Universidade do Estado do Rio de Janeiro
Centro Biomédico
Faculdade de Ciências Médicas

Marcela Ignacchiti Lacerda Ávila

Análise dos desfechos maternos, fetais e neonatais na gestação de pacientes com lúpus eritematoso sistêmico

Rio de Janeiro
2021

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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

Coorientador: Prof. Dr. Guilherme Ribeiro Ramires de Jesús

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DEDICATÓRIA

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Platão

RESUMO

ÁVILA, Marcela Ignacchiti Lacerda. *Análise dos desfechos materno, fetal e neonatal na gestação de pacientes com lúpus eritematoso sistêmico.* 2021. 132 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2021.

Gestação em mulheres com lúpus é um assunto que vem sendo, há décadas, estudado em virtude das potenciais complicações maternas, fetais e neonatais que podem ocorrer. Atualmente observamos aumento do número de gestações bem-sucedidas e diminuição das taxas de perdas fetais, todavia ainda há eficácia limitada na prevenção de outras complicações e a associação do LES com a gestação continua sendo considerada de alto risco, podendo ter prognóstico reservado. O objetivo desta tese foi avaliar os resultados gestacionais em uma coorte de gestantes com lúpus eritematoso sistêmico, com enfoque no impacto da nefrite lúpica, especialmente glomerulonefrite proliferativa (GNP) e do conhecimento dos danos permanentes (SDI) acumulados previamente à gravidez, como fatores de risco associados a desfechos maternos, fetais e neonatais adversos. O estudo 1 analisou as variáveis clínicas e laboratoriais maternas potencialmente associadas à ocorrência de recém-nascidos pequenos para a idade gestacional (PIG), e demonstrou que a atividade do LES na gestação, especificamente a nefrite proliferativa e o emprego de pulsoterapia com metilpredinisolona foram preditores independentes de risco, para recém-nascidos pequenos para a idade gestacional. O estudo 2 analisou o impacto da presença dos danos permanentes nas gestantes com LES e evidenciou que existe uma associação entre os danos permanentes e os resultados gestacionais adversos.

Palavras-chave: Lúpus eritematoso sistêmico. Glomerulonefrite proliferativa. Pequeno para a idade gestacional. Dano permanente. SDI. Resultado gestacional adverso.

ABSTRACT

ÁVILA, Marcela Ignacchiti Lacerda. *Analysis of maternal, fetal and neonatal outcomes in the pregnancy of patients with systemic lupus erythematosus.* 2021. 132 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2021.

Pregnancy in women with lupus is a subject that has been studied for decades because of the potential maternal, fetal and neonatal complications that can occur. Currently, we observe an increase in the number of successful pregnancies and a decrease in fetal loss rates, but there is still limited effectiveness in preventing other complications and the association of SLE with pregnancy continues to be considered high risk and may have a poor prognosis. The aim of this thesis was to evaluate pregnancy outcomes in a cohort of pregnant women with systemic lupus erythematosus, focusing on the impact of lupus nephritis, especially proliferative glomerulonephritis (GNP) and knowledge of permanent damage (SDI) accumulated prior to pregnancy, as factors of risk associated with adverse maternal, fetal and neonatal outcomes. Study 1 analyzed the maternal clinical and laboratory variables potentially associated with the occurrence of small-for-gestational age (SGA) newborns, and demonstrated that the activity of SLE during pregnancy, specifically proliferative nephritis and the use of pulse therapy with methylpredinisolone were independent risk predictors for small-for-gestational-age newborns. Study 2 analyzed the impact of the presence of permanent damage in pregnant women with SLE and showed that there is an association between permanent damage and adverse pregnancy outcomes.

Keywords: Systemic Lupus Erythematosus. Proliferative glomerulonephritis. Small for gestational age. Permanent damage. SDI. Adverse gestational outcomes.

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

AC	Anticorpo
ACL	Anticardiolipina
ACR	*American College of Rheumatology*
ANA	Anticorpos Antinucleares
Apl	Anticorpo antifosfolipídeo
APS	*Antiphospholipid Syndrome*
CI	*Confidence Interval*
CNS	*Central Nervous System*
ELISA	*Enzyme Linked Immuno Sorbent Assay*
FAN	Fator Anti-Nuclear
GN	Glomerulonefrite
GNP	Glomerulonefrite proliferativa
HAS	Hipertensão Arterial Sistêmica
HELLP	*Hemolytic Elevated Liver Enzymes Low Plalet*
HUPE	Hospital Universitário Pedro Ernesto
IG	Idade Gestacional
ISN/RPS	*International Society of Nephrology / Renal Pathology Society*
IUGR	*Intrauterine Growth Restriction*
LAC	Anticoagulante Lúpico
LES	Lúpus Eritematoso Sistêmico
LN	*Lupus Nephritis*
NICU	*Neonatal Intensive Care Unit*
NL	Nefrite Lúpica
NP	*Neuropsychiatric*
NPSLE	*Neuropsychiatric Systemic Lupus Erythematosus*
PE	Pré-eclâmpsia
PIG	Pequenos para a Idade Gestacional
PIGF	*Placental Growth Factor*
RCF	Restrição do Crescimento Fetal

RN	Recém-nascido
RNP	Ribonucleoproteína
RPMO	Ruptura Prematura de Membranas Ovulares
SAF	Síndrome do Anticorpo Antifosfolipídeo
sFlt-1	*Soluble Fms-like tyorine 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	*Systemic Lupus International Collaborating Clinics*
SLICC/ACR-SDI	*SLICC/ACR Damage Index*
SNC	Sistema Nervoso Central
TFG	Taxa de Filtração Glomerular
UTI	Unidade de Terapia Intensiva
VEGF	*Vascular Endotelial Growth Factor*
VHS	Velocidade de Hemossedimentação

LISTA DE SÍMBOLOS

%	Porcentagem
$\pm$	Mais ou menos
$\geq$	Maior ou igual
$\leq$	Menor ou igual
Cm	Centímetro
cm^3	Centímetros cúbicos
DP	Desvio Padrão
H	Hora
Mg	Miligrama
mmHg	Milimetros de mercúrio
Ml	Mililitro
N	número

SUMÁRIO

REVISÃO DA LITERATURA

lúpus eritematoso sistêmico (LES)

O lúpus eritematoso sistêmico (LES) é uma doença inflamatória crônica, que acomete diversos órgãos e sistemas, com ampla gama de manifestações clínicas (1). Entretanto, uma revisão detalhada destas, não faz parte do escopo desse projeto, ainda que adiante citemos algumas importantes.

A doença evolui com manifestações clínicas pleomórficas, períodos de atividade e remissão. Seu fenótipo é heterogêneo, a gravidade e prognóstico variáveis de acordo com o tipo e o órgão/sistema afetado.

Tem natureza autoimune e sua fisiopatologia envolve a formação de autoanticorpos, especialmente o anticorpo antinuclear (FAN), recentemente denominado anticorpo anticélula (2), além de imunocomplexos, linfócitos autorreativos e a ativação de mecanismos da imunidade inapta (1).

De etiologia, ainda, obscura, o desenvolvimento da doença está ligado a ativação do sistema imunológico (células B e T), predisposição genética, epigênetica, presença de hormônios sexuais e fatores ambientais, como a radiação ultravioleta (1).

Incide mais frequentemente em mulheres jovens (26 a 40 anos), ou seja, na fase reprodutiva, na proporção de nove a dez mulheres para um homem, com incidência para o sexo e para a idade de 2,8 a 4,6 casos por 100.000 pessoas na América do Norte (3) e prevalência variando de 62,2 a 84,8/100.000 habitantes no mundo (1).

Nos Estados Unidos há tendência a maior prevalência em grupos de ascendências hispânica ou asiática e africana, além de maior risco de manifestações em órgãos vitais como sistema nervoso central (cérebro) e rins (1).

No Brasil a incidência estimada foi de 4,8 (4) a 8,7 (5) casos por 100.000 pessoas por ano e a prevalência de 98/100.000 habitantes em Minas Gerais em um estudo com metodologia COPCORD (6).

Sua sobrevida global é menor, quando comparada com a população geral, principalmente quando há acometimento renal, embora na maioria das pacientes o curso seja relativamente benigno. Nas últimas décadas houve aumento das taxas de sobrevivência,

respectivamente de 90 a 95% em 5 anos e 70 a 80% em 10 anos, tendendo a taxas menores nos países em desenvolvimento e em pacientes com acometimento renal. Embora haja um acréscimo na expectativa de vida a mortalidade continua alta e a morbidade (danos permanentes) em ascensão à medida que aumenta a sobrevida (1, 7-12).

A mortalidade é 2-3 vezes maior do que na população geral ocorrendo devido a infecções (principalmente pneumonia e septicemia) e atividade da doença- mortalidade precoce (1-2 anos a partir do diagnóstico de LES) e doença cardiovascular, lesão renal e neoplasias – mortalidade a partir de 5 anos ou mais após o diagnóstico. (7, 8, 10-12).

Nefrite lúpica

A nefrite lúpica (NL) acomete aproximadamente de 50 a 60% dos pacientes com LES, com apresentação clínica e gravidade variáveis de hematúria e / ou proteinúria assintomática a síndrome nefrótica e glomerulonefrite (GN) rapidamente progressiva com perda da função renal (13,14). Clinicamente se apresenta com hipertensão, proteinúria e nos casos mais graves insuficiência renal. É a principal manifestação clínica relacionada a internação hospitalar e aumento da mortalidade, apresentando assim como outras manifestações sistêmicas períodos de atividade e remissão (14, 15).

A prevalência da NL é maior em afroamericanos e hispânicos, com sobrevida em 10 anos de cerca de 88%, menor quando comparada com a de pacientes sem nefrite (7, 16).

Para determinação de marcadores diagnósticos e prognósticos, bem como avaliação da extensão, tipo de acometimento renal (tubular, intersticial, vascular e glomerular) e decisão terapêutica pode ser necessária a realização da biópsia em acordo com indicações especificas (14, 17-21). São avaliados: 1) tipo de proliferação: mesangial ou endocapilar- presente ou ausente; 2) natureza da lesão- ativa (inflamatória) ou crônica (esclerosante); 3) nos glomérulos- tipo de lesão- global ou segmentar, local de acúmulo dos imunocomplexos e extensão do acometimento- focal ou difuso (20,21).

A análise e padrão histopatológico permitirá a distinção e classificação de acordo com os critérios da *Society of Nephrology/Renal Pathology Society 2003* (ISN/RPS 2003) em NL mesangial mínima (classe I), NL membranosa (classes II – mesangial proliferativa e V- membranosa), NL proliferativa (classes III- focal e IV- difusa) e NL esclerosante avançada

(classe VI) sendo possível, ainda, a diferenciação por inferência clínica, segundo critérios previamente estabelecidos e publicados (14, 20, 21).

Lesões permanentes- SDI

Proporcional ao aumento da sobrevida observou-se, nas últimas décadas, aumento também das internações hospitalares e morbidade, danos permanentes em pacientes com LES e NL, principalmente em virtude das complicações próprias da doença, do seu tratamento e comorbidades como aterosclerose, diabetes mellitus e osteoporose (22).

Os danos crônicos aos órgãos, acumulados, podem predizer maior risco de morbidade e mortalidade futura. Estudos descrevem, por exemplo, que em 10 anos, 25 % dos pacientes com SDI $\geq$ 1 morrem versus 7,3% com SD = 0 (22).

Para avaliar, quantificar e analisar o dano(s) permanente (s) acumulado (s) em pacientes com LES e medir suas variações ao longo do tempo, a *Systemic Lupus Collaborating Clinics* (SLICC) e o *American College of Rheumatology* (ACR) propuseram e validaram um índice de dano específico, o SLICC / ACR *Damage Index* (SDI) (Anexo C) (23, 24).

O índice de danos (SDI) reflete os danos irreversíveis, atribuídos e acumulados durante o curso da doença e desenvolvidos a partir do diagnóstico do LES tendo valor prognóstico. O SDI é quantificado e definido por sistemas/órgãos: ocular, neuropsiquiátrico, renal, pulmonar, cardiovascular, vascular periférico, gastrointestinal, musculosquelético, pele, endócrino (diabetes), gónada e malignidades, somando um máximo (total) de 47 pontos.

As lesões permanentes devem estar presentes por pelo menos 6 meses quando passíveis de reversão como as disfunções cognitivas ou convulsões ou apenas identificadas como por exemplo o infarto do miocárdio, osteonecrose e acidente vascular cerebral que são registrados assim que ocorrem.

Dentre os fatores de risco para SDI temos: no diagnóstico do LES- idade avançada e atividade moderada a grave; no curso do lúpus- maior duração (tempo) da doença, mais episódios de (re) atividades e comorbidades associadas (25, 26).

Atividade do LES

A apresentação clinica e ou laboratorial do lúpus ativo deve ser sempre diferenciada do (s) dano (s) acumulado (s) e da manifestação de outras comorbidades associadas. Com o intuito de padronizar esse diagnóstico, facilitar pesquisas clínicas e diagnósticos diferenciais foram desenvolvidos, desde o início da década de 90, sistemas de pontuação. Estes visam aferir a atividade do LES e nortear a terapêutica, como: o Índice de Atividade de Doença de Lúpus Eritematoso Sistêmico-2K (SLEDAI-2K) (Anexo A), a Medida de Atividade de Lúpus Sistêmica Revisada (SLAM-R) e a Medição de Atividade de Lúpus de Consenso Europeu (ECLAM) (27-31), entre outros, entretanto descrever e discutir especificamente esses índices e suas diferenças, não faz parte do propósito deste trabalho.

Apesar de não haver um padrão ouro isolado para avaliação da atividade do lúpus, em nossos manuscritos, utilizamos o SLEDAI como referência por ser a medida de atividade da doença específica do LES mais comumente empregada (32). O SLEDAI foi validado inicialmente em 1985 sendo após modificado para SELENA- SLEDAI que adicionou maior detalhamento a dados descritores (27) e posteriormente em 2002 foi revisado e modificado para SLEDAI-2K (33) No SLEDAI-2K, a atividade contínua persistente nos descritores de erupção (s) cutânea (s), alopecia, úlceras orais e proteinúria passaram a pontuar em contraste com apenas novas ocorrências no SLEDAI “original”.

Ainda assim, persistem discussões e diversas definições para reativação e índices de aferição padronizados e apesar de não haver consenso, a maioria concorda que deve-se levar em consideração a história clínica, o exame físico, os exames laboratoriais e sorológicos, bem como, quando necessário, exames complementares dirigidos para o órgão suspeito de acometimento, somado a avaliação da necessidade de adição e ou modificação da terapêutica medicamentosa instituída (27, 34-36).

Diversos estudos correlacionam ou tentam estabelecer preditores clínicos e ou laboratoriais para a (re) ativação da doença, como idade precoce do diagnóstico (antes 25 anos), acometimento renal, hematológico ou neurológico, além de títulos elevados de anti-DNA e consumo de complementos séricos especialmente C3, C4 e C1q associado a nefrite ativa. Porém nem todos os pacientes com esses marcadores tem doença ativa e para determinar a ativação, não está recomendada a fundamentação apoiada apenas em um desses parâmetro em virtude da natureza multissistêmica do lúpus e da flutuação da atividade (s) intra e inter pacientes ao longo do tempo (37-39). O diagnóstico de (re) atividade da doença pode ser

dificultado em alguns casos, especialmente nas gestantes em função das alterações fisiológicas e dos sinais e sintomas próprios da gestação.

LES e gestação

Gestação em mulheres com lúpus é um assunto que vem sendo, há décadas, estudado em virtude das potenciais complicações maternas e ou fetais, que incluem respetivamente (re) atividade do lúpus (em particular a nefrite), pré-eclâmpsia, rotura prematura de membranas ovulares (RPMO), abortamento, natimortalidade, parto prematuro, restrição do crescimento fetal (RCF) e lúpus neonatal (incluindo bloqueio cardíaco congênito) (40).

Atualmente temos observamos aumento do número de gestações bem-sucedidas que pode variar de 65 a 92% (38) e diminuição das taxas de perdas fetais de 40% para 17% (42), todavia ainda há eficácia limitada na prevenção das demais complicações (43) e a associação do LES com a gestação continua sendo considerada de alto risco, podendo ter prognóstico reservado.

A frequência da (re) atividade na gestação pode variar de 25 a 60% de acordo com o grupo e desenho de estudo analisado (44- 47), a maioria tende a ser leve, embora cerca de 30% possa evoluir com gravidade seja na gestação, parto e ou puerpério (47).

A reativação no ciclo gravídico puerperal, entre outros fatores, pode estar relacionada a atividade pré-gestacional (concepção) e a aferição adequada da atividade do LES na gestação (48).

O diagnóstico diferencial entre a atividade do lúpus e as alterações fisiológicas próprias da gestação pode ser complicado na prática clínica, sobretudo quando essas situações coexistem e devem ser interpretadas com cautela, como por exemplo: o edema devido ao acúmulo gradual de sódio e água corporal; a anemia leve por hemodiluição; a trombocitopenia até cerca de 80.000 plaquetas/ml e o aumento da velocidade de hemossedimentação (VHS).

Cabe ainda ressaltar que algumas condições patológicas desenvolvidas durante a gestação também podem apresentar alterações clínicas e/ou laboratoriais semelhantes àquelas presentes na atividade do lúpus e no acometimento renal, como por exemplo: anemia hemolítica e plaquetopenia na síndrome *HELLP*; a hipertensão arterial e proteinúria na pré-eclâmpsia; as convulsões na eclâmpsia; as lesões cutâneas na face no melasma gravídico, além de artralgia e alopecia leves.

Deve-se ainda considerar que os níveis dos complementos séricos aumentam na

gestação e, portanto, tornam-se menos informativos para avaliar a atividade lúpica, e também a interpretação da função renal considerando o aumento fisiológico do volume plasmático e da taxa de filtração glomerular.

A distinção entre estas alterações fisiológicas, gestação complicada com determinadas patologias como por exemplo PE e a atividade do LES, deve ser realizada, sempre que possível, uma vez que a abordagem terapêutica e a conduta são distintas e podem influenciar no desfecho e prognóstico materno, fetal e ou neonatal.

Como ferramenta para auxiliar essa diferenciação e diagnóstico, alguns critérios foram propostos e ajustados para a avaliação da atividade do lúpus durante a gestação (49). Um dos índices mais frequentemente empregados em pesquisa e prática clínica, o SLEDAI, foi adaptado para uso na gestação, sendo denominado de SLEPDAI (*Systemic Lupus Erythematosus Pregnancy Disease Activity Index*) (Anexo B).

Atividade na gestação

O lúpus ativo, principalmente no período da concepção e no início da gravidez, aumenta significativamente o risco de complicações maternas e ou fetais e neonatais (48).

Os mecanismos fisiopatológicos da reativação na gestação são semelhantes aos do puerpério: maior concentração dos hormônios estrogênio e prolactina (híper) ao longo dos trimestres gestacionais, aliados a presença de autoanticorpos hiperreativos, anticorpos antifosfolipídeos (principalmente anticoagulante lúpico-LAC), diminuição das citosinas Th1 e aumento das Th2 e seus receptores solúveis, quimosinas e outras glicoproteínas solúveis. As células T reguladoras e dendríticas, e a interação destas com os hormônios próprias da gestação e suas oscilações em cada trimestre gestacional ainda precisam ser elucidadas em mais pesquisas (50).

A probabilidade de reativação do LES na gestação e puerpério é variável podendo chegar aproximadamente 25 a 60% (45, 51, 52), com aproximadamente 21% de crises leves a moderadas e 6% de crises graves na gestação e respetivamente 27,7 e 1,7% no puerpério (53). Quando consideramos pacientes em remissão no momento da concepção, temos redução de 50% para 10-30% nas chances de exacerbação do lúpus. Na maior parte dos casos, quando ocorre reativação na gravidez, esta tende a ser leve e predominantemente cutâneo-articulares (54), entretanto há também acometimento de outros sistemas como renal e hematológico (52).

Os fatores de risco, classicamente, relatados para (re) atividade na gravidez são: o tempo de remissão antes do início da gestação, a maioria dos estudos recomenda seis meses antes da concepção, entretanto há alguns relatos em torno de três a quatro meses (55); ter acometimento renal (nefrite) prévio e suspender medicações em uso, principalmente a hidroxicloroquina e a azatioprina (40, 50, 56). Outros fatores de risco descritos são: ser primigesta (56), ter menor média de idade (±29,56) em anos, ter complementos consumidos (C4) (50, 57) e positividade para anticorpos anti-DNA (50).

As complicações obstétricas mais frequentemente ligadas a atividade do LES são PE (7,6 a 25%), abortamento (16 a 17%), prematuridade (17 a 49%) e RCF (12,7 a 15%). Nestas gestantes, existe também maior frequência de outros desfechos adversos (45) entre eles destacam-se: Maternos - hipertensão gestacional (16,3 a 27,5%), eclâmpsia (0,8 a 4,6%) e rotura prematura de membranas ovulares (40,42,45); fetais, neonatais e infantis - natimortalidade (3,6%), neomortalidade (2,5%) e presença de alterações neurológicas como atraso no neurodesenvolvimento, deficit de atenção e transtorno do espectro autista (40,45, 52, 56-58).

Nefrite ativa na gestação

A paciente com acometimento renal tem maior frequência de (re) atividade na concepção do que as sem (25% vs. 6,6%, p=0,009) (56), isto acontece porque menos de 50% atingem a remissão completa após os primeiros 6 meses de tratamento, apesar dos esquemas terapêuticos atuais (14). Em uma revisão sistemática e metanálise incluindo 37 estudos, foi descrito risco de 16% de reativação renal em gestantes com NL (45). Valor similar (19,7%) foi encontrado em estudo prospectivo que incluiu 71 gestações em 61 pacientes (59). Ambos os estudos apresentavam pacientes com nefrite em remissão, com taxas de reativação renal próximas de 10-15% semelhantes as descritas na literatura (60).

Nos estudos com NL ativa, as taxas de reativação renal são mais elevadas, variando de 44 - 48% (60, 61), em uma análise retrospectiva de 73 gestações, foi descrita reativação em 61,6% (p=0,001) das pacientes, sendo 50% delas *flare* renal (p<0,01).

De uma forma geral, as pacientes com NL, apresentam maior morbidade materna, incluindo eclâmpsia, acidente vascular encefálico e morte (45).

Do ponto de vista prognóstico, bem como para fins terapêuticos as formas mais graves

da NL na gestação são as proliferativas, principalmente quando ativas e associadas a HAS, onde há maior comprometimento da função renal, característico das glomerulonefrites (GN) classes III e IV e menos intensamente das GN membranosas (14,45, 61, 62) sendo provável que a presença de NL mesangial pouco ou nada interfira com os resultados gestacionais, conforme discutido no artigo que consta no ANEXO F.

A GNP, principalmente se ativa durante a gestação, aumenta o risco de desfechos adversos fetais como parto prematuro (39%), crescimento intrauterino restrito (12%), óbito fetal (3,6 a 11%) e neonatal (2,5 a 6,5%) (62-65).

No que se relaciona à saúde materna a GN, mesmo que em remissão, está independentemente associada ao maior risco de desfechos adversos como reativação renal e pré-eclâmpsia (PE) (63-65).

A PE em pacientes com LES varia de 9% a 35%, podendo ser mais alta e precoce naquelas com nefrite ativa (20 a 32 %), em comparação aos percentuais 5 a 8% em mulheres saudáveis (45, 59, 60). Além da nefrite propriamente dita, o risco de PE nessas pacientes, também está associado à presença de hipertensão arterial sistêmica (HAS) prévia, redução da taxa de filtração glomerular (TFG), mesmo que de pequena monta, presença do anticorpo antifosfolipídeo e síndrome do anticorpo antifosfolipídeo (SAF) (41, 59) gestações não planejadas e primeiro episódio de nefrite diagnosticada na gestação (61).

A diferenciação entre pré-eclâmpsia e nefrite ativa pode ser difícil. A positividade do anti-DNA e o consumo de complemento falam a favor de nefrite ativa (66). A pesquisa de marcadores angiogênicos (PLGF - fator de crescimento placentário, VEGF- fator de crescimento de endotélio vascular) e antiangiogênicos (sFlt1- tirosinoquinase 1 solúvel fms-simile) auxiliam na diferenciação entre as duas condições conforme discutido no artigo que consta no ANEXO F. Entretanto uma discussão minuciosa sobre esses marcadores não faz parte dos objetivos da presente tese.

Dano permanente (SDI) e gestação

Até o momento, existem poucos estudos publicados sobre os danos permanente (SDI) e a gestação, os que encontram-se disponíveis, avaliam sumariamente se a própria gravidez tem algum impacto no acúmulo de danos e concluem que apesar dessas gestações terem duração mais curta (em meses), ou seja, mais partos prematuros, elas por si só não predizem o

aumento da pontuação do SDI (67).

O estudo Lumina encontrou 76,2% de desfechos fetais e / ou neonatais adversos, porém essa coorte avaliou apenas 63 gestações e se limitou aos desfechos de aborto, parto prematuro e natimorto, sem avaliar resultados maternos e ou outros desfechos fetais e neonatais (67).

O estudo Luna que apesar de incluir 104 pacientes, sendo 3 com SDI $\geq$1, avaliou apenas 13 gestações após o diagnóstico de LES e não discriminou os desfechos de acordo com o dano permanente. Destas, 12 nasceram vivos e 33% tiverem desfechos adversos (4 nascimentos prematuros e PIGs e 1 óbito fetal) (68).

Um outro estudo, desenvolvido em um centro de Israel, com 61 pacientes, relatou 138 internações, 29 (47,5%) tiveram SDI $\geq$ 1, e a segunda causa de internação foi por complicações na gravidez e no parto 18,9% (26/138), com 1 óbito materno e 4 partos prematuros sendo 1 por PE e PIG. Como os outros citados acima, também não se destinou a correlacionar a pontuação do SDI com resultados adversos e analisou um pequeno número de mulheres grávidas (20/61) (69).

O estudo 2 desta tese, entretanto, analisou o potencial impacto do SDI $\geq$ 1 no início do acompanhamento pré-natal sobre os desfechos gestacionais adversos e demonstrou que gestantes com SDI$\geq$ 1 podem ter maior risco de desfechos maternos, fetais e neonatais adversos quando comparadas àquelas com SDI = 0.

1 **JUSTIFICATIVA**

A maioria das pacientes com LES é acometida pela doença na fase reprodutiva da vida e uma gravidez neste grupo não é infrequente na prática clínica.

