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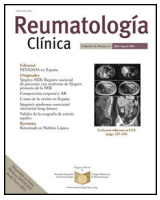

Original Article

Is lupus nephritis a prognosis factor for pregnancy? Maternal and foetal outcomes☆

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ABSTRACT

Background: Pregnancy in women with systemic lupus erythematosus (SLE) and nephritis (LN) is at risk of foetal and maternal complications.
Objective: To evaluate the effect of LN on pregnancy with respect to foetal and maternal outcome.
Methods: We retrospectively studied all pregnant SLE patients with and without diagnosis of LN, who attended the Materno Neonatal Hospital in Cordoba city, Argentina, from January 2015 to April 2017. Demographic, clinical, and laboratory data were collected. The presence of antiphospholipid syndrome (APS) and antiphospholipid antibodies (AAF), and maternal and foetal outcome were evaluated.
Results: 121 pregnancies in 79 patients were included. Pregnancies were divided into those with LN (69) and those without LN (52). The presence of APS and AAF was more frequent in the LN group as well as higher basal SLEDAI. The LN group received more immunosuppressive therapy and increased steroid dose treatment. Of the patients, 47.5% had Class IV LN. Lupus flares occurred more frequently in the LN group 25.8% vs 10.9% in the group without LN ($P = .041$), mainly renal flares in the LN group. No patients developed end-stage renal failure. Preeclampsia was more frequent in the LN group, 18.8% vs 6.3% in the group without LN ($P = .047$). There was only one maternal death. A caesarean section was required in 68.5% of the LN group vs 31.5 in the group without LN, and urgent caesarean section was also performed in the LN group. There were no differences in foetal outcomes in either group: live birth, gestational age, weight birth, perinatal death, foetal distress.
Conclusions: Patients with LN experienced more maternal complications such as lupus flares and preeclampsia. However, LN does not lead to a worse pregnancy and foetal outcome. Patients should be strictly monitored before and after conception.

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¿Es la nefritis lúpica un factor pronóstico en el embarazo? Resultados maternos y fetales

Palabras clave:
Lupus eritematoso sistémico
Nefritis lúpica
Embarazo
Pronostico materno fetal

RESUMEN

Introducción: La preexistencia de nefritis lúpica (NL) es un factor de riesgo importante al planificar un embarazo debido al riesgo de complicaciones.
Objetivo: Evaluar complicaciones maternas y fetales en la gestación de mujeres con lupus eritematoso sistémico (LES) con y sin NL previa a la concepción.

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Métodos: Se estudiaron retrospectivamente todas las pacientes lúpicas embarazadas con y sin NL previa, asistidas desde enero de 2015 hasta abril de 2017. Se analizaron datos demográficos, clínicos y de laboratorio, presencia de anticuerpos antifosfolípidos (AAF) y síndrome antifosfolípido (SAF) según criterios de Sydney, resultados maternos y fetales.
Resultados: Se incluyeron 79 pacientes, 40 con NL previa y 39 sin NL, sumando 121 embarazos (52 sin NL y 69 con NL). El grupo NL registró mayor porcentaje de presencia de AAF, SAF y mayor SLEDAI basal, además recibieron más terapia inmunosupresora y corticoidea. En NL fue más frecuente la clase IV (47,5%): 25,8% en el grupo NL vs 10,9% (p = 0,041) tuvieron reactivaciones, especialmente renales, sin desarrollo de enfermedad renal terminal. La preeclampsia fue mayor en el grupo con NL: 18,8% vs 6,3% sin NL (p = 0,047). Registramos una muerte materna en el grupo NL. La vía de finalización fue cesárea (68,5% en el grupo NL y 31,5% en grupo sin NL), siendo más frecuente de urgencia en el grupo con NL. En resultados fetales, no hubo diferencia en porcentaje de nacidos vivos, peso del neonato ni edad gestacional. Se registraron 3 muertes fetales: 2 en el grupo con NL y 1 en el otro.
Conclusión: Las pacientes con NL sufrieron más complicaciones maternas como brote lúpico y preeclampsia. Sin embargo, la NL no conduciría a peores resultados obstétricos ni fetales.
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Introduction

