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Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management

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EXPERT REVIEWS

Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management

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Systemic lupus erythematosus is a systemic autoimmune disease that primarily affects women in their reproductive age years. Pregnancy in systemic lupus erythematosus now has favorable outcomes for the majority of women. However, flares of disease activity, preeclampsia, fetal loss, intrauterine growth retardation and preterm birth are established risks of such pregnancies. Active lupus nephritis at the time of conception poses the greatest risk for disease flares and poor obstetric outcomes. Patients should delay conception until their lupus has been in remission for at least 6 months. In addition, certain lupus medications are potentially teratogenic and need to be stopped before conception. The signs and symptoms of a lupus flare may mimic those of normal pregnancy, impeding its recognition during pregnancy. Hydroxychloroquine, low-dose prednisone, pulse intravenous methylprednisolone and azathioprine are commonly used to treat lupus flares during pregnancy.

Keywords: disease activity • lupus • preeclampsia • pregnancy • systemic lupus erythematosus

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Learning objectives

Upon completion of this activity, participants will be able to:

- Analyze the effects of SLE on pregnancy outcomes
- Assess the clinical presentation of lupus flares during pregnancy
- Compare alterations in laboratory values associated with SLE and pregnancy
- Distinguish primary treatments for SLE during pregnancy

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that primarily affects women of childbearing age. This chronic disease is distinguished by its multiorgan involvement, characteristic inflammatory lesions of the skin, joints, serous membranes, kidneys and CNS, and its association with high titers of autoantibodies to an array of autoantigens. Its clinical course is often one of disease flares followed by variable periods of remission. The 1982 American College of Rheumatology Criteria for Classification of SLE are commonly used as guidelines for diagnosis [1] but have limited utility in the diagnosis of patients with early disease or limited forms of lupus, such as patients with isolated lupus nephritis.

Pregnancy in a woman with SLE is associated with an increased risk of adverse maternal and fetal outcomes. This observation prompted physicians in the past to advise their lupus patients not to consider childbirth. However, the prevention and management of maternal complications has improved dramatically. The frequency of pregnancy loss in SLE has dropped over the last 40 years from levels as high as 43% in 1960–1965 to 17% in 2000–2003, a level now commensurate with that of the general US population [2]. Pregnancy is thus an option for many women with lupus and can usually be managed successfully in a high-risk clinic, with the close collaboration of a maternal–fetal medicine specialist and a rheumatologist. At present, women with SLE account for approximately 4500 pregnancies in the USA each year [3]. In this article, the authors reviewed pregnancy outcomes in lupus, the frequency and types of lupus flares during pregnancy and the puerperium, the differentiation of lupus flares from normal physiologic changes of pregnancy and serious pregnancy-related complications, and the management of lupus during pregnancy.

Pregnancy outcomes in systemic lupus

Pregnancy in the setting of SLE is prone to complications and must, therefore, be considered high risk. In a recent US study of 16.7 million pregnancies, 13,555 occurred in lupus patients and were associated with a 20-fold increase in maternal mortality and increased risks for maternal morbidity, including cesarean sections (odds ratio [OR]: 1.7), preterm labor (OR: 2.4) and preeclampsia (OR: 3.0) [4]. These increased risks persisted when adjusted for maternal age. Preeclampsia complicates 13–35% of lupus pregnancies, compared with 5–8% of pregnancies in the general US population [3,5,6]. Fetal morbidity and mortality in SLE pregnancies were recently tallied in a systematic review and meta-analysis of case series from throughout the world. Among 29 observational studies with 2751 pregnancies, the rate of premature birth was 39.4%, spontaneous abortion 16%, intrauterine growth restriction (IUGR) 12.7%, stillbirth 3.6% and neonatal deaths 2.5% [7]. More reassuring data are emerging from the PROMISSE study, an ongoing prospective multicenter study of lupus pregnancy. In a preliminary analysis, 80% of 333 pregnant women had a favorable pregnancy outcome, defined as the absence of fetal/neonatal death, IUGR and birth prior to 36 weeks due to placental insufficiency, hypertension or preeclampsia [8]. A summary of the fetal outcomes of lupus pregnancies in eight case series is given in (**Table 1**).

Risk factors for poor pregnancy outcomes in lupus

Adverse fetal outcomes in a lupus pregnancy relate to a variety of maternal disease factors (**Box 1**). Risk factors for first trimester fetal loss include proteinuria (>500 mg/day), the presence of antiphospholipid antibody syndrome, thrombocytopenia and hypertension [9]. The risk for fetal loss in pregnant women with active lupus nephritis has been reported to range from 8 to 36% [6,10–12]. However, pregnancy outcomes can be favorable in patients with a past history of lupus nephritis, particularly if the renal disease is in complete remission and renal function is normal at the time of conception [13,14]. Women with a serum creatinine of >2.8 mg/dl at the time of conception only have a 20–30% chance of pregnancy success [15]. Active lupus nephritis and hypertension during the first trimester increase the risk of preterm birth (delivery before 37 weeks) and IUGR.

Table 1. Pregnancy and fetal outcomes in systemic lupus erythematosus.

Study (year)	Pregnancies (n)	Live births (n)	Therapeutic abortions	Spontaneous abortions, n (%)	Fetal deaths, n (%)	Total pregnancy losses, n (%)	Ref.
Mintz *et al.* (1987)	102	80 (78%)	0	17 (17%)	5	22 (22%)	[28]
Huong *et al.* (1997)	62	51 (77%)	2 (3%)	10 (16%)	2 (3%)	12 (19%)	[105]
Lima *et al.* (1995)	108	89 (82%)	2 (2%)	7 (7%)	10 (9%)	19 (18%)	[106]
Georgiu *et al.* (2000)	59	36 (61%)	3 (5%)	9 (15%)	1 (2%)	13 (22%)	[107]
Cortes-Hernandez *et al.* (2002)	103	68 (66%)	8 (8%)	15 (15%)	12 (12%)	35 (34%)	[12]
Liu *et al.* (2012)	111	83 (75%)	23 (20%)	2 (2%)	8 (9%)	10 (11%)	[108]
Gladman *et al.* (2011)	193	114 (59%)	31 (16%)	42 (21%)	3 (2%)	79 (41%)	[109]
Al Arfaj *et al.* (2010)	383	269 (70.2%)	NA	94 (25%)	20 (5%)	114 (30%)	[110]
Ko *et al.* (2011)	183	152 (83%)	NA	17 (9%)	12 (7%)	29 (16%)	[111]
Clowse *et al.* (2006)	267	229 (86%)	NA	19 (7%)	19 (7%)	27 (14%)	[38]

NA: Not available.

