**Universidade do Estado do Rio de Janeiro**

Centro Biomédico

Faculdade de Ciências Médicas

Guilherme Ribeiro Ramires de Jesús

# Lúpus eritematoso sistêmico e gestação: análise dos desfechos maternos em uma coorte de um hospital terciário

Rio de Janeiro

2019

Guilherme Ribeiro Ramires de Jesús

# Lúpus eritematoso sistêmico e gestação: análise dos desfechos maternos em uma coorte de um hospital terciário

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Evandro Mendes Klumb

Rio de Janeiro

2019

CATALOGAÇÃO NA FONTE
UERJ/REDE SIRIUS/CBA

R173 Ramires de Jesús, Guilherme Ribeiro.
Lúpus eritematoso sistêmico e gestação : análise dos desfechos maternos em uma coorte de um hospital terciário / Guilherme Ribeiro Ramires de Jesús – 2019.
87 f.

Orientador: Evandro Mendes Klumb.
Tese (doutorado) – Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas. Programa de Pós-graduação em Ciências Médicas.

1. Lúpus eritematoso sistêmico - Teses. 2. Nefrite lúpica - Teses. 3. Pré-eclâmpsia - Teses. 4. Gravidez de alto risco - Teses. 5. Gravidez - Complicações e sequelas – Teses. 6. Fator de crescimento placentário – Teses. I. Klumb, Evandro Mendes. III. Universidade do Estado do Rio de Janeiro. Faculdade de Ciências Médicas. III. Título.

CDU 616.5-002.52:618.2

Bibliotecária: Kalina Silva CRB7/4377



_____ _____

Assinatura Data

Guilherme Ribeiro Ramires de Jesús

# Lúpus eritematoso sistêmico e gestação: análise dos desfechos maternos em uma coorte de um hospital terciário

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Aprovada em 09 de dezembro de 2019.

Banca Examinadora:

_____

Prof. Dr. Evandro Mendes Klumb (Orientador)

Faculdade de Ciências Médicas - UERJ

_____

Prof. Dr. Geraldo da Rocha Castelar Pinheiro

Faculdade de Ciências Médicas - UERJ

_____

Prof.ª Dra. Denise Leite Maia Monteiro

Faculdade de Ciências Médicas - UERJ

_____

Prof. Dr. Fernando Maia Peixoto Filho

Instituto Fernandes Figueira

_____

Prof. Dr. Carlos Augusto Ferreira de Andrade

Instituto de Pesquisa Clínica Evandro Chagas

Rio de Janeiro

2019

## DEDICATÓRIA

Dedico esta tese à minha família e à Universidade do Estado do Rio de Janeiro, como forma de retribuição pelo conhecimento que me foi concedido ao longo destes anos.

## AGRADECIMENTOS

À minha família, pela compreensão e apoio nos momentos que não pude estar presente.

Ao professor Evandro Klumb, orientador e exemplo desde a graduação, sempre com o mesmo entusiasmo para ensinar e aprender.

Ao meu pai, professor Nilson, que criou toda a estrutura para que pudéssemos chegar até aqui.

Às doutoras Flávia Cunha, Marcela Lacerda e Bruna Rodrigues, companheiras de quinta-feira e que tornaram todo este trabalho possível mesmo com todos os percalços encontrados ao longo do caminho.

Ao professor Roger Levy, pelos conhecimentos reumatológicos durante o pré-natal e pelas oportunidades profissionais.

Ao professor Luis Cristóvão Porto, pela disponibilidade com as amostras e com os testes realizados.

Aos demais colegas obstetras do Núcleo Perinatal – HUPE, pela assistência prestada às nossas gestantes mais complicadas que o habitual.

Aos residentes, que estimulam diariamente a busca pelo conhecimento.

Aos reumatologistas, pela paciência com um intruso na sua especialidade.

Às gestantes do Hospital Universitário Pedro Ernesto, que sempre foram solicitas e atenciosas com a nossa equipe.

*The only true wisdom is in knowing you know nothing.*

*Socrates*

# RESUMO

RAMIRES DE JESÚS, Guilherme Ribeiro. *Lúpus eritematoso sistêmico e gestação*: análise dos desfechos maternos em uma coorte de um hospital terciário. 2019. 87 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2019.

Devido à maior prevalência do lúpus eritematoso sistêmico (LES) em mulheres em idade fértil, a gestação nessas pacientes não é uma condição incomum. Contudo, gestantes com LES possuem uma maior morbimortalidade materna e fetal do que o restante da população, necessitando de cuidados diferenciados ao longo do pré-natal. É descrito maior risco de atividade da doença durante a gravidez, além de maior frequência de pré-eclâmpsia (PE), parto prematuro, crescimento intrauterino restrito e perda gestacional. As manifestações clínicas do LES, além de estarem associadas a um resultado gestacional adverso, podem mimetizar complicações obstétricas e dificultar a adequada assistência prestada para a gestante. O objetivo desta tese foi avaliar os desfechos clínicos maternos em uma coorte de gestantes com lúpus eritematoso sistêmico, com maior enfoque nas manifestações neurológicas e renais, e analisar o uso de fatores angiogênicos (VEGF, PlGF) e antiangiogênicos (sFlt-1) no diagnóstico diferencial entre nefrite do LES e pré-eclâmpsia. No estudo 1, apenas um pequeno número de pacientes apresentou doença neurológica ativa durante a gravidez, sendo que a alta incidência de PE e prematuridade estava diretamente relacionada com a manifestação renal concomitante. O estudo 2 avaliou o impacto das diferentes classes de nefrite nos resultados gestacionais maternos e fetais. Concluiu-se que as gestantes com nefrite proliferativa (classes III/IV) apresentaram com maior frequência atividade da doença durante a gestação, doença ativa contínua durante a gravidez e o puerpério, hospitalização, cesariana e PE em comparação com pacientes sem nefrite, inclusive com maior morbidade fetal em comparação com gestantes com nefrite não proliferativa (classes II e V). No estudo 3, foi feita a análise dos níveis séricos de fatores angiogênicos (VEGF, PlGF) e antiangiogênicos (sFlt-1) em gestantes com LES e doença inativa, doença renal ativa e PE. Foi demonstrado que as gestantes com LES que desenvolvem PE apresentaram elevação do sFlt-1 e queda do PlGF, ambos estatisticamente significativos, da mesma forma que pacientes com PE sem LES. As pacientes com nefrite ativa apresentaram elevação do VEGF em comparação com os outros dois grupos, o que sugere o potencial uso destes marcadores na prática clínica para diferenciação entre PE e nefrite lúpica.

Palavras-chave: Lúpus eritematoso sistêmico. Nefrite lúpica. Pré-eclâmpsia. Fator de crescimento placentário. Gravidez de alto risco.

## ABSTRACT

RAMIRES DE JESÚS, Guilherme Ribeiro. *Systemic lupus erythematosus and pregnancy*: analysis of maternal outcomes in a cohort of a tertiary hospital. 2019. 87 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2019.

Due to the higher prevalence of systemic lupus erythematosus (SLE) in women of childbearing age, pregnancy in these patients is not an uncommon condition. However, pregnant women with SLE have higher maternal and fetal morbidity and mortality than the rest of the population, requiring differentiated prenatal care. There is a higher risk of disease activity during pregnancy, as well as a higher frequency of preeclampsia (PE), premature birth, intrauterine growth restriction, and gestational loss. The clinical manifestations of SLE, in addition to being associated with adverse gestational outcomes, can mimic obstetric complications and hinder appropriate care provided to pregnant women. The aim of this thesis was to evaluate maternal clinical outcomes in a cohort of pregnant women with systemic lupus erythematosus, focusing more on neurological and renal manifestations, and to analyze the use of angiogenic (VEGF, PlGF) and antiangiogenic (sFlt-1) factors in the differential diagnosis between SLE nephritis and preeclampsia. In study 1, only a small number of patients had active neurological disease during pregnancy, and the high incidence of PE and prematurity were directly related to concomitant renal manifestation. Study 2 evaluated the impact of different classes of nephritis on maternal and fetal gestational outcomes. It was concluded that pregnant women with proliferative nephritis (classes III / IV) presented more frequently disease activity during pregnancy, continuous active disease during pregnancy and the puerperium, hospitalization, cesarean section and PE compared to patients without nephritis, also with higher fetal morbidity compared to pregnant women with nonproliferative nephritis (classes II and V). In study 3, analysis of serum levels of angiogenic (VEGF, PlGF) and antiangiogenic (sFlt-1) factors was performed in pregnant women with SLE and inactive disease, active renal disease and PE. It was shown that pregnant women with SLE who develop PE had statistically significant elevation in sFlt-1 and lower levels of PlGF, the same pattern as PE patients without SLE. Patients with active nephritis had increased VEGF compared to the other two groups, suggesting the potential use of these markers in clinical practice for differentiation between PE and lupus nephritis.



Keywords: Systemic Lupus Erythematosus. Lupus Nephritis. Preeclampsia. Placenta Growth Factor. Pregnancy, High-Risk.

## LISTA DE ABREVIATURAS E SIGLAS

| | |
|---|---|
| ADMA | *Asymmetric dimethylarginine* |
| ACR | *American College of Rheumatology* |
| APS | *Antiphospholipid Syndrome* |
| BAFF | *B-cell activating factor* |
| BLyS | *B lymphocyte stimulator* |
| CI | *Confidence Interval* |
| CNS | *Central Nervous System* |
| CSF-1 | *Colony-stimulating factor-1* |
| ELISA | *Enzyme Linked Immuno Sorbent Assay* |
| Flt-1 | *Fms-like tyrosine kinase-1* |
| HAS | Hipertensão arterial sistêmica |
| HUPE | Hospital Universitário Pedro Ernesto |
| IFN | Interferon |
| IL | Interleucina |
| ISN/RPS | *International Society of Nephrology / Renal Pathology Society* |
| IUGR | *Intrauterine growth restriction* |
| LES | Lúpus eritematoso sistêmico |
| LN | *Lupus nephritis* |
| mRNA | *messenger RNA* |
| NICU | *Neonatal Intensive Care Unit* |
| NP | *Neuropsychiatric* |
| NPSLE | *Neuropsychiatric Systemic Lupus Erythematosus* |
| NK | *Natural Killer* |
| PE | Pré-eclâmpsia |
| PlGF | *Placental growth factor* |
| PROMISSE | *Predictors of Pregnancy Outcome: Biomarkers in APL Syndrome and SLE* |
| ROC | *Receiver Operating Characteristic* |
| SDI | *Systemic Lupus International Collaborative Clinics Damage Index* |
| sEng | *Soluble endoglin* |
| sFlt-1 | *Soluble Fms-like tyrosine kinase-1* |

| | |
|---|---|
| SGA | *Small for gestational age* |
| SLE | *Systemic lupus erythematosus* |
| SLEDAI | *Systemic Lupus Erythematosus Disease Activity Index* |
| SLEPDAI | *Systemic Lupus Erythematosus in Pregnancy Disease Activity Index* |
| SLICC-DI | *Systemic Lupus International Collaborative Clinics Damage Index* |
| SNC | Sistema Nervoso Central |
| sVEGFR-1 | *Soluble vascular endothelial growth factor receptor 1* |
| TGF | *Transforming growth factor* |
| TNF | *Tumor necrosis factor* |
| VEGF | *Vascular endotelial growth factor* |

**SUMÁRIO**

## INTRODUÇÃO

O lúpus eritematoso sistêmico (LES) é uma doença autoimune cuja fisiopatologia envolve mecanismos imunológicos, incluindo distúrbios nos processos de morte celular e nos mecanismos de eliminação de autoantígenos e de tolerância (central e periférica), acompanhados da formação de autoanticorpos patogênicos. Apesar de permanecer obscura a razão pela qual muitos desses mecanismos se desenvolvem, existe evidência robusta na literatura que demonstram serem eles secundários à interação entre fatores genéticos, hormonais e ambientais. A maioria das pacientes com LES está em idade reprodutiva (entre 26 e 40 anos) e as manifestações clínicas podem ser leves ou graves com acometimento de múltiplos órgãos, incluindo rins (nefrite), pulmões (pneumonite), fígado (hepatite) e cérebro (1, 2). É característica a evolução com períodos de atividade (inflamatória) e outros de remissão dos sintomas e, apesar de a maioria dos pacientes com LES terem um curso evolutivo relativamente benigno, a mortalidade média em comparação com a população é maior do que pessoas do mesmo sexo e idade, sendo que os que têm acometimento renal têm caracteristicamente maior morbimortalidade (3).

# 1 **REVISÃO DA LITERATURA**

## 1.1 **Aspectos clínicos e fisiopatológicos do acometimento renal do LES**

A nefrite associada ao LES pode ocorrer clinicamente em até 60% dos pacientes, com acometimento tubular, intersticial, vascular e glomerular. A sua presença é um fator de alta morbidade, visto que 10% a 30% dos pacientes irão desenvolver doença renal terminal ao longo da vida, sendo mais comum naqueles com glomerulonefrite proliferativa (4). A mortalidade também está aumentada, sendo em torno de três vezes maior do que os pacientes com LES sem acometimento renal, e eles tendem a falecer mais precocemente. No entanto, caso a remissão da doença renal seja alcançada a sobrevida em 10 anos se eleva de 46% para 95% (5).

Assim como as manifestações de outros sistemas no LES, a nefrite intercala períodos de atividade e remissão, o que pode modificar a terapêutica a ser escolhida de acordo com apresentação atual (4). As manifestações mais comuns da nefrite do LES são hipertensão, proteinúria inclusive em nível nefrótico em alguns casos, hematúria dismórfica e insuficiência renal nas formas mais graves (5).

A classificação mais utilizada para a nefrite do LES foi descrita pelas Sociedade Internacional de Nefrologia e Sociedade de Patologia Renal (ISN/RPS, do inglês *International Society of Nephrology / Renal Pathology Society*). Neste sistema, a nefrite é classificada de acordo com os seguintes achados histopatológicos, obtidos através de biópsia renal: localização de acúmulo dos imunocomplexos nos glomérlulos; presença ou ausência de proliferação mesangial ou endocapilar; extensão do acometimento glomerular (focal ou difuso) e lesão glomerular (global ou segmentar); e se a lesão é ativa (inflamatória) ou crônica (esclerótica) (6).

A diferenciação entre as classes propostas pela ISN/RPS claramente influencia no tratamento recomendado. Pacientes com doença limitada ao mesangio (classe II) geralmente não precisam de terapia específica para a doença renal assim como as pacientes com doença renal terminal (classe VI), enquanto os pacientes com doença renal proliferativa (classes III e IV) são frequentemente tratadas com imunossupressores potentes. A classe V, chamada de membranosa, pode ser

tratada com terapia antiproteinúria ou imunossupressão, de acordo com a intensidade da proteinúria (5).

A glomerulonefrite, que é a forma mais típica de acometimento renal no LES, tem fisiopatologia complexa e envolve principalmente a deposição de imunocomplexos na membrana basal glomerular. Sequencialmente, ocorre a ativação do sistema de complemento, proliferação de células residentes e migração de leucócitos, em associação à produção de matriz extracelular, de quimiocinas e de citocinas pró-inflamatórias. Algumas dessas moléculas têm sido associadas à fisiopatologia da autoimunidade como o estimulador de linfócito B (BLyS, do inglês *B lymphocyte stimulator*)/fator ativador da célula B (BAFF, do inglês *B-cell activating factor*), interleucina (IL)-17, IL-23, IL-6, IL-10, fator de necrose tumoral (TNF, do inglês *Tumor necrosis factor*) alfa e interferon (IFN) alfa. Outras estão mais diretamente relacionadas às alterações teciduais como o fator de transformação do crescimento (TGF, do inglês *Transforming growth factor*) beta, o fator estimulador de colônias-1 (CSF-1, do inglês *Colony-stimulating factor-1*), o IFN tipo I produzido pelas células renais residentes (3) e o fator de crescimento endotelial vascular (VEGF, do inglês *vascular endotelial growth factor*). O resultado deste processo inflamatório são as alterações histopatológicas observadas à biópsia renal que incluem aumento da matriz extracelular e da celularidade no mesângio, proliferação de células endocapilares, inflitração de polimorfonucleares, linfócitos, monócitos e formação de crescentes celulares associados a depósitos de imunocomplexos. Também são frequentes as alterações vasculares ainda que estas não sejam empregadas para definir a classe histológica (6). As alterações mais frequentes incluem as lesões necrosantes na parede vascular, com depósito imune e redução da luz, e necrose fibrinoide em vasos de pequeno e médio calibre com infiltração inflamatória mural (7).

Estudo realizado por Avihingsanon et al. (6) investigou a expressão do RNA mensageiro (mRNA) do VEGF renal em material obtido através de biópsia para caracterização de nefrite em 35 pacientes com lúpus. Vinte e sete pacientes tiveram o diagnóstico histopatológico de nefrite lúpica classe IV e oito pacientes foram diagnosticadas como portadoras de nefrite classe III segundo a classificação da ISN/RPS. Os níveis de mRNA VEGF foram menores nas pacientes com nefrite lúpica quando comparados com o controle, apresentando correlação negativa com formação de crescentes, com altos valores do índice de atividade medido através de

achados patológicos descritos por Austin et al. (8) e com proliferação difusa endocapilar. No entanto, amostras com mais de 25% de infiltração neutrofílica glomerular não mostraram diferença no VEGF. Os autores encontraram, através da análise de uma curva ROC, nível de mRNA capaz de predizer 53% dos casos de perda de função renal (dobrando a creatinina sérica ou doença renal crônica com necessidade de terapia renal substitutiva) em 12 meses (9).

Formulou-se a hipótese que a redução intrarrenal de VEGF seria causada pela perda de células podócitárias na urina, já que o mesmo autor demonstrou em estudo anterior aumento de VEGF urinário em pacientes com nefrite lúpica comprovadas por biópsia (10). Os autores analisaram as amostras urinárias de 21 pacientes no dia da realização da biópsia utilizada para medir o VEGF mRNA intrarrenal e encontraram aumento de WT-1, um marcador podocitário, e de VEGF quando comparadas com o controle (9).

## 1.2 **Aspectos clínicos e fisiopatológicos do acometimento neurológico do LES**

O acometimento do sistema nervoso central (SNC) do lúpus é uma das formas mais graves da doença, sendo responsável por 13% das mortes assim como um número significativo das morbidades (11). Sua frequência é variável na literatura, visto que não há uniformidade nos seus critérios diagnósticos. Alguns sintomas, como cefaleia e alterações de humor, são frequentes na população geral e provavelmente não são causados pelo LES. Quando apenas manifestações neurológicas maiores são incluídas, estima-se que entre 5 e 10% dos pacientes apresentarão uma manifestação neurológica atribuível ao LES no momento de diagnóstico e outros 5% apresentarão este tipo de sintoma nos primeiros três anos da doença. As mais comuns são convulsões, acidente vascular cerebral, mielopatia, meningite, psicose, disfunção cognitiva e neuropatia periférica (12).

O conhecimento sobre a fisiopatologia do acometimento neurológico do lúpus ainda continua bastante limitado, estando relacionado com fatores genéticos, ambientais e hormonais. Os principais mecanismos descritos até o momento seriam relacionados com neurotoxicidade mediada por autoanticorpos, vasculopatia

trombótica relacionada principalmente com anticorpos antifosfolipídeos, neurotoxicidade induzida por citocinas e perda de neuroplasticidade (13).

