0.008. SLE: systemic lupus erythematosus; IQR: interquartile range; eGFR: estimated glomerular filtration rate; aPL: antiphospholipid antibody; APS: antiphospholipid syndrome; LMWH: low molecular weight heparin.

PN was low (0 and 60%, respectively) but specificity was higher (100% and 87%, respectively). The negative predictive value was 47% for women with PN and 85% for women without PN.

Fetal and neonatal outcomes. Fetal and neonatal outcomes of women with SLE with and without LN are shown in Table 4. One unexplained stillbirth occurred in a woman with discoid lupus, anti-Ro, normal fetal cardiology and growth scans, and a single notch on midtrimester uterine artery Doppler. At 36 + 5 weeks' gestation she had a small antepartum hemorrhage, and fetal heartbeat was undetectable. The morphologically normal infant weighed 2.71 kg, and postmortem was declined.

One fetus (3%) of 35 women with anti-Ro/SSA antibodies developed congenital heart-block, and 1 baby (3%) developed neonatal cutaneous lupus.

Mothers with PN had significantly shorter gestation periods and higher rates of deliveries with < 34 weeks' gestation. The proportion of spontaneous and iatrogenic preterm delivery did not differ between the groups. Those with PN and preeclampsia were more likely to have preterm deliveries (7/12, 58% vs 6/31, 19%, p = 0.02) than those with PN without preeclampsia. The presence of preeclampsia in women without PN was not associated with a higher rate of preterm delivery (p = 0.6). Of the 7 women with PN and preeclamp-

Table 3. Maternal outcome of a cohort of women with SLE with and without lupus nephritis.

Characteristics	No Previous Lupus Nephritis, n = 64	Previous Lupus Nephritis, n = 43
Preeclampsia, n (%)	10 (16)	12 (28)
Gestation of preeclampsia onset, weeks, median (range)	37.5 (35–38)	34.5 (32–37)†
Mode of delivery, n (%)		
Caesarean birth	22 (34)	17 (40)
Emergency	17 (27)	14 (33)
Flare, n (%)	25 (40)	14 (36)
Renal flare	1 new (1.5)	6 (14)
Time to first flare, weeks		
Median (range)	22 (16–28)	20 (16–24)
Postnatal flare	2	0
Treatment given during flare		
Prednisolone started	3	0
Prednisolone increased	17	12
Azathioprine increased	0	2
Prednisolone declined	4	0
Hydroxychloroquine started	1	0
No immunosuppression during pregnancy, n (%)	20 (31)	3 (7)††
Bilateral uterine artery notches to predict preeclampsia/SGA	9/58 (16%)	0/40 (0%)
Sensitivity	60%	0%
Specificity	87%	100%
PPV	44%	—
NPV	85%	47%
Postpartum creatinine	n = 45	n = 38
Median (IQR)	62 (56–71)	67* (58–94)
Postpartum eGFR, ml/min/1.73m^2, median (IQR)	105 (94–123)	95** (68–118)
Months followup, median (IQR)	39 (23–63)	39 (19–64)

† p = 0.047, †† p = 0.002, * p = 0.04, ** p = 0.024. SLE: systemic lupus erythematosus; IQR: interquartile range; eGFR: estimated glomerular filtration rate; SGA: small for gestational age; PPV: positive predictive value; NPV: negative predictive value.

Table 4. Fetal and neonatal outcome of women with SLE with and without lupus nephritis. Data are n (%) unless otherwise indicated.

Characteristics	No Previous Lupus Nephritis, n = 64	Previous Lupus Nephritis (PN), n = 43
Live birth	63 (98)	43 (100)
Intrauterine death	1 (1.6)	0
Gestation, weeks		
Median (IQR)	39.0 (38.3–39.8)	37.9 (34.9–39.3)†
Percent < 37/40	7 (11)	13 (30)*
Spontaneous	3 (43)	7 (54)
Percent < 34/40	2 (3)	8 (19)**
Spontaneous	0 (0)	4 (50)
Mean birth weight, g, median (IQR)	2990 (2797–3455)	2845 (1980–3300)
SGA (< 10th customized centile)	14 (22)	14 (33)
Apgar score	n = 62	n = 42
< 7 at 1 min	5 (8)	9 (21)
< 7 at 5 min	0	1 (2.4)

† p = 0.005, * p = 0.029, ** p = 0.016. SLE: systemic lupus erythematosus; IQR: interquartile range; SGA: small for gestational age.

sia-associated preterm delivery, 5 were induced, 1 had an abruption, and 1 went into spontaneous labor. One woman with cerebral APS without PN had a preeclampsia-associated preterm emergency caesarean delivery for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome at 25 weeks' gestation. Another also had a premature caesarean delivery, at 36 weeks.