Additional risk factors include other forms of increased lupus activity at the time of conception and during the first trimester, antiphospholipid antibodies and a prior pregnancy loss. IUGR may occur even in lupus patients with mild disease, suggesting an effect of lupus on fetal growth irrespective of disease activity or complications [16]. In one study, the neonates of lupus patients were noted to weigh less than normal controls at every gestational age, even when controlling for maternal hypertension and renal disease [17].

Adverse maternal outcomes in a lupus pregnancy include preeclampsia and disease flares. Preeclampsia is most common in women with active lupus nephritis and renal insufficiency at the time of conception. Other risk factors for preeclampsia include maternal age ≥40 years, previous personal or family history of preeclampsia, pre-existing hypertension or diabetes mellitus, and obesity (BMI ≥35 kg/m^2), as well as SLE-specific factors such as sustained use of prednisone in doses of 20 mg per day or greater during the pregnancy and thrombocytopenia [5,18–20]. The latter can be both a predictor of preeclampsia in lupus patients and a manifestation of preeclampsia [5]. Clowse *et al.* observed that women who discontinued hydroxychloroquine prior to conception were at an increased risk of SLE flares [21]. Predictors of renal flare during pregnancy include a serum creatinine greater than 1.2 mg/dl or proteinuria of 500 mg or greater in a 24-h collection at the time of conception [22].

A genetic predisposition for the development of preeclampsia is being defined. A maternal susceptibility site for preeclampsia on chromosome 2p has been identified with genome-wide association studies using cohorts from Iceland, Australia and New Zealand [23,24]. Multiple candidate genes have been reported to confer an increased susceptibility for preeclampsia, including those encoding angiotensinogen, the angiotensinogen receptors, factor V Leiden variant, methylene tetrahydrofolate reductase, nitric oxide synthase and TNF-α. However, none of these genetic factors proved to be associated with a high risk of preeclampsia in a study of 657 British women affected by preeclampsia [25]. Over the past year, liver X receptor-β (NR1H2), a key player in lipid metabolism, has been implicated in preeclampsia through modulation of trophoblast invasion and regulation of the expression of the endoglin (*CD105*) gene, a marker of preeclampsia [26]. The PROMISSE study was the first to look at specific genetic risk factors that may predispose SLE patients to preeclampsia. The investigators hypothesized that impaired capacity to limit complement activation predisposes pregnant women with SLE or antiphospholipid antibodies to preeclampsia. They sequenced the genes for three complement regulatory proteins: membrane cofactor protein, complement factor H and complement factor I. In normal pregnancies, these regulatory proteins are highly expressed on trophoblast membranes and prevent excessive complement activation. Of the 40 patients who developed preeclampsia, seven (18%) were found to have heterozygous mutations in membrane cofactor protein and complement factor I [27].

The identification of modifiable risk factors for poor pregnancy outcomes in lupus mandates the need for pregnancy planning in women with SLE. Thus, the outcomes of such pregnancies are far better if conception is delayed until more serious lupus disease activity has been absent for at least 6 months and the patient's medication regimen has been adjusted in advance (see below). Women with certain forms of advanced organ damage should be advised against considering conception [19]. Prior to considering pregnancy, a woman with SLE should meet with

Box 1. Risk factors for pregnancy loss in lupus patients.

- Active disease within 6 months prior to conception
- Active disease during pregnancy
- Systemic lupus erythematosus onset during pregnancy
- Secondary antiphospholipid antibody syndrome
- Hypocomplementemia
- Double-stranded DNA antibodies
- Thrombocytopenia
- Chronic hypertension
- Pre-existing renal disease and first-trimester proteinuria

Table 2. Flare rates in systemic lupus erythematosus.

Study (year)	Pregnancies (n)	Controls	Flare definition	Pregnancy flares (%)	Ref.
Flare rate similar in and out of pregnancy					
Lockshin *et al.* (1984)	33	Matched, nonpregnant	Custom	27	[33]
Mintz *et al.* (1986)	92	Matched, nonpregnant	Custom	59	[28]
Urowitz *et al.* (1993)	79	Matched, nonpregnant with and without active SLE	Custom	70	[34]
Tandon *et al.* (2004)	78	Matched, nonpregnant	Renal activity	45	[35]
Increased flare rate in pregnancy					
Petri *et al.* (1991)	40	Matched, nonpregnant	PGA	60	[29]
Wong *et al.* (1991)	29	Nonpregnant	Custom, modified from Lockshin	58	[33,36]
Ruiz-Irastroza *et al.* (1996)	78	Matched, nonpregnant and postpregnancy course	LAI	65	[37]

LAI: Lupus activity index; PGA: Physician global assessment; SLE: Systemic lupus erythematosus.

both her rheumatologist and a maternal–fetal medicine specialist in order to be apprised of the risk of both maternal and fetal problems, to receive advice about the advisability and timing of pregnancy, and receive a specific management plan concerning alterations in her medication regimen (if necessary) and monitoring.

