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Review

Systemic Lupus Erythematosus and Pregnancy Outcomes

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease. It is characterized by the development of autoantibodies and immune complexes in association with a wide variety of clinical manifestations and tissue damage. Several defects of multiple immunological components play a role in the pathogenesis of SLE. Despite the advent in the management of SLE pregnant patients, SLE poses a higher risk of prenatal morbidity and mortality when compared to normal pregnant females. Pregnancies for patients with SLE pose a greater risk of fetal loss, intrauterine growth retardation, prematurity, preeclampsia, and low birth weight. Pregnancy can both trigger and cause SLE flares. In this review we will discuss the effect of SLE on pregnancy, fertility, when and how to time pregnancy, organ involvement during pregnancy (eg. Lupus nephritis), clinical and serological factors associated with adverse maternal and fetal outcomes in SLE. At last the management of pregnant female patient with SLE.

Keywords: pregnancy, SLE, maternal outcomes, fetal outcomes

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. It is characterized by the development of autoantibodies and immune complexes in association with a wide variety of clinical manifestations and tissue damage. Several defects of multiple immunological components play a role in the pathogenesis of SLE (D'Cruz et al., 2007).

Effect of SLE on pregnancy

Fertility

Usually SLE does not affect the fertility of patients but it might decrease in patients with renal failure, an ovulatory cycles due to active disease or high dose corticosteroids and cyclophosphamide treatment. It is better to give cyclophosphamide intravenously by pulse therapy intermittently than daily oral cyclophosphamide for preservation of gonadal function as the chances of permanent amenorrhea are higher with the latter (Mok and Wong, 2001).

In lupus patients undergoing cyclophosphamide treatment in order to preserve fertility we can use oral contraceptives to put the ovary to rest, or use of gonadotrophin releasing factor (Petri, 2000).

For infertile women with lupus invitro fertilization (IVF) might be a solution for these cases. Oestrogens given as part of IVF regimens may exacerbate SLE but these flares can be controlled (Guballa et al., 2000).

When and how to get safe pregnancy?

It is better to plan pregnancy in SLE patients and is better when the disease is in remission for at least 6 months. For patients who need contraceptive methods, barrier contraception (condom, diaphragm etc.) is the safest method (Petri, 2000).

Intra-uterine devices might cause infection, especially in women on immunosuppressives and that is why they are best avoided. The low dose oestrogen oral pills are usually safe in SLE patients except for patients with antiphospholipid syndrome (APL). Authors who reported SLE exacerbation with oral pills explained this by high dose of oestrogens. Women who do not want to get pregnant any more can safely undergo tubal ligation (Guballa et al., 2000).

Organ Involvement in SLE and Pregnancy

Lupus nephritis

Lupus nephritis (LN) is a major complication of SLE therefore pregnant patients with active LN is at higher risk for pregnancy complications than those without LN. They should be advised to have renal remission of at least 6 months, and if possible, 12–18 months before getting pregnant according to recommendations (Rahman et al., 2005).

Women with quiescent disease (proteinuria <500mg/day and inactive urinary sediment) and unaffected renal function are at reasonably low risk during pregnancy but should be closely monitored. In normal pregnancy, the glomerular filtration rate increases by 30–50% and creatinine clearance rises to<100 mL/min, causing a decrease in serum creatinine. Tubular reabsorption of protein is decreased during pregnancy, and this is why an increase in the normal proteinuria level to150–180mg/24h is possible. However, new-onset proteinuria>300mg/24 h may be considered pathological in pregnant patients without proteinuria at baseline. The rate of fruitful pregnancies in SLE ladies with LN went in the vicinity of 65% and 92%, and the frequency of flares extended in the vicinity of 8% and 30% (Bramham et al., 2011).

Maternal hypertension during pregnancy and the rate of premature birth are commonly presented in patients with LN as proved by systematic review and meta-analysis. During pregnancy renal flare may determine further loss of kidney function in the short and the long term, with potential accelerated progression to end stage renal disease (Smyth et al., 2010).

Respiratory system and cardiovascular system

Cardiovascular disease (CVD) is a main source of morbidity and mortality in SLE. SLE patients with restrictive pulmonary disease may worsen during pregnancy because of thoracic pressure by the developing uterus. Also, women with cardiac affection may be at risk of heart failure due to volume overload caused by the normal increase in circulating volume. A past report found that SLE patients with a background marked by pulmonary embolism PE had a very nearly fourfold increment in the rate of subclinical CVD (Oakley and Warnes, 2007).

