

# A Critical Review on Obstetric Follow-up of Women Affected by Systemic Lupus Erythematosus

## *Uma Revisão Crítica Sobre o Acompanhamento Obstétrico de Mulheres com Lúpus Eritematoso Sistêmico*

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### Abstract

**Objective** To review the existing recommendations on the prenatal care of women with systemic lupus erythematosus (SLE), based on currently available scientific evidence.

**Methods** An integrative review was performed by two independent researchers, based on the literature available in the MEDLINE (via PubMed), EMBASE and The Cochrane Library databases, using the medical subject headings (MeSH) terms “systemic lupus erythematosus” AND “high-risk pregnancy” OR “prenatal care.” Studies published in English between 2007 and 2017 were included; experimental studies and case reports were excluded. In cases of disagreement regarding the inclusion of studies, a third senior researcher was consulted. Forty titles were initially identified; four duplicates were excluded. After reading the abstracts, 7 were further excluded and 29 were selected for a full-text evaluation.

**Results** Systemic lupus erythematosus flares, preeclampsia, gestation loss, preterm birth, fetal growth restriction and neonatal lupus syndromes (mainly congenital heart-block) were the major complications described. The multidisciplinary team should adopt a specific monitoring, with particular therapeutic protocols. There are safe and effective drug options that should be prescribed for a good control of SLE activity.

**Conclusion** Pregnant women with SLE present an increased risk for maternal complications, pregnancy loss and other adverse outcomes. The disease activity may worsen and, thereby, increase the risk of other maternal-fetal complications. Thus, maintaining an adequate control of disease activity and treating flares quickly should be a central goal during prenatal care.

### Keywords

- systemic lupus erythematosus
- pregnancy
- prenatal care
- maternal outcomes
- fetal outcomes

### Resumo

**Objetivo** Revisar as recomendações existentes sobre o cuidado pré-natal às mulheres com lúpus eritematoso sistêmico (LES), com base em evidências científicas atualmente disponíveis.

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**Palavras-chave**

- lúpus eritematoso sistêmico
- gravidez
- cuidado pré-natal
- resultados maternos
- resultados fetais

**Métodos** Revisão integrativa realizada por dois pesquisadores independentes, com base na literatura disponível nos bancos de dados MEDLINE (via PubMed), EMBASE e The Cochrane Library, usando os cabeçalhos de assuntos médicos, ou termos MeSH, “systemic lupus erythematosus” E “high-risk pregnancy” OU “prenatal care.” Estudos publicados em inglês entre 2007 e 2017 foram incluídos; estudos experimentais e relatos de caso foram excluídos. Em caso de desacordo, um terceiro pesquisador sênior foi consultado. Quarenta títulos foram inicialmente identificados; quatro duplicatas foram excluídas. Após leitura dos resumos, mais 7 artigos foram excluídos e 29 foram selecionados para uma avaliação de texto completo.

**Resultados** Surtos de LES, pré-eclâmpsia, perda de gestação, parto prematuro, restrição de crescimento fetal e síndromes de lúpus neonatal foram as principais complicações descritas. A equipe multidisciplinar deve adotar um monitoramento específico, com protocolos terapêuticos apropriados. Há drogas seguras e eficazes que devem ser prescritas para um bom controle do LES.

**Conclusão** Gestantes com LES apresentam risco aumentado de complicações maternas, perda de gravidez e outros desfechos adversos. A atividade da doença pode piorar e, assim, aumentar o risco de outras complicações. Assim, manter um controle adequado da atividade da doença e tratar rapidamente os surtos deve ser um objetivo central durante o pré-natal.

## Introduction

### General Aspects

Systemic lupus erythematosus (SLE) is an autoimmune and multisystemic disorder of the connective tissue that mainly affects women of childbearing age (about nine women for each man). Immune anomalies, particularly the production of a series of antinuclear antibodies, are another prominent feature of the disease.<sup>1</sup>

The SLE prevalence varies from 40 to 200 cases per 100,000 inhabitants, more common among Africans and Asians descendants. In Brazil, its prevalence is around 8.7 per 100,000 inhabitants.<sup>1,2</sup>

The broad spectrum of clinical presentations includes mucous-cutaneous, muscle-skeletal, hematological, cardiopulmonary, renal and central nervous system manifestations. The most severe forms of organ involvement are lupus nephritis and neuropsychiatric lupus, and these conditions may result in a significant reduction in life expectancy.<sup>1</sup> Lupus nephritis is one of the leading causes of death along with infections.<sup>3</sup>

The most common general symptoms are weight loss, anemia, arthralgia and/or arthritis, being the involvement of the osteoarticular system the most frequent clinical manifestation.<sup>1</sup> Antiphospholipid syndrome can occur in association with SLE, and it is characterized by arterial and venous thromboses, as well as recurrent morbidity in pregnancy.<sup>4</sup>

The American College of Rheumatology (ACR) proposed the criteria for the diagnosis of SLE (– **Table 1**).<sup>5</sup> To be classified as SLE, at least four criteria should occur in series or simultaneously.<sup>1,4,6</sup>

A consensus group of experts on SLE, the Systemic Lupus International Collaborating Clinics (SLICC), has proposed revised criteria for the diagnosis of SLE (– **Table 2**). It requires either that a patient satisfies at least 4 out of 17 criteria,

including at least one of the 11 clinical criteria and one of the 6 immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE and positivity to antinuclear antibodies (ANA) or anti-double-stranded DNA (dsDNA) antibodies.<sup>7</sup>

### Systemic Lupus Erythematosus and Pregnancy

Considering the predilection of SLE in affecting women of childbearing age, pregnancy is of particular importance, with

**Table 1** American College of Rheumatology (ACR) criteria for the classification of systemic lupus erythematosus

1.	Erythema malar.
2.	Discoid lupus.
3.	Photosensitivity.
4.	Oral ulcers.
5.	Arthritis.
6.	Serositis (pleuritis or pericarditis).
7.	Nephropathy (persistent proteinuria greater than 0.5 g/day and/or glomerular hematuria).
8.	Neurological disorders (convulsion or psychosis).
9.	Hematologic disorders (hemolytic anemia, leucopenia, thrombocytopenia).
10.	Immune disorder (presence of LE cells, anti-DNA or anti-Sm antibodies, false positive VDRL test, anticardiolipin IgG or IgM antibodies, lupus anticoagulant).
11.	Antinuclear antibody (ANA).

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; LE, lupus erythematosus; Sm, smith; VDRL, venereal disease research laboratory.