Factors associated with the development of preeclampsia

or preterm delivery before 37 weeks are presented in Table 5.

The use of previous immunosuppression, histological class, aPL, parity, or ethnicity were not associated with higher rates of preeclampsia or preterm delivery in women with or without PN. Proteinuria at booking was associated with SGA < 10th centile in women with PN. Booking proteinuria was not persistent throughout pregnancy in women without PN; thus booking urinalysis is likely to be falsely positive.

Postpartum creatinine and eGFR are shown in Table 6. Women with PN had higher prepregnancy and postpartum creatinine and lower eGFR than women without PN, but neither group experienced significant deterioration in renal function at a median of 39 months (IQR 19-64) followup. None required renal replacement therapy. Women with PN were no more likely than women without PN to have a significant fall in eGFR (> 30 ml/min/1.73 m^2) during followup, nor was their rate of decline in eGFR more rapid. No women with a fall in eGFR > 30 ml/min/1.73 m^2 developed chronic kidney disease Stage 3 (eGFR 30-59 ml/min/1.73 m^2). Prepregnancy eGFR, disease flare, preeclampsia, and proteinuria were not predictors of a decline in eGFR.

Table 6. Renal outcome in women with SLE with and without lupus nephritis.

Clinical Measures	No Previous Lupus Nephritis	Previous Lupus Nephritis (PN)
Prepregnancy creatinine, µmol/l	n = 38	n = 33
Median (IQR)	63 (55–71)	69* (62–94)
Prepregnancy eGFR, ml/min/1.73m^2	n = 38	n = 33
Median (IQR)	115 (100–125)	99** (75–122)
Prepregnancy eGFR, ml/min/1.73m^2	n = 38	n = 33
< 90	5 (21%)	12 (49%)***
< 60	0	4 (12%)
Postpartum creatinine, µmol/l	n = 45	n = 38
Median (IQR)	62 (56–71)	67† (58–94)
Postpartum eGFR, ml/min/1.73m^2	n = 45	n = 38
Median (IQR)	113 (102–124)	105‡ (71–117)
Months followup	n = 30	n = 31
Median (IQR)	39 (23–63)	39 (19–64)
Fall in eGFR	n = 13	n = 17
Median (range)	9 (3–38)	11 (2–22)
Rate of fall in eGFR, ml/min/1.73m^2/month	n = 13	n = 17
Median (range)	0.56 (0.06–5.40)	0.29 (0.06–2.26)
Fall in eGFR, > 30 ml/min/1.73m^2	n = 30	n = 31
No. (%)	2 (6%)	0 (0%)

* p = 0.015, ** p = 0.051, *** 0.022, † p = 0.038, ‡ p = 0.01. SLE: systemic lupus erythematosus; IQR: interquartile range; eGFR: estimated glomerular filtration rate.

DISCUSSION

Our study shows that with modern care, women with SLE and PN can achieve successful pregnancies without an effect on longterm renal function, although they experience significantly higher rates of preterm delivery than those without PN.

The evolution of immunosuppression has reduced mortality and dramatically improved outcomes for individuals with PN. Together with prepregnancy counseling, this has resulted in women entering pregnancy with increased likelihood of success. Reported rates of fetal loss fell from 40% in 1960-65 to 17% in 2000-3[22]. Previous studies included women with

Table 5. Factors associated with preeclampsia and preterm delivery in women with SLE with and without lupus nephritis.

