

**OBSTETRIC EMERGENCIES**

# Management of lupus flare

If disease is handled quickly, mother and fetus usually fare well, but loss of mother, fetus, or both is not always avoidable

It was not that long ago that systemic lupus erythematosus (SLE) was considered a contraindication to pregnancy. With improved understanding and improved treatment options, many women with SLE have successful pregnancies.

Still, lupus flare during pregnancy is a medical and obstetric emergency, and a persistent obstetric dilemma. The most difficult dilemma is how to differentiate a lupus flare from preeclampsia, as both may present with worsening blood pressure, proteinuria and deteriorating renal function, and edema.<sup>1</sup>

If anticipated and handled quickly, most outcomes will be good for mother and fetus, but occasional severe consequences of lupus flare resulting in loss of mother, fetus, or both, are not always avoidable.

**90% of lupus cases are in reproductive-age women**

SLE is an autoimmune disease that affects virtually all organ systems. Specific clinical and laboratory criteria must be met to establish the diagnosis. About 90% of all cases are in women in the reproductive age range, with an overrepresentation of African Americans. The overall prevalence of lupus is approximately 15 to 50 per 100,000 population (both sexes, all ages).

**Counsel the patient, gauge the risks**

The most important first step is the preconception visit. While early prenatal care is better than late presentation, the best option is a preconception visit so that the relative risks of pregnancy may be assessed and discussed, and alterations to medication regimens can be made prior to establishment of a pregnancy (TABLE 1).<sup>2</sup>

As lupus patients are at increased risk for early pregnancy loss, the preconception visit may also allow for identification of risk factors and risk assessment. A recent study<sup>3</sup> proposed the acronym **PATH** to help identify high-risk patients:

- Proteinuria
- Antiphospholipid syndrome
- Thrombocytopenia
- Hypertension

**Disease quiescence is not an infallible sign**

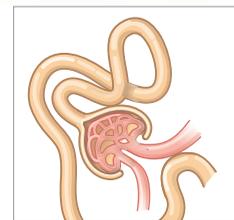
One of the better indicators of a favorable prognosis for pregnancy is disease quiescence for at least 6 months, and preferably more than 12 months, prior to conception. A number of factors go into the definition of “disease quiescence” including blood pressure control, need for immunosuppressive medication, renal function, and overall physician global assessment,

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to name but a few, and these factors will be briefly reviewed.

## Renal disease and hypertension

### Nephritis

Patients with SLE not infrequently have hypertension secondary to renal involvement, specifically lupus nephritis. Nephritis is generally the most serious of lupus manifestations, and if not aggressively treated can lead to nephrotic syndrome, edema and end-stage renal disease in more than 50% of patients within 2 to 3 years.<sup>4</sup> Patients with this complication, especially in the setting of proliferative glomerulonephritis, have a poorer prognosis for pregnancy.

**Accelerated atherosclerotic vascular disease** may also affect these patients—in addition to nephritis—and may herald poor placental function and fetal growth.

### Hypertension

When there is coexisting hypertension, antihypertensive agents that are safe for use in pregnancy are preferred, such as beta-blockers, calcium channel blockers, and alpha methyl dopa. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be avoided during the second and third trimester due to adverse effects on fetal renal function.

## Diagnosis of antiphospholipid syndrome

Patients with SLE may have associated antiphospholipid antibodies. Screening tests such as antinuclear antibodies (ANA) and activated partial thromboplastin times (aPTT) are not very reliable and have relatively poor positive predictive value, although in the case of ANA, when the diagnosis of lupus is suspected, repetitive negative ANA titers make SLE unlikely. Anti-double stranded DNA is quite specific to SLE, and elevations in the Anti-ds-

**TABLE 1**

### Factors that increase the likelihood of a good outcome

- **Disease quiescence** for more than 6 months prior to conception
- **Normal renal function** (creatinine less than 0.7 mg/dL, but not more than 1.2 mg/dL)
- **Normal preconception blood pressure**, preferably without the need for antihypertensive medication
- **Minimal doses or no need for immunosuppressive therapy** (prednisone less than or equal to 10 mg/day)
- **Absence of antiphospholipid antibodies/antiphospholipid syndrome**
- **No history of adverse pregnancy outcome**
- **No history of thrombosis** (not a factor specific to lupus)

DNA titers correlate well with SLE disease activity, and can be helpful in making the diagnosis of a lupus flare.