**Table 2** Systemic lupus international collaborating clinics (SLICC) criteria for the classification of systemic lupus erythematosus (4 of 17 criteria, including at least one clinical criterion and one immunologic criterion; OR biopsy-proven lupus nephritis)<sup>7</sup>

Criterion	Clinical criteria
Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); <b>OR</b> subacute cutaneous lupus (nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; <b>OR</b> discoid lupus/lichen planus overlap
Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral or nasal ulcers	Palate, buccal, tongue, <b>OR</b> nasal ulcers (in the absence of other causes, such as vasculitis, Behçet disease, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Joint disease	Synovitis involving two or more joints, characterized by swelling or effusion <b>OR</b> tenderness in two or more joints and at least 30 minutes of morning stiffness
Serositis	Typical pleurisy for more than one day, pleural effusions, or pleural rub, <b>OR</b> typical pericardial pain (pain with recumbency improved by sitting forward) for more than one day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler's syndrome
Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, <b>OR</b> red blood cell casts
Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); <b>OR</b> acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hemolytic anemia	Hemolytic anemia
Leukopenia or lymphopenia	Leukopenia ( $< 4,000/\text{mm}^3$ at least once) (in the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension), <b>OR</b> lymphopenia ( $< 1,000/\text{mm}^3$ at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
Thrombocytopenia	Thrombocytopenia ( $< 100,000/\text{mm}^3$ ) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
<b>Immunologic criteria</b>	
ANA	ANA level above laboratory reference range
Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or $> 2$ -fold the reference range if tested by ELISA)
Anti-Sm	Presence of antibody to Sm nuclear antigen
Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti- $\beta$ 2-glycoprotein I (IgA, IgG, or IgM)
Low complement	Low C3; low C4; <b>OR</b> low CH50
Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

Abbreviations: ANA, antinuclear antibodies; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus.

relevant impact in maternal and perinatal health.<sup>8</sup> The incidence of SLE among pregnant women ranges from 1:660 to 1:2,952; therefore, an understanding on how to manage these patients is essential.<sup>9</sup>

Although advances in the treatment of obstetric complications and improvements in neonatal care have enabled lupus women to have pregnancies with better outcomes, SLE persists associated with significant fetal and maternal morbidity.<sup>8</sup>

Conditions with elevated levels of estrogen, such as pregnancy, have the potential to exacerbate SLE. The incidence of disease outbreaks during pregnancy varies between 15 and 63%.<sup>10</sup>

The impact of pregnancy in the course of lupus remains controversial, especially in relation to the incidence of flares. In contrast, the impact of lupus on gestation is more clearly understood. Women with lupus are no less fertile; outcomes are characterized by higher rates of fetal loss, preterm birth,

and fetal growth restriction (FGR), higher incidence of hypertensive disorders and maternal intensive care admission. Multiple factors have been identified in association with adverse outcomes, such as lupus activity during pregnancy, previous nephropathy, maternal hypertension, and positivity for anti-phospholipid antibodies.<sup>8</sup>

Thus, adopting a specific protocol of care for pregnant women with lupus should contribute to reduce the frequency of maternal and fetal adverse outcomes, directly or indirectly related to SLE, improving care standards and ensuring successful pregnancies. This review aims to disclose the existing recommendations on prenatal care among health professionals attending pregnant women affected by SLE, based on currently available scientific evidence.

## Methods

Integrative reviews were conducted to develop an evidence-based context in relation to different perspectives of clinical science studies. The following medical subject headings (MeSH) terms were used for research: “systemic lupus erythematosus” AND “high-risk pregnancy” OR “prenatal care.” Different scientific databases were analyzed: MEDLINE (via PubMed), EMBASE and The Cochrane Library.

The inclusion criteria comprised studies published in English language, between 2007 and 2017. Experimental articles and case reports were excluded. Two independent researchers performed the search strategy in the scientific databases and, if there were disagreements regarding the final inclusion, a third senior researcher was consulted.

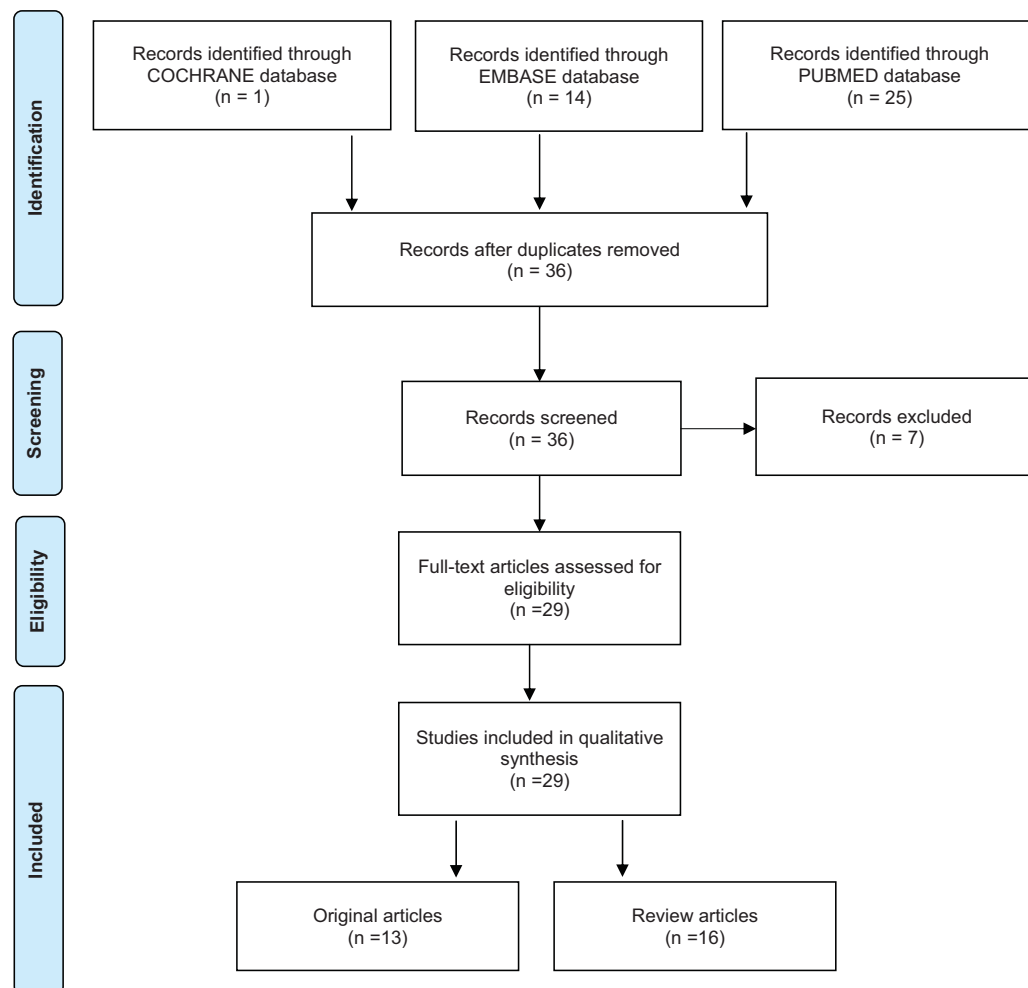
We found a total of 40 articles; 29 were accessed in full-text and selected for a qualitative synthesis (► **Fig. 1**). ► **Table 3** summarizes their methodologies, results and conclusions.

## Results

### Preconception Orientation

Adequate counselling, planning and care before, during and after the pregnancy must be the goal of health professionals who look after women with SLE. Luckily, multidisciplinary units are increasingly integrating different medical specialists (including obstetricians, immunologists, rheumatologists, hematologists and nephrologists), which may allow for a more coordinated management of pregnancy along with disease activity.<sup>35</sup>

The care of pregnant women with SLE must focus on three mainstays: a coordinated medical-obstetrical care, a well-defined management protocol and a well-structured



**Fig. 1** PRISMA 2009 flow diagram for article's inclusion on obstetric follow-up of women affected by systemic lupus erythematosus.