Clinical and Serological Factors Associated with Adverse Maternal and Fetal Outcomes in SLE (G´omez-Puerta et al., 2013)

Clinical factors

SLE activity 6 months before and during pregnancy, onset of disease during pregnancy, chronic kidney disease (creatinine> 2.8mg/dL), active LN, hypertension, Previous fetal loss, and Catastrophic antiphospholipid syndrome (CAPS) which is a rare complication but is a life-threatening.

Serological factors

Positive Antiphospholipid-antibodies and anti-double-stranded DNA antibodies.

Biochemical factors

Low complement levels, proteinuria, and Thrombo-cytopenia.

Maternal outcome

The danger of pre-eclampsia (PE) in lupus patients is (5-38%) when compared with ladies without SLE. There are numerous hazard factors for pre-eclampsia, for instance, previous hypertension, LN and presence of antiphospholipid antibodies (APL). Clinical, separation between PE to hypertension, proteinuria, edema and deterioration in renal function. Preeclampsia and renal lupus may exist together in a similar patient. The treatment for pre-eclampsia and eclampsia are the same as in the non-lupus patients (Mok and Wong, 2001).

Neonatal Outcome

There is a risk of obstetric and neonatal complications in SLE pregnancy than in general population, on the other hand in the last decades there was improvement in these

complications. Also women with SLE have fewer live births compared with the general population especially in patients with high disease activity. Major obstetrical complications are usually associated with lupus activity with the presence of APS (Vinet et al., 2011). There is fetal loss in about 20% of pregnancies in women with SLE (Clowse et al., 2005).

Patients with SLE have higher risk of PE, IUGR, fetal loss, and preterm delivery when compared to general population, especially in those with active nephritis (Carvalheiras et al., 2010). A study done in multicenter revealed that PE rising to 22% if there were positive APL even without severe disease activity (Salmon et al., 2011).

The difficulties during pregnancy as revealed by The European Registry on Obstetric Antiphospholipid Disorder (EUROAPS) of 247 ladies were repetitive first trimester premature delivery took after by fetal loss. Different difficulties which did not prompt fetal demise were in 52% of the cases. The most common finding was prematurity followed by stillbirth, fetal loss, miscarriage, fetal growth restriction, and early and late onset PE in a percentage of 47%, 22.5%, 16%, 14%, 13% and 12% respectively. The strongest marker related to poor obstetric outcomes was the presence of lupus anticoagulant (LAC), isolated or in combination with anticardiolipin (aCL) and/or anti-beta2-glycoprotein I (anti-β2GPI) (Alijotas-Reig et al., 2015). Also, the higher the number of positive LAC the more association of thrombosis (Sciascia et al., 2013). In about 50% of the complicated cases there was low complement levels. Usually outcomes of the mother or the upcoming baby were good when the accepted treatment was given (Alijotas-Reig et al., 2015).

The investigation of 76 pregnancies in 63 lupus patients there was 15% with PE, 30% hypertension and 27% of babies had chronic fetal distress. The mean gestational age was 35 weeks and fetal passing was more continuous in patients with nephritis when contrasted with patients without nephritis (37% versus 12.2%) (Klumb et al., 2005). Low complement titre and positive anti-DNA in the second trimester in SLE patients were reported to have higher rate of fetal loss and preterm delivery regardless of the clinical activity, but when combined with clinical activity this was more predictive of fetal loss and prematurity (Clowse et al., 2011).

In a cohort of 96 patients, Borella et al. evaluated 132 pregnancies of 96 patients with SLE and reported that there were live births, PE and premature rupture of membranes 22%, 12% and 8% respectively. Hypertension at conception was found to be predictor of fetal loss, while presence of APS and the titre of anti-dsDNA before pregnancy were predictors of preterm birth. Interestingly, the presence of APS was not related with pregnancy loss, the fact that could be explained by the use of low dose aspirin and heparin in patients with APS and/or positive APL (Borella et al., 2014). In cases of PE or fetal distress usually to protect the fetus and/or the mother the doctors induce premature rupture of membranes (Clark et al., 2003).

Disease activity 6 months prior to and during pregnancy with high anti-DNA titre and low serum complement levels is another risk factor for preterm delivery (Clowse et al., 2011).

