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Managing lupus patients during pregnancy

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease, primarily affecting young females. Pregnancy in a woman with SLE remains a high risk situation with higher maternal and fetal mortality and morbidity. Although live births are achieved in majority of the pregnancies, active disease and major organ involvement can negatively affect the outcomes. Higher risk of fetal loss, pre-term birth, intra-uterine growth restriction and neonatal lupus syndromes are major fetal issues. Mothers are faced with disease flares, pre-eclampsia and other complications. Disease flares during SLE pregnancy pose the unique issue of recognition and differentiation between physiologic changes and disease state. Similarly pre-eclampsia and lupus nephritis may lead to diagnostic confusion. Treatment choices during pregnancy are limited to a few safe drugs, further restricting the options. Refractory pregnancy loss associated with anti-phospholipid antibodies and complete heart block associated with anti-Ro antibodies remain unresolved issues. A multidisciplinary approach, with close monitoring, is essential for optimal outcomes.

Keywords

Systemic lupus erythematosus; anti-phospholipid antibodies; pregnancy; fetal loss; pre-eclampsia; neonatal lupus syndromes

Introduction

Systemic lupus erythematosus (SLE) is an auto-immune disease with significant female predominance. The onset during reproductive years, coupled with improved survival, has led to increased numbers of pregnancies in SLE. The pregnancy outcomes have also significantly improved. The rate of pregnancy loss has decreased from 43% to 17% in recent years [1]. However, SLE patients have fewer children than their normal counterparts and SLE pregnancy still carries a high risk of complications [2-4]. A multidisciplinary approach, with close medical, obstetric and neonatal monitoring, is essential for optimal outcomes. This chapter will highlight major issues in SLE pregnancy and discuss the management strategies to minimize maternal and fetal risks.

Pregnancy planning in SLE

Active SLE at the time of conception is known to be the strongest predictor of adverse pregnancy outcomes [5]. Hence, ideally, all pregnancies in women with SLE should be planned during periods of disease control. Unplanned pregnancies during periods of disease activity highlight the often neglected need of effective contraceptive counseling of all young women with SLE [6]. Natural and barrier methods of contraception have a high failure rate and may not be sufficient in a patient with active disease. Safety of oral contraceptives has been documented in two large randomized controlled trials [7, 8]. However, patients with severely active disease were excluded from the studies. Patients with anti-phospholipid antibodies (aPL) are at high risk of thrombosis and should avoid estrogen containing contraceptives [9]. Certain drugs interfere with the oral contraceptive efficacy. This fact has recently been added to the FDA labeling of mycophenolate mofetil. Although effective, progesterone-only contraceptives have to be used judiciously. Long term use, especially of depot preparations, leads to negative effects on bone mineral density [10]. The intra-uterine contraceptive device remains a viable and safe option for many patients with SLE [8].

Pre-conception evaluation

Preconception assessment is an essential component of pregnancy planning in SLE. In a limited number of patients, pregnancy may pose an unacceptably high maternal risk, justifying an advice to defer or avoid pregnancy (Table 1). If there are no contra-indications, patient should undergo pre-conception counseling, maternal and fetal risk assessment, and medication review, before conception (Figure 1). A complete set of autoantibodies should be as certain specific maternal antibodies (aPL and anti-Ro antibodies) in mother poses unique fetal risks. Every effort should be made to ensure optimal disease control for at least 6 months prior to conception. Medications should be reviewed and adjusted to achieve good disease control on permitted medication. Thyroid function should be assessed as hypothyroidism in SLE is associated with poorer outcomes [11].

Pre-pregnancy Counseling

SLE pregnancies are considered to be high risk. All patients should be counseled about the possible issues including risk of disease flares, higher rates of pregnancy complications, sub-optimal obstetric outcomes, and the risk of neonatal lupus syndromes. The need for optimal disease control with safe medications during pregnancy should be explained.

Disease activity during pregnancy

One of the major issues is SLE pregnancy is the risk of disease exacerbation. Although it is generally agreed that pregnancy may lead to higher rates of disease flares, widely variable flare rates of between 25-65% have been reported [12-17]. Different organ systems may have variable response to pregnancy; musculoskeletal flares are less common while renal and hematologic flares are more common [18]. Majority of the flares in pregnancy are mild-to-moderate, with only small percentage of patients developing severe flares [16]. Active disease during the 6 months prior to conception, history of lupus nephritis and discontinuation of anti-malarial significantly increase the risk of flares during the pregnancy [14, 19-21].