**Table 3** Original articles and review articles included on this integrative review

<i>Original Articles</i>				
Author, Year (Country)	Study Design	Population Description	Main Results	
Zhan et al. (2017) <sup>11</sup> (China)	Retrospective observational study	251 SLE patients with 263 pregnancies assisted at the First Affiliated Hospital of Sun Yat-Sen University, from 2001 to 2015.	APOs occurred in 70.0% of pregnancies, in which pregnancy loss in 28.5%; PTB in 21.3%; IUGR in 12.2%; and fetal distress in 8.0%. The use of antimalarial medications was associated with lower risk for APOs (OR 0.3, 95% CI 0.1–0.7, $p = 0.01$ ). Fetal umbilical artery Doppler in the third trimester showed higher resistance among SLE patients with APOs than the ones without APOs ( $2.9 \pm 0.9$ versus $2.4 \pm 0.5$ , $p = 0.001$ ).	
Simard et al. (2017) <sup>12</sup> (Sweden)	Retrospective observational study	742 births to women with SLE and 10,484 births to non-SLE women from the Swedish Lupus Linkage (SLINK) cohort, with at least one pregnancy/birth in the Medical Birth Register, from 2001 to 2012.	Among births to women with SLE, there were 32 (4.3%) diagnoses of early-onset PE, and among births to non-SLE women, there were 55 (0.5%). SLE was associated with an increased risk of early onset PE (RR 7.8, 95% CI 4.8–12.9, all pregnancies). The association remained similar upon restriction to women without pregestational hypertension.	
Chiu et al. (2016) <sup>13</sup> (Taiwan)	Retrospective cohort study	Records of pregnant (1,526) and non-pregnant (2,932) women with SLE, and pregnant (3,052) and non-pregnant (3,052) women without SLE obtained from the Taiwan National Health Insurance Research Dataset, from 1997 to 2010.	Pregnant patients with SLE exhibited significantly increased risk of ESRD after adjusting for other confounders, like immunosuppressant and parity (HR = 3.19, 95% CI: 1.35 ± 7.52 for pregnant non-SLE; and HR = 2.77, 95% CI: 1.24 ± 6.15 for nonpregnant non-SLE patients). No significant differences in the ESRD incidence were observed in pregnant and nonpregnant SLE patients. Pregnant SLE patients exhibited better clinical condition at the baseline and a significantly lower risk of overall mortality than nonpregnant SLE patients.	
Hussein Aly et al. (2016) <sup>14</sup> (Egypt)	Prospective observational study	91 pregnancies (84 women) with SLE attending the antenatal clinic at the high-risk pregnancy unit at Cairo University Hospitals, from 2010 to 2015.	The most common manifestations of SLE were cutaneous (93%), articular (92%), lupus nephritis (53%), hypertension (39%) and secondary APS (38%). Incidence rates: abortion 15%, FGR 32%, PTB 13%, PE 12%, fetal death 8%, neonatal admission ICU 15%, LBW 22%, SLE antenatal flares 44%. There was association between hypertension and abortion ( $p = 0.04$ ), PE ( $p = 0.0001$ ) and SLE flares ( $p = 0.0001$ ). Lupus nephritis and hypertension were predictors of PE ( $p = 0.01$ and $p = 0.002$ respectively) and SLE flares ( $p = 0.048$ and $p = 0.003$ respectively).	
Tedeschi et al. (2016) <sup>15</sup> (USA)	Retrospective observational study	114 SLE pregnant women referred to Brigham and Women's Hospital Lupus Center (Harvard Medical School), from 1990 to 2013.	Most pregnancies resulted in a live term delivery (76.5%). Factors significantly associated with adverse pregnancy outcomes were Nephritis (OR 3.6, 95% CI 1.0–12.8), cytopenias (OR 3.9, 95% CI 1.3–11.4), and serositis (OR 5.9, 95% CI 1.0–34.0).	
Buyon et al. (2015) <sup>16</sup> (USA, Canada)	Prospective cohort study	385 patients (49% non-Hispanic white; 31% with prior nephritis) with SLE in the PROMISSE study, from 2003 to 2012	APOs occurred in 19.0% (95% CI, 15.2% to 23.2%) of pregnancies; fetal death in 4%, neonatal death in 1%, PTB in 9%, and SGA neonate in 10%. Severe flares in the second and third trimesters occurred in 2.5% and 3.0%, respectively. Baseline predictors of	(Continued)

**Table 3** (Continued)

Original Articles				
Author, Year (Country)	Study Design	Population Description	Main Results	
Chen et al. (2015) <sup>17</sup> (China)	Retrospective observational study	83 pregnancies in 80 women with SLE attended at the Zhangzhou Affiliated Hospital of Fujian Medical University, from 2008 to 2013.	<p>APOs included presence of LAC (OR 8.32; CI 3.59 to 19.26), antihypertensive use (OR 7.05; CI 3.05 to 16.31), and platelet count (OR 1.33; CI, 1.09 to 1.63 per decrease of <math>50 \times 10^9</math> cells/L). Non-Hispanic white race was protective (OR 0.45; CI, 0.24 to 0.84). Maternal flares, higher disease activity, and smaller increases in C3 level later in pregnancy also predicted APOs. Among women without baseline risk factors, the APO rate was 7.8%. For those who were either LAG-positive or were LAG-negative but nonwhite or Hispanic and using antihypertensives, the APO rate was 58.0% and the fetal or neonatal mortality was 22.0%.</p> <p>The sample was divided into three groups: group A (patients in remission for &gt; 6 months before pregnancy, proteinuria &lt; 0.5 g per day, without renal failure and discontinuation of cytotoxic drugs for &gt; one year); group B (patients with SLE disease activity in the six months before pregnancy); group C (patients with new onset SLE during pregnancy). In group A, 76.47% pregnancies achieved full-term deliveries and 80.39% achieved live born infants. In group B and C, the outcome was poor. Among 62 patients (64 pregnancies) diagnosed as SLE before pregnancy, SLE flares occurred in 27 (42.19%) pregnancies. SLE disease activity in the six months before pregnancy was significantly associated with lupus flare (OR 5.00, 95% CI 1.14–21.87, <math>p = 0.03</math>) and fetal loss. New onset lupus during pregnancy was independently associated with obstetric complications (OR 7.22, 95% CI 2.14–24.38, <math>p = 0.001</math>).</p>	
Jakobsen et al. (2015) <sup>18</sup> (Denmark)	Retrospective observational study	84 pregnancies in 39 women diagnosed with SLE referred to a Danish University Hospital during 1990–2010 (registered at the Danish National Registry)	SLE flares developed in 46.4%, PE in 8.3%, and HELLP syndrome in 4.8% of cases. Significantly higher rates of premature delivery ( $p = 0.0032$ ), C-section ( $p = 0.015$ ), hypertension ( $p = 0.025$ ), and IUGR ( $p = 0.003$ ) were found. Disease activity ( $p = 0.021$ ) increased the risk of prematurity 3-fold. Two NLS and one congenital heart block were described. Birth weight and length were significantly lower in the SLE cohort.	
Tedeschi et al. (2015) <sup>19</sup> (USA)	Retrospective observational study	147 pregnancies among 113 women followed at the Brigham and Women's Lupus Center (Harvard Medical School), between 1990 and 2013.	Among women with organ-specific lupus activity during the 6 months before conception, the crude odds for the same type of activity during pregnancy was 7.7- to 32.5-fold higher compared with women without that type of activity immediately before conception.	