In SLE pregnancies it is common to find low birth weight babies (<2500 g) or babies smaller than gestational age in a percent ranging from 6 to 35% (Yuen et al., 2009).

Neonatal Lupus Syndrome (NLE)

Neonatal lupus syndromes (NLE) are a rare condition in infants born to mothers with positive Ro/SSA and La/SSB autoantibodies. It consists of cutaneous, cardiac, and systemic abnormalities observed in newborn infants. It is usually self-limited, but may sometimes have serious consequences. It is due to passive transfer of anti-Ro/SSA and/or anti-La/SSB antibodies in some babies of mothers with autoimmune disease which may damage the developing tissues (Lun Hon and Leung, 2012).

Approximately 98% of affected infants have maternal transfer of autoantibodies against Ro/SSA, La/SSB, and less commonly U1-RNP. However, only 1-2% of mothers with these autoantibodies have neonates with NLE, regardless of whether the mothers are symptomatic or not**.** The finding is typically made in light of the clinical highlights and the exhibit of (NLE) related antibodies in the serum of the mother or influenced baby. The most widely recognized clinical signs of NLE are, in diminishing request of recurrence, dermatologic, heart, and hepatic variations from the norm. A few babies may likewise have hematologic, neurologic, or splenic variations from the normal. The most serious complication in the neonate is Complete heart block (CHB) is the most dangerous complication of these babies which occurs in about 2% of SLE pregnancies. This may require a pacemaker in about 60% and cardiomyopathy develop in 10% despite pacemaker placement. 10-year mortality rate is 20–35% (Izmirly et al., 2010).

Pregnancy in Mothers with Anti-Ro Antibodies

The high-danger of CHB is the most critical issue identified with the presence of anti-Ro antibodies during pregnancy.CHB develops between 18 and 24 weeks of pregnancy. Early treatment may be a way to reverse this condition which may be noticed by a lesser degrees of conduction delays (Izmirly et al., 2010).

However, conduction abnormalities may progress very rapidly and CHB is often the first rhythm abnormality detected. Various tools have been developed for the

early detection of lesser degrees of heart block, including fetal Doppler echocardiography, fetal kineto cardiogram, and trans-abdominal fetal electrocardiogram. Fetal Doppler echocardiography is the most commonly used. Monitoring is usually done weekly between 16 and 26 weeks of pregnancy and biweekly there after (Buyon et al., 2009).

An early detection of conduction defect (as prolonged PR interval) should be considered as dangerous signal. In these cases prophylactic treatment ought to be given in thought. Fluorinated corticosteroids may help fetal survival in a few examinations, yet then again there is a higher danger of IUGR and preterm birth (Friedman et al., 2009).

Treatment of established CHB remains even more unsatisfactory. A study done in 2004 found that after giving the mother dexamethasone and betaadrenergic stimulants there is improved fetal outcomes (Jaeggi et al., 2004). Tunks et al found that hydroxychloroquine reduces the risk of cardiac NLS in at-risk fetuses (Tunks et al., 2013), also decreases the risk of recurrence in subsequent pregnancies (Izmirly et al., 2010).

Contraindications to pregnancy

Severe pulmonary hypertension (estimated systolic PSAP > 50mmHg or symptomatic), advanced heart failure, severe restrictive lung disease, moderate/severe chronic renal failure (creatinine>2,8mg/dL), current use of (clophosphamide, mycophenolate mofetil, methotrexate, leflunomide, statins and angiotensin converting enzyme inhibitor),active renal (24 h urinary protein > 0.5 g) or CNS disease in the past6 months, recent major thrombosis (<2 years), and cardiovascular disease (CVD) (Lin et al., 2014).

Morbidity and Mortality

SLE women are subjected to more serious complications and mortality than other non-SLE women. These comorbidities as pregestational diabetes, arterial hypertension, pulmonary hypertension, renal failure, and thrombophilia**.** The risk of complications in SLE patients is about 2–4-fold increase in the rate of caesarean section, PE, and eclampsia, especially in women with preexisting hypertension and/or renal insufficiency taking high-dose prednisone (Clowse et al., 2008).

Patients with postpartum or antepartum haemorrhage, anaemia at delivery and thrombocytopenia which are common in SLE patients might require blood transfusion (Salmon et al., 2011).