Pregnancy Complications

Pregnancy in the setting of SLE is associated with a higher risk of complications, compared to normal women. A large national data base study of 16.7 million deliveries reported many fold increased risk of maternal death, preeclampsia, preterm labor, thrombosis, infection, and hematologic complications during SLE pregnancy [2]. However, these results have to be

interpreted with caution. Non- pregnant SLE patients also have higher risk of medical complications and mortality rate. In addition, women with SLE in this study were older and had significantly higher rates of co-morbidities.

The biggest issue is the 3-5 times higher risk of pre-eclampsia, complicating 16-30% of SLE pregnancies [22-24]. The predisposing factors for pre-eclampsia include advanced maternal age, previous personal or family history of preeclampsia, pre-existing hypertension or diabetes mellitus, and obesity [25]. In SLE, additional specific risk factors include active or history of lupus nephritis, presence of anti-phospholipid antibodies, declining complement levels, and thrombocytopenia [22-24, 26]. A genetic predisposition with heterozygous mutations in complement regulatory proteins was reported in the PROMISSE cohort, but needs further evaluation [27].

Obstetric Outcomes

The main obstetric issues in SLE pregnancy are higher rates of fetal loss, preterm birth, intra-uterine growth restriction (IUGR), and neonatal lupus syndromes. However, the rate of fetal loss has declined and live births rates of 80-90% have recently been reported [12, 14, 15]. Active disease and lupus nephritis increase the risk of fetal loss and other adverse outcomes [13, 20, 28, 29]. Proteinuria, hypertension, thrombocytopenia, and presence of anti-phospholipid antibodies are other negative predictors for fetal survival [13, 28, 30].

Pre-term births, and the morbidity associated with it, are the most frequent problems of SLE pregnancy. Variable rates have been reported but in the presence of the mentioned adverse prognostic factors, up to half of the pregnancies may end in premature delivery. Thyroid disease is also associated with higher risk of pre-term birth in SLE pregnancy [11]. About 10-30% of SLE pregnancies are complicated with fetal growth restriction and small for gestational age babies [14, 21].

Neonatal Lupus Syndromes

Neonatal Lupus Syndromes (NLS) is a form of passively acquired fetal autoimmunity from maternal antibodies, anti-Ro and anti-La antibodies. Majority of the manifestations, such as rash, hematologic and hepatic abnormalities, parallel the presence of maternal antibodies in the neonatal circulation. They tend to resolve with the clearance of the antibodies by six to eight months of life. In contrast, cardiac complications are a result of permanent damage to the fetal cardiac conduction system by maternal antibodies.

The cardiac manifestations of NLS include conduction defects, structural abnormalities, cardiomyopathy and congestive cardiac failure [31]. However, the most common issue is congenital heart block (CHB). CHB leads to high fetal mortality; rates of 15-30% have been reported. The majority of survivors require pacemakers, adding to the significant morbidity [32, 33]. CHB affects about 2% of children born to primigravid women with anti-Ro antibodies [34]. However, the risk rises to about 16-20% in subsequent pregnancies, after the birth of an affected child [35, 36]. Other suggested risk factors include higher levels of maternal antibodies, maternal hypothyroidism, and fetal genetic polymorphisms [36, 37].

Medication use during pregnancy

An essential component of pre-pregnancy counseling is discussion about the use of appropriate medications during the pregnancy. Unfortunately, concerns over presumed toxicity often lead to discontinuation of necessary therapy with resultant increase in disease activity, worsening the outcomes. The United States Food and Drug Administration (FDA) categories are often not helpful as they are mostly derived from animal data or are outdated.

Although majority of SLE therapeutics are potentially harmful and contra-indicated, safe options exist and should be continued during the pregnancy (Table 2).

Non-steroidal anti-inflammatory drugs (NSAIDS) were considered safe during the first and second trimesters [38]. However, moderate associations between NSAID use in first trimester and specific birth defects were recently reported [39, 40]. There is also an increased risk of impaired fetal renal function with use after 20 weeks of gestation. Hence, caution needs to be exercised when using NSAIDs during early pregnancy. Continued use after the 32 week of gestation can increase the risk of premature closure of the ductus arteriosus by almost 15-fold, and should be avoided [41]. The data on the cyclooxygenase 2 inhibitors in pregnancy is very limited, and they are best avoided during pregnancy.