Diferentemente da nefrite do LES, a classificação das manifestações neurológicas da doença ocorre a partir de síndromes ao invés de mecanismos fisiopatológicos. Isto dificulta o entendimento do lúpus neurológico e influencia diretamente o tratamento assim como o prognóstico (12). Além disso, condições clínicas frequentes em pacientes com LES podem mimetizar o acometimento neurológico da doença, como infecções, tumores de sistema nervoso central, efeitos colaterais de medicações, vasculopatias isquêmicas e outras comorbidades, como a esclerose múltipla (14). Na gestação, a convulsão associada à eclâmpsia é um diagnóstico diferencial importante e muitas vezes difícil na prática clínica (15).

## 1.3 **Gestação em pacientes com LES**

Devido à maior prevalência do LES em mulheres em idade fértil, a gestação nessas pacientes não é uma condição incomum e ao mesmo tempo é interessante notar que diversos achados clínicos e laboratoriais na nefrite lúpica são semelhantes àqueles encontrados em pacientes com pré-eclâmpsia (PE) grave, especificamente hipertensão arterial sistêmica (HAS), proteinúria e edema (16, 17). As reativações do LES durante a gestação são na maioria das vezes leves (18), no entanto a reativação grave da doença pode ocorrer em 25-30% das gestantes com lúpus (16), podendo a doença surgir durante a gravidez ou no período pós-parto (18).

As complicações obstétricas são mais frequentes nas gestantes com lúpus, com grande morbimortalidade materna e fetal. As mais frequentemente associadas são PE, parto prematuro, perda gestacional e crescimento intrauterino restrito, sendo que os principais preditores para estes eventos obstétricos adversos são atividade da doença materna, nefrite, proteinúria, hipertensão, trombocitopenia e a presença de anticorpos antifosfolipídeos, especialmente o anticoagulante lúpico (18). Mais recentemente, foi descrito um aumento da incidência de atraso de neurodesenvolvimento em filhos de pacientes com lúpus (19).

Considerando a forma neurológica, há relatos de mielite transversa com progressão para paraplegia, vasculite sistêmica com necrose cerebral, convulsões,

déficit cognitivo e desorientação associados ao LES (20-22). Apesar disso, são poucos os estudos sobre as repercussões neurológicas do LES durante a gravidez, sendo grande parte deles relatos ou séries de casos.

Em revisão sistemática de 2751 gestações em 1842 pacientes com LES, foi encontrada reativação da doença em 25,6% dos casos, HAS em 16,3%, nefrite em 16,1%, PE em 7,6%, eclâmpsia em 0,8% e prematuridade em 39,4% dos partos. Houve associação positiva entre parto prematuro e nefrite ativa, assim como entre HAS e nefrite ativa ou história de nefrite (23).

A revisão de 76 gestações em 63 pacientes com lúpus acompanhadas no Hospital Universitário Pedro Ernesto (HUPE) identificou que 15% das pacientes desenvolveram PE e 30% possuíam HAS. Neste mesmo estudo, 14 pacientes precisaram aumentar as doses de corticosteroides durante a gestação e 27% dos fetos apresentaram sofrimento fetal crônico. Os partos ocorreram numa idade gestacional média de 35 semanas e foi notada maior incidência de óbito fetal em pacientes com nefrite comparadas às pacientes sem nefrite (37% x 12,2%) (24).

Uma coorte multicêntrica de 71 gestações em 61 mulheres com LES e nefrite descreveu 19,7% de ativação da doença, seis casos de pré-eclâmpsia (8,4%) e dois casos de síndrome HELLP. Cinquenta e seis casos (78,9%) estavam em remissão renal completa no início do pré-natal e 15 pacientes possuíam atividade leve da nefrite. Os preditores da atividade renal durante o pré-natal encontrados neste estudo foram baixos níveis de C3 e C4 e altos títulos de anticorpos anti-DNA e anti-C1q, enquanto a presença de atividade renal no início do pré-natal não teve relação com a reativação do LES. Além disso, o índice de massa corpórea (IMC) foi associado com a atividade tardia da doença (25).

A presença de proteinúria durante o pré-natal foi associada a um risco 2.45 vezes maior de PE durante a gestação, assim como a creatinina sérica maior do que 1,2 mg/dl aumentou o risco em 1.25 vezes. Na análise composta de eventos adversos, uma taxa de filtração glomerular menor que 90 ml/min foi associada a um risco de 18.73 para o desenvolvimento de PE, crescimento intrauterino restrito e parto prematuro (26).

Além dos resultados adversos maternos e perinatais associados à PE e ao LES, o diagnóstico diferencial entre as duas condições é complexo, pois ambas podem apresentar aumento de proteinúria, HAS, trombocitopenia e deterioração da função renal. Nos casos de eclâmpsia, a diferenciação deve ser feita com o

acometimento neurológico do LES. A queda dos níveis das proteínas do complemento sérico, que pode ocorrer principalmente na reativação das glomerulonefrites proliferativas no lúpus e auxiliariam no diagnóstico diferencial com a PE, pode não ser observada em decorrência do aumento fisiológico das proteínas do sistema complemento durante a gestação (17).

Os estudos 1 e 2 que compõem esta tese foram desenvolvidos para investigar a influência do acometimento neurológico e renal do lúpus, respectivamente, nos resultados gestacionais adversos, além analisar a atividade do LES durante a gestação.

## 1.4 **Pré-eclâmpsia**

### 1.4.1 Epidemiologia

A PE é uma desordem multifuncional de causa desconhecida que é exclusiva da gestação humana. É caracterizada pela resposta vascular anormal à placentação, levando ao aumento da resistência vascular periférica, da agregação plaquetária, ativação do sistema de coagulação e disfunção endotelial. Os achados clínicos de PE podem se manifestar como uma síndrome materna, com HAS e proteinúria com ou sem outras anormalidades multissistêmicas, e/ou uma síndrome fetal, apresentando restrição do crescimento intrauterino, oligodramnia e oxigenação deficiente (27).

Apesar dos avanços nos cuidados perinatais, a frequência de pré-eclâmpsia não tem mudado e não houve melhora substancial nos métodos de predição ou de prevenção da patologia independente das pesquisas das últimas décadas. Um grande impedimento para tais métodos é o fraco entendimento dos vários mecanismos patológicos que levam à pré-eclâmpsia assim como o critério inconsistente para definí-la (27).

A PE é uma das principais causas de morbimortalidade materna, morte perinatal, parto pré-termo e restrição de crescimento intrauterino. Apesar de um bom desfecho para a maioria das gestantes, o atraso no seu diagnóstico pode favorecer

a evolução para sua forma mais grave, a eclâmpsia, caracterizada por uma ou mais convulsões sobrepostas aos achados de PE. Enquanto nos países desenvolvidos a frequência de eclâmpsia é de uma para duas mil gestações, nos países em desenvolvimento pode chegar até a uma em cada cem gestações. Calcula-se que pacientes gestantes em países desenvolvidos apresentam um risco médio de mortalidade por causas obstétricas durante a vida de um para quatro mil a um para dez mil, enquanto nos países com baixa renda esse risco varia entre um para quinze e um para cinquenta, apresentando uma taxa de mortalidade cem a duzentas vezes maior que na Europa e América do Norte (28).

Vários estudos sugerem que as mulheres que desenvolvem PE possuem um risco cardiovascular aumentado no restante da vida, sendo a disfunção endotelial uma peça fundamental no achado fisiopatológico e que persiste após o parto (29-31). A gestação que apresenta esta complicação pode identificar as mulheres em risco para doença cardiovascular e dar a oportunidade para mudança nos fatores de risco e estilo de vida (27).

### 1.4.2 Aspectos fisiopatológicos da pré-eclâmpsia

Apesar do grande número de pesquisas, a etiologia da pré-eclâmpsia continua desconhecida. Existem duas correntes de pensamento atuais, que são discordantes: o modelo isquêmico, no qual a isquemia e a reperfusão resultam em estresse oxidativo e doença vascular; e o modelo imunológico, que considera uma má adaptação imune entre a gestante e seu companheiro, isto é, uma reação aloimune materna disparada pela rejeição do aloenxerto fetal (27).

Durante o desenvolvimento placentário normal, o citotrofoblasto invade as arteríolas espiraladas maternas e promove um remodelamento, tornando esses vasos de grande capacitância e de baixa resistência. Esta invasão endovascular do citotrofoblasto envolve a troca do endotélio e da túnica média das arteríolas. No modelo isquêmico, a hipótese formulada é que ocorre uma invasão superficial das arteríolas espiraladas pelo citotrofoblasto, não permitindo o remodelamento vascular e levando a uma perfusão placentária deficiente e consequentemente insuficiência placentária (32). Além disso, não ocorre uma mudança da expressão das integrinas

superficiais epiteliais das células trofoblásticas para um fenótipo endotelial, limitando seu potencial invasivo (33).

A disfunção endotelial generalizada pode ser responsável por todos os aspectos clínicos encontrados na pré-eclâmpsia e a identificação de fatores circulantes que servem como mediadores desta disfunção tornou-se assunto de grande interesse nas últimas décadas. Diversos grupos publicaram alterações em citocinas, fatores de crescimento e químicos, como TNF-α, IL-6, IL-1α, IL-1β, ligante de Fas, produtos lipídicos oxidados, neuroquinina-B e dimetilarginina assimétrica (ADMA), que são liberados pela placenta e/ou outras fontes maternas na pré-eclâmpsia (32).

Já no modelo imunológico, a deposição do sêmen no trato genital feminino provoca uma cascata de eventos celulares e moleculares que são semelhantes à reposta inflamatória clássica, permitindo um processamento dos antígenos paternos e uma forte reação imune tipo 2. Ao iniciar este tipo de resposta imune em relação aos antígenos paternos, o TGFβ1 encontrado no sêmen pode inibir a indução de respostas tipo 1 contra o concepto semi-alogênico; a pequena exposição ao sêmen levaria a resposta imune tipo 1 que seria a causa do desenvolvimento placentário e fetal deficiente (27).

### 1.4.3 Fatores angiogênicos e antiangiogênicos na pré-eclâmpsia

Independentemente do modelo proposto como causa da pré-eclâmpsia, sabe-se que na gestação normal existe uma interação do trofoblasto endovascular e dos leucócitos deciduais, especialmente células natural-killer (NK), resultando na liberação de mitógenos responsáveis pela angiogênese necessária para o desenvolvimento placentário, principalmente o VEGF e o fator de crescimento placentário (PlGF, do inglês *placental growth factor*). Concentrações elevadas de VEGF livre também são importantes para manter em repouso o endotélio, apesar do estresse inflamatório típico que envolve uma gestação normal (27). Outras funções do VEGF incluem induzir a produção de óxido nítrico e prostaciclinas vasodilatadoras pelas células endoteliais, reduzindo o tônus vascular e a pressão arterial; promover a recuperação glomerular em modelo animal de glomerulonefrite e

microangiopatia trombótica; e aumentar a permeabilidade vascular (34). Estudos sobre fatores antiangiogênicos demonstraram que o bloqueio de seus sinalizadores resultou em HAS e proteinúria (34). Considerando estes dados, o VEGF apresenta um papel importante não apenas na regulação da pressão sanguínea mas também em manter a integridade da barreira de filtração glomerular durante a gestação (33, 34).

Maynard et al. (34) pesquisaram, em tecido placentário de mulheres com e sem pré-eclâmpsia, o mRNA do receptor *Fms-like* tirosina quinase-1 solúvel (sFlt-1, do inglês *soluble Fms-like tyrosine kinase-1*) e encontraram aumento de sua expressão apenas nas mulheres com pré-eclâmpsia. O sFlt-1, também chamado de sVEGFR-1, é um dos dois receptores solúveis para o VEGF (35) e possui alta afinidade pelo VEGF, à semelhança do que ocorre com o receptor de membrana VEGFR-1. O sFlt-1 é uma variante solúvel do receptor de VEGF Flt-1 que não possui domínios transmembrana e citoplasmáticos, agindo como potente antagonista de VEGF e PlGF, apresentando, portanto, um perfil inibidor da ação dessas duas citocinas, o que poderia ser considerado uma atividade antiangiogênica. O mesmo grupo formulou a hipótese que o sFlt-1 circulante em excesso secretado pela placenta na PE levaria a disfunção endotelial, HAS e proteinúria ao antagonizar o VEGF e PlGF circulantes (34).

Continuando seu estudo, Maynard demonstrou que os níveis de sFlt-1 sérico medidos pelo método ELISA em pacientes com pré-eclâmpsia eram maiores que os de gestantes com pressão arterial normal, chegando o aumento a cinco vezes no caso de PE grave. Este achado foi confirmado por outros autores (36). Foi demonstrado neste grupo de pacientes que os valores séricos das frações livres de VEGF e PlGF estavam reduzidos proporcionalmente ao aumento de sFlt-1, sugerindo que o sFlt-1 atuaria como antagonista ao se ligar a essas citocinas e impedir a ligação do VEGF e PlGF aos seus receptores de superfície celular. Por fim, utilizando um modelo animal no qual foi administrado um adenovirus recombinante produtor de sFlt-1, houve desenvolvimento de hipertensão e proteinúria em ratas gestantes e não gestantes, inclusive com análise histopatológica renal evidenciando endoteliose glomerular, lesão característica da PE (34).

Posteriormente a este estudo, Levine et al. (37) utilizaram o banco de soros de um estudo prévio e compararam os valores de sFlt-1, PlGF e VEGF das

pacientes com PE pareadas com pacientes normotensas de mesma idade gestacional na primeira coleta sérica (120 casos e 120 controles), utilizando o mesmo procedimento de Maynard (método ELISA). O autor comprovou que as pacientes analisadas após o diagnóstico de pré-eclâmpsia possuíam níveis séricos maiores de sFlt-1 e menores de PlGF e VEGF que o grupo controle. Essas alterações foram mais pronunciadas quando as pacientes apresentaram pré-eclâmpsia precoce (<34 semanas) ou restrição do crescimento intrauterino. Depois, em análise longitudinal, ele observou que, durante a gestação normal, a concentração de sFlt-1 manteve-se constante até 33 a 36 semanas, apresentando posterior elevação semanal até o parto; a de PlGF manteve-se constante nos dois primeiros trimestres, apresentou pico entre 29 a 32 semanas e posterior queda contínua; o VEGF manteve-se baixo durante toda gestação.

Avaliando o grupo de pacientes com PE, Levine relatou que, antes do diagnóstico, houve elevação da concentração de sFlt-1 entre 21 e 24 semanas de gestação, sendo esta elevação mais rápida de 11 a 9 semanas antes da abertura do quadro, chegando ao pico 5 semanas antes e mantendo-se neste patamar até o diagnóstico. Os níveis de PlGF encontrados foram menores a partir das 13 a 16 semanas e também apresentaram queda 11 a 9 semanas antes do diagnóstico, com redução substancial nas 5 semanas antes do aparecimento de hipertensão ou proteinúria. As concentrações de VEGF mantiveram-se baixas durante toda gestação sem diferença entre os grupos, exceto nos casos de coleta de material entre 37 e 41 semanas das pacientes que posteriormente desenvolveram pré-eclâmpsia e nos casos em que o soro foi colhido entre 21 e 32 semanas e até 5 semanas antes do aparecimento do quadro. Essas alterações foram mais pronunciadas quando a paciente apresentou PE precoce (<34 semanas) ou restrição do crescimento intrauterino (37).

O autor sugere que, fisiologicamente, o estado pró-angiogênico do segundo trimestre (aumento de PlGF com sFlt-1 baixo) seria convertido para um estado anti-angiogênico (aumento do sFlt-1 e queda do PlGF e VEGF) e que nas pacientes com pré-eclâmpsia esta conversão seria mais precoce e abrupta, como um exagero do processo normal de controle do crescimento e funcionamento placentário (37).

Diversos autores continuaram esta linha de pesquisa, estudando fatores angiogênicos e antiangiogênicos urinários (38, 39), a associação dos fatores séricos com achados ultrassonográficos (40-42) e principalmente a possibilidade de utilizar

estes marcadores como preditores da pré-eclâmpsia (43-46). Entre estas novas aplicações, sem dúvidas a predição da pré-eclâmpsia no primeiro trimestre da gestação, especialmente a sua forma grave e precoce, é a mais promissora e já está sendo utilizada na prática clínica em alguns países (47), inclusive no Brasil.

Além da dificuldade de predição e de entendimento da fisiopatologia, a PE apresenta semelhança clínica e laboratorial com várias doenças que acometem o ciclo gravídico-puerperal, tanto clínicas quanto cirúrgicas, como por exemplo o fígado gorduroso agudo da gravidez, a púrpura trombocitopência trombótica, a síndrome hemolítica urêmica, a sepse e a reativação do LES. O tratamento difere entre estas enfermidades e o diagnóstico incorreto pode levar a uma elevada morbimortalidade materna e fetal (48).

Há, portanto, necessidade de melhorar a acurácia do diagnóstico diferencial entre pré-eclâmpsia e LES com nefrite e a medida dos marcadores angiogênicos e antiangiogênicos como sFlt-1, VEGF e PlGF poderia contribuir para discriminar as duas condições (49) mas estudos prospectivos que incluam pacientes com LES durante a gestação ainda são aguardados (50).

## 1.5 **Fatores angiogênicos e antiangiogênicos em pacientes com LES**

Um estudo caso-controle contendo pacientes gestantes com LES estudou os níveis de sFlt-1 em pacientes com diagnóstico de PE, tendo encontrado concentrações elevadas em comparação às das pacientes com LES sem pré-eclâmpsia. No entanto, o estudo incluiu um pequeno número de pacientes (18 casos e 34 controles), não incluiu pacientes com nefrite e não avaliou os títulos dos fatores angiogênicos VEGF e PlGF (51).

Um relato de caso publicado sugere o potencial uso da dosagem de PlGF e sFlt-1 como auxiliar para o diagnóstico diferencial entre reativação do LES e PE. Uma gestante com diagnóstico prévio de LES e nefrite foi internada com quadro de HAS progressiva, trombocitopenia e piora na proteinúria. Tendo em vista o diagnóstico inicial de reativação da doença de base, a paciente foi tratada com corticosteroides mas não ocorreu melhora clínica e houve evolução para o óbito fetal. Após o parto, a rápida melhora clínica sugeriu a hipótese de PE e a

mensuração dos níveis séricos de PlGF e sFlt-1 coletados no momento da internação foi sugestiva deste diagnóstico, revelando o sFlt-1 acima do percentil 95 para a idade gestacional com o PlGF abaixo do nível de detecção para o exame (52).

Rhee et al. (52) também mencionam que estudos clínicos prospectivos são necessários para a melhor caracterização dos fatores angiogênicos e antiangiogênicos em situações clínicas reais em gestantes com comorbidades que dificultem o diagnóstico diferencial com a PE. Em relação ao LES, cuja fisiopatologia envolve dano vascular, e principalmente nos casos com glomerulonefrite, em que a inflamação envolve caracteristicamente as alças capilares do glomérulo, é preciso melhor conhecimento quanto a variação dos níveis séricos dessas citocinas em diferentes condições, incluindo os períodos de atividade e inatividade da doença durante a gravidez.