Table 3 (Continued)

Original Articles				
Author, Year (Country)	Study Design	Population Description	Main Results	
Madažli et al. (2014) <sup>20</sup> (Turkey)	Retrospective observational study	65 consecutive cases of SLE and pregnancy referred to a University Hospital, from 2002 to 2011.	Disease flare-up occurred in 7.7% of patients. Mean GA at delivery was $36.6 \pm 4.2$ and mean birth weight was $2,706 \pm 927$ g. Stillbirth, FGR, PE and PTB rates were 4.6, 18.5, 9.2 and 27.6%, respectively. Cases with uterine artery Doppler abnormalities had significantly poorer obstetric outcomes.	
Fatemi et al. (2013) <sup>21</sup> (Iran)	Retrospective observational study	72 pregnancies in 65 patients attending at Lupus Clinic in Isfahan University of Medical Sciences between 1998 and 2012.	No woman with LN experienced preterm labor or stillbirth. 16 pregnancies either ended in abortion or experienced PE of which seven had LN. Lupus nephritis and positive ANA were related to PE, whereas age of SLE development was associated with preterm labor. LN was associated with PE and SLE flare.	
Gaballa et al. (2012) <sup>22</sup> (Egypt)	Case-control study	40 SLE pregnant women from inpatient and outpatient clinics of the rheumatology & rehabilitation and Ob&Gyn Departments of Zagazig University Hospitals; another 35 non-pregnant SLE patients attending rheumatology outpatient clinics were taken as a control group. The study was conducted from 2008 to 2010	Pregnant women comprised group A and non-pregnant women comprised group B. SLEDAI was increased in both groups, more in group A. Lupus flares were increased during pregnancy as it occurred in 62.5% of group A compared with 37.14% in group B. Severe flares were more frequent in group A. Gestational hypertension and SLEDAI showing disease activity were risk factors for poor maternal outcome. Fetal outcome included full term 37.5%, PTB 25%, FGR 22.5%, stillbirth 12.5%, abortion 7.5% and congenital heart block 2.5%. Factors associated with poor fetal outcome were severe flares and active renal disease. Full term pregnancy was more common in patients with no flares.	
Surita et al. (2007) <sup>23</sup> (Brazil)	Observational cohort study	67 women with lupus (76 pregnancies) who received care at a tertiary clinic for high-risk pregnancies, at Universidade do Estado de Campinas, Brazil, between 1995 and 2002.	Flare-ups occurred in 85.3% of cases, especially when there was renal involvement (being the most significant). This was related to greater numbers of women with PE and poor perinatal outcome. In cases when there was active disease, IUGR was more common. The placental weight was significantly lower in the women with renal involvement. Flare-ups and renal involvement in lupus patients during pregnancy are associated with increased maternal and perinatal complications.	

Review Articles			
Author, Year	Type of Review	Main Results	Conclusions and Recommendations
Knight and Nelson-Piercy (2017) <sup>24</sup>	Narrative review	SLE provides challenges in pre-pregnancy, antenatal, intrapartum, and postpartum periods for the medical, obstetric, and midwifery teams. Women are at risk of lupus flares, worsening renal impairment, onset of or worsening hypertension, PE, miscarriage, FGR, PTB, and/or neonatal lupus syndrome.	In pregnancy, early referral for hospital-coordinated care, involvement of obstetricians and rheumatologists, an individual management plan, regular reviews, and early recognition of flares and complications are all important. A C-section may be required in certain obstetric contexts (e.g., preterm delivery for maternal and/or fetal well-being), but vaginal birth should be the aim for the majority of women. Postnatally, an ongoing individual management plan remains important.
Lateef and Petri (2017) <sup>25</sup>	Narrative review	Outcomes for pregnancy in the setting of SLE have considerably improved but the maternal and fetal risks remain high. Disease flares, PE, pregnancy loss, PTB, FGR and neonatal lupus syndromes (especially heart block) remain the main complications.	Specific monitoring and treatment protocols need to be used for situations such as presence of specific antibodies (antiphospholipid antibodies and anti-SSA/SSB). Safe and effective treatment options exist and should be used to control disease activity during pregnancy. Close monitoring and judicious use of medications are the key to achieve optimal outcomes.
Ostensen (2017) <sup>26</sup>	Narrative review	Ideal conditions for pregnancy are conception at a stage of remission or minimal disease activity while on stable, pregnancy-compatible medication.	Points discussed during preconception counseling should be shared with all doctors and health professionals involved in the care of a pregnant patient. Address family planning in all patients of fertile age. Physicians should actively offer information on reproduction issues to all patients. Address medication concerns and the benefits of optimal disease control in pregnancy with all patients.
Moroni and Ponticelli (2016) <sup>27</sup>	Narrative review	Pregnancy is not contraindicated in women with SLE. However, pregnant patients with lupus nephritis may run increased risk of PE and PTB. The maternal and fetal outcome are strongly correlated with lupus activity, kidney function and the presence of aPL antibodies.	Ideally, a woman should plan a pregnancy only until her lupus has been under control for at least 6 months.
Yamamoto and Aoki (2016) <sup>28</sup>	Narrative review	Maternal and fetal risks are higher in females with SLE than in the general population. However, with appropriate management of the disease, sufferers may have a relatively uncomplicated pregnancy course.	Factors such as appropriate preconception counseling and medication adjustment, strict disease control prior to pregnancy, intensive surveillance during and after pregnancy by both the obstetrician and rheumatologist, and appropriate interventions play a key role.
Jesus et al. (2015) <sup>29</sup>	Narrative review	The risk of flares depends on the level of maternal disease activity in the 6–12 months before conception and is higher in women with repeated flares before conception, in those who discontinue useful medications and in women with active glomerulonephritis at conception.	It is a challenge to differentiate lupus nephritis from PE and, in this context, the angiogenic and antiangiogenic cytokines are promising. Prenatal care of pregnant patients with SLE requires close collaboration between rheumatologist and obstetrician. Planning pregnancy is essential to increase the probability of success.