The risk for both venous thromboembolism and stroke was 6.5- fold higher than that of healthy pregnant women, and the excess maternal mortality rate was estimated at 20 times higher than in the general population. These data, collected using the discharge diagnosis, may be not comparable with those derived from tertiary referral centers in which careful multidisciplinary management of pregnant women with SLE allows better maternal and fetal outcomes (Tincani et al., 2008).

Pregnancy and lupus flares

An important aspect of pregnancy in SLE patients is the risk of disease flares. It is not simple to quantify the incidence of these complications because many clinical studies were performed using individual definitions of flare. Recently, efforts have been made to create a “pregnancy-version” of existing activity indexes, such as the systemic lupus erythematosus activity index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) aimed at making studies more comparable (Doria et al., 2008).

One of the reliable indexes for pregnant SLE females is the British Isles Lupus Assessment Group (BILAG) 2004-Pregnancy index (Yee et al., 2012).

The results of prospective, controlled observational studies show some discordance: some studies found that women are at increased risk of lupus flares when pregnant, while other studies found no difference between pregnant SLE patients and controls. This error might be clarified by the set number of patients enlisted in SLE-pregnancy studies, the absence of criteria for characterizing lupus flares, disease heterogeneity, and the different medicines utilized during pregnancy. Also there are some normal manifestation of pregnancy that might be considered as flares but they are not as arthralgia, myalgia, facial and palmar rash, hearing loss, and edema in the face, hands, and lower limbs. Similarly, some serological variations as complement and erythrocyte sedimentation rate might be physiologically adjusted during pregnancy (Doria et al., 2008).

The disease flare is unpredictable but usually in third trimester. The risk of flares increase in case of disease activity 6–12 months before pregnancy, women with repeated flares before conception, women who stopped medications (particularly hydroxychloroquine) or in women with active glomerulonephritis at time of pregnancy (Imbasciati et al., 2009).

A study done by Clowse et al. (2011) found that the rate of pregnancy loss increases when there is disease activity 6 months before conception, also when there is low complement or positive anti-dsDNA (Clowse et al., 2011).

Authors examined indicators of SLE flare during pregnancy were distinguished by stepwise logistic regression analysis in 132 pregnancies in 96 SLE patients and found that maternal lupus flares happened in 57% of pregnancies and were best anticipated by the quantity of flares before conception. Likewise, dermatological flares by previous skin rash, renal flares

by previous nephritis, and haematological flares by previous haematological abnormalities (Borella et al., 2014).

Higher disease activity, serious organ damage, early onset preeclampsia, and higher pregnancy loss are generally connected with thrombocytopenia during pregnancy. Central nervous system (CNS) lupus in pregnancy represents serious sign of SLE and may include extraordinary maternal and fetal dangers. Compared with nonpregnant active female SLE patients, active pregnant-related lupus, including new-onset lupus and flare lupus, had a higher rate of renal and hematological association yet less mucocutaneous and musculoskeletal affection (Yang et al., 2014).

Pregnancy and Lupus Nephritis (LN)

The presence of renal disease of any reason is a significant risk factor for obstetric complications (Stanhope et al., 2012). What's more, even little decreases in the glomerular filtration rate (GFR) may expand the possibility of pregnant ladies to develop PE (Bramham et al., 2011). LN is among the findings that most often induces increased morbidity and mortality during pregnancy, patients with LN who takes high doses of corticosteroids and immunosuppressive agents have a higher incidence of severe infections and hospitalization and also have an increased mortality rate (Li and Isenberg, 2006).

Active LN demonstrates positive relationship with premature delivery, increased recurrence of hypertension, and of PE .To recognize clinical markers of LN activity from pregnancy physiological appearances and those identified with PE can be a test. In the first trimester of pregnancy, maternal systemic circulation suffers remarkable physiological vasodilation and relaxin, a hormone produced by the corpus luteum, is a major contributor. One of the consequences of these progressions is a physiological increase of the GFR and resulting serum creatinine diminishment, so estimations of 0.9mg/dL may recommend a hidden renal disease requiring further examination. Protein discharge in the urine is additionally increased and rates equivalent to or over 300 mg/24 hours are viewed as pathological. Hence, during pregnancy patients with LN may have disconnected rise of proteinuria that isn't really characteristic of active nephritis. The patients with LN have 2-3 times higher rate of flare when contrasted with patients without LN, both systemic and renal disease activity (Smyth et al., 2010).