Other antibodies such as Anti-Ro (SS-A) and Anti-La (SS-B) may be useful for predicting and managing for neonatal lupus syndromes, but are not very useful in maternal management.

Additional tests for anticardiolipin, lupus anticoagulant (Russell viper venom test), and beta-2-glycoprotein are also of use. **Diagnosis of APLS** requires positive serologies (at least twice, separated by a minimum of 2 weeks), thrombosis, and/or recurrent early pregnancy loss.

## Does pregnancy bring on lupus flare?

Whether or not pregnancy increases the incidence of lupus flare is a continuing controversy, stemming from variable definitions of “flare.” Universally accepted criteria have been lacking in published studies.<sup>5</sup> Consensus indicates, however, that lupus flares are more common in pregnancy than in nonpregnant controls.

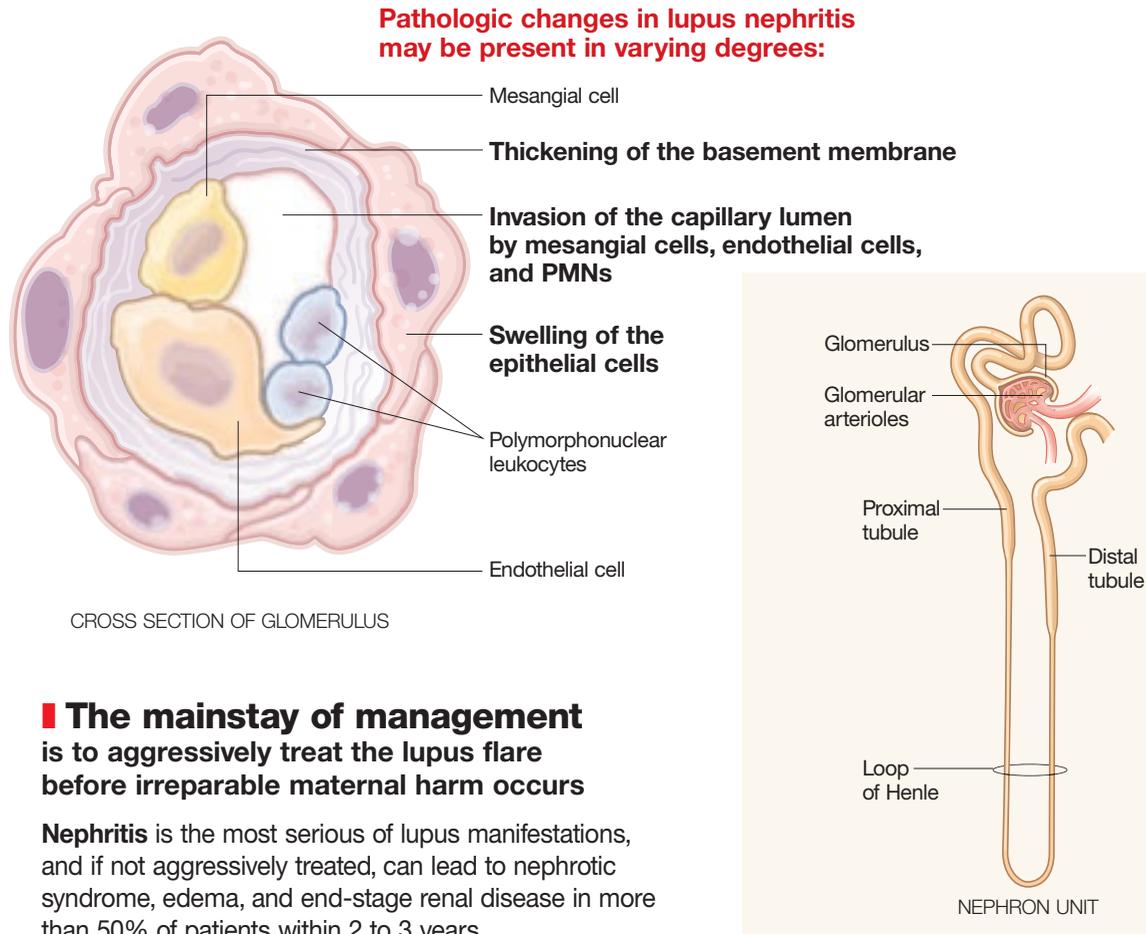
Some studies suggest that SLE flares are more common in the second and third trimesters, but the data are not clear on this point.<sup>6</sup> This variability is due in part to