Em pacientes não gestantes, alguns autores demonstraram o aumento do VEGF no LES ativo comparado com doença inativa ou com o controle (8), assim como em outras doenças inflamatórias como artrite reumatoide, polimiosite e dermatomiosite (8). Esta elevação do VEGF é esperada após a lesão endotelial presente na fisiopatologia da doença, considerando seu papel como modulador da angiogênese, proliferação e migração celular endotelial, quimiotaxia e permeabilidade capilar.

Outros mecanismos também podem ser responsáveis pela elevação do VEGF em pacientes com LES. Níveis elevados de IL-17 foram descritos em pacientes com LES e esta citocina pró-inflamatória determinam aumento na produção de VEGF (53). Em pacientes com nefrite lúpica, sua elevação pode estar associada com o reparo capilar dos glomérulos danificados (54). Frieri et al. (55) observaram, através de coloração imunohistoquímica, a presença de VEGF nos glomérulos e túbulos renais obtidos a partir de biópsias em pacientes com LES e nefrite, mas não identificaram este fator em amostras de pacientes saudáveis.

Robak et al. (56) e, mais recentemente, Zhou et al. (57), avaliaram a medida de PlGF nas pacientes com LES não gestantes. Os dois grupos encontraram valores aumentados dessa citocina tanto na doença ativa quanto na doença inativa em relação ao controle. O PlGF, membro da família VEGF, também possui um papel expressivo na neovascularização em adultos, contribuindo na cicatrização de feridas através da angiogênese, além de promover quimiotaxia de monócitos, crescimento

de vasos colaterais, mobilização de células precursoras na medula óssea e aumento da atividade do VEGF (56).

Já o receptor solúvel do VEGF-1, sFlt-1, foi descoberto recentemente e o seu papel fisiológico ainda não está bem estabelecido. Sabemos que ele é normalmente encontrado na circulação de homens e mulheres, é produzido por células endoteliais e monócitos e sua produção é aumentada quando estas duas células são ativadas (58). O sFlt-1 possui uma grande afinidade pelo VEGF e acredita-se que ele funcione como regulador negativo de sua disponibilidade do VEGF (35). Foi demonstrado que este receptor solúvel faz parte de um sistema vascular intrínseco que guia os brotos vasculares para longe do vaso parental, em conjunto com o VEGF (59).

Em relação ao sFlt-1, Hrycek et al. (60) e Robak et al. (35) o estudaram em pacientes adultos com LES não gestantes e relataram não haver diferença da medida nas pacientes com doença inativa em relação ao controle. Por outro lado, o primeiro grupo descreveu valores menores em pacientes com a doença ativa enquanto o segundo grupo relatou valores maiores no mesmo cenário, ambos com diferença estatisticamente significativa. Provavelmente diferenças na população estudada resultaram em resultados tão divergentes.

Um estudo avaliando crianças e adolescentes com LES encontrou valores maiores para sFlt-1 nos pacientes com nefrite ativa quando comparados com pacientes com história de nefrite em remissão e com um grupo controle sem LES. Os valores de VEGF encontrados foram maiores para as pacientes que tinham nefrite ativa, mas estavam inversamente relacionados com o sFlt-1 tanto nos pacientes com nefrite ativa quanto com nefrite inativa. A redução do VEGF circulante resultaria em diminuição de seu efeito protetor endotelial e glomerular, o que tornaria o sFlt-1 um possível agente causador de lesão endotelial (61).

De Jesús et al. (62) avaliaram os valores séricos médios de VEGF, PlGF e sFlt-1 pacientes não gestantes com LES. A maior parte das pacientes incluídas neste estudo (47 pacientes, 82,4%) possuía história clínica, laboratorial e/ou histopatológica de nefrite lúpica, incluindo mais da metade (66,6%) das pacientes com a doença em remissão. Estes autores demonstraram que os valores séricos médios de VEGF, PlGF e sFlt-1 foram maiores em pacientes não gestantes com LES em comparação ao grupo controle composto por mulheres sem doença autoimune. As pacientes com LES ativo apresentaram os valores séricos médios

das três citocinas maiores do que o grupo controle, enquanto não houve diferença estatística entre os valores séricos médios do VEGF, PlGF e sFlt-1 quando as pacientes com LES inativo foram comparadas ao grupo controle de mulheres saudáveis.

Quando os dois grupos de pacientes com LES foram comparados neste mesmo estudo, apenas os valores séricos médios do sFlt-1 foram significativamente maiores no grupo com doença ativa em comparação ao grupo com doença em remissão, enquanto não houve diferença entre os dois grupos em relação aos valores séricos médios de VEGF e PlGF (62).

O padrão de elevação de VEGF e PlGF com a atividade da doença descrito por De Jesús et al. (62) favorece a aplicação destes fatores angiogênicos como método para auxílio no diagnóstico diferencial entre nefrite lúpica e PE em gestantes com LES, visto que estas citocinas estão reduzidas em pacientes com PE (25). A elevação do sFlt-1 em pacientes com doença ativa indica a necessidade de analisar o comportamento desta citocina especificamente em mulheres com LES e nefrite durante a gestação para que ela possa ser empregada como biomarcador na diferenciação entre nefrite ativa e PE.

Vários estudos demonstraram que alterações nos fatores angiogênicos e antiangiogênicos estão relacionadas com a fisiopatologia da PE e possuem um papel provável no diagnóstico e prognóstico da doença. Apesar de a dosagem destas citocinas ainda não estar amplamente disponível, muitos autores já recomendam seu uso em mulheres com sinais e sintomas de PE ou em gestantes assintomáticas que apresentam alto risco de desenvolver a doença (63).

Leaños-Miranda et al. (64) estudaram 117 gestantes com lúpus, analisando amostras de sangue venoso coletadas a cada quatro semanas a partir de 12 semanas de gestação. O grupo identificou que as mulheres que desenvolveram PE posteriormente apresentaram níveis séricos menores de PlGF e maiores de sFlt-1 e endoglina solúvel (sEng) 12 semanas antes do surgimento da doença, tanto na PE precoce (menor que 34 semanas) quanto na tardia (maior que 34 semanas). Este grupo, no entanto, não analisou os resultados dos fatores em pacientes com LES ativo, inclusive excluindo do estudo pacientes com doença renal ativa.

De forma similar, Mayer-Pickel et al. (65) analisaram níveis séricos de sFlt-1, PlGF e sEng com intervalos de quatro semanas em 23 mulheres com LES. Duas delas desenvolveram PE e também apresentaram níveis elevados de sFlt-1 e sEng

com níveis baixos de PlGF, sendo que estas alterações se tornaram estatisticamente significativas a partir de 12 semanas de gestação.

Um estudo multicêntrico americano, chamado PROMISSE (*Predictors of Pregnancy Outcome: Biomarkers in APL Syndrome and SLE*), apresentou desenho similar à pesquisa mencionada anteriormente. A dosagem do sFlt-1 isoladamente e a combinação do sFlt-1 e do PlGF em gestantes com LES e/ou anticorpos antifosfolipídeos no primeiro trimestre foram fortes preditores de resultados gestacionais adversos graves, definidos como PE menor que 34 semanas, morte fetal/neonatal e indicação de parto pré-termo antes de 30 semanas (66).

Em outra publicação do mesmo estudo multicêntrico, Andrade et al. (67) descreveram que os altos níveis séricos de sFlt-1 e o baixo PlGF precederam o desenvolvimento da PE em gestantes com LES apenas quando o IFN-alfa estava diminuído. As alterações nas citocinas mencionadas não foram identificadas nas gestantes com LES e PE quando o IFN-alfa estava normal. Os autores sugerem, a partir de estudos *in vitro*, que o IFN-alfa poderia amplificar a resposta endotelial ao sFlt-1, o que resultaria em PE com níveis menores deste fator antiangiogênico.

Uma grande limitação do estudo PROMISSE, assim como no estudo de Leaños-Miranda, é a exclusão de pacientes com nefrite ativa, o que impede a análise destes fatores nas pacientes com acometimento renal relacionado ao LES. Outro ponto importante é que os estudos anteriores não excluíram pacientes com síndrome antifosfolipídeo, que aumenta o risco de PE e pode ser um fator de confusão na análise do papel do LES nestes casos (49).

O estudo 3 foi desenvolvido com o objetivo de utilizar fatores angiogênicos (PlGF e VEGF) e antiangiogênicos (sFlt-1) na diferenciação entre nefrite do LES durante a gravidez e PE.

# 2 **OBJETIVOS**

## 2.1 **Objetivo geral**

Avaliar os desfechos clínicos maternos em uma coorte de gestantes com lúpus eritematoso sistêmico.

## 2.2 **Objetivos específicos**

Analisar os desfechos gestacionais em gestantes com lúpus eritematoso sistêmico e acometimento neuropsiquiátrico (estudo 1).

Analisar os desfechos gestacionais em gestantes com lúpus eritematoso sistêmico de acordo com a classificação da manifestação renal da doença (estudo 2).

Analisar o uso de fatores angiogênicos (VEGF, PlGF) e antiangiogênicos (sFlt-1) no diagnóstico diferencial entre nefrite do LES e pré-eclâmpsia (estudo 3).

# 3 **MATERIAL E MÉTODOS**

Os três estudos aqui apresentados foram desenvolvidos a partir da coorte de gestantes com LES do Hospital Universitário Pedro Ernesto. O atendimento pré-natal especializado em gestantes com doenças autoimunes foi iniciado em 1994 e é uma referência no estado do Rio de Janeiro. Nos últimos anos, uma média de 30 gestantes com LES são atendidas por ano, o que representa uma das maiores coortes em um único centro quando comparamos com outros locais e também com publicações internacionais.

O atendimento pré-natal, conduzido por médicos e residentes do departamento de Obstetrícia, possui apoio de médicos reumatologistas durante a consulta, o que é um grande diferencial em relação a outras instituições. As pacientes são avaliadas sobre a doença de base na primeira consulta, a partir do histórico do LES e exames laboratoriais disponíveis. Uma nova avaliação laboratorial é feita buscando marcadores que possam alterar o resultado gestacional, como por exemplo anticorpos antifosfolipídeos e proteinúria. As pacientes que não apresentam intercorrências são atendidas mensalmente até 28 semanas, com consultas quinzenais após este período e semanais após 36 semanas. A avaliação laboratorial é repetida a cada três meses ou se houver alguma intercorrência clínica ou obstétrica. As pacientes mais graves são internadas na enfermaria de Obstetrícia para acompanhamento conjunto com a Reumatologia.

# 4 ESTUDO 1 - GESTATIONAL OUTCOMES IN PATIENTS WITH NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (Artigo publicado)*

**Abstract**

This study analyzed maternal and fetal outcomes of pregnancies of NPSLE patients followed in a reference unit. A retrospective cohort study between 2011 and 2015 included 26 pregnancies with history and/or active NPSLE among 135 pregnancies. Three patients had active NPSLE at conception, but only one remained with neurological activity during gestation, characteristically related to the inadvertent suspension of medications. Twenty six percent of newborns were small for gestational age and 40% of live births were premature, with no neonatal death or early complications of prematurity. Nine pregnancies presented preeclampsia, with two cases of early severe form that resulted in intrauterine fetal death. Patients with NPSLE had more prematurity and preeclampsia compared to patients without NP disease. However, patients with NPSLE without lupus nephritis had favorable outcomes.

**Keywords**

Neuropsychiatric Systemic Lupus Erythematosus, Central Nervous System Lupus, preeclampsia, preterm birth, pregnancy.

## Introduction

The risk of obstetric complications in systemic lupus erythematosus (SLE) patients is significant, with higher rates of abortion, intrauterine fetal death, preeclampsia, fetal growth restriction and preterm birth (1). Pregnancy, in turn, may increase the frequency of lupus flares and worsen renal function in the short and long term and may lead to end-stage renal disease (2).

Neuropsychiatric (NP) SLE has variable prevalence, ranging from 9.5 to 95%, depending on the geographic and ethnic characteristics, as well as the diagnostic criteria considered (3). NPSLE manifestations are associated with worse prognosis in

* De Jesús GR et al. Gestational outcomes in patients with neuropsychiatric systemic lupus erythematosus. Lupus 2017;26(5):537-42. DOI: 10.1177/0961203317693929.

SLE, including multiple organs disease activity and early death. Up to 13% of deaths in SLE patients are attributed to central nervous system (CNS) involvement, as well as a major cause of morbidity (4-10). However, there are few studies in the literature evaluating perinatal outcomes in patients with NPSLE. The present study analyzed maternal and fetal outcomes of pregnancies of NPSLE patients followed in a reference unit.

**Patients and methods**

This is a retrospective cohort study, based on the review of medical records of patients followed at Hospital Universitário Pedro Ernesto at the State University of Rio de Janeiro, between 2011 and 2015. All patients were diagnosed with SLE according to American College of Rheumatology criteria (11). Evaluated clinical outcomes were disease activity at the time of conception, activity or reactivation of lupus during pregnancy and puerperium and association with comorbidities, such as antiphospholipid syndrome (APS) and chronic hypertension. Disease manifestations were analyzed according to the organ or system involved, separated in cutaneous, articular, serositis, renal, haematological and CNS.

The obstetric outcomes evaluated were abortion, fetal death, premature rupture of membranes, preeclampsia, intrauterine growth restriction, and prematurity. Immediate neonatal outcomes, such as neonatal intensive care unit (NICU) admission, complications of prematurity, and occurrence of neonatal lupus were also analyzed.

**Results**

Of the 135 single pregnancies followed in the study period, history and/or active NPSLE were identified in 26 (21 patients). The mean maternal age was 28 years, with an average disease duration of 9.6 years. Table 1 describes the characteristics of the study patients.

Of the 21 studied patients, 17 had history of cutaneous manifestations (80%), including one with discoid lupus, 17 presented articular manifestations (80%), 14 had lupus nephritis (66%), 13 had haematological manifestations (61%) and 10 had serositis (47%). Six patients had detectable circulating anti-Ro/SSA (28%) and none had anti-La/SSB.

Table 1 - Characteristics of studied patients, including general and neuropsychiatric SLE manifestations (continua)

| Patient # | Maternal age (year) | Duration of SLE (year) | Neuropsychiatric manifestations | Other SLE manifestations | Comorbidities |
|---|---|---|---|---|---|
| **1**[a] | 24<br>26<br>28 | 4<br>6<br>8 | Depression, psychosis | Serositis, renal | Chronic hypertension, renal failure |
| **2** | 18 | 8 | Headache, chorea, psychosis, hemiparesis | Cutaneous, arthritis, serositis, hematological | - |
| **3** | 24 | 8 | Transverse mielitis, seizures, neurogenic bladder | Cutaneous, arthritis | Recurrent UTI |
| **4** | 31 | 14 | Tetraparesis with altered level of consciousness | Cutaneous, arthritis | - |
| **5** | 31 | 17 | Peripheral neuritis, headache | Cutaneous, arthritis, serositis, hematological | aPL + (aCL) |
| **6** | 21 | 6 | Depression, psychosis | Cutaneous, arthritis | Recurrent UTI |
| **7**[a] | 32<br>33 | 10<br>11 | Ischemic stroke, seizures | Cutaneous, arthritis, serositis, renal | APS |
| **8** | 40 | 8 | Depression, psychosis | Cutaneous, arthritis | Chronic hypertension |
| **9**[a] | 27<br>28 | 15<br>16 | Seizures, psychosis, amnesia | Cutaneous, arthritis, serositis, renal, hematological | - |
| **10** | 28 | 11 | Seizures | Cutaneous, arthritis, renal, hematological | - |
| **11** | 24 | 3 | Seizures, depression | Cutaneous, arthritis, serositis, renal, hematological | aPL + (LA) |
| **12** | 20 | 6 | Seizures | Cutaneous, arthritis, serositis, renal, hematological | - |
| **13**[a] | 20<br>29 | 0<br>9 | Ischemic stroke | Cutaneous, serositis, renal, hematological | APS |
| **14** | 31 | 2 | Ischemic stroke | Arthritis | - |
| **15** | 33 | 13 | Ischemic stroke | Cutaneous, arthritis, renal, hematological | Chronic hypertension |
| **16** | 38 | 25 | Depression, apathy | Cutaneous, arthritis, renal | Chronic hypertension |
| **17** | 31 | 14 | Seizures, depression | Cutaneous, arthritis, serositis, renal, hematological | APS |

Table 1 - Characteristics of studied patients, including general and neuropsychiatric SLE manifestations (conclusão)

| Patient # | Maternal age (year) | Duration of SLE (year) | Neuropsychiatric manifestations | Other SLE manifestations | Comorbidities |
|---|---|---|---|---|---|
| **18** | 31 | 17 | Seizures | Cutaneous, arthritis, serositis, renal, hematological | - |
| **19** | 32 | 3 | Depression, psychosis | Cutaneous, arthritis, renal, hematological | Hypothyreoidism |
| **20** | 23 | 10 | Ischemic stroke, headeache | Cutaneous, arthritis, renal, hematological | HIV positive (without AIDS manifestations) |
| **21** | 27 | 8 | Seizures, headache | Cutaneous, arthritis, serositis, renal, hematological | - |

[a] Patients with more than one pregnancy during the study period. LA = lupus anticoagulant, aCL = anticardiolipin; UTI = urinary tract infection; APS = antiphospholipid syndrome; aPL = antiphospholipid antibody.

Three patients had APS (14%), all three with positive lupus anticoagulant. Of these, all had previous thrombotic events (deep vein thrombosis and stroke) and two had previous fetal deaths. Two other patients had isolated circulating antiphospholipid antibodies (aPL), without APS. Four pregnant women had chronic hypertension (19%), including one with chronic renal failure on haemodialysis.

**Disease activity**

Activity of SLE at conception, during gestation and in puerperium were documented according to the physician's overall assessment at these times, including clinical and laboratorial analysis. In eleven pregnancies the disease was considered active at conception (42%), three with NP manifestation (11%). However, only in one patient the neurological activity remained during gestation, in the form of chorea, characteristically related to the inadvertent suspension of medications.

Of those with active SLE at conception, seven remained active during gestation and puerperium, with unfavorable fetal outcome in six cases (two intrauterine fetal deaths and four preterm deliveries, including two small for gestational age [SGA] infants). Only one patient was in remission at conception and

had SLE flare during pregnancy, but it was not related to NP manifestations (cuteaneous/serositis). Similarly, eight pregnancies presented SLE activity in the puerperium (30%), but none NP. Table 2 lists those who presented disease activity at conception, gestation or puerperium and their gestational outcome.

Table 2 - Relation of patients who had active SLE at conception, during pregnancy and during puerperium, with sites of activity and outcome of gestation

| Patients | SLE Activity at conception | during pregnancy | during puerperium | Gestational outcome |
|---|---|---|---|---|
| 1 [a] | Neurological, renal | Renal | Renal | Fetal death at 16 weeks |
| 1 [b] | Renal | Renal | Renal | Preterm birth at 35 weeks, NICU |
| 1 [c] | Renal | Renal | Renal | Preterm birth at 34 weeks |
| 2 | Neurological, serositis | Neurological, serositis | --- | Term delivery, uneventful |
| 5 | --- | Serositis, arthritis | --- | Preterm birth at 36 weeks, NICU |
| 6 | Serositis | --- | Cutaneous, arthritis | Term delivery, uneventful |
| 7 [a] | Serositis, arthritis | Serositis, renal | --- | Fetal death at 30 weeks, SGA |
| 7 [b] | Arthritis | Renal | Renal | Preterm birth at 34 weeks, NICU, SGA |
| 9 [b] | --- | --- | Serositis | Fetal death at 27 weeks, preeclampsia |
| 13 [a] | Neurological, arthritis, renal | Renal, arthritis | --- | Fetal death at 18 weeks |
| 15 | Renal | Renal | Renal | Term delivery, uneventful |
| 19 | Cutaneous | Cutaneous, arthritis, renal | Cutaneous | Preterm birth at 34 weeks, NICU, SGA |
| 21 | Renal | Renal | Renal | Fetal death at 23 weeks, preeclampsia, SGA |

[a] first pregnancy; [b]second pregnancy. NICU: Neonatal intensive care unit admission. SGA: small for gestational age infant.