Ao mesmo tempo, as gestações nesta população são consideradas de alto risco obstétrico devido a elevada frequência de complicações, incluindo a possibilidade de reativação do lúpus e o maior risco de desfechos adversos.

Ainda que diversos estudos tenham analisado a evolução e os fatores associados aos desfechos gestacionais adversos em pacientes com LES, poucos foram realizados em países em desenvolvimento como o Brasil. Além disso, diversos fenótipos clínicos e laboratoriais da doença como o impacto das diferentes classes histológicas da nefrite lúpica e a presença de danos permanentes ainda não foram analisados por completo como variáveis potenciais para os desfechos adversos maternos, fetais e neonatais, razão pela qual esta coorte foi desenhada.

Neste contexto e para fins de desenvolvimento do presente trabalho selecionamos dois aspectos estudados nesta coorte, especificamente a ocorrência de PIG e o impacto dos danos permanentes sobre os desfechos gestacionais, para uma avaliação mais minuciosa.

2 **OBJETIVOS**

2.1 **Objetivo geral**

Avaliar os desfechos maternos, fetais e neonatais em uma coorte de gestantes com lúpus eritematoso sistêmico.

2.2 **Objetivos específicos**

Analisar as variáveis clínicas e laboratoriais maternas potencialmente associadas à ocorrência de recém-nascidos pequenos para a idade gestacional (estudo 1).

Avaliar o potencial impacto dos danos permanentes (SDI) sobre os desfechos maternos, fetais e neonatais (estudo 2).

3 **PACIENTES E MÉTODOS**

3.1 **Delineamento do estudo**

Estudo de coorte com coleta prospectiva e retrospectiva de dados, realizado no Hospital Universitário Pedro Ernesto (HUPE) da Universidade do Estado do Rio de Janeiro (UERJ), no período de 2011 a 2020.

3.2 **População do estudo**

Foram selecionadas todas as gestações de pacientes com LES, de acordo com os critérios de classificação do *American College of Rheumatology* (ACR) revisados por Hochberg em 1997 (70), acompanhadas no ambulatório de pré-natal de doenças reumáticas imunomediadas (previamente ambulatório de pré-natal de colagenoses) do HUPE, no período de 2011 a 2020. Foram excluídas as gestações múltiplas, os abortamentos e as aneupleudias (Apêndice A).

Os dados foram obtidos por entrevista pessoal e revisão dos prontuários físicos e eletrônicos com o emprego de um questionário semiestruturado (Apêndice B) impresso e digitalizado. Quando necessário, foi feito contato telefônico para confirmação e ou obtenção de informações complementares. O presente estudo foi aprovado pelo CEP sob o número CAAE: 50726115.40000.5259, incluindo a emenda versão 4 de 08 de abril de 2020 que abrange a mudança do título do estudo para: “Análise dos desfechos maternos, fetais, neonatais e infantis das gestações de mulheres com LES acompanhadas na UERJ-Coorte GELES (Apêndice C). Todas as pacientes assinaram o termo de consentimento livre e esclarecido (TCLE) previamente aprovado pelo comitê de ética do HUPE (Apêndice D).

As variáveis maternas para análise da potencial associação com os desfechos adversos maternos, fetais e neonatais foram: dados sociodemográficos (a cor da pele foi definida por autodeclaração), manifestações clínicas, medicações em uso no início do acompanhamento pré-natal e ao longo da gestação, ocorrência de uma ou mais internações durante a gravidez, dados da (s) internação (s) (etiologia, duração, terapêutica), presença de comorbidades, duração da

gestação, tipo de parto (cesariana, vaginal ou fórceps) e características especificas do trabalho de parto (espontâneo ou indicado; eletivo ou de urgência).

Todos os exames laboratoriais disponíveis foram verificados e conferidos no prontuário e no laboratório do HUPE. Os métodos utilizados para avaliação sorológica dos autoanticorpos, foram respectivamente: imunofluorescência indireta, substrato de células HEp2 para o fator antinuclear (FAN); imunofluorescência indireta, substrato de *Crithidia luciliae* para anti-DNA de fita dupla e fluoroenzima imunoensaio para anti- Ro, anti-La, anti-SM e anti-RNP. Para os anticorpos antifosfolipídeos (Apl): imunoensaio enzimático para anticardiolipina (ACL) e anti-Beta 2 glicoproteína I e anticoagulante lúpico (LAC), método I- tempo de veneno de víbora de *Russel* diluído (dRVVT) e método II- tempo de tromboplastina parcial ativado com ativação sílica (S-TTpa).

Os métodos utilizados para avaliação dos complementos foram: imunoturbimetria para os complementos séricos C3 e C4 e imunoensaio enzimático (ELISA) para complemento total CH-50.

A avaliação da atividade do lúpus no início do acompanhamento pré-natal e ou no primeiro trimestre da gestação, no segundo e terceiro trimestres e no pós-parto, foi avaliada com o emprego do escore de SLEPDAI (Anexo B). Foram consideradas com doença ativa aquelas pacientes com SLEPDAI $\geq$ 4 (48).

O índice de dano permanente, na primeira consulta do pré-natal, foi avaliado com o emprego do escore SDI (Anexo C). Foram consideradas com dano irreversível aquelas pacientes com pontuação SDI $\geq$ 1 na primeira consulta do pré-natal.

As pacientes com história de nefrite lúpica (NL) submetidas previamente a biópsias renais foram classificados de acordo com a classificação ISN / RPS (20,21) e aquelas sem biópsia, foram classificados por inferência, realizada pelo reumatologista, baseada em análises clínicas e laboratoriais de acordo com os critérios publicados (14). A NL ativa foi definida como o desenvolvimento de nova proteinúria (> 500 mg / 24h); quando a prévia era < 500 mg / 24h ou > 2.000 mg / 24h, nos casos > 500 mg / 24h ou presença de sedimento urinário ativo (> 5 glóbulos vermelhos ou leucócitos por campo de grande ampliação 400X ou presença de cilindros celulares), presença de hematúria dismórfica de padrão glomerular (> 50% entre as hemácias urinárias) ou creatinina sérica elevada devido a nefrite (60, 64, 65-71)

As medições de proteinúria foram obtidas a partir de amostras isoladas de urina usando a relação proteinúria / creatinina urinária ou medidas em 24 horas respectivamente pelos métodos parcial/colorimétrico e colorimétrico com vermelho de pirogalol.

A pré-eclâmpsia (PE) foi definida, de acordo com os critérios propostos pelo *American*

College of Obstetricians and Gynecologists 2013, como a ocorrência de hipertensão e proteinúria acima de 300 mg / 24h após 20 semanas de gestação ou o início ou piora da hipertensão (aumento ≥ 15 mmHg) e um aumento de duas vezes no valor da proteinúria em um paciente com proteinúria prévia, sem nefrite ativa (72).

A restrição do crescimento fetal, foi definida como o feto que não atingiu o seu potencial de crescimento e que tinha peso estimado abaixo do 10º percentil para a idade gestacional durante a avaliação ultrassonográfica (73,74), sendo mais graves aqueles abaixo do 3º percentil.

Ao nascimento, os recém-nascidos com peso abaixo do 10º percentil para a idade gestacional foram definidos como pequenos para a idade gestacional (PIGs). As curvas de Fenton (Anexo D) e as curvas de crescimento do *International Fetal and Newborn Growth Consortium for the 21st Century* (*INTERGROWTH-21*) foram usadas para classificar o peso ao nascer (Anexo E).

3.3 **Resultados**

Na presente coorte foram incluídas 274 gestações em 260 pacientes com LES (Apêndice A). As principais características demográficas, clínicas e laboratoriais estão descritas na tabela 1 (Apêndice E).

Segue abaixo os resultados dos estudos 1 ("*The association between active proliferative lupus nephritis during pregnancy and small for gestational age newborns*") e 2 ("*The SLICC/ACR Damage Index (SDI) may predict adverse obstetric events in patients with Systemic Lupus Erythematosus (SLE*)") que representam a análise de parte dos dados obtidos na coorte de gestantes com LES (UERJ-GELES) e nos Anexos F e G manuscrito de outros estudos desenvolvidos no período da pós-graduação.

4 **ESTUDO 1**

a. Autores

Artigo publicado na revista Clin Exp Rheumatol em 18 de Outubro de 2020. Referência:1. Ignacchiti Lacerda M, Costa Rodrigues B, Ramires de Jesús G, Cunha Dos Santos F, Ramires de Jesús N, Levy RA, Mendes Klumb E. The association between active proliferative lupus nephritis during pregnancy and small for gestational age newborns. Clin Exp Rheumatol. 2020 Oct 18. Epub ahead of print. PMID: 33124562.

b. Artigo Title

The association between active proliferative lupus nephritis during pregnancy and small for gestational age newborns

Abstract

OBJECTIVE: To analyze maternal variables associated with occurrence of small for gestational age (SGA) newborns in pregnancies of women with systemic lupus erythematosus (SLE), considering clinical and laboratory characteristics prior to conception, during gestation and comorbidities. METHODS: Retrospective cohort study with SLE pregnant patients and singleton deliveries after 22 weeks. SGA newborn was defined as birth weight below 10^{th} percentile and SLE activity at conception and during gestation was measured using SLE Pregnancy Disease Activity Index (SLEPDAI). Univariate analysis was employed to evaluate individual influence of demographic and clinical variables on the SGA newborn outcome, while variables with $p < 0.20$ were included in multivariate regression. RESULTS: Among 151 pregnancies, 28 (18.5%) had SGA newborns. History of proliferative nephritis (RR=3.84) and positivity for anti-RNP and anti-Sm antibodies (RR=2.67,2.78) were more frequent in the study group. Active proliferative nephritis at conception (RR=3.29) and during gestation (RR=3.63), as well as complement C3 consumption (RR=2.70) and venous pulse therapy with methylprednisolone (RR=20.3), were also associated with SGA newborns, the latter being

independently associated in multivariate regression. Adverse perinatal outcomes, such as stillbirths (4.3 times) and neonatal intensive care unit admissions (3.2 times), were more frequent among SGA infants. CONCLUSION: Active proliferative lupus nephritis during pregnancy was associated with SGA newborns, while its treatment with venous pulse therapy with methylprednisolone may play a significant role in this context. Presence of previous proliferative nephritis, SLEPDAI > 4, C3 consumption and presence of anti-RNP and anti-Sm antibodies were additional variables associated with SGA newborns in this population.

Keywords

Systemic Lupus Erythematosus, Lupus Nephritis, Birth Weight, Small for Gestational Age.

4.1 **Introduction**

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad spectrum of clinical presentation and severity. It primarily affects women at reproductive age and typically presents periods of activity and remission that clearly interferes with gestational outcomes (1). Despite recent advances in therapy and improved survival rates, pregnant women with SLE still have a higher frequency of maternal and fetal morbidity (2, 3), such as utero-placental dysfunction, represented a fetal growth restriction (FGR) during ultrasound evaluation and small for gestational age (SGA) newborns.

Incidence of FGR in pregnancies with SLE is greater than in general population (5 to 30% versus 7 to 15%) (4, 5), with a perinatal mortality rate 10 times higher than normal fetuses. Those who survive are more prone to neonatal morbidity, delayed neurological development, learning disabilities, behavioral changes, and cerebral palsy (6). In adulthood, there is still an increased risk of arterial hypertension, type 2 diabetes, obesity, atherosclerosis, hypercholesterolemia, and cardiovascular disease (7, 8).

The present study aimed to analyze maternal variables associated with occurrence of SGA newborns in a cohort of SLE patients followed at a high-risk prenatal clinic for rheumatic and autoimmune diseases.

4.2 **Materials and methods**

This is a retrospective cohort study with analysis of clinical and laboratory variables in pregnant SLE patients, followed in Pedro Ernesto University Hospital (Rio de Janeiro, Brazil).

All patients classified with SLE according to the American College of Rheumatology (ACR) criteria (9), presenting singleton pregnancies and deliveries after 22 weeks of gestation between January 2011 and December 2016 were included. Besides SLE classification criteria, other inclusion criteria were: available data about the disease state at conception and during gestation (activity score); gestational age at delivery; and newborn's birth weight and gender. Pregnancies whose fetuses presented congenital malformations or aneuploidies were excluded. SLE activity at conception and during gestation was measured with Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) (10, 11), as well as steroids and/or immunosuppressive adjustments due to active disease. Patients were classified with active SLE if SLEPDAI was $\geq$ 4 and inactive disease was defined as SLEPDAI < 4 (12). Previous lupus nephritis (LN) was confirmed when the patient had biopsy proven classes II, III, IV and V LN, according to the ISN/RPS 2003 classification (13). For those patients without biopsy, LN was established by the presence of proteinuria greater than or equal to 500 mg/24h or urinary protein/creatinine ratio higher than 0.5.

In those patients, histologic classification was made by clinical inference according to previously published criteria (1). Currently accepted definition of FGR is a fetus with estimated weight below the 10^{th} percentile for gestational age during ultrasound evaluation (7, 14, and 15), being considered as severe those classified below the 3^{rd} percentile. The clinical confirmation of a growth restricted fetus is a SGA newborn, defined as birth weight below the 10^{th} percentile (16). The International Fetal and Newborn Growth Consortium for the 21^{st} Century (INTERGROWTH-21) growth curves were used to classify birth weight (17, 18). In four cases of births at 22 and 23 weeks, the Fenton curve was used to classify growth, since the INTERGROWTH-21 curves start at 24 weeks (19). Univariate analysis was employed to evaluate individual influence of demographic and clinical variables on the SGA newborn outcome. In the multivariate analysis, independent predictors were selected by stepwise forward selection method. Through univariate analysis, explanatory variables with $p < 0.20$ were included in the multivariate regression.

Comparison between the groups with SGA and non-SGA newborns was analyzed by Student's t-test (parametric) or Mann-Whitney test (non- parametric) for numerical data, and by the chi-square test ($\chi 2$) or Fisher's exact test for categorical data. Statistical analysis was performed using statistical software SAS® System, version 6.11 (SAS Institute, Inc., Cary, North Carolina). The institution's ethics committee review board approved the study.

4.3 **Results**

A total of 151 gestations in 139 SLE patients were analyzed. Twenty- eight pregnancies resulted in SGA newborns (18.5%) and 123 were classified as non-SGA newborns. Among the 28 SGA infants, 19 (67.9%) were below the 3rd percentile and/or had abnormalities in fetal Doppler velocimetry, which may represent greater severity and worse prognosis. All these severe cases were already identified as FGR by routine ultrasound and the positive predictive value for ultrasound FGR diagnosis was 90.5% (19/21), with a negative predictive value of 93% (121/130).

Clinical and demographic variables of included patients are described in Table I. Considering the total sample, mean maternal age at delivery was 28.4 ± 6.0 years, with no difference between SGA and non-SGA groups. There was also no statistical difference when mean gestational age at delivery of excluded patients (29.2 $\pm$ 6.7) was compared to the whole sample or even to the groups included in the analysis. Fourteen patients with SGA newborns were nulliparous (14/28, 50%), a similar proportion to the patients that had adequate for gestational age newborns (58/123, 47.1%) (p 0.39).

Regarding clinical and laboratorial manifestations that occurred during the whole course of disease, 43% (64/151) had a past history of nephritis (SGA 18/28, non-SGA 46/123) and 20.5% had neuropsychiatric manifestation. In those patients with history of nephritis, mean serum creatinine levels were within normal range but statistically higher in the SGA group (0.89 $\pm$ 0.31 excluding one patient on dialysis vs 0.64 $\pm$ 0.24 on non-SGA group). Twenty-nine (19.2%) patients had chronic hypertension, 19 (12.6%) patients had antiphospholipid syndrome (APS) and 13 (8.6%) only had positive antiphospholipid antibodies (aPL) without APS. Low serum complements (C3 and C4) was identified in 32.4% of the patients.

Table 1. Demographic, clinical and immunological features of patients according to SGA NB outcomes.

Variable	SGA (n = 28) n	%	non-SGA (n =123) n	%	RR	CI 95%	*p* value
Maternal age at delivery (years) mean ± SD	28.3 ± 7.1		28.5 ± 5.7		1.00	0.93 - 1.07	0.90
Duration of SLE (years) median (Q1 - Q3)	6.5 (3-10)		7 (3-11)		0.97	0.89 - 1.05	0.45
Permanent damage by SDI ≥ 1	11	39.3	27	22	2.30	0.96 – 5.49	0.061
SLE involvement before pregnancy							
Cutaneous	23	82.1	11	90.2	0.50	0.16 - 1.55	0.23
Articular	25	89.3	11	90.2	0.90	0.24 - 3.43	0.88
Haematological	14	50	77	62.6	0.60	0.26 - 1.36	0.22
Neuropsychiatric	7	25	24	19.5	1.37	0.52 - 3.61	0.52
Serositis	9	2.1	44	35.8	0.85	0.35 - 2.04	0.72
Nephritis	18	64.3	46	37.4	2.99	1.27 - 7.28	0.005
Proliferative (classes III/IV)	17	94.4	35	28.4	3.84	1.63 - 9.30	0.0009
Non-proliferative (classes II/V)	1	5.6	11	8.9	0.37	0.01 - 2.37	0.19
Immunological profile							
Anti-RNP	11	39.3	24	19.5	2.67	1.11 - 6.43	0.029
Anti-Sm	9	32.1	13	10.5	2.78	1.44 - 5.32	0.004
Anti-Ro/SSA	12	42.9	60	48.8	0.79	0.34 - 1.80	0.57
Anti-La/SSB	2	7.1	13	10.6	0.65	0.14 - 3.06	0.59
Antiphospholipid syndrome	3	10.7	16	13	0.80	0.22 - 2.97	0.74
Positive aPL* without APS	2	7.1	11	8.9	0.78	0.11 - 3.40	0.40

Categorical data were expressed by frequency (n) and percentage (%) and numerical data by mean ± standard deviation (SD) or median and interquartile range (Q1-Q3). Relative risk (RR) and its confidence interval f 95% (CI 95%) according to individual binary logistic regression. SLE: systemic lupus erythematosus. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index *aPL: antiphospholipid antibodies.

Forty-three patients (28.5%) had active lupus at conception. Twenty-one (49%) of these had active lupus nephritis, with nineteen being classified with proliferative nephritis (classes III/IV). Five patients were submitted to methylprednisolone intravenous pulse therapy during pregnancy, all due to active nephritis classes III or IV.

Variables related to LN (active nephritis at conception and during pregnancy, pulse therapy), increased SLEPDAI at the end of gestation, low C3, positivity for anti-RNP and anti-Sm were significantly associated with the main outcome (Table II).

Table 2. Disease activity by clinical judgment and serological markers at the beginning and at the end of gestation according to SGA NB outcome.

Variable	SGA (n= 28)		non-SGA (n=123)		RR	CI 95%	*p*-value
	n	%	n	%			
Active SLE at conception	10	35.7	33	26.8	1.52	0.63 – 3.62	0.35
Non-renal activity	5	17.8	27	21.9	0.80	0.33 – 1.95	0.42
Active nephritis at conception	9	32.1	12	9.75	2.93	1.53 – 5.59	0.004
Proliferative (classes III/IV)	9	100	10	83.3	3.29	1.75 – 6.18	0.001
Non-proliferative (classes II/V)	0	0	2	16.7	0	0 – 15.39	0.33
Active SLE during gestation	10	35.7	34	27.6	1.35	0.67 – 2.69	0.26
Non-renal activity	4	14.3	27	21.9	0.64	0.24 – 1.72	0.26
Active nephritis during gestation	10	35.7	14	11.4	2.94	1.44 – 5.56	0.003
Proliferative (classes III/IV)	10	100	10	71.5	3.63	1.97 – 6.71	0.0003
Non-proliferative (classes II/V)	0	0	4	28.4	0	0 – 54.5	0.21
SLEPDAI at the beginning of gestation (points) - median (Q1-Q3)	2 (0 – 6)		1 (0 – 4)		1.09	0.99 – 1.19	0.088
Anti-DNA	10	35.7	26	21.1	2.07	0.85 – 5.03	0.10
C3 consumption	7	25.0	22	17.9	1.53	0.58 – 4.04	0.39
C4 consumption	6	21.4	11	8.9	0.36	0.12 – 1.08	0.067
SLEPDAI at the end of gestation (points) - median (Q1-Q3)	4 (0 – 7.5)		1 (0 – 3)		1.10	1.01 – 1.20	0.026
Anti-DNA	9	32.1	25	20.3	1.86	0.75 – 4.60	0.18
C3 consumption	10	35.7	21	17.1	2.79	1.09 – 6.67	0.031
C4 consumption	6	21.4	12	9.8	2.52	0.86 – 7.44	0.094

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and this confidence interval of 95% (CI 95%) according to individual binary logistic regression. SLE: systemic lupus erythematosus; SLEPDAI: Pregnancy Disease Activity Index

There was no statistically significant difference between groups for other clinical manifestations, including non-renal activity, active mesangial and membranous nephritis (classes II and V), immunological features and co-morbidities, as well as for other treatments besides pulse therapy during pregnancy (Table III).

Table 3. Treatment during pregnancy according to SGA NB outcome.

Variable	SGA (n=28)		non-SGA (n = 123)				
	n	%	n	%	RR	CI 95%	*p-value*
Methylprednisolone intravenous pulse therapy	4	14.3	1	0.81	20.3	2.18 - 190	0.008
Oral prednisone	19	67.9	77	62.6	1.26	0.53 -3.02	0.60
Azathioprine	14	50	54	43.9	1.28	0.56 -2.91	0.56
Hydroxychloroquine	27	96.4	121	98.4	0.45	0.04 -5.10	0.52
Low Dose Aspirin	24	85.7	106	86.2	0.96	0.30 -3.12	0.95
Heparin	5	17.9	20	16.3	1.12	0.38 -3.29	0.84

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.

Neonatal intensive care unit (ICU) admission (50% versus 15.4%, p <0.0001) and stillbirths (14.3% versus 3.3%, p = 0.039) were more frequent among SGA infants (Table IV). All stillbirths in the SGA group had severe growth restriction (birth weight below 3rd percentile), with a median gestational age at intrauterine death of 26.5 weeks and mean birth weight of 763.5 ± 580g. In all SGA stillbirths, the mother had active nephritis at conception and half of them (2/4) received intravenous pulse therapy with methylprednisolone during pregnancy.

Perinatal mortality was 7.3% (8 intrauterine deaths and 3 neonatal deaths), with a survival rate of 92.7% of newborns in the total sample. Survival among SGA newborns was 84% and in the non-SGA newborns was 93.2%, with no significant difference between the groups (p = 0.10).

All statistically significant variables, previously mentioned in univariate analysis, were selected for multivariate analysis by logistic regression. Administration of intravenous pulse therapy with methylprednisolone for active proliferative nephritis during pregnancy was found as an independent risk factor for the SGA newborn outcome (RR = 24.5, 95% CI 2.1 - 283, p = 0.010).

Table 4. Characteristics of birth and newborn according to SGA classification.

Variable	SGA (n=28)		non- SGA (N=123)		P-value
	n	%	n	%	
Gestational age at delivery (weeks)					
median (Q1 - Q3)	36.5 (3-38)		38 (3-39)		0.05
Preterm birth	10	41.6	38	31.9	0.17
Birth weight (g) mean ± SD	1831 ± 687		2794 ± 741		<0.0001
Neonatal ICU admission	14	50	19	15.4	<0.0001
Stillbirth	4	14.3	4	3.3	0.039
Neonatal death	0	-	3	2.6	0.31

Categorical data were expressed by frequency (n) and percentage (%).
Numerical data were expressed by mean ± SD (standart deviation) or median and interquartile Range; ICU: Intensive care unit.

4.4 **Discussion**

In this study, the rate of SGA newborns was 18.5%. This is in accordance with published rates for patients with SLE (5 to 30%) and higher than that observed in general population (7 to 15%) (4, 5, 7).

The presence of active lupus at conception is associated with worse maternal and fetal prognosis (20), and can be a predictor of perpetuation of activity throughout gestation. Patients who have active SLE at conception may have up to twice as much risk of activity during pregnancy and 3.5 times higher risk of FGR (21-23).

In our cohort, almost one third of patients who had SGA newborns presented active disease at conception and 35% had active proliferative nephritis during pregnancy, while this frequency was 10% and 11%, respectively, in patients with non-SGA newborns. The local adherence to lupus treatment and contraceptive methods in Brazil is low and discontinuation of all medications due to potential risk of teratogenicity is frequent, which results in higher frequency of activity at conception (25). It is important to note that sixty-five percent of pregnancies in Brazil are not planned (26).

Considering pregnant women with active nephritis at conception, 81% (17/21) remained with active disease during pregnancy, demonstrating an activity perpetuation rate

higher than that previously described in the literature (17, 27, 29). Seventeen of the 18 patients with a history of nephritis and SGA newborns had proliferative LN (classes III and IV), and four of them required intravenous pulse therapy. Proliferative LN has a more aggressive behavior, is associated with a higher risk of reactivation in pregnancy and a greater frequency of activity at conception due to the lower rates of complete remission (1, 24 and 30). The results of the current study are in consonance our previously publication, that adverse fetal and neonatal outcomes appear to be more related to active proliferative lupus nephritis rather than non-renal disease or even different classes of renal involvement (classes II and V) (24).

Usual acute treatment for active SLE is corticosteroids and, during pregnancy, high doses may influence placental angiogenesis. Glucocorticoids can affect the expression of VEGF receptor and also reduce the production of TNF and interleukin 6, placental cytokines that have a regulatory effect on angiogenesis. Disturbances in the development and functioning of the villous vascular system generate reduction of uteroplacental blood flow and contribute to the pathogenesis of fetal growth restriction (31).

SLE activity measured by SLEPDAI score at the end of gestation was also significantly higher in the SGA group (32). Scales of disease activity during pregnancy are not often used in clinical practice, but the observed association suggests that they may be useful in identifying pregnant women at increased risk of developing FGR.

Complement C3 consumption can be related to the high frequency of activity during gestation in the sample, around 30%. Of the 31 patients with C3 consumption at the end of gestation, 17 had active disease (54.8%). There are publications that correlate hypocomplementemia during gestation with other adverse obstetric outcomes, such as pregnancy loss and preterm birth, regardless of SLE activity (33). In the same way, a prospective study with 47 patients with APS described hypocomplementemia as an independent predictor of lower birth weight and lower gestational age at delivery (34).

