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Lupus Activity in Pregnancy

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Systemic lupus erythematosus (SLE) primarily affects women in their reproductive years, making the issue of pregnancy important to many patients. There are an estimated 4500 pregnancies in women with SLE each year in the United States [1,2].

The impact of pregnancy on SLE activity has been debated in the literature, but the majority of studies endorse an increase in disease activity during pregnancy. In some patients, this will mean a dramatic worsening of symptoms that can be life threatening. Most patients, however, will have a modest increase in symptoms making pregnancy uncomfortable but not affecting their long-term survival.

Women with SLE have complicated pregnancies: one third will result in a cesarean section, 33% will have preterm birth, and more than 20% will be complicated by preeclampsia [1,3]. Increased lupus activity, particularly before conception and early in pregnancy, significantly increases the risks for these complications. For this reason, timing pregnancy to coincide with a period of SLE quiescence is a worthy goal.

This article will address the impact of pregnancy on SLE activity, of SLE activity on pregnancy outcome, and the treatment of women with SLE to minimize these effects.

Systemic lupus erythematosus activity during pregnancy

Whether SLE activity increases during pregnancy has been debated widely in the literature. In murine models, increasing doses of estrogen, like those seen in pregnancy, promote physiologic and immunologic changes associated with increased lupus activity [4,5]. Different methods to determine a flare and active lupus were used in many of the cohort studies of SLE pregnancy in the literature. Therefore, it is difficult to draw clear

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conclusions about the impact of pregnancy on SLE activity. Several small studies that matched pregnant lupus patients with nonpregnant lupus patients found no significant increase in SLE activity during pregnancy [6–9]. However, more recent studies have found a two- to threefold increase in SLE activity during pregnancy (Box 1) [10–13]. Based on these studies, it appears that between 35% and 70% of all pregnancies will have measurable SLE activity, with most studies showing the risk to be between 40% and 50% [8,9,11–16]. The risk for a moderate to severe flare is lower and ranges between 15% and 30% [14–16].

The risk of lupus flare is increased drastically if the woman has had active lupus in the 6 months before pregnancy. Two hundred sixty-five pregnancies to women with lupus were seen in the Hopkins Lupus Pregnancy Cohort between 1987 and 2002. In this cohort, the risk for significant SLE activity during pregnancy was 7.25-fold higher if the patient had recently active lupus before conception (58% versus 8%, $P < .001$) [16]. Other studies have found a twofold increase in risk for lupus flare during pregnancy among women with active SLE at conception [8,14]. Other risk factors for increased lupus activity in pregnancy include the discontinuation of antimalarial therapy and a history of highly active lupus in the years before pregnancy [13,17].

Types of disease activity

Fortunately, the majority of SLE activity in pregnancy is not severe. In most studies, skin, joint, and constitutional symptoms are most commonly

Box 1. Impact of pregnancy on systemic lupus erythematosus activity

Pregnancy probably increases lupus activity:
- About 50% of women will have measurable SLE activity during pregnancy
- Most of the disease activity will be mild to moderate
- 15% to 30% of women will have highly active SLE in pregnancy

Most common types of SLE activity in pregnancy:
- Cutaneous disease
- Arthritis
- Hematologic disease

Risk factors for increased lupus activity:
- Active lupus within the 6 months before conception
- Multiple flares in the years before conception
- Discontinuation of hydroxychloroquine

reported. The risk for skin disease ranges from 25% to 90%, depending on the severity measured [12,18,19]. The rates for arthritis during pregnancy are similarly disparate between studies, based on the severity measured. However, 2 large cohorts show a 20% risk of significant arthritis, although many more women will have an increase in less-severe joint pain [12]. Hematologic disease, in particular thrombocytopenia, is also common during pregnancy, with the risk ranging from 10% to 40% in different cohorts [12,18].

The risk for lupus nephritis during lupus ranges from 4% to 30%, based on the cohort characteristics and the definition of lupus nephritis [9,10,13,20]. Women with a prior history of lupus nephritis have 20% to 30% risk of relapse during pregnancy [9,13]. For women who have worsening renal function because of SLE nephritis during pregnancy, an estimated 25% had continuing renal damage after pregnancy, despite aggressive therapy [11,13,15]. Fortunately, very few women require lifelong dialysis.