**Intrauterine fetal death**

Of the 26 pregnancies, intrauterine fetal death occurred in six (23%), three before 22 weeks (15, 16 and 18 weeks) and three at 22 weeks or more (23, 27 and 30 weeks). The patients with fetal death at 16 and 18 weeks had active renal disease during conception that persisted during pregnancy. Two patients with stillbirths after

22 weeks had severe early preeclampsia (23 and 27 weeks) and the third stillborn had severe intrauterine growth restriction with 30 weeks, in a patient with associated APS.

**Intrauterine growth restriction / small for gestational age newborns**

Of the 23 newborns with gestational age over 22 weeks, six were SGA (26%); three born prematurely and two stillborn. Ultrasonographic findings of intrauterine growth restriction (IUGR), oligohydramnios and/or altered fetal Dopplervelocimetry were observed in 5/6 fetuses, representing an antenatal detection rate of 83%. The cohort's mean birth weight was of 2,443g (394-3,605g), with 78% of newborns weighing more than 2,000g. In the group of SGA newborns, the mean birth weight was 1,462g (394-2,445g).

**Prematurity - delivery between 22 and 36 weeks and 6 days**

Mean gestational age at delivery was 35.6 weeks (23-40 weeks), with 12 births over 37 weeks (52%), seven between 32 and 36 weeks and 6 days (30%), and four deliveries < 32 weeks (17%). Considering only the live births, the frequency of prematurity was 40% (8 in 20 live births). The SGA infants and patients with preeclampsia had mean gestational age at delivery of 32.5 weeks (23-38) and 33.6 weeks (23-40), respectively.

**Preeclampsia**

Nine pregnancies had preeclampsia (39%). The onset of early severe form, below 32 weeks, was observed in two patients, both evolving with intrauterine fetal death. The mean birth weight of newborns in pre-eclampsia patients was 1,889g (394-3,205g), with four SGA newborns. There were no cases of eclampsia, placental abruption or HELLP syndrome in this group.

**Neonatal Outcome**

Of the 26 pregnancies studied, 20 resulted in the live births (76%). Among them, fourteen were healthy and discharged in 24 to 72 hours (70%). As previously described, three were stillborns and there was no neonatal death.

Six newborns were admitted to NICU, three classified as SGA at birth. The main causes of NICU admission were prematurity, low birth weight and respiratory

distress. No newborn had early complications of prematurity (cardiorespiratory disorders, retinopathy, necrotizing enterocolitis, cerebral haemorrhage) and/or secondary to NICU (neonatal infection, severe respiratory disorder, renal insufficiency).

No newborn had diagnosis of neonatal lupus among six pregnant women with positive anti-Ro/SSA, although one of the babies had a 48-hour skin rash with no other signs, symptoms suggesting neonatal lupus.

**Obstetric outcomes in NPSLE without lupus nephritis**

Considering the seven patients with NPSLE without lupus nephritis, five had term deliveries, including one patient with mild preeclampsia, and the two preterm birth occurred with 36 weeks due to premature rupture of membranes. Only one newborn was SGA and there was no NICU admission in this group.

**Comparison of adverse events between patients with NP and non-NP disease**

Table 3 compares the frequency of SLE activity and adverse obstetric events between patients with NPSLE and patients without those manifestations, excluding those who had abortions. Patients with NPSLE had more prematurity and preeclampsia, with also a trend for more disease activity during pregnancy and SGA infants.

Table 3 - Frequency of SLE-related and adverse obstetric events between patients with neuropsychiatric (NP) manifestations of SLE and patients without NP SLE, excluding abortions (continua)

| At conception | NP SLE (23 pregnancies) | Non-NP manifestations (109 pregnancies) | p value (CI 95%) [a] |
|---|---|---|---|
| SLE Activity during pregnancy | 9 (39%) | 25 (22%) | 0.08 |
| Prematurity | 11 (48%) | 30 (27%) | **0.01** |
| Small for gestational age infant | 6 (26%) | 27 (24%) | 0.87 |
| Preeclampsia | 9 (39%) | 17 (15%) | **0.01** |
| Stillbirth | 3 (13%) | 4 (3%) | 0.10 |
| Gestational age at delivery in weeks (mean $\pm$ SD) | 35.6 $\pm$ 4.3 | 37.0 $\pm$ 3.5 | 0.09 |

Table 3 - Frequency of SLE-related and adverse obstetric events between patients with neuropsychiatric (NP) manifestations of SLE and patients without NP SLE, excluding abortions (conclusão)

| At conception | NP SLE (23 pregnancies) | Non-NP manifestations (109 pregnancies) | p value (CI 95%) [a] |
|---|---|---|---|
| Birth weight in grams (mean) | 2443.4 ± 915 | 2703.5 ± 805 | 0.17 |

[a] Chi square, Fischer exact test and T student test when applicable

**Discussion**

Despite literature reports on maternal-fetal complications of pregnancies in SLE patients, especially with renal manifestations, there are few publications addressing NPSLE in pregnancy. These are included in cohorts or retrospective analysis, but infrequently NPSLE gestational results are studied separately.

Some reports illustrate the potential severity of NPSLE in pregnancy, like the occurrence of transient myelitis with progression to paraplegia and systemic vasculitis with cerebral necrosis, resulting in maternal death (12,13). Another case report described a patient with an uneventful pregnancy, with term cesarean section for active genital herpes, that presented chorea three days postpartum (14).

El-Sayed and colleagues analyzed five NPSLE pregnancies, with three developing neurological activity during pregnancy. In the first case, there were frequent episodes of seizure and headache, with cognitive deficit, disorientation and memory and speech alterations within a year. The gestation occurred without other maternal complications but oligohydramnios was detected at 39 weeks. The second case presented seizures during pregnancy and puerperium, preeclampsia and signs of chronic fetal distress, which resulted in premature delivery. The last patient had chorea and altered mental status since 11 weeks, with posterior severe preeclampsia and fetal growth restriction that required delivery of at 26 weeks. The infant died at 71 days of life (15).

In our cohort, those with NPSLE had a disease activity rate of 42% during pregnancy, higher than described by Smyth et al (25.6%) (2), but lower than reported by Borella et al (57%) (16). The results show disagreement in literature, with some studies evidencing an increased risk of SLE activity during pregnancy and puerperium, while others report a similar risk of reactivation compared to non-pregnant SLE patients (17). This can be explained by the disease heterogeneity,

limited number of patients involved, lack of homogeneous criteria to define disease activity and different treatments used during pregnancy (1).

Most of disease activity reported was related to lupus nephritis, which is directly related to adverse obstetric outcomes (2). Despite the small number of patients, the analysis of gestational results of patients with NPSLE without renal disease in our cohort suggests a favorable outcome overall, without significant morbidity for the mother or the child.

Two patients with NP manifestations during conception had no neurological symptoms during pregnancy, but remained with renal flare and had fetal loss with less than 20 weeks. The third case with NPSLE at conception, although remained with chorea during pregnancy, had favourable outcome with a term healthy newborn. This patient had poor treatment adherence, so chorea was rapidly controlled after medication adjustment.

Considering clinical characteristics of the study population, we found a frequent association of NPSLE and articular manifestation (arthritis/arthralgia) in our cohort, present in 80% of the patients (seventeen cases). The available data on this issue are conflicting and old, with some publications suggesting a negative association between neurological and joint manifestations (10,18), some others suggesting a positive association (19), and others not (20).

Among cutaneous manifestations, only one of the 21 included patients had discoid lesion. Such finding may represent a milder course of SLE and could be a protective factor for NPSLE. Different pathophysiological mechanisms, such as small-vessel non-inflammatory proliferative vasculopathy in NP disease instead of perivascular inflammatory infiltrate that is found in cutaneous lesions, may explain this negative correlation (10).

Studies with non-pregnant patients have found an association of NPSLE with APS, mainly arterial thrombotic events (10,20). Karassa and colleagues found a 44% association between APS and NP manifestations in non-pregnant women. In our study, we did not find such significant association, with only 3 patients presenting an association of NPSLE with APS (10). The same authors described anti-Ro/SSA positivity in 38% of the non-pregnant population, as well as association between anti-Ro/SSA and NP manifestations.

About 20% of pregnancies in patients with lupus end in first trimester abortion or intrauterine fetal death in the second and third trimesters (21). In this study, we

found 23% of gestational losses (six cases): two of the three abortions were associated with severe renal disease at conception and pregnancy, two stillbirths occurred with early preeclampsia and IUGR and the third stillbirth had severe IUGR. Disease activity, specially renal flares, and/or other placenta-mediated obstetric complications (preeclampsia, IUGR) were clearly related to fetal losses.

Intrauterine growth restriction in lupus is observed in up to 30% of pregnancies (2,21,22), similar to our finding of 26%. This justifies screening for IUGR in all SLE patients after 26 weeks of pregnancy (1). IUGR suspicion should be confirmed with appropriate birth weight curves after delivery, which will denote a SGA infant. The 23% rate of SGA newborns in our study is in agreement with the literature for SLE patients.

The preeclampsia incidence in this study was 39%, somewhat higher of the previously described rates 14 to 30% in SLE (4,6,21). As mentioned earlier, the high prevalence of lupus nephritis in this group may have influenced these results. Most of the cases (7/9) occurred with 34 or more weeks and, although three newborns required NICU admission, all had good outcomes, with Apgar's score of $\geq$7 with 5 minutes of birth and no apparent morbidity after discharge. Both cases of preeclampsia with very early presentation (23 and 27 weeks) had also severe renal flare and intrauterine fetal death. This data underscores the necessity of a high-risk pregnancy center prenatal care for those patients, as hypertensive disorders are the first cause of maternal death in Latin America and still a serious public health problem in Brazil (23).

In the same fashion, prematurity plays a significant role in neonatal morbimortality in SLE pregnancies. The prognosis of preterm infants is influenced by gestational age and birth weight and, although 40% of the live births in our analysis were premature, only two cases occurred before 32 weeks. Deliveries before this cut-off, classified as extreme prematurity, confer a higher risk of neurological sequelae, with cerebral palsy rates reaching 12% (24). Despite a NICU admission rate of 30% of live births, all but one related to prematurity, no significant morbidity observed in these concepts.

We did not find newborns with confirmed diagnosis of neonatal lupus despite six pregnant women having anti-Ro/SSA, probably because it is a rare complication (25).

In conclusion, this analysis of a cohort of pregnant SLE patients suggests that NP manifestations during pregnancy are infrequent and not directly related to adverse obstetrical events. The renal disease overlap seems to confer a greater risk to pregnancy outcomes. Further studies, with larger number of patients, are needed to better evaluate the behavior of NPSLE patients during pregnancy and optimize treatment.

**References**

1. de Jesus GR, Mendoza-Pinto C, de Jesus NR et al. Understanding and managing Pregnancy in patients with lupus. Autoimm Dis 2015; 2015:943490.

2. Smyth A, Oliveira GHM, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic Review and Meta-Analysis of pregnancy outcomes in patients with Systemic Lupus Erythematosus and Lupus Nephritis. Clin J Am Soc Nephrol. 2010; 5:2060-2068.

3. Hajighaemi F, Eternadifar M, Bonakdar ZS. Neuropsychiatric manifestations in patients with systemic lupus erythematosus: a study from Iran. Adv Biomed Res 2016; 5:43.

4. Gimovsky ML, Montoro M. Systemic lupus erythematosus and other connective tissue diseases in pregnancy. Clin Obstet Gynecol. 1991; 34:35-50.

5. Abel T, Gladman DD, Urowitz MB. Neuropsychiatric lupus. J Rheumatol 1980; 7:325-33.

6. Buchbinder R, Littlejohn GO, Hall S. Neuropsychiatric manifestations of systemic lupus erythematosus. Aus N Z J Med.1988; 679-84.

7. Estes D, Larson DL. Systemic lupus erythematosus and pregnancy. Clin Obstet Gynecol 1965; 8:307-21.

8. Lee P, Urowitz MB, Bookman AA et al. Systemic lupus erythematosus. A review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis, and prognosis. Q J Med 1977;181:1-32.

9. Feng PH, Cheah PS, Lee YK. Mortality in systemic lupus erythematosus: a 10-year review. Br Med J 1973;4;772-4.

10. Karassa FB, Joannidis JPA, Toulomi G, Boki KA, Moutsopoulos HM. Risk factors for central nervous system involvement in systemic lupus erythematosus. Q J Med 2000; 93:169-174.

11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

12. Inslicht DV, Stein AB, Pomerantz F Ragnarsson KT. Three women with lupus transverse myelitis: case reports and differential diagnosis. Arch Phys Med Rehabil. 1998; 79:456-9.

13. Suzuki Y, Kitagawa Y, Matsuoka Y, Fukuda J, Mizushima Y. Severe cerebral and systemic necrotizing vasculitis developing during pregnancy in a case of systemic lupus erythematosus. J Rheumatol 1990; 17:1408-11.

14. Wolf RE, Mc Beath JG. Chorea gravidarum in systemic lupus erythematosus. J Rheumatol 1985; 12:992-3.

15. El-Sayed YY, Lu EJ, Genovese MC, Lambert RE, Chitkara U, Druzin ML. Central nervous system lupus and pregnancy: 11-year experience at a single center. J Mat-Fetal Neonat Med 2002; 12(2): 99-103

16. Borella E, Lojacono M, GattoM et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunol Res 2014; 60 (no2-3);170-176.

17. Doria A, Tincani A, Lockshin M. Challenges of lupus pregnancies. Rheumatol 2008; 47(3): iii9-iii12.

18. Vlachoyiannopoulos PG, Karassa FB, Karakostas KX, Drosos AA, Moutsopoulos HM. Systemic lupus erythematosus in Greece. Clinical features, evolution and outcome: a descriptive analysis of 292 patients. Lupus 1993; 2:303-12.

19. West SG, Emlen W, Werner MH, Kotzin BL. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am J Med. 1995; 99:153-63.

20. Toubi E, Khamashta MA, Panarra A, Hughes GRV. Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. Am J Med 1995; 99:397-401.

21. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol. 2013; 27(3):435-47.

22. Soh MC, Dib F, Nelson-Piercy C, Westgren M, McCowan L, Pasupathy D. Maternal-placental syndrome and future risk of accelerated cardiovascular events in Parous Swedish women with systemic lupus erythematosus - a population-based retrospective cohort study with time-to-event analysis. Rheumatology (Oxford) 2016; 55(7):1235-42.

23. Barbosa IR, Silva WB, Cerqueira GS, Novo NF, Almeida FA, Novo JL. Maternal and fetal outcome in women with hypertensive disorders of pregnancy: the impact of prenatal care. Ther Adv Cardiovasc Dis. 2015 Aug; 9(4):140-6.

24. Baschat AA. Neurodevelopment after fetal growth restriction. Fetal Diagn Ther 2014; 36:136-142.

25. Burch JM, Lee LA, Weston WL. Neonatal lupus erytematosus. Dermatol Nurs 2002; 14:157-160.

# 5 ESTUDO 2 - THE IMPACT OF DIFFERENT CLASSES OF LUPUS NEPHRITIS ON MATERNAL AND FETAL OUTCOMES: A COHORT STUDY OF 147 PREGNANCIES (Artigo publicado)*


## Abstract

**Objective** To analyze the impact of different classes of lupus nephritis (LN) as risk variables for maternal and fetal adverse outcomes in a cohort of pregnant lupus patients.

**Methods:** This is a cohort study with retrospective and prospective data collection, conducted in the University Hospital of State University of Rio de Janeiro, Brazil, from 2011 to 2016. A total of 147 pregnancies of 137 systemic lupus erythematosus (SLE) patients of whom 66 had LN were included. Demographic and clinical features, as well as maternal and fetal outcomes were observed for each nephritis histological class among SLE patients and compared with those without nephritis. Categorical variables were expressed as absolute and relative frequencies and numerical variables as means and standard deviation. The chi-square test with Fisher's correction and Student's *t*-test were used for statistical analysis. A *P* value of < 0.05 was considered statistically significant.

**Results:** SLE patients with proliferative nephritis (Classes III / IV, n=54) presented more frequently disease flares (*P* =0.02), continuous active disease during pregnancy and puerperium (*P*=0.006), hospitalization due to SLE (p<0.001), hospitalization not directly associated to SLE (*P*=0.04), higher frequency of cesarean delivery (*P*=0.03) and preeclampsia (*P*=0.01) than patients without nephritis. Permanent damage, measured by SLICC/ACR damage index (SDI) was more frequent in classes III / IV than among the other patients. The frequency of adverse fetal outcomes such as prematurity and admission to neonatal intensive care unit were not different among SLE patients with or without nephritis. However, perinatal deaths were more frequent in patients with all classes of nephritis (*P*=0.003).

**Conclusion:** SLE patients with proliferative nephritis (classes III / IV) have a higher frequency of adverse maternal outcomes. This is probably due to the major impact of


*Rodrigues BC et al. The impact of different classes of lupus nephritis on maternal and fetal outcomes: a cohort study of 147 pregnancies. Lupus 2019;28(4):492-500. DOI: 10.1177/0961203319829825.

proliferative forms of nephritis on women global heath, which is corroborated by the higher SDI found, although we can not exclude the ominous influence of disease activity for the maternal adverse events. The findings indicate a need for further LN classification beyond the nonspecific term nephritis in the context of lupus pregnancy as the impact on maternal and fetal outcomes varies according to histological classes.

**Keywords**

Systemic lupus erythematosus, renal lupus, nephritis, pregnancy

## Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that has a variable clinical course, ranging from mild to severe forms. Lupus nephritis (LN) occur in about 60% of patients and is the most common indication for high doses of steroids, immunosuppressive therapy and hospitalization, leading to the highest morbidity and mortality among SLE manifestations (1-3).

During pregnancy, history of LN has been independently associated with increased risk of adverse maternal outcomes, which are even more frequent when nephritis is active at conception (4-6). Increased fetal morbidity is also found in association with LN, regardless of the presence of antiphospholipid antibodies (5, 6).

However, the term "lupus nephritis" encompasses a broad spectrum of renal involvement that are different from one another regarding clinical manifestations including levels of proteinuria, potential risk of renal insufficiency and the need of therapeutic immunosuppression. From a prognostic point of view and for treatment purposes, LN is classified according to histological findings in renal biopsy (classes I-VI). However, it may not be possible to perform a biopsy and for therapeutic purposes, renal involvement is classified by inference based on clinical and laboratory parameters, despite its inaccuracy (3).