Then again, the utilization of azathioprine during pregnancy by patients with LN was related with a lower recurrence of flare (Fischer-Betz et al., 2013).

Varying outcomes have been accounted for on pregnancy results in SLE women with prior LN. The rate of successful pregnancies ranged between 65% and 92% and the incidence of flares ranged between 8% and 30% (Bramham et al., 2011).

A systematic review and meta-analysis of pregnancy results showed a significant relationship between active LN and both the onset of maternal hypertension during pregnancy and the rate of premature birth**.** Preeclampsia (PE) which is more common in women with SLE, identified in up to 20% versus 7.6% in healthy pregnant controls. This obstetric complication have clinical and laboratory appearances that can be completely super imposable to the active LN, which is in turn a risk factor for the development of PE (Smyth et al., 2010). Furthermore, patients with LN have a tendency to develop PE earlier compared with women with SLE without nephritis (Bramham et al., 2011).

One of the most complex and challenging aspects during a pregnancy of a woman with lupus is the precise characterization of the LN activity and the differentiation of PE. In the two confusions hypertension, proteinuria and edema are present. The differential conclusion is basic, as the treatment shifts fundamentally: in PE, delivery should be considered, while immunosuppressive medications should be administered to patients with SLE nephritis. LN is likely to be related with positive anti-dsDNA antibodies (particularly in high titers), serum complement utilization, and dysmorphic hematuria and/or red blood cell cylinders. In this situation, the likely diagnosis is a proliferative kidney disease (Klumb et al., 2015).

During clinical assessment, the onset of fever, presence of discoid or subacute cutaneous lupus lesions, vasculitis, oral ulcers, polyserositis, lymphadenomegaly, positive direct Coombs, myocarditis, and pneumonitis additionally demonstrate lupus flare. In contrast, if the gestational age is more than22 weeks, with no signs of SLE activity and hyperuricemia is present, we can express the determination of PE with relative exactness. A few highlights, if introduce, may recognize the two conditions. However, in many circumstances the patients' manifestations are not complete. Renal biopsy is a important research tool for accurate characterization of LN, but it is usually avoided during pregnancy because of the technical difficulties of this method in pregnant women. A current report found that renal biopsy gives valuable data to the administration of patients with LN during pregnancy (Chen et al., 2015).

Management of SLE

Follow up of pregnant SLE patient

Prenatal Care

Ideally, all patients with SLE that who wants to get pregnant should have a preconception visit, when the doctor assesses the dangers related to the pregnancy,

drugs that are contraindicated during pregnancy and if the patient is in the best moment to get pregnant indicated by underlying disease activity and complications. Arranged pregnancies have shown reduced flare rates and better obstetric results in women with SLE**.** After conception, antenatal management of pregnant patients with SLE requires close joint effort from the rheumatologist and obstetrician (Lateef and Petri, 2013).

Antinatal care

The woman with SLE who gets pregnant should be submitted to clinical and laboratory evaluations during the first visit, keeping in mind the end goal to recognize SLE disease activity and circumstances that increase risk of fetal complications.

Recommended visits

Obstetrician visits are as follows

(A) monthly until 20 weeks,
(B) Every two weeks until 28 weeks,
(C) Weekly after 28 weeks until delivery.

Rheumatologist visits are as follows

(A) Ideally, a rheumatologist should support the obstetrician during prenatal care;
(B) If not possible, the rheumatologist should see the patient every 4–6 weeks.

Laboratory Tests

First visit tests are as follows

(A)Complete blood count, platelet count, prothrombin time, and partial thromboplastintime;
(B)Lupus anticoagulant; anticardiolipin antibody IgG and IgM; and anti-β2 glycoprotein I IgG and IgM (which must be repeated in 12 weeks if positive).
(C)Anti-Ro/SS-A, anti-La/SS- B, anti-Sm, and anti-RNP.
(D)Blood glucose, BUN, creatinine, uric acid, AST and ALT.
(E)Anti-DNA, C3, C4, and CH50.
(F)Urinary sediment; 24-hour proteinuria or protein/creatinine ratio in a single urine sample, creatinine clearance and urine culture.

Quarterly visit tests are as follows

(A) Complete blood count, platelet count;
(B) Anti-DNA, C3, C4, and CH50;
(C) Blood glucose, BUN, creatinine, uric acid, AST and ALT;
(D) 24-hour proteinuria or protein/creatinine ratio in a single urine sample if preeclampsia orlupus nephritis is suspected, as well as research erythrocyte dysmorphism.