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease that primarily affects women of childbearing age. The recommendation in the past was to avoid pregnancy due to maternal and foetal complications[1]. However, better outcomes are now being achieved[2,3]. Factors that contribute to complications have been identified as lupus activity at the time of conception, the presence of previous lupus nephritis (LN), antiphospholipid antibodies (APA), anti-SSA/Ro and anti-SSB/La antibodies and maternal hypertension (HTN) prior to pregnancy[4,5].

Pre-existing LN when planning a pregnancy carries an increased risk of developing pre-eclampsia, delayed intrauterine growth, stillbirth, small for gestational age babies, and preterm delivery[5,6]. HTN and kidney failure are predictors of poor maternal and foetal prognosis, and it is sometimes difficult to determine whether an increase in proteinuria or onset of HTN is due to pregnancy or a renal flare. This may explain the incidence of renal flares in pregnancy and the puerperium at between 8% and 70% in different studies, while reactivations accompanied by impaired kidney function are between 0% and 23%[5–10].

It is important to highlight that the presence of moderate and severe kidney failure at conception increases the risk of developing severe HTN and impaired kidney function. In normotensive patients with mild and stable impaired kidney function, the risk of progression to irreversible kidney failure is low. In contrast, the prognosis is worse if kidney function is moderately impaired (serum creatinine 1.4–3.0 mg/dl), and impaired kidney function will persist in one third of these patients[10–12].

The aim of this study was to evaluate maternal and foetal outcomes in pregnant patients with SLE with and without a previous diagnosis of LN and its influence on prognosis.

Materials and methods

Using ACR 1997 classification criteria[13], we retrospectively studied all pregnant patients with a diagnosis of SLE with and without previous LN, attended in the autoimmune diseases and pregnancy clinic of the Maternal and Neonatal Hospital of the city of Córdoba, Argentina, from January 2015 to April 2017. LN was confirmed by biopsy and classified according to NL ISN/RPS 2004 criteria[14]. All patients were assessed in the clinic by a rheumatologist and an obstetrician under high-risk pregnancy follow-up. Demographic data, duration of SLE, clinical and laboratory data were recorded. Antiphospholipid syndrome (APS) was classified according to the Sydney criteria[15].

Routine laboratory work-up was performed at each trimester visit, including complete cytology, serum albumin, urea, creatinine, plasma ionogram, hepatogram, uraemia, complete urine and 24 h proteinuria. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence assay using Hep-2, anti-dsDNA by indirect immunofluorescence test with Crithidia Luciliae, anti-ENA antibodies (Sm, RNP, Ro, La) by ELISA and then confirmed by Immunoblot assay, complement C3 and C4 levels by immunoturbidimetry, and anti-dsDNA and C3 and C4 levels were tested during each trimester.

Anti-cardiolipin (aCL) IgG and IgM and anti-B2 glycoprotein I antibodies were measured by ELISA and moderate and high titres were considered positive. The presence of lupus anticoagulant (LA) was assessed according to the criteria of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis[16].

All patients underwent a first trimester ultrasound. Doppler ultrasound to evaluate the uterine arteries was performed at 20 and 24 weeks to assess the presence of a protodiastolic notch that could predict pre-eclampsia or delayed intrauterine growth. Pre-eclampsia laboratory profile was performed every 3 weeks from the second trimester, glycaemia, and an oral glucose tolerance test (OGTT) at 28 and 32 weeks of pregnancy, toco/gynaecological ultrasound every 3 weeks to evaluate the growth curve, and Doppler ultrasound of the umbilical artery and middle cerebral artery every 2 weeks after the 30th week of pregnancy, as necessary.