The most severe forms of LN are the proliferative classes (III and IV), while mesangial glomerulonephritis (classes I and II) show little or no interference with renal function, have generally low levels of proteinuria and probably have no impact in pregnancy. Patients with membranous LN (class V) have characteristically high levels of proteinuria, without significant reduction of glomerular filtration rate, no dysmorphic hematuria on urinalysis, no hypertension, normal complement levels and

no anti-dsDNA antibodies. Due to the great variability of morbidity among distinct lupus glomerulonephritis, it is reasonable that the studies on the impact of nephritis on gestation should take into account the different histological classes. Nevertheless, most studies about lupus pregnancy include all LN classes as a single variable. At the same time, currently available data come mostly from small samples of Caucasian women whose disease is frequently in remission (4, 9, 10). Thus, in order to allow a more accurate interpretation of the actual influence of LN on gestational outcomes, it is necessary to include data of LN histological classification besides disease activity and other clinical variables.

The present study aims to analyze risk variables for maternal and fetal adverse outcomes in a cohort of pregnant patients with SLE followed at a tertiary referral center for high-risk pregnancies, comparing patients with different histological classes of lupus nephritis to those without LN.

**Methods**

A total of 176 pregnancies in SLE patients were identified in the cohort of patients with rheumatic diseases, followed at the State University of Rio de Janeiro Obstetrics Unit between 2011 and 2016. Twenty-nine patients were excluded for the following reasons: ten did not meet four American College of Rheumatology (ACR) SLE classification criteria (11); eight delivered before 22 weeks (miscarriages), three with fetal aneuploidy, one with fetal malformations due to mother's use of mycophenolate at conception, two with twin pregnancies and five cases that have not been submitted to renal biopsy (four presented nephrotic syndrome and one, acute renal failure probably not related to SLE) and despite presenting LN, we were not able to establish appropriately nephritis classes by inference. Thus, we included 147 pregnancies from 137 SLE patients whose socio-demographic data, outcome of the maternal disease (SLE) and gestational complications were obtained by a review of medical records including the period prior to gestation, during pregnancy and puerperium. Data were collected retrospectively from 2011 to 2015 and prospectively in 2016. There were 81 patients without LN and 66 cases of LN, among which 6 cases were mesangial (class II) LN, 54 cases were proliferative (classes III or IV) LN and 6 cases were membranous (class V). Fifty three patients (80,3%) with LN who have been submitted to renal biopsies were classified according to the ISN/RPS classification (7) and 13 out of the 66 SLE patients with nephritis, were classified by

inference based on clinical and laboratory findings according to published criteria (3) and rheumatologist judgement (3 with mesangial and 10 with proliferative LN). The local Institutional Ethics Commitee approved the study. Demographic and clinical features were recorded, including maternal age at delivery, parity and ethnicity, years since the diagnosis of SLE, disease activity at conception, association with antiphospholipid (aPL) syndrome and/or aPL antibodies, systemic arterial hypertension and permanent damage defined by SLICC/ACR - damage index (SDI) (12). Maternal and fetal complications were described and compared among patients with different LN classes and those without LN. The outcomes were: SLE activity during pregnancy (continuous since conception or flare); hospitalization related and not related to SLE, maternal infection, preeclampsia, cesarean delivery for maternal or fetal compromise, peripartum hemorrhage and adverse fetal outcomes such as prematurity, small for gestational age newborns, admission to NICU and perinatal death.

Disease activity was defined by a rheumatologist experienced on evaluating pregnant SLE patients at each visit and it took into consideration clinical and laboratory findings as well as specific therapeutic adjustments due to disease activity (initiation or increase of dose of steroids and/or immunosuppressive agents) as a binary variable. Nephritic and proteinuric flares were analyzed together as renal activity. Active nephritis was defined as the development of new proteinuria (> 500 mg/24h) when it was previously under 500 mg/24h or > 2,000 mg/24h when it was previously over 500 mg/24h or presence of active urinary sediment (> 5 red blood cells or leukocytes per large magnification field 400X or presence of cell casts), presence of glomerular pattern dysmorphic hematuria (> 50% among urinary red blood cells) or elevated serum creatinine due to LN (2-5).

Proteinuria measurements were obtained from isolated urine samples using proteinuria/creatinine ratio or measured in 24 hours. Preeclampsia was defined as the occurrence of hypertension and proteinuria above 300 mg/24h after 20 weeks of gestation or the onset or worsening of hypertension (increase ≥ 15 mmHg) and twice the proteinuria in a patient with previous proteinuria, without active nephritis (10,13). All cases classified as preeclampsia had the diagnosis confirmed after delivery.

For statistical analysis, categorical variables were treated as absolute and relative frequencies and numerical variables as means and standard deviation (SD), after the performance of Shapiro-Wilk normality test. The chi-square test with Fisher's

correction and Student's *t*-test were used to analyze the variables among the groups. A *P* value of < 0.05 was considered statistically significant.

## Results

A total of 147 pregnancies of 137 patients with SLE were analyzed. The majority were Afro-descendant (56.1%) and primiparous (52.1%). The mean maternal age at delivery was 28.4 ± 6.1 years and the mean duration of SLE was 7.4 ± 5.3 years. These variables were not different (*P*>0.05) among the different classes of LN and patients without LN (Class II = 29.0 ± 6.1 and 6.8 ± 5.6; Classes III and IV = 27.3 ± 6.8 and 7.8 ± 5.0; Class V = 27.4 ± 6.2 and 7.9 ± 5.0; without nephritis = 28.9 ± 6.1 and 6.9 ± 5.6, in years, respectively). Permanent damage measured by SDI ≥ 1 was present in 38 (25.9%) of all SLE patients, in 15 (18.5%) without nephritis and was higher among proliferative LN patients (22 cases, 40.7%, *P* =0.02 in comparison to all patients). Antiphospholipid syndrome was present in 18 (12.2%) among 147 SLE patients, 2 (33.3%) in mesangial LN patients, 7 (13%) in proliferative LN patients and in 9 (11.1%) patients without nephritis. Systemic arterial hypertension was found in 28 (19.1%) SLE patients, in 1 (16.7%) with mesangial LN patients, in 22 (40.7%) with proliferative LN patients and in 5 (6.2%) patients without nephritis. Table 1 shows the demographic and clinical data.

Table 1 - Main clinical and demographic features (continua)

| **Variable** | **All SLE$^{\alpha}$ pregnancies** | **Class II*** | **Classes III / IV**** | **Class V***** | **Without LN $^{\beta}$** |
|---|---|---|---|---|---|
| | **n=147** | **n=6** | **n=54** | **n=6** | **n=81** |
| Maternal age (years) $^{\#}$ mean ± SD | 28.4 ± 6.1 | 29.0 ± 6.1 | 27.3 ± 6.8 | 27.4 ± 6.2 | 28.9 ± 6.1 |
| Ethnicity Afrodescendent | 82 (56.1%) | 5 (83.3%) | 27 (50%) | 2 (33.3%) | 48 (60%) |
| Parity | | | | | |
| 0 | 76 (51.7%) | 4 (66,7%) | 30 (55.5%) | 5 (83.3%) | 37 (45.7%) |
| ≥ 1 | 71 (48.3%) | 2 (33,3%) | 24 (44.5%) | 1 (16.7%) | 44 (54.3%) |
| SLE duration (years) mean ± SD | 7.4 ± 5.3 | 6.8 ± 5.6 | 7.8 ± 5.0 | 7.9 ± 5.0 | 6.9 ± 5.6 |
| SDI $^{\Omega}$ ≥ 1 | 38 (25.9%) | 0 | 22 (40.7%) | 1 (16.7%) | 15 (18.5%) |

Table 1 - Main clinical and demographic features (conclusão)

| Variable | All SLE[α] pregnancies | Class II* | Classes III / IV** | Class V*** | Without LN [β] |
|---|---|---|---|---|---|
| | n=147 | n=6 | n=54 | n=6 | n=81 |
| Non-renal SDI [Ω] ≥ 1 | 31 (21.1%) | 0 | 15 (27,8%) | 1 (16.7%) | 15 (18.5%) |
| Active disease at conception | 41 (27.9%) | 0 | 19 (35.2%) | 2 (33.3%) | 20 (25%) |
| Systemic activity | 30 (20.5%) | 0 | 10 (18.5%) | 0 | 20 (25%) |
| Renal activity | 21 (14.3%) | 0 | 19 (35.1%) | 2 (33.3%) | 0 |
| Antiphospholipid syndrome | 18 (12.2%) | 2 (33.3%) | 7 (13%) | 0 | 9 (11.1%) |
| Systemic arterial hypertension | 28 (19.1%) | 1 (16.7%) | 22 (40.7%) | 0 | 5 (6.2%) |

Categorical data were expressed by frequency (n) and percentage (%) and numerical data by means and standard deviation. α- SLE- systemic lupus erythematosus; β LN - lupus nephritis; SD- Standard deviation; Ω- SLICC/ACR-DI- Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. *Class II- mesangial. **Class III- focal proliferative. **Class IV-diffuse proliferative. ***Class V-membranous. # age at delivery compared with Student t test.

Permanent damage measured by SDI ≥ 1 was more frequent in the group of proliferative LN compared to the group of all lupus patients (*P*=0.001). Systemic arterial hypertension was also significantly more frequent in proliferative LN than in patients without LN (*P*=0.001) and these patients (classes III and IV) presented more frequently global disease activity at conception (35.2% versus 25%; *P*=0.02).

In reference to maternal outcomes, the group with proliferative LN also presented more commonly persistent disease activity along pregnancy and puerperium (33.3% versus 14.8%; *P*=0.006) and SLE flares during pregnancy and puerperium (20.4% versus 8.6%; *P*=0.02) when compared to patients without nephritis. Considering the 44 patients with active SLE during pregnancy, 35 (79%) were treated with prednisone associated with azathioprine, 7 (16%) were treated with prednisone alone and 1 (2%) with azathioprine alone. Among patients with LN classes III/IV and active SLE, 92% received prednisone associated with azathioprine, 48% of them used prednisone in doses greater than or equal to 20 mg / day. Five patients received methylprednisolone pulse therapy for severe renal activity, four of them with biopsy-proven proliferative nephritis.

Hospitalization directly associated with SLE (35.1% versus 16%; *P*<0.001) and due to problems not specifically associated with SLE (33.3% versus 19.7%; *P*=0.04) were also more frequent in the proliferative LN group, as well as preeclampsia (31.5% versus 16%; *P*=0.01) and cesarean delivery for maternal or fetal compromise (*P*=0.03). There was a trend to higher risk of peripartum hemorrhage (*P*=0.07) in the proliferative LN group and no difference in the frequency of infection between proliferative LN patients and patients without LN (Table 2).

Table 2 - Adverse outcomes among SLE patients with lupus nephritis according to histological classes and without nephritis (continua)

| **Variable** | **Without Nephritis** **n=81** | **Nephritis All Classes** **n=66** | ***P* value** | **Classes II* and V**** **n=12** | **P value** | **Classes III# and IV##** **n=54** | ***P* value** |
|---|---|---|---|---|---|---|---|
| SLE flare in pregnancy or puerperium α | 7 (8.6%) | 12 (18.2%) | 0.04 | 1 (8.3%) | 0.47 | 11 (20.4%) | 0.02 |
| Maintenance of active SLE in pregnancy / puerperium | 12 (14.8%) | 19 (28.8%) | 0.02 | 1 (8.3%) | 0.30 | 18 (33.3%) | 0.006 |
| Hospitalization due to SLE during pregnancy | 13 (16%) | 20 (30.3%) | 0.02 | 1 (8.3%) | 0.27 | 19 (35.1%) | <0.001 |
| Hospitalization not related to SLE | 16 (19.7%) | 21 (31.8%) | 0.04 | 3 (25%) | 0.33 | 18 (33.3%) | 0.04 |
| Infection | 25 (30.9%) | 24 (36.4%) | 0.26 | 5 (41.7%) | 0.23 | 19 (35.2%) | 0.30 |
| Preeclampsia | 13 (16.0%) | 18 (27.3%) | 0.05 | 1 (8.3%) | 0.27 | 17 (31.5%) | 0.01 |
| Cesarean delivery Ω | 12 (14.8%) | 17 (25.8%) | 0.05 | 2 (16.7%) | 0.4 | 15 (27.8%) | 0.03 |
| Peripartum hemorrhage | 9 (11.1%) | 11 (16.7%) | 0.17 | 0 | 0.13 | 11 (20.3%) | 0.07 |
| Adverse fetal outcome (except perinatal death) | 32 (39.5%) | 28 (42.4%) | 0.36 | 2 (16.7%) | 0.06 | 26 (48.1%) | 0.16 |

Table 2 - Adverse outcomes among SLE patients with lupus nephritis according to histological classes and without nephritis (conclusão)

| Variable | Without Nephritis n=81 | Nephritis All Classes n=66 | *P* value | Classes II* and V** n=12 | P value | Classes III# and IV## n=54 | *P* value |
|---|---|---|---|---|---|---|---|
| Perinatal death | 2 (2.5%) | 10 (15.1%) | 0.003 | 3 (25%) | 0.007 | 7 (13%) | 0.01 |

Categorical data were expressed by frequency (n) and percentage (%) and compared by the Chi-square. Comparisons were made between each nephritis group versus group without nephritis. * Class II- mesangial. ** Class V-membranous. # Class III- focal proliferative. ## Class IV-diffuse proliferative. α- SLE flares with inactive disease at conception. SLICC/ACR-DI= Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Ω Cesarean delivery due to maternal and/or fetal compromise. Adverse fetal outcome included prematurity, small for gestational age newborn, admission to neonatal intensive care unit.

As disease activity might have influenced maternal outcomes, we analyzed data controlling for the presence of disease activity. Among the 44 patients with active SLE during pregnancy (25 with LN classes III/IV in comparison to 17 without LN) we found a higher frequency of PE (28% *versus* 11%), hospitalization directly associated to SLE (68% *versus* 41%) and infections during pregnancy (56% *versus* 47%) but the differences did not achieve statistical significance.

The analysis of main maternal adverse outcomes (systemic disease activity, hypertension, hospitalizations, preeclampsia and hemorrhage) in patients with mesangial and membranous lupus nephritis showed no significant differences in comparison to the group without nephritis (*P*>0,05 for all variables). These two classes of LN were put together for analysis purposes due to small number of cases (6 each) in the present cohort and similarity of clinical behavior during pregnancy.

In order to analyze if LN class inference could have influenced the results, we proceeded a full analysis of data considering only the patients who have been submitted to renal biopsy. Most of the results did not change significantly and SLE patients with classes III/IV LN in comparison to those without nephritis, still presented more frequently disease flare, maintenance of disease activity, hospitalization due to SLE, cesarean delivery, peripartum hemorrhage, adverse fetal outcome and perinatal death all with statistical significance. However the frequency of preeclampsia and hospitalization not related to SLE was not statistically different between the groups. Considering the current practice of LN classification by inference for clinical purposes, we assume that inclusion of patients whose classification was done by

inference is more accurate for clinical practice and pregnancy management among SLE patients.

The frequency of adverse fetal outcome (including perinatal deaths) was higher among LN patients (57.6%) in comparison to patients without LN (42%; *P*=0.03). Nonetheless, the same comparison of adverse fetal outcomes between groups (with and without LN) excluding unsuccessful pregnancies (complicated by perinatal deaths), showed no differences (39.5% for those without LN and 42.2% for LN; *P*=0.36) and perinatal deaths analyzed as a specific adverse outcome were significantly higher among LN patients (15.1% *versus* 2.5%; *P*=0.003; table 2).

Within patients with LN, the analysis of fetal morbidity among mesangial and membranous nephritis (classes II / V) in comparison to those with proliferative nephritis (III / IV) evidenced a higher frequency of fetal morbidity in the latter (16.7% *versus* 48.1%; *P*=0.02), but not of perinatal deaths (*P*=0.16), as shown on table 3.

Table 3 - Comparison of adverse outcomes between SLE patients with nephritis classes II and V and nephritis classes III and IV (continua)

| **Variable** | **Classes II* and V** n=12** | **Classes III# and IV## n=54** | ***P* value** |
|---|---|---|---|
| SLE α flare in pregnancy / puerperium (inactive at conception) | 1 (8.3%) | 11 (20,4%) | 0.18 |
| Maintenance of active SLE in pregnancy / puerperium | 1 (8.3%) | 18 (33.3%) | 0.04 |
| Hospitalization due to SLE during pregnancy | 1 (8.3%) | 19 (35.1%) | 0.03 |
| Hospitalization not related to SLE | 3 (25%) | 18 (33.3%) | 0.30 |
| Infection | 5 (41.7%) | 19 (35.2%) | 0.33 |
| Preeclampsia | 1 (8.3%) | 17 (51.5%) | 0.05 |
| Cesarean delivery for maternal or fetal compromise | 2 (16.7%) | 15 (27.8%) | 0.23 |
| Peripartum Hemorrhage | 0 | 11 (20.3%) | 0.04 |

Table 3 - Comparison of adverse outcomes between SLE patients with nephritis classes II and V and nephritis classes III and IV (conclusão)

| Variable | Classes II* and V** n=12 | Classes III# and IV## n=54 | *P* value |
|---|---|---|---|
| Adverse fetal outcome (except perinatal death) | 2 (16.7%) | 26 (48.1%) | 0.02 |
| Perinatal death | 3 (25%) | 7 (13%) | 0.16 |

Categorical data were expressed by frequency (n) and percentage (%) and compared by the Chi-square. * Class II- mesangial. ** Class V-membranous. # Class III- focal proliferative. ## Class IV-diffuse proliferative. α - SLE- systemic lupus erythematosus.

The presence of any permanent damage (SDI ≥ 1) was associated with more frequent hospitalization due to active disease during pregnancy (*P*=0.02), hospitalization not related to SLE (*P*=0.03), cesarean delivery for maternal or fetal compromise (*P*=0.02) and peripartum hemorrhage (*P*=0.02). The non-renal SDI did not present any statistical association with maternal or fetal adverse outcome (table 4).

Table 4 - Maternal and fetal adverse outcomes between SLE patients with and without permanent damage by SDI (continua)

| Variable | SDI α =0 n= 109 | SDI α ≥ 1 n= 38 | *P* value | Non-renal SDI α ≥ 1 n= 15 | *P* value |
|---|---|---|---|---|---|
| SLE β flare in pregnancy / puerperium (inactive at conception) | 10 (9.1%) | 5 (13.1%) | 0.24 | 0 | 0.08 |
| Maintenance of active SLE in pregnancy / puerperium | 1 (0.9%) | 1 (2.6%) | 0.25 | 1 (6.6%) | 0.28 |
| Hospitalization due to SLE during pregnancy | 20 (18.3%) | 13 (34.2%) | 0.02 | 5 (33.3%) | 0.48 |
| Hospitalization not related to SLE | 23 (21.1%) | 14 (36.8%) | 0.03 | 7 (46.6%) | 0.26 |
| Infection | 35 (32.1%) | 14 (36.8%) | 0.29 | 7 (46.6%) | 0.26 |

Table 4 - Maternal and fetal adverse outcomes between SLE patients with and without permanent damage by SDI (conclusão)

| Variable | SDI $^{\alpha}$ =0 n= 109 | SDI $^{\alpha}$ ≥ 1 n= 38 | *P* value | Non-renal SDI $^{\alpha}$ ≥ 1 n= 15 | *P* value |
|---|---|---|---|---|---|
| Infection | 35 (32.1%) | 14 (36.8%) | 0.29 | 7 (46.6%) | 0.26 |
| Preeclampsia | 26 (23.8%) | 11 (28.9%) | 0.26 | 4 (26.6%) | 0.44 |
| Cesarean delivery for maternal or fetal compromise | 63 (57.7%) | 15 (39.4%) | 0.02 | 8 (53.3%) | 0.19 |
| Peripartum Hemorrhage | 11 (10.1%) | 9 (23.6%) | 0.02 | 2 (13.3%) | 0.22 |
| Adverse fetal outcome (except perinatal death) | 42 (38.5%) | 18 (47.3%) | 0.17 | 4 (26.6%) | 0.09 |
| Perinatal death | 8 (7.3%) | 4 (10.5%) | 0.27 | 1 (6.6%) | 0.36 |

Categorical data were expressed by frequency (n) and percentage (%). and compared by the Chi-square. $^{\alpha}$ - SLICC/ACR-DI- Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. $^{\beta}$ - SLE-systemic lupus erythematosus.