Table 3 (Continued)

Review Articles			
Author, Year	Type of Review	Main Results	Conclusions and Recommendations
Singh and Chowdhary (2015) <sup>30</sup>	Narrative review	Established risk factors for adverse pregnancy outcomes include active disease within 6 months prior to conception and during pregnancy, active nephritis, maternal hypertension, antiphospholipid antibodies and hypocomplementemia.	Certain aspects such as prevention of PTB, treatment of congenital heart block due to neonatal lupus and recurrent pregnancy loss despite best management, remains challenging. Pregnant patients with SLE should be followed in a high-risk obstetric clinic, and care should be closely coordinated between the obstetrician and rheumatologist.
Lateef and Petri (2013) <sup>31</sup>	Narrative review	Although live births are achieved in the majority of the pregnancies in women with SLE, active disease and major organ involvement can negatively affect the outcomes. Disease flares during SLE pregnancy pose the unique issue of recognition and differentiation between physiologic changes and disease state. Similarly, PE and lupus nephritis may lead to diagnostic confusion.	A multidisciplinary approach, with close monitoring, is essential for optimal outcomes. Safe treatment options exist and should be appropriately used for disease activity during pregnancy.
Lateef and Petri (2012) <sup>32</sup>	Narrative review	Maternal and fetal mortality and morbidity are considerably increased among pregnancies with SLE, compared with the general population. Active maternal disease, renal involvement, specific autoantibody subsets and advanced organ damage are predictors of poor outcome.	Multidisciplinary care, close monitoring, high-risk surveillance, and judicious use of medications are essential to achieve good outcomes.
Stanhope et al. (2012) <sup>33</sup>	Narrative review	Renal involvement in the form of either active LN at the time of conception, or a LN new onset or flare during pregnancy increases the risks of PTB, PE, maternal mortality, fetal/neonatal demise, and FGR.	The major goal of immunosuppressive therapy in pregnancy is control of disease activity with medications that are relatively safe for a growing fetus. Therefore, the use of mycophenolate mofetil, due to increasing evidence supporting its teratogenicity, is contraindicated during pregnancy.
Baer et al. (2011) <sup>34</sup>	Narrative review	The frequency of pregnancy loss in lupus has dropped to a level commensurate with that of the general population. The outcomes of lupus pregnancies are better if conception is delayed until the disease has been inactive for at least 6 months, and the medication regimen has been adjusted in advance.	Monitoring should include baseline and monthly laboratory tests, serial ultrasonography, fetal surveillance tests, and fetal m-mode echocardiography for mothers with SSA (Ro) or SSB (La) antibodies. If hydroxychloroquine was in use before conception, it should be maintained throughout pregnancy. If a woman with SLE has antiphospholipid antibodies, prophylactic treatment with aspirin and/or low-molecular weight heparin is indicated to prevent fetal loss. Lupus flares during pregnancy are generally treated with hydroxychloroquine, low-dose prednisone, pulse intravenous methylprednisolone, and azathioprine. High-dose prednisone and cyclophosphamide are reserved for severe lupus complications.

(Continued)

**Table 3** (Continued)

Review Articles			
Author, Year	Type of Review	Main Results	Conclusions and Recommendations
Ruiz-Iratorza and Khamashta (2011) <sup>35</sup>	Narrative review	Women with severe active disease or a high degree of irreversible damage, such as those with symptomatic pulmonary hypertension, heart failure, severe restrictive pulmonary disease or severe chronic renal failure should best avoid pregnancy.	Adequate pregnancy care of women with SLE rests on three pillars: a coordinated medical-obstetrical care, an agreed and well-defined management protocol and a good neonatal unit. Pregnancy should be planned following a preconceptional visit for counselling.
Buyon (2009) <sup>36</sup>	Narrative review	Flare rates are generally low for patients who are clinically stable at conception. For patients who have never had renal disease, there is no firm evidence that they will develop active renal disease simply due to being pregnant. For women with anti-SSA antibodies, the risk of having a child with congenital heart block is 2%, which rises to a recurrence rate of 18%.	For patients with aPL antibodies detected in the first trimester of pregnancy, the lupus anticoagulant is the strongest predictor of serious pregnancy complications.
Doria et al. (2008) <sup>37</sup>	Narrative review	Most SLE patients experience uncomplicated pregnancies. One of the major risks for SLE mothers is the occurrence of a disease flare during pregnancy. Another major risk of SLE relapse during pregnancy is glomerulonephritis, especially if active at the time of conception.	To reduce the risk of maternal and fetal complications, pregnancies must be planned when SLE is inactive and must be closely and appropriately monitored. Specific blood tests predict some pregnancy complications.
Clowse (2007) <sup>38</sup>	Narrative review	Pregnancy in a woman with SLE can be complicated by lupus activity and pregnancy mishaps. Recent studies found an increase in lupus activity during pregnancy, possibly worsened by hormonal shifts required to maintain pregnancy. An elevated risk for poor pregnancy outcomes, such as stillbirth, preterm birth, low birth weight and preeclampsia, is related to an increased lupus activity.	A rheumatologist and a high-risk obstetrician are best equipped to care for women with lupus who become pregnant. Careful planning and treatment may be required to achieve success of gestation.
Witter (2007) <sup>39</sup>	Narrative review	Interactions between SLE and pregnancy include the overall activity of lupus and pregnancy outcome, the effect of lupus nephritis on pregnancy, the effect of pregnancy on the progression of lupus nephritis, and the differentiation of hypertension related to lupus nephritis from PE.	A live birth can be achieved by close coordination of care between the patient's rheumatologist, obstetrician, and, in the case of renal involvement, her nephrologist.

Abbreviations: ANA, antinuclear antibodies; aPL, antiphospholipid; APOs, adverse pregnancy outcomes; APS, antiphospholipid syndrome; CI, confidence interval; ESRD, end-stage renal disease; FGR, fetal growth restriction; GA, gestational age; HR, hazard ratio; ICU, intensive care unit; IUGR, intrauterine growth retardation; LAC, lupus anticoagulant; LBW, low birth weight; LN, lupus nephritis; NLS, neonatal lupus syndrome; OR, odds ratio; PE, preeclampsia; PTB, preterm birth; PTD, preterm delivery; RR, relative risk; SGA, small for gestational age; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

neonatal unit. Preconception counselling is vital to assess the chance of both potential fetal and maternal complications; that way, consistent information regarding specific risk for complications and the expected management plan should be provided (►Table 3).<sup>35</sup>

Pregnancy planning is a key-point for women with SLE. Postponing conception until the disease is considered inactive for at least six months significantly improves the outcomes of these pregnancies.<sup>26,31,34,35</sup> Women who present some form of irreparable organ injury are more likely to undergo complications and even additional damage during and after pregnancy. Some conditions should advise to delay pregnancy, such as severe disease flare within the previous six months, recent stroke and active lupus nephritis.<sup>32</sup> In some situations, pregnancy may be contraindicated (►Table 4).<sup>26,34,35</sup>

At the preconception visit, obtaining a complete set of autoantibody profile is recommended, including antiphospholipid (aPL) antibodies (anticardiolipin and lupus anticoagulant), complement serum levels, anti-SSA and anti-SSB antibodies. Evaluating the pregnancy risk and assessing the SLE activity and the organ function is important to maintain disease control only in safe medications.<sup>32</sup>

A higher risk of complications is found among women with severe impairment of organ function, with or without preexisting severe organ damage.<sup>24</sup> Besides, the diagnosis of SLE during pregnancy is also related to the occurrence of complications, significantly affecting maternal and fetal outcomes.<sup>30</sup>

