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Risk factors associated with infections in pregnant women with systemic lupus erythematosus

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SUMMARY

OBJECTIVE: The aim of this study was to analyze the occurrence and risk factors associated with infections during pregnancy in patients with systemic lupus erythematosus.

METHODS: This is a retrospective cohort study using the data of pregnant women who were followed up between 2011 and 2018 at a university hospital.

RESULTS: The data of 221 pregnant women with systemic lupus erythematosus were analyzed. The incidence of infections was 22.6% (50/221), with the urinary tract being the most frequent site of infection (32/221, 14.5%) followed by the respiratory tract (15/221, 6.8%). The bivariate analysis showed that active disease, hematological systemic lupus erythematosus, reduced complement, and use of prednisone ≥5 and ≥10 mg increased the chance of infection during early pregnancy (p=0.05, p=0.04, p=0.003, p=0.008, and p=0.02, respectively), while disease activity and anti-DNA positivity increased it at the end of pregnancy (p=0.03 and p=0.04, respectively). Prednisone at a dose ≥5 mg increased the chance of infection in the beginning (p=0.01) and at the end of pregnancy (p=0.008). Multivariate analysis showed that increasing the dose of prednisone from 5 to 10 mg tripled the chance of developing infections in pregnant women with lupus (p=0.02).

CONCLUSION: The study showed an increased chance of infections in pregnant women with systemic lupus erythematosus and it was associated with the use of prednisone.

KEYWORDS: Systemic lupus erythematosus. Infection. Pregnancy. Risk factors.

INTRODUCTION

Systemic lupus erythematosus (SLE) is common in women of reproductive age[1]. There is a higher incidence of infection in pregnant women with SLE than in those without SLE[2]. The relationship between disease activity and infection has already been described, suggesting that an unbalanced immune response increases the vulnerability to infections[2]. Together, these factors increase the incidence of infections, which are the cause of 30% of all deaths in patients with SLE and are the leading cause of mortality in this population[3]. Evidence suggests that in pregnant women with SLE, there is a higher risk of maternal death due to serious infections[1].

The main objective of this study was to evaluate the incidence of infections in pregnant women with SLE and to identify the sites of infections and the associated risk factors.

METHODS

This is an observational cohort study based on retrospective data. It included pregnant women with SLE according to the classification criteria proposed by the American College of Rheumatology[4]. These women were followed up at the prenatal clinic for autoimmune diseases at Pedro Ernesto University Hospital (HUPE), State University of Rio de Janeiro, from 2011 to 2018.

Data were obtained through the review of physical and electronic medical records. The data of all pregnant women from the first medical appointment until the time of delivery were collected.

Sociodemographic and reproductive factors, such as the age at diagnosis and delivery, ethnicity, number of pregnancies and live births, and risk factors related to infection in patients with SLE, such as disease activity, clinical and laboratory parameters,

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and medications used in the treatment of the underlying disease, were evaluated.

Disease activity in early and late pregnancy was established using the pregnancy-adapted SLE Disease Activity Index (SLEPDAI)[5]. SLEPDAI values ≥3[5] were considered indicative of disease activity, and their association with potential infection was analyzed. Disease activity was categorized following the SLEPDAI values: inactive disease=0, mild activity=1–2, moderate activity=3–5, and high activity ≥6. For the clinical analysis of the underlying disease, the clinical manifestations were categorized into cutaneous, articular, serous, hematological, renal, pulmonary, and neuropsychiatric involvement. Laboratory evaluation was performed to detect the presence of lymphopenia at diagnosis, consumption of C3 and/or C4, and the presence of positive anti-DNA at the beginning and end of pregnancy.

Lupus nephritis was defined as proteinuria ≥500 mg in a 24-h urine sample or protein/creatinine ratio ≥0.5 in a single urine sample, the presence of nephrotic syndrome or acute or chronic renal failure due to SLE, or confirmation on renal biopsy, according to the 2003 International Society of Nephrology/Renal Pathology Society classification.

The use of prednisone, hydroxychloroquine, and azathioprine in the beginning of and during pregnancy was analyzed. The intake of prednisone at the dosage levels of ≥5, ≥10, and ≥40 mg/day was also analyzed.