Steroid exposure should be limited to a minimum during the pregnancy. High doses during pregnancy are associated with an increased risk of diabetes, hypertension, pre-eclampsia and premature rupture of membranes [38]. However, in the case of disease flares, short courses of high doses and/or intravenous pulse methylprednisolone can be used. Patients on long term steroid therapy should also receive stress doses at the time of delivery. Use of fluorinated compounds, such as dexamethasone and betamethasone should be limited to a single course for fetal lung maturity, in cases of premature delivery. Repeated use has been associated with impaired neuro-psychological development of the child in later life, and should be avoided [42].

Hydroxychloroquine should be continued in all pregnant women with SLE. Multiple studies have proven the beneficial effects of hydroxychloroquine in SLE, including during pregnancy. Reduction in disease activity was noted with no harmful effects on the baby with use during pregnancy, while discontinuation led to an increase in disease flares [19, 43, 44]. The risk of CHB and neonatal lupus syndromes was also significantly reduced in at-risk pregnancies with sustained use of hydroxychloroquine [45, 46].

Azathioprine is one of the only few immunosuppressive agents that has documented safety during pregnancy [38]. The dose should be limited to maximum of 2mg/kg/day, to avoid risk of fetal cytopenias and immune suppression [38]. An association between maternal azathioprine therapy during pregnancy and late developmental delays in offspring was suggested by a recent study [47]. However, the confidence intervals were very wide and the study had serious limitations (small sample size, retrospective nature, lack of validated measures). Azathioprine can still be considered safe during pregnancy but it is prudent to counsel the women about the possible association. Other immunosuppressive drugs with no reported increase in fetal risk are the calcineurin inhibitors, tacrolimus and cyclosporine [48]. Leflunomide was considered to be teratogenic and traditional advice has been to discontinue for 2 years or perform a wash out procedure before conception. Recently, 2 cohort studies reported no increase in risk of malformations after inadvertent exposure during pregnancy [49, 50]. However, caution needs to be exercised and routine use of leflunomide during pregnancy is not recommended. Most other agents, such as cyclophosphamide, methotrexate, and mycophenolate, are contraindicated during pregnancy and should be discontinued at least 3 months before conception. Data on the biologics, such as rituximab or belimumab, during pregnancy are very limited, and they should be discontinued before conception.

Most of the commonly used antihypertensive drugs have to be either avoided or used with extreme caution during pregnancy [51, 52]. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers can cause specific malformations, the ACE-inhibitor fetopathy. In addition, neonatal arterial hypotension, renal failure, and death have been reported. Beta-adrenergic blockers have been associated with IUGR and fetal

bradycardia. Diuretics can lead to maternal volume depletion and reduced uteroplacental perfusion. Hence, the safe armamentarium against hypertension during pregnancy is quite limited, including drugs such as hydralazine, methyl-dopa, nifedipine, and labetalol [51, 52].

Low-dose aspirin as an antiplatelet agent is safe during pregnancy but data on other antiplatelet agents are limited [53]. Heparin does not cross the placenta and is the anticoagulant of choice during pregnancy. Low-molecular weight heparin (LMWH) has similar efficacy and safety to unfractionated heparin (UFH). The ease of administration, higher antithrombotic to anticoagulant ratio, and predictable bioavailability has led to widespread use of LMWH instead of UFH [54]. Warfarin should be avoided during pregnancy, especially during the first trimester, due to the risk of warfarin embryopathy syndrome [55]. The data on direct factor Xa inhibitor, fondoparinux, are limited but reassuring. It does not cross placenta and may be a possible choice in women intolerant to heparin [54].

Calcium supplementation should be routinely provided to all pregnant women with SLE, especially those receiving corticosteroids and heparin. Insufficient vitamin D levels during pregnancy are associated with higher pregnancy morbidity including gestational diabetes, pre-eclampsia, and small for gestational age infants [56]. However, supplemental vitamin D during pregnancy did not consistently or significantly reduce the risk [57, 58]. Although guidelines differ, currently the safest approach is to supplement vitamin D during pregnancy in women at higher risk [59]. Bisphosphonates should be discontinued 6-12 months prior to pregnancy. Animal data showed higher maternal and fetal mortality and morbidity, albeit at levels many times higher than clinical doses. Limited human data did not show any serious adverse maternal or fetal effects but some reports of fetal hypocalcaemia and growth retardation have been noted [60].