The patients were divided according to renal function into mild kidney failure (KF) with a serum creatinine level <1.5 mg%, moderate KF with a creatinine level between 1.5 mg% to 2.4 mg%, and severe KF with a creatinine level >2.5 mg%. Lupus activity was assessed in all patients with SELENA-SLEDAI adapted to pregnancy at conception[17], in each trimester and in the puerperium. Lupus reactivation was considered a change of more than 4 on the SELENA SLEDAI compared to the previous visit. Persistent activity was defined by a score of 4 (excluding serology alone) at two or more consecutive visits. Pre-eclampsia was differentiated from renal lupus flare by urinary sediment and the presence of other characteristics of lupus flare[18].

Renal flares in pregnancy were defined by the presence of active urinary sediment, increased proteinuria >2 g/24 h if baseline was <3.5 g/24 h or double the proteinuria if baseline was >3.5 g/24 h and an increase in serum creatinine to 30% from baseline[19]. Complete remission was considered when serum creatinine was normal (according to gender and body weight), proteinuria less than .2–.5 g/24 h, and urinary sediment inactive; partial remission: normal serum creatinine, proteinuria greater than .2–.5 g/24 h but less

than 2 g/24 h, or a decrease in proteinuria (greater than 50% from baseline with urinary protein excretion less than 3.5 g/24 h)[20].

Clinical remission on treatment was defined according to DORIS (prednisone less than or equal to 5 mg/day, immunosuppressive therapy allowed; SLEDAI (clinical without serology) = 0 PGA less than 5[18].

Adverse pregnancy outcome was defined as any maternal or foetal complication during pregnancy and in the immediate postpartum period (up to 6 weeks); the maternal complications assessed were pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, plateletopenia)[21], gestational diabetes[22], spontaneous premature rupture of membranes, chorioamnionitis, arterial and venous thrombosis, reactivation of disease and LN, infections, and maternal mortality.

Foetal outcome was assessed as live birth, preterm delivery (birth before 37 weeks gestation), spontaneous abortion (spontaneous foetal loss before 20 weeks gestation), stillbirth (intrauterine foetal death after 20 weeks), low birth weight (live birth less than 2500 g [LBW]), and neonatal death (neonatal death up to 28 days after birth).

The route of delivery, whether vaginal, forceps or caesarean section, and the indication for caesarean section, as well as the treatment received during gestation and puerperium, were determined.

Statistical analysis

Statistical analysis of clinical and demographic data was expressed as mean and standard deviation for continuous variables or as frequency and percentage for categorical variables. Comparisons between patients with previous LN and controls, lupus patients without previous nephritis, were made using the Student's t-test for continuous variables and Pearson's chi-squared test for categorical variables. Measures were presented as OR with 95% confidence interval. Values of $P < .05$ were considered significant.

Results

Seventy-nine medical records of pregnant women with a diagnosis of SLE were reviewed, two of which were excluded as they were lost to follow-up. Seventy-nine patients were included in the analysis, 39 without LN and 40 with a previous diagnosis of LN, with a total of 121 pregnancies (52 without LN and 69 with LN). Seventy percent were residents of the city of Córdoba and 77.2% had no social security. Fifty-eight percent were Caucasian. The mean maternal age at first pregnancy was 26.8 years (16–38 years) in the group without LN and 27.2 years (15–39 years) for the LN group; disease duration in years was similar in both SLE groups, as was the number of previous abortions. Maternal characteristics are described in Table 1.

The kidney biopsies were: 5 (12.5%), class II; 9 (22.5%) class III; 19 (47.5%) class IV; 5 (12.5%) class V, 1 (2.5%) class III + V, and 1 with no data.

Table 2 shows treatment at baseline and during pregnancy. Nephritis was the main reason for steroid pulses in the patients with LN, and in the 3 patients without LN the indications were thrombocytopenia in 2, and serositis in one.

During follow-up, the patients with LN had more frequent changes to their therapy with increased doses of prednisone, methylprednisolone pulses and increased immunosuppression.