Timing of systemic lupus erythematosus flares in pregnancy

Lupus flares can occur at any time during pregnancy, as well as in the several months after delivery. Although several studies have reported on the timing of activity in trimesters, a consistent pattern is not apparent [8,16,18]. It is important to keep in mind, however, that lupus patients remain at risk of flare in the months after delivery [8,18].

Impact of systemic lupus erythematosus activity on pregnancy outcome

Pregnancy loss

Overall, about 20% of pregnancies to women with SLE will end with a miscarriage or stillbirth [3]. The risk of miscarriage (a pregnancy loss before 20 weeks gestation) is not markedly elevated over the general population. The risk of stillbirth (a pregnancy loss after 20 weeks gestation), however, is elevated in several studies. The two most important risk factors for pregnancy loss are increased lupus activity and antiphospholipid syndrome (APS). In a Greek cohort of SLE pregnancies, six of eight (75%) pregnancies with high-activity SLE resulted in a fetal loss, whereas only 14% of pregnancies without active lupus and 5% of non-SLE pregnancies ended with a loss [18]. In the Hopkins Lupus Pregnancy Cohort, increased lupus activity did not increase the risk for miscarriage, but the stillbirth rate was threefold higher (Table 1) [16]. The timing of lupus activity affects the pregnancy loss rate, with activity early in pregnancy being the most dangerous. Proteinuria, thrombocytopenia, and hypertension in the first trimester are each independent risk factors for pregnancy loss. A woman with any of these risk factors has a 30% to 40% chance of suffering a pregnancy loss [21].

Table 1
Increased lupus activity in pregnancy increases pregnancy complications

Complication	Moderate to severely active SLE (n = 57)	Inactive or mildly active SLE (n = 210)	*P*-value
Miscarriage	7%	7%	0.9
Stillbirth	16%	5%	<0.01
Extreme preterm (<28 weeks' gestation)	17%	6%	0.09
Late preterm (28 to 37 weeks' gestation)	49%	26%	<0.001
Small for gestational age baby (<10th percentile weight for gestational age)	30%	21%	0.23

Data from Clowse MEB, Magder L, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005;52(2):514–21.

Preterm birth

The risk for preterm birth (delivery before 37 weeks gestation) is estimated to be 33% in all lupus pregnancies [3]. In a population-based study of 555 lupus deliveries in California, 21% were preterm, which was almost sixfold higher than the rate in healthy women [22]. Among cohorts at tertiary referral centers, however, the rate tends to be higher, ranging from 20% to 54% [3,9,11–16,20]. Preterm premature rupture of membranes (PPROM) is a prominent cause of preterm birth among lupus patients [11,23]. Although most of the preterm births are spontaneous, a significant proportion of them are induced to protect the health of either the mother or the baby [3,11].

Risk factors for preterm birth include lupus activity before and during pregnancy, higher prednisone dose, and hypertension. In the Hopkins Lupus Pregnancy Cohort, 66% of pregnancies with active lupus were delivered preterm versus 32% of pregnancies without active lupus ($P < .05$) (see Table 1). Babies born before 28 weeks' gestation are at highest risk for long-term medical complications and neonatal death. Within this cohort, 17% of all pregnancies with active SLE were born between 24 and 28 weeks' gestation, but only 6% of those without SLE activity were born during this risky period ($P = .09$) [16].

In women without SLE, an estimated one third of spontaneous preterm births are associated with infection within the uterus. The inflammation associated with chorioamnitis is postulated to promote dissolution of the amniotic sac, ripening of the cervix, and uterine contractions, which all lead to preterm birth. Unfortunately, no data have been published about the rate of chorioamnititis in SLE pregnancies. Placenta studies, however, do not show increased rates for infection on pathology [24]. We can hypothesize that the inflammation seen in active lupus may have a similar effect on the uteroplacental unit, thereby increasing preterm labor and rupture of membranes. Research to study this hypothesis is in its infancy, but in the future we hope that the role of inflammation in preterm birth will be more clearly

elucidated. Once this mechanism is understood, improved methods of therapy may be developed.