Lupus flares associated with pregnancy

Lupus disease activity may flare during pregnancy or in the immediate postpartum period. Several prospective studies have suggested that the frequency of these flares may be lowest in the third trimester [28–30]. Reported rates of such flares range from 13.5–65% of pregnancies in affected women [31]. The frequency of flares during lupus pregnancies has been the subject of seven prospective comparative studies that have used nonpregnant lupus patients as controls (Table 2). Four of these studies did not identify an increased rate of flares, while three did [28,29,32–37]. This disparity reflects variability in the severity of lupus among the patients in the study cohorts and in the criteria for defining a lupus flare. Some symptoms and laboratory findings of a normal pregnancy can mimic those of SLE (see later), making it more difficult to diagnose a lupus flare during pregnancy. More recent prospective studies have utilized validated measures of disease activity and have found a two- to three-fold increase in lupus disease activity during pregnancy [12,38,39]. The most common organs affected in lupus flares during pregnancy are skin, kidney, blood and joints. Relative to nonpregnant SLE patients, joint flares are less common, while renal and hematological flares are increased in frequency during a lupus pregnancy [40]. Approximately 15–30% of patients who flare will have severe disease manifestations, with involvement of the kidneys and other internal organs [38]. Tandon *et al.* used a nested case–control design to determine whether renal flares were increased during pregnancy among lupus patients with renal disease prior to conception [35]. Seventy eight pregnancies among 53 women with renal disease were matched with 78 nonpregnant lupus patients with renal disease. There were no significant differences in the percentage of patients whose renal disease activity changed or whose renal function deteriorated between the two groups [35].

Pathophysiology of lupus flares during pregnancy

Flares of lupus during pregnancy are generally attributed to the progressive increase in serum estrogen levels during pregnancy, especially in the third trimester. Estrogens augment immunologic reactivity and this observation is often cited as the basis for the increased risk of autoimmune disease in women. Thus, increased estrogen levels during pregnancy have been postulated to lead to an increased risk of lupus flares. However, such an increase in estrogen levels was not documented in a study of 17 pregnant lupus patients, possibly as a result of placental compromise [41]. Additionally, an elegant mouse model system has been created recently that allows an analysis of the effects of the sex chromosome complement without the confounding effects of differences in gonadal type. With this model, Smith-Bouvier *et al.* showed that the expression of SLE is augmented in mice with the XX sex chromosome complement, when compared with that of the XY chromosome complement, within a common gonadal type [42]. Thus, there is evidence in murine models for a direct role for the sex chromosome complement, independent of the sex hormone milieu, in the female bias noted in lupus and other autoimmune diseases.

Treg cells are a subset of T lymphocytes that have a key role in the regulation of the immune response and the induction of self-tolerance [43]. They express the surface markers CD4 and CD25 at high levels, as well as a specific Treg marker, the transcription factor FOXP3. The main role of Treg cells is to suppress the immune system, via inhibition of B, $CD4^+$ and $CD8^+$ T, and natural killer cells, and suppression of cytokine and antibody production. The activation of Treg cells is antigen specific, but once activated, these cells are able to exert suppressive effects on other local cells in an antigen-independent manner. In SLE, Treg cell numbers are reduced and their function is impaired. Treg

cells isolated from patients with SLE had reduced migratory ability and a reduced ability to suppress $CD4^+CD25^-$ effector T-cell proliferation [43–45]. The maternal Treg cell population was shown to expand in murine pregnancy [46]. A high proportion of maternal Treg cells was identified within the pregnant uterus, with the highest levels found in the decidua, which is the fulcrum of the maternal–fetal interface [46,47]. Lower levels of Treg cells have been described in decidua obtained from first trimester pregnancies that aborted spontaneously compared with those obtained from elective terminations [48], implying that a reduced Treg cell response is involved in abnormal pregnancy. Pregnancy complications in lupus may thus be the result of an intrinsically dysfunctional Treg cell. This intriguing hypothesis is the subject of ongoing investigation.

Recognition of a lupus flare during pregnancy

The recognition of a lupus flare during pregnancy may be difficult since the signs and symptoms may mimic those of normal pregnancy. Examples of this apply to most organ systems, as tabulated (Table 3) and discussed below.

Table 3. Assessment of lupus flares in pregnancy.

Feature	Findings indicative of a lupus flare	Findings of normal pregnancy that can mimic a flare
Clinical	Active rash of lupus Inflammatory arthritis Lymphadenopathy	Fatigue Arthralgias Bland effusions of knees
	Fever >38°C (not related to infection or drug)	Myalgias Malar and palmar erythema Postpartum hair loss
	Pleuritis	Carpal tunnel syndrome Edema of hands, legs, and face Mild resting dyspnea
	Pericarditis	
ESR	Increased	18–46 mm/h <20 weeks gestation 30–70 mm/h ≥20 weeks gestation [112]
Anemia	Hemoglobin <10.5 g/dl	Hemoglobin >11 g/dl during first 20 weeks gestation Hemoglobin >10.5 g/dl after 20 weeks gestation [113]
Thrombocytopenia	Platelet count <95,000/µl	Mild in approximately 8% [55]
Urinalysis	Hematuria or cellular casts	Rare hematuria from vaginal contamination
Proteinuria	≥300 mg/day	<300 mg/dl
dsDNA antibodies	Rising titers	Negative or stable titers
Complement	≥25% drop	Usually increased

ESR: Erythrocyte sedimentation rate.
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Fatigue is reported by more than 80% of SLE patients, independent of pregnancy, and correlates with fibromyalgia and depression but not SLE disease activity [49]. Its presence during pregnancy has little diagnostic import since this symptom has a weekly prevalence of close to 50% in the third trimester [50].

Melasma affects up to 75% of pregnant women and presents as symmetric hyperpigmentation of the skin on the cheeks, forehead, upper lip, nose and chin (centrofacial pattern); the cheeks and nose (malar pattern); or the ramus of the mandible (mandibular pattern) [51]. By contrast, the lupus malar rash consists of edematous and erythematous plaques that may have some fine scaling on the surface without atrophy. Postpartum telogen effluvium should not be confused with the scarring or nonscarring alopecia that may occur as a manifestation of SLE. Palmar erythema develops during pregnancy as a result of estrogen-induced vasodilatation and may mimic vasculitis.