## Discussion

SLE patients with proliferative nephritis presented more frequently adverse maternal and fetal outcomes, including disease activity during pregnancy and puerperium, need for hospitalization, preeclampsia and adverse fetal outcomes including unsuccessful pregnancies in comparison to SLE pregnant patients without nephritis. On the other hand, the frequencies of maternal and fetal adverse outcomes in patients with mesangial and membranous nephritis were not different in comparison to those found among patients without nephritis, except for fetal deaths, which may have been due to APS present in two among the three patients of this latter group.

These data brings light to the need for more detailed LN classification whenever leading with pregnancy among patients with SLE and nephritis. The few studies that included histological classes as a variable to interpret pregnancy course emphasized the presence of LN classes III and IV as risk factors for adverse outcomes, including a higher risk of maternal complications, a higher risk of systemic

and renal reactivation (17). Activity at conception was found to confer a 50-fold risk of flare occurrence during gestation (18) and patients with LN are described to have a higher frequency of activity at conception than those without LN (17). In fact, one fourth of all SLE patients in this cohort had active disease at conception, which demonstrate the low adherence to pregnancy planning including the use of inappropriate contraception methods in the scenario of LN treatment.

Despite the similar frequency of disease activity at conception, patients with proliferative classes presented more frequently flares and continuous activity in comparison to patients without nephritis or with classes II or V. It is possible that it may have occurred due to the restriction to employ more effective agents to treat most patients with proliferative disease. Disease activity at conception is probably also related to the low frequency of complete remission achieved by LN patients, especially for those with proliferative classes (3), aggravated by a local adherence rate to pharmacological therapy found to be of 31.7% for non-pregnant SLE patients (19). In this study, 31.8% of patients with LN had active disease at conception.

Previous studies also demonstrated that almost half of patients with active LN at conception present renal flares and up to 20% of patients with LN on remission at conception will present renal reactivation during pregnancy (1, 2, 8-10). Renal activity may require hospital admission due to the risk imposed for both mother and fetus, which explains the higher rate of hospitalization directly related to SLE in patients with proliferative LN (35.1%). Although patients with proliferative nephritis had more hospital admissions, there was no case of maternal death. This outcome has been reported by different authors to be present in up to 1% of LN patients (8).

The impact of LN class II and V on pregnancy has not been thoroughly studied as most series have included small number of cases. We have also included few cases of mesangial and membranous nephritis, but we could identify that these patients behave more like the ones without nephritis and did not develop most maternal and fetal adverse outcomes found among proliferative classes. The three cases of fetal death among patients with LN class II and V were probably more associated to the antiphospholipid syndrome present in two SLE mothers in this group. We might interpret that mesangial and membranous LN might not influence pregnancy outcomes, but studies with larger number of patients with LN classes II and V are needed to adequately clarify this issue.

The incidence of preeclampsia (PE) in the United States ranges from 9-35% in SLE patients, compared to 5-8% in healthy women (1, 2, 9, 10, 20). In this study, 31.5% of patients with proliferative LN had PE, despite the prophylactic use of low-dose aspirin in the majority of patients (70%) (21).The highest rates of PE are reported in unplanned pregnancies with active LN before conception (1), which unfortunately is the reality of our population and could have contributed to this elevated frequency. Despite the possible influence of disease activity, nephritis activity and even APS on the increased frequency of preeclampsia found among patients with proliferative nephritis, we cannot exclude the potential impact of systemic arterial hypertension (SAH) *"per se"* on the development of PE, as 40% of patients with proliferative nephritis presented SAH, a common clinical feature of this class of nephritis (10).

Despite it has not been previously described, the association between permanent damage according to SDI and pregnancy morbidity is in accordance to the morbidity and mortality previously associated with accrual damage reported in non pregnant SLE patients (15). We identified an association of SDI ≥ 1 with all causes of hospitalization during pregnancy, cesarean delivery for maternal or fetal compromise and peripartum hemorrhage which may confirm its value as a marker of higher morbidity. However, we could not assure that the attributed value (SDI ≥ 1) is an independent marker of risk, as it may be too strictly associated with the clinical course of proliferative nephritis that presents frequently proteinuria for six months and the analysis of non-renal SDI was not associated with any adverse outcome. On the other hand, its use as a variable of analysis may help to identify those patients with higher risk for obstetric complications.

Even though SLE activity during conception can represent a flaw in preconception counseling, unplanned pregnancy is not infrequent in Brazil (14). This, however, allowed this study to better estimate the impact of disease activity during conception compared to other studies, when a significant number of patients became pregnant during remission.

The study published by Bramham et al. (1) did not find any association between LN classes and adverse maternal events despite the higher rates of maternal complications among patients with LN in comparison to patients without nephritis. The series included mainly patients with quiescent LN and preserved renal function even considering a 60 % of cases with classes III/IV (26/43). It is possible

that the absence of any difference among histological classes and maternal outcomes be due to the small sample of LN included, lower frequency of active disease at conception and also due to the lower severity of the SLE patients studied.

Although some previous studies intended to evaluate gestational results according to histologic subclass of nephritis and suggested a more unfavorable outcome in patients with proliferative forms of nephritis, the whole amount of patients enrolled in such analysis, including the present one is relatively small (8).

This study has limitations. This is a real world cohort of pregnant SLE patients with multiethnic origin followed at a single center that included a large group of different LN classes many with active disease at the time of conception.

Not all patients were submitted to renal biopsy in order to histologically confirm the class of nephritis, which may lead to erroneous interpretation of the results as inference was employed for 13 out of 66 patients (19.6%). Most cases were assumed as proliferative nephritis (10 patients), which is the more typical severe nephritis presentation. Despite its inaccuracy, inference of class is a commonly employed expedient during clinical practice mainly for guiding therapeutic protocols and to establish prognosis (3). It is possible that we could not find association of classes II and V LN with adverse maternal and fetal outcome because of the small number of patients in each class.

The disease activity definition relied on the rheumatologists' interpretation, including the need for intensifying treatment and observation of results along the time course during pregnancy. This can be troublesome in some scenarios, specially differentiating nephritis from preeclampsia (16), but all current available clinical and laboratorial parameters were employed to provide the definite diagnosis through discussions between rheumatologists and obstetricians. In addition, retrospective analysis of data allowed the authors to review some initial diagnosis provided by assistant physicians, as new data could have emerged later.

In conclusion, SLE patients with proliferative nephritis (classes III and IV) but not mesangial (class II) and membranous (class V) have a higher frequency of adverse maternal and fetal outcomes in comparison to SLE patients without nephritis. This is probably due to the major impact of proliferative nephritis on the health of the pregnant woman, corroborated by a higher permanent damage measured by SDI, although as these patients also presented higher frequency of disease flares during pregnancy, we can not exclude the ominous influence of

disease activity for the maternal adverse events. The adequate attribution of risk for different classes of lupus nephritis may contribute to more specific approaches depending on the histological classification, including appropriate information on risk factors to adverse outcomes to the patients.

**References**

1. Bramham K, Hunt BJ, Bewley S, Germain S, Calatayud I, Khamashta MA, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol. 2011;38(9):1906-13.

2. Koh JH, Ko HS, Lee J, Jung SM, Kwok SK, Ju JH, et al. Pregnancy and patients with preexisting lupus nephritis: 15 years of experience at a single center in Korea. Lupus. 2015;24(7):764-72.

3. Klumb EM, Silva CA, Lanna CC, Sato EI, Borba EF, Brenol JC, et al. [Consensus of the Brazilian Society of Rheumatology for the diagnosis, management and treatment of lupus nephritis]. Rev Bras Reumatol. 2015;55(1):1-21.

4. Buyon JP, Kim MY, Guerra MM, Lu S, Reeves E, Petri M, et al. Kidney Outcomes and Risk Factors for Nephritis (Flare/De Novo) in a Multiethnic Cohort of Pregnant Patients with Lupus. Clin J Am Soc Nephrol. 2017;12(6):940-6.

5. Stanhope TJ, White WM, Moder KG, Smyth A, Garovic VD. Obstetric nephrology: lupus and lupus nephritis in pregnancy. Clin J Am Soc Nephrol. 2012;7(12):2089-99.

6. Blom K, Odutayo A, Bramham K, Hladunewich MA. Pregnancy and Glomerular Disease: A Systematic Review of the Literature with Management Guidelines. Clin J Am Soc Nephrol. 2017;12(11):1862-72.

7. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15(2):241-50.

8. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5(11):2060-8.

9. Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. Rheumatology (Oxford). 2013;52(6):1070-6.

10. Moroni G, Doria A, Giglio E, Tani C, Zen M, Strigini F, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. J Autoimmun. 2016;74:6-12.

11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

12. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol. 2000;27(2):373-6.

13. Gianfreda D, Quaglini S, Frontini G, Raffiotta F, Messa P, Moroni G. Does pregnancy have any impact on long term damage accrual and on the outcome of lupus nephritis? J Autoimmun. 2017;84:46-54.

14. Prietsch SO, Gonzalez-Chica DA, Cesar JA, Mendoza-Sassi RA. [Unplanned pregnancy in Southern Brazil: prevalence and associated factors]. Cad Saude Publica. 2011;27(10):1906-16.

15. Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis. 2015;74(9):1706-13.

16. de Jesus GR, de Jesus NR, Levy RA, Klumb EM. The use of angiogenic and antiangiogenic factors in the differential diagnosis of pre-eclampsia, antiphospholipid syndrome nephropathy and lupus nephritis. Lupus. 2014;23(12):1299-301.

17. Saavedra MA, Cruz-Reyes C, Vera-Lastra O, Romero GT, Cruz-Cruz P, Arias-Flores R, et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. Clin Rheumatol. 2012;31(5):813-9.

18. Borella E, Lojacono A, Gatto M, Andreoli L, Taglietti M, Iaccarino L, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunol Res. 2014;60(2-3):170-6.

19. Oliveira-Santos M, Verani JF, Klumb EM, Albuquerque EM. Evaluation of adherence to drug treatment in patients with systemic lupus erythematosus in Brazil. Lupus. 2011;20(3):320-9.

20. Lv J, Wang W, Li Y. Clinical outcomes and predictors of fetal and maternal consequences of pregnancy in lupus nephritis patients. Int Urol Nephrol. 2015;47(8):1379-85.

21. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010;116(2 Pt 1):402-14.

# 6 ESTUDO 3 - VEGF, PLGF AND SFLT-1 SERUM LEVELS ALLOW DIFFERENTIATION BETWEEN ACTIVE NEPHRITIS AND PREECLAMPSIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (Artigo submetido)*

## Introduction

Pregnancy in patients with systemic lupus erythematosus (SLE) is associated with significant morbidity and mortality compared to general population, including increased risk of disease activity, hypertension, pregnancy loss, preterm delivery, intrauterine growth restriction and preeclampsia (1, 2). Active lupus nephritis (LN) during pregnancy makes the differential diagnosis with preeclampsia (PE) troublesome in clinical practice, as both can present with hypertension, edema, proteinuria, low platelet count and worsening of renal function. The classical biomarkers, such as anti-dsDNA and complement plasmatic levels are not always able to differentiate the two conditions that require different treatment approaches (3).

The use of angiogenic factors measurement, like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and antiangiogenic factors, such as soluble Fms-like tyrosine kinase-1 (sFlt-1), has been proposed to help the differentiation between these two conditions, however there is little available data about the behavior of these cytokines among pregnant SLE patients who present quiescent or active nephritis and most come from case reports (4). The objective of this study was to evaluate serum levels of VEGF, PlGF and sFlt-1 in SLE pregnant women with inactive disease, active lupus nephritis and preeclampsia.

## Materials and Methods

This was a cross-sectional study of SLE patients, diagnosed according American College of Rheumatology criteria (5), with singleton pregnancies followed at a high risk prenatal care clinic in a tertiary health unit – Universidade do Estado do Rio de Janeiro, Brazil. Patients were prospectively included according to regular prenatal follow-up visits and were accompanied by obstetricians and rheumatologists

---

* O resumo deste estudo foi aceito para apresentação oral no *American College of Rheumatology Annual Meeting* (2019) e publicado na revista *Arthritis and Rheumatology*. O artigo completo foi submetido para publicação na revista *Annals of Rheumatic Diseases*.

experienced in evaluating pregnant SLE patients. Women with other autoimmune diseases, including antiphospholipid syndrome, and with end stage renal disease were excluded as these conditions could influence with the results of the tests.

Disease activity was established according to the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) (6) and occurrence of preeclampsia followed the American College of Obstetricians and Gynecologists proposed criteria (7). All clinical data was obtained by physical examination and medical charts review and all diagnosis of PE versus LN were confirmed after delivery according to clinical outcome. Information about SLE characteristics (clinical and laboratory manifestations before pregnancy, medications, SLICC/ACR damage index) and outcomes of current pregnancy (gestational age at delivery, birth weight, Apgar score) were also recorded.

Blood samples were collected through venous puncture at the third trimester of pregnancy, within 3 weeks of delivery, during regular prenatal visit for patients with inactive SLE or if disease activity or preeclampsia was suspected. Serum samples aliquots were frozen at -80oC for subsequent blinded analysis by ELISA kits (PlGF – DRG Instruments, Marbug, Germany; sFlt-1 and VEGF – R&D systems, Minneapolis, United States) according to manufacturers' recommendations.

The results were compared between groups, using Pearson chi-square, Mann-Whitney's U test and ANOVA as appropriate. This study was approved by the institutions' review board.

**Results**

Seventy four women were prospectively included according to the inclusion criteria. One patient with a diagnosis of secondary antiphospholipid syndrome and two patients who presented non-renal SLE activity were excluded from this analysis. Forty one patients had inactive or mildly active SLE (Group 1, SLEPDAI < 4), 15 had active lupus nephritis (Group 2, SLEPDAI $\geq$ 4, including renal criteria) and 15 had preeclampsia (Group 3) at the time of blood collection. Two patients who had been initially classified as active LN were reclassified as preeclampsia due to subtle normalization of hypertension and proteinuria few days after delivery without considerable change of medications. Demographics and clinical characteristics of included patients are described in Table 1.

Table 1 - Demographic, clinical characteristics and gestational results of patients with Inactive SLE, SLE nephritis and SLE with Preeclampsia

| | Inactive SLE (n = 41) | Active SLE Nephritis (n = 15) | SLE with Preeclampsia (n = 15) | p value (C.I. 95%) (ANOVA) |
|---|---|---|---|---|
| Age at inclusion Mean ± SD | 27.2 ± 6 | 29.4 ± 4.4 | 30.1 ± 5.8 | 0.17 |
| Gestational age at blood collection Mean ± SD | 36.8 ± 1.7 | 33.7 ± 4.2 | 34.5 ± 2.5 | **<0.001** |
| Gestational age at delivery Mean ± SD | 38.7 ± 1.9 | 35.7 ± 3.8 | 35.8 ± 2.5 | **<0.001** |
| SLICC Damage Index (SDI) Mean ± SD | 0.3 ± 0.6 | 0.3 ± 0.5 | 0.1 ± 0.4 | 0.45 |
| History of SLE nephritis n (%) | 15 (35.7%) | 15 (100%) | 8 (53.3%) | NA |
| Birth weight Mean ± SD | 2976.8 ± 532.4 | 2448.4 ± 759.2 | 2174.3 ± 834.6 | **<0.001** |
| 5$^{th}$ min Apgar score Mean ± SD | 9.0 ± 0.6 | 8.7 ± 2.5 | 8.7 ± 0.6 | 0.60 |
| Small for gestational age (SGA) newborn n (%) | 5 (12.1%) | 4 (26.6%) | 9 (60%) | NA |

Blood sample collections were performed at a mean gestational age of 36.8, 33.7 and 34.5 weeks respectively in groups 1, 2 and 3, and delivery occurred at 38.7, 35.7 and 35.8 weeks, respectively. Both were significantly higher in patients with inactive SLE ($p<0.001$ for both). The mean SLICC/ACR damage index was similar in all groups as were 5th minute Apgar scores. Mean birth weight was

considerably lower in patients with active SLE nephritis and even more in those with preeclampsia ($p<0.001$).

Medications used during pregnancy are described in Table 2. Patients in group 2 (active LN) used prednisone and azathioprine more frequently compared to the other groups. Only two patients in the study were not using hydroxychloroquine and over 80% were using low dose aspirin.

Table 2 - Medications used by included patients of patients with Inactive SLE, SLE nephritis and SLE with Preeclampsia

| | Inactive SLE (n = 41) | Active SLE Nephritis (n = 15) | SLE with Preeclampsia (n = 15) | p value (C.I. 95%) (ANOVA) |
|---|---|---|---|---|
| Prednisone<br>n (%)<br>Mean dose ± SD | <br>24 (57.1%)<br>9.4 + 6.9 | <br>14 (93.3%)<br>27.9 + 23.7 | <br>8 (53.3%)<br>10.3 + 6.6 | <br><br>**<0.0001** |
| Hydroxychloroquine<br>n (%)<br>Mean dose ± SD | <br>40 (95.2%)<br>385.0 ± 53.3 | <br>15 (100%)<br>400.0 ± 0 | <br>15 (100%)<br>386.7 ± 51.6 | <br><br>0.56 |
| Azathioprine<br>n (%)<br>Mean dose ± SD | <br>18 (42.8%)<br>111.1 ± 36.6 | <br>13 (86.6%)<br>130.8 ± 38.4 | <br>6 (40.0%)<br>100.0 ± 31.6 | <br><br>0.06 |
| Antihypertensive medication<br>n (%) | <br>1 (2.3%) | <br>4 (26.6%) | <br>4 (26.6%) | <br>NA |
| Low dose Aspirin<br>n (%) | <br>34 (80.9%) | <br>14 (93.3%) | <br>12 (80%) | <br>NA |

Mean levels of VEGF, PlGF and sFlt-1 of each group are reported on Table 3. Patients with SLE and preeclampsia had significantly lower mean serum levels of PlGF, while sFlt-1 was significantly higher in patients with PE compared to pregnant patients with inactive SLE or active lupus nephritis. The sFlt-1/PlGF ratio was also significantly higher in patients of Group 3 (Preeclampsia) compared to other patients with SLE (Groups 1 and 2). VEGF was higher in patients with SLE nephritis

compared to inactive SLE and SLE with preeclampsia, while PlGF and sFlt-1 were similar when both groups with SLE without preeclampsia were compared.