Anti-RNP and anti-Sm antibodies are highly specific for the diagnosis of SLE and may be present in about 30% of patients. Some authors have described that Anti-RNP antibodies, especially when associated to anti-Sm, are more frequent in patients with lupus nephritis, which can justify the higher frequency of these antibodies in the SGA group (35). Anyhow, this association between anti-RNP and anti-Sm antibodies and SGA newborns, found in our study, is not described in the literature and deserves further investigation.

Recent reports have demonstrated that hydroxychloroquine may reduce the incidence of FGR and prematurity in patients with SLE (36), however not all publications have reached the same conclusion (37). The universal use of hydroxychloroquine medication in the studied

population (98% of the cohort was using the medication at the end of gestation) did not allow to use it as a variable of discrimination between the groups. Similarly, the administration of low dose aspirin to pregnant women with high risk for pre-eclampsia, perinatal death and SGA newborns significantly decreases the occurrence of these events when started before 16 weeks (38,39,40). Despite the use of aspirin by more than 85% of patients during gestation, the frequency of FGR was still high in this study.

When FGR is identified in antenatal screening, fetal well-being surveillance increases and delivery is scheduled at the most opportune moment, balancing the risk of intrauterine death with the morbidity and mortality of prematurity (41). In our study, all severe cases (birth weight below 3rd percentile and/or Doppler abnormalities) were accurately identified during routine ultrasound screening, performed monthly after 24 weeks in our center. This diagnostic accuracy for FRG is better when fetal biometry evaluation is associated with the analysis of uterine and fetus-placental circulation by Doppler velocimetry, which was used in all cases (19, 21). The evaluation of anti-angiogenic and angiogenic cytokines, such as sFlt-1 and PIGF, may also help identify women at higher risk of placenta-mediated complications like FGR, as they are strongly associated with Doppler velocimetry changes and histological signs of placental hypoperfusion (21, 22, 42).

Regarding fetal death, placenta-mediated obstetric complications are the leading cause in patients with SLE (42). Intrauterine deaths in women with SLE occur earlier than in controls (median 29 weeks in patients with SLE versus 35 weeks in healthy patients) and are more frequent in cases of severe FGR (below the 3rd percentile) or altered flow at fetal Doppler velocimetry (43, 44). In this study, fetal deaths in patients with FGR were even earlier (26 weeks), with all SGA stillborn below the 3rd percentile and 75% of them presented abnormalities in Doppler velocimetry. Neonatal deaths and prematurity were not statistically different between groups in this study.

The retrospective analysis and the single center characteristic are limitations of this study. Although it is a cohort of 151 pregnancies in 139 women with SLE, some variables had a small number of events, which lead to high relative risks and wide confidence intervals. On the other hand, all patients were evaluated by both obstetricians and rheumatologists with experience in pregnant patients with SLE, which may increase the accuracy of reported diagnosis.

In conclusion, this study demonstrates that active proliferative nephritis during pregnancy was associated with SGA newborns, while its treatment with intravenous pulse therapy with methylprednisolone may play a significant role in this context. Presence of

previous proliferative nephritis, SLEPDAI $\geq$ 4, complement C3 consumption, presence of anti-RNP and anti-Sm antibodies were additional variables associated with SGA newborns in this population. Regular screening with ultrasound and Doppler velocimetry may identify fetuses at higher risks for adverse perinatal events.

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5 ESTUDO 2

a. Submissão

Artigo submetido para publicação na revista Lupus em 12 de Maio de 2021 (Apêndice F- The SLICC/ACR Damage Index (SDI) may predict adverse obstetric events in patients with Systemic Lupus Erythematosus (SLE)).

b. Artigo Title

The SLICC/ACR Damage Index (SDI) may predict adverse obstetric events in patients with Systemic Lupus Erythematosus (SLE)

Abstract

Objective: The objective of this study was to evaluate the potential impact of irreversible damage accrual in women with systemic lupus erythematosus (SLE) and adverse maternal and/or fetal/neonatal outcomes.

Methods: Retrospective cohort study with SLE pregnant patients, carried out from January 2011 to January 2020 at the Hospital University Pedro Ernesto (HUPE) of the State University of Rio de Janeiro, Brazil. Irreversible damage was defined according to SLICC/ACR damage index (SDI). The association of SDI on pregnancy outcomes was established by univariate and multivariate regression models and included demographic and clinical variables.

Results: This study included data from 260 patients in their first pregnancies after SLE diagnosis, with a quarter of them (67/260) scoring one or more points on SDI at the beginning of prenatal care. These patients presented more frequently adverse maternal events, namely disease activity during pregnancy (p=0.004) and puerperium (p=0.001), active lupus nephritis (p=0.04) and hospitalizations (p=0.004), than those with no SDI score. Similarly, the risks of adverse fetal and neonatal outcomes were also higher among the patients with SDI $\geq$ 1 (59.7% vs. 38.3 % p=0.001) even after controlling data for disease activity (SLEPDAI $\geq$ 4). Patients with SDI $\geq$ 1 presented more frequently preterm deliveries (46.3% vs 31.6%; p=0.01), small for gestational age infants (28.3% vs 18.1%; p=0.04), and neonatal intensive care unit admission (26.9% vs 1.5%; $p < 0.001$). The multivariate analyses showed that SDI $\geq$ 1 is an

independent risk factor for hospitalization due to obstetric complications (p=0.0008) and preterm delivery (p=0.009).

Conclusion: Pregnant SLE patients who present irreversible damage accrual may have higher risk of maternal and fetal adverse outcomes, independently of disease activity.

Keywords

Systemic Lupus Erythematosus, SLICC, SDI, Irreversible Damage Accrual, Pregnancy, Adverse Pregnancy Outcomes.

5.1 **Introduction**

Systemic lupus erythematosus (SLE) mainly affects women in reproductive age and pregnancy is common in this population. Over the past decades, the proportion of successful pregnancies increased considerably among these patients (1), with decreasing rates of fetal loss (2) and adverse pregnancy outcomes (3). However, ominous events related to lupus activity during pregnancy remain a major challenge. While evaluating pregnant patients with SLE, some disease aspects should be considered as predictors of adverse pregnancies outcomes, such as active or the history of lupus nephritis (4,5,6), moderate or high disease activity, pulmonary hypertension, presence of antiphospholipid syndrome (APS) or antiphospholipid antibodies (aPL), chronic kidney disease and chronic arterial hypertension.

Among SLE patients, irreversible organ damage is assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI), which has been extensively validated. The presence of permanent damage accrual, measured by the SDI, is associated with increased risk of further damage, reduced health-related quality of life and higher socio-economic burden and early mortality (7), especially when there is early damage and renal or cardiovascular impairment (8).

Although there have been, in the last decades, many studies that searched for predictors of adverse gestational results in women with SLE, to our knowledge, there is no published data that analyzed the impact of damage (SDI) at the beginning of prenatal care, on pregnancy outcomes. The aim of the present study is to evaluate this potential association in a cohort of SLE pregnant patients.

5.2 **Materials and Methods**

This is an observational single-center cohort study, approved by the Institutional Ethics Committee. The studied population was selected among the two hundred and ninety women with SLE followed at the high-risk prenatal care clinic for autoimmune diseases and thrombophilia (PrAT) at Hospital Universitário Pedro Ernesto in Rio de Janeiro, Brazil, during a 9-year period between 2011 and 2020. Data were obtained retrospectively by medical charts' review and personal interviews when necessary.

All pregnant patients that fulfilled ACR 1997 classification criteria for SLE (9) were included. For this study, all data referred exclusively to the first pregnancy of each patient after the SLE diagnosis in order to avoid duplication of SDI count and its potential bias for patients with more than one pregnancy. Cases with congenital malformations or aneuploidies, miscarriages, twin pregnancies, second or more pregnancies and lack of adequate data for analysis were excluded.

5.3 **Definitions**

5.3.1. Definition of maternal variables

SLE activity was defined as Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) $\geq$ 4 during pregnancy (11) and/or a rheumatologist and obstetrician consensual judgement with a need for increasing steroid and/or azathioprine doses. Irreversible organ damage was assessed in the first visit using the SDI (12, 13, 8, 14). Patients with SDI score of 1 or more were grouped and compared to pregnant women with score of zero.

Lupus nephritis was classified according to ISN/RPS histological criteria (15), while patients with nephritis without renal biopsy were classified by clinical inference according to previously published criteria (16). Pre-eclampsia was diagnosed according to the criteria proposed by the American College of Obstetricians and Gynecologists (17).

For this study, maternal adverse pregnancy outcomes (APO) were defined as: lupus disease activity (SLEPDAI $\geq$4), hypertensive disorders related to pregnancy (gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, placental abruption), need for

hospitalizations due to SLE or obstetric complications not directly related to lupus, obstetric complications during puerperium (infections, hemorrhage, blood transfusion, surgical complications) and Cesarean section.

5.3.2. Definition of fetal and neonatal variables

Adverse fetal and neonatal variables were defined as: small for gestational age (SGA) at delivery, preterm birth, stillbirth, admission to neonatal intensive care unit (NICU), neonatal death and neonatal lupus. SGA newborns were classified as birthweight below the 10th percentile according to the INTERGROWTH-21st (between 24 and 42 weeks and 6 days) and Fenton (between 22 and 24 weeks) curves (18, 19).

5.4 **Statistical analysis**

The descriptive analysis will be presented in the form of tables, the data observed will be expressed by measures of central tendency and dispersion (mean, standard deviation, median and interquartile range) for numerical data, and frequency and percentage (n , and%) for categorical data.

In order to assess the individual influence and the association of demographic, clinical variables, laboratory markers, treatment and comorbidities relationship between adverse pregnancy outcome (APO) and chronic damage (SLICC/ACR-DI), univariate analysis was used.

Once identified, in the univariate analysis, the variables with significant association and p value of up to 0.20 were adjusted to the logistic regression models for the multivariate analysis. In this, initially, all predictors were evaluated individually and later they were selected by the stepwise forward selection method and then choose the multiple statistical model with only the significant variables (p value $\leq$0.05). Thus, the final logistic regression estimated the relative risks and their corresponding 95% confidence intervals.

The comparison of childbirth and newborn characteristics between subgroups with and without SDI was assessed by Student's t test for independent samples or Mann-Whitney (nonparametric), and for categorical data the $\chi 2$ test or Fisher's exact test was applied. The chi-square test was used for categorical data and Fisher's exact test was used as an alternative to the chi-square when at least one of the variables was <5. A nonparametric method was applied, as some numerical variables that did not have a normal distribution (Gaussian), due to the rejection

of the hypothesis of normality according to the Shapiro-Wilk test. The database was implemented in a Microsoft Excel 2007 spreadsheet. The statistical analyzes were processed using free program R version 3.3.2 (www.r-project.org).

5.5 **Results**

The first pregnancies of 283 SLE patients that occurred from January 2011 to January 2020 were reviewed. Twenty-three patients were excluded, the reasons were: malformed or aneuploid fetuses (5 patients), twin pregnancies (2), miscarriage (12) and pregnant SLE patients for whom adequate data was not available (4). Therefore, 260 patients in their first pregnancies after SLE diagnosis were included. At the beginning of the prenatal care follow-up, a quarter of the patients (67/260) had a SDI score $\geq$1 with the following results: 50/67 (74.6%) scoring 1; nine (13.4%) patients with score of 2; three (4.5%) with score 3 and five patients (7.5%) scoring 4. The most commonly affected systems were: neurological (24.7%), peripheral vascular (21%) and renal (19.4%) cardiovascular (10.4%), pulmonary (6%) and infarction or resection of bowel (below duodenum), spleen, liver or gallbladder (6%). These patients with SDI $\geq$1 constituted the Group 1.

Demographics and clinical variables are shown in Table 1. Mean maternal age at delivery, duration of SLE and skin color were similar in both groups, while patients in Group 1 were older at the diagnosis of SLE (21.7 vs 19.7 years; p=0.04) and presented more frequently neuropsychiatric involvement (p=0.00007), hematological disorders (p=0.008), history of nephritis (p=0.001) and APS (p=0.0003).

There were no statistical differences in other SLE-related clinical manifestations, plasma complement levels, anti-dsDNA positivity, type of medication currently used and presence of other co-morbidities at the beginning of the prenatal care follow-up.

Table 5. Demographics and clinical variables of pregnant in SLE with and without SDI.

Variables	SDI ≥ 1 (n=67)		SDI = 0 (n=193)		RR	CI 95%	p *(value)*
	Mean	**± SD**	**Mean**	**± SD**			
Maternal age at delivery (years)	28.3	(± 5.84)	28.4	(± 6.16)	-	-	0.9
Min/Max	18	41	15	39			
Age at diagnosis of SLE	21.7	(± 7.80)	19.7	(± 6.60)	-	-	0.04
Min/Max	5	36	4	48			
Duration of SLE	8.1	(± 5.47)	7.9	(± 4.94)	-	-	0.8
Min/Max	0	48	0	48			
	n	**%**	**n**	**%**			
Ethnicity (Skin color)							
Caucasian	28	41.8	85	44.0	-	-	0.4
Afro-descendant	35	52.2	108	55.9			
Clinical variables							
Neurolupus	23	34.3	24	12.4	3.65	1.87 - 7.14	0.00007
Hematologic disorder	24	35.8	40	20.7	2.12	1.14 - 3.91	0.008
History of nephritis	39	58.2	72	37.3	2.33	1.32 - 4.14	0.001
Antiphospholipid syndrome (APS)	16	23.8	14	7.2	3.98	1.80 - 8.86	0.0003

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.

Table 2 describes adverse maternal outcomes in this cohort. SDI ≥1 was associated with adverse maternal outcomes [35/67 (46.3%) vs. 62/193 (32.1%), p = 0.002)], even when SLE activity and chronic hypertension were well excluded [19/67 (28.4%) vs. 33/193 (17%), p = 0.02; 21/67 (31.3%) vs 23/193 (11.9%), p = 0.0001]. Disease activity was more frequent in patients with SDI ≥ 1 [21/67 (31.3%) vs. 40/193 (20.7%), p = 0.004], including active nephritis [19 (28.3%) vs. 35 (18.1%), p = 0.04]. All other studied maternal variables were also significantly more frequent in patients with SDI ≥1, except for hypertensive disorders related to pregnancy and obstetric complications during puerperium that had no statistical difference.

Table 6. Maternal outcomes of pregnant in SLE with and without SDI.

Variables	**SDI ≥ 1 (n=67)**		**SDI = 0 (N=193)**		RR	**CI 95%**	**p *(value)***
Active SLE	n	%	n	%			
Score SLEPDAI ≥ 4	21	31.3	40	20.7	1.74	0.92 - 3.24	0.04
Active nephritis during gestation	19	28.3	35	18.1	1.78	0.92 - 3.39	0.04
Active non-renal during gestation	2	3.0	5	2.6	1.15	0.15 - 6.01	0.4
Complications							
Adverse Outcomes	35	46.3	62	32.1	2.30	1.30 - 4.08	0.002
Excluding SLEPDAI ≥4 and/or activity SLE	19	28.4	33	17.0	1.95	1.05 - 3.73	0.02
Hypertensive disorders	19	28.4	44	22.8	1.33	0.70 - 2.50	0.1
Hospitalization due to Obstetric complications	20	29.9	34	17.6	1.98	1.03 - 3.76	0.01
Obstetric complications during puerperium	19	28.4	46	23.8	1.26	0.66 - 2.35	0.23
Hospitalization due to SLE	22	32.8	33	17.0	2.36	1.24 - 4.45	0.004
Pathological puerperium (activity)	14	20.9	14	7.2	3.35	1.48 - 7.61	0.001
Cesarean section (urgency/emergency)	37	55.2	70	36.3	2.16	1.22 - 3.82	0.003

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.

Similarly, the risk of adverse fetal and neonatal outcomes was higher [40/67 (59.7%)] in patients with SDI ≥1 compared to patients with no damage accrual as established by SDI [74/193 (38.3), p=0.001], a difference that was still observed even after excluding for disease activity (SLEPDAI ≥4, p=0.03) (Table 3) and chronic hypertension [31/67 (46.3%) vs. 62/193 (32.1%), p=0.02]. Patients in Group 1 had more frequently premature deliveries [31 (46.3%) vs 61 (31.6%); p=0.01], SGA newborns [19 (28.3%) vs. 35(18.1%), p=0.04], lower mean gestational age at delivery (36.1 vs. 37.2, p=0.004) and more NICU admissions (18 (26.9%) vs. 3 (1.5%), p<0.0000001).

Considering fetal and neonatal outcomes, only 4/40 patients had permanent damage that was related to these systems (cataract, scaring chronic alopecia and deforming arthritis). Likewise, only 5/35 patients with adverse maternal outcomes had ocular and skin

SDI. This suggests that cardiovascular and neurological permanent damage are more related to adverse events.

Table 7. Adverse fetal/neonatal outcomes in pregnant with SLE, with and without SDI.

Variables	SDI ≥ 1 (n=67)		SDI = 0 (n=193)		RR	CI 95%			p *(value)*
	n	%	n	%					
Adverse fetal/neonatal outcomes	40	59.7	74	38.3	2.37	1.34	-	4.22	0.001
Excluding SLEPDAI ≥4 and/or activity SLE	21	31.3	39	20.2	1.79	0.95	-	3.35	0.03
Except activity nephritis	19	28.3	34	17.6	1.79	0.95	-	3.35	0.03
Fetal	**n**	**%**	**n**	**%**					
Stillbirth	4	5.9	8	4.1	1.46	0.37	-	5.02	0.2
Preterm birth	31	46.3	61	31.6	1.85	1.04	-	3.29	0.01
Gestational age at delivery (weeks) mean ± SD	36.1 ± 4	-	37.2 ± 3						0.04
Neonatal									
SGA	19	28.3	35	18.1	1.78	1.09	-	3.39	0.04
Birth weight (g) mean ± SD	2541	± 805	2794	± 741					0.01
Neonatal death	1	1.5	3	1.5	0.95	0.03	-	9.16	0.4
NICU admission	18	26.9	3	1.5	4.18	3.08	-	5.67	<0.000001

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.

On multivariate analysis, SDI ≥1 was an independent risk factor for hospitalization due to obstetric complication during pregnancy non-related to SLE (RR 4.42; CI 1.75-11.47, p=0.0008) and preterm birth (RR 3.76; CI 1.39- 10.69, p=0.009).

5.6 **Discussion**

The present study that analyzed a single center obstetric cohort of women with SLE and included 260 pregnancies unveiled that organ damage accrual according to SDI may be potently interpreted as a risk factor for adverse maternal and fetal outcomes. Scoring one or more on SDI at the beginning of pregnancy was associated with adverse maternal and fetal outcomes.

Due to the typical disease activity and chronic hypertension impact on both maternal and fetal adverse outcomes, we have controlled these variables and the association between damage accrual and adverse outcomes was still observed, suggesting that it was not a random finding. Adverse obstetric events related to SDI may be partially attributed to cardiovascular and renal function impairments, well-known factors for pregnancy complications (20).

A number of studies have demonstrated an increased frequency of maternal and fetal complications even during disease remission, but, to the best of our knowledge, there is no data directly correlating the SDI score with gestational outcomes. Few studies analyzed if pregnancy in SLE had any impact in damage accrual (14, 21). In the Lumina cohort study (14), the authors described that pregnancy was not associated with an increase in damage accrual and they could not find any interactions between maternal and/or fetal outcomes and SDI score prior to pregnancy. They also reported 76.2% of fetal and/or neonatal adverse outcomes, a considerably higher percentage, this cohort evaluated 63 pregnancies and was limited to the outcomes of miscarriage, premature birth and stillbirth, not reporting other fetal and maternal adverse outcomes.

In the same context, a nested case-control analysis (21) that included 104 patients, but evaluated only 13 pregnancies after the diagnosis of SLE, did not find any impact of pregnancy on the development of de novo damage accrual (21).

Previous publications have associated damage accrual in patients with age at disease onset, disease duration, serositis, neurological disorder, hypertension, cumulative dose of glucocorticoids and/or immunosuppressants, uncontrolled disease activity and the presence of antiphospholipid antibodies (22). In our cohort, there were no significant associations between SDI and maternal age, chronic hypertension prior to pregnancy and the use of specific medications. This may be due to the young age of the patients studied (mean 28 years-old). However, and in agreement with other studies, we also found a correlation between SDI >1 and higher age at diagnosis, higher disease activity, mostly nephritis, and/or positive aPL (23, 24, 25, 26).

The presence of any permanent damage measured by the SDI in non-pregnant patients has been shown to predict new damage accrual and complications like hospitalizations, disease activity, organ failure and even death (22, 27- 32). Although part of these events is infrequent during pregnancy, such as mortality, some of the other mentioned complications related to damage accrual for non-pregnant SLE patients were also identified in this pregnant population, which corroborates the findings of the study.

This study has some clear limitations. It is a retrospective analysis from a single center, which may hinder extrapolation of results, and it was not possible to assess modifiable risk factors such as smoking, since most of patients discontinue or reduce their use during pregnancy. Stratification within the SDI >1 group was not possible as almost 75% of patients had a score of 1, limiting comparison with patients with higher scores. Also, evaluation of SDI occurred at beginning of prenatal care and its modification during pregnancy was not analyzed, despite the short period of pregnancy course, as this was not the purpose of this study.

On the other hand, to the best of our knowledge, this is the first study to point out a possible correlation between SDI>1 and adverse gestational outcomes. The SDI is straight forward to calculate in the routine clinical settings and identifies SLE patients with or without damage accrual. When the damage is present at the beginning of the prenatal care follow-up it may be interpreted as a risk factor for adverse obstetric outcomes in patients with SLE.

5.7 **Conclusion**

In this single center cohort study that compares adverse maternal, fetal and neonatal outcomes of pregnant women with SLE, damage at the beginning of pre-natal care, as measured by the SDI, can be a predictor of future adverse obstetrics outcomes. These complications were still more frequent in patients with damage accrual even when patients with active disease were removed from analysis as a potential bias. Further studies with larger and different populations are required to determine if these results are reproducible and to allow risk stratification inside the SDI scoring group and types of organ involved.

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CONCLUSÕES

O estudo 1, que analisou o desenvolvimento de recém natos PIG (*"The association between active proliferative lupus nephritis during pregnancy and small for gestational age newborns"*) demonstrou que a atividade do LES na gestação, especificamente a nefrite proliferativa e o emprego de pulsoterapia com metilpredinisolona foram preditores independentes de risco, para recém-nascidos pequenos para a idade gestacional (PIG). Adicionalmente a análise univariada evidenciou associação de PIG com a presença de nefrite proliferativa prévia à gestação, atividade de doença medida pelo SLEPDAI ($\geq$ 4), consumo de complemento (C3), presença de anticorpos anti-RNP e anti-Sm.

O estudo 2, que analisou o impacto da presença dos danos permanente nas gestantes com LES (*"The SLICC/ACR Damage Index (SDI) may predict adverse obstetric events in patients with Systemic Lupus Erythematosus (SLE)")* evidenciou que pode existir uma associação entre os danos permanentes e os resultados gestacionais adversos.

Os demais estudos realizados ao longo do período de desenvolvimento desta tese, permitiram a identificação de outras variáveis clínicas e ou laboratoriais associadas à evolução da gestação de pacientes com LES. A população que compõe esta coorte apresenta particularidades como, incluir muitas mulheres com doença grave, acompanhadas com intensa colaboração interdisciplinar, incluindo não só a obstetrícia e a reumatologia, mas também outras especialidades afins como a nefrologia e a hematologia, estar estruturada em uma unidade pública de referência para gestações de alto risco, cuja criação ocorreu há mais de 30 anos.

Ainda que existam outros grupos de pesquisa que estudem gestações em pacientes com LES, poucos incluíram populações de menor renda e foram realizados em países em desenvolvimento onde as complicações inerentes a própria doença e a gestação são mais frequentes.

Revisamos e identificamos neste grupo, ao longo dos últimos 10 anos de seguimento sistematizado (2011 a 2020), o maior risco de desfechos desfavoráveis, classicamente descritos na literatura, como (re) atividade do LES, incluindo a nefrite, PE, prematuridade e restrição do crescimento fetal e ainda adicionamos, mais evidências do potencial ominoso da manifestação renal, especialmente na forma proliferativa (classes III e IV), ressaltando a importância da diferenciação das classes histológicas e do conhecimento dos danos permanentes adquiridos previamente à gestação como fatores de risco associados a resultados maternos, fetais e neonatais adversos.

Assim, os resultados destes trabalhos e outros preliminares desta coorte ainda em andamento, reforçam a necessidade da continuidade das investigações em gestantes com LES e estimulam a formulação de novas perguntas e desenhos de estudos para que possamos colaborar com a melhoraria dos resultados maternos, fetais e neonatais das gestantes com LES.