## Prenatal Follow-up

### General Findings

The prenatal care of a woman with SLE requires close collaboration between the obstetrician and the clinicians (rheumatologist, nephrologist or hematologist), and management in a high-risk referral center. An evaluation by the clinician should occur every 4–6 weeks, whereas the obstet-

ric visit should be every 4 weeks until 20 weeks of gestation; then, every 2 weeks until 28 weeks, and then, weekly until the expected delivery date.<sup>34</sup>

At every prenatal visit, blood pressure, weight gain, uterine size, fetal heart rate and urinalysis (through a quick outpatient analysis with the dipstick testing) should be assessed, as well as inquiring about symptoms related to lupus flares.<sup>34</sup>

The differential diagnosis of complications that may arise during pregnancy is not easy. Signs and symptoms of lupus flares often mimic the ones of normal pregnancy. Those flares are less frequent in the third trimester, although they may occur at any time during pregnancy or in the immediate postpartum period.<sup>34</sup>

### Laboratory Evaluation during Prenatal Care

In addition to routine pregnancy booking, blood tests (which include a full blood count), baseline tests of renal and hepatic function and baseline urinary protein quantified by a 24-hour collection should be obtained.<sup>24</sup> Complement studies should comprise further tests (C3, C4, CH50), anticardiolipin antibodies, anti-dsDNA, lupus anticoagulant and anti-SSA and SSB.

### Disease Activity during Prenatal Care (Flares)

Changes in hormonal levels through pregnancy prompt to a shift from Th1 to Th2 lymphocyte dominance; consequently, autoimmune disorders involving Th2-response, such as SLE, are expected to flare.<sup>24</sup>

It is generally agreed that pregnancy may lead to higher rates of disease flares, with rates from 25 to 65% being reported.<sup>18,31,37</sup> Different organ systems may have variable response to pregnancy; musculoskeletal flares are less common, whereas renal and hematological flares are more common.<sup>31</sup> The risk of flare seems to be related to the occurrence of disease activity 6–12 months before conception.<sup>15,19,22,24,30</sup>

**Table 4** Preconception visit checklist and contraindications to pregnancy in women with SLE<sup>35</sup>

Preconception visit checklist	Contraindications to pregnancy
Age?	Severe lupus flare within the previous 6 months
Any previous pregnancy?	Severe restrictive lung disease (FVC < 1 L)
Previous pregnancy complications?	Heart failure
Presence of severe irreversible damage?	Chronic renal failure (Cr > 28 mg/dL)
Recent or current lupus activity?	Stroke within the previous 6 months
Presence of antiphospholipid antibodies/syndrome?	Previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin
Other chronic medical conditions? (Hypertension, diabetes, etc.)	Severe pulmonary hypertension (estimated systolic PAP > 50 mm Hg or symptomatic)
Current treatment: any "forbidden" drugs? (including cyclophosphamide, methotrexate, mycophenolate, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and statins)	
Positivity of anti-SSA /anti-SSB?	
Smoking?	

Abbreviations: FVC, forced vital capacity; PAP, pulmonary arterial pressure.

A higher risk of flare during pregnancy is noticed when lupus nephritis occurs at conception, even in women in remission.<sup>13,21,24,30</sup> One study showed a 30% flare rate during pregnancy or postpartum among 113 pregnancies in women with preexisting lupus nephritis evaluated; other studies suggest a likelihood of up to 60%.<sup>24</sup> Besides, different reports in the literature indicate lupus nephritis as a predictive of poor prognosis for pregnancy.<sup>23</sup>

It may be difficult to distinguish pregnancy-related signs and symptoms from those of SLE. Therefore, an appropriate assessment by experienced physicians is important.<sup>24,37,38</sup> Ambiguous manifestations include fatigue, headaches, arthralgia, edema, hair loss, dyspnea, malar and palmar erythema, anemia and thrombocytopenia. Hence, baseline blood counts and urinalysis with measurement of proteinuria assessed early in gestation are helpful to monitor disease status and identify flares.<sup>24</sup>

During pregnancy, liver production of serum C3 and C4 increases, so their levels may persist within the range of normality in cases of active SLE. Relative variations are more important, rather than absolute levels, with a drop of  $\geq 25\%$  in serum complement levels suggesting lupus flare.<sup>24</sup>

Pregnancy-specific disease activity scales (such as systemic lupus erythematosus pregnancy disease activity index [SLEPDAI] and lupus activity index in pregnancy [LAI-PI]) have been developed, but mostly remain as research tools. In practice, the clinical judgment of an experienced clinician is still considered the gold standard.<sup>25,31,32</sup> The SLEPDAI scale is a similar instrument to the systemic lupus erythematosus disease activity index (SLEDAI) for assessment of lupus activity, assigning different scores for the various clinical and laboratory manifestations of lupus activity, however taking into account the physiological changes of gestation and the main pathologies of the pregnancy-puerperal cycle that can mimic SLE in activity. Its score ranges from zero to 105 and stratifies the disease activity: absent (up to 4 points), mild to moderate (5–12 points) and severe (up to 12 points) (→ **Table 5**).<sup>36</sup>

A recent meta-analysis reported rates ranging from 1.5 to 83% for a lupus nephritis flare during pregnancy,<sup>33</sup> corroborating with data from previous studies.<sup>38</sup> Thus, it is strongly recommended a close monitoring, with monthly assessments of disease activity (with special attention to renal function). Besides, the risk of hypertensive disorders of pregnancy increases in the setting of active lupus nephritis.<sup>14,33</sup>

The frequency of preeclampsia varies from 7.5 to 22.5% for all women with SLE.<sup>12,15,18,20,39</sup> Lupus renal involvement is often associated with hypertension, and the preeclampsia diagnosis is difficult, since it may be superimposed on chronic hypertension.<sup>39</sup>

Likewise, in cases of SLE women with glomerular lesions, increased proteinuria may be observed, due to the enlarged glomerular filtration rate during pregnancy, with this fact not being related to preeclampsia. Thus, the diagnosis of preeclampsia can get more difficult because of increasing blood pressure and proteinuria at term.<sup>38,39</sup>

The differential diagnosis of preeclampsia in lupus patients may be facilitated by changes in the measures of C3, C4 and CH50, since a reduction in those levels is expected

during lupus activity.<sup>39</sup> Other laboratory test findings may be helpful to successfully perform a differential diagnosis: abnormal urinary sedimentation with the presence of erythrocyte dysmorphism or cell casts and increased anti-DNA antibody titers (all found in lupus nephritis).<sup>23</sup>

New onset SLE during pregnancy can be considered as SLE activity and might be associated with worse outcome. Differentiating the diagnosis of preeclampsia from new onset SLE during pregnancy is a challenge and frequently delays the diagnosis of SLE. However, a Chinese study indicated that new onset SLE during the third trimester of pregnancy might have a better outcome.<sup>17</sup>

Among patients with stable condition at the time of conception, it is expected that disease activity will not worsen, and even if so, the flare is usually mild and occasionally involves some kind of treatment modification.<sup>28</sup>

### Evaluation of Fetal Growth and Vitality

Fetal complications are frequently observed in patients with SLE. Overall, miscarriages and stillbirth may occur in  $\sim 20\%$  of pregnancies in SLE patients.<sup>11,15,26,30</sup> Patients with a history of nephritis, in special, have an increased risk for such adverse outcomes.<sup>14,16</sup>