The positive predictive value (PPV) for PE with a sFlt-1/PlGF ratio of 62 was 76.1%, while the negative predictive value (NPV) for PE with a sFlt-1/PlGF ratio of 38 was 97.9%.

Table 3 - Mean values of VEGF, PlGF and sFlt-1 for patients with Inactive SLE, SLE nephritis and SLE with Preeclampsia (PE)

| | Inactive SLE (n = 41) | Active SLE Nephritis (n = 15) | SLE with Preeclampsia (n = 15) | p value (C.I. 95%) (Mann-Whitney's U test) |
|---|---|---|---|---|
| VEGF (pg/mL) Mean ± SD | 5.6 ± 7 | 12.3 ± 10.1 | 4.1 ± 5 | Inactive SLE x SLE nephritis: **0.006** Inactive SLE x PE: 0.45 SLE Nephritis x PE: **0.009** |
| PlGF (pg/mL) Mean ± SD | 189.8 ± 146.1 | 198.7 ± 134.8 | 61.4 ± 127.3 | Inactive SLE x SLE nephritis: 0.83 Inactive SLE x PE: **0.003** SLE Nephritis x PE: **0.007** |
| sFlt-1 (pg/mL) Mean ± SD | 1804.2 ± 668.3 | 1832.1 ± 760.9 | 2517.0 ± 431.9 | Inactive SLE x SLE nephritis: 0.90 Inactive SLE x PE: **<0.001** SLE Nephritis x PE: **0.006** |
| Ratio sFlt-1/PlGF Mean ± SD | 22.9 ± 25.1 | 23.3 ± 35.5 | 781.1 ± 1211.3 | Inactive SLE x SLE nephritis: 0.96 Inactive SLE x PE: **0.02** SLE Nephritis x PE: **0.02** |

## Discussion

The differential diagnosis between active LN and preeclampsia in SLE patients is crucial for better outcomes, as the first one is treated with immunosuppressive therapy and the latter has considerable improvement of manifestations after delivery (2). This study provides new insights for this conundrum, as serum levels of sFlt-1 and sFlt-1/PlGF ratio were higher in patients with preeclampsia while PlGF levels

were significantly lower compared to pregnant SLE patients without this obstetric morbidity.

Levine et al described, in a case-control study of healthy nulliparous women, increased serum levels of sFlt-1 in patients with preeclampsia compared to controls, while PlGF and VEGF were significantly lower. The authors suggest that physiological proangiogenic state of second trimester (high PlGF and low sFlt-1) is converted to an antiangiogenic state during late pregnancy, with higher sFlt-1 and lower PlGF to control placental vascular growth. Patients with preeclampsia would have this conversion at an earlier stage and more abruptly, with an exaggeration of normal process of placental growth and function (8).

Two publications have validated, in a prospective fashion, the use of angiogenic and antiangiogenic factors in patients with SLE and preeclampsia, demonstrating the same pattern of healthy women and also the possibility to predict patients who will develop this obstetric condition (9, 10). Nonetheless, they did not evaluate the levels of those cytokines in patients with active SLE, precluding the use for differential diagnosis between nephritis and preeclampsia, and did not include VEGF in their analysis.

We have previously reported that, although non-pregnant patients with history of SLE nephritis had increased sFlt-1 compared to controls, PlGF was also higher in these patients, which is a different pattern compared to preeclampsia (11). The current study confirms the potential use of these angiogenic and antiangiogenic factors as differential diagnosis of preeclampsia and lupus nephritis, also demonstrating that serum VEGF is higher in patients with active nephritis compared to inactive lupus and preeclampsia. This result is in consonance with previous publications that demonstrated increased serum VEGF in non-pregnant SLE patients with active disease compared to SLE controls (12).

Our results may promptly help physicians on prenatal care of SLE pregnant patients, considering that differential diagnosis between SLE nephritis and preeclampsia can be challenging – sometimes impossible – using current available methods. Serum complement levels, usually low in patients with proliferative glomerulonephritis, may be normal due to physiological changes of pregnancy. Dysmorphic hematuria is not always present in nephritis and anti-dsDNA can be persistently positive in some SLE patients, while serum uric acid is normally elevated in preeclampsia, but not specific for the disease (3).

Two patients in this study had initial diagnosis of lupus nephritis at inclusion, but maintenance of abnormalities despite early immunosupressive treatment and rapid reversal of hypertension and proteinuria after delivery switched this diagnosis to preeclampsia. Retrospective blinded analysis of studied cytokines also pointed for the diagnosis of preeclampsia in both patients (high sFlt-1 and low PlGF), suggesting that this information could have changed the initial recommended treatment. Similarly, Hirashima et al published a case report about a woman with initial diagnosis of preeclampsia that did not reverse proteinuria and hypertension for more than 30 days after delivery, receiving a final diagnosis of new onset of lupus nephritis during pregnancy. Evaluation of blood samples retrieved before delivery demonstrated normal serum levels of sFlt-1 and sFlt-1/PlGF ratio, so the authors suggest that if these results were available at the time they could have ruled out preeclampsia and proceeded to appropriate diagnosis and treatment (4).

The small number of patients is a limitation of this study, however the exclusion of patients with SLE activity without nephritis and women with other autoimmune diseases, specially antiphospholipid syndrome, makes the results more reliable for the intended differential diagnosis. Either way, this is the largest study evaluating these cytokines for this purpose, led by obstetricians and rheumatologists with considerable experience in prenatal care of lupus patients.

In conclusion, this study demonstrated that pregnant SLE patients that developed preeclampsia had similar angiogenic and antiangiogenic profile of patients with preeclampsia without SLE – low PlGF and high sFlt-1, with high sFlt-1/PlGF ratio. This pattern differs from patients with inactive SLE or active lupus nephritis, this one the main differential diagnosis during gestation. Evaluation of angiogenic and antiangiogenic factors, specially PlGF and sFlt-1, can be a new tool to differentiate preeclampsia from lupus nephritis during pregnancy in clinical practice.

**References**

1. Lateef A, Petri M. Systemic Lupus Erythematosus and Pregnancy. Rheum Dis Clin North Am. 2017;43(2):215-26.

2. Lightstone L, Hladunewich MA. Lupus Nephritis and Pregnancy: Concerns and Management. Semin Nephrol. 2017;37(4):347-53.

3. de Jesus GR, Mendoza-Pinto C, de Jesus NR, Dos Santos FC, Klumb EM, Carrasco MG, et al. Understanding and Managing Pregnancy in Patients with Lupus. Autoimmune Dis. 2015;2015:943490.

4. Hirashima C, Ogoyama M, Abe M, Shiraishi S, Sugase T, Niki T, et al. Clinical usefulness of serum levels of soluble fms-like tyrosine kinase 1/placental growth factor ratio to rule out preeclampsia in women with new-onset lupus nephritis during pregnancy. CEN Case Rep. 2019;8(2):95-100.

5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

6. Andreoli L, Gerardi MC, Fernandes M, Bortoluzzi A, Bellando-Randone S, Brucato A, et al. Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. Autoimmun Rev. 2019;18(2):164-76.

7. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):e1-e25.

8. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672-83.

9. Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M. Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus. J Reprod Immunol. 2018;127:19-23.

10. Leaños-Miranda A, Campos-Galicia I, Berumen-Lechuga MG, Molina-Pérez CJ, García-Paleta Y, Isordia-Salas I, et al. Circulating Angiogenic Factors and the

Risk of Preeclampsia in Systemic Lupus Erythematosus Pregnancies. J Rheumatol. 2015;42(7):1141-9.

11. de Jesus GR, de Jesus NR, Levy RA, Klumb EM. The use of angiogenic and antiangiogenic factors in the differential diagnosis of pre-eclampsia, antiphospholipid syndrome nephropathy and lupus nephritis. Lupus. 2014;23(12):1299-301.

12. Zhou L, Lu G, Shen L, Wang L, Wang M. Serum levels of three angiogenic factors in systemic lupus erythematosus and their clinical significance. Biomed Res Int. 2014;2014:627126.

## CONSIDERAÇÕES FINAIS

A maioria das pacientes com LES é acometida pela doença na fase reprodutiva da vida e uma gravidez neste grupo de pacientes não é infrequente na prática clínica. Por outro lado, essas pacientes apresentam risco aumentado de PE, hipertensão gestacional, prematuridade e ativação da doença, incluindo da nefrite. Os estudos aqui apresentados, a partir de uma grande coorte de gestantes com LES, fornecem novos conhecimentos para auxiliar na assistência e no acompanhamento destas pacientes durante o período gestacional, contribuindo para que o progresso obtido nas últimas décadas seja ainda mais aprimorado.

O estudo 1 consistiu em analisar os resultados gestacionais maternos e fetais em pacientes com manifestações neuropsiquiátricas do LES, sendo descrito um pequeno número de pacientes com doença ativa durante a gravidez. Apesar de uma alta incidência de PE e prematuridade em comparação com pacientes sem acometimento neurológico, grande parte destas pacientes apresentava nefrite associada. A retirada da manifestação renal concomitante na análise resultou em resultados gestacionais mais favoráveis.

O estudo 2 tinha como objetivo analisar o impacto das diferentes classes de nefrite nos resultados gestacionais maternos e fetais. As gestantes com nefrite proliferativa (classes III/IV) apresentaram com maior frequência atividade da doença durante a gestação, doença ativa contínua durante a gravidez e o puerpério, hospitalização, cesariana e PE em comparação com pacientes sem nefrite. Estas pacientes também apresentaram maior morbidade fetal em comparação com gestantes com nefrite não proliferativa (classes II e V). Os resultados sugerem que a diferenciação da nefrite de acordo com a classe é importante, visto que os resultados maternos e fetais são consideravelmente diferentes de acordo com a classe histológica.

No estudo 3, foi feita a análise dos níveis séricos de fatores angiogênicos (VEGF, PlGF) e antiangiogênicos em gestantes com LES e doença inativa, doença renal ativa e PE. Foi demonstrado que as gestantes com LES que desenvolvem PE apresentam elevação do sFlt-1 e queda do PlGF, ambos estatisticamente significativos, da mesma forma que pacientes com PE sem LES. Este resultado sugere que as citocinas estudadas, que já estão disponíveis para uso comercial,

podem ser utilizadas no diagnóstico diferencial entre PE e nefrite do LES, situação de difícil diferenciação na prática clínica considerando a similaridade clínica e laboratorial entre as duas condições. Da mesma forma, a elevação do VEGF em pacientes com nefrite ativa em comparação com os outros dois grupos também pode ser uma ferramenta para este tipo de análise.

Apesar dos conhecimentos adquiridos ao longo do desenvolvimento dos estudos apresentados, é importante ressaltar que eles representam apenas uma pequena parte do que ainda podemos aprender sobre gestantes com LES e que novos questionamentos foram gerados ao longo do processo. Desta forma, torna-se imperativo a continuidade dos estudos sobre esta população, encerrando-se aqui apenas um ciclo.

# REFERÊNCIAS


1. Cortes-Hernandez J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology (Oxford). 2002;41(6):643-50.

2. Larosa M, Del Ross T, Calligaro A, Favaro M, Zanatta E, Iaccarino L, et al. Clinical outcomes and predictors of maternal and fetal complications in pregnancies of patients with systemic lupus erythematosus. Expert Rev Clin Immunol. 2019;15(6):617-27.

3. Saxena R, Mahajan T, Mohan C. Lupus nephritis: current update. Arthritis Res Ther. 2011;13(5):240.

4. Klumb EM, Silva CA, Lanna CC, Sato EI, Borba EF, Brenol JC, et al. Consenso da Sociedade Brasileira de Reumatologia para o diagnóstico, manejo e tratamento da nefrite lúpica. Rev Bras Reumatol. 2015;55(1):1-21.

5. Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-35.

6. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15(2):241-50.

7. Barber C, Herzenberg A, Aghdassi E, Su J, Lou W, Qian G, et al. Evaluation of clinical outcomes and renal vascular pathology among patients with lupus. Clin J Am Soc Nephrol. 2012;7(5):757-64.

8. Austin HA, 3rd, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int. 1984;25(4):689-95.

9. Avihingsanon Y, Benjachat T, Tassanarong A, Sodsai P, Kittikovit V, Hirankarn N. Decreased renal expression of vascular endothelial growth factor in lupus nephritis is associated with worse prognosis. Kidney Int. 2009;75(12):1340-8.

10. Avihingsanon Y, Phumesin P, Benjachat T, Akkasilpa S, Kittikowit V, Praditpornsilpa K, et al. Measurement of urinary chemokine and growth factor messenger RNAs: a noninvasive monitoring in lupus nephritis. Kidney Int. 2006;69(4):747-53.

11. Karassa FB, Ioannidis JP, Touloumi G, Boki KA, Moutsopoulos HM. Risk factors for central nervous system involvement in systemic lupus erythematosus. QJM. 2000;93(3):169-74.

12. McGlasson S, Wiseman S, Wardlaw J, Dhaun N, Hunt DPJ. Neurological Disease in Lupus: Toward a Personalized Medicine Approach. Front Immunol. 2018;9:1146.

13. Kivity S, Agmon-Levin N, Zandman-Goddard G, Chapman J, Shoenfeld Y. Neuropsychiatric lupus: a mosaic of clinical presentations. BMC Med. 2015;13:43.

14. de Amorim JC, Torricelli AK, Frittoli RB, Lapa AT, Dertkigil SSJ, Reis F, et al. Mimickers of neuropsychiatric manifestations in systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2018;32(5):623-39.

15. Maethasith I, Sathirapanya P. Cerebral lupus presented with late postpartum eclampsia and atypical reversible leucoencephalopathy. Neuroradiology. 2017;59(11):1063-4.

16. Tandon A, Ibanez D, Gladman DD, Urowitz MB. The effect of pregnancy on lupus nephritis. Arthritis Rheum. 2004;50(12):3941-6.

17. de Jesus GR, Mendoza-Pinto C, de Jesus NR, Dos Santos FC, Klumb EM, Carrasco MG, et al. Understanding and Managing Pregnancy in Patients with Lupus. Autoimmune Dis. 2015;2015:943490.

18. Lateef A, Petri M. Systemic Lupus Erythematosus and Pregnancy. Rheum Dis Clin North Am. 2017;43(2):215-26.

19. Vinet É, Pineau CA, Clarke AE, Scott S, Fombonne É, Joseph L, et al. Increased Risk of Autism Spectrum Disorders in Children Born to Women With Systemic Lupus Erythematosus: Results From a Large Population-Based Cohort. Arthritis Rheumatol. 2015;67(12):3201-8.

20. Inslicht DV, Stein AB, Pomerantz F, Ragnarsson KT. Three women with lupus transverse myelitis: case reports and differential diagnosis. Arch Phys Med Rehabil. 1998;79(4):456-9.

21. Suzuki Y, Kitagawa Y, Matsuoka Y, Fukuda J, Mizushima Y. Severe cerebral and systemic necrotizing vasculitis developing during pregnancy in a case of systemic lupus erythematosus. J Rheumatol. 1990;17(10):1408-11.

22. El-Sayed YY, Lu EJ, Genovese MC, Lambert RE, Chitkara U, Druzin ML. Central nervous system lupus and pregnancy: 11-year experience at a single center. J Matern Fetal Neonatal Med. 2002;12(2):99-103.

23. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5(11):2060-8.

24. Klumb EM, Barros LMS, Romeiro L, Jesús NR, Levy RA, Albuquerque EMN. Impacto da nefrite sobre os resultados gestacionais de mulheres com lúpus eritematoso sistêmico. Revista Brasileira de Reumatologia. 2005;45(3):107-13.

25. Moroni G, Doria A, Giglio E, Tani C, Zen M, Strigini F, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. J Autoimmun. 2016;74:6-12.

26. Mecacci F, Simeone S, Cirami CL, Cozzolino M, Serena C, Rambaldi MP, et al. Preeclampsia in pregnancies complicated by systemic lupus erythematosus (SLE) nephritis: prophylactic treatment with multidisciplinary approach are important keys to prevent adverse obstetric outcomes. J Matern Fetal Neonatal Med. 2019;32(8):1292-8.

27. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.

28. Duley L. Pre-eclampsia and the hypertensive disorders of pregnancy. Br Med Bull. 2003;67:161-76.

29. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, et al. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records: A CALIBER Study. Circulation. 2019;140(13):1050-60.

30. Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. Am J Med Sci. 2007;334(4):291-5.

31. Edlow AG, Srinivas SK, Elovitz MA. Investigating the risk of hypertension shortly after pregnancies complicated by preeclampsia. Am J Obstet Gynecol. 2009;200(5):e60-2.

32. Davison JM, Homuth V, Jeyabalan A, Conrad KP, Karumanchi SA, Quaggin S, et al. New aspects in the pathophysiology of preeclampsia. J Am Soc Nephrol. 2004;15(9):2440-8.

33. Silasi M, Cohen B, Karumanchi SA, Rana S. Abnormal placentation, angiogenic factors, and the pathogenesis of preeclampsia. Obstet Gynecol Clin North Am. 2010;37(2):239-53.

34. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649-58.

35. Robak E, Sysa-Jedrzejewska A, Robak T. Vascular endothelial growth factor and its soluble receptors VEGFR-1 and VEGFR-2 in the serum of patients with systemic lupus erythematosus. Mediators Inflamm. 2003;12(5):293-8.

36. Koga K, Osuga Y, Yoshino O, Hirota Y, Ruimeng X, Hirata T, et al. Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia. J Clin Endocrinol Metab. 2003;88(5):2348-51.

37. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672-83.

38. Levine RJ, Thadhani R, Qian C, Lam C, Lim KH, Yu KF, et al. Urinary placental growth factor and risk of preeclampsia. JAMA. 2005;293(1):77-85.

39. Buhimschi CS, Norwitz ER, Funai E, Richman S, Guller S, Lockwood CJ, et al. Urinary angiogenic factors cluster hypertensive disorders and identify women with severe preeclampsia. Am J Obstet Gynecol. 2005;192(3):734-41.

40. Stepan H, Walther T. Questionable role of the angiotensin II receptor subtype 1 autoantibody in the pathogenesis of preeclampsia. Hypertension. 2007;50(1):e3; author reply e4.

41. Schlembach D, Wallner W, Sengenberger R, Stiegler E, Mortl M, Beckmann MW, et al. Angiogenic growth factor levels in maternal and fetal blood: correlation with Doppler ultrasound parameters in pregnancies complicated by pre-eclampsia and intrauterine growth restriction. Ultrasound Obstet Gynecol. 2007;29(4):407-13.

42. Crispi F, Dominguez C, Llurba E, Martin-Gallan P, Cabero L, Gratacos E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol. 2006;195(1):201-7.

43. Thadhani R, Mutter WP, Wolf M, Levine RJ, Taylor RN, Sukhatme VP, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. J Clin Endocrinol Metab. 2004;89(2):770-5.

44. Romero R, Nien JK, Espinoza J, Todem D, Fu W, Chung H, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med. 2008;21(1):9-23.

45. Espinoza J, Romero R, Nien JK, Gomez R, Kusanovic JP, Goncalves LF, et al. Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor. Am J Obstet Gynecol. 2007;196(4):326 e1-13.

46. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn. 2011;31(1):66-74.

47. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol. 2017;50(4):492-5.

48. Sibai BM. Imitators of severe pre-eclampsia. Semin Perinatol. 2009;33(3):196-205.

49. de Jesus GR, de Jesus NR, Levy RA, Klumb EM. The use of angiogenic and antiangiogenic factors in the differential diagnosis of pre-eclampsia, antiphospholipid syndrome nephropathy and lupus nephritis. Lupus. 2014;23(12):1299-301.