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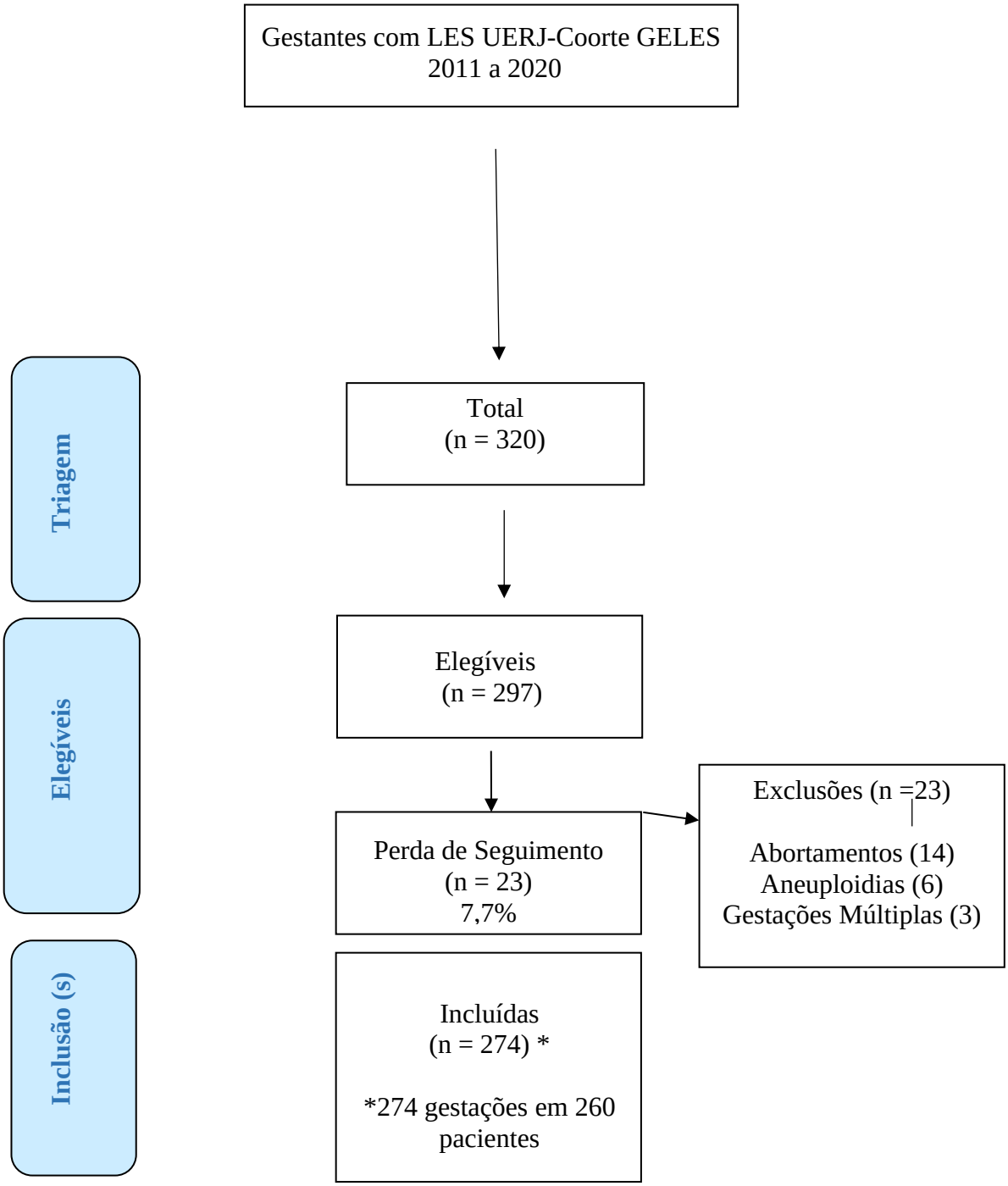
APÊNDICE A – Fluxograma UERJ- Coorte GELES



APÊNDICE B – Questionário utilizado para coleta de dados das gestantes com lúpus eritematoso sistêmico

1 - Identificação:

Nome_____

Prontuário_____

Data de nascimento ___ / ___ / ___ Estado civil _____

Naturalidade _____

Endereço _____

Bairro _____ Cidade_____ CEP_____

Telefone _____

Data do preenchimento ___/___/___

Avaliação de Nível Social pela ABEP: _____;

Renda per capita em U$: _____; Nº de anos de estudo: _____

Cor da pele: branca ( ); parda ( ); negra ( ); amarela ( ); indígena ( );

Outra ( ) _____

Local de acompanhamento do LES até a gestação: _____

Idade gestacional no momento de início do Pré-natal na UERJ_____ semanas.

Tempo de remissão do LES antes da concepção: _____ meses;

Gestação Programada: ( )

Atividade da doença no momento da concepção: ( ) - Cutânea: ( );

Articular ( ); Pleuris ( ), Pericardite ( ); AHAI ( ); Trombocitopenia ( ); Neuropsiquiátricas: ( ); Renais: ( )

2 - Manifestações Clínicas: (em qualquer momento):

Data do início dos sintomas: ___ / ___ / ___;

Data do diagnóstico: ___ / ___ / ___; SLICC-DI (/ /): _____

Eritema malar: ( ) Lesão discóide: ( ); Úlcera oral: ( );

Fotossensibilidade: ( ); Poliartrite: ( ); Pleuris: ( ); Pericardite: ( );

Ascite: ( ); Neuropsiquiátricas ( ); Renais: ( ) - Classe Histológica: _____

OU tipo de manifestação: PTNúria > 1 gr. ( ); IRA ( ); S. Nefrótica: ( );

Hematológicas: ( ) - Tipo: AHAI ( ); Leucopenia < 4000/mm^3, em > 2 ocasiões ( ); Linfopenia < 1000/ mm^3 , em > 2 ocasiões ( ); Trombocitopenia < 100 000/ mm^3 na ausência de medicamentos ofensivos ( );

Imunológicas: anti-DNA nativo ( ); anti-Sm ( ); anti- SS-A (Ro) ( ); anti-SS-B (La) ( ); anticardiolipina ( ) _____; VDRL Falso + ( ); complemento -C3 ou C4 ou CH 50 ou CH 100 ( ); FAN ( ) Título:_____ Padrão:_____

SAF Associada: ( )

Evento Clínico: _____

Anticardiolipina ( ) Subtipo: _____ Valor: _____data: _____

LAC ( ) data: _____

Evento Obstétrico: _____

Anticardiolipina ( ) Subtipo: _____ Valor: _____data: _____

LAC ( ) data: _____

3 – Medicamentos em uso no início do pré-natal:

Prednisona (Classe C/D): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

Hidroxicloroquina (Classe C): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

Azatioprina (Classe D): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

Metotrexato: (Classe X): ( ) dose diária: _____mg;

Suspenso ( ) – IG: ____sem. ; Uso últimos 3 meses: ( )

Micofenolato mofetil (Classe X): ( ) dose diária: _____mg;

Suspenso ( ) – IG: ____sem. ; Uso últimos 3 meses: ( )

Ciclofosfamida i.v. (Classe D): ( ) dose por infusão: _____mg

Inicio: __ / __ / __ última infusão: __ /__ / __

AAS (Classe D): ( ) dose diária: _____mg,

Cálcio: ___; Vit. D: ___;

Inibidores da ECA (Classe X): ( ) dose diária: _____mg,

Substância: _____; suspenso ( )- IG: ____sem.

Antagonistas da ATII (Classe B/D): ( ) dose diária: _____mg,

Substância: _____; suspenso ( )- IG: ____sem.

Diuréticos (Classe D): ( ) dose diária: _____mg,

Substância: _____; suspenso ( )- IG: ____sem.

Outros medicamentos: _____

4-Evolução durante gestação:

Atividade durante a gravidez: ( )

SLEPDAI no início da gravidez: _____ (___ / ___ / ___)

SLEPDAI no final da gravidez: _____ (___ / ___ / ___)

Reativação: ( )

Cutânea: ( ); Articular ( ); Pleuris ( ), Pericardite ( ); AHAI ( ); Trombocitopenia ( ); Neuropsiquiátricas: ( ); Renal: ( )

( ) proteinúria R P/C _____; PTNÚRIA/24 H: _____ - 1º trimestre

( ) proteinúria R P/C _____; PTNÚRIA/24 H: _____ - 2º trimestre

( ) proteinúria R P/C _____; PTNÚRIA/24 H: _____ - 3º trimestre

( ) cilindrúria (hemático, leucocitário, granular, tubular ou misto) – ( ) microscopia de fase

( ) Dismorfismo eritrocitário - ( ) microscopia de fase

( ) outras alterações no EAS _____; ( ) microscopia de fase

( ) creatinina antes (até 90 dias) da gestação: _____ mg/dl; ( ) creatinina após (até 90 dias) a gestação: _____ mg/dl;

Complicações:

Infecção: ( ) – Local: _____

Nº de internações por complicações **não** relacionadas ao LES: ( );

Período da internação: ___ semanas

Nº de internações por complicações relacionadas ao LES: ( );

Período da internação: ___ semanas

Motivo: _____

OBS: Internação por causa administrativa? Especificar_____

5 – Antecedentes obstétricos:

Pré-diagnóstico de LES (sintomas):

Ab. Espontâneo: _____ ( ) 1º.tri - ≤ 14sem ( ) 2º. tri > 14 sem

Parto termo (n) – _____ vivo _____ natimorto _____ neomorto

Parto Prematuro (n): _____ vivo _____ natimorto _____ neomorto

Malformação _____ Hipertensão/Pré-eclâmpsia ( ) CIUR ( ) Peso ao nascer _____ IG ao nascer

Pós-diagnóstico de LES (sintomas):

Ab. Espontâneo: _____ ( ) 1º.tri - ≤ 14sem ( ) 2º. tri > 14 sem

Parto termo (n) – _____ vivo _____ natimorto _____ neomorto

Parto Prematuro (n): _____ vivo _____ natimorto _____ neomorto

Malformação _____ Hipertensão/Pré-eclâmpsia ( ) CIUR ( ) Peso ao nascer _____ IG ao nascer

6 – Gestação atual:

Abortamento:

Espontâneo ( ) IG _____sem. Complicação: _____

Pré-natal:

N° de consultas _____

Oligodramnia: ( ) IG: _____ sem CIUR: ( ) IG: _____ sem

RPMO: ( ) IG: _____ sem

Pré-eclâmpsia :( ) IG: _____ sem S. HELLP: ( ) IG: _____ sem DPP: ( ) IG: _____ sem

HAS gestacional: ( ) IG: _____ sem Diabetes: ( ) Gest. / ( ) Tipo l /( ) Tipo II

Último Doppler (antes do parto): Norm. ( ) Centralizado ( ) D Zero ( ) D reversa ( ) DV alterado ( ) IG _____ sem

Última CTG: ( )Reativo ( )Ñ Retaivo ( ) Comp ( ) Lisa Dip III ( ) Dip II ( )

7 - Medicamentos em uso no fim do pré-natal:

Prednisona (Classe C/D): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

Hidroxicloroquina (Classe C): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

Azatioprina (Classe D): ( ) dose diária: _____mg

Uso nos últimos 3 meses: ( )

AAS (Classe D): ( ) dose diária: _____mg,

Cálcio: ___; Vit. D: ___;

Outros medicamentos: _____

8 - Parto:

Data: _____ /_____/_____

Início: ( ) Esp ( ) Induzido – Método _____ ( ) Ces. Elet.

Indicação: _____

Término: ( ) Vag ( ) Ces. Indic. _____

IG _____ sem Peso: _____ g Ballard _____ sem

Classif: ( ) PIG ( ) AIG ( ) GIG Sexo: ( ) M ( ) F

APGAR: 1° _____ 5° _____

( ) betametasona - nº de doses: ____ ( ) dexametasona - nº de doses: ____

Registro do RN: _____

Memb. Hialina: ( ) Respirador: ( ) Asfixia: ( ) Infec. Cong.: ( ) Infec. Adq.: ( )

Lúpus Neonatal ( ) Pele ( ) Coração ( ) Fígado ( ) Hematológica ( )

UTI: ( ) Tempo _____ dias Malformação ( )

Tempo de permanência no berçário _____dias

Óbito: ( ) Causa _____

9 - Puerpério:

Normal ( ) Infecção ( )

Atividade: ( ) - Cutânea: ( ); Articular ( ); Pleuris ( ), Pericardite ( ); AHAI ( );

Trombocitopenia ( ); Neuropsiquiátricas: ( ); Renais: ( )

APÊNDICE C – Aprovação do Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto

HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação De Fatores Angiogênicos E Antiangiogênicos Como Método De Diagnóstico Diferencial Entre Pré-Eclâmpsia E Lúpus Eritematoso Sistêmico Com Nefrite

Pesquisador: Guilherme Ribeiro Ramires de Jesús

Área Temática:

Versão: 1

CAAE: 50726115.4.0000.5259

Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ

Patrocinador Principal: CERPE CENTRO DE ESTUDOS EM REUMATOLOGIA PEDRO ERNESTO
FUN CARLOS CHAGAS F. DE AMPARO A PESQUISA DO ESTADO DO RIO DE JANEIRO - FAPERJ

DADOS DO PARECER

Número do Parecer: 1.319.997

Apresentação do Projeto:

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, acompanhados da formação de autoanticorpos
patogênicos. Ele acomete principalmente mulheres jovens e a gestação nestas pacientes apresenta significativa morbimortalidade. Os achados
clínicos e laboratoriais na nefrite lúpica são semelhantes àqueles encontrados em pacientes com pré-eclâmpsia (PE), especificamente hipertensão
arterial, proteinúria e edema. Foi proposto o uso de fatores angiogênicos, como o fator de crescimento vascular endotelial (VEGF) e o fator de
crescimento placentário (PlGF), e antiangiogênicos, como o receptor Fms-like tirosina quinase 1 solúvel (sFlt -1), para o diagnóstico diferencial entre
estas duas condições, no entanto não existem dados na literatura sobre os valores séricos destas citocinas em gestantes com LES. Este estudo de

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caráter transversal foi desenhado para avaliar se existe diferença entre os níveis séricos de VEGF, PlGF e sFlt-1 em gestantes com lúpus
eritematoso sistêmico com e sem atividade sistêmica da doença que estão em acompanhamento regular no pré-natal de doenças reumatológicas do
Hospital Universitário Pedro Ernesto. Os valores séricos destas citocinas em gestantes com LES serão comparados com os valores encontrados em
gestantes sem doença autoimune com pré-eclâmpsia e sem pré-eclâmpsia, avaliando se há diferença entre os resultados. Outra parte do estudo
consiste em avaliar se há diferença entre os resultados encontrados em pacientes com LES gestantes e não gestantes. Os resultados gestacionais
das pacientes com lúpus serão analisados para identificar a frequência de eventos gestacionais adversos.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar se existe diferença entre os níveis séricos de VEGF, PlGF e sFlt-1 em gestantes com lúpus eritematoso sistêmico com e sem atividade
sistêmica da doença e em pacientes com lúpus eritematoso sistêmico com pré-eclâmpsia.

Objetivo Secundário:

Avaliar se existe diferença entre os valores séricos de VEGF, PlGF e sFlt-1 em gestantes com lúpus eritematoso sistêmico em comparação com os
níveis séricos dessas citocinas em gestantes sem doença autoimune com e sem pré-eclâmpsia.Avaliar se existe diferença entre os valores séricos
de VEGF, PlGF e sFlt-1 em gestantes com lúpus eritematoso sistêmico em comparação com os níveis séricos dessas citocinas em pacientes não
gestantes com lúpus eritematoso sistêmico.Avaliar se existe diferença entre os valores séricos de VEGF, PlGF e sFlt-1 em gestantes com lúpus
eritematoso sistêmico em comparação com os níveis séricos dessas citocinas em gestantes sem doença autoimune com e sem pré-
eclâmpsia.Avaliar o resultado gestacional das gestantes com lúpus eritematoso sistêmico em acompanhamento no Hospital Universitário Pedro
Ernesto.Avaliar o resultado histopatológico das placentas em gestantes com lúpus eritematoso sistêmico em acompanhamento no Hospital

Universitário Pedro Ernesto.

Avaliação dos Riscos e Benefícios:

Riscos

Os únicos riscos envolvidos com o projeto estão na coleta de sangue venoso para análise dos fatores VEGF, PlGF e sFlt-1, que pode resultar em
hematoma e dor. Todos os outros dados utilizados no estudo serão provenientes de exame físico, exames laboratoriais e análise histopatológica da
placenta feitos de rotina no acompanhamento pré-natal de gestantes de alto risco do Hospital Universitário Pedro Ernesto ("standard of care"),
coletados a partir da revisão do prontuário.

Benefícios:

Este estudo poderá criar uma nova ferramenta no acompanhamento de gestantes com lúpus eritematoso sistêmico, permitindo um melhor
diagnóstico e consequentemente melhor tratamento destas pacientes.

Comentários e Considerações sobre a Pesquisa:

Pesquisa com potencial impacto na prática clínica, Foram avaliadas as informações contidas na Plataforma Brasil e as mesmas se encontram dentro das normas vigentes e sem riscos eminentes ao participante de pesquisa envolvido.

Considerações sobre os Termos de apresentação obrigatória:

Em conformidade, Foram analisadas as documentações e as mesmas se encontram dentro das normas.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

O trabalho pode ser realizado da fora como está apresentado. Diante do exposto e à luz da Resolução CNS nº466/2012, o projeto pode ser enquadrado na categoria – APROVADO. Para ter acesso ao PARECER CONSUBSTANCIADO: Clicar na "LUPA" (DETALHAR) - Ir em "DOCUMENTOS DO PROJETO DE PESQUISA ", clicar na opção da ramificação (pequeno triangulo no entrocamento do organograma) de pastas chamada – "Apreciação", e depois na Pasta chamada "Pareceres", o Parecer estará nesse local.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente, o CEP recomenda ao Pesquisador: 1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas. 2. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes. 3. O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais e anuais referentes ao andamento da pesquisa ao término da pesquisa encaminhe a esta comissão um sumário dos resultados do projeto.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_530156.pdf	14/10/2015 15:06:25		Aceito
Declaração de Pesquisadores	img006.jpg	14/10/2015 15:06:07	Guilherme Ribeiro Ramires de Jesús	Aceito
Folha de Rosto	FolhaderostoCEP.pdf	29/09/2015 23:40:59	Guilherme Ribeiro Ramires de Jesús	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Doutorado_19_10_14_Plaintext.docx	22/09/2015 18:07:03	Guilherme Ribeiro Ramires de Jesús	Aceito
Parecer Anterior	Aprovacao_CEP.jpg	22/09/2015 18:06:16	Guilherme Ribeiro Ramires de Jesús	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_final.doc	22/09/2015 18:02:24	Guilherme Ribeiro Ramires de Jesús	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RIO DE JANEIRO, 12 de Novembro de 2015

Assinado por:
DENIZAR VIANNA ARAÚJO
(Coordenador)

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APÊNDICE C – Aprovação do Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto- Emenda Versão 4

UERJ - HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Avaliação De Fatores Angiogênicos E Antiangiogênicos Como Método De Diagnóstico Diferencial Entre Pré-Eclâmpsia E Lúpus Eritematoso Sistêmico Com Nefrite

Pesquisador: Guilherme Ribeiro Ramires de Jesús
Área Temática:
Versão: 4
CAAE: 50726115.4.0000.5259
Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ
Patrocinador Principal: CERPE CENTRO DE ESTUDOS EM REUMATOLOGIA PEDRO ERNESTO
FUN CARLOS CHAGAS F. DE AMPARO A PESQUISA DO ESTADO DO RIO DE JANEIRO - FAPERJ

DADOS DO PARECER

Número do Parecer: 3.960.404

Apresentação do Projeto:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Objetivo da Pesquisa:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Avaliação dos Riscos e Benefícios:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Comentários e Considerações sobre a Pesquisa:
Justificativa da Emenda:
Solicitação de substituição do título do projeto e do TCLE para adequação aos novos objetivos incluídos na pesquisa, devido a adequação do projeto inicial que passará a permitir a análise da coorte de gestantes com lúpus eritematoso sistêmico (LES) de forma mais ampla, incluindo novos desfechos maternos e fetais.
Título atual (já aprovado): Avaliação dos fatores angiogênicos e antiangiogênicos como método de

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diagnóstico diferencial entre pré-eclâmpsia e lúpus eritematoso sistêmico e nefrite. Título proposto (novo): Análise dos desfechos maternos, fetais, neonatais e infantis das gestações em mulheres com LES acompanhadas na UERJ-Coorte GELES

Considerações sobre os Termos de apresentação obrigatória:

Os documentos enviados a este Comitê estão dentro das boas práticas em pesquisa e apresentando todos dados necessários para apreciação ética.

Conclusões ou Pendências e Lista de Inadequações:

A emenda apresenta todas as informações necessárias para avaliação ética. Diante do exposto e à luz da Resolução CNS nº466/2012, a Emenda pode ser enquadrada na categoria – APROVADO.

Considerações Finais a critério do CEP:

Em consonância com a resolução CNS 466/12 e a Norma Operacional CNS 001/13, o CEP recomenda ao Pesquisador: Comunicar toda e qualquer alteração do projeto e no termo de consentimento livre e esclarecido, para análise das mudanças; Informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa; O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais de andamento a cada 06 (seis) Meses da pesquisa e ao término, encaminhe a esta comissão um sumário dos resultados do projeto; Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1483903_E3.pdf	13/02/2020 15:03:31		Aceito
Folha de Rosto	FolhadeRosto.pdf	28/07/2019 20:12:08	Guilherme Ribeiro Ramires de Jesús	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Gestantes.doc	05/01/2017 17:23:32	Guilherme Ribeiro Ramires de Jesús	Aceito
Declaração de Pesquisadores	img006.jpg	14/10/2015 15:06:07	Guilherme Ribeiro Ramires de Jesús	Aceito

Projeto Detalhado / Brochura Investigador	Projeto_Doutorado_19_10_14_Plaintext.docx	22/09/2015 18:07:03	Guilherme Ribeiro Ramires de Jesús	Aceito
Parecer Anterior	Aprovacao_CEP.jpg	22/09/2015 18:06:16	Guilherme Ribeiro Ramires de Jesús	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RIO DE JANEIRO, 08 de Abril de 2020

Assinado por:
WILLE OIGMAN
(Coordenador(a))

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APÊNDICE D –Termo de consentimento livre e esclarecido (TCLE)- Avaliação da evolução e desfecho da gestação de pacientes com lúpus eritematoso sistêmico

Nome:_____Idade:_____anos.

Data: ___ / _____ / ____ Data de Nac.: ___ / ___ / ___

Doc. de Identidade: _____

Endereço: _____

CEP: _____

Telefones: _____ / _____ / _____ / _____

Você está sendo convidada a participar deste projeto porque está sendo atendida pelo serviço de Obstetrícia e Reumatologia do Hospital Universitário Pedro Ernesto. Este projeto tem por objetivo principal estudar a evolução e o desfecho das gestações de mulheres com lúpus eritematoso sistêmico (LES).

Para participar, é preciso responder a um questionário e caso necessário, ter coletada amostra de sangue e/ou urina para exames complementares. Este estudo será desenvolvido por médicos do Hospital Universitário Pedro Ernesto (HUPE).

A participação neste estudo não é obrigatória e, mesmo aceitando participar, você poderá sair do estudo a qualquer momento, sem que isto leve a alguma punição ou restrição no seu tratamento. Todos os dados deste estudo serão mantidos em segredo, mas poderão ser publicados em revistas científicas sem qualquer identificação dos participantes.

Participando deste estudo, você terá nenhum custo diferente dos que já vinha tendo com o seu tratamento e também não terá qualquer custo com os exames que poderão ser realizados. Participando deste estudo você também não receberá qualquer tratamento diferenciado em relação às outras pacientes acompanhadas no HUPE.

Qualquer dúvida antes, durante ou após o estudo poderá ser esclarecida pelo seu médico assistente e/ou médicos responsáveis pelo estudo.

Declaro que concordei em participar deste projeto, de acordo com os esclarecimentos acima:

Nome: _____ Assinatura: _____

Médicos responsáveis pelo projeto:

Dr. Evandro M. Klumb (tel: 2868 8216), Dr. Nilson R. de Jesús (tel: 2868 8451), Dr. Guilherme R. R. de Jesús (tel: 2868 8451), Dra. Marcela I. L. Ávila (tel: 2868 8451), Dra. Bruna C. Rodrigues (tel: 2868 8451).

Comitê de ética em Pesquisa do HUPE: (tel: 2868 8253).

Testemunha: _____ Testemunha: _____

Nome: _____ Nome: _____

APÊNDICE E – Tabela 1. Características demográficas, clínicas e sorológicas na 1º consulta de pré-natal UERJ-Coorte GELES

Tabela 1. Características demográficas, clínicas e sorológicas na 1º consulta de pré-natal UERJ- Coorte GELES

Variáveis relacionadas ao Lúpus	**n = 320**	
Idade no parto (anos)		
Média ± DP	28,43 ± 5,99	
Idade no diagnóstico LES (anos)		
Média ± DP	20,51 ± 6,72	
Duração LES (anos)		
Média + DP	7,43 ± 4,93	
Mínima	15	
Máxima	47	
Cor da Pele	n	%
Branca	169	53
Parda	74	23
Negra	77	24
Indígena	0	0
SDI* ≥ 1	80	25
Manifestações clínicas (n=260)	**n**	**%**
Cutâneo-mucosas	22	81,5
Hematológicas	12	54,6
Articulares	26	86,9
Serosites	13	43,5
Neurológicas	67	25,8
Nefrite	13	51,2
Perfil Sorológico (n=260)	**n**	**%**
AC anti-DNA*	18	41,5
AC Anti-Ro**	99	38
AC Anti-La **	22	8,5
AC Anti-Sm **	33	12,7
AC Anti-RNP **	52	20
Apl	58	22,3

DP: Desvio Padrão; LES: Lupus EritematosoSistêmico; SDI: SLICC Damage Index; AC: anticorpo; aPL: anticorpos Antifosfolipídios; * método: imunofluorescência indireta; **método:Elisa.