### **FAST TRACK**

**It is impossible to predict who will have a lupus flare, when, and to what level of severity**

## How lupus damages kidneys

Changes in glomerular capillaries in lupus renal disease compromise kidney function



**■ The mainstay of management is to aggressively treat the lupus flare before irreparable maternal harm occurs**

**Nephritis** is the most serious of lupus manifestations, and if not aggressively treated, can lead to nephrotic syndrome, edema, and end-stage renal disease in more than 50% of patients within 2 to 3 years

IMAGE: RICH LAROCCO

differences in disease activity of the patients when they entered the studies.

One may conclude that for any given patient it is impossible to accurately predict whether she will experience a lupus flare, and if she does, when it will occur, and to what level of severity it will rise.

**Potential adverse outcomes**

Predicting who will have a lupus flare and its degree of severity may be difficult if not impossible, but there is little doubt that a significant percentage of women with SLE will experience a flare of some degree. How a lupus flare will affect the pregnan-

cy is uncertain, as well. SLE activity in pregnancy has been linked to adverse outcomes ranging from increased risk of miscarriage to preterm delivery.

**■ Diagnosis and initial management**

**Preventive treatments**

**Steroids.** SLE flares being somewhat more common in pregnancy than in the non-pregnant patient has led to the belief in some centers that prophylactic administration of steroids to prevent flares would

**TABLE 2**

**Clinical features of preeclampsia vs lupus flare\***

FEATURE	PREECLAMPSIA	LUPUS FLARE
Hypertension	Present	Present
Proteinuria	Present	Present
Edema	Present	Present
Malar rash	Absent	Present
Arthritis	Absent	Present
Photophobia	Absent	Present
Oral ulcers	Absent	Present
Serositis	Absent	Present
Seizures	Present	Present

\*Denoting presence or absence does not suggest absolute presence or absence, but rather, the likely compatibility with the diagnosis.

**TABLE 3**

**Tests that help tell lupus flare from preeclampsia**

TEST	PREECLAMPSIA	LUPUS FLARE
PTT	Usually normal	May be abnormal
Platelet count	Normal or reduced	Normal or reduced
Urinalysis	Normal sediment	Active sediment
ANA	Usually negative	Usually positive
Anti-ds-DNA	Usually negative	Usually positive
AST	May be abnormal	May be abnormal
ALT	May be abnormal	May be abnormal
Lupus anticoagulant	Negative	May be positive
Hemolysis	May be present	Usually absent
Complement levels	Usually normal	Usually reduced
WBC	Increased	Decreased
SFlt-1*	Increased	Normal

\*Investigational and not widely available for clinical use.

have beneficial pregnancy effects. To date, however, no conclusive evidence supports this approach. In fact, steroid use in particular has been associated in some series with higher rates of premature rupture of membranes (both term and preterm), preeclampsia, and gestational diabetes.

**Hydroxychloroquine.** It has been suggested that SLE patients whose disease has been controlled with hydroxychloroquine need not discontinue this therapy due to the pregnancy.

The risks of this agent in pregnancy—which are not thought to be significant—are far outweighed by the potential maternal and fetal benefits of averting a lupus flare.

**■ The differential diagnosis**

It is imperative, before starting a management strategy, to determine if in fact a lupus flare is the correct diagnosis. Many features of a lupus flare can be confused with features of normal pregnancy, or pregnancy associated complications such as preeclampsia (TABLE 2). The differential diagnosis includes most commonly preeclampsia, but diagnoses such as immune thrombocytopenia, poststreptococcal glomerulonephritis, and hemolytic-uremic syndrome must also be considered.