Data were descriptively evaluated, and the analysis of the normal distribution of variables, and the proportions, means, standard deviations, medians, and the respective 95% confidence intervals (CI) were estimated. Categorical variables were expressed as frequency (n) and proportion (%), and continuous variables were expressed as mean and standard deviation or median. The relative proportions were calculated for two distinct groups, with and without infection. Medians were used to define the cutoff value used to convert numerical to categorical variables. The association between infection during pregnancy and the clinical and sociodemographic variables was determined by the bivariate analysis and multiple logistic regression, and the performance of the adjusted model was evaluated using the receiver operating characteristic (ROC) curve. The response variable of the adjusted model was the presence of infection, and the explanatory variables were the initial SLEPDAI score and final dose of prednisone. Missing data were excluded from the statistical analysis.

The chi-square (χ^2) and Fisher's exact tests were used to compare categorical variables and outcomes (infection in pregnant women with SLE). Continuous variables were compared using Student's t-test. The level of associations was evaluated by calculating the measures of associations (odds ratio [ORs]) and their respective 95%CIs. Statistical analyses were performed using Epi-info version 3.5.2 and R-Projeto version 3.3.1. A hypothesis test was used to compare proportions, using a significance level of 5%.

This study was approved by the Research Ethics Committee of HUPE (CAAE: 00407518.8.0000.5259).

RESULTS

A total of 221 pregnancies were analyzed. The age of patients with SLE at the time of delivery ranged between 15 and 47 years (mean=28.5±6.2; median=29 years). The mean age at the time of diagnosis of SLE was 20.3±6.8 years (from 4 to 47 years, median=20 years). The duration of disease remission ranged from 0 to 108 months (9 years), with a median of 6 months. Of the 221 patients, 42.5% (94) were Caucasian.

The most frequent clinical manifestations of the underlying disease over the years in the 221 patients analyzed were cutaneous-mucosal manifestations in 87.3% (193), hematological manifestations in 57.9% (123), and renal manifestations in 44.3% (98), with a predominance of proliferative forms (classes III and IV) and class V, arthritis in 91.4% (202), and serositis in 35.8% (79).

Laboratory tests performed during pregnancy and the frequency of disease activity evaluated by a SLEPDAI value ≥3 were classified, as shown in Table 1.

All patients were on medication for the treatment and/or control of SLE during early pregnancy. Of these, 136 (61.5%) used prednisone, with a minimum dose of 2.5 mg/day and a maximum dose of 80 mg/day, with a mean of 8.7±13.3 mg and a median of 5 mg.

Hydroxychloroquine was used by 92.3% (205/221) of the patients. Azathioprine was used by 37.6% (83/221) of the patients.

Of the 221 patients, 22.6% (50) had pregnancy-related infections. Urinary tract infections were the most common and seen in 14.5% (32/221), and respiratory tract infections were the second most common and seen in 6.8% (15/221). Of these, 4.5% (10/221) had community-acquired pneumonia.

Other infections with a lower incidence included skin infections in 2.3% (5/221), with herpes zoster occurring in 1.8% (4/221) and being the most frequent infection, gastroenteritis in 0.9% (2/221), meningitis in 0.5% (1/221), bloodstream infections caused by a dialysis catheter in 0.5% (1/221), and reactivation of ocular toxoplasmosis in 0.5% (1/221) of the patients.

Clinical and laboratory variables, as well as individual medications (Table 1) and their relationship with infections, were evaluated.

Disease activity, in general, was not associated with infections. However, an increased risk of active disease at the end of pregnancy in women with a SLEPDAI value 3–5 was identified (p=0.03).

Table 1. Clinical/laboratory variables and medications potentially associated with infection.