APÊNDICE F–Comprovante de submissão do artigo -Estudo 2

Lupus

SAGE

! Home " Author # Review

Author Dashboard / Submission Confirmation

Submission Confirmation

Thank you for your submission

Submitted to	Lupus
Manuscript ID	LUP-21-289
Title	The SLICC/ACR Damage Index (SDI) may predict adverse obstetric events in patients with Systemic Lupus Erythematosus (SLE)
Authors	Lacerda, Marcela de Jesus, Guilherme Cunha, Flavia de Jesús, Nilson Levy, Roger Klumb, Evandro
Date Submitted	12-May-2021

Author Da

ANEXO A – Índice de Atividade da Doença no Lúpus Eritematoso Sistêmico (SLEDAI)

Descrição	Definição	Pontos
Convulsão	Início recente. Excluir infecção metabólica ou causas devido ao medicamento	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 incluindo défict cognitivo 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 do 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.	8
Cefaléia lúpica	Dor de cabeça severa persistente; pode ser enxaqueca, mas não deve ser responsiva à analgesia narcótica.	8
Acidente vascular cerebral (AVC)	Novo início de acidente(s) vascular (es) cerebral (is). Excluir arteriosclerose.	8
Vasculite	Ulceração, gangrena, nódulos moles dos dedos, infarto periungueal, hemorragia splinter, ou biópsia ou arteriografia de vasculite.	8
Artrite	Mais de 2 articulações com dor e sinais de inflamação (isto é, sensibilidade, inchaço e efusão).	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.	4
Proteinúria	> 0,5 g por 24 horas. Novo início ou aumento recente de mais que 0,5 g por 24 horas.	4
Piúria	> 5 leucócitos por campo. Excluir infecção.	4
Nova erupção	Novo início ou recorrência de erupção do tipo inflamatório	2
Alopecia	Novo início ou recorrência de perda anormal de cabelo difusa ou em placa.	2
Úlceras na mucosa	Novo início ou recorrência de ulcerações nasais ou orais.	2
Pleurisia	Dor torácica pleurítica com atrito pleural ou efusão ou espessamento pleural	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.	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	1
Leucopenia	< 3000 leucócitos por mm^3. Excluir causada por medicamento.	1

ANEXO B – Índice de Atividade da Doença Lúpus Eritematoso Sistêmico na gestação (SLEPDAI)

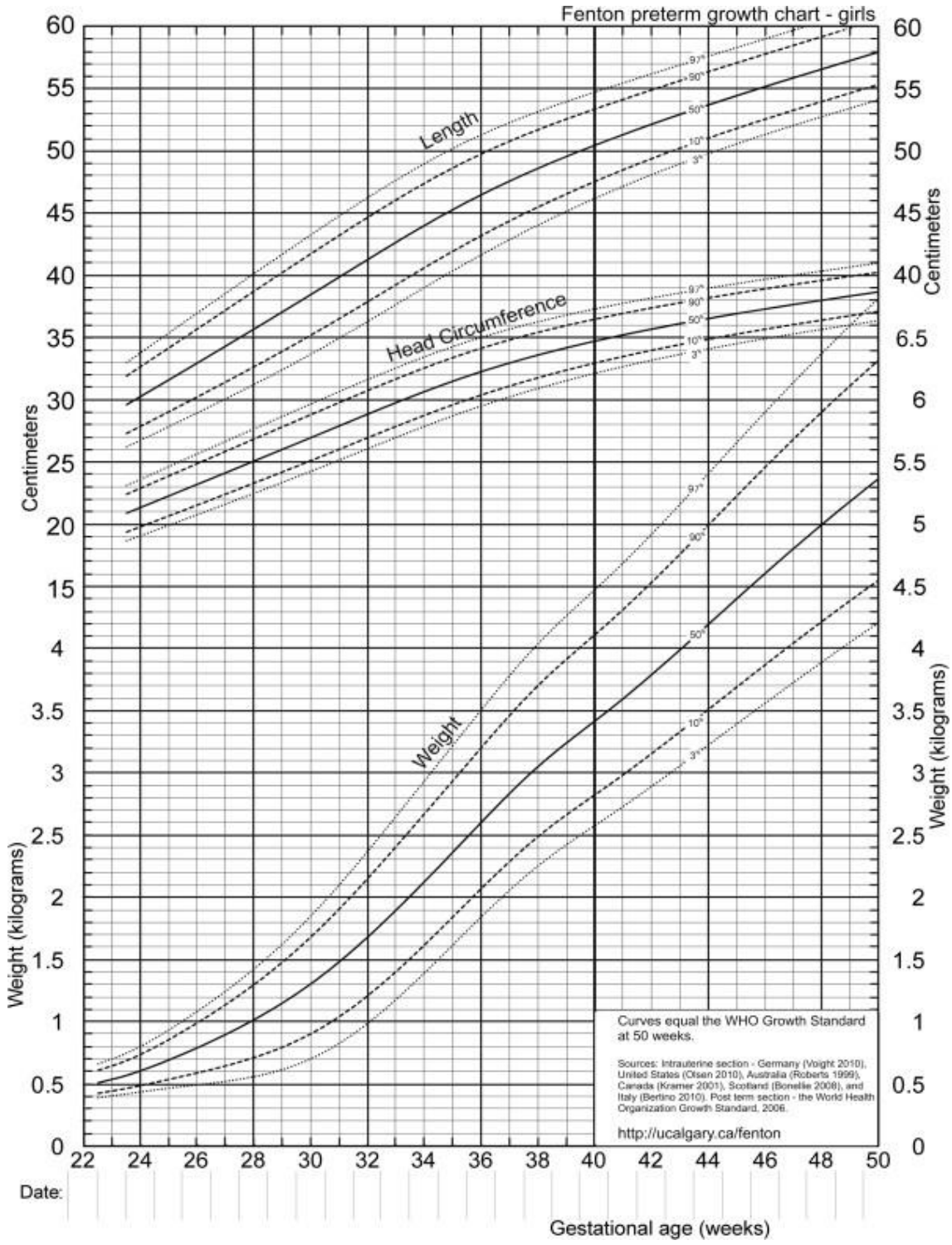
Descrição	Definição	Pontos
Convulsão	Início recente. Excluir infecção metabólica ou causas devido ao medicamento. **Excluir eclâmpsia.**	8
Psicose	Capacidade alterada para função em atividade normal devido a distúrbio severo na percepção da realidade. Inclui alucinação, incoerência, perda marcante de 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 eclâmpsia.**	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
Úceras 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

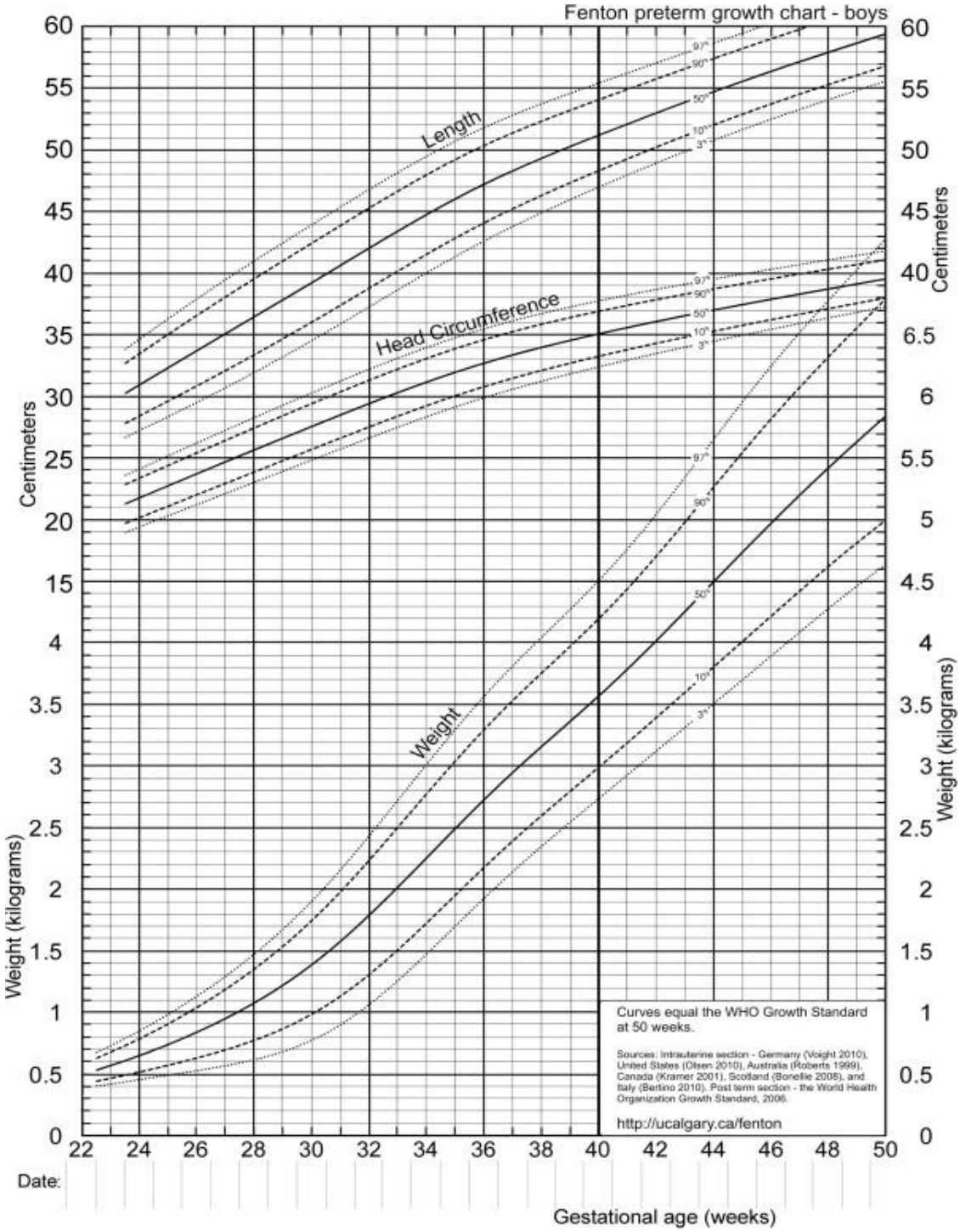
ANEXO C – Índice de dano cumulativo (SLICC-DI)

	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 diastólico > 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)		

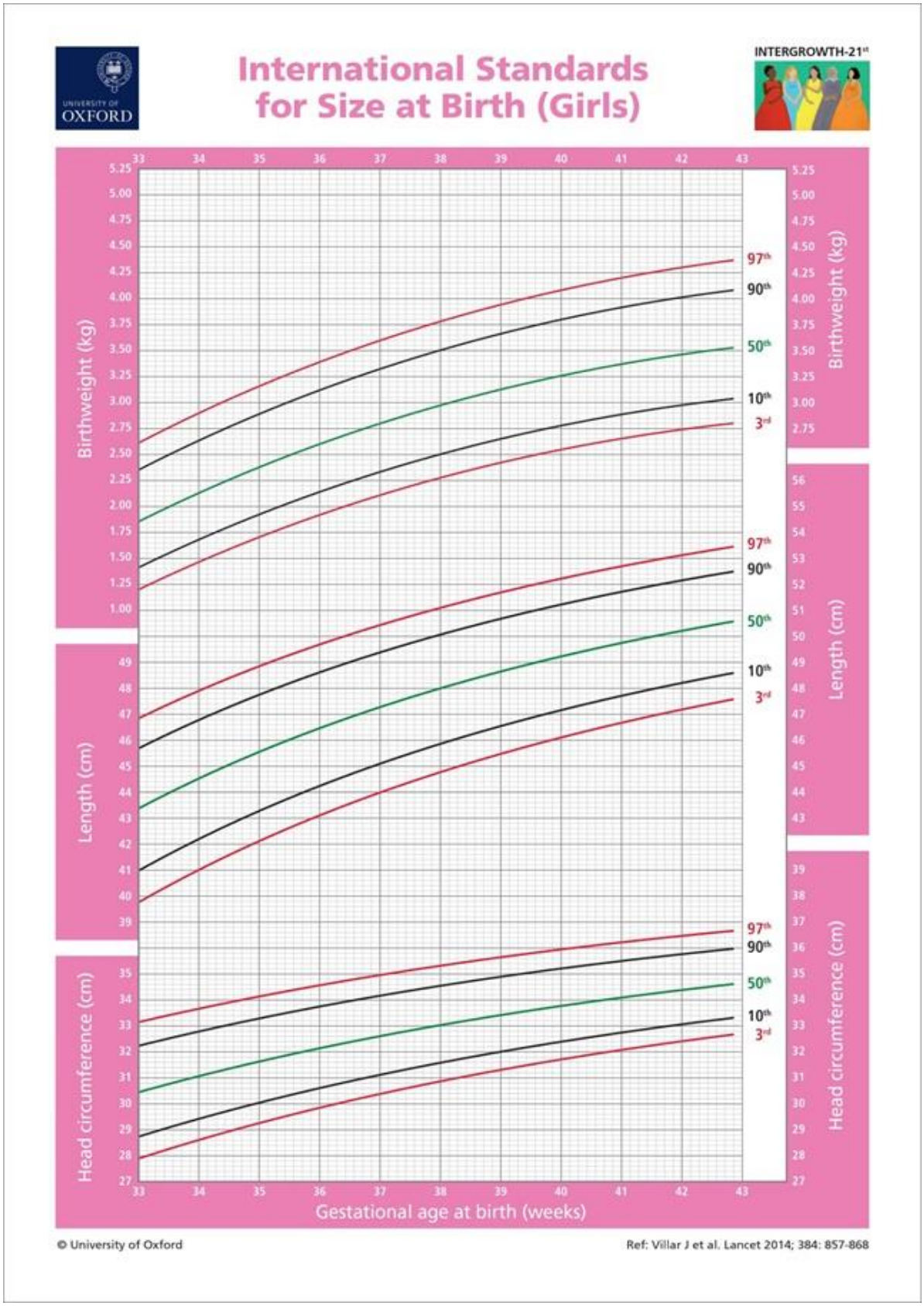
ANEXO D – Curvas de Fenton 2013 (*Girls)*



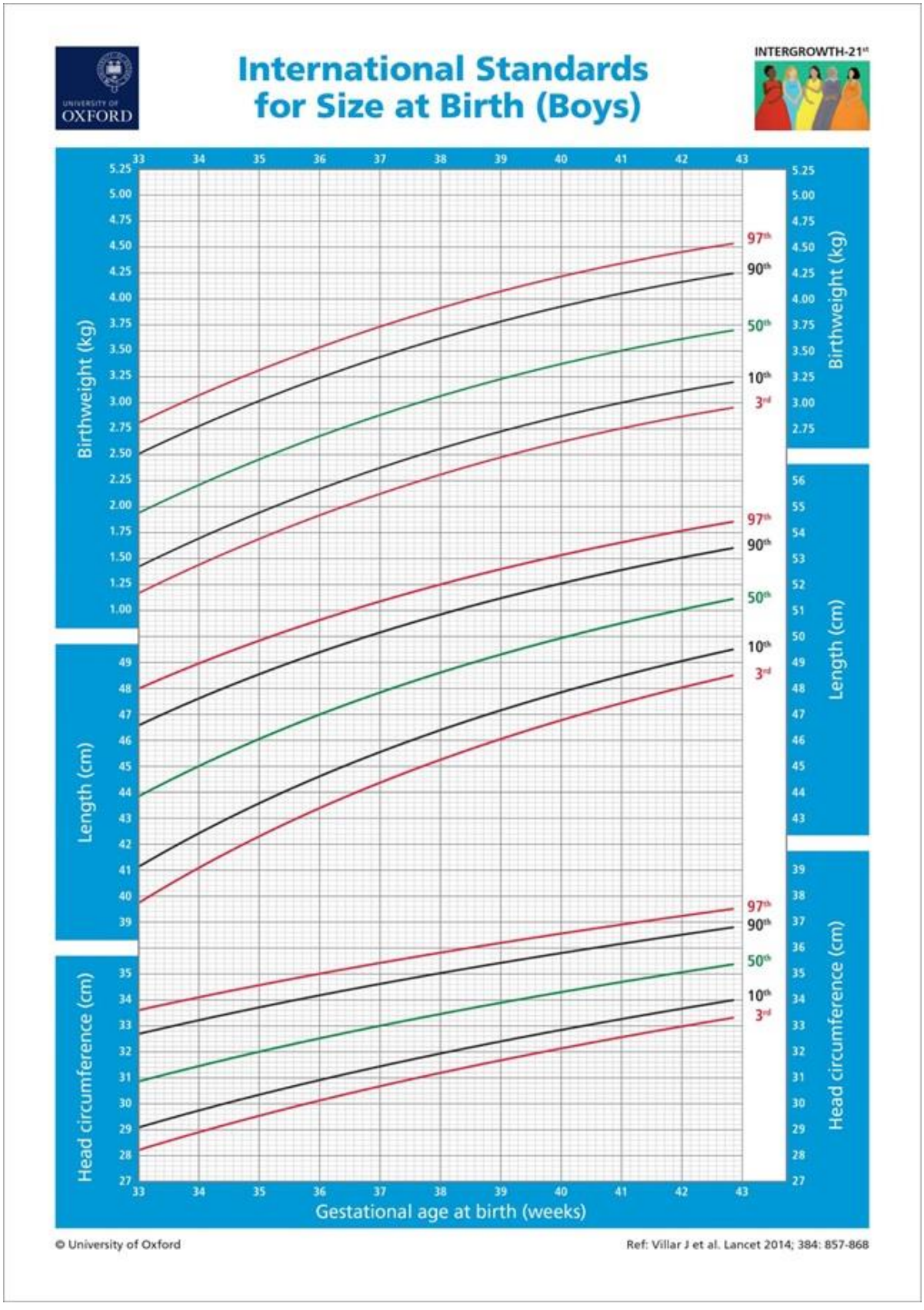
ANEXO D – Curvas de Fenton 2013 (*Boys)*



ANEXO E– Curvas do Intergrowth-21st (*Girls*)



ANEXO E– Curvas do Intergrowth-21st (*Boys*)



ANEXO F – Outros Artigos com Temas Afins Publicados Durante o Período da Pós-Graduação

Grein et al. Pediatric Rheumatology (2016) 14:12
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Pediatric Rheumatology

REVIEW Open Access

HPV infection and vaccination in Systemic Lupus Erythematosus patients: what we really should know

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Abstract

Patients with Systemic Lupus Erythematosus (SLE) are at increased risk for infections. Vaccination is a powerful tool to prevent infections, even in immunocompromised patients. Most non-live vaccines are immunogenic and safe in patients with SLE, even if antibody titres are frequently lower than those of healthy controls. Human papillomavirus (HPV) infections are more prevalent in SLE patients when compared to the healthy population. Low-risk types of this virus cause anogenital warts, while high risk types are strongly related to pre-malignant cervical abnormalities and cervical cancer. HPV vaccines have been developed to prevent these conditions. Although little is known about HPV vaccination in SLE, few studies in patients with autoimmune rheumatic diseases (AIRDs) have shown that HPV vaccines are safe, and capable to induce an immunogenic response in this group of patients. To date, available data suggest that HPV vaccines can be given safely to SLE patients. Given the increased incidence of cervical abnormalities due to HPV in SLE patients, this vaccination should be encouraged.

Keywords: Human papillomavirus infection, HPV, Systemic lupus erythematosus, SLE, Immunosuppression, Cervical dysplasia, Cervical cancer, Vaccines

Background

Systemic lupus erythematosus (SLE) is an immune disorder that predominantly affects women of reproductive age. The disease is characterized by chronic inflammation, circulating autoantibodies, and heterogeneous multisystemic involvement. It is well known that SLE patients are at increased risk for infections [1–7]. This might be due to the dysregulation of their immune system as well as the immunomodulatory therapy used by these patients [2, 4, 7–10].

Vaccines present one of the most effective tools to prevent infectious diseases. Ideally, vaccines should be immunogenic (i.e., capable to induce an antibody response), effective (i.e., provide protection) and safe. Vaccine safety in patients with chronic inflammatory conditions can be broken down into two separate concerns. Firstly, there is a potential risk of causing an exacerbation of the underlying disease. Secondly, in case of live-attenuated vaccines, there is a possibility to induce overt infection [9, 11]. When considering vaccinating a SLE patient, these issues should be addressed [2, 4, 8–11].

Protective immunity is dependent on a functional immune system that induces both adequate antibody levels as well as memory to achieve short term and long-term protection [2, 8, 9, 11]. As SLE patients have a dysfunctional immune system, there is a risk that their immune response to vaccination could be impaired. However, studies have demonstrated that most vaccines are efficacious in patients with SLE, even if specific immune responses may be reduced when compared to the responses of the healthy population [4, 5, 11–13].

In this review, we aim to give an overview of the risks of contracting oncogenic HPV infections in patients with SLE. Additionally, we describe the importance and relevance of the HPV vaccines in this group of patients. Three non-live protein subunit vaccines for HPV were

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approved in the last decade: bivalent (bHPV), quadrivalent (qHPV), and most recently, 9-valent (9vHPV) vaccines [14–16]. These vaccines were developed to prevent pre-malignant cervical lesions and cervical cancer. qHPV and 9vHPV also prevent benign conditions caused by HPV, like anogenital warts. All these conditions are more common in patients with SLE when compared to healthy population [17–27].

Vaccination in patients with Systemic Lupus Erythematosus

The European League Against Rheumatism (EULAR) has published general recommendations for the use of vaccines in autoimmune rheumatic diseases (AIRDs) [28, 29]. When indicated in national guidelines, non-live vaccines can be administered independent of medication use. It is recommended to withhold live-attenuated vaccines in patients on high-dose disease modifying anti-rheumatic drugs (DMARDs), high-dose glucocorticosteroids or biological agents. Boosters vaccinations can be considered in patients receiving a low dose of immunosuppressive medications [28, 29].

Irrespective of the AIRD, the majority of immunosuppressive drugs do not seem to have a detrimental effect on the immune response against vaccines, especially when the drug is administered in low doses [28, 29]. There is one important exception: rituximab, an anti CD-20 antibody. This drug acts through depletion of lymphocytes B and therefore strongly impairs the humoral immune response to vaccines. For this reason, it is recommended to vaccinate before or at least six months after administration of this medication [11, 28, 29].

Pneumococcal polysaccharide vaccine (PPSV23) and influenza vaccines have been researched extensively in patients with SLE, as these pathogens are responsible for the most common infections in patients with SLE [1, 4, 5]. Studies show that these two non-live composite vaccines are safe in this patient population. Vaccinated patients show hardly any change in disease activity. Patients did have a lower specific immune response when compared to the general population, but the majority of them produced protective antibody levels. No clear effect of immunosuppressive drugs or biological agents on the antibody titres was reported [1, 4, 5]. In pediatric patients, only influenza vaccines have been studied, with similar results to the adults trials [1, 11, 30–33].

The Hepatitis B Virus (HBV) vaccine, another non-live composite vaccine, has been studied in this population as well. One adult study with 28 patients and one pediatric study with 64 patients had showed lower antibody seroconversion rates, but still adequate humoral response against the virus in patients with SLE. There were no significant exacerbation of disease, nor adverse effects after HBV vaccination [1, 11–13].

The most important concern regarding live-attenuated vaccines in patients with SLE relates to the risk of developing overt infections of live-attenuated pathogens in the vaccine [3]. Only two prospective studies using a live attenuated virus vaccine in SLE patients have been published. One studied the varicella-zoster virus (VZV) vaccine in childhood-onset SLE patients who were previously immune to varicella virus. This study showed adequate immunogenicity and safety [34]. The other also studied the VZV-vaccine, in 10 SLE patients older than 50 years. The vaccine was safe: no episodes of herpes zoster or vesicular rash, no serious adverse events or SLE flares were reported [6].

Vaccination in immunocompromised patients can reduce the burden of infections [11, 28]. As these patients have many benefits from effective vaccination strategies, new vaccines should be assessed in this population as well. The most recent example are vaccines against the human papillomavirus (HPV), that have been studied in healthy and immunocompromised individuals in the last years, with satisfactory results.

Human Papillomavirus infections and vaccination in the healthy population

HPV infection is the most common sexually transmitted disease (STD) in the world [35–39]. The virus is able to infect the skin, mucous membranes of the anogenital region, as well as conjunctiva, oral and nasal mucosas, larynx and pharynx [37, 40]. Depending on the subtype, the virus can cause pre-malignant cervical abnormalities and cervical cancer as well as benign conditions such as anogenital warts. Besides sexual transmission, there are studies reporting transplacental and perinatal transmission [41–43]. It seems that the transmission is significantly lower when caesarean section is performed. In the majority of cases, the viral DNA does not persist in the newborn for more than 6 months [41–45]. Recurrent laryngeal papillomatosis, which is the most important clinical consequence of infantile HPV 6 and 11 infections, is a rare consequence of HPV chronicity in the newborn [44, 45].

The prevalence of HPV infection varies according to gender, age, population and geographic region. A large systematic review about HPV prevalence in women encompassed data from 70 countries worldwide [46]. Age is the strongest predictor, as the highest HPV prevalence in all studies around the world is found in women between 16 and 24 years old [35–37, 39, 46]. The review showed an age-stratified HPV prevalence that varied considerably across geographical regions and study population, ranging from less than 2 % to approximately 70 %, even in the same continent. Women under 25 were the most affected group in all study populations. Some regions, especially in America and Africa, showed a second peak among women older than 45 years old [46].

HPV is a DNA virus from the papillomavirus family, which covers over 120 genotypes classified according to the organization of DNA sequences and their oncogenic potential. About 40 of them are able to infect the human anogenital tract [35–38]. The most important types are showed in Table 1. The low risk subtypes are responsible for benign abnormalities such as anogenital warts. The subtypes 16 and 18 are responsible for 70 % of all cervical cancers, around 50 % of high-grade intraepithelial lesions (HSIL) and 30–50 % of low-grade intraepithelial lesions (LSIL). Together with the other high risk subtypes, they encompass 99.7 % of all cervical dysplasias, pre-malignant abnormalities, and cervical cancers [35–38]. A system for reporting these cervical cytologic diagnoses is the Bethesda System, created in 1988 and last updated in 2014 (Table 2) [47, 48].

Cancers caused by HPV include all cancers of the cervix, most anal (88 %) and vaginal (70 %) cancers, and part of vulvar (43 %), penile (50 %), and oropharyngeal cancers (26 %) [40]. The most recent estimate of the worldwide incidence and mortality of 27 major types of cancer, ranked cervical cancer as the fourth most common cancer in women. Interestingly, 84 % of the cases as well as 87 % of the deaths due to cervical cancer occurred in the more poorly developed regions [40, 49]. This is a consequence of more effective programs of population screening in developed countries, which provide early diagnosis and treatment and a higher chance of curing this cancer [40]. In the absence of screening programmes as in poorer countries is often the case, simple vaccination strategies could thus be extra effective.

HPV infection alone is not sufficient to develop cervical abnormalities. The combination of the virus' oncogenicity, its persistence in the infected tissue and the response of the host immune system determine the evolution of the infection [35–38, 40, 50]. In a large number of cases, the immune system is capable of clearing the virus in 1 to 5 years, without any treatment. Thus, only a minority of individuals infected with HPV develop clinical complications (Fig. 1). Women who are younger at first sexual intercourse or who have multiple sexual partners have a higher risk to develop HPV abnormalities, since they are more likely to be exposed to oncogenic subtypes as well as to a high charge of the virus. Smoking and hormonal contraception can cause immunological dysregulations that facilitate the genetic expression of HPV. The presence of other STDs increases the risk of disease development as well. In addition, immunosuppression or immunodeficiency can facilitate viral persistence in the host [35–38, 40, 50].

Table 1 Classification of HPV genotypes by cervical oncogenicity

Oncogenic potential	HPV genotypes
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably/Possible high risk	26, 53, 66, 68, 73, 82

Abbreviations: *HPV* human papillomavirus
Adapted from Eriksson et al. [37]

As the evolution of HPV infection to pre-malignant cervical abnormalities and cervical cancer takes decades in health women, it is possible to identify pre-malignant lesions by conducting screening tests. Conventional cytology tests (Papanicolaou test or Pap test) are the most widespread method used in cervical cancer screening. The test should be performed at each 3-year interval [16, 50–52]. In the past years, HPV DNA tests have been incorporated by developed countries for the screening of HPV infections. These tests have a higher sensitivity and are slightly less specific when compared with Pap test. The new guidelines suggest that the cervical screening of women 30 and over can be extended to 5-year interval when negative Pap test is combined with HPV DNA test [16, 50–52]. For women younger than 30 years, HPV DNA testing alone or in combination with Pap test are not recommended due to the high prevalence of HPV infection at this age, as well as the rarity of progression of those infections to invasive cancer [52].