Low birth weight

Any study of low birth weight babies, in particular among lupus pregnancies, is complicated by the high rate of preterm birth. Therefore, the correction of the weight by gestational age is generally used. A small for gestational age (SGA) baby weighs less than the tenth percentile based on national norms [25]. On average, 9.4% of all SLE pregnancy cohort births were SGA, comparable to what would be expected in the general population [3]. However, some cohorts had significant increases over the expected rate, with some as high as 35% [11,16]. Given the relatively small risk for SGA, clear risk factors have not been identified. When a pregnancy is complicated by placental insufficiency, the baby may grow slowly and fail to gain adequate weight. Placental studies report a higher incidence of thrombosis among pregnancies affected by SLE [24]. For this reason, it is not surprising that some SLE pregnancies produce growth-restricted infants.

Preeclampsia

Preeclampsia is characterized as elevated blood pressure and proteinuria starting in the latter half of pregnancy. Preeclampsia places a woman and her fetus at considerable risk for stroke, preterm birth, and even death. In severe situations, preeclampsia may evolve into eclampsia with the addition of grand mal seizures in the mother. Definitive treatment for preeclampsia is delivery of the pregnancy; once the fetus (and probably more importantly the placenta) is removed, the hypertension, proteinuria, and risks subside.

Pregnant women with SLE are at increased risk for preeclampsia. Preeclampsia complicates 5% to 8% of pregnancies in the United States. However, among lupus pregnancy cohorts, the rate of preeclampsia ranges from 13% to 35% [2,14,26,27]. Preeclampsia is thought to arise from vascular dysfunction in the placenta. Several experimental markers for preeclampsia, including sFlt-1 (soluble FMS-like tyrosine kinase) and PIGF (placental growth factor), have been found to correspond to preeclampsia in lupus patients as they do in women with SLE [28]. Women at particular risk for preeclampsia are in their first pregnancy, have a history of preeclampsia or renal disease, have active SLE at conception, have positive anti–double-stranded DNA antibody (dsDNA) or antiribonucleoprotein antibodies, have low complement, are obese, and/or have hypertension (Table 2) [11,14,26,27].

Lupus nephritis in pregnancy

Among cohorts of patients with a history of lupus nephritis before pregnancy, pregnancy loss rates range from 8% to 36%, excluding pregnancies that are electively terminated [26,29,30]. In patients with active lupus

Table 2
Factors that distinguish between preeclampsia and systemic lupus erythematosus activity

	Preeclampsia	SLE activity
Risk factors		
1st pregnancy	Increases risk	No impact
Preeclampsia in prior pregnancy	Increases risk	No impact
Multifetal gestation	Increases risk	Unknown impact
History of lupus nephritis	Increases risk	Increases risk
Timing in pregnancy	Always after 20 weeks, usually after 30 weeks' gestation	Any time in pregnancy
Laboratory findings		
Active urine sediment (white blood cells, red blood cells, casts)	Usually negative	Positive
Coombs test	Usually negative	May be positive
Antiplatelet antibody	Usually negative	May be positive
Complement (C3 & C4)	Usually normal	May be low
Anti-dsDNA antibody	Usually negative	May be positive
Serum uric acid	>5.5 mg/dL	No change
Urine calcium	Low	Normal
sFlt-1 (soluble FMS-like tyrosine kinase 1)	High	Unknown
PlGF (Placental Growth Factor)	Low	Unknown
Physical findings: signs and symptoms of active SLE		
Dermatologic disease ■ vasculitic rash ■ discoid or subacute cutaneous rash ■ mouth ulcers ■ alopecia	Not present	Present
Arthritis	Not present	Present
Serositis	Not present	Present

nephritis in pregnancy, fetal loss occurs in 36% to 52% of the pregnancies [30,31]. Among patients with prior lupus nephritis but with stable creatinine and minimal proteinuria during pregnancy, 11% to 13% result in a fetal loss [30,31]. Prematurity occurs in 16% to 75% of pregnancies, with most series reporting around 35% to 40% preterm [26,29,30,32,33]. Although a history of lupus nephritis does not preclude pregnancy, it does increase the risks for reactivation of lupus activity, preeclampsia, and pregnancy loss.

