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Morbidities in pregnancy associated with systemic lupus erythematous

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Abstract

The association between systemic lupus erythematosus (SLE) and pregnancy is not a rare event, but these pregnacy are associated with an increased risk of preeclampsia, fetal growth restriction, fetal stillbirth, prematurity and neonatal death. Nephritis is an important complication of SLE and a factor for maternal and fetal morbidity. Studies of the impact of SLE and pregnancy morbidities generate conflicting results. The aim of these study was to realize a systematic analysis in the literature concerning the pregnancy outcome in women with SLE and SLE associated with lupus nephritis. We searched the electronic database in literature and random effects of analytycal methods were used to evaluate pregnancy complications rates. Also the association between pregnancy and nephritis it is not very often encountered in different articles. Active SLE and the presence of antiphospholipid antibodies (APA) are considered the most powerful predictors of perinatal morbidity. We found that a significant number of pregnancies occur during periods of active nephritis (19%), and have positive APAs (26.2%). Up to 75% of patients with SLE have clinically evident renal disease. Lupus flare in pregnancy is one of the major issues associated with SLE. However, studies report variable flare rates in pregnancy between 25-65%. Other important perinatal complications associated with SLE in pregnancy are: gestational hypertension (16.3%), fetal growth restriction (12,7%), preeclampsia (7,6%), preterm delivery (39,4%), stillbirth (3,6%), neonatal death (2,5%). Neonatal lupus syndromes is a form of passively acquired fetal autoimmunity from maternal antibodies, anti-Ro and anti-La antibodies with important cardiac involvement, most commonly congenital heart block. Previous and actual lupus nephritis is associated with negative effects on preganancy and with a deterioration of renal function. Despite considerable improvement in success rates, suboptimal obstetrical outcomes still remain a cause for concern. Best pregnancy results can be obtained if appropriately managed by a multidisciplinary team of physicians.
Keywords: *systemic lupus erythematosus, pre-eclampsia, lupus flare, hypertension*

Introduction

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease that affects predominantly women. The onset of the disease at a childbearing age, coupled with the improvement in the survival rates has led to an increased number of pregnancies in SLE. Early reported outcomes of these pregnancies were poor, and the rates of therapeutic abortions were high; recent studies report significantly improved outcomes. The rate of pregnancy loss has decreased from 43% to 17% in recent years[(1)]. Fecundity in SLE is not modified compared to a healthy population except for the association of SLE with antiphospholipid syndrome, advanced renal impairment (creatinine ≥3 mg/dl), and also women treated with cytotoxic alkylating agents[(1)]. Published data have pinpointed several risk factors that prompt to poor pregnancy outcomes, including hypertension, anti-phospholipid syndrome, and renal involvement of SLE. The influence of lupus nephritis (LN) on maternal and fetal mortality and morbidity is not fully comprehended and is the subject of dispute. Stable renal disease has been noted in a group of pregnant SLE patients, even in those complicated with LN and diffuse glomerular lesions[(2,3)]. Contrastingly the rate of pregnancy loss in patients with SLE and acute nephritis was reported to be as high as 60%[(2)]. Treatment choices during pregnancy are limited to a few drugs, confining the treatment options. Thus close monitoring of the mother and the fetus by a multidisciplinary team including an obstetrician, neonatologist, rheumatologist, nephrologist, should be initiated for better obstetrical outcomes.

SLE and pregnancy: pre-conception planning, counseling

Active SLE and the presence of antiphospholipid antibodies (APA) are considered the most powerful predictors of perinatal morbidity[(2)]. And thus pregnancy planning is very important in these patients. Ideally the pregnancy should be planned in periods of disease control. A recent meta-analysis shows that a significant number of pregnancies occur during periods of active nephritis (19%), and have positive APAs (26.2%)[(2)]. Natural and barrier methods of contraception are not considered sufficient for these patients. Oral contraceptives have been studied in randomized controlled trials[(2,3)], highlighting the risk of thrombosis in patients with positive APAs. Intrauterine devices are considered the preferred option for most patients who wish to postpone pregnancy[(4)].

A thorough preconceptional assessment of the patients is an essential component of pregnancy planning in SLE with the purpose of optimizing their health before beco-

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ming pregnant. Preconceptional evaluations should contain physical examination. Blood pressure measurement, urinalysis, determination of proteinuria, complete blood count, serum creatinine, antiphospholipid antibodies (Anti-SSA/Ro and anti-SSB/La antibodies), complement studies, liver function tests[5,6]. The recommended disease free interval before conception is 6 months, without flares, and discontinuation of hydroxychloroquine. Medication should be reviewed and adjusted to obtain disease control with accepted medications in pregnancy. Similarly antihypertensive medication known to be teratogenic for the fetus (i.e. angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) should be changed to safe alternates[7].