Clinical/laboratory variables				
Variables		**Infection**	**Without infection**	**p-value**
		n (%)	**n (%)**	
Cutaneous mucous SLE	Present	44 (19.9)	149 (67.4)	0.87
	Absent	6 (2.71)	22 (9.95)	
Hematological SLE	Present	35 (15.8)	93 (43.0)	0.04*
	Absent	15 (67.9)	78 (35.3)	
Renal SLE	Present	21 (9.5)	77 (34.8)	0.7
	Absent	29 (13.1)	94 (42.5)	
Neuropsychiatric SLE	Present	13 (5.9)	31 (14.3)	0.22
	Absent	37 (16.7)	140 (63.3)	
Joint SLE	Present	48 (21.7)	154 (69.6)	0.19
	Absent	2 (0.9)	17 (7.7)	
Serositis	Present	19 (8.6)	60 (27.1)	0.7
	Absent	31 (14.0)	111 (50.2)	
Initial C3 and/or C4	Consumed	22 (9.9)	47 (21.3)	0.03*
	Normal	28 (12.7)	124 (56.1)	
Final C3 and/or C4	Consumed	15 (6.8)	43 (19.5)	0.49
	Normal	35 (15.8)	128 (57.9)	
Initial Anti-DNA	Positive	21 (9.5)	49 (22.2)	0.07
	Negative	29 (13.1)	122 (55.2)	
Final Anti-DNA	Positive	26 (11.8)	61 (27.6)	0.04*
	Negative	24 (10.9)	110 (49.8)	
Initial SLEPDAI	≥3	22 (9.9)	50 (22.6)	0.05
	<3	28 (12.7)	121 (54.8)	
Final SLEPDAI	≥3	23 (10.4)	55 (24.9)	0.44
	<3	27 (12.2)	116 (54.5)	
Medications:				
Prednisone	Present	38 (17.2)	98 (44.3)	0.02*
	Absent	12 (5.4)	73 (33.0)	
Final prednisone	Present	39 (17.6)	98 (4.4)	0.008*
	Absent	11 (5.0)	73 (33.0)	
Initial prednisone ≥5 mg/day	Present	37 (16.7)	93 (42.1)	0.01*
	Absent	13 (5.8)	78 (35.3)	
Final prednisone ≥5 mg/day	Present	37 (16.7)	91 (41.2)	0.008*
	Absent	13 (5.8)	80 (36.2)	
Initial prednisone ≥10 mg/day	Present	22 (9.9)	46 (20.8)	0.02*
	Absent	28 (12.7)	125 (56.6)	
Final prednisone ≥10 mg/day	Present	23 (10.4)	54 (24.4)	0.06
	Absent	27 (12.2)	117 (51.5)	
Initial prednisone ≥40 mg/day	Present	3 (1.4)	10 (4.5)	0.93
	Absent	47 (21.3)	161 (72.8)	
Final prednisone ≥40 mg/day	Present	3 (1.4)	15 (6.8)	0.56
	Absent	47 (21.3)	156 (70.6)	
Initial hydroxychloroquine	Present	46 (20.8)	159 (72)	0.79
	Absent	4 (1.8)	12 (5.4)	
Final hydroxychloroquine	Present	48 (21.7)	169 (76.5)	0.26
	Absent	2 (0.9)	2 (0.9)	
Initial azathioprine	Present	21 (9.5)	62 (28.1)	0.46
	Absent	29 (13.1)	109 (49.3)	
Azatioprina final	Present	27 (1.2)	71 (32.1)	0.12
	Absent	23 (10.4)	100 (45.2)	

SLE: systemic lupus erythematosus; SLEPDAI: Pregnancy-adapted SLE Disease Activity Index. *Systemic Lupus Erythematosus Prenancy Disease Activity Index.

Hematological involvement also increased the chance of infection (p=0.04) and was associated with a twofold increase in the chance. Reduced complement during early pregnancy contributed to an increased chance of infection (p=0.003).

The presence of anti-DNA antibodies at the end of pregnancy was associated with an increased chance of infection (p=0.04).

Increased chance of infection with the use of prednisone, regardless of the dose, was observed at the beginning and end of pregnancy (p=0.008 and p=0.03, respectively).