Distinguishing lupus activity from the signs and symptoms of pregnancy

Systemic lupus erythematosus versus pregnancy: signs and symptoms

Many of the signs and symptoms of pregnancy can be easily mistaken for signs of active SLE (Table 3). For this reason, when the SLE disease activity

Table 3
Symptoms of pregnancy that can mimic lupus activity

Constitutional	• Fatigue that can be debilitating throughout entire pregnancy.
Skin	• Palmar erythema and a facial blush from increased estrogen.
Face	• Melasma: "mask of pregnancy." A macular, photosensitive hyperpigmented area over cheeks and forehead.
Hair	• Increased hair growth and thickness during pregnancy. • Hair loss in the weeks to months postpartum.
Pulmonary	• Increased respiratory rate early in pregnancy from progesterone. • Dyspnea from enlarging uterus late in pregnancy.
Musculoskeletal	• Back pain in second and third trimesters. ○ Relaxin loosens sacroiliac joint and symphysis pubis ○ Gravid uterus increases lumbar lordosis. • Joint effusions: noninflammatory in lower extremities.
Central nervous system	• Headache can be part of normal pregnancy or associated with hypertension. • Seizures occur in eclampsia. • Cerebral vascular accidents can be caused by preeclampsia or antiphospholipid syndrome.

From Tsokos GC, Gordon C, Smolen JS, editors. Systemic lupus erythematosus—a companion to rheumatology. St. Louis: Mosby; 2007; with permission.

index (SLEDAI) was modified for pregnancy, several caveats were included to rule out pregnancy-related complications, thus allowing for a clearer measure of true SLE activity [34]. Symptoms such as severe fatigue, melasma (the "mask of pregnancy"), postpartum hair loss, increased shortness of breath, arthralgias, and headaches frequently accompany normal pregnancy.

Arthralgias are common among pregnant women because of increased weight as well as the effect of relaxin on the joints. A study comparing pregnant women with and without rheumatoid arthritis documented that even women without arthritis have significant pain. The HAQ (Health Assessment Questionnaire) score for healthy pregnant women increased from 0.02 in the first trimester to 0.16 in the second and 0.48 in the third (score ranges from 0 to 3) [35].

Because up to 30% of SLE patients are also affected by fibromyalgia, it is important to distinguish between the aches and pains of fibromyalgia and an arthritis that is accompanied by inflammation. There is very limited published information about the change in fibromyalgia symptoms in pregnancy. A single study comparing 22 pregnant women with fibromyalgia and 22 pregnant women without found a significant worsening of fibromyalgia symptoms during pregnancy [36]. Because steroids do not have a role in treating fibromyalgia, they should not be given if inflammation is not present.

In normal pregnancy, the woman's blood volume increases by 50%, which alters several laboratory parameters. The hematocrit level frequently decreases because of hemodilution. Up to 50% of pregnancies in healthy

women may have some degree of anemia. Hemolytic anemia, however, is not considered normal and could be a sign of a lupus flare or HELLP syndrome (a severe derivative of preeclampsia with hemolysis, elevated liver tests, and low platelets). Mild thrombocytopenia, usually with a platelet count around 100,000, can occur in up to 8% of healthy pregnancies. A platelet count below this, however, is more likely to be from lupus activity, severe preeclampsia, or HELLP syndrome.

The creatinine level normally decreases secondary to the increased glomerular filtration rate required to accommodate the increased blood volume. In fact, a creatinine level that remains stable throughout pregnancy and does not decrease could be a sign of renal insufficiency. In women with prior renal damage from lupus nephritis, the degree of urine protein may increase. This is, again, secondary to increased blood flow through the kidneys, resulting in increased tubular flow. Therefore, alarm should not be raised unless baseline proteinuria doubles. Even in healthy pregnancies, a small degree of proteinuria (<300 mg/24 hr) can be considered within the normal range.

Complement levels (C3 and C4) may decrease with increased lupus activity, because these proteins are consumed in the inflammatory process [37]. In pregnancy, however, the complement levels may increase 10% to 50% in response to increased hepatic protein synthesis [38]. Therefore, the utility of complement measurement in pregnancy is unclear. In the Hopkins Lupus Pregnancy Cohort, half of the pregnancies had hypocomplementemia at some point. Low complement alone was not particularly predictive of either lupus activity or pregnancy outcome. However, the combination of low complement and high-activity lupus led to a three- to fivefold increase in pregnancy loss and preterm birth [39].