Characteristics	Preeclampsia, OR (95% CI)		< 37 Weeks, OR (95% CI)	
	No Previous Lupus Nephritis, n = 64	Previous Lupus Nephritis, n = 43	No Previous Lupus Nephritis, n = 64	Previous Lupus Nephritis, n = 43
Maternal age, yrs				
≤ 35	1.00	1.00	1.00	1.00
> 35	3.55 (0.87–14.13)	2.08 (0.47–9.29)	0.91 (0.17–5.02)	1.78 (0.41–7.80)
BMI, kg/m^2				
≤ 30	1.0	*	*	*
> 30	10.70 (1.5–75.8)			
Prepregnancy eGFR, ml/min/1.73m^2				
≥ 90	1.00	1.00	*	1.00
< 90	22.5 (1.86–271.95)	12.00 (2.16–66.55)		1.25 (0.27–5.77)
Proteinuria at booking				
Trace or none	1.00	1.00	*	1.00
1 + or more	1.18 (0.12–11.42)	5.7 (1.25–25.92)		4.05 (0.99–16.57)
Systolic BP, mmHg at booking				
≤ 130	1.00	1.00	1.00	1.00
> 130	2.12 (0.20–23.02)	3.71 (0.83–16.55)	2.94 (0.26–32.97)	5.57 (1.22–25.36)
Diastolic BP, mmHg at booking				
≤ 80	1.00	1.00	1.00	1.00
> 80	7.29 (1.22–43.41)	4.82 (1.02–22.84)	4.33 (0.65–28.86)	4.06 (0.88–19.86)

* No women in one or more outcome category, therefore OR not calculated. SLE: systemic lupus erythematosus; BMI: body mass index; eGFR: estimated glomerular filtration rate; BP: blood pressure.

severe renal impairment and/or active disease on older immunosuppressive regimes; they are less relevant to modern counseling for women with SLE and PN[7,11,14]. Our study adds to the literature regarding pregnancy outcome in women with predominantly quiescent PN and relatively preserved renal function[7,11,14]. Our study is important because there are few data regarding pregnancy complications in women with SLE and PN managed in the 21st century.

Other authors have studied only white women[14] or not reported ethnicity. Our cohort includes an ethnically diverse population, about one-third of African or Afro-Caribbean origin, which has previously been associated with worse pregnancy outcome for LN[23]. However, this study shows that black ethnicity was not a predictor of preeclampsia, preterm delivery, or SGA.

Limitations of the research include its retrospective design, which precluded the use of disease activity indices, and study size, which prevented identification of subtle associations with pregnancy complications. The exclusion of women who delivered at other hospitals may have introduced bias toward women with more complex medical and obstetric histories.

Differentiation between a flare of LN and preeclampsia in women with PN is a challenging clinical dilemma, particularly in late pregnancy. The definition of proteinuria used for a flare of LN in pregnancy is not evidence-based but has been published by other authors[2]. Our study demonstrated a temporal difference in presentation; preeclampsia occurred between 30-37 weeks, while first episodes of renal flare occurred at 9-25 weeks and responded to adjustment in immunosuppression. In 1 woman, LN presented *de novo* several days postpartum, and therefore differentiation from preeclampsia was possible by renal biopsy.

Because of retrospective analysis, only pregnancies 10–13 weeks after the 8-12 weeks' antenatal visit were included, thus missing early miscarriages, so that total fetal loss rates cannot be reliably reported.

In our study, preterm delivery rates were significantly higher in women with SLE who had PN than in women who did not have PN (30% vs 11%), in agreement with a recent metaanalysis of women with SLE PN showing a rate of 39%[4]. Our data suggests that even if active renal disease has resolved with normal GFR and urinalysis, women with PN remain at risk for preterm delivery.

About half of preterm deliveries were spontaneous in another series of SLE pregnancies including 35% with PN[24]. Premature rupture of membranes was identified as the most common cause of preterm delivery in a larger series of women with SLE, more commonly than in controls[25]. Others report a similar rate of preterm delivery (27%) to our cohort for women who entered pregnancy in complete remission[14]; women with preterm deliveries tended to be induced because of deterioration in renal function or progressive preeclampsia. In our study, women with PN were more likely to have preterm deliveries but over half had spontaneous labor, demonstrating that medical intervention is not always a factor in pregnancy outcome.

Only 10–13 weeks systolic BP > 130 mmHg in women with PN was a predictor of preterm delivery, independent of the development of preeclampsia. Hypertension has been seen to be a predictor of fetal death in women with PN[2], as well as a predictor of preterm delivery in all with SLE[24]. Others have found these predictors of preterm delivery: the use of prednisolone[24,26], lack of aspirin[14], Afro-Caribbean race[23], Raynaud's phenomenon[27], and aPL[26,28]. Oviasu, *et al* found that preterm deliveries occurred only in women with WHO Class III, IV, and V LN[3], although other studies, like ours, found no association with histological class of nephritis[1,7,14,29]. This is in keeping with recent evidence suggesting that proteinuria may not always be consistent with histological disease activity in nonpregnant individuals[30]. Active nephritis has been shown in several studies[24,27,31,32], including a metaanalysis of 2751 pregnancies, to be associated with increased rates of early delivery[4]; however, we report high rates of preterm delivery despite the majority of women with PN having quiescent disease.