Ultrasound and Doppler Velocimetry Studies

(1) Monthly after 24 weeks: evaluation of fetal growth, amniotic fluid, and umbilical artery (fetal-placental flow),
(2) Uterine artery evaluation at 24 weeks: screening tests for preeclampsia and intrauterine growth restriction.

Intervals of the visits and frequency of laboratory tests may be smaller in case of disease activity or suspected PE. Laboratory tests should be interpreted in the light of the knowledge of the changes imposed by pregnancy itself. Despite being used as a marker of inflammatory disease activity, erythrocyte sedimentation rate (ESR) rises by pregnancy itself, so it should not be used in pregnant women with SLE. Serum complement levels tend to increase during pregnancy and its fall should be assessed relative to a baseline test. By chance, thrombocytopenia may happen in around 10%of pregnant women and it becomes difficult to distinguish from lupus activity. The urinary excretion of proteins, which normally rises during pregnancy, can reach about 300mg/24hours without having clinical significance (Lateef and Petri, 2013). Likewise, pregnant women generally have a tendency to have urinary tract infections, and the use of immunosuppressant agents may inhibit cellular deviation and leukocytosis. Renal function should be evaluated even in patients without nephritis history as it can be asymptomatic or begin during pregnancy, and also the requirement for a pattern for examination on account of kidney damage throughout pregnancy. Hepatic involvement is uncommon in patients with SLE, but the assessment of their role is required particularly in patients taking azathioprine because of its hepatotoxicity, with repeat tests at least every 3 months (References).

Regarding the mentioned antibodies, aPL (LAC, aCL, and anti-β2GPI) is markers of adverse pregnancy outcomes and may be useful on account of a thrombotic event during pregnancy. It ought to be recollected that the presence of aPL in lupus patients without obstetric (repetitive spontaneous abortion, fetal loss) or thrombotic occasions (deep vein thrombosis, arterial thrombosis) does not give the diagnosis of APS or even justifies the prescription of heparin to these patients. Most of authors suggest the use of low dose aspirin during pregnancy for patients with SLE and positive aPL (de Jesus et al., 2012).

Lupus flares are probably going to be related with hypocomplementemia and increased titers of anti-DNA antibodies; in comparison, complement levels are as a rule (yet not generally)increased in patients with

preeclampsia. The anti-Ro/SSA and anti-La/SSB are in charge of neonatal lupus and anti-Smith the antibody specific for SLE. Patients with positive anti-Ro/SSA or anti-La/SSB ought to perform fetal echocardiography week after week from 16 to 26 weeks and every other week thereafter (Lateef and Petri, 2013).

ANA, anti-Ro/SS-A, anti-La/SS-B, anti-Sm, and anti-RNP do not change with disease activity and therefore do not need to be repeated later. Current standard of care in SLE pregnancy incorporate Doppler investigations of uterine arteries and umbilical artery, which are useful to evaluate placental capacity and to avoid the event of difficulties, for example, PE and fetal distress (Ruiz-Irastorza and Khamashta, 2011).

Uterine Doppler studies are valuable as screening test for PE and the 24th week is the best moment for the assessment. Abnormal uterine artery Doppler studies have been distinguished inpatients with SLE with history of fetal loss, PE, IUGR, and preterm labor (Pagani et al., (2015).

Umbilical Doppler ultrasound gives a more precise meaning of the placental function, indicating different degrees of impairment such as increased resistance, absent or even reverse diastolic flow, which is a reasonable sign of placental insufficiency and fetal distress (Ruiz-Irastorza and Khamashta, 2011).

Follow-up with month to month ultrasound and Doppler velocimetry studies beginning at 24 weeks to assess fetal growth, amniotic fluid, and fetal-placental flow is recommended thinking about the high occurrence of fetal growth restriction and chronic distress (Le ThiHuong et al., 2006).

Treatment of pregnant SLE patient

Antimalarial

The utilization of hydroxychloroquine during pregnancy is suggested by the American College of Rheumatology and the European League Against Rheumatism (EULAR). Hydroxychloroquine (200-400mg daily) utilized during pregnancy decreases the quantity of flares and hypertensive disorders so its utilization should be kept during pregnancy or prescribed for those that are not utilizing (Hahn et al., 2012).