The anti–double-stranded DNA antibody (dsDNA) is very sensitive for the diagnosis of lupus and can be indicative of increased lupus activity, especially in the kidney. A rising level of dsDNA during pregnancy may correspond to increasing lupus activity. In the Hopkins Lupus Pregnancy Cohort, 43% of women had a positive dsDNA during pregnancy. Women with a positive dsDNA had a higher incidence of increased lupus activity (28%) than those without this antibody (16%, $P<.05$) [39]. However, this antibody did not predict pregnancy outcomes. Instead, the combination of a positive dsDNA titer and highly active SLE contributed toward a four- to sixfold increase in perinatal mortality and a two- to threefold decrease in full-term birth [39].

The erythrocyte sedimentation rate (ESR) is unreliable in pregnancy because it increases significantly in normal pregnancy. The C-reactive protein (CRP), however, may be more useful during pregnancy. In non-SLE pregnancies, an increased CRP level in the second trimester has been associated with preterm birth [40]. The CRP does not increase in all pregnancies and may be more reflective of the degree of overall inflammation during pregnancy. In nonpregnant SLE patients, the CRP may increase with a lupus

flare [41–43]. The use of CRP has not been systematically tested in SLE pregnancies yet.

Distinguishing lupus nephritis from preeclampsia

One of the greatest challenges of caring for pregnant SLE patients is distinguishing between preeclampsia and a lupus nephritis flare. Both present with proteinuria, hypertension, and lower extremity edema and may have more systemic effects as well (see Table 2). The treatment of these two conditions is different: preeclampsia will remit with delivery of the fetus, but active SLE will require immunosuppression.

Preeclampsia is diagnosed when a pregnant woman has a blood pressure $>140/90$ and proteinuria >0.3 g per 24 hours after 20 weeks' gestation. Severe preeclampsia can be accompanied by severe hypertension ($\geq 160/110$); microangiopathic hemolytic anemia with thrombocytopenia, anemia, and an elevated lactate dehydrogenase level; liver damage with elevated liver enzymes and epigastric pain; CNS ischemia causing headache, visual changes, and stroke; and renal pathology with nephrotic range proteinuria and an increasing serum creatinine level. Eclampsia is the addition of grand mal seizures to preeclampsia.

The breadth of symptoms that can be attributed to severe preeclampsia makes it clear that distinguishing it from active lupus is difficult and, in some situations, impossible. Table 2 outlines some risk factors, laboratory, and physical findings that may clarify the diagnosis. Prior lupus nephritis increases the risk for both a renal SLE flare in pregnancy as well as preeclampsia.

Treatment of systemic lupus erythematosus in pregnancy

All pregnant women should take a prenatal multivitamin with at least 400 mg of folic acid each day. Folic acid supplementation is very important for women who have taken methotrexate before pregnancy, because folate deficiency can lead to neural tube defects (Table 4).

Prevention of systemic lupus erythematosus activity

The best prevention of SLE flares during pregnancy is the delay of conception until a woman has had quiescent SLE for at least 6 months. In many situations, however, this is not possible. The continuation of medications for SLE during pregnancy helps to prevent SLE flares.

Many women with SLE will be taking hydroxychloroquine (HCQ) (Plaquenil) before pregnancy. This medication has been proven to decrease the risk of SLE flare, improve the prognosis of SLE nephritis, and prevent death [44–46]. It is also very well tolerated with arguably the best side-effect profile of any medication available to treat SLE. An expert panel, comprised of 29

Table 4
Medications to prevent and treat lupus activity in pregnancy

Treatment	FDA classification[a]	Recommended use in SLE pregnancy
Prenatal multivitamin	A	All women.
Acetaminophen	A	As needed for pain control.
NSAID	B first and second trimesters. D third trimester	As needed for pain control in the latter first trimester and second trimester only. Discontinue use in third trimester.
Prednisone and Prednisolone	B	As needed to control lupus activity.
Dexamethasone and Betamethasone	C	Not for treatment of lupus. As needed to treat the fetus.
Hydroxychloroquine	C	For all women if on before pregnancy or to treat mild flares in pregnancy.
IVIg	C	As needed to control lupus activity.
Mycophenolate mofetil	C	Only if no other options.
Azathioprine	D	Continue if on before pregnancy. May help treat flares.
Cyclophosphamide	D	Only if no other options.
Methotrexate	X	No use.
Leflunomide	X	No use.