Prednisone at a dose ≥5 mg/day was associated with an increased chance of infection in general (p=0.01) at the beginning, as well as at the end of pregnancy (p=0.008). A high chance of infection (p=0.02) in those on a dose ≥10 mg/day of prednisone was observed in early pregnancy. Multivariate analysis showed that increasing the dose of prednisone from 5 to 10 mg tripled the chance of developing infections in pregnant women with lupus in the study group (adjusted OR=3.15 [1.22–8.12]; p=0.02) (Table 2).

The goodness-of-fit of the model was evaluated using the ROC curve. The ROC curve graph for the infection outcome showed an area below the curve of 68%. The point of greatest sensitivity (Ŝ) and specificity (Ê) of the model was Ŝ=70% and Ê=62% (Figure 1). These values indicate the moderate performance of the adjusted model in differentiating the presence and absence of infection in pregnant women with lupus.

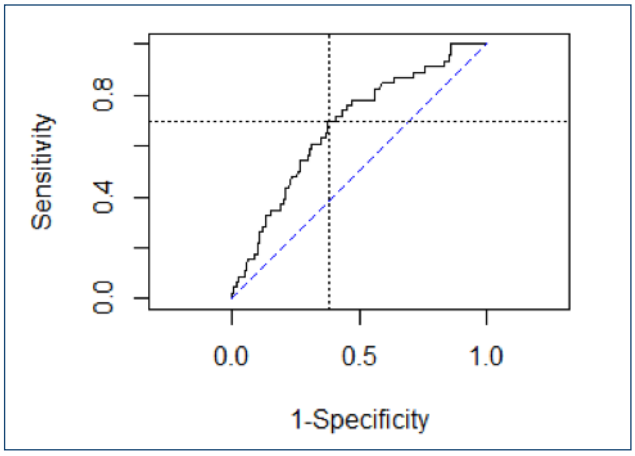

Figure 1. Performance of the model adjusted in the recevier operating characteristic curve for infection in general.

Table 2. Crude and adjusted odds ratio (OR) of infections in general in pregnant women with systemic lupus erythematosus.

	Crude OR (95%CI)	p-value	Adjusted OR	p-value
Initial SLEPDAI*	1.28 (0.88–1.81)	0.21	1.01 (0.65–1.57)	0.96
Initial SLEPDAI*	1.24 (0.88–1.75)	0.21		
Initial prednisone (mg)				
0	1			
5	2.32 (0.98–5.47)	0.05		
10	3.25 (1.39–7.62)	0.01		
40	2.18 (0.52–9.17)	0.29		
Final prednisone (mg)				
0	1			
5	2.82 (1.17–6.80)	0.02	3.05 (1.20–7.77)	0.02
10	3.27 (1.41–7.57)	0.01	3.15 (1.22–8.12)	0.02
40	1.49 (0.37–5.99)	0.57	1.57 (0.35–7.02)	0.56
Initial azathioprine (mg)				
0	1			
50	0.51 (0.06–4.24)	0.53		
100	2.09 (0.97–4.48)	0.06		
150	0.82 (0.28–2.36)	0.71		
200	3.44 (0.72–16.5)	0.12		
Final azathioprine (mg)				
0	1			
50	1.37 (0.41–4.58)	0.61		
100	1.19 (0.51–2.80)	0.68		
150	1.08 (0.37–3.16)	0.89		
200	2.06 (0.18–23.5)	0.56		

*Log transformation. Logistic regression models whose response variable was "infection in general." The explanatory variables of the multiple model were initial SLEPDAI and final prednisone. SLEPDAI; Pregnancy-adapted SLE Disease Activity Index.

DISCUSSION

Infections are a frequent concern in patients with SLE, being the major cause of mortality in this population[6]. They can increase morbidity, requiring the use of high doses of glucocorticoids (GCs) and the use of immunosuppressants in some situations. High disease activity, frequent reactivations, anti-DNA positivity, serum complement consumption, and renal impairment at diagnosis are also associated with a higher risk of infection[7].

The study population was homogeneous, showing no significant difference in terms of sociodemographic factors.

Our study found a higher rate of urinary tract infection than that reported in previous studies, which have reported the rate of urinary infection in pregnant women without SLE between 1% and 2%[8]. Our study showed a rate of pyelonephritis similar to that reported in the literature, with a frequency of 0.5–2%[8].