Maternal and kidney outcomes

Considering the first trimester SELENA SLEDAI, 22 (55%) patients became pregnant while in the active nephritis group and 4 (10%) patients in the group without LN.

Table 1
Maternal, demographic, clinical and serological characteristics.

	LN (n = 40)	Without LN (n = 39)
Age at first gestation (years)	27.2 (15–39)	26.8 (16–38)
Years of SLE duration at first gestation (years)	5.86 (SD 5.108)	5.06 (SD 3.971)
Without social security, n (%)	33 (82.5)	27 (62.2)
Race		
Caucasian, n (%)	29 (72.5)	17 (43.5)
Mixed, n (%)	11 (27.5)	22 (56.4)
Previous abortions, n (%)	16 (40)	15 (38.5)
Nulliparous, n (%)	29 (72)	24 (61)
Anti-Ro antibody, n (%)	16 (41)	15 (38.5)
Anti-La antibody, n (%)	3 (7.7)	2 (5.1)
Anti-Sm antibody, n (%)	8 (20.5)	9 (23.1)
Anti-RNP antibody, n (%)	8 (20.5)	8 (20.5)
Associated APS, n (%)	9 (22.5)	7 (17.9)
APA, n (%)	12 (30)	9 (23.1)
Average baseline creatinine in mg%	.80	.83
Mild kidney failure, n (%)	2 (4)	0
Moderate kidney failure, n (%)	2 (4)	0
Malar rash, n (%)	26 (65)	24 (61)
Discoid lupus, n (%)	2 (5)	4 (10)
Photosensitivity, n (%)	27 (67)	22 (56)
Mouth ulcers, n (%)	11 (27)	16 (41)
Arthritis, n (%)	35 (87)	36 (92)
Serositis, n (%)	6 (15)	1 (2)
Neurological involvement, n (%)	0	1 (2)
Haemolytic anaemia, n (%)	8 (20)	8 (20)
Leukopenia, n (%)	7 (17)	11 (27)
Lymphopenia, n (%)	0	5 (12)
Thrombocytopenia, n (%)	2 (5)	10 (25)

APA: antiphospholipid antibodies; SD: standard deviation.

Table 2
Medical treatment during pregnancy.

	LN (n = 69)	Without LN (n = 52)	*P*
Prednisone <10 mg, n (%)	49 (71%)	33 (63.5)	.247
Increase in dose	17 (27.9)	8 (15.4)	.085
Methylprednisolone pulses, n (%)	8 (13.3)	3 (5.8)	.153
Hydroxychloroquine, n (%)	68 (98.6)	52 (100)	.570
Azathioprine, n (%)	50 (73.5)	14 (26.9)	.000
ASA, n (%)	61 (88.4)	50 (96.2)	.114
Heparin sodium prophylaxis, n (%)	2 (2.9)	4 (7.8)	.210
Enoxaparin prophylaxis, n (%)	22 (32.4)	11 (21.6)	.137

ASA: acetylsalicylic acid.

Table 3
Lupus activity according to SELENA SLEDAI in pregnancy.

	LN	Without LN	*P*
SS 1st trimester (SD)	2.18 (3.580)	.52 (1.529)	.001
SS 2nd trimester (SD)	1.95 (3.311)	.94 (2.428)	.060
SS 3rd trimester (SD)	1.94 (3.296)	.86 (2.213)	.036
SS puerperium (SD)	1.98 (3.132)	.70 (1.764)	.006

SD: standard deviation; SS: SELENA SLEDAI.

The patients with previous LN had significantly higher rates of lupus reactivation (without LN 10.9% vs LN 25.8%, $P = .041$), especially in the renal domain (10 patients); LN class IV was the most frequent, with 4 patients, followed by classes II, III and V, with 2 patients each. One patient with no previous kidney involvement had renal reactivation during gestation.