Women with PN developed preeclampsia at significantly earlier gestations than those without. Markers of renal disease (prepregnancy eGFR < 90 ml/min/1.73 m^2, proteinuria at booking) and hypertension at booking (diastolic BP > 80 mmHg) were predictors of preeclampsia in women with PN, and have been noted[2,33]. BMI > 30 and hypertension at booking were predictors of preeclampsia in women without PN. Preeclampsia affects between 21-30% of SLE pregnancies[24,27,29,34,35], particularly in the presence of aPL[36,37] and renal disease[1,24,33,38]. Preeclampsia occurred in 21% of our SLE cohort but tended to be more frequent in women with PN (28% vs 16%).

Others have also found more maternal complications in women with PN, including preeclampsia, eclampsia, and HELLP syndrome, than in those with SLE without PN[4,7]. Preeclampsia has been associated with LN WHO Class III and IV rather than Class II and V[29] but no associations were found in a metaanalysis of 9 studies of women with PN[4]. We found no relationship between preeclampsia and disease class, but we found a significantly earlier onset of preeclampsia in women with renal involvement, which is important for prepregnancy counseling.

Bilateral midtrimester uterine artery notches have been associated with impaired trophoblast migration and consequent preeclampsia, growth restriction, and placental abruption[39]. In 100 pregnancies complicated by SLE and/or APS, including 19 women with PN, Le Thi Huong, *et al* found unilateral or bilateral notching was the only predictor of adverse pregnancy outcome, including fetal death, FGR, and preeclampsia, using multivariate analysis[40]. Although not comparable, in our study there was a < 50% negative predictive value for the development of preeclampsia, an important negative finding for the management of these women in clin-

ical practice (i.e., not to be reassured by the presence of normal Dopplers).

Moreover, our recent review of the utility of uterine artery Dopplers in a cohort of women with APS (which included 10 women from our study) found high sensitivity and specificity for placental dysfunction[41]. Given that uterine artery Doppler is a surrogate assessment of placental function, one could speculate that women with PN have relatively adequate placentation, but other preexisting maternal abnormalities such as endothelial dysfunction may be the predominant underlying pathophysiology for developing preeclampsia and/or SGA.

Rates of SGA < 10th customized centile were higher than background. Other studies have reported varying proportions of noncustomized SGA in infants of women with PN (4-24%). FGR has been shown to be more common in pregnancies complicated by SLE than in healthy controls, regardless of gestational age, even when controlled for hypertension and renal disease[42], and those with mild disease[32]. Another recent report identified 46% and 20% of infants of women with and without current nephritis were SGA, according to customized centiles[11]. There was no significant deterioration in renal function in women with SLE with or without PN at a median of 39 months followup postpartum. Factors previously reported to be associated with worsening renal impairment did not predict postpartum decline in eGFR, i.e., prepregnancy eGFR, disease activity during pregnancy, and preexisting hypertension. In a review of 17 studies of pregnancy in 276 women with PN, including some from over 20 years ago, 11% developed acute renal failure. In 3% the decline in renal function was permanent, without requiring dialysis, and 6% progressed to endstage renal failure or death[43].

A recent study of 81 women managed between 1985-2004, which included 11% with chronic kidney disease (CKD) stage 3, found 2% of women suffered a progressive deterioration in eGFR and 1% needed dialysis[14]. Reassuringly, 12% of our cohort had CKD stage 3 but none required renal replacement therapy nor experienced a permanent loss of eGFR. A deterioration in GFR > 20 ml/min/1.73 m^2 was found in 10% and 16% of women with and without PN respectively, suggesting that PN prior to pregnancy carries no greater risk of progression of renal disease.

Women with PN can have successful pregnancies in tertiary centers with multidisciplinary teamwork. However, women should be counseled before conception about early onset preeclampsia, preterm delivery, and SGA. Women with PN and prepregnancy eGFR < 90 ml/min/1.73 m^2, proteinuria, and diastolic BP > 80 mmHg at booking have increased risk of preeclampsia. Systolic BP > 130 mmHg at booking predicts preterm delivery. Reassurance can be provided about the low risk of permanent decline of renal function during and after pregnancy. A normal uterine artery Doppler is of limited value in prediction of preeclampsia and/or SGA in women with PN.

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