Musculoskeletal discomfort is expected in pregnancy, the most common symptom being low back pain. Bland knee effusions do occur in normal pregnancy and may be mistaken for an inflammatory arthritis, such as occurs in lupus. Fibromyalgia tends to worsen during pregnancy and in the postpartum period, often leading to prolonged leave from work due to chronic pain [52]. In the absence of signs of joint inflammation (tenderness, swelling and/or effusion), the musculoskeletal symptoms of pregnancy should not be confused with a lupus flare.

Dyspnea during pregnancy is attributed to central effects of progesterone. It should be differentiated from respiratory symptoms suggestive of lupus pleurisy. The neural mechanisms underlying the stimulation of respiration by progesterone are similar to those mediating its reproductive effects [53].

In a normal pregnancy, the maternal blood volume increases by 50%, and the red cell mass increases by 35% [54]. As a result, a mild anemia resulting from hemodilution is present in up to 50% of patients. Hemolytic anemia manifested by a positive Coombs test, low haptoglobin, high reticulocyte count and/or increased lactate dehydrogenase level is a manifestation of lupus. The white blood cell count begins to increase in the first trimester and reaches a plateau at approximately 30 weeks of pregnancy. The normal range for pregnancy is 5000–12,000/mm^3, although values as high as 15,000/mm^3 are not uncommon [54]. This increase is mainly the result of neutrophilia. Lymphopenia, defined as a lymphocyte count <1000/mm, retains its significance in the assessment of lupus flares. The platelet count usually falls during pregnancy. Mild thrombocytopenia (100,000–150,000/mm^3) is present in approximately 8% of normal pregnancies and is of no clinical significance [55]. Before attributing thrombocytopenia to SLE disease activity, several pregnancy-related causes must be excluded, including preeclampsia/eclampsia; hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; abruptio placentae and antiphospholipid antibody syndrome.

During normal pregnancy, there is a 10–50% increase in the level of the complement components, probably as a result of estrogen-driven increased hepatic synthesis [56]. Complement activation is a manifestation of lupus flares during pregnancy; however, total complement levels may remain in the 'normal' range, but below the level seen in uncomplicated non-lupus pregnancies. Hypocomplementemia should be attributed to lupus disease activity in pregnancy when the levels of C3, C4 or CH50 are below the normal range or when levels of C3, C4, or CH50 fall by 25% or more as pregnancy progresses, but remain within the normal range [57]. Anti-dsDNA antibodies are a highly sensitive and specific diagnostic test for lupus. A positive anti-dsDNA test in the second trimester is associated with a higher rate of pregnancy loss and preterm birth [58].

Renal blood flow and the glomerular filtration rate increase by more than 50% during pregnancy to accommodate the increased blood volume, resulting in a decreased serum creatinine level [59]. A serum creatinine level of >0.8 mg/dl and blood urea nitrogen level of >13 mg/dl are indicative of renal impairment in pregnancy [60]. A creatinine level that remains stable throughout pregnancy and does not decrease can also be a sign of renal insufficiency. Proteinuria in amounts of 300 mg/day or less is considered as normal in pregnancy. In women with prior renal damage from lupus nephritis, the degree of urine protein loss may increase as a result of increased renal blood flow. However, a doubling in the amount of the baseline urine protein should prompt further investigation.

The erythrocyte sedimentation rate is a useful marker of disease activity in SLE; however, it normally rises in pregnancy and it has been omitted from all the pregnancy-specific disease activity scales. C-reactive protein levels have not been systematically studied in lupus pregnancies.

Validated measures of lupus disease activity during pregnancy

The established lupus activity scales, for example, the Lupus Activity Index (LAI), the SLE Disease Activity Index (SLEDAI), and the Systemic Lupus Activity Measure (SLAM), were validated with populations that excluded pregnant women and included men. Their shortcomings in distinguishing between physiologic changes seen in pregnancy and true lupus manifestations led to the development of lupus activity scales specific for pregnant women. Adaptations of the SLEDAI, LAI and SLAM for pregnancy were proposed in 1999 and were given the acronyms SLE Pregnancy Disease Activity Index, LAI in Pregnancy (LAI-P) and modified SLAM (mSLAM) [57]. The features of the modified LAI and SLEDAI are shown in Tables 4 & 5, respectively. The LAI-P is a modified version of the LAI created by Ruiz-Irastorza *et al.* and was the first to be validated [61]. Physician's Global Assessment and asthenia were eliminated from the original LAI due to the high prevalence of fatigue and lack of objective measures to discern between asthenia related to lupus and a physiologic change in pregnancy. Asthenia was replaced by fever, a more objective measure. The more severe manifestations, such as CNS disease, could only be scored as 3.0. By contrast, anti-DNA antibodies and complement levels score a maximum of 2.0, in order to eliminate flares based only on laboratory findings (see Table 4). The renal system was given added weight, because 'renal' and 'proteinuria' were considered separately. LAI-P was validated in a study of 38 pregnant lupus patients and had a sensitivity and specificity >90% compared with Physician's Global Assessment as the gold standard [61].

SLEPDAI is a revision of SLEDAI, a lupus activity scale comprised of 24 descriptors, 15 of which were modified in order to optimize differentiation of lupus activity signs and symptoms from changes related to pregnancy. Importantly, it included preeclampsia/eclampsia as a differential diagnosis of several of the CNS descriptors including seizure, headache and cerebral infarction. HELLP syndrome was added as a differential diagnosis of the descriptor of thrombocytopenia (see Table 4). SLEPDAI has not been formally validated, although it has been used in a study assessing the effect of hydroxychloroquine on SLE exacerbations in pregnant women [62].

Table 4. Lupus Activity Index in Pregnancy.