The data on lupus activity assessed in the 2 groups throughout the entire pregnancy are shown in Table 3; the disease was always more active in the patients with LN, except for the second trimester. Completion of pregnancy was indicated due to lupus flare without response to treatment in 7 patients with LN and one without previous renal involvement. The mean creatinine in the LN group was .80 mg/dl (.42–1.1 mg/dl), 2 patients had mild KF at the beginning

Table 4
Maternal outcomes.

	LN (n = 69)	Without LN (n = 52)	*P*	OR	95% CI
Preeclampsia, n (%)	12 (18.8)	3 (6.3)	.047	3,46	.91–13
Eclampsia, n (%)	1 (1.6)	1 (2.1)	.676	.74	.04–12.23
HELLP, n (%)	1 (1.6)	0 (0)	.571	Not defined	
Preterm delivery, n (%)	20 (31.3)	14 (29.2)	.490	1.10	.48–2.49
Gestational diabetes, n (%)	2 (3.1)	1 (2.1)	.607	1.51	.13–17.22
REM, n (%)	3 (4.7)	4 (8.3)	.343	.54	.11–2.53
Lupus flares, n (%)	17 (25.8)	5 (10.9)	.041	2.84	.96–8.37

SRM: spontaneous rupture of membranes.

Table 5
Foetal outcomes.

	LN (n = 69)	Without LN (n = 52)	*P*	OR	95% CI
Spontaneous abortion, n (%)	4 (5.3)	4 (7.7)	.17	.73	.17–3.1
Foetal death, n (%)	2 (2.9)	1 (1.9)	.11	1.52	.13–17.25
Live births, n (%)	63 (91.3)	47 (90.4)	.552	1.11	.32–3.88
Appropriate for gestational age, n (%)	48 (76.2)	38 (80.9)	.365	1.18	.53–2.6
Small for gestational age, n (%)	15 (23.8)	9 (19.1)	.365	1.31	.52–3.34

Table 6
Completion of pregnancy.

	LN (n = 69)	Without LN (n = 52)	*P*	OR	95% CI
Normal delivery, n (%)	26 (37)	16 (30.7)	.35	1.36	.63–2.9
Forceps, n (%)	1 (14)	0 (0)	.577		
Caesarean, n (%)	31 (44.9)	36 (69.2)	.004	.36	.17–.77
Emergency caesarean, (%)	11 (15.9)	0 (0)	.0005		

of pregnancy that persisted during pregnancy, and 2 had moderate KF at the beginning of pregnancy who, although they suffered renal reactivations, did not require dialysis, or develop end-stage kidney disease.

Table 4 shows the maternal complications. One maternal death was recorded in the LN group, from malignant HTN complicated by acute myocardial infarction.

Foetal outcomes

Table 5 shows the foetal outcomes. One hundred and ten live births were documented, 47 without LN and 63 with LN (90.4% vs 91.3%, *P* = .552), a total of 83 children were appropriate for gestational age (without LN 80.9% vs LN 76.2%, *P* = .365). Three patients had twin pregnancies, one in the LN group and one in the group without LN, and there were three foetal deaths, 2 in the LN group and one in the other group.

None of the pregnancies with Ro had neonatal lupus. In the group of patients without nephritis there was one miscarriage and 3 LBW, whereas in the LN group there was one stillbirth and 4 LBW.

Of the patients who received corticosteroid pulses, the maternal outcomes in the LN group were: 5 preterm deliveries, one of them twin, 2 pre-eclampsia; among the foetal outcomes there was one stillbirth and 4 LBW. In the group without LN there was one pre-eclampsia, one preterm delivery and one LBW.

Regarding route of delivery, caesarean section was the most frequent, with a significant difference in emergency caesarean section in the LN group (Table 6). The indications for emergency caesarean section were 4 for pre-eclampsia, 2 for premature rupture of membranes, 2 for delayed intrauterine growth and oligohydramnios, one for polyserositis and one for placental abruption and breech presentation.