Evidence from current studies suggests that the periodic tests should be complemented with HPV vaccination, aiming at primary prevention of infection with the virus [16, 40, 51]. Currently, three types of prophylactic HPV vaccines are available. The bHPV vaccine is directed against two high-risk genotypes, 16 and 18. The qHPV vaccine is also directed against these two high-risk HPV genotypes, but also provides protection against the low risk genotypes 6 and 11. Clinical data shows that both vaccines are safe and generate adequate antibody levels up to 4.5 years after vaccination [53–56]. A 9-valent HPV vaccine was licensed in December 2014 by the Food and Drug Administration (FDA), and in March 2015 by the European Medicine Agency. This vaccine offers protection against an additional five HPV high-risk genotypes. This should increase prevention of cervical cancer from 70 to 90 %, as well as prevent 85–95 % of HPV-related vulvar, vaginal and anal cancers. As this vaccine has just been approved, no clinical effectiveness data is yet available [14, 15, 57, 58].

The HPV vaccines have been incorporated in National Immunization Programs (NIP) across the globe, targeting 9 to 13 years old girls, with an original three dose regimen [40, 59]. Recently, the World Health Organization (WHO) updated its HPV vaccines position paper to recommend a two dose regimen with a 6-month interval between doses for immunocompetent girls younger than 15 years at the time of the first dose [59]. Different from European countries, The United States, Canada and Australia have incorporated HPV vaccination for boys from 9 to 12 years old in

Table 2 Bethesda System (Last update in 2014)

Terminology	Interpretation
Negative for intraepithelial lesion or malignancy	No cellular evidence of neoplasia
Squamous cells:	
Atypical squamous cells:	
Of undetermined significance (ASC-US)	Undetermined
Cannot exclude HSIL (ASH-H)	Cannot exclude pre-malignant lesion
Low-grade squamous intraepithelial lesion (LSIL)	HPV/mild dysplasia/CIN-1
High-grade squamous intraepithelial lesion (HSIL)	Moderate and severe dysplasia/CIN-2 and CIN-3/CIS
Squamous cell carcinoma	Invasive cancer
Glandular cells:	
Atypical glandular cells	Undetermined or cannot exclude pre-malignant lesion
Endocervical adenocarcinoma in situ	CIS
Adenocarcinoma	Invasive cancer

Abbreviations: CIN cervical intraepithelial neoplasia, CIS carcinoma in situ, HPV human papillomavirus
Adapted from Nayar and Wilbur [48]

their NIP [14, 40]. Women younger than 26 years and men younger than 21 years can also be benefited by the HPV vaccination [14, 40, 59].

All three vaccines show high efficacy in prevention of vaccine-specific HPV-type infection and associated high-grade cervical dysplasia in HPV-naïve women (Table 3) [57]. Despite bHPV and qHPV vaccines having been approved only 10 years ago, a meta-analysis of 20 studies performed in developed countries has already showed significant decrease of HPV prevalence in young vaccinated men and women [60]. Due to the lag-time between HPV infection and the development of cancer, a decreased incidence of HPV-related cancers can only be determined after several decades. In order to reduce the incidence and mortality from cervical cancer globally, these vaccines should have a high coverage in the population [40]. Figure 2 shows the most important events in the history regarding the screening and prevention of HPV infection and cervical cancer.

Human Papillomavirus infections and vaccination in Systemic Lupus Erythematosus patients

Studies from all over the world showed that HPV infections are more prevalent in patients with SLE [17–27]. Santana et al. performed a systematic review of 33 studies. They concluded that the diagnosis of SLE directly increases the risk of developing cervical dysplasias and pre-malignant lesions [20]. Although the majority of the studies showed that SLE patients had more pre-malignant lesions than healthy women, the prevalence of cervical cancer was similar between SLE patients and healthy populations in almost all studies [20]. Only one study included in the review found an increased prevalence of cervical cancer in SLE patients [20, 21]. The increased risk of pre-malignant lesions in this population was confirmed in a meta-analysis performed by Zard et al. [23]. Seven studies about the prevalence of pre-malignant cervical lesions in patients with SLE were included. They showed a 9-fold increase risk on pre-malignant cervical lesions in this population when

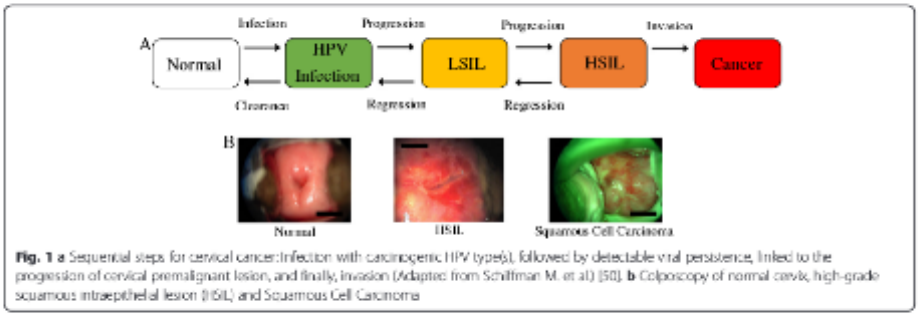

Fig. 1 **a** Sequential steps for cervical cancer: Infection with carcinogenic HPV type(s), followed by detectable viral persistence, linked to the progression of cervical pre-malignant lesion, and finally, invasion (Adapted from Schiffman M. et al.) [50]. **b** Colposcopy of normal cervix, high-grade squamous intraepithelial lesion (HSIL), and Squamous Cell Carcinoma

Table 3 HPV vaccines efficacy and cervical cancer coverage

Vaccine	HPV genotypes	Vaccine efficacy	Cervical cancer coverage
bHPV	6 and 18	>98 % for HPV disease related to genotypes 6 and 18	70 %
qHPV	6, 11, 16 and 18	>99 % for HPV disease related to genotypes 6, 11, 16 and 18 (women) 90 % for external genital disease (men)	70 %
9vHPV	6, 11, 16 and 18 31, 33, 45, 52 and 58	>99 % for HPV disease related to genotypes 6, 11, 16 and 18 96,7 % for HPV disease related to genotypes 31, 33, 45, 52 and 58	90 %

Abbreviations: bHPV bivalent vaccine, *qHPV* quadrivalent vaccine, *9vHPV* 9-valent vaccine, *HPV* human papillomavirus
Adapted from Committee Opinion number 641 [57]

compared to healthy individuals [23]. The studies included in this meta-analysis did not include any long term follow-up data. Whether these pre-malignant lesions progress to cervical cancer remains unclear. An explanation for the higher prevalence of cervical dysplasia in SLE patients is that clearance of HPV could be related to adequate innate and adaptative immune responses. As these are impaired in patients with SLE, clearance of the virus could also be impaired or merely delayed, resulting in persistent carriage of HPV, as well as persistent lesions [20, 23, 24, 61].

There is no consensus in the literature regarding the role of immunosuppressive drugs as a predisposing factor for the cervical abnormalities caused by HPV [19, 20, 25]. The majority of the studies showed no association. However, some evidence suggests azathioprine and intravenous cyclophosphamide use could contribute to the development of persistent HPV infections and subsequent complications [19, 20, 25–27].

It is clear that patients with SLE are at increased risk to develop HPV infections. Thus, it is reasonable that more rigorous criteria should be applied to cervical cancer screening in SLE patients, with shorter intervals in between examinations than the general population, associated to HPV vaccination [19]. The introduction of the HPV vaccines presents an opportunity for cervical cancer prevention. SLE patients should benefit from preventive vaccination. Therefore, it is essential that the safety, immunogenicity and efficacy of the HPV vaccine in this specific population will be studied.

The EULAR recommendations for both children and adults with rheumatic diseases state that the HPV vaccine should be considered in patients with autoimmune diseases. An association with venous thromboembolic events (VTE) and the qHPV vaccine had been reported, which led to a side note on this in the recommendations regarding the vaccine [62]. However, current evidence from 997.585 girls did not show any association between HPV vaccination and possible VTE. In this large cohort, no associations between HVP vaccination and autoimmune or neurological adverse events could be shown either [63].

Since the HPV vaccines were licensed, six original articles and one systematic review have been published regarding the safety and immunogenicity of these vaccines in patients with autoimmune disease [53, 54, 64–67]. Three articles studied the safety and immunogenicity of the vaccine in SLE patients [66–68], two in juvenile

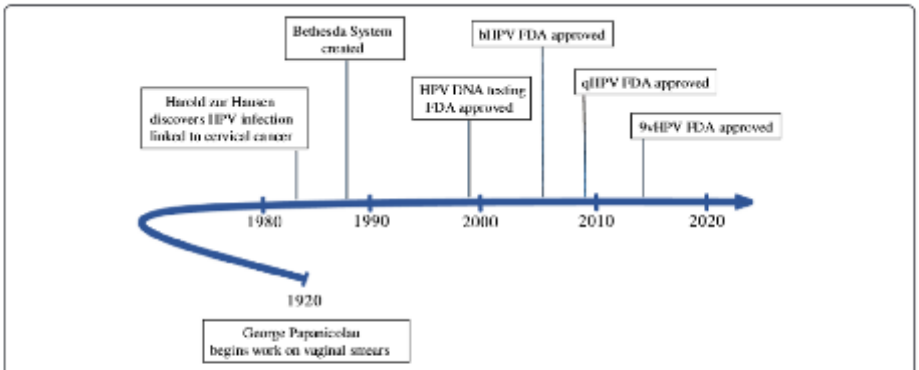

Fig. 2 Important events regarding cervical cancer and HPV. Abbreviations: bHPV, bivalent vaccine; qHPV, quadrivalent vaccine; 9vHPV, 9-valent vaccine; HPV, human papillomavirus; FDA, Food and Drug Administration. Adapted from Lees et al. [16]

idiopathic arthritis (JIA) patients [64, 69], one in patients with juvenile dermatomyositis (JDM) [68] and one in patients with inflammatory bowel disease (IBD) [65]. Overall, the vaccine seems to be safe and immunogenic in patients with an autoimmune disease.

The largest study assessing immunogenicity and safety of the HPV vaccine in patients with SLE included 50 SLE patients and 50 healthy controls between the age of 18 and 35 years. At twelve months after receiving the first vaccination, seroconversion rates in both groups were adequate (Patients vs Controls: HPV 6: 82 % vs 98 %, HPV11: 89 % vs 98 %, HPV16: 95 % vs 98 %, HPV18: 98 % vs 80 %). A lower immunogenicity of the vaccine was associated with the use of low-dose prednisolone or mycophenolate mofetil. Adverse events were not different between patients and controls. No significant difference in rate of flares in the vaccinated group and a control group of unvaccinated SLE patients was found [66].

A pilot study included 6 patients with childhood-onset SLE who were vaccinated in the context of the national vaccination program [68]. The vaccine induced seropositivity for all isotypes in a high proportion of patients, although the geometric mean titres were lower in patients than those in healthy controls. An uncontrolled study in 20 SLE patients also showed a high seropositivity rate for all isotypes [67]. In both studies, disease activity was measured with the SLE Disease Activity Index (SLEDAI). Prior to vaccination, disease activity was low in all patients. During follow-up, disease activity remained low. Ten mild/moderate flares were reported. These flares were generally similar to the flares the patients had in the year prior to vaccination.

One study evaluated the change in hospitalizations for SLE in the United States since the introduction of the HPV vaccine, to assess its safety [70]. In this study, no evidence of an increased amount of hospitalizations for SLE was found since the introduction of the HPV vaccine.

The HPV vaccines have been studied in small groups of patients with autoimmune diseases. In these groups, the vaccines are shown to be immunogenic and safe. As antibody titres are a proxy for protection for most vaccines, larger, controlled studies are needed to compare the antibody titres in patients and in controls. When antibody titres are low, an adequate immunologic memory could still indicate that individuals are adequately protected when they encounter the virus. Therefore, specific memory against HPV also needs to be assessed in patients with SLE. Additionally, long-term studies are necessary to assess the effect of HPV vaccination on the prevalence of persistent high-risk HPV infections in patients with SLE.

Conclusion

Infections represent the main cause of death in patients with SLE. Vaccination is the most important tool in the prevention of infections, and for this reason it is an important topic to be discussed in order to improve the care of SLE patients. Although some questions still remain, diverse studies have shown the immunogenicity and safety of non-live vaccines in patients with SLE. Therefore, use of these vaccines should be encouraged by health professionals.

Evidence about the immunogenicity and safety of live-attenuated vaccines in SLE patients is still scarce. More studies are needed to elucidate the level of immunosuppression that turns out patients to be at risk from live agents present in the vaccines, as well as the pattern of immune system response and memory production after vaccination.

HPV is essential in the pathophysiology of premalignance cervical abnormalities and cervical cancer, conditions that are highly prevalent among women in all the world. Women with SLE present even higher risk of development HPV diseases. SLE predominantly affects women of reproductive age, that is the same group where the occurrence of HPV infection is increased. As the immune system of SLE patients is abnormal, the clearance of the virus is impaired. The result is the persistence of HPV virus in the cervix of SLE patients more often than in healthy women, what leads to higher prevalence of cervical dysplasia and cancer in SLE female population.

Non-live HPV vaccines are safe and able to produce a protective response even in patients with autoimmune diseases. These findings represent a great benefit for public health. Especially in poorer countries with absent screening programs, HPV vaccination strategies should be implemented. Despites the vaccines have been approved only 10 years ago, studies performed in developed countries already showed significant decrease of HPV prevalence in young vaccinated men and women [40, 60]. Future studies will have to be performed to evaluate the reduction in incidence of cervical cancer and other HPV-related cancers after decades of HPV vaccines implementation, as well as the HPV vaccines' long term efficacy in patients with SLE.

Abbreviations

9vHPV: 9 valent HPV vaccine; ARDs: autoimmune rheumatic diseases; bHPV: bivalent HPV vaccine DMARDs: disease modifying anti-rheumatic drugs; EULAR: European League Against Rheumatism; HBV: Hepatitis B Virus; HPV: human papillomavirus; HSIL: high grade intraepithelial lesions; IBD: inflammatory bowel disease; JDM: Juvenile dermatomyositis; JIA: juvenile idiopathic arthritis; LSIL: low-grade intraepithelial lesions; PPSV23: pneumococcal polysaccharide vaccine; qHPV: quadrivalent HPV vaccine; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; STD: sexually transmitted disease; VTE: venous thromboembolic events; VZV: varicella-zoster virus; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IHRG drafted the manuscript and designed the figures and tables. NC drafted the manuscript and participated in the design of the study. MIL drafted the manuscript and provided photos from Fig. 1. NW conceived the study, and participated in its design and coordination. GP drafted the manuscript, designed the figures and tables and participated in the design and coordination of the study. All authors read and approved the final manuscript.

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SPECIAL ARTICLE

Gestational outcomes in patients with neuropsychiatric systemic lupus erythematosus

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This study analyzed maternal and fetal outcomes of pregnancies of neuropsychiatric systemic lupus erythematosus patients followed in a reference unit. This retrospective cohort study included 26 pregnancies of patients seen between 2011 and 2015 included with history and/or active neuropsychiatric systemic lupus erythematosus among 135 pregnancies. Three patients had active neuropsychiatric systemic lupus erythematosus at conception, but only one remained with neurological activity during gestation, characteristically related to the inadvertent suspension of medications. Twenty six percent of the newborns were small for gestational age and 40% of live births were premature, with no neonatal death or early complications of prematurity. Preeclampsia was diagnosed in nine pregnancies, with two cases of early severe form that resulted in intrauterine fetal death. Patients with neuropsychiatric systemic lupus erythematosus had more prematurity and preeclampsia compared to patients without neuropsychiatric disease. However, when concomitant lupus nephritis was excluded, the gestational results of neuropsychiatric systemic lupus erythematosus patients were more favorable. *Lupus* (2017) **26,** 537–542.

Key words: 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 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

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according to the organ or system involved, separated into cutaneous, articular, serositis, renal, hematological and CNS.

The obstetric outcomes evaluated were abortion, fetal death, premature rupture of membranes, preeclampsia, intrauterine growth restriction (IUGR) 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 hematological manifestations (61%) and 10 had serositis (47%). Six patients had detectable circulating anti-Ro/SSA (28%) and none had anti-La/SSB.

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

Table 1 Characteristics of studied patients, including general and neuropsychiatric SLE manifestations

Patient #	*Maternal age (year)*	*Duration of SLE (year)*	*Neuropsychiatric manifestations*	*Other SLE manifestations*	*Comorbidities*
1[a]	24	4	Depression, psychosis	Serositis, renal	Chronic hypertension, renal failure
	26	6			
	28	8			
2	18	8	Headache, chorea, psychosis, hemiparesis	Cutaneous, arthritis, serositis, hematological	—
3	24	8	Transverse myelitis, 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	31	6	Depression, psychosis	Cutaneous, arthritis	Recurrent UTI
7[b]	32	10	Ischemic stroke, seizures	Cutaneous, arthritis, serositis, renal	APS
	35	11			
8	40	8	Depression, psychosis	Cutaneous, arthritis	Chronic hypertension
9[b]	27	15	Seizures, psychosis, amnesia	Cutaneous, arthritis, serositis, renal, hematological	—
	28	16			
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	0	Ischemic stroke	Cutaneous, serositis, renal, hematological	APS
	29	9			
14	31	2	Ischemic stroke	Arthritis	—
15	35	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
18	31	17	Seizures	Cutaneous, arthritis, serositis, renal, hematological	—
19	32	3	Depression, psychosis	Cutaneous, arthritis, renal, hematological	Hypothyroidism
20	33	10	Ischemic stroke, headache	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.
SLE: systemic lupus erythematosus; LA: lupus anticoagulant; aCL: anticardiolipin; UTI: urinary tract infection; APS: antiphospholipid syndrome; aPL: antiphospholipic antibody.

women had chronic hypertension (19%), including one with chronic renal failure on hemodialysis.

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 analyses. In eleven pregnancies, the disease was considered active at conception (42%), three with NP manifestation (11%). However, the neurological activity remained during gestation in only one patient, 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 a SLE flare during pregnancy, but it was not related to NP manifestations (cutaneous/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.

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 IUGR at 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 IUGR, oligohydramnios and/or altered fetal Doppler-velocimetry were observed in five of six fetuses, representing an antenatal detection rate of 83%. The cohort's mean birth weight was 2443 g (394–3605 g), with 78% of newborns weighing more than 2000 g. In the group of SGA newborns, the mean birth weight was 1462 g (394–2445 g).

Prematurity – delivery between 22 and 36 weeks and six 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 six days (30%), and four deliveries <32 weeks (17%). Considering only the live births, the frequency of prematurity was 40% (eight 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.

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[a]	—	—	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.
SLE: systemic lupus erythematosus; NICU: neonatal intensive care unit admission; SGA: small for gestational age infant.

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 preeclampsia patients was 1889 g (394–3205 g), 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 live births (76%). Among them, 14 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 hemorrhage) and/or secondary to NICU (neonatal infection, severe respiratory disorder, renal insufficiency).

No newborn had a 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 or symptoms that suggested 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 births occurred at 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.

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 NPSLE gestational results are infrequently 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, who presented with 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

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

At conception	*NPSLE (24 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%)	**0.04**
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 delivers in weeks (mean ± SD)	35.6 ± 4.3	37.0 ± 3.5	0.09
Birth weight in grams (mean)	2443.4 ± 915	2703.5 ± 805	0.17

[a] Chi squared, Fisher's exact test and Student's t test when applicable.
SLE: systemic lupus erythematosus; NP: neuropsychiatric; NPSLE: neuropsychiatric systemic lupus erythematosus.

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 from 11 weeks, with posterior severe preeclampsia and fetal growth restriction that required delivery 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] Results show disagreement in the 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 the 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 at less than 20 weeks. The third case with NPSLE at conception, although chorea remained during pregnancy, had a favorable outcome with a term healthy newborn. This patient had poor treatment adherence, so chorea was rapidly controlled after medication adjustment.

Considering the 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 (17 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 lesions. Such a 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 the 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 three 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 an 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.

IUGR 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 than the previously described rates of 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 (seven of nine) occurred at 34 or more weeks and, although three newborns required NICU admission, all had good outcomes, with Apgar's scores of >7 within five minutes of birth and no apparent morbidity after discharge. Both cases of preeclampsia with very early presentation (23 and 27 weeks) also had severe renal flare and intrauterine fetal death. These data underscore the necessity of high-risk pregnancy center prenatal care for those patients, as hypertensive disorders are the primary 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 was 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 numbers of patients, are needed to better evaluate the behavior of NPSLE patients during pregnancy and optimize treatment.

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Challenging cases in rheumatic pregnancies

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Abstract

This article describes three complicated cases in rheumatology and pregnancy. The first case elucidates the challenges in treating SLE in conjunction with pulmonary arterial hypertension, while the second case features an SLE-affected pregnancy with development of portal hypertension secondary to portal vein thrombosis related to APS. The third case is a pregnant woman with stable SLE who developed thrombotic microangiopathy caused by atypical haemolytic uraemic syndrome, and failed to improve despite multiple measures including biopsy and elective preterm delivery. There are grave and unique challenges for women with autoimmune disease, but adverse outcomes can sometimes be avoided with careful and multidisciplinary medical management. Pre-conception counselling with regard to medications and disease treatment should also include discussion of the advisability of pregnancy, which may be difficult for a patient, but present the best course for optimizing health outcomes.

Key words: anti-phospholipid syndrome, portal vein thrombosis, portal hypertension, pregnancy, pulmonary arterial hypertension, scleroderma, stillbirth, systemic lupus erythematosus

Rheumatology key messages

- Rheumatic diseases in pregnancy present with a wide range of symptoms and present significant clinical challenges.
- Cases presented demonstrate that keeping a broad differential diagnosis is essential to providing the best care.

REVIEW

Introduction

Women with rheumatic disease can present with a myriad of symptoms, some causing catastrophic illness. The three cases presented here demonstrate that pregnancy can be complicated by a wide range of ailments and that keeping an open mind and a wide differential diagnosis can be essential to providing the best care. Each patient described has a serious underlying rheumatic disease that, taken alone, can often be successfully managed in pregnancy with careful planning, strong medications and close attention. But each woman described developed an unexpected and rare complication that put her life—and the life of her unborn child—in peril.

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Case 1

The patient is a 24-year-old African American female diagnosed with SLE at age 18 years after presenting with arthritis, malar rash, leucocytoclastic vasculitis, fevers, fatigue, anaemia and lymphopenia. At diagnosis she had a high titre ANA and positive Smith, RNP, SmRNP and aPL. At age 21 years she was diagnosed with WHO class IV/V LN causing chronic proteinuria of 2 g/l and had been prescribed mycophenolate. After an unplanned pregnancy resulting in miscarriage while on mycophenolate at age 22 years, this medication was stopped and she was started on tacrolimus and AZA. Her medications at presentation included AZA, HCQ, prednisone 15 mg/day, aspirin, lisinopril and tacrolimus.

Table 1 Objective parameters of PAH in a pregnant patient while on epoprostenol

Gestational age	20 weeks 4 days	23 weeks 3 days	27 weeks 6 days
Epoprostenol dose	None	6 ng/kg/min	12 ng/kg/min
6MWT predicted distance (m)	477	478	470
6MWT actual distance (m)	332	375	424
6MWT distance predicted (%)	70	78	90
Borg score[a]	3	2	2
BMI (kg/m^2)	40.9	40.7	41.8

[a]Borg Rating of Perceived Exertion Scale, 0 = none 10 = maximum. PAH: pulmonary arterial hypertension; 6MWT: 6 min walk test.

At a routine rheumatology appointment, she reported a dry cough and dyspnoea on exertion. A chest radiograph revealed perihilar congestion and cardiomegaly. Her echocardiogram was notable for a preserved ejection fraction, an enlarged right ventricle (RV) with reduced contractility, moderate tricuspid regurgitation and a small pericardial effusion. Out of concern for pulmonary hypertension, right heart catheterization (RHC) was scheduled. Per protocol, a pre-procedure urine pregnancy test was collected and returned positive. The procedure was cancelled. The cardiologist started furosemide, discontinued her lisinopril and she was continued on the rest of her outpatient medication regimen.

Three months later, at 20 weeks gestation, she was seen in the pulmonary hypertension clinic at a different medical facility with dyspnoea on exertion, rapid weight gain, peripheral oedema, hypertension (149/94 mmHg) and a BMI of 41. Cardiac auscultation found a split S2, accentuated P2 and 1/6 systolic murmur at the left lower sternal border. She had 1$^+$ pitting pretibial oedema, trace oedema in the hands and periorbital oedema. Her labs were notable for mild anaemia, low albumin (1.4 g/dl), hypocomplementaemia and 2.5 g/l proteinuria with normal creatinine, platelets and liver enzymes. Consistent with her prior history, she had a high titre ANA and positive Smith, Sm/RNP and RNP antibodies, however, she also had a low-positive dsDNA titre and her aPL testing was negative.

She was admitted to the hospital from the clinic for further workup. Her echocardiogram had a preserved ejection fraction but volume overload, a moderately enlarged RV and RA, and a small pericardial effusion. The RV systolic pressure was 63 mmHg. Echocardiogram findings were concerning for moderate pulmonary hypertension. A ventilation–perfusion scan was read as low probability. RHC was performed and demonstrated a pulmonary arterial pressure of 42 mmHg, consistent with moderate pulmonary arterial hypertension (PAH), presumably type 1, secondary to her SLE. Epoprostenol was initiated at 2 ng/kg/min, with near resolution of her peripheral oedema and dyspnoea. Lengthy discussions were had with the patient, her medical teams and her family due to the mortality risk that PAH conveys to both mother and foetus as well as the theoretical threat of pre-term labour with epoprostenol therapy. She desired to continue the pregnancy. Enoxaparin was started due to the likelihood of thrombosis secondary to SLE, gravid state, PAH, obesity, proteinuria, indwelling central line and prostacyclin use. Discharge medications included higher-dose furosemide, metoprolol, continuous epoprostenol and an increased dose of tacrolimus, in addition to her prior SLE medications. Epoprostenol was titrated to 12 ng/kg/min after discharge, with subjective and objective improvement, illustrated in Table 1.