[a] FDA pregnancy risk categories: A, no risk in controlled clinic trials of humans; B, human data reassuring or when absent, animal studies show no risk; C, human data are lacking and animal studies show risk or are not done; D, positive evidence of risk but the benefit may outweigh the risks; X, contraindicated in pregnancy.

international leaders in the research and care of women with SLE, recently recommended the continuation of HCQ during pregnancy [47]. Among more than 300 pregnancies described in the literature that were exposed to HCQ for the treatment of autoimmune disease, there has been no elevation of fetal anomalies identified. When chloroquine is taken at supratherapeutic doses, there may be ocular or auditory damage. However, no such changes were seen among 133 babies exposed to HCQ in utero [48].

In nonpregnant SLE patients, the cessation of HCQ is associated with a 2-fold risk of SLE flare within the following 6 months [46]. Among pregnant SLE patients, as well, the risk for flare increases when HCQ use is discontinued. In the Hopkins Lupus Pregnancy Cohort, 38 women discontinued HCQ use just before or early in pregnancy because of concern about fetal exposure, and 56 women continued HCQ therapy throughout pregnancy (Table 5) [17]. Among women who discontinued the medication, the risk for increased lupus activity, whether measured by absolute physician's estimate of activity, change in this scale, or the SLEDAI, was

Table 5
Lupus activity during pregnancy based on the use of hydroxychloroquine

	Continued HCQ	Discontinued HCQ	P value
Total pregnancies	56	38	
High PEA	6 (11%)	9 (24%)	.05
Flare rate	17 (30%)	21 (55%)	.05
SLEDAI ≥ 4	29 (52%)	32 (84%)	.007
Prednisone use	35 (63%)	34 (89%)	0.002
Maximum prednisone dose (mean $\pm$ SD)	16 $\pm$ 12 mg	21 $\pm$ 16 mg	0.06

Abbreviation: PEA, physician's estimate of activity.

Data from Clowse MEB, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54(11):3640–7.

significantly increased. More of these women required corticosteroid therapy at higher doses than women who continued taking HCQ. Within this cohort, as in other reports, there was no increase in fetal abnormalities after HCQ exposure. The pregnancy outcomes among women who continued and discontinued taking HCQ were similar. This likely reflects the type of SLE activity that women who discontinued taking HCQ suffered: they did not have increased rates of lupus nephritis, anemia, or thrombocytopenia. Instead, women who discontinued taking HCQ had increased incidence of fatigue and joint symptoms. Although these symptoms are uncomfortable, they are generally not life threatening nor do they require cytotoxic therapy. They may, however, prompt the institution or increase of corticosteroid therapy mid-pregnancy.

Azathioprine (Imuran) may be the safest immunosuppressant medication taken during pregnancy. The fetal liver does not have the enzyme required to metabolize azathioprine into its active form [47]. A report of three women who took azathioprine throughout pregnancy for inflammatory bowel disease or autoimmune hepatitis showed comparable levels of 6-thioguaninenucleoties (6-TGN) but no evidence of 6-methylmercaptopurine (6-MMP) in fetal blood at the time of delivery [49]. The level of 6-TGN is associated with myelosuppression in adults, and may rarely prompt transient myelosuppression after in utero exposure [50]. Series of pregnancies exposed to azathioprine for inflammatory bowel disease or renal transplants show no significant increase in fetal abnormalities [47]. Among renal transplant patients, however, up to 40% of the offspring were small for gestational age. It is not clear if this was a product of the underlying illness, corticosteroids, or azathioprine use [47,51].

Little data are available about the use of azathioprine in SLE pregnancy. In the Hopkins Lupus Pregnancy Cohort, 31 pregnancies were exposed to azathioprine [52]. Among the women who conceived while taking azathioprine and continued it through pregnancy, 2 of the 13 ended in a pregnancy loss, both in women who had active SLE in pregnancy. Among the 10 women who maintained low lupus activity and azathioprine throughout

pregnancy, all resulted in live births at greater than 34 weeks' gestation. Based on these data, we recommend the continuation of azathioprine treatment throughout pregnancy if the woman required it before pregnancy to treat her lupus. We also recommend switching women from mycophenolate mofetil (MMF) to azathioprine therapy before conception to avoid the teratogenic effects of the MMF.