The presence of pneumonia was also frequent in this study. Lim et al. reported a rate of pneumonia of 0.01% in pregnant women[9].

Disease activity was not associated with infection in our study. Disease activity has been previously reported as a risk factor for infection. Jeong et al. found an association between infection and SLEPDAI value ≥12[7]. However, the authors reported that the infection was attributed to medications used in the treatment of reactivations and not directly related to the disease activity[2,10]. However, Pimentel-Quiroz et al. found an association between infection and SLEPDAI values ≥4[11].

In this study, the only clinical manifestation of SLE that increased risk of infection was hematological involvement of the disease. A similar result was reported in recent study[12], and the presence of hematological manifestations was considered a factor for poor prognosis in these patients[2].

Renal involvement was not a risk factor for infection in this study. It is known that the presence of kidney disease due to SLE is typically defined as a risk factor for infection[10]. Despite the significant number of patients having previous kidney disease (almost 50% of the study cohort), it was not associated with infection in the present study, which can be explained by the small number of patients using high doses of GCs, since only a small proportion of the patients had active kidney disease.

Serosal involvement was not associated with infection in the present study. However, Jung et al. found a higher frequency of serositis in patients with infection[2].

Complement consumption and positive anti-DNA are markers of disease activity and were also associated with infection in this study. This finding agrees with that reported in the previous study[7]. In the bivariate analysis in this study, both were significantly associated with infections in general; however, this was not seen in the multivariate analysis. However, these two markers of disease activity cannot always be easily dissociated. In some cases, an analysis of variation >25% is already predictive of reactivation[13], albeit mild and without clinical repercussions.

Glucocorticoids at variable doses are the first-line therapy to treat reactivations. In mild cases, prednisone is usually used at a maximum dose of 20 mg/day, with a dose between 5 and 10 mg considered safe during pregnancy[14]. Higher doses and pulse therapy with GCs are reserved for cases of moderate-to-severe activity[14]. In contrast to the safety of the 5–10 mg dose reported in the literature, we observed that the chance of infection was three times higher with an increase in the dose from 5 to 10 mg of prednisone. Jung et al. found an association between infection and the use of prednisone at a dose ≥7.5 mg/day[2]. The fact that our study did not find an association between high doses of GCs and the risk of infection can be explained by the small number of patients using doses ≥40 mg/day.

The present study found no association between the use of azathioprine and the risk of infection in pregnant women with lupus. Previous reports on this association are conflicting; hence, further studies are necessary. Feldman et al. also reported this association without defining the duration of use, while Jung et al. did not find this correlation[2,15].

A limitation of the present study is that some patients were followed up at the HUPE only during pregnancy, with data on the diagnosis of SLE being limited. Underdiagnosis of some infections during the period between the consultations that were not witnessed or reported at the time of the consultation might also have occurred. The infection was made by clinical diagnosis in some cases due to the limitations of performing the imaging tests during pregnancy. Some laboratory tests were not performed in the hospital laboratory, making it difficult to access information that was not in the medical records.

CONCLUSIONS

The present study clearly showed an association between some risk factors and infections. An increase in the number of infections was observed in the group of pregnant women with SLE. The most significant finding was the threefold increase in the risk of infection with an increase in the dose of prednisone from 5 to 10 mg. Therefore, conducting further studies and confirming the current evidence will help professionals who deal with pregnancy and SLE, thereby improving the quality of life and reducing the morbidity and mortality in this patient group. This study is relevant considering the scarce literature on this topic.

AUTHORS' CONTRIBUTIONS

DMJV: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, and Writing – review & editing. **DLMM**: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, and Writing – review & editing. **NRJ**: Conceptualization, Data curation, and Writing – original draft. **GRRJ**: Conceptualization, Data curation, Formal Analysis, and Writing – original draft. **FCS**: Conceptualization, Data curation, and Writing – original draft. **MIL**: Conceptualization, Data curation, and Writing – original draft. **NCPR**: Conceptualization, Data curation, Formal Analysis, and Writing – original draft. **EMK**: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, and Writing – review & editing.

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