Ante-natal management in SLE patients

Ante-natal management of pregnant patients will SLE requires close collaboration between rheumatologist and obstetrician. The monitoring should be more frequent and detailed than the usual standard of care. Each visit should include thorough physical examination, routine laboratory tests and specific investigations, tailored to the risk profile of the particular pregnancy (Table 3). Certain situations, such as disease flare or presence of specific antibodies, require specific strategies, as discussed below.

Pregnancy in the presence of anti-phospholipid antibodies

Presence of aPL during pregnancy is associated with significant risk of pregnancy morbidity and loss. Although aPL are present in about a quarter to half of patients with SLE, only a fraction of these patients develop antiphospholipid syndrome (APS), defined by the persistence of medium-to-high titre aPL (anticardiolipin, anti-β2 glycoprotein and/or the lupus anticoagulant) on at least two laboratory tests, 12 weeks apart, in the presence of at least one clinical criterion of thrombosis and/or pregnancy morbidity [61]. However, even asymptomatic women with aPL, not fulfilling the criteria, have higher rates of pregnancy loss. In addition, aPL increase the risk of pre-eclampsia, placental insufficiency, IUGR, and preterm delivery. Lupus anticoagulant is more specific in predicting the risk of adverse pregnancy outcomes, compared with other aPL [30].

The outcomes of pregnancies exposed to aPL have significantly improved and live birth rates of over 80% have been recently reported [62]. The management strategies differ, based on the risk profile of each pregnancy. Low dose aspirin alone is generally recommended for asymptomatic women with only persistently positive aPL and no prior event, despite limited evidence [63, 64]. The group with recurrent early losses or one or more late fetal loss, but no

history of systemic thrombosis, is termed Obstetric APS. Aspirin, in combination with prophylactic doses of heparin, significantly reduces the risk of pregnancy loss in this group [65, 66]. Low-molecular weight heparin (LMWH) has similar efficacy to unfractionated heparin, but requires twice daily administration at all doses during pregnancy [67]. Low-molecular weight heparin must be transitioned to unfractionated heparin prior to delivery. Heparin treatment needs to be continued for 6 weeks post-partum [68]. The patients with prior systemic thrombosis should receive full therapeutic doses of heparin throughout pregnancy.

Some patients are refractory to the aspirin and heparin treatment and continue to have recurrent losses. The management of these patients requires individualized approach; all decisions have to be made in discussion with the woman and her partner. Addition of steroids has been reported to improve outcomes [69]. IVIg and plasmapheresis have been tried with benefit in case reports, but data are limited [70-72].

Pregnancy in the presence of anti-Ro antibodies

The biggest issue with exposure to the anti-Ro antibodies during pregnancy is the high risk of CHB. Most often CHB develops between 18–24 weeks of gestation. It is usually preceded by lesser degrees of conduction delays which may be reversed with early treatment [33]. However, conduction abnormalities can progress very rapidly and many times the first rhythm abnormality detected is CHB. Many tools have been developed for early detection of lesser degrees of heart block, including fetal doppler echocardiography, fetal kinetocardiogram and transabdominal fetal electrocardiogram [73-75].

Fetal doppler echocardiography remains the most commonly used modality. All exposed fetuses should be monitored weekly between 16–26 weeks of gestation, and bi-weekly thereafter [33]. Detection of an early conduction defect such as prolonged PR interval should be considered a danger signal. Although some early blocks are transient, the progression to CHB remains unpredictable. Prophylactic treatment should be discussed if the PR interval remains persistently prolonged. Maternal administration of fluorinated corticosteroids has shown fetal survival benefit in some studies. However, the results have not been consistent and the benefits have to be weighed against the higher risk of IUGR and preterm birth [76-78]. Treatment of established CHB remains even more unsatisfactory. Improved fetal outcomes were reported after trans-placental treatment with dexamethasone and beta-adrenergic stimulants in one study, but these findings were not replicated [76-78]. Hydroxychloroquine during pregnancy reduces the risk of cardiac NLS in at-risk fetuses [45, 79].