Group	Parameter	Point values				Values to calculate LAI-P
1	Fever	0	1			(a) Mean
	Rash	0		2		
	Arthritis	0		2	3	
	Serositis	0	1	2	3	
2	Neurologic	0			3	(b) Maximum
	Renal	0		2	3	
	Lung	0			3	
	Hematologic	0	1	2	3	
	Vasculitis	0			3	
	Myositis	0			3	
3	Prednisone, NSAID, HCQ	0	1	2	3	(c) Mean
	Immunosuppressor	0			3	
4	Proteinuria	0	1	2	3	(d) Mean
	Anti-DNA	0	1	2		
	C3, C4	0	1	2		

Point value of LAI-P = (a + b + c + d)/4.
HCQ: Hydroxychloroquine; LAI-P: Lupus Activity Index in Pregnancy.

Differentiation of preeclampsia from a lupus nephritis flare

The accepted definition of preeclampsia includes a blood pressure >140/90 mmHg and proteinuria >300 mg in a 24-h urine specimen detected for the first time after 20 weeks of gestation. The differentiation of preeclampsia from active lupus nephritis is often difficult, since both entities may present with increasing proteinuria, hypertension, lower extremity edema, deterioration in renal function,

Table 5. Modification of SELENA–SLEDAI for assessment of systemic lupus erythematosus disease activity in pregnancy.

SELENA–SLEDAI		SLEPDAI	Comment
Descriptor	*Score*	*Modified for pregnancy*	
Seizure	8	Yes	r/o eclampsia
Psychosis	8	No	
Organic brain syndrome	8	No	
Visual disturbance	8	Yes	Hypertension
Cranial nerve disorder	8	Yes	r/o Bell's palsy
Lupus headache	8	Yes	r/o eclampsia, preeclampsia
CVA	8	Yes	r/o eclampsia
Vasculitis	8	Yes	Consider palmar erythema
Arthritis	4	Yes	Consider bland knee effusions
Myositis	4	No	
Urinary casts	4	No	
Hematuria	4	Yes	r/o cystitis and vaginal bleeding reflective of placental problems
Proteinuria	4	Yes	r/o eclampsia
Pyuria	4	Yes	r/o infection
Rash	2	Yes	Consider chloasma
Alopecia	2	Yes	Consider normal postpartum alopecia
Mucosal ulcers	2	No	
Pleurisy	2	Yes	Hyperventilation secondary to progesterone, dyspnea secondary to enlarging uterus
Pericarditis	2	No	
Low complement	2	Yes	Complements normally rise during pregnancy
Increased DNA binding	2	No	
Fever	1	No	
Thrombocytopenia	1	Yes	r/o preeclampsia, HELLP, incidental thrombocytopenia of pregnancy
Leukopenia	1	Yes	Consider normal rise of leukocyte count during pregnancy

Total score (sum of weights next to descriptors marked present).
CVA: Cerebrovascular accident; HELLP: Hemolysis elevated liver enzymes low platelet count; r/o: Rule out; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.
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and thrombocytopenia. The two conditions may also coexist. The early recognition of preeclampsia may also be hindered if a pregnant woman with lupus has hypertension and/or proteinuria in the first half of pregnancy. In these situations, diagnostic criteria for superimposed preeclampsia established by the American College of Obstetricians and Gynecologists are applicable. They include new-onset proteinuria in a woman with hypertension before 20 weeks of gestation, a sudden increase in proteinuria if already present in early gestation, a sudden increase in hypertension, or the development of HELLP syndrome [20]. The development of a headache, scotomata or epigastric pain in a pregnant woman with chronic hypertension should also raise concern for superimposed preeclampsia.

Features of preeclampsia that help to distinguish it from active lupus nephritis are summarized in (Table 6). These include a serum uric acid >5.5 mg/dl, a urine calcium level of <195 mg/day, and rising liver enzyme levels. Features of active lupus nephritis include a rise in dsDNA antibody titer, low or dropping complement levels (see earlier), increased lupus activity in other organs, and an active urinary sediment. Complement-split products, such as C3a, may also indicate a flare, but their measurement is not routinely available. A renal biopsy may be needed to define the presence of active lupus glomerulonephritis [63]; however, the increased risk of bleeding following such biopsies in pregnancy is a consideration. On occasion, this diagnostic dilemma demands resolution with delivery of the fetus or a trial of empiric therapy.

Doppler ultrasound of the uterine and umbilical arteries allows assessment of the perfusion of the uteroplacental and fetoplacental circulations, respectively. In 21 pregnancies of mothers with SLE and/or antiphospholipid antibody syndrome, Benifla *et al.* found that abnormal uterine blood flow velocity waveforms on Doppler examinations performed between 20 and 30 weeks of gestation

Table 6. Differentiation of active lupus nephritis from preeclampsia.

Clinical and laboratory features	Active lupus nephritis	Preeclampsia
Hypertension	Onset before 20 weeks	Onset after 20 weeks
Proteinuria	≥300 mg/day	≥300 mg/dl
Urinary sediment	Active	Inactive
Uric acid	≤5.5 mg/dl	>5.5 mg/dl
DNA antibody levels	Rising	Stable or negative
24 h urine calcium	≥195 mg/day	<195 mg/day
Complement levels	≥25% drop	Normal

Reproduced with permission from [114].

predicted later adverse fetal and neonatal events [64]. In a prospective study of 116 pregnant French SLE patients with a second trimester Doppler ultrasound examination, the only predictor of adverse pregnancy outcome by multivariate analysis was uterine artery notching (OR: 13.84). A normal umbilical artery waveform, the absence of a notched uterine artery waveform and of IUGR had a positive predictive value of close to 100% for a good pregnancy outcome [65]. In a study of 26 pregnant lupus patients who underwent uterine–umbilical artery Doppler velocimetry, Guzman *et al.* showed that all patients with normal flow velocity in both vessels had normal outcomes [66]. Four patients with reduced flow velocity in both vessels had the poorest outcome, with all fetuses being small for gestational age and three dying in the perinatal period. Despite an excellent negative predictive value, uterine–umbilical artery Doppler velocimetry has a relatively poor positive predictive ability when used alone [67].