At her 33 week prenatal visit, she described worsening dyspnoea and the inability to lay supine. On examination, she had 3$^+$ pitting oedema to the thigh, edematous hands and a blood pressure of 141/99 mmHg. She had gained 15 pounds since her recent appointment. Her brain natriuretic peptide, platelets, liver enzymes and creatinine were normal, however, her urine total protein was very elevated at 16 g/l and complements were lower than at her PAH diagnosis (Table 2). Urinalysis returned with 15 white blood cells (WBCs)/high-power field (hpf), 5 red blood cells (RBCs)/hpf, hyaline and cellular and granular casts. The tacrolimus level was low. An echocardiogram showed a hyperdynamic left ventricle, severely dilated RV and RA and a moderate pericardial effusion. All SLE medications were continued, tacrolimus increased and diuresis was attempted. She remained on epoprostenol 12 ng/kg/min. She was given betamethasone for foetal lung maturation. Increasing doses of metoprolol and methyldopa were trialled due to worsening hypertension. Out of concern for SLE flare manifesting as worsening proteinuria, hypocomplementaemia and pericardial effusion, prednisone was increased from 15 to 60 mg/day. Three days after this increase, she began having headaches and blurred vision with systolic blood pressures >180 mmHg. Magnesium infusion was begun with concern for superimposed preeclampsia, although uric acid, liver enzymes and platelet count did not suggest this aetiology.

Due to her worsening clinical picture as well as new foetal heart rate decelerations, an urgent caesarean delivery under general anaesthesia was performed at 33 weeks 4 days gestation. She received intraoperative stress-dose steroids. Cardiothoracic surgery, cardiac and obstetric anaesthesia and the extracorporeal membrane oxygenation team, as well as obstetrics, neonatology and pulmonary specialists were present for her uncomplicated delivery and bilateral tubal ligation. A healthy boy, Apgar scores 8/9, was delivered. After delivery she was admitted to the surgical intensive care unit (ICU) and her course was complicated by a large postpartum haemorrhage. While his mother was recovering,

TABLE 2 Laboratory value at initial PAH visit and subsequent worsening 13 weeks later

Lab	20 weeks gestation	33 weeks gestation
WBC count ($\times 10^9$/l)	5.4	4.8
Haemoglobin (g/dl)	10.5 low	9.8 low
Platelets ($\times 10^9$/l)	260	369
Creatinine (mg/dl)	0.42	0.50
Albumin (g/dl)	1.6 low	1.4 low
AST (U/l)	18	18
ALT (U/l)	14	15
C3 (mg/dl)	57	48 low
C4 (mg/dl)	12 low	11 low
Anti-dsDNA (IU/ml)	10.0 positive	6.0 positive
Spot urine protein (g/l)	4.0 high	16.5 high

ALT: alanine transaminase; AST: aspartate transaminase.

the newborn spent 1 week in the neonatal ICU receiving routine care and had no significant events or interventions. The patient was continued on her prior outpatient medication regimen, including epoprostenol with a prednisone taper, and demonstrated no evidence of post-partum SLE flare. Both were discharged from the hospital at 1 week post-partum, at which time her spot urine total protein was 4.5 g/l.

Discussion

This case presents many challenging clinical dilemmas. In general, those with SLE can and do have successful pregnancies. Patients should be counselled, however, that improved outcomes for both mother and baby occur when pregnancies are planned, allowing for the cessation of teratogenic medications and disease control, making reproductive health counselling an essential part of their rheumatologic care. Initially our patient was denied an RHC due to her gravid state, however, this is not a contraindication for this procedure [1]. As an RHC does not use contrast or fluoroscopy, risks for the foetus are low when compared with left heart catheterization. RHC complications include bleeding or bruising, pneumothorax and more rarely air embolism, arrhythmia, thrombosis, infection, tamponade and pulmonary artery rupture, but there are no reports of these being more frequent in pregnancy; in fact, pulmonary artery catheters are common in obstetric intensive care. Echocardiography in pregnancy actually overestimates pulmonary pressures, potentially leading to too-frequent diagnosis of PAH, highlighting the need for RHC in obstetric patients [2, 3].

While pregnancy and the diagnosis of PAH occurred concurrently in this case, PAH itself is an indication to advise against conception in those with or without CTD [4]. The European societies for cardiology and respiratory diseases have limited guidelines about PAH and pregnancy, but these include that pregnancy should be discouraged and contraception, including medical sterilization, is indicated; termination should be discussed if a woman is pregnant; and 'disease-targeted therapies, planned elective delivery and effective close collaboration between obstetricians and the PAH team' are important [5]. Patients with PAH should be offered medical sterilization and reliable contraception modalities. Based on the greatly increased risk for morbidity and mortality, termination of pregnancy should be offered independent of functional status or objective findings. This recommendation is based on the known increased risk of morbidity and mortality.

Studies prior to prostaglandin therapy estimate a 50% chance of mortality to both mother and baby [6]. More recent studies estimate the probability of death to be 18–40% [7–11], and it is higher in women with rheumatologic disorders, often due to complications from pre-eclampsia and disease flare. A majority of these deaths are attributed to RV failure, although they are often multifactorial, involving respiratory failure, kidney failure and haemorrhage. International case studies reporting PAH and prostacyclin administration in pregnancy have demonstrated that starting this medication early in pregnancy leads to an improved survival rate [10, 12–18], although pre-term delivery is still present in >50% of cases. It does not appear from these case studies that prostacyclin therapy has a teratogenic effect. The preferred prostacyclin delivery is parental. This mode of delivery is the most efficacious, has a rapid onset of action, titrates easily and has been successfully paired with oral phosphodiesterase 5 inhibitors sildenafil and tadalafil. Both epoprostenol and treprostinil are classified as pregnancy category B, iloprost is category C. Inhaled prostacyclins have been used but are recommended for mild classes of heart failure without significant RV changes. Calcium channel blockers have also been used with success and are safe in pregnancy. On the other hand, endothelin receptor antagonists and soluble guanylate cyclase stimulator are not recommended in pregnancy due to teratogenicity concerns.

Regarding delivery mode, there is no expert consensus whether caesarean or vaginal delivery is safest for women with PAH [5, 19, 22]. Theoretically vaginal deliveries have more haemodynamic complications due to Valsalva manoeuvres and associated natural neurologic sequela of childbirth. Anaesthesia for caesarean delivery must be chosen carefully as there are also inherent haemodynamic risks with general anaesthesia. PA catheterization may be useful in either mode of delivery, but is not standard. No matter the mode, delivery should be planned and performed at a centre with a multidisciplinary team able to care for both mother and baby. Of note, the highest incidence of thrombosis, cardiac decompensation and death in reported cases of PAH is within the first week post-partum. Patients should remain hospitalized during this period and anticoagulation considered [19]. Anticoagulation is controversial in PAH, even independent of the pregnant state, due to side effects, particularly bleeding, as was seen in this patient [4]. All patients should be closely followed post-partum, as they are still at risk for haemodynamic compromise.

Table 3 Serum complement reference ranges in healthy pregnant females

Complement	Non-pregnant adult	First trimester	Second trimester	Third trimester
C3	83–177	44–116	68–118	60–126
C4	16–47	9–45	10–42	17–37

Information summarized from Gronowski [20]. All units are milligram per decilitre.

It is difficult to determine whether this patient had pre-eclampsia or if her clinical worsening was an evolution of her lupus. Arguing for pre-eclampsia was her gestational age, rising blood pressure, headaches, dramatic increase in proteinuria, the absence of other lupus symptoms, as well as her rapid improvement following delivery. Arguing against pre-eclampsia was that her platelets, hepatic function and uric acid were all normal, her tacrolimus level was low, putting her at risk for renal disease flare, and she had declining complement levels. Complicating the latter aetiology, C3 and C4 can be low during pregnancy even without a diagnosis of SLE [20] (Table 3). Out of concern for a lupus flare, she received an increased prednisone dose, which has a known side effect of hypertension, which possibly led to her headaches and vision changes and confounded her case. Aetiological consideration was also given to cardiac tamponade or worsening pulmonary hypertension. Her moderate pericardial effusion improved quickly with concurrent diuresis and prednisone, ruling out tamponade, but without further elucidation of the causation of her decompensation. While she did not undergo an RHC or have a pulmonary artery catheter placed, she improved without titration of her epoprostenol, making worsening PAH unlikely. PAH affects the ability to increase cardiac output and increases pulmonary vascular resistance. These altered haemodynamics, accompanied by the cardiovascular effects of pregnancy and the theoretical pathophysiology of pre-eclampsia involving increased plasma volume and reduced systemic vascular resistance due to the uterine spiral artery failure, may explain the decompensation seen in this patient and others with PAH.

This case is an example of a successful, unplanned pregnancy and concurrently diagnosed PAH in a patient with well-controlled SLE with baseline proteinuria. This patient's course emphasizes the importance of recognizing PAH and pursuing a full evaluation as well as beginning treatment early in pregnancy for improved outcomes. Parenteral prostanoids have been shown to be safe and advantageous in pregnancy, as seen in this case. Without this treatment, mortality rates are unacceptably high, but with therapy the risks may be modified, although data do not exist to demonstrate the extent of the improvement. This case also highlights the challenges of determining whether a patient has pre-eclampsia or a lupus flare—patients with SLE being at risk for both.

Case 2

A 29-year-old Brazilian Afro-descendant patient, born and living in Rio de Janeiro, was admitted to our high-risk pregnancy clinic for women with systemic autoimmune diseases at the Hospital Universitário Pedro Ernesto in Rio de Janeiro, Brazil, in January 2016. It was her fifth pregnancy; she reported having one healthy 11-year-old son, one previous neonatal death due to congenital heart disease and two stillbirths at 29 and 32 weeks of gestation, respectively, with the last delivery complicated by pre-eclampsia and placental abruption. The patient was first examined at our clinic at 23 weeks of gestation presenting with ascites, recent upper gastrointestinal bleeding and haemodynamic instability (syncope and dyspnoea). She was admitted to the hospital and managed with clinical support, blood transfusion, removal of 2 l of ascitic fluid by paracentesis and endoscopic ligation of oesophageal varices for extra-hepatic portal vein obstruction (EHPVO). She reported presenting the same signs and symptoms during the previous two pregnancies that resulted in stillbirths. At that time her physicians treated the oesophageal varices with endoscopic sclerotherapy, but no further investigation was performed. The patient had a history of alcohol use from ages 20 to 24 years, but denied present consumption of alcohol. The laboratory workup revealed high titre aCL (145 G phospholipids and 129 M phospholipids), that were persistent, with negative anti-beta 2 glycoprotein I, LA and ANA tests. A complete blood cell count showed anaemia and thrombocytopenia (haemoglobin 6.8 mg/dl, platelet count 82 000 cells/mm^3); serologic tests for syphilis; hepatitis viruses A, B and C and HIV were negative. The cultures of the ascitic fluid were negative and cytology showed the absence of neoplastic cells. Abdominal Doppler US identified partial recanalization of an old portal vein thrombosis (cavernomatous transformation of the portal vein), homogeneous splenomegaly, voluminous ascites and no signs of chronic liver disease. An upper gastrointestinal endoscopy showed thin and intermediate thickness oesophageal varices and mild portal hypertensive gastropathy. The final diagnosis was portal hypertension secondary to portal vein thrombosis related to APS type 2 [21] with thrombotic and obstetric events as classical manifestations and thrombocytopenia as a non-criteria manifestation [22–24].

After 13 days of hospitalization and no further bleeding event, the patient was discharged in stable condition, with prescriptions for enoxaparin 40 mg/day, diuretics (furosemide and spironolactone), a β-blocker (propranolol) and an iron supplement. She was followed for prenatal care at our centre and remained stable until term, undergoing labour induction at 39 weeks of pregnancy, with a live-born baby girl of 2800 g. The Apgar scores were 9 at the 1 and 5 min following an uncomplicated vaginal delivery. There was no need for ICU admission for the mother or the infant. Both were discharged 48 h after delivery with routine observation. She was asymptomatic at the follow-up visits at 20 and 48 days after delivery. The use of s.c. enoxaparin was kept at 40 mg/day for 6 weeks post-partum, as well as the remainder of the

medications for portal hypertension treatment. The patient was referred back to the gastroenterology and rheumatology clinics for ongoing follow-up.

We decided not to add low-dose aspirin to enoxaparin due to the high bleeding risk in this patient. Twenty-one pregnancies in 12 patients with EHPVO were studied in a single centre in New Delhi, India [25]. The authors called attention to the fact that the increase in blood volume and cardiac output related to pregnancy overloads the portal flow, aggravating pre-existing portal hypertension and increasing the risk of variceal bleeding during pregnancy. It has been previously demonstrated that pregnancy is safe in women that have undergone endoscopic sclerotherapy or endoscopic ligation of oesophageal varices [26]. In the study mentioned above [25], there was no significant difference between those that had variceal ligation or endoscopic sclerotherapy in terms of pregnancy outcome and complications. There were no stillbirths or maternal mortality. The authors concluded that pregnant EHPVO patients should be managed in a tertiary care centre with a multidisciplinary approach. In the case reported here, we determined the cause of EHPVO and managed the patient according to the recommendations of Subbaiah *et al.* [25], in addition to treating the patient for APS-related obstetric complications.

Case 3

A 27-year-old G2P1 Hispanic woman with a history of SLE presented to the hospital at 25 weeks 6 days gestation with a 1 week history of worsening shortness of breath, productive cough, fatigue and rhinorrhoea. The patient was diagnosed with SLE at age 17 years when she presented with discoid lesions, arthritis, mononeuritis multiplex, RP in the setting of a positive ANA titre and dsDNA. At age 21 years she developed biopsy-proven class II and V LN and was treated with high-dose steroids, MMF and enalapril. Her serologies are notable for an ANA of 1:2560; positive Ro, RNP, Smith and dsDNA antibodies; hypocomplementaemia and negative aPL panel. Her past medical history is remarkable for primary biliary cirrhosis treated with ursodiol. Previous treatments include AZA (complicated by pancreatitis), MMF (discontinued due to insurance), CYC (complicated by severe cytopenia), rituximab (ineffective), tacrolimus (ineffective) and belimumab. Her prior obstetrical history is significant for one previous planned pregnancy in 2013. Six months prior to her first pregnancy the patient transitioned from MMF to ciclosporin. The pregnancy was complicated by anaemia, pleuritis, increased blood pressure, 8 g/day of proteinuria and worsening skin rashes. Treatment during pregnancy included prednisone of 30 mg/day and several IVIG infusions, in addition to the aforementioned medications. The patient was delivered by caesarean section at 36 weeks for breech position and premature rupture of the membranes. The post-partum period was complicated by hypertension.

Following the first pregnancy, the patient had the placement of an intrauterine device (IUD) and resumed MMF at 3 g/day. After missing one cycle of her menses, the patient was found to be pregnant by a urine pregnancy test. Vaginal US revealed that the IUD had been dispelled and the presence of an intrauterine gestational sac of 7 weeks 4 days. Active medications included ciclosporin 100 mg by mouth twice a day, HCQ 200 mg/day by mouth, calcium and vitamin D, ursodiol 300 mg by mouth three times a day, labetalol 400 mg by mouth twice a day, levothyroxine 150 μg/day by mouth, aspirin 81 mg/day by mouth and prednisone 20 mg/day by mouth. At the time of her pregnancy diagnosis her skin disease was active and her urine protein:creatinine ratio was 7.48 with a serum albumin of 2.0 g/l, C3 was 65 mg/dl and C4 was 15 mg/dl. She was counselled on both the high-risk nature of the pregnancy and the potential risks to the foetus associated with MMF exposure: the patient elected to continue the pregnancy. MMF was discontinued and ciclosporin was initiated and increased to a dose of 125 mg twice a day (selection of ciclosporin was based on its successful use during her first pregnancy). Her prednisone dose was increased to 20 mg/day and labetalol and furosemide were added.

At week 22 of gestation she presented as an outpatient with worsening shortness of breath and was diagnosed with fluid overload. Her furosemide dose was increased to 80 mg/day. Three weeks later at gestational age 25 weeks 6 days, she presented with a 1 week history of worsening shortness of breath, productive cough, fatigue and rhinorrhoea. Her creatinine was 0.88 mg/dl, 24 h urine protein was 1.6 g, C3 was 102 mg/dl and C4 was 18 mg/dl. Her urinalysis showed no casts, 0 RBCs/hpf and 5–10 WBCs/hpf. Her chest radiograph showed a left lower lobe consolidation consistent with pneumonia and the sputum culture grew methicillin-sensitive *Staphylococcus aureus*. The patient had been on prednisone of 10–20 mg for weeks and therefore infection was one of the greatest concerns. As therapy with vancomycin and ceftriaxone was initiated, prednisone was switched to methylprednisolone 16 mg/day i.v. to ensure appropriate systemic absorption and her ciclosporin was discontinued. Despite this therapy, she developed acute respiratory distress syndrome requiring intubation and subsequently became oliguric and required renal replacement therapy. Attempts at extubation were complicated by tachycardia and tachypnea. In an effort to improve her respiratory status, at 26 weeks 6 days the patient underwent an emergency caesarean section with delivery of a boy with Apgar scores of 2 and 4 and a weight of 670 g. Shortly after her caesarean section, her labs were notable for decreased complements (C3, 46 mg/dl; C4, 10 mg/dl), dsDNA of 22 IU/ml, 24 h urinary protein of 2.2 g, haemoglobin of 6.8 g/dl with 1+ schistocytes on a smear, platelets of 136×10^3/μl and urinalysis with granular casts. A renal biopsy was performed 3 days after delivery to elucidate the nature of her renal failure and demonstrated thrombotic microangiopathy (TMA), stable class V LN, with superimposed acute tubular necrosis. Workup of the TMA revealed negative aPL and negative ADAMTS13 and the presumptive diagnosis of atypical haemolytic uraemic syndrome (aHUS) was made. Therapy with plasmapheresis and eculizumab was initiated and with this

combination she was able to be extubated and weaned off of supplemental oxygen. Her renal function improved during the subsequent 2 weeks and she no longer required renal replacement therapy. She was pending discharge to a rehabilitation facility when she developed an irreversible coagulopathy of unknown aetiology and died. Autopsy was not performed as per family wishes.

Discussion

The differential diagnosis of acute renal failure in this pregnant SLE patient includes LN, pre-eclampsia, acute tubular necrosis, hypertensive emergency and thrombotic microangiopathies. While renal biopsy has an increased rate of complication during pregnancy, it is not contraindicated [27]. LN was a distinct possibility given her prior history of class V LN. Tedaschi *et al.* [28] showed that in SLE, a patient's flare during pregnancy is likely to follow the same organ pattern as disease activity within 6 months of pregnancy. However, this patient's low dsDNA level and normal complements at the start of her clinical presentation with minimally active urine sediment made LN flare less likely. Pre-eclampsia, manifesting with hypertension and proteinuria, is a complication reported in >20% of SLE pregnancies [29]. Patients with LN and/or APS are at an even higher risk of pre-eclampsia during pregnancy, and this patient was on low-dose aspirin as recommended by the EULAR [30] for prevention of pre-eclampsia or pre-term labour. The official recommendations support initiation of low-dose aspirin prior to conception or before 16 weeks gestation, and this patient was placed on it after learning of the pregnancy at 7 weeks gestation. While this patient certainly was at risk for pre-eclampsia, during much of her hospitalization she was hypotensive due to sepsis. This patient was a risk for thrombosis with her ongoing proteinuria but was not anticoagulated. Thus the renal biopsy was crucial in identifying and appropriately treating the active pathology in this patient. The predominant biopsy finding in this patient was TMA without glomerular endotheliosis.

TMA is a clinical syndrome associated with thrombocytopenia, microangiopathic haemolytic anaemia and renal failure with a characteristic appearance on biopsy specimen [31]. Our patient possessed all of these features. Thrombotic thrombocytopenia purpura, a more common cause of acquired primary TMA, was ruled out in this patient with a normal ADAMTS13 level. TMA can be seen in cases of pre-eclampsia, but it is more commonly associated with glomerular endotheliosis in which the glomeruli appear enlarged and hardened due to the inability of blood to pass through the narrowed capillaries [32]. The HUSs are a class of conditions also associated with TMA and should be considered in a case of TMA associated with hypocomplementaemia. These include typical HUS (Shiga toxin mediated), aHUS, secondary HUS and idiopathic HUS [33]. Causes of secondary HUS include pregnancy; haemolysis, elevated liver enzymes and low platelet count syndrome; drug associated; sepsis; disseminated intravascular coagulation; autoimmune disorders including SLE; APS; malignancy and streptococcal infections [34]. Her stable SLE clinical manifestations suggested that SLE was not the primary driver of her HUS. Her sepsis had responded to antibiotics, making this too an unlikely cause of secondary HUS, and the patient lacked aPL on several occasions, ruling out APS. The findings of TMA on renal biopsy in the setting of low complement levels with improved sepsis, no evidence of active SLE and negative ADAMTS13 were consistent with aHUS.

aHUS is a disorder in the complement alternative pathway system and is responsible for an estimated 10% of HUS in adults [35]. First-line treatment is plasmapheresis, but the evidence for the success of plasmapheresis in aHUS is not as robust as the evidence for treatment in thrombotic thrombocytopenic purpura [36]. Plasmapheresis was initiated in this patient, however, after 3 days she had not improved and discussions were initiated regarding anti-complement therapy with eculizumab. Eculizumab is a mAb to C5 and a terminal complement inhibitor, preventing formation of the membrane attack complex (C5b-C9) and thus halting the cytokine activation and pro-inflammatory effects of complement consumption [36]. This medication is an approved treatment for paroxysmal nocturnal haemoglobinuria and aHUS. While there are no randomized clinical trials to evaluate the use and safety of eculizumab in pregnancy, case reports for aHUS [37] and case series and a review of paroxysmal nocturnal haemoglobinuria [38–40] suggest no increased risk in complications with the medication during pregnancy. The decision to proceed with this treatment after the diagnosis was made following delivery was driven by her critical clinical status and absence of alternative therapies. With eculizumab therapy her haemolytic anaemia and renal insufficiency reversed, suggesting that complement activation was driving her renal disease.

Conclusion

The differential diagnosis for a patient with SLE and renal failure is broad, particularly in the setting of sepsis. Pregnancy, autoimmunity and infection can result in renal insufficiency, however, decreased complement levels and biopsy-proven TMA in the setting of stable SLE and treated infection should prompt the consideration of aHUS. There have been some successes in treating this entity with eculizumab, a C5a blocker. While this medication's safety during pregnancy is not established, in morbid situations such as the case described, it can be considered as an option.

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PAPER

The impact of different classes of lupus nephritis on maternal and fetal outcomes: a cohort study of 147 pregnancies

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Objective: To analyze the impact of different classes of lupus nephritis 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 at 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 patients of whom 66 had lupus nephritis were included. Demographic and clinical features, as well as maternal and fetal outcomes were observed for each nephritis histological class among systemic lupus erythematosus 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 < 0.05 was considered statistically significant. **Results:** Systemic lupus erythematosus patients with proliferative nephritis (classes III/IV, $n = 54$) presented more frequent disease flares ($p = 0.02$), continuous active disease during pregnancy and puerperium ($p = 0.006$), hospitalization due to systemic lupus erythematosus ($p < 0.001$), hospitalization not directly associated to systemic lupus erythematosus ($p = 0.04$), higher frequency of cesarean delivery ($p = 0.03$) and preeclampsia ($p = 0.01$) than patients without nephritis. Permanent damage measured by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index 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 systemic lupus erythematosus patients with or without nephritis. However, perinatal deaths were more frequent in patients with all classes of nephritis ($p = 0.003$). **Conclusion:** Systemic lupus erythematosus patients with proliferative nephritis (classes III/IV) have a higher frequency of adverse maternal outcomes. This is probably due to the major impact of proliferative forms of nephritis on women's global heath, which is corroborated by the higher Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index findings, although we cannot exclude the negative influence of disease activity for the maternal adverse events. The findings indicate a need for further lupus nephritis classification beyond the nonspecific term nephritis in the context of lupus pregnancy as the impact on maternal and fetal outcomes varies according to histological class. *Lupus* (2019) **0**, 1–9.

Key words: 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) occurs 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

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fetal morbidity is also found in association with LN, regardless of the presence of antiphospholipid antibodies.[5,6]

However, LN 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 for 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), whereas 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, to allow a more accurate interpretation of the actual influence of LN on gestational outcomes, it is necessary to include data on 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 LN 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: 10 did not meet four American College of Rheumatology (ACR) SLE classification criteria;[11] eight delivered before 22 weeks (miscarriages); three had fetal aneuploidy; one had fetal malformations due to the mother's use of mycophenolate at conception; two 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 appropriate 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 six cases were mesangial (class II), 54 cases were proliferative (classes III or IV) and six cases were membranous (class V). In total, 53 patients (80.3%) with LN who have been submitted to renal biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (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 (three with mesangial and 10 with proliferative LN). The local Institutional Ethics Committee 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 Systemic Lupus International Collaborating Clinics/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 (PE), cesarean delivery for maternal or fetal compromise, peripartum hemorrhage, and adverse fetal outcomes such as prematurity, small for gestational age newborns, admission to a neonatal intensive care unit and perinatal death.

Disease activity was defined by a rheumatologist experienced in evaluating pregnant SLE patients at

each visit and 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/24 h) when it was previously under 500 mg/24 h or >2,000 mg/24 h when it was previously over 500 mg/24 h or presence of active urinary sediment (>5 red blood cells or leukocytes per large magnification field 400× 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 a proteinuria/creatinine ratio or measured in 24 hours. PE was defined as the occurrence of hypertension and proteinuria above 300 mg/24 h 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 PE 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 <0.05 was considered statistically significant.

Results

A total of 147 pregnancies of 137 patients with SLE were analyzed. The majority were of African descent (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 (APS) was present in 18 (12.2%) among 147 SLE patients, two (33.3%) in mesangial LN patients, seven (13%) in proliferative LN patients and in nine (11.1%) patients without nephritis. Systemic arterial hypertension was found in 28 (19.1%) SLE patients, in one (16.7%) with mesangial LN patients, in 22 (40.7%) with proliferative LN patients and in five (6.2%) patients without nephritis. Table 1 shows the demographic and clinical data.

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 frequent 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 in 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, seven (16%) were treated with prednisone alone and one (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 per 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 PE (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).