Discussion

The demographic characteristics of our series, age and disease duration are like those described by Janardana et al.[4], Aggarwal et al.[23], Chen et al.[24], and Buyon et al.[25]. However, in our study the percentage of patients with LN was higher due to the design. Of note, 55% of patients in the nephritis group had disease activity at the start of pregnancy, whereas only 10% in the group without nephritis. However, in other series reviewed, 90% of patients were in remission. When compared with the Janardana et al.[4] and Aggarwal et al.[23] series in India, 67% and 47%, respectively, had live births despite a better start to pregnancy. Our foetal outcomes resemble Buyon's series[25], perhaps similar ethnicity could explain this. This coincides with the literature, which describes the average number of successful pregnancies in different series as between 65%–90%, with a less favourable prognosis when the patient became pregnant with active disease[4,26]. In our sample, the rates of baseline disease activity were significantly higher in the LN group from the start, which correlated with higher reactivation, higher doses of immunosuppressants and higher emergency caesarean section outcomes when compared with the lupus group without nephritis. However, foetal outcomes remained the same in both groups.

In line with other studies, a significantly higher rate of lupus flares was observed here in patients with previous nephritis compared to those without renal involvement[26]. Despite the renal reactivations in this group, few developed kidney failure, as in other series[2,6]. LN, mainly diffuse proliferative (class IV), has been associated with various complications in pregnancy, especially if active[27]. In this study, most of the patients with LN were class IV, and despite being on immunosuppressive therapy with azathioprine and steroids, four patients in this class had reactivations. Only one reactivation with kidney involvement was documented in a patient in the group without nephritis.

In terms of treatment received, the LN group required higher doses of steroids and immunosuppressive therapy for disease control, like that shown in other series[26]. Although no significant differences were found, probably due to the number of patients, patients in the LN group received more antithrombotic prophylaxis with heparin.

Pre-eclampsia is a frequent complication compared to the general population and notably higher in patients with previous nephritis[27,28]. In this study we found significant differences in the frequency of pre-eclampsia in patients with previous LN, in line with other studies[11,25,29]. This could be related to the higher disease activity at the start of gestation and the presence of APA. Despite receiving ASA, the rate of pre-eclampsia remains high, in agreement with other similar series: 11.9%–18.1%[4,24].

Preterm delivery is a common complication in pregnant women with lupus, estimated to occur in about one third of pregnancies[27]. A high rate of preterm delivery was recorded in both groups in this study, slightly higher in the LN group, and this could be related to the development of pre-eclampsia, greater disease activity and the need for steroids to control it[28].

Regarding foetal prognosis, the most important predictors are disease activity prior to pregnancy, the presence of kidney failure and the presence of APA[3,15,28]. In this series, the LN group has a greater history of associated APS and APA, and despite this, favourable results were found in more than 90% of pregnancies,

with similar numbers of live births in both groups, which contrasts with other series[4,23], as mentioned above. This could be due to the treatment received with the combination of heparin and aspirin prophylaxis. More foetal deaths were documented in the LN group, which may be related to the abovementioned factors.

Caesarean section was the main route of delivery in both groups, and its emergency indication was significantly higher in the LN group. This was due to the coexistence of pre-eclampsia, as described by Saavedra[21] and Rodrigues et al.[30].

However, compared with Asian, North American, or Canadian series, the number of caesarean sections is unusually high, and there could be some cultural bias[23–25].

A strength of our study is that we could compare patients with a major manifestation such as LN with lupus patients without nephritis. We consider the retrospective design to be a weakness, as it did not allow us to reliably collect data on previous disease and treatment, and therefore we do not have data on preconception counselling and family planning, or the number of patients.

Conclusions

The patients with LN experienced more maternal complications such as lupus flare and pre-eclampsia. However, LN would not lead to worse obstetric or foetal outcomes. Patients should be closely monitored before and after pregnancy.

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Conflict of interests

The authors have no conflict of interests to declare.

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