The recurrence risk of CHB in subsequent pregnancies after an affected pregnancy is many-fold higher. Hydroxychloroquine reduced this risk by 65% in one study [45]. Open label data showed beneficial effects of intravenous immunoglobulin (IVIG), but two large randomized controlled trials showed negative results [80-82]. The study design, dose of IVIG used and different composition of IVIG may have contributed to the negative outcomes [83]. In summary, currently there is no satisfactory treatment for established CHB.

Disease flare during pregnancy

An important management issue is the difficultly of recognizing disease flare in pregnant SLE patients. Many physiological changes of pregnancy may overlap with features of active disease, making differentiation difficult (Table 4). Some common laboratory tests also become less reliable: mild anemia and thrombocytopenia are common, erythrocyte sedimentation rate is raised, and up to 300mg/day proteinuria can occur during normal pregnancy. Complement levels rise by 10–50% during normal pregnancy and may appear to

remain in the 'normal' range, despite disease activity. Thus, the trend of complement levels becomes more important than absolute values. Low and declining levels of complement during pregnancy have been associated with poor pregnancy outcomes [26, 84]. Anti-dsDNA antibodies may be helpful in evaluation of disease activity [84].

The SLE disease activity indices have similar limitations. They were derived in non-pregnant populations and physiologic pregnancy changes were not accounted in these indices. Pregnancy-specific disease activity scales, SLE Pregnancy Disease Activity Index (SLEPDAI), LAI in Pregnancy (LAI-P), and BILAG2004-Pregnancy index, have been developed with modifications to descriptors. However, they mostly remain as research tools. In real life, a combination of laboratory parameters coupled with the clinical judgment may the best tool to evaluate disease activity.

Treatment of flares during pregnancy is guided by the severity and organ involvement, similar to the non-pregnant state. However, the choice of agents is limited to safe drugs, as discussed above. Steroids in the lowest possible doses should be used, but short courses of high doses can be used for flares. NSAIDS can be used for mild symptoms in the first and second trimester. However, caution needs to be exercised in view of recent data on associations with malformations. Hydroxychloroquine should be continued throughout the pregnancy. Other safe immunosuppressants that can be used include azathioprine and calcineurin inhibitors. Although developmental delays in offsprings were recently reported with azathioprine, more studies are required to further evaluate this association. IVIG and plasmapheresis remain alternative options but the higher risk of thrombosis with IVIG and fluid overload have to be considered.

Pre-eclampsia during SLE pregnancy

Differentiation between pre-eclampsia and lupus nephritis flares during pregnancy may become difficult; both can present with increasing proteinuria, deteriorating renal function, hypertension, and thrombocytopenia. Certain features, if present, can help in distinguishing between the 2 conditions (Table 5). Multiple guidelines for diagnosis of pre-eclampsia have been proposed but are neither highly sensitive nor specific [85]. Abnormal uterine artery waveforms have been associated with a higher risk of pre-eclampsia and poor obstetric outcomes [86, 87]. However, the lack of standardization and limited data restricts the diagnostic value [88]. Multiple biomarkers, such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), soluble fms-like tyrosine kinase-1 (sFLT1), and soluble endoglin (sENG), have been evaluated as possible predictors and diagnostic tools. However, the sensitivities remain low and data in SLE are very limited [89, 90]. Prediction models incorporating clinical characteristics, uterine artery Doppler and biomarker levels have been developed but await prospective validation studies [91]. In certain situations, it may become extremely difficult to differentiate lupus nephritis and pre-eclampsia and they may also co-exist. Renal biopsy could help to differentiate but the higher risk of complications during pregnancy limits the use in advanced pregnancy. Sometimes, delivery of the baby may be the only definitive answer.

Summary

Pregnancy in women with SLE is a high risk condition. Despite considerable improvement in success rates, substantially high maternal and fetal morbidity and mortality still remain a cause for concern. Disease activity may worsen during the pregnancy and in turn may increase the risk of other maternal and fetal complications. Recognition and treatment of disease flares and pre-eclampsia, during SLE pregnancy, is fraught with difficulties including overlapping features, lack of specific diagnostic markers, and drug toxicities. Increased fetal loss, especially in the presence of aPL, pre-term births, IUGR, and neonatal

syndromes including CHB are major unresolved issues. The key to success lies in the multidisciplinary care with close monitoring. Early detection of threats to maternal and fetal well-being, with judicious use of appropriate medications, is essential to achieve good outcomes.