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

Table 1 Main clinical and demographic features of the studies

Variable	*All SLE pregnancies* n = 147	*Class II*[a] n = 6	*Classes III/IV*[b] n = 54	*Class V*[c] n = 6	*Without LN* n = 81
Maternal age (years)[d]					
Mean ± SD	28.4 ± 6.1	29.0 ± 6.1	27.3 ± 6.8	27.4 ± 6.2	28.9 ± 6.1
Ethnicity					
African descent	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 ≥ 1	38 (25.9%)	0	22 (40.7%)	1 (16.7%)	15 (18.5%)
Non-renal SDI ≥ 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.
a-SLE: systemic lupus erythematosus; βLN: lupus nephritis; SD: standard deviation; Ω-SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
[a]Class II – mesangial.
[b]Class III – focal proliferative; class IV – diffuse proliferative.
[c]Class V – membranous.
[d]Age at delivery compared with Student's *t* test.

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

Variable	*Without nephritis* n = 81	*Nephritis all classes* n = 66	p value	*Classes II*[a] *and V*[b] n = 12	p value	*Classes III and IV*[c] n = 54	p value
SLE flare in pregnancy or puerperium[e]	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[f]	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
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.
[a]Class II – mesangial.
[b]Class V – membranous.
[c]Class III – focal proliferative.
[d]Class IV – diffuse proliferative.
[e]SLE flares with inactive disease at conception.
[f]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.
SLE: Systemic lupus erythematosus; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

associated to SLE (68% versus 41%) and infections during pregnancy (56% versus 47%) among the patients with proliferative LN, but the differences did not achieve statistical significance.

The analysis of main maternal adverse outcomes (systemic disease activity, hypertension, hospitalizations, PE and hemorrhage) in patients with mesangial and membranous LN 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 the small number of cases (six each) in the present cohort and similarity of clinical behavior during pregnancy.

To analyze if LN class inference could have influenced the results, we proceeded to 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 frequent 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 PE 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 in Table 3.

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 outcomes (Table 4).

Discussion

SLE patients with proliferative nephritis presented more frequent adverse maternal and fetal outcomes, including disease activity during pregnancy and puerperium, need for hospitalization, PE and adverse fetal outcomes including unsuccessful pregnancies in comparison to SLE pregnant patients without nephritis. In contrast, the frequencies of maternal and fetal adverse outcomes in patients with mesangial and membranous nephritis were not different in comparison to those found among

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

Variable	*Classes II[a] and V[b]* n = 12	*Classes III[c] and IV[d]* n = 54	p value
SLE 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%)	0.02
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 (31.5%)	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
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 χ^2 Chi-square test.
[a]Class II – mesangial.
[b]Class V – membranous.
[c]Class III – focal proliferative.
[d]Class IV – diffuse proliferative.
SLE: systemic lupus erythematosus.

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

Variable	*SDI = 0* n = 109	*SDI ≥ 1* n = 38	p *value*	*Non-renal SDI ≥ 1* n = 15	p *value*
SLE 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
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 cChi- square test.
SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE: systemic lupus erythematosus.

patients without nephritis, except for fetal deaths, which may have been due to APS present in two of the three patients of this latter group.

These data shed light on the need for more detailed LN classification when dealing 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, and 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 as having a higher frequency of activity at conception than those without LN.[17] In fact, a quarter of all SLE patients in this cohort had active disease at conception, which demonstrates the low adherence to pregnancy planning including the use of appropriate contraception methods in the scenario of LN treatment.

Despite the similar frequency of disease activity at conception, patients with proliferative classes presented more frequent 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 in employing 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 investigated as most studies have included a 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 those 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 a larger number of patients with LN classes II and V are needed to adequately clarify this issue.

The incidence of 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 PE 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 having 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 be sure 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 frequent proteinuria for 6 months and the analysis of non-renal SDI was not associated with any adverse outcome. In contrast, its use as a variable of analysis may help to identify those patients with a higher risk of 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 class 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 60% of cases with classes III/IV (26/43). It is possible that the absence of any difference among histological classes and maternal outcomes could be due to the small sample of LN included, lower frequency of active disease at conception and due to the lower severity of the SLE patients studied.

Although some previous studies intended to evaluate gestational results according to the histologic subclass of nephritis and suggested a more unfavorable outcome in patients with proliferative forms of nephritis, the overall number of patients enrolled in such analysis, including the present study, is relatively small.[8]

This study has limitations. This is a real-world cohort of pregnant SLE patients with multiethnic origins 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 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 PE,[16] but all currently 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 diagnoses 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 higher permanent damage measured by SDI; however, as these patients also presented higher frequency of disease flares during pregnancy, we cannot exclude the negative influence of disease activity for maternal adverse events. The adequate attribution of risk for different classes of LN may contribute to more specific approaches depending on the histological classification, including appropriate information on risk factors of adverse outcomes to the patients.

Contribution to authorship

BCR and MIL contributed equally to the article.

BCR: data acquisition, study design, writing, literature review and statistical analysis.

MIL: data acquisition, study design, writing, literature review and statistical analysis.

GRJ: data acquisition, study design, writing, literature review.

FCS: data acquisition, writing and literature review.

NRJ: study design, writing and literature review.

RAL: study design, writing and literature review.

EMK: study design, writing, literature review and statistical analysis.

Ethics approval

This study approved by the ethics committee in research of University Hospital Pedro Ernesto, State University of Rio de Janeiro on 22 September 2015, number 1.319.997-50726115.4.0000.5259.

Disclaimer

The authors state that the views expressed in this article are the authors' own and not an official position of the State University of Rio de Janeiro.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Roger Abramino Levy is a licensed professor of rheumatology at the State University of Rio de Janeiro and is currently working as a global medical expert for GSK in Upper Providence, PA, USA. The other authors declare that there are no conflicts of interest.

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BRIEF REPORT

Soluble Flt-1, Placental Growth Factor, and Vascular Endothelial Growth Factor Serum Levels to Differentiate Between Active Lupus Nephritis During Pregnancy and Preeclampsia

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Objective. To evaluate mean serum levels of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and soluble Flt-1 (sFlt-1) in pregnant patients with systemic lupus erythematosus (SLE) with inactive disease, active lupus nephritis, and preeclampsia for differential diagnosis between these conditions.

Methods. Pregnant women with SLE, with singleton pregnancies and no other autoimmune diseases, were classified according to disease activity (inactive SLE and active lupus nephritis) and the presence of preeclampsia. Serum samples were collected within 3 weeks of delivery and frozen for subsequent blinded analysis through the enzyme-linked immunosorbent assay method.

Results. A total of 71 women were included, with 41 classified as having inactive SLE (group 1; Systemic Lupus Erythematosus Pregnancy Disease Activity Index [SLEPDAI] score <4), 15 with a diagnosis of active lupus nephritis (group 2, SLEPDAI score ≥4, including renal criteria), and 15 with a diagnosis of preeclampsia (group 3). Patients in group 3 had higher mean levels of sFlt-1 and lower mean levels of PlGF compared to groups 1 and 2, both findings with statistical significance. The sFlt-1:PlGF ratio was also significantly higher in patients with preeclampsia, while mean VEGF levels were higher in pregnant woman with active lupus nephritis compared to patients with preeclampsia or inactive SLE.

Conclusion. Evaluation of serum VEGF, PlGF, and sFlt-1 levels can differentiate between preeclampsia, inactive SLE, and active lupus nephritis during pregnancy.

INTRODUCTION

Pregnancy in patients with systemic lupus erythematosus (SLE) is associated with significant morbidity and mortality compared to the general population, including an 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 troublesome in clinical practice, because both conditions can present with hypertension, edema, proteinuria, low platelet count, and worsening of renal function. The classical biomarkers, such as anti–double-stranded DNA (anti-dsDNA) and complement plasma levels, are not always able to differentiate the 2 conditions, which require different treatment approaches (3).

Evaluation of serum angiogenic factors, like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and antiangiogenic factors, such as soluble Flt-1 (sFlt-1), has been proposed to help the differentiation between these 2 conditions (4,5). VEGF and PlGF are necessary for physiologic development of pregnancy, because they promote angiogenesis and induce the vasodilatory prostacyclins and nitric oxide in endothelial cells, resulting in reduced vascular tone and blood pressure. They have also been related to glomerular healing and accelerated renal recovery in animal models (6).

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SIGNIFICANCE & INNOVATIONS

- Pregnant patients with lupus and preeclampsia have increased serum levels of soluble Flt-1 and lower levels of placental growth factor when compared to inactive systemic lupus erythematosus (SLE) and active lupus nephritis.
- Levels of vascular endothelial growth factor were higher in patients with active lupus nephritis compared to inactive SLE and preeclampsia.
- Evaluation of angiogenic and antiangiogenic factors can be a new tool to differentiate preeclampsia from lupus nephritis during pregnancy in clinical practice.

On the other hand, sFlt-1 is a splice variant of VEGF endothelial receptor Flt-1, but it lacks transmembrane and cytoplasmatic domains. It works as a strong antagonist of VEGF- and PlGF- and induces hypertension, endothelial dysfunction, and nephrotic proteinuria when administered to animal models (6). In humans, previous publications have demonstrated an angiogenic imbalance (increased serum sFlt-1 with low PlGF and VEGF) in patients who develop preeclampsia (7), including patients with lupus (8,9).

Although promising for the differential diagnosis with preeclampsia, few data are available regarding the behavior of these cytokines among pregnant patients with SLE who present quiescent or active LN, and most data come from case reports (4). The objective of this study was to evaluate serum levels of VEGF, PlGF, and sFlt-1 in pregnant women with SLE with inactive disease, active LN, and preeclampsia.

PATIENTS AND METHODS

This was a cross-sectional study of patients with SLE, diagnosed according to American College of Rheumatology (ACR) criteria (10), 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 experienced in evaluating pregnant patients with SLE. Women with other autoimmune diseases, including antiphospholipid syndrome, and with end-stage renal disease, were excluded because these conditions could influence the results of the tests.

Disease activity was established according to the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) (11), and the occurrence of preeclampsia followed the American College of Obstetricians and Gynecologists proposed criteria (12). Clinical data were obtained by physical examination and medical chart reviews, with an initial classification of activity or preeclampsia performed at the time of blood collection by both rheumatologist and obstetrician in all cases. After delivery, all initial diagnostic results were retrospectively reviewed to ensure that there was no misdiagnosis at first impression. Information about SLE characteristics (clinical and laboratory manifestations before pregnancy, medications, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SDI]) and outcomes of current pregnancy (gestational age at delivery, birth weight, Apgar score) were also recorded.

Blood samples were collected through venous puncture, within 3 weeks of delivery, during regular prenatal visits for patients with inactive SLE, or if disease activity or preeclampsia was suspected during the third trimester. Serum sample aliquots were frozen at −80°C for subsequent blinded analysis by enzyme-linked immunosorbent assay kits (PlGF: DRG Instruments; sFlt-1 and VEGF: R&D Systems) according to manufacturers' recommendations. All samples were run in duplicate in 2 batches in the same laboratory, and average rates were reported. Manufacturers' controls were used, and the assay was repeated if there was a variation >10% between duplicates.

The results were compared between groups, using Pearson's chi-square test, the Mann-Whitney U test, and analysis of variance as appropriate. A receiver operating characteristic curve was created for the sFlt-1:PlGF ratio and VEGF to determine cutoff values and analyze the accuracy of the tests. This study was approved by the Universidade do Estado do Rio de Janeiro Institutional Review Board.

RESULTS

A total of 74 women were prospectively added according to the inclusion criteria. One patient with a diagnosis of secondary antiphospholipid syndrome and 2 patients who presented with nonrenal SLE activity were excluded from this analysis. For the purpose of this study, only patients with active renal manifestations were included in the active SLE group.

A total of 41 patients had inactive or mildly active SLE (group 1: SLEPDAI score <4), 15 had active LN (group 2: SLEPDAI score ≥4, including renal criteria), and 15 had preeclampsia (group 3) at the time of blood collection. Among patients of group 1, 36.5% had a history of LN but had no clinical or laboratory manifestations of active renal disease. Patients with active LN and preeclampsia had higher proteinuria and serum creatinine levels compared to patients with inactive SLE, although there were no cases of severe renal disfunction (all patients had creatinine <1.2 mg/dl). Patients with active LN more frequently had positive anti-dsDNA than the other 2 groups (11 of 15 versus 10 of 56; $P < 0.001$), but there was no significant difference in the number of patients with hypocomplementemia (6 of 15 versus 13 of 56; $P = 0.19$).

Two patients who had been initially classified as having active LN were reclassified as having preeclampsia due to subtle normalization of hypertension and proteinuria a few days after delivery without considerable change of medications. Demographics and clinical characteristics of included patients are described in Table 1.

Table 1. Demographic and clinical characteristics and gestational results of patients with inactive SLE, active LN, and SLE with preeclampsia*

	Inactive SLE (n = 41)	Active LN (n = 15)	SLE with preeclampsia (n = 15)	P†
Age at inclusion, years	27.2 ± 6	29.4 ± 4.4	30.1 ± 5.8	0.17
Gestational age at blood collection, weeks	36.8 ± 1.7	33.7 ± 4.2	34.5 ± 2.5	<0.001‡
Gestational age at delivery, weeks	38.7 ± 1.9	35.7 ± 3.8	35.8 ± 2.5	<0.001‡
SDI	0.3 ± 0.6	0.3 ± 0.5	0.1 ± 0.4	0.45
History of LN, no. (%)	15 (35.7)	15 (100)	8 (53.3)	NA
Birth weight	2,976.8 ± 532.4	2,448.4 ± 759.2	2,174.3 ± 834.6	<0.001‡
Serum creatinine at inclusion, mg/dl	0.57 ± 0.14	0.76 ± 0.22	0.67 ± 0.21	<0.001‡
Proteinuria at inclusion, grams/24 hours	0.2 ± 0.1	2.2 ± 1.5	1.7 ± 1.9	<0.001‡
5th-minute Apgar score	9.0 ± 0.6	8.7 ± 2.5	8.7 ± 0.6	0.60
Small for gestational age newborn, no. (%)§	5 (12.1)	4 (26.6)	9 (60)	NA

* Values are the mean ± SD unless indicated otherwise. LN = lupus nephritis; NA = not applicable; SLE = systemic lupus erythematosus; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
† *P* values by analysis of variance.
‡ Statistically significant.
§ Defined as birth weight below 10th percentile.

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. The mean gestational age of blood collection and delivery was significantly higher in patients with inactive SLE ($P < 0.001$ for both). The mean SDI score was similar in all groups, as were 5th-minute Apgar scores. The mean birth weight was considerably lower in patients with active LN 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 2 patients in the study were not using hydroxychloroquine and >80% were using low-dose aspirin.

Mean levels of VEGF, PlGF, and sFlt-1 of each group are reported on Table 3 and Supplementary Figures 1–4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24380/abstract. Patients with SLE and preeclampsia had significantly lower mean serum levels of PlGF, while sFlt-1 was significantly higher in patients with preeclampsia compared to pregnant patients with inactive SLE or active LN. 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 LN 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 preeclampsia with a sFlt-1:PlGF ratio of 44 was 56.5% (13 of 23), with a negative predictive value (NPV) of 95.8% (46 of 48). The sensitivity was 86.6% (13 of 15) and specificity was 80.3% (45 of 56). For a VEGF cutoff of 10.4 pg/ml, the sensitivity for active LN was 53.3% (8 of 15) and specificity of 87.5% (49 of 56), with a PPV of 53.3% (8 of 15) and an NPV of 87.5% (49 of 56).

DISCUSSION

The differential diagnosis between active LN and preeclampsia in patients with SLE is crucial for better outcomes, because the first condition is treated with immunosuppressive therapy and the latter has considerable improvement of manifestations after delivery (2). This study provides new insights for this conundrum, because serum levels of sFlt-1 and the sFlt-1:PlGF ratio were higher in patients with preeclampsia, while PlGF levels were significantly lower compared to pregnant patients with SLE without this obstetric morbidity.

Table 2. Medications used by included patients with inactive SLE, active LN, and SLE with preeclampsia*

	Inactive SLE (n = 41)	Active LN (n = 15)	SLE with preeclampsia (n = 15)	P†
Prednisone	24 (57.1); 9.4 ± 6.9	14 (93.3); 27.9 ± 23.7	8 (53.3); 10.3 ± 6.6	<0.0001†
Hydroxychloroquine	40 (95.2); 385.0 ± 53.3	15 (100); 400.0 ± 0	15 (100); 386.7 ± 51.6	0.56
Azathioprine	18 (42.8); 111.1 ± 36.6	13 (86.6); 130.8 ± 38.4	6 (40.0); 100.0 ± 31.6	0.06
Antihypertensive, no. (%)	1 (2.3)	4 (26.6)	4 (26.6)	NA
Low-dose aspirin, no. (%)	34 (80.9)	14 (93.3)	12 (80)	NA

* Values are the number (%); mean ± SD unless indicated otherwise. LN = lupus nephritis; SLE = systemic lupus erythematosus; NA = not applicable.
† *P* values by analysis of variance.
‡ Statistically significant.

Table 3. Mean values of VEGF, PlGF, sFlt-1, and sFlt-1:PlGF ratio for patients with inactive SLE, active LN, and SLE with preeclampsia*

	Inactive SLE (n = 41)	Active LN (n = 15)	SLE with preeclampsia (n = 15)	P†		
				Inactive SLE × LN	Inactive SLE × PE	LN × PE
VEGF, pg/ml	5.6 ± 7	12.3 ± 10.1	4.1 ± 5	0.006‡	0.45	0.009‡
PlGF, pg/ml	189.8 ± 146.1	198.7 ± 134.8	61.4 ± 127.3	0.83	0.003‡	0.007‡
sFlt-1, pg/ml	1,804.2 ± 668.3	1,832.1 ± 760.9	2,517.0 ± 431.9	0.90	<0.001‡	0.006‡
sFlt-1:PlGF ratio	22.9 ± 25.1	23.3 ± 35.5	781.1 ± 1,211.3	0.96	0.02‡	0.02‡

* Values are the mean ± SD unless indicated otherwise. LN = lupus nephritis; PE = preeclampsia; PlGF = placental growth factor; sFlt-1 = soluble Flt-1; SLE = systemic lupus erythematosus; VEGF = vascular endothelial growth factor.
† *P* values by Mann-Whitney U test.
‡ Statistically significant.

Levine et al described a case–control study of healthy nulliparous women, with increased serum levels of sFlt-1 in patients with preeclampsia compared to controls, while PlGF and VEGF were significantly lower. The authors suggest that the physiologic proangiogenic state of the 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 the normal process of placental growth and function (7).

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 as healthy women and also the possibility to predict patients who will develop this obstetric condition (8,9). Nonetheless, the researchers did not evaluate the levels of those factors in patients with active renal SLE, precluding the use for differential diagnosis between LN and preeclampsia and did not include VEGF in their analysis.

Angiogenic factor imbalance can also be used as predictor of adverse obstetric outcomes, such as preeclampsia, fetal/neonatal death, fetal growth restriction, and indicated preterm delivery. In the Predictors of Pregnancy Outcome: Biomarkers in APL Syndrome and SLE study, sFlt-1 and PlGF levels between 12 and 16 weeks were significantly altered in patients with SLE with severe adverse obstetric outcomes (13). Another publication identified a higher sFlt 1:PlGF ratio between 24 and 29 weeks in women with SLE who developed adverse obstetric outcomes compared to uncomplicated pregnancies and 5 patients with SLE flare, none with renal activity (14).

We have previously reported that, although nonpregnant patients with a history of LN had increased sFlt-1 levels compared to controls, PlGF was also higher in these patients, which is a different pattern compared to preeclampsia (15). The current study confirms the potential use of these angiogenic and antiangiogenic factors for a differential diagnosis of preeclampsia and LN, also demonstrating that serum VEGF is higher in patients with active LN compared to those with inactive lupus and preeclampsia. This result is in consonance with previous publications that demonstrated increased serum VEGF in nonpregnant patients with SLE with active disease compared to SLE controls (16). Some authors have suggested that a low sFlt-1:PlGF ratio may rule out preeclampsia for a few weeks in patients without SLE, based on the very high reported NPV of this ratio (17), a result that was also found in this study.

Considering the fact that that hydroxychloroquine treatment for pregnant patients with SLE may reduce the incidence of preeclampsia (18), in vitro studies have investigated the effect of this medication on human placental explants from term gestations exposed to hypoxic injury. A protective effect on endothelial function has been described, but there was no influence on sFlt-1 and soluble endoglin release (19). In a similar study, azathioprine significantly increased sFlt-1 and PlGF expressions on term placenta explants after 24 hours of incubation when compared to controls (20). However, there are no studies evaluating whether these drugs affect angiogenic and antiangiogenic levels in pregnant women.

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

Two patients had an initial diagnosis of LN at inclusion, but maintenance of abnormalities despite early immunosuppressive treatment, in addition to rapid reversal of hypertension and proteinuria after delivery, switched this diagnosis to preeclampsia. Retrospective blinded analysis of studied factors also indicated a 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 an initial diagnosis of preeclampsia who did not reverse proteinuria and hypertension for >30 days after delivery, receiving a final diagnosis of new onset of LN during pregnancy (4). Evaluation of blood samples retrieved before delivery demonstrated normal serum levels of sFlt-1 and a sFlt-1:PlGF ratio, so the authors suggest that if these results had

been 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, but the exclusion of patients with SLE activity without LN and women with other autoimmune diseases, especially antiphospholipid syndrome, makes the results more reliable for the intended differential diagnosis. Either way, this is the largest study evaluating these factors for this purpose, led by obstetricians and rheumatologists with considerable experience in prenatal care of lupus patients.

In conclusion, this study demonstrated that pregnant patients with SLE who developed preeclampsia had similar angiogenic and antiangiogenic profile of patients with preeclampsia without SLE, low serum PlGF, and high serum sFlt-1, with a high sFlt-1:PlGF ratio. This pattern differs from patients with inactive SLE or active LN, the latter condition being the main differential diagnosis during gestation of SLE patients. In addition, there is an increase in serum VEGF in patients with active LN, which is not expected in preeclampsia. Evaluation of angiogenic and antiangiogenic factors can be a new tool to differentiate preeclampsia from LN during pregnancy in clinical practice.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. G. R. de Jesús had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. G. R. de Jesús, N. R. de Jesús, Levy, Klumb.

Acquisition of data. G. R. de Jesús, Lacerda, Rodrigues, dos Santos, do Nascimento, Porto, N. R. de Jesús, Levy.

Analysis and interpretation of data. G. R. de Jesús, Lacerda, N. R. de Jesús, Levy, Klumb.

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ANEXO G – Outros Artigos com Temas Afins Submetidos Aguardando Resposta dos Revisores

1. *"Premature Rupture of Membranes- A Cause of Fetal Complications Among Lupus: A Cohort Study, Systematic Review and Meta-Analysis"*

LUPUS

Lupus
An international Journal

PREMATURE RUPTURE OF MEMBRANES – A CAUSE OF FETAL COMPLICATIONS AMONG LUPUS: A COHORT STUDY, SYSTEMATIC REVIEW AND META-ANALYSIS

Journal:	*Lupus*
Manuscript ID	LUP-21-119
Manuscript Type:	Paper
Date Submitted by the Author:	25-Feb-2021
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Keyword:	Pregnancy, Systemic Lupus Erythematosus, Nephritis
Abstract:	Objective: The aims of the present study were to analyze premature rupture of ovular membranes occurrence among 190 women with SLE followed at Hospital Universitário Pedro Ernesto, from 2011 to 2018 and review the literature of PROM in SLE pregnancy Methods: A cohort study of SLE patients was carried out with analysis of the following variables: sociodemographic characteristics, clinical manifestations of lupus, modified disease activity index for pregnancy (SLEPDAI), used drugs during pregnancy, intercurrent maternal infections, and obstetric outcome. Additionally, analyzes of seven electronic databases (Pubmed, Embase, Cochrane, Scielo, Scielo Brazil, Virtual Health Library Regional Portal and Google Scholar) were systematically searched. The search was updated on February 3rd, 2020. Results: Infection (Relative risk (RR) - 3.26 IC 95% 1.5-6.7, p=0.001), serositis history (RR- 2.59 IC 95% 1.31-5.11, p=0.006) and anti-RNP (RR- 3.08 IC 95% 1.39-6.78, p=0.005) were associated risk factors for PROM and anti-RNP (RR- 3.37 IC 95% 1.35-8.40, p=0.009) for PPROM. The prevalence of PROM and PPROM were respectively 28.7% and 12.9%. Among all studies, the prevalence of PROM ranged from 2.7 to 35% (I2= 87.62%) and of PPROM from 2.8 to 20% (I2=79.56%). Conclusions: PROM, both at term and preterm, occurred more frequently than reported in women with lupus. Immunosuppression during

	pregnancy may increase susceptibility to PROM. The systematic review didn't find any study with the main objective of evaluate PROM / PPROM in women with lupus.

2. "Risk Factors Associated with Infections in Pregnant Women with Systemic Lupus Erythematosus"

LUPUS

Lupus
An international Journal

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

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Keyword:	Systemic Lupus Erythematosus, Infection, Immunosuppressants, Pregnancy, Risk factors
Abstract:	Objective: To analyze the occurrence and risk factors associated with infections during pregnancy in patients with systemic lupus erythematosus (SLE). Methods: Retrospective cohort study using the data of pregnant women followed up between 2011 and 2018 at a university hospital. Results: The data of 221 pregnant in women with SLE were analyzed. The incidence of infections was 22.6% (50/221), with the urinary tract being the most frequent site of infection (32/221, 14.5%) followed by the respiratory tract (15/221, 6.8%). The bivariate analysis showed that active disease, hematologic SLE, reduced complement and use of prednisone □ ▯ mg and □ ▱▱mg increased the risk of infection during early pregnancy (p=0.05, p=0.04, p=0.003, p=0.008, and p=0.02), while disease activity and anti-DNA positivity increased it at the end of pregnancy (p=0.03 and p=0.04). Prednisone at a dose □ 5 mg increased the risk of infection in the beginning (p=0.01) and at the end of pregnancy (p=0.008). Multivariate analysis showed that increasing the dose of prednisone from 5 mg to 10 mg tripled the risk of developing infections in pregnant women with lupus (p=0.02), while pregnancy-adapted SLE Disease Activity Index values showed no association with the risk of infections.

Conclusion: The study showed an increased risk of infections in pregnant women with SLE. The risk was associated with an increase in the dose of prednisone and not associated with disease activity.
Keywords: Systemic Lupus Erythematosus; infection; immunosuppressants; pregnancy; risk factors.