Its utilization during pregnancy is safe, without reported malformations, growth restriction and ocular, auditory, orneurological toxicity in exposed fetus (Ruiz-Irastorza and Khamashta, 2011). Chloroquine has smaller information when compared to hydroxychloroquine, but no long-term sequel was additionally illustrated (Makol et al., 2011). In addition, a systematic review did not report any visual abnormality in children born from mothers treated with chloroquine or hydroxychloroquine during pregnancy (Osadchy et al., 2011). Both are secreted in breast-milk, however there was no reportof adverse effects in breastfed children whose mothers used hydroxychloroquine (Makol et al., 2011).

Corticosteroid

Corticosteroids are the treatment of choice in cases of flare of SLE during pregnancy and can be utilized as prednisone or prednisolone. Most specialists prescribe starting with prednisone at the least dose possible. These compounds are inactivated by the enzyme 11-β-hydroxysteroid dehydrogenase and reduce fetal exposure to approximately 10% of maternal dosage (Jain and Gordon, 2011). In this way, the utilization of these medications does not replace the utilization of betamethasone or dexamethasone when they are demonstrated for fetal lung development. The dose should be the minimum dose needed and depends on the impaired organ, using the same criteria recommended for non-pregnant women. The utilization of doses above 10mg/day of prednisone is associated with increased danger of developing arterial hypertension, dyslipidemia, fluid retention, and maternal hyperglycemia. Intravenous pulses of methylprednisolone can be utilized safely if indicated for severe activity. Corticosteroids do not enter breast milk in large quantities and there is no contraindication to breastfeeding in women who are on corticosteroid therapy (Ward et al., 2001).

Women that are breastfeeding and utilizing higher doses of corticosteroids should hold up 4 hours after taking the pill to breast-feed, reducing the drug concentration in the breast-milk (Makol et al., 2011).

There is no confirmation that the prophylactic utilization of corticosteroids in SLE pregnant women without activity counteracts exacerbations during pregnancy, so this conduct is considered in appropriate. The nonsteroidal anti-inflammatory drugs can be given for the management of arthralgia or serositis in the most minimal measurements workable for a brief timeframe and it is prescribed to be totally ceased after the 32th week. After this time, there is high risk of fetal and maternal hemorrhage in addition to fetal renal dysfunction, and premature closure of arterial duct (50).

Azathioprine

Azathioprine in doses up to 2.5mg/kg/day stays one of the helpful treatments in cases of SLE activation during pregnancy, being the immunosuppressant of choice for the treatment of severe maternal disease or refractory to isolated use of corticosteroids. This immunosuppressant and steroid sparing agent is not related with teratogenicity in humans, as the fetal liver isn't equipped for processing azathioprine in to its active form. The

treatment with azathioprine is safe with breastfeeding, with no risks for the child (Makol et al., 2011).

Tacrolimus and Cyclosporine

Since, Cyclosporin (4mg/kg/d) and Tacrolimus (0.075mg/kg/d-0.2mg/kg/d) both are safe during pregnancy and during breastfeeding, these may be used for controlling of disease activity (Armenti et al., 2008).

Anti-hypertensive drugs

Medications safe in pregnancy are Methyldopa, Labetalol, Nifedipine, Hydralazine. Acetaminophen: It is protected during pregnancy. Heparin: I t does not cross placenta and is safe during pregnancy. Simplicity of administration, higher anti-thrombotic to anticoagulant ratio and predictable bioavailability makes low-molecular weight heparin (LMWH) the anti-coagulant of choice(Hahn et al., 2012).

Anti-platelets

Aspirin is the only anti-platelet drug safe in pregnancy and may be continued if indicated, Low-dose aspirin (less than 160 mg/day) has been used safely in the treatment of pregnant women with antiphospholipid syndrome (Østensen et al., 2006).

Drugs which contraindicated during pregnancy

Cyclophosphamide, mycophenolatemofetil, leflunomide, and methotrexate have teratogenic effects and should not be used during pregnancy (Fischer-Betz et al., 2013). Mycophenolatemofetil should be stopped at least 6months prior to conception and changed to azathioprine, with a small risk of flare during this period (Fischer-Betz et al., 2013).

CONCLUSIONS

SLE women are subjected to more serious complications and mortality than other non-SLE women. Also, fetal complications in SLE patients have higher risk of preeclampsia, intra uterine growth retardation, fetal loss, and preterm delivery. So, planned pregnancy is mandatory.

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