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Practice points

- Pregnancy in the setting of SLE remains a high risk situation
- Multidisciplinary care with close monitoring is essential for good outcomes
- Active disease at conception is associated with adverse maternal and fetal outcomes
- Pregnancy should be planned at times of disease quiescence with effective use of contraception
- Preconception assessment should be done prior to the planned pregnancy
- Specific monitoring and treatment protocols are required in high risk situations such as presence of specific antibodies (aPL and anti-Ro)
- Disease flares, pre-eclampsia, fetal loss, prematurity, intra-uterine growth restriction and neonatal lupus syndromes (including CHB) remain the main issues
- Safe treatment options exist and should be appropriately used for disease activity during pregnancy

Research agenda

- Adverse obstetric outcomes including refractory pregnancy loss associated with aPL, and CHB associated with anti-Ro antibodies, remain a challenge.
- The pathophysiologic mechanisms of these complications are now being understood such as the role of complement activation in aPL associated pregnancy loss. However, further studies are required for in depth understanding of these mechanisms.
- There is an unmet need to develop targeted therapies, based on the underlying mechanisms, for pregnancy loss and CHB in at-risk pregnancies.
- Late neuropsychiatric effects on children exposed to maternal anti-Ro antibodies and immunosuppressants in utero, need further evaluation.
- The significance of thyroid abnormalities and benefits of thyroid replacement in pregnant women with SLE needs further evaluation.

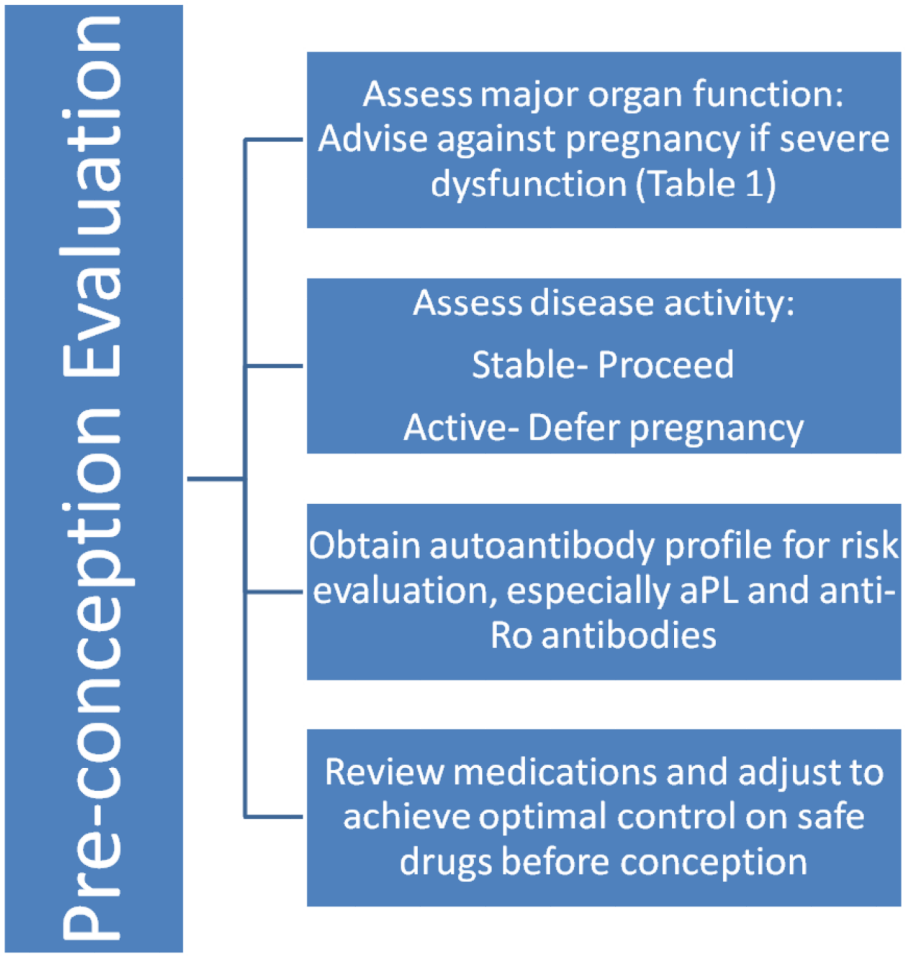

Figure 1. Planning a pregnancy in the setting of SLE

Table 1
Situations where pregnancy is not advisable in patient with SLE

Contra-indications to pregnancy:
Severe pulmonary hypertension (systolic pulmonary artery pressure > 50mm Hg)
Severe restrictive lung disease (Forced vital capacity < 1 L)
Advanced renal insufficiency (creatinine >2.8 mg/dL)
Advance heart failure
Previous severe preeclampsia or HELLP despite therapy
Pregnancy should be deferred:
Severe disease flare within last 6 months
Active lupus nephritis
Stroke within the previous 6 months