Placental factors have been studied as possible predictors for preeclampsia. These include: ADAM12, a member of the ADAM protein family [68], present in the syncytiotrophoblast and involved in placental growth and development; free β-subunit of human chorionic gonadotropin, involved in the maintenance of the decidual spiral arteries and the vascular supply of the placenta [69]; inhibin A and activin A, which regulate hCG levels during pregnancy [70]; PP13, which plays a major role in the implantation of the blastocyst [71]; angiogenic factors, including antiangiogenic factors such as sFlt-1 and sEng secreted into the maternal circulation by a poorly implanted and ischemic placenta, and proangiogenic factors, such as PlGF and VEGF [72] and PAPP-A, which regulates the bioavailability of free IGF at the placenta–decidua interface during human implantation [73]. In a systematic review assessing the predictive potential of first trimester serum markers and of uterine artery Doppler findings, Kuc *et al.* determined that the screening potential for each single serum marker was limited by a detection rate of approximately 10%, making them unsuitable for clinical practice [74]. However, a combination of inhibin A, PlGF, PAPP-A, uterine artery Doppler findings, and maternal characteristics (e.g., maternal age, BMI and ethnicity) increased the detection rates to almost 100% [75]. Unfortunately, most of the studies assessing combination markers have been underpowered with a very low number of preeclampsia patients. Although several studies assessed the predictive value of uterine artery Doppler studies for late pregnancy outcomes in SLE [65,66], the predictive value of a combination of serum markers and Doppler findings in SLE remains unknown.

Table 7. Differentiation of microangiopathies in lupus pregnancy.

Features	HELLP	AFLP	TTP	CAPS
Fever	-	++	+++	+
Jaundice	+	+++++	+	+
Lung involvement	-	-	-	++++
Elevated liver enzymes	+++++	+++++	+++	+
Impaired renal function	+++	+++++	++	++++
Elevated bilirubin	+++	+++++	+++++	+
Hepatic infarcts	+	-	-	+
Hypertension	++++	++	+++	+
DIC	+++	++++	-	+
Microangiopathic hemolytic anemia	+++++	+	+++++	+
Thrombocytopenia	+++	-	+	+++
Hypoglycemia	-	+++	-	-
ADAMTS13 <5%	-	-	+++++	-

+: 0–20% approximate frequency; ++: 20–40%; +++: 40–60%; ++++: 60–80%; +++++: 80–100%; -: Does not occur; ADAMTS: A disintegrin and metalloproteinase with thrombospondin type-1 motifs; AFLP: Acute fatty liver of pregnancy; CAPS: Catastrophic antiphospholipid antibody syndrome; DIC: Disseminated intravascular coagulation; HELLP: Hemolysis, elevated liver enzymes and low platelets; TTP: Thrombotic thrombocytopenic purpura.
Adapted from [84,103,115,116].

Microangiopathies in pregnancy

Different types of microangiopathies can occur in pregnancy and may mimic or overlap with certain types of lupus flares (Table 7). The differentiation of these microangiopathies in pregnancy is critical, since the management will vary depending on the type (see later).

The HELLP syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia and liver injury in the setting of pregnancy, with a peak frequency between the 27th and 37th week of gestation. It develops postpartum in approximately a third of cases. It has a prevalence of 0.5–0.9% in all pregnancies and 10–20% in cases of severe preeclampsia [76]. The Tennessee Classification System diagnostic criteria for HELLP are hemolysis with increased lactate dehydrogenase (>600 U/l), aspartate aminotransferase; (≥70 U/l), and platelets <100,000/μl [77]. The prothrombin time remains normal unless there is evidence of disseminated intravascular coagulation or severe liver injury.

Acute fatty liver of pregnancy is a microvesicular fatty infiltration of hepatocytes that develops during the second half of pregnancy. It is a rare complication and resembles Reye's syndrome in its presentation with vomiting, hypoglycemia, lactic acidosis, hyperammonemia, elevated hepatic transaminases, conjugated hyperbilirubinemia and evidence of disseminated intravascular coagulation [78]. Hypertension, proteinuria and

thrombocytopenia are present in some cases, raising concern for preeclampsia and/or the HELLP syndrome. However, the finding of hypoglycemia points strongly to acute fatty liver as the correct diagnosis.

Thrombotic thrombocytopenic purpura (TTP) is a syndrome of microangiopathic hemolytic anemia, severe thrombocytopenia, fever, CNS and renal disease. Unfortunately, the presenting signs and symptoms are nonspecific. Fever is uncommon and many patients have no neurologic abnormalities on presentation [79]. In a patient with hemolytic anemia and thrombocytopenia, support for a diagnosis of TTP includes an elevated unconjugated bilirubin level, marked elevation of lactate dehydrogenase, a negative Coombs test, schistocytes on peripheral blood smear and a normal prothrombin time [80]. The diagnostic value of ADAMTS13 deficiency has been a matter of heated debate over the years. Although invariably present in the inherited forms of TTP, low ADAMTS13 activity has a reported frequency of 18–72% in acquired TTP [79,81]. TTP may occur rarely in conjunction with systemic lupus [82]. This is usually associated with severe deficiency of ADAMTS13 activity and with the presence of anti-ADAMTS13 IgG antibodies [83].

The rare entity of catastrophic antiphospholipid antibody syndrome (CAPS) is characterized by an acute thrombotic microangiopathy affecting the small vessels of at least three organ systems. In one case series of CAPS occurring in association with pregnancy, seven of 15 patients had systemic lupus. The CAPS occurred during pregnancy in seven patients, postpartum in six patients and 2 days after a dilatation and curettage for fetal death at 18 weeks of gestation in one patient [84]. The kidneys, lungs and brain were the most commonly affected organs. The specific pregnancy-related manifestations of CAPS included placental thrombosis, myometrial thrombotic angiopathy and pelvic vein thrombosis [84].