The rate of FGR is estimated to be near of 30%, observed even in mild disease, with an increased risk if there is renal involvement. Small-for-gestational-age is a more common outcome in those born prematurely, but can occur at all gestational ages.<sup>20,22,37,39</sup> Several studies concluded that the small-for-gestational-age rate outcome among SLE women tends to be higher, condition strongly associated to the presence of disease flare-ups during pregnancy.<sup>23</sup>

Serial obstetric sonography is the most important method to guide surveillance for fetal growth. Crown-rump length measurement in the first trimester presents as the most precise measurement. At 16 to 22 weeks of gestation, an anatomic survey considering diagnosis of fetal anomalies should be followed, also serving to allow the first monitoring of growth. At each 4-week periods, new scans should take place, with measurement of amniotic fluid volume. If preeclampsia or FGR are diagnosed, the interval can be reduced to 3 weeks.<sup>39</sup>

Fetal vitality surveillance is an important part of the prenatal care of SLE patients. This should include the nonstress test (NST), the biophysical profile (BPP), and fetal umbilical artery Doppler velocimetry, starting at 26 to 28 weeks and continuing weekly until birth.<sup>39</sup>

In patients with SLE, alterations of umbilical artery Doppler velocimetry should be managed similarly to those without the condition. Normal evaluation of these tests has a high negative predictive value for fetal death.<sup>29</sup> Association between abnormal uterine artery Doppler and later fetal loss, preeclampsia, FGR and preterm labor were also described.<sup>29</sup>

Because of the risk of fetal congenital heart block, for women with anti-SSA/SSB antibodies, a fetal echocardiography should be performed at 18–20 weeks and 26–28 weeks to exclude fetal congenital heart block. An urgent referral to a tertiary care center should be prompted in case of any fetal heart rate abnormality, mostly a slow heart rate.<sup>24</sup>

**Table 5** Systemic lupus erythematosus pregnancy disease activity index (SLEPDAI) instrument to stratify SLE activity during pregnancy<sup>36</sup>

Score	Descriptor	Modified for pregnancy	Considerations
8	Seizure	Yes	(r/o eclampsia)
8	Psychosis	No	
8	Organic brain syndrome	No	
8	Visual disturbance	No	(hypertension is already considered an exclusion in SELENA-SLEDAI and SLEDAI)
8	Cranial nerve disorder	Yes	(r/o Bell palsy)
8	Lupus headache	Yes	(r/o Bell palsy)
8	CVA	Yes	(r/o eclampsia)
8	Vasculitis	Yes	(consider palmar erythema)
4	Arthritis	Yes	(consider bland knee effusions)
4	Myositis	No	
4	Urinary casts	No	
4	Hematuria	Yes	(r/o cystitis and vaginal RBC reflective of placental problems)
4	Proteinuria	Yes	(r/o eclampsia)
4	Pyuria	Yes	(r/o infection)
2	Rash	Yes	(consider chloasma)
2	Alopecia	Yes	(consider normal postpartum alopecia)
2	Mucosal Ulcers	No	
2	Pleurisy	Yes	(hyperventilation may be secondary to progesterone, dyspnea secondary to enlarging uterus)
2	Pericarditis	No	
2	Low complement	Yes	(complements normally rise during pregnancy)
2	Increased DNA binding	No	
1	Thrombocytopenia	Yes	(r/o preeclampsia, HELLP syndrome, incidental thrombocytopenia of pregnancy)
1	Leukopenia	Yes	(consider normal rise of leukocyte count during pregnancy)
1	Fever	No	

Abbreviation: CVA, cerebrovascular accident; RBC, red blood cell; r/o: rule out, SELENA-SLEDAI, safety of estrogens in lupus erythematosus national assessment- systemic lupus erythematosus pregnancy activity index; SLEDAI, systemic lupus erythematosus pregnancy activity index.

### Recommended SLE Treatment during Pregnancy

Considering the harmful effects of active disease on both mother and fetus, an appropriate reflection between the risks and benefits of this treatment must take place.<sup>26,30</sup>

In practice, it is frequent that SLE women to discontinue their medication before conception, due to fear of fetotoxicity, without proper doctor counseling. However, discontinuation of the medication may lead to active SLE and unfavorable pregnancy outcomes.<sup>28</sup>

Usually, the immunosuppressive treatment in pregnant women with quiescent lupus should not be changed. The most frequently used agents in lupus patients are glucocorticoids and hydroxychloroquine, which should be maintained.<sup>27</sup>

Prednisone at a dosage of 5–10 mg per day is usually considered safe.<sup>27</sup> Lupus flares that fit into mild activity can be treated with low-dose prednisone (less than 20 mg/d). Higher doses of corticosteroids, including pulse dose steroids, are options to treat moderate to severe lupus activity.<sup>37,38</sup>

Hydroxychloroquine is not a teratogenic drug. Its use is recommended to prevent disease activity and reduce the risk of cardiac-neonatal lupus in patients who are carriers of anti-SSA/-antibody.<sup>11,27,28</sup> In addition, it improves the prognosis of SLE nephritis and prevents death.<sup>38</sup>

Azathioprine is considered safe, especially if compared with other immunosuppressive drugs. Many studies sustain a transition to this option if the patient wishes to conceive. However, some other reports recently pointed out concerns about late developmental delays in children who were exposed to azathioprine during pregnancy,<sup>28,38</sup> as well as neonatal leucopenia and/or thrombocytopenia.<sup>27</sup>

Regarding cyclosporine and tacrolimus, the FDA classifies as category C; however, some meta-analysis studies did not find significant differences related to birth defects when pregnant women were exposed to them.<sup>27,37</sup>

Cyclophosphamide should not be prescribed during the first trimester, because of its association to chromosomal



impairment. During the second or third trimester, it should be reserved only to severe flares unamenable with methylprednisolone pulses or other drugs. The use of cyclophosphamide during the second and third trimesters does not seem to increase the risk for congenital abnormalities. Nevertheless, miscarriages and preterm birth may be more frequent.<sup>27,37</sup>

Leflunomide is associated to teratogenic and fetotoxic effects in animals, and its metabolite is detectable in plasma up to 2 years after discontinuation. Thus, in pregnant women, it is formally contraindicated; and pregnancy must be excluded before starting it.<sup>27</sup>

Methotrexate is another teratogenic drug, classified by the FDA as X (contraindicated in pregnancy). If used in the first trimester, it is associated to FGR and some major malformations, such as absence or hypoplasia of the frontal bones, craniosynostosis, large fontanelle and ocular hypertelorism.<sup>27</sup>

During the first trimester, rituximab has very low transplacental transfer, with some studies reporting safe pregnancies and deliveries in those cases of exposure. However, during the second or third trimester, it can cross the placenta and induce severe neonatal lymphopenia.<sup>27,37</sup> Hence, in these cases, live vaccines should be avoided in those children during the first 6 months of life.<sup>27</sup>

Handling some complications that often affect pregnant women with SLE justifies a short statement. Since arterial hypertension is a common condition among patients with lupus nephritis, an appropriate management of blood pressure in pregnancy may reduce the progression of the disease and avoid several adverse pregnancy outcomes. Labetalol, nifedipine or methyldopa are safe drugs for treating hypertension. Angiotensin-converting-enzyme inhibitors should be avoided due to their association to multiple congenital abnormalities.<sup>27</sup>