Table 2
Medications safe for use during SLE Pregnancy

Drugs	Comments	Recommendations
Non-steroidal anti-inflammatory drugs (NSAIDS)	First trimester use may be associated with higher risk of congenital malformations, fetal renal impairment and premature closure of ductus arteriosus with use in last trimester	Use with caution during the first and second trimester Discontinue during last trimester
Corticosteroids • Prednisolone/ Pulse methyl prednisolone • Flourinated compounds (Betamethasone/ dexamethasone)	High doses can lead to higher maternal complications Some association with impaired neuro-psychological development of the child	Use lowest possible dose Pulse therapy can be used for acute flares Limit to one course, for fetal lung maturation
Antimalarials • Hydroxychloroquine	Reduced risk of disease flares, CHB and NLS	Should be continued in all SLE pregnancies
Immunosuppressants • Azathioprine • Calcineurin inhibitors (cyclosporine/ tacrolimus)	Used in large number of transplant recipients. Recent report of late developmental delays in off springs with azathioprine	Limit azathioprine dose to 2mg/kg/ day Explain the probability of late effects in the child to mother
Anti-Hypertensives • Methyldopa • Labetalol • Nifedipine • Hydralazine	Concerns about growth retardation with labetalol and impaired utero-placental blood flow with hydralazine	Generally safe and preferred drugs for hypertension during pregnancy

Table 3
Ante-natal monitoring in SLE pregnancy

Clinical review	Investigations	Specific Monitoring
• Rheumatologist: 4-6 weekly, more frequent if activedisease or flare • Obstetrician: Monthly till week 20, then 2 weekly till week 28, and weekly thereafter	• Each visit: Blood count, serum uric acid, urea, creatinine, electrolyte levels, liverfunction tests, urinalysis, spot urine protein/creatinine ratio, complement levels and dsDNAantibodies • Ultrasound: early pregnancy forgestational dating, between week 16-20 to screen for fetal anomalies, 4 weekly thereafter to monitor growth • Fetal surveillance tests (FST): weekly form week 26	• Poitive anti-Ro antibodies: Fetal echocardiography, weekly from week 16-26 and biweekly thereafter, continuing till delivery • Pre-eclampsia: Uterine artery Doppler study (week 20 and 4 weekly thereafter), Fetal umbilical artery Doppler velocimetry (weekly from week 26 onwards) • IUGR: Increase frequency of growth monitoring by ultrasound and FST

Table 4
Differentiation of SLE flare from physiological pregnancy changes

Characteristic	Pregnancy-related changes	SLE flare
Mucocutaneous	Facial flush Palmar erythema Postpartum hair loss	Photosensitive rash Oral or nasal ulcers
Musculoskeletal	Arthralgias Myalgias	Inflammatory arthritis
Hematologic	Mild anemia, Mild thrombocytopenia	Leucopenia, lymphopenia Immune hemolytic anemia Thrombocytopenia
Renal	Physiologic proteinuria <300mg/day	Active urinary sediment Proteinuria >300mg/day
Immunologic	Higher complement levels	Falling complement levels Rising anti DNA levels
Others	Fatigue Mild edema Mild resting dyspnea	Fever Lymphadenopathy Pleuritis

Table 5
Features differentiating Pre-eclampsia and Lupus nephritis

Clinical and Laboratory Features	Pre-eclampsia	Lupus nephritis
Hypertension	After 20 weeks of gestation	Any time during the pregnancy
Platelets	Low - normal	Low - normal
Complements	Normal - low	Low
Anti dsDNA	Absent or unchanged	Rising titers
Creatinine	Normal - raised	Normal to raised
Serum Uric Acid	Elevated (>5.5mg/dl)	Normal
24 hour Urine Calcium	<195mg/dl	>195mg/dl
Urinary Sediment	Inactive	Active
Other Organs Involved	Occasionally CNS or HELLP	Evidence of active non-renal SLE
Response to steroids	No	Yes