Pregnancy counseling is also important for the patient because it informs the future mother about maternal and fetal complications that could arise (pregnancy induced hypertension, preeclampsia, prematurity, stillbirth, SLE flare, and nephritis flare). SLE pregnancies are considered high risk and the patients should be informed about the risk of flares, suboptimal obstetric outcomes and the risk of neonatal lupus syndrome[8].

Disease activity during pregnancy

Up to 75% of patients with SLE have clinically evident renal disease; active renal involvement is defined as the presence of urine sediment (≥5 red and white blood cells per high-powered field and/or ≥1 cellular casts) and/or proteinuria ≥0.5 g/d, with or without an elevation in serum creatinine[3].

Preexisting renal disease is an important risk factor and studies show an increase in maternal and fetal complications including spontaneous abortion, premature delivery (with the associated neonatal morbidity), intrauterine growth restriction and pre-eclampsia.

Lupus flare in pregnancy is one of the major issues associated with SLE. Studies report variable flare rates in pregnancy between 25-65%[5,6]. The most common flares are renal and hematologic with the musculoskeletal flares being less common. The progression of pregnancy in patients with pre-existing renal disease may be accompanied by an increase in proteinuria, and either de novo or worsening of hypertension. It is very important to differentiate between lupus renal flare and other obstetrical conditions like pre-eclampsia (hypertension and proteinuria) (Table 1).

Pregnancy complications

A large national database 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(3, 9).

Maternal morbidity and mortality in the setting of active LN: a recent meta-analysis reported frequencies of 16.3% for hypertension and 7.6% for pre-eclampsia among pregnant LN patients. Progressive renal impairment can occur, but it is generally mild, and the necessity for hemodialysis is rare[10,11].

Fetal and neonatal complications are also increased in pregnancies complicated by LN. Studies report increased

Table 1 Differentiation of pre-eclampsia and active lupus nephritis

	Pre-eclampsia	Active Lupus Nephritis
Timing in pregnancy	After 20w of gestation	All gestational ages
Complement (C3, C4)	Normal	Typically decreased
Thrombocytopenia	Absent	Present
Neutropenia	Absent	Present
Active urine sediment	Absent	Present (may be benign in membranous lupus nephritis)
Other organ involvement	Absent	Present
Anti-double-stranded DNA antibodies	Absent	Present
Anti-C1q antibodies		May be high
Serum uric acid	Increased	Normal (may be elevated with reduced GFR)
Hypertension (BP ≥140/90 mmHg)	Present	Variable
Elevation in creatinine (≥1.2 mg/dl)	Typically absent	Commonly present

risk for preterm birth as high as 39.4 %, intrauterine growth restriction 12.7%, stillbirth 3.6 %, neonatal death 2.5%.

Neonatal lupus syndromes is a form of passively acquired fetal autoimmunity from maternal antibodies, anti-Ro and anti-La antibodies. It is manifested by cutaneous rash, hepatic and hematologic abnormalities and 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[3,12].

The cardiac manifestations of neonatal lupus syndromes include conduction defects, structural abnormalities, cardiomyopathy and congestive cardiac failure. However, the most common issue is congenital heart block (CHB). CHB leads to high fetal mortality; rates of 15-30% have been reported[13,14].

Antepartum management

Pregnancies complicated by SLE and LN are best managed with a multidisciplinary approach including an obstetrician (maternal fetal medicine specialist), rheumatologist, and nephrologist. Close maternal disease monitoring should be conducted by periodically obtaining laboratory studies and serial fetal ultrasound is recommended to observe fetal growth. Also in case of thrombocytopenia and/or coagulation abnormalities an anesthesiologist should be consulted for the appropriate intrapartum analgesia[15,16].

As we mentioned earlier the distinction between renal flare, preeclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome can be challenging manifesting similar signs like hypertension, proteinuria. The management of these pregnancy complications differs so it is essential to make the differential diagnosis - LN flare is managed with immunosuppression whereas delivery is indicated in cases of superimposed preeclampsia or HELLP syndrome[17].

Delivery may be best in a tertiary care center where neonatologists are available, particularly if a patient is likely to deliver before 37 weeks of gestation. Cesarean section should be reserved for obstetrical indications[18].

Conclusions

Pregnancy in women with SLE is a high risk condition for neonatal and maternal morbidity. Despite considerable improvement in success rates, suboptimal obstetrical outcomes still remain a cause for concern. Best pregnancy results can be obtained if appropriately managed by a multidisciplinary team of physicians, with appropriate preconception counseling and monitoring. Increased fetal loss, especially in the presence of aPL, pre-term births, and neonatal syndromes including CHB are major unresolved issues. ■

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