Treatment of systemic lupus erythematosus flares during pregnancy

Women without any signs or symptoms of active SLE require no specific treatment during pregnancy. Prior recommendations for prophylactic corticosteroids have been rescinded because of increased hypertension, preterm birth, and low birth weight seen with excess use of this medication.

Mild activity can be treated with low-dose prednisone (less than 20 mg/d) as required. The side effects of low-dose corticosteroids include increased risk for hypertension and diabetes, just as in a nonpregnant woman. There may be a 2-fold increased risk for cleft lip or palate with systemic corticosteroid use, although the absolute risk for this remains low (about 20 per 10,000 babies with corticosteroid exposure) [53,54].

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used during the latter part of the first trimester and during the second trimester. There is evidence in a murine model that COX enzymes are important for embryo implantation, which may explain the increased risk for early miscarriage in women taking NSAIDs around the time of conception [47,55,56]. NSAIDs are considered fairly safe in the second trimester, although they may decrease fetal renal excretion and therefore promote oligohydramnios [57,58]. NSAIDs should be stopped in the third trimester for 2 reasons: they can prolong labor and may promote premature closure of the ductus arteriosis [47].

Moderate lupus activity can be treated with higher doses of corticosteroids, including pulse–dose steroids. Only a small percentage of each dose of prednisone and prednisolone cross the maternal–fetal membranes. However, fluorinated glucocorticoids, such as dexamethasone and betamethasone, easily transfer to the fetus. These steroids can be helpful in treating the fetus, in particular in promoting fetal lung maturity before a preterm delivery. However, they have also been associated with lasting adverse effects on the offspring. Children exposed to these corticosteroids may have increased blood pressure and cognitive deficits [59,60]. Therefore, dexamethasone and betamethasone should not be used to treat lupus activity during pregnancy.

The commencement of azathioprine mid-pregnancy for a lupus flare may be risky. In the Hopkins Lupus Pregnancy Cohort there was an increase in pregnancy loss among woman who used azathioprine to treat a moderate to severe flare: of the 8 pregnancies with moderate to severe flare treated with azathioprine, five (63%) resulted in a pregnancy loss, whereas only 1 of 9

(11%) of those with severe SLE activity but treated without azathioprine were lost ($P = .02$) [52].

Another option for treatment mid-pregnancy is intravenous immunoglobin (IVIg). IVIg can be particularly helpful in controlling hematologic and renal disease [61,62]. There are no published series of IVIg use for lupus during pregnancy; however, there are multiple reports of IVIg use to prevent recurrent miscarriage. In these cases, the primary outcome is live birth, and there is no change in this rate with the use of IVIg. Little has been published on the effects of IVIg on the offspring, but cell count levels seem to be stable, and no congenital anomalies have been reported. IVIg that contains sucrose can prompt renal insufficiency, but this has not hampered the treatment of nonpregnant women with lupus nephritis [62]. Some women will have headaches, rigors, or fevers with IVIg therapy, but more severe side effects are rare.

Cyclophosphamide (Cytoxan) and MMF (Cellcept) should be avoided during pregnancy. First trimester exposure to cyclophosphamide causes fetal abnormalities in a significant minority of patients. Exposure in the second and third trimesters does not increase the risk for fetal anomalies among women treated for breast cancer during pregnancy. Of the three pregnancies women with SLE who had cyclophosphamide treatment during mid-pregnancy reported in the literature, however, only one resulted in a live birth [63,64]. Cyclophosphamide should only be used when all other options are exhausted, and a frank a discussion about the risk for pregnancy loss has been discussed with the mother. The data on MMF in pregnancy are scarce but worrisome. There appears to be an elevated risk for both fetal anomalies and pregnancy losses [47].

Summary

The hormonal and physiologic changes that occur in pregnancy can induce lupus activity. Likewise, the increased inflammatory response during a lupus flare can cause significant pregnancy complications. Distinguishing between lupus activity and signs of both healthy and pathologic pregnancy can be difficult. A rheumatologist and a high-risk obstetrician are best equipped to care for women with lupus who become pregnant. Fortunately, most women with lupus remain well throughout pregnancy and deliver healthy babies. However, careful planning and treatment may be required to achieve this success.

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