Hepatic infarction is a rare complication that deserves special mention. The diagnosis should be considered in any pregnant woman presenting with right upper quadrant abdominal pain in the setting of preeclampsia and complete or incomplete HELLP. Fever, significant leukocytosis, jaundice, nausea and vomiting may be present. Underlying antiphospholipid antibody syndrome always needs to be considered. The diagnosis may be confirmed with Doppler ultrasound, but computed tomography or MRI may be indicated if the ultrasound is negative. Termination of pregnancy is obligatory in this setting. The role of corticosteroids is not clear and the use of heparin poses risks of major hemorrhage or rupture of the liver and thus must be monitored closely [85].

Therapy of lupus flares during pregnancy

Management of lupus flares in pregnancy must be individualized and take into account the severity and type of organ involvement. The use of NSAIDs after 20 weeks of pregnancy is avoided since it has been associated with reversible oligohydramnios, premature closure of the patent ductus arteriosus, gastrointestinal bleeding or perforation, increased risk of necrotizing enterocolitis, intracranial bleeding, pulmonary hypertension and prolongation of labor [86]. Hydroxychloroquine is typically used to treat the arthritis and skin manifestations of lupus, although additional benefits are being realized. Its safety and ability to decrease flare rates during pregnancy has prompted the recommendation to continue its use throughout pregnancy, particularly if it was being used prior to conception [62]. A recent case series suggested that in mothers with anti-SSA/Ro and/or anti-SSB/La antibodies and a previous child with neonatal lupus, exposure to hydroxychloroquine during a subsequent pregnancy may decrease the risk of congenital heart block [87]. An interventional study is in progress to confirm this observation (Congenital Heart Block with Hydroxychloroquine study).

When symptoms and signs of lupus are not adequately controlled with acetaminophen and hydroxychloroquine, corticosteroids are generally required. More aggressive therapy is indicated for anemia (hemoglobin <8 g/dl), sustained fever (>38.5°C), and low serum albumin levels (<3 g/dl), since these findings threaten the developing fetus [88]. Prednisone is inactivated by the placenta and is thus the preferred corticosteroid for use during pregnancy. The fluorinated glucocorticoids, dexamethasone and betamethasone, cross the placenta easily and should be avoided unless there is a need to induce fetal lung maturation before preterm delivery. These steroids are also given in an effort to treat early stages of *in utero* fetal heart block, but proof of their efficacy has not been established [89]. Doses of prednisone less than 20 mg/day are used to treat mild lupus activity and higher doses, including pulse intravenous methylprednisolone, are used to treat more severe lupus activity [90]. A twofold increased risk for cleft lip or palate has been linked with systemic corticosteroid use in the first trimester, although the risk of these birth defects remains low (~2/1000 babies with corticosteroid exposure) [91,92]. Adverse effects of corticosteroids in pregnancy include hypertension, osteopenia, osteonecrosis, susceptibility to infection and an increased risk of gestational diabetes [86].

A second-line agent may be used in conjunction with prednisone for the long-term management of moderate to severe lupus activity. This second-line agent may provide a 'steroid-sparing' effect, facilitating the tapering of the prednisone to a lower dose. Azathioprine at a daily dose not exceeding 2 mg/kg is the preferred second-line agent, although its use during pregnancy has been associated with IUGR and an increased rate of pregnancy loss [86,93,94].

Cyclosporine can be used to treat renal disease during pregnancy. It is safe for the fetus, but poses risks of maternal nephrotoxicity. Tacrolimus, a calcineurin inhibitor that is 100 times more potent *in vitro* compared with cyclosporine, has recently been found to be a safe and effective treatment for lupus nephritis. In a trial of 18 patients with class V lupus nephritis, induction treatment with tacrolimus and prednisone for 6 months was compared with historical controls treated with oral cyclophosphamide induction therapy [95]. Tacrolimus proved to be safe and effective and resulted in faster resolution of proteinuria and a lower risk of lupus flare within 1 year when compared with cyclophosphamide. There are few data concerning the use of calcineurin inhibitors in pregnancy. A recent case report describes a patient with class II lupus nephritis who failed trials of mycophenolate

and azathioprine only to have a renal flare in the 10th week of her pregnancy [96]. She received tacrolimus 3 mg twice daily as induction therapy and enjoyed a complete remission with no adverse effects for the mother or child. On the other hand, there is extensive experience with tacrolimus in pregnant transplant patients and many successful pregnancies have been reported in patients with various solid organ transplantations, without any increased risk of congenital abnormalities compared with the general population [97]. Tacrolimus inhibits T-cell receptor stimulation-induced cell division of conventional $CD4^+$ T cells, while promoting the cell division of $CD4^+$ Treg cells; from a pharmacodynamics standpoint, it is thus intriguing to contemplate the efficacy of tacrolimus in pregnant patients, since Treg cells may play a crucial role in the genesis of pregnancy complications in lupus.

Intravenous immunoglobulin has an accepted indication for the treatment of thrombocytopenia during pregnancy. No fetal adverse effects of intravenous immunoglobulin have been reported [86].

Mycophenolate has been associated with the development of fetal anomalies and should be avoided during pregnancy [98,99]. Cyclophosphamide is reserved for the treatment of severe manifestations of lupus, but poses significant risks to the fetus. These include fetal malformation when used in the first trimester and growth retardation and suppression of fetal hematopoiesis when used in the second and third trimesters [98]. Its use is appropriate when it is understood that the fetus may not survive without treatment of the mother.

The safety of belimumab in pregnancy has not been studied, but animal data are encouraging since teratogenic effects were not identified. The current US FDA recommendations are to discontinue belimumab 4 months prior to anticipated conception. Rituximab is a chimeric monoclonal IgG antibody directed against the CD20 antigen on B lymphocytes. It is detectable in serum 3–6 months after completion of the treatment infusions. IgG molecules are known to cross the placenta and rituximab has been detected in the serum of infants exposed *in utero*. To date, studies of children who were exposed to rituximab early in pregnancy have not demonstrated any adverse outcomes. By contrast, second- and third-trimester exposure causes B-cell depletion in the fetus with unknown long-term effects [100]. Although few congenital malformations or neonatal infections were seen among exposed neonates, women should continue to be counseled to avoid pregnancy for 6–12 months after rituximab exposure [101,102].