**Is it lupus flare or preeclampsia?**

The most frequent cause for uncertainty is whether the diagnosis is lupus flare or preeclampsia. It is important to find their distinguishing features, because therapy for these 2 conditions is radically different. **A few easy tests** can help (TABLE 3), but the most important are:

- **positive ANA screen,**
- **active urinary sediment,**
- **hypocomplementemia** (C3, C4, or CH 50—the latter is an assay of total serum hemolytic complement), and
- **high titers of anti-ds-DNA.**

Additional tests for anticardiolipin antibody, anti-Ro and anti-La, and lupus anticoagulant may be of some prognostic importance, but do not help differentiate a lupus flare from other similar entities.<sup>7</sup>

**■ Aggressive drug therapy is imperative**

Management of lupus flare depends on aggressive drug therapy. The choice of therapy is determined by whether the patient is currently on an immunosuppressive regimen, and if so, the types and doses of medications, and whether this is her first

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## Without warning, a catastrophe

Even a healthy lupus patient who fulfills all the accepted criteria for a safe pregnancy can take a disastrous turn

**A** 28-year-old G0 with SLE since age 11 presented for preconception consultation. She was on no medications, with normal blood pressure and no evidence of disease activity for more than 2 years. Physical examination and laboratory findings were normal, including serum creatinine 0.7 mg/dL; less than 30 mg protein in a 24-hour urine collection; creatinine clearance 110 mL/min; and lupus anticoagulant, anti-cardiolipin antibodies, anti-Ro, and anti-La were negative.

### Green light

One year later, she returned for follow-up and to inform her obstetrician that she was getting married and wished to conceive. She had had no SLE activity since her last visit. Repeat laboratory studies were unchanged. She was given medical clearance to attempt conception, and told that she met all the criteria that would make her a suitable candidate for pregnancy.

### 7 weeks All findings normal

Three months later, a single intrauterine gestation of approximately 7 weeks was confirmed. Laboratory studies and physical examination were normal, and she reported no SLE-related symptoms.

### 11 weeks Lupus flare

Four weeks later, at her next prenatal visit, a 3+ proteinuria and blood pressure of 140/90 mm Hg were noted. Her rheumatologist made a diagnosis of lupus flare with probable nephritis. Oral prednisone was begun, with rapid taper. Clinical response was good. She remained on prednisone, 10 mg/day.

### 14 weeks Recurrence

A recurrence of lupus flare with probable nephritis was diagnosed and her oral prednisone dose was increased. One week later the patient seemed to worsen. She was admitted for steroid pulse therapy. Initially, she improved, but then continued to worsen.

### 16 weeks Cyclophosphamide therapy

After counseling, she was begun on cyclophosphamide, but her condition continued to deteriorate. Renal function worsened and the patient, now with nephrotic proteinuria, was profoundly edematous and hypoalbuminemic with a rising serum creatinine.

### 18 weeks Dilatation and evacuation

Ultrasound evaluation of the fetus revealed evidence of early growth restriction. After much discussion, the patient underwent dilatation and evacuation.

### Cerebral infarct and anticoagulation

Her lupus flare did not abate. More aggressive medical therapy ensued. Transfer to the intensive care unit with intubation was necessary. She subsequently had an ischemic cerebral infarct requiring anticoagulation.

### The next 7 weeks Lupus remission

Over the next several weeks, the patient improved. She had some residual sequelae from the cerebral infarct, but was doing well, with her lupus flare in remission. She was responding well to rehabilitation therapy.

### Fatal cerebrovascular accident

One day before anticipated discharge to home, she had a massive cerebrovascular accident and died.

### A vivid reminder

This case vividly illustrates the difficulties we must be prepared to manage in lupus pregnancies.

**The foremost concern** is that even the best candidates for pregnancy can have unfavorable outcomes when this highly unpredictable disease flares.

**These women can become severely ill.** Ideally, their care should be provided at a facility where expertise in maternal-fetal medicine, anesthesiology, rheumatology, neonatology, and critical care medicine can be readily mobilized to deal with the occasionally catastrophic complications. Even with all of this expertise available, maternal and fetal mortality will not be preventable in all cases.

**Pregnancy termination** does not necessarily result in amelioration of the lupus flare or its sequelae.

**Patients with SLE must be informed** of the unpredictability of this disease during pregnancy. The entire family, where appropriate and desired, should be included in the information-sharing process.