50. Day CJ, Lipkin GW, Savage CO. Lupus nephritis and pregnancy in the 21st century. Nephrol Dial Transplant. 2009;24(2):344-7.

51. Qazi U, Lam C, Karumanchi SA, Petri M. Soluble Fms-like tyrosine kinase associated with preeclampsia in pregnancy in systemic lupus erythematosus. J Rheumatol. 2008;35(4):631-4.

52. Rhee JS, Young BC, Rana S. Angiogenic factors and renal disease in pregnancy. Case Rep Obstet Gynecol. 2011;2011:281391.

53. Colombo BM, Cacciapaglia F, Puntoni M, Murdaca G, Rossi E, Rodriguez G, et al. Traditional and non traditional risk factors in accelerated atherosclerosis in systemic lupus erythematosus: role of vascular endothelial growth factor (VEGATS Study). Autoimmun Rev. 2009;8(4):309-15.

54. Frieri M. Accelerated atherosclerosis in systemic lupus erythematosus: role of proinflammatory cytokines and therapeutic approaches. Curr Allergy Asthma Rep. 2012;12(1):25-32.

55. Frieri M, Samih MA, Dzhindzhikhashvili M, Liu H, Balsam L, Rubinstein S. Toll-like receptor 9 and vascular endothelial growth factor levels in human kidneys from lupus nephritis patients. J Nephrol. 2012;25(6):1041-6.

56. Robak E, Kulczycka L, Sysa-Jedrzejowska A, Wierzbowska A, Robak T. Circulating proangiogenic molecules PIGF, SDF-1 and sVCAM-1 in patients with systemic lupus erythematosus. Eur Cytokine Netw. 2007;18(4):181-7.

57. Zhou L, Lu G, Shen L, Wang L, Wang M. Serum levels of three angiogenic factors in systemic lupus erythematosus and their clinical significance. Biomed Res Int. 2014;2014:627126.

58. Barleon B, Reusch P, Totzke F, Herzog C, Keck C, Martiny-Baron G, et al. Soluble VEGFR-1 secreted by endothelial cells and monocytes is present in human serum and plasma from healthy donors. Angiogenesis. 2001;4(2):143-54.

59. Luft FC. Soluble fms-like tyrosine kinase-1 and atherosclerosis in chronic kidney disease. Kidney Int. 2014;85(2):238-40.

60. Hrycek A, Janowska J, Cieslik P. Selected angiogenic cytokines in systemic lupus erythematosus patients. Autoimmunity. 2009;42(5):459-66.

61. Edelbauer M, Kshirsagar S, Riedl M, Billing H, Tonshoff B, Haffner D, et al. Soluble VEGF receptor 1 promotes endothelial injury in children and adolescents with lupus nephritis. Pediatr Nephrol. 2012;27(5):793-800.

62. De Jesús, GR. Avaliação de fatores angiogênicos e antiangiogênicos em pacientes com lúpus eritematoso sistêmico [tese]. Rio de Janeiro: Universidade do Estado do Rio de Janeiro; 2014. 83 f. Doutor em Ciências Médicas.

63. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol. 2015;45(3):241-6.

64. Leaños-Miranda A, Campos-Galicia I, Berumen-Lechuga MG, Molina-Pérez CJ, García-Paleta Y, Isordia-Salas I, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia in Systemic Lupus Erythematosus Pregnancies. J Rheumatol. 2015;42(7):1141-9.

65. Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M. Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus. J Reprod Immunol. 2018;127:19-23.

66. Kim MY, Buyon JP, Guerra MM, Rana S, Zhang D, Laskin CA, et al. Angiogenic factor imbalance early in pregnancy predicts adverse outcomes in patients with lupus and antiphospholipid antibodies: results of the PROMISSE study. Am J Obstet Gynecol. 2015.

67. Andrade D, Kim M, Blanco LP, Karumanchi SA, Koo GC, Redecha P, et al. Interferon-α and angiogenic dysregulation in pregnant lupus patients who develop preeclampsia. Arthritis Rheumatol. 2015;67(4):977-87.

**ANEXO A** – Aprovação do Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto

**UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO**
**HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO**
**COMITÊ DE ÉTICA EM PESOUISA**

Rio de Janeiro, 03 de maio de 2011

Do: Comitê de Ética em Pesquisa
Prof.: Wille Oigman
Para: Coord. Prof. Evandro Mendes Klumb

Registro CEP/HUPE: 2866/2011 (este número deverá ser citado nas correspondências referentes ao projeto)
CAAE: 0017.0.228.000-11

O Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto, após avaliação, considerou o projeto, "AVALIAÇÃO DOS FATORES ANGIOGÊNICOS E ANTIANGIOGÊNICOS COMO MÉTODO DE _DIAGNÓSTICO DIFERENCIAL ENTRE PRÉ-ECLÂMPSIA E LÚPUS ERITEMATOSO SISTÊMICO E NEFRITE" aprovado, encontrando-se este dentro dos padrões éticos da pesquisa em seres humanos, conforme Resolução n.º196 sobre pesquisa envolvendo seres humanos de 10 de outubro de 1996, do Conselho Nacional de Saúde, bem como o termo de consentimento livre e esclarecido.

O pesquisador deverá informar ao Comitê de Ética qualquer acontecimento ocorrido no decorrer da pesquisa.

O Comitê de Ética solicita a V. Sª., que ao término da pesquisa encaminhe a esta comissão um sumário dos resultados do projeto.

Prof. Wille Oigman
Presidente do Comitê de Ética em Pesquisa

CEP - COMITÊ DE ÉTICA EM PESQUISA
AV. VINTE E OITO DE SETEMBRO, 77 TÉRREO - VILA ISABEL - CEP 20551-030
TEL: 21 2587-6353 – FAX: 21 2264-0853 - E-mail: cep-hupe@uerj.br

**ANEXO B –** Medida da Atividade da Doença Lúpus Eritematoso Sistêmico na gestação (SLEPDAI)

| Descrição | Definição | Pontos |
|---|---|---|
| Convulsão | Início recente. Excluir infecção metabólica ou causas devido ao medicamento. **Excluir eclampsia.** | 8 |
| Psicose | Capacidade alterada para função em atividade normal devido a distúrbio severo na percepção da realidade. Inclui alucinação, incoerência, perda marcante de associações, empobrecimento do conteúdo do pensamento, pensamento ilógico marcante, comportamento bizarro, desorganizado ou catatônico. Excluir uremia e causas devido ao medicamento. | 8 |
| Síndrome cerebral orgânica | Função mental alterada com orientação prejudicada, memória ou outra função intelectual com início rápido e características clínicas instáveis. Inclui estado alterado da consciência com redução da capacidade de foco e incapacidade de manter a atenção no ambiente mais pelo menos 2 dos seguintes: distúrbio de percepção, fala incoerente, insônia ou sonolência durante o dia ou aumento ou diminuição da atividade psicomotora. Excluir causas devido ao medicamento, infecção ou metabólicas. | 8 |
| Distúrbio visual | Alterações retinianas de LES . Incluir corpos citóides, hemorragia retiniana, exsudato seroso ou hemorragia na coróide, ou neurite óptica. Excluir causas devido ao medicamento, infecção ou hipertensão. | 8 |
| Distúrbio dos nervos cranianos | Novo começo de neuropatia motora ou sensorial comprometendo nervos cranianos. **Excluir paralisia de Bell.** | 8 |
| Dor de cabeça lúpica | Dor de cabeça severa persistente; pode ser enxaqueca, mas não deve ser responsiva à analgesia narcótica. **Excluir pré-eclâmpsia.** | 8 |
| Acidente vascular cerebral (AVC) | Novo início de acidente(s) vascular(es) cerebral(is). Excluir arteriosclerose. **Excluir eclampsia.** | 8 |
| Vasculite | Ulceração, gangrena, nódulos moles dos dedos, infarto periungueal, hemorragia *splinter*, ou biópsia ou arteriografia de vasculite. **Não considerar eritema palmar.** | 8 |
| Artrite | Mais de 2 articulações com dor e sinais de inflamação (isto é, sensibilidade, inchaço e efusão). **Não considerar derrame nos joelhos** | 4 |
| Miosite | Músculo proximal dolorido ou fraqueza associada com aldolase ou creatina fosfoquinase elevada, ou alterações de eletromiograma, ou uma biópsia apresentando miosite. | 4 |
| cilindros urinários | Cilindros de hemácias ou heme-granular | 4 |
| Hematúria | > 5 hemácias por campo. Excluir cálculo, infecção ou outras causas. **Excluir cistite ou cilindros hemáticos vaginais originados de patologias placentárias.** | 4 |
| Proteinuria | > 0,5 g por 24 horas. Novo início ou aumento recente de mais que 0,5 g por 24 horas. **Excluir pré-eclâmpsia.** | 4 |
| Piúria | > 5 leucócitos por campo. Excluir infecção. | 4 |
| Nova erupção | Novo início ou recorrência de erupção do tipo inflamatório. **Não considerar cloasma.** | 2 |
| Alopecia | Novo início ou recorrência de perda anormal de cabelo difusa ou em placa. **Não considerar alopecia puerperal.** | 2 |
| Ulceras na mucosa | Novo início ou recorrência de ulcerações nasais ou orais. | 2 |
| Pleurisia | Dor torácica pleurítica com atrito pleural ou efusão ou espessamento pleural. **Hiperventilação pode ser secundário a progesterona, dispnéia secundário ao aumento do útero** | 2 |

| | | |
|---|---|---|
| Pericardite | Dor pericárdica com pelo menos 1 dos seguintes: efusão de atrito ou confirmação por eletrocardiograma. | 2 |
| Baixo complemento | Diminuição no CH50, C3 ou C4 abaixo do limite mínimo do normal para exame de laboratório. **Aceitar queda de 25%** | 2 |
| Ligação ao DNA aumentada | ligação > 25 % pelo ensaio de Farr ou acima da faixa normal para exame de laboratório. | 2 |
| Febre | > 38 °C. Excluir causas infecciosas. | 1 |
| Trombocitopenia | < 100 000 plaquetas por $mm^3$ **Excluir pré-eclâmpsia, HELLP, trombocitopenia gestacional.** | 1 |
| Leucopenia | < 3000 leucócitos por $mm^3$. Excluir causas devido ao medicamento. **Considerar <1000 linfócitos por $mm^3$** | 1 |

**ANEXO C –** Índice de dano cumulativo (SLICC-DI)

Nome_____ Prontuário_____

| | | Escore | Paciente | Data |
|---|---|---|---|---|
| Ocular | Catarata | 1 | | |
| | Mudança na retina ou atrofia óptica | 1 | | |
| Neuropsiquiátrico | Déficit cognitivo* | 1 | | |
| | Convulsões tratadas por 6m | 1 | | |
| | AVC (score 2>1) | 1 (2) | | |
| | Neuropatia craniana ou periférica (exceto óptica) | 1 | | |
| | Mielite transversa | 1 | | |
| Renal | TFG medida ou estimada < 50% | 1 | | |
| | Proteinúria > 3,5 g/24horas | 1 | | |
| | OU | | | |
| | Doença renal terminal (aguardando diálise ou transplante) | 3 | | |
| Pulmonar | Hipertensão pulmonar (HVD ou P2 > A2 ) | 1 | | |
| | Fibrose pulmonar (exame físico ou radiográfico) | 1 | | |
| | Síndrome dos pulmões encolhidos | 1 | | |
| | Fibrose pleural (radiográfico) | 1 | | |
| | Infarto pulmonar (radiográfico) | 1 | | |
| Cardiovascular | Angina ou cirurgia de revascularização miocárdica | 1 | | |
| | IAM (score 2 se > 1) | 1 (2) | | |
| | Cardiomiopatia (disfunção ventricular) | 1 | | |
| | Doença Valvar (sopro sistólico ou sopro diast´locio > 3/6) | 1 | | |
| | Pericardite por 6m ou pericardiectomia | 1 | | |
| Vascular periférico | Claudicação por 6m | 1 | | |
| | Perda pequena de tecido (polpa digital) | 1 | | |
| | Qualquer perda significativa de tecido (dedo ou membro) (score 2 se > 1) | 1 (2) | | |
| | Trombose venosa com edema, ulceração ou estase venosa | 1 | | |
| Gastrointestinal | Infarto ou ressecção do intestino abaixo do duodeno, esplênico, hepático ou da vesícula biliar, por qualquer causa ( score 2 se >1 lugar) | 1 (2) | | |
| | Insuficiência mesentérica | 1 | | |
| | Peritonite crônica | 1 | | |
| | Estreitamento ou qualquer cirurgia do TGI superior | 1 | | |
| Musculoesquelético | Atrofia ou fraqueza muscular | 1 | | |
| | Artrite deformante ou erosiva ( incluindo deformidades redutíveis, com exceção de necrose avascular ) | 1 | | |
| | Osteoporose com fratura ou colapso vertebral ( com exceção avascular ) | 1 | | |
| | Necrose avascular (score 2 se > 1) | 1 (2) | | |
| | Osteomielite | 1 | | |
| Pele | Alopecia crônica cicatricial | 1 | | |
| | Cicatriz extensa ou de paniculum que não seja escalpo polpa digital | 1 | | |
| | Ulceração de pele (excluindo trombose) por 6 m | 1 | | |

| | | | |
|---|---|---|---|
| Insuf. Gonadal prematura | 1 | | |
| Diabetes Mellitus (apesar de tratamento) | 1 | | |
| Malignidade (excluindo displasia) (score 2 se > 1 lugar) | 1 (2) | | |

**ANEXO D –** Outros Artigos com Temas Afins Publicados Durante o Período de Pós-Graduação

BJOG. 2019 Apr;126(5):656-661. doi: 10.1111/1471-0528.15469. Epub 2018 Oct 24.

## Factors associated with first thrombosis in patients presenting with obstetric antiphospholipid syndrome (APS) in the APS Alliance for Clinical Trials and International Networking Clinical Database and Repository: a retrospective study.

de Jesús GR[1], Sciascia S[2], Andrade D[3], Barbhaiya M[4], Tektonidou M[5], Banzato A[6], Pengo V[6], Ji L[7], Meroni PL[8], Ugarte A[9], Cohen H[10], Branch DW[11], Andreoli L[12], Belmont HM[13], Fortin PR[14], Petri M[15], Rodriguez E[16], Cervera R[17], Knight JS[18], Atsumi T[19], Willis R[20], Nascimento IS[3], Rosa R[3], Erkan D[4], Levy RA[21,22]; APS ACTION.

Author information

### Abstract

**OBJECTIVE:** To evaluate the subsequent rate of thrombosis among women with obstetric antiphospholipid syndrome (Ob-APS) in a multicentre database of antiphospholipid antibody (aPL)-positive patients, and the clinical utility of the adjusted Global Antiphospholipid Syndrome Score (aGAPSS), a validated tool to assess the likelihood of developing new thrombosis, in this group of patients.

**DESIGN:** Retrospective study.

**SETTING:** The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Clinical Database and Repository.

**POPULATION:** Women with Ob-APS.

**METHODS:** Comparison of clinical and laboratory characteristics and measurement of aGAPSS in women with Ob-APS, with or without thrombosis, after initial pregnancy morbidity (PM).

**MAIN OUTCOME MEASURES:** Risk factors for thrombosis and aGAPSS.

**RESULTS:** Of 550 patients, 126 had Ob-APS; 74/126 (59%) presented with thrombosis, and 47 (63%) of these women developed thrombosis after initial PM, in a mean time of 7.6 ± 8.2 years (4.9/100 patient years). Younger age at diagnosis of Ob-APS, additional cardiovascular risk factors, superficial vein thrombosis, heart valve disease, and multiple aPL positivity increased the risk of first thrombosis after PM. Women with thrombosis after PM had a higher aGAPSS compared with women with Ob-APS alone [median 11.5 (4-16) versus 9 (4-13); P = 0.0089].

**CONCLUSION:** Based on a retrospective analysis of our multicentre aPL database, 63% of women with Ob-APS developed thrombosis after initial obstetric morbidity; additional thrombosis risk factors, selected clinical manifestations, and high-risk aPL profile increased the risk. Women with subsequent thrombosis after Ob-APS had a higher aGAPSS at entry to the registry. We believe that aGAPSS is a valid tool to improve risk stratification in aPL-positive women.

**TWEETABLE ABSTRACT:** More than 60% of women with obstetric antiphospholipid syndrome had thrombosis after initial pregnancy morbidity.



**KEYWORDS:** Antiphospholipid antibodies; antiphospholipid syndrome; fetal death; miscarriage; pre-eclampsia; thrombosis

BJOG. 2018 Sep;125(10):1271. doi: 10.1111/1471-0528.15310. Epub 2018 Jul 6.

# Bringing stillbirths out of the shadows in Latin America.

de Jesús G[1], Flenady V[2].

Author information

**Comment on**

Stillbirth rates in 20 countries of Latin America: an ecological study. [BJOG. 2018]

PMID: 29878622 DOI: 10.1111/1471-0528.15310

Autoimmune Dis. 2015;2015:943490. doi: 10.1155/2015/943490. Epub 2015 Jul 12.

# Understanding and Managing Pregnancy in Patients with Lupus.

de Jesus GR[1], Mendoza-Pinto C[2], de Jesus NR[1], Dos Santos FC[1], Klumb EM[3], Carrasco MG[2], Levy RA[3].

Author information

## Abstract

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune disease that occurs predominantly in women of fertile age. The association of SLE and pregnancy, mainly with active disease and especially with nephritis, has poorer pregnancy outcomes, with increased frequency of preeclampsia, fetal loss, prematurity, growth restriction, and newborns small for gestational age. Therefore, SLE pregnancies are considered high risk condition, should be monitored frequently during pregnancy and delivery should occur in a controlled setting. Pregnancy induces dramatic immune and neuroendocrine changes in the maternal body in order to protect the fetus from immunologic attack and these modifications can be affected by SLE. The risk of flares depends on the level of maternal disease activity in the 6-12 months before conception and is higher in women with repeated flares before conception, in those who discontinue useful medications and in women with active glomerulonephritis at conception. It is a challenge to differentiate lupus nephritis from preeclampsia and, in this context, the angiogenic and antiangiogenic cytokines are promising. Prenatal care of pregnant patients with SLE requires close collaboration between rheumatologist and obstetrician. Planning pregnancy is essential to increase the probability of successful pregnancies.

PMID: 26246905 PMCID: PMC4515284 DOI: 10.1155/2015/943490

BJOG. 2015 Apr;122(5):606-9. doi: 10.1111/1471-0528.13119. Epub 2014 Oct 20.

# Caesarean rates in Brazil: what is involved?

Ramires de Jesus G[1], Ramires de Jesus N, Peixoto-Filho FM, Lobato G.

Author information

Comment in

We have met the enemy, and he or she is us. [BJOG. 2015]

Thromb Haemost. 2015 Aug 31;114(3):651-2. doi: 10.1160/TH15-02-0156. Epub 2015 May 7.

# Limited evidence for diagnosing and treating "non-criteria obstetric antiphospholipid syndrome".

Ramires de Jesús G[1], Levy RA, Porter TF, Branch DW.

Author information

Comment on
Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. [Thromb Haemost. 2015]