The management of microangiopathy in a lupus pregnancy is dependent on diagnosis and gestational age. Thus, immediate delivery is the treatment of choice for the HELLP syndrome at 34 weeks of gestation [77]. At 27–34 weeks of gestation, an initial attempt should be made to stabilize the patient in a tertiary care unit with close maternal and fetal surveillance, thereby allowing the administration of corticosteroids (e.g., two doses of 12 mg betamethasone 24 h apart or 6 mg of dexamethasone 12 h apart) to promote fetal lung maturation. However, delivery should occur within 48 h. Prior to 27 weeks of gestation, the patient may be managed expectantly for more than 48–72 h, but immediate delivery is indicated if the condition of the mother or fetus deteriorates. Corticosteroids may serve to increase the platelet count and allow vaginal delivery but do not appear to reduce maternal morbidity in the HELLP syndrome. Acute fatty liver of pregnancy is managed with delivery as soon as the patient is stabilized; the latter generally involves the administration of fresh frozen plasma and other blood products for the bleeding disorder and/or severe coagulopathies, and aggressive correction of hypoglycemia and electrolyte abnormalities [103]. TTP is treated with plasma exchange or plasmapheresis [104]. CAPS during pregnancy is managed with heparin anticoagulation and prompt delivery. An attempt to promote fetal lung maturation with corticosteroids prior to delivery should be made if the patient's condition allows. High-dose corticosteroids, intravenous immunoglobulin therapy, and plasma exchange are adjunctive treatments that were often used in the reported cases of this rare entity [84].

Expert commentary

Successful pregnancies can now be realized for the majority of women with SLE. However, the management of such pregnancies requires careful preconception planning and advanced adjustment of medications. The best outcomes for a lupus pregnancy occur when the disease has been in remission for at least 6 months prior to conception. Unfortunately, access to prenatal care and family planning is inadequate for many young women with lupus, particularly if they are of lower socioeconomic status. This leads to continued morbidity and mortality for both the mother and fetus in lupus pregnancies. Ensuring access to basic prenatal care and to the advancements in management of SLE pregnancies is the foremost task for healthcare providers and policy makers.

Five-year view

Although the improvement in SLE pregnancy outcomes over the years is evident, there remains a large gap between the better understanding of the pathophysiological mechanisms leading to complications and the available clinical markers for predicting, measuring and treating these complications. The bench-to-bedside translation of new discoveries related to genetic markers and the implementation of an optimal combination of serum markers and imaging modalities may allow us to identify high-risk SLE patients with precision and implement early therapeutic measures. A better understanding of the pharmacodynamics of available drugs may also allow us to use targeted therapy for specific lupus complications.

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Key issues

- The immunological and hormonal changes that occur in pregnancy may lead to increased lupus activity.
- The majority of lupus pregnancies can be managed successfully with minimal maternal or fetal morbidity or mortality.
- Women in sustained lupus remission prior to conception have a low rate of pregnancy flares.
- The most common organs affected in lupus flares during pregnancy are the skin, kidneys, blood and joints.
- Pregnancy complications in lupus may be the result of dysfunctional Treg cells.
- Recognition of a lupus flare during pregnancy may be difficult since the signs and symptoms may mimic those of normal pregnancy.
- The Lupus Activity Index in Pregnancy is a validated, pregnancy-specific lupus activity scale.
- Careful differentiation between lupus flares and mimics, including preeclampsia, other hypertensive pregnancy disorders, and microangiopathies is necessary.
- Maternal characteristics, genetic and serum markers and uterine artery Doppler may help identify women at high risk for poor pregnancy outcomes.
- Hydroxychloroquine is safe and beneficial when continued during a lupus pregnancy.

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Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing a 30-year-old woman with a 5-year history of systemic lupus erythematosus (SLE). Her last menstrual period was 3 months ago, and a urine pregnancy test is positive. She is concerned regarding how SLE will affect her pregnancy. What can you tell her?

- ☐ **A** Rates of pregnancy loss among women with SLE have remained stagnant over the past 4 decades
- ☐ **B** SLE is associated with higher risks for preterm labor, preeclampsia, and delivery via cesarean section
- ☐ **C** Increased serum complement levels indicate a high risk for first-trimester fetal loss
- ☐ **D** The degree of control of SLE in the pre-conception period does not generally affect pregnancy outcomes

2. What should you consider regarding the activity of SLE during pregnancy?

- ☐ **A** SLE flares are most common during the third trimester
- ☐ **B** SLE flares during pregnancy are more likely to involve joints
- ☐ **C** SLE flares during pregnancy are more likely to involve the kidneys
- ☐ **D** The presence of proteinuria at levels of more than 300 mg/dl differentiates preeclampsia from acute lupus nephritis

3. The patient initiates prenatal care and then presents 4 weeks later to your clinic with a 3-day history of malaise and nausea with vomiting. What should you consider regarding recognizing lupus flares during pregnancy?

- ☐ **A** The presence of fatigue usually indicates a lupus flare
- ☐ **B** A white blood cell (WBC) count of 15,000/mm^3 probably indicates a lupus flare
- ☐ **C** Serum creatinine levels in excess of 0.8 mg/dl are indicative of renal impairment in pregnancy
- ☐ **D** The erythrocyte sedimentation rate is the easiest means to follow SLE disease activity during pregnancy

4. The patient is confirmed to have a lupus flare which involves her skin and joints. What is the first-line therapy for most pregnant women with lupus flares?

- ☐ **A** Mycophenolate
- ☐ **B** Prednisone
- ☐ **C** Cyclosporine
- ☐ **D** Hydroxychloroquine