**A team approach**, both pre- and postconception, will help to maximize (but not guarantee) the likelihood of a successful outcome for mother and child.

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flare during the pregnancy.

**The usual initial therapy** is glucocorticoids, or the so-called steroid “pulses,” typically consisting of very high doses of steroids administered either orally or intravenously over a 3-day period. This strategy has had some success in ameliorating lupus flares, particularly lupus nephritis.

**Dosage.** Methylprednisolone, 1,000 mg/day intravenously, for 3 days followed by oral prednisone, 0.5 to 1.0 mg/kg per day, provides better survival than lower steroid doses in patients with diffuse proliferative glomerulonephritis.

The intravenous route is preferred because of its rapid response, though long-term outcome is probably not altered.

### ■ Refractory flares: Focus on damage control

In pregnancy, most lupus flares involve nephritis and the systemic effects of nephritis, such as hypertension, proteinuria, and renal failure. In some cases, however, steroid pulse therapy fails to suppress these sequelae, or recurrent flares seem to become refractory to steroid pulse therapy.

**Any evidence for pregnancy termination?** In such cases it is essential that appropriate medical decisions be made on behalf of the mother. No conclusive data suggest that pregnancy termination ameliorates a lupus flare, although some anecdotes suggest this possibility.

**The mainstay** of management is to aggressively treat the lupus flare before irreparable maternal harm occurs.<sup>8</sup>

### ■ Early delivery: When and how

In advanced pregnancies it may be worthwhile considering early delivery so that the fetus may be spared any adverse consequences of maternal cytotoxic therapy, which would be the next step in management.

**Amniocentesis** for gestations earlier than 34 weeks may assist in guiding the decision

for betamethasone administration for the purpose of accelerating maturation of fetal lungs.

**Tertiary care facilities are needed.** Generally, if aggressive cytotoxic therapy is indicated, delivery of the fetus is indicated after 32 weeks. Such deliveries should occur at tertiary or quaternary care facilities where both adult and neonatal intensivists are available.

Cesarean section may be reserved for accepted obstetric indications.

### ■ Cytotoxic therapy

Remote from term, it may be necessary to commence cytotoxic therapy while allowing gestation to progress.

#### Cyclophosphamide

This is the preferred agent with respect to efficacy, especially for management of glomerulonephritis.<sup>9</sup> Unlike steroid therapy, which may show effects within 24 hours, cyclophosphamide therapy may take from 2 to 3 weeks to several months to achieve a satisfactory clinical response.

**Warn of potential ovarian failure.** It is important that the patient be informed that prolonged therapy with cyclophosphamide might lead to premature ovarian failure and subsequent infertility.

#### Azathioprine

An alternative, less toxic immunosuppressive agent that can be used is azathioprine. However, it is also less efficacious in treating severe nephritis. In pregnancy, the preferred role for azathioprine may be in the management of an initial, mild flare. Like cyclophosphamide, azathioprine may take several weeks to be effective.

**The combination of glucocorticoids and azathioprine** may be more effective than glucocorticoids alone in preventing recurrence of lupus flares, data indicate.

#### Methotrexate

Although this agent has also been used to manage lupus flares, it is generally effective

### FAST TRACK

**Pregnancy termination doesn't necessarily ameliorate lupus flare**

# Women's<sup>TM</sup> Health Experience

Enhancing the patient/  
physician dialogue



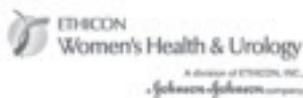
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## ► Management of lupus flare

in treating symptoms of arthritis and dermatitis, with little or no efficacy for life-threatening forms of SLE flares.

### ■ Thrombosis requires swift anticoagulation

In patients with SLE and antiphospholipid antibodies, the risk of thrombosis is increased. The ideal management during pregnancy is debatable, if the patient has no history of thrombosis. But in the setting of a lupus flare with either arterial or venous thrombosis, there is no debate. These patients require swift anticoagulation with either unfractionated or low molecular weight heparin. (Long-term therapy with a combination of heparin and glucocorticoids increases the risk of maternal osteoporosis.<sup>10</sup>) ■

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