Low-dose aspirin is recommended, since it reduces the risk of preeclampsia and perinatal death; besides, it is associated with an increase in the birth weight of those with risk factors, including renal disease. Full anticoagulation with low-molecular weight heparin (LMWH) is recommended if there has been a previous thromboembolic event.<sup>27</sup>

Calcium supplementation is required, mainly for those women in use of corticosteroids and heparin. Supplemental vitamin D does not reduce the risks of unfavorable outcomes.<sup>25</sup>

### Delivery Assistance

Women with SLE have an increased risk of preterm delivery. This may occur spontaneously or because of maternal and/or fetal complications (such as severe lupus flare, preeclampsia and FGR).<sup>24</sup>

In gestational age between 24 weeks and 34 weeks and 6 days, accelerating of fetal lung maturation is essential, with two intramuscular steroid injections (preferably, betamethasone), independently of any maternal steroids administered before.<sup>24</sup>

Magnesium sulfate should be considered when gestational age is < 32 weeks, due to its neuroprotective benefits to the fetus. As it is well known, it ought to be administered in cases of severe preeclampsia.<sup>24</sup>

The aim in a pregnant SLE patient should be to accomplish a spontaneous labor at term with vaginal delivery. However, available data have revealed that women with SLE are more expected to undergo a cesarean section (> 33%; odds ratio [OR] 1.7; confidence interval [CI] 95% 1.6–1.9). In spite of that, it is recommended that C-sections should be reserved only for obstetric indications, due to its extra risk factor for venous thromboembolism (VTE), blood loss and infection, as well as repercussions for future gestations.<sup>24</sup>

Adjusting maternal medication for labor may be required. Intravenous hydrocortisone may be necessary to overcome the physiological stress of labor if long-term oral steroids have been taken. If a woman receives standard prophylactic LMWH, it should be discontinued at the onset of spontaneous labor, as well as on the night before induced labor or elective cesarean section. Regional anesthesia (epidural or spinal) can be performed 12 hours after the last LMWH dose.<sup>24</sup>

### Postpartum Care

Rigorous monitoring for severe maternal exacerbations is strongly recommended for those who had anticipated delivery because of a SLE flare or coexisting preeclampsia. The treatment for postpartum active SLE is similar to that for non-pregnant women. Nonetheless, it should be noticed that several medications for aggressive therapy are not recommended during breastfeeding. Thus, the risks and benefits of continuing breastfeeding must be clarified to the lactating mother.<sup>28</sup>

All women who received antenatal LMWH should continue its use for 6 weeks postpartum, in a prophylactic dosage, since puerperium is also a period of increased VTE risk. Afterward, the postpartum VTE risk should be assessed.<sup>24</sup>

In patients with SLE, postpartum counseling to offer safe contraception is particularly important. Good choices are long-acting reversible contraception (LARC) methods. They are considered reliable and less dependent on patient commitment.<sup>24</sup> Progestogen-only methods are safe and may become a suitable option.<sup>24</sup>

Estrogen-containing contraceptives must not be used by women with aPL antibodies or antiphospholipid syndrome (APS), moderate to severe active SLE (including lupus nephritis) and some other conditions, such as hypertension, smoking, obesity or previous VTE, since they increase a woman's VTE risk. In cases of well-defined SLE with stable and/or low-active disease, the use of combined oral contraceptive may be suitable if wished.<sup>24</sup> Barrier methods present a high failure rate (15–32%); thus, they should not be used as single methods.<sup>24</sup>

### Discussion

It is well established that pregnant women with SLE present a higher risk for maternal complications and pregnancy wastage, in spite of significant progress concerning success rates lately. During pregnancy, the disease activity may worsen and consequently rise the risk of other maternal and fetal complications. Therefore, holding an adequate control of disease activity and treating flares quickly must be a core-objective during prenatal care.



Multidisciplinary care, coordinated by obstetricians and clinicians, with close monitoring, should allow for early diagnosis of complications.

Considering the data obtained on this review, the disease activity should be systematically evaluated by SLEP-DAI,<sup>25,31,32,36</sup> since it presents as the factor that guides adjustment or change in medication. All pregnant women with clinical suspicion of active or poorly controlled disease should be hospitalized due to the severity of the maternal condition and fast deterioration of fetal vitality conditions that may be associated with this event.<sup>24,25</sup>

Regarding the appropriate treatment, prednisone is an immunosuppressant that can be safely used during pregnancy. The association with gestational diabetes in lupus is low and is not a limiting factor for the use of medication. However, pregnant women using high doses should be screened for gestational diabetes.<sup>24</sup> Hydroxychloroquine may be used during gestation, since it is associated with reduced disease activity.<sup>27,40,41</sup>

Azathioprine, tacrolimus and cyclosporine could be used as a therapeutic option in cases resistant to prednisone. Non-steroidal anti-inflammatory drugs, leflunomide, cyclophosphamide, methotrexate and mycophenolate mofetil should not be prescribed.<sup>27,28,37,40,41</sup>

Furthermore, prophylaxis of preeclampsia should be performed with AAS 100mg/d between 12 and 34 weeks of gestation and calcium carbonate 1.5 g/d throughout the entire gestational period.<sup>24,40</sup>

We strongly recommend follow-up of fetal growth and vitality with serial sonography (at least one per trimester), Doppler velocimetry assessment from 26 weeks (repeated every 2 weeks if normal and weekly if altered), NST from 28 weeks and fetal echocardiography between 24 and 30 weeks for patients with anti-SSA.<sup>29,39,42</sup>

Labor delivery must be determined according to obstetric indication and should occur no later than full-term. In the cases of patients taking corticosteroids at immunosuppressive dose (1 mg/kg), we recommend prophylactic antibiotics due to the risk of infections and sepsis.<sup>27,31</sup>

Contraceptive counseling may include LARC or progestogen-only methods and surgical sterilization (with social or medical indication). Combined oral contraceptives present relative contraindication, considering the risk of VTE.<sup>24,40</sup>

After all, it is important to notice that the present study had some limitations: randomized trials did not integrate this review, which would certainly increase its degree of evidence. However, it should be emphasized that SLE in pregnancy is a condition whose incidence is not so high, which could justify the lack of these trials. In addition, one cannot deny the existence of a publication bias, with often the best results disclosed to the scientific community.

On the other hand, there are strengths of this study that should be underlined: a wide variety of studies performed in different countries, with the opinions of several experts, each with varied backgrounds, were part of this integrative review. Besides, the lack of available meta-analysis reinforces the importance of including other reviews made by these specialists.

## Conclusion

In conclusion, SLE pregnant women present an increased risk for maternal complications, pregnancy loss and other adverse perinatal outcomes. The diagnosis of the disease during pregnancy may be highly difficult, as well as the identification of worsening disease activity. These conditions, therefore, increase the risk of other maternal-fetal complications. Thus, close prenatal care, multidisciplinary team, adequate control of disease activity and treating flares quickly should be a central goal for better results

## Conflicts of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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