World Journal of Rheumatology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5499/wjr.v3.i3.32

World J Rheumatol 2013 November 12; 3(3): 32-39
ISSN 2220-3214 (online)

MINIREVIEWS

Hot topics in lupus pregnancy

Javier A Cavallasca, Cecilia A Costa, Maria del Rosario Maliandi, Jorge L Musuruana

Javier A Cavallasca, Cecilia A Costa, Maria del Rosario Maliandi, Jorge L Musuruana, Sección Reumatología y Enfermedades Autoinmunes Sistémicas, Hospital JB Iturraspe, CP 3000, Santa Fe, Argentina
Author contributions: All the authors contributed equally to the analysis and interpretation of the data as well as to the preparation of the manuscript.
Correspondence to: Javier A Cavallasca, MD, Sección Reumatología y Enfermedades Autoinmunes Sistémicas, Hospital JB Iturraspe, Bv. Pellegrini 3551, CP 3000, Santa Fe, Argentina. jcavallasca@yahoo.com.ar
Telephone: +54-342-4555019 Fax: +54-342-4555019
Received: June 27, 2013 Revised: September 30, 2013
Accepted: November 1, 2013
Published online: November 12, 2013

Abstract

Systemic lupus erythematosus (SLE) typically affects women in their childbearing age, who have the same fertility rates as the healthy population. The effect of pregnancy on the disease and the effect of SLE on pregnancy and the fetus are highly important issues for the attending physician. Whether lupus flares are more frequent during pregnancy remains controversial. Among the possible effects of SLE on pregnancy are a greater number of abortions, fetal loss, pre-term deliveries and perinatal mortality. The newborn may be affected by the onset of neonatal lupus erythematosus (neonatal LE), either as a skin or blood disease, or by the presence of congenital heart block. The frequent association between SLE and antiphospholipid syndrome represents another risk situation for the mother and the product of conception. Multiples drugs used in SLE patients should be evaluated. Those with teratogenic potential should be withdrawn before pregnancy, and when necessary, appropriate medications should be indicated to treat the mother without compromising the safety of the baby. In conclusion, pregnancies in lupus patients represent a challenge for the physician and must be closely followed up and treated if necessary, during all trimesters and in the puerperium period, to improve outcome.

Key words: Systemic lupus erythematosus; Pregnancy; Pre-eclampsia; Lupus nephritis; Neonatal lupus erythematosus; Congenital heart block

Core tip: Systemic lupus erythematosus (SLE) typically affects women in their childbearing age. The effect of pregnancy on the disease and the effect of SLE on pregnancy and the fetus are highly important issues for the attending physician. The newborn may be affected by the onset of neonatal lupus erythematosus, either as a skin or blood disease, or by the presence of congenital heart block. The frequent association between SLE and antiphospholipid syndrome represents another risk situation. Optimization of pharmacological therapy before and during pregnancy should be done in order to reduce adverse events to the mother and the baby.

Cavallasca JA, Costa CA, Maliandi MR, Musuruana JL. Hot topics in lupus pregnancy. *World J Rheumatol* 2013; 3(3): 32-39 Available from: URL: http://www.wjgnet.com/2220-3214/full/v3/i3/32.htm DOI: http://dx.doi.org/10.5499/wjr.v3.i3.32

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that typically affects women in their childbearing age. The peak incidence of SLE occurs between the ages of 15 and 40 years, with an estimated female to male incidence of 9:1. Multiple reports have researched the impact of pregnancy on SLE with dissimilar results. While some authors hold that pregnancy is not a cause of disease exacerbations[1] other researchers have found exacerbations in 74% of cases[2]. There is no consensus on the management of pregnancy in SLE patients[3]; therefore pregnancy is a challenge for lupus patients and their physicians.

Although pregnancy in SLE currently has favorable

outcomes for the majority of women, the potential for maternal and fetal complications still exists[4]. Next we summarize the latest bibliographical data of SLE and pregnancy.

FERTILITY: IS FERTILITY IMPAIRED IN LUPUS PATIENTS?

Women with SLE have normal fertility, even if disease is active. However, fertility may be reduced in the presence of impaired renal function. Cyclophosphamide has previously been associated with ovarian failure. However, it has now been demonstrated that cumulative dose of cyclophosphamide on patients over 32 is the most important predictor of anovulation[5]. On the other hand, the use of azathioprine, cyclosporine and methotrexate is not associated with ovarian failure[6].

WHICH ARE THE BEST CHOICES FOR BIRTH CONTROL?

Patients with SLE should be encouraged to delay pregnancy until their disease is inactive for at least 6 mo, to avoid major complications and fetus exposure to potentially teratogenic medications.

Effective and safe birth control is essential to the care of these patients, especially in the group that have high risk of complications, where pregnancy is contraindicated (Table 1)[7].

Barrier methods are the most common form of contraception in these patients. However, they are not the most appropriate choice because they have a relatively high rate of failure compared to, the significantly lower failure rate of hormonal contraceptives. Oral contraceptives are safe for about two thirds of SLE patients, according to OC-SELENA trial which demonstrated that oral contraceptives do not appreciably increase the risk of a severe flare as compared with placebo[8]. The exception would be unstable lupus, hypercoagulability due to antiphospholipid antibodies or to nephrotic syndrome or past history of thrombosis. Although estrogen containing contraceptives are contraindicated for this risk group, other contraceptive methods can be recommended. Progestin-only methods, including the levonorgestrel-containing intrauterine devices (IUD) do not increase the risk of thrombosis in the general population.

The lowest failure rates are achieved with IUD, a method that offers effective, reversible contraception without increasing vascular risk. Besides, this method is considered safe for all women with SLE. Previous concerns about an increased risk of infection in immunocompromised patients appear unfounded[9].

HOW DOES PREGNANCY AFFECT LUPUS PATIENTS?

The influence of pregnancy on disease activity in women with SLE is variable. This variability may be due to the differences in study populations, the number of patients included in the series, the methodological differences in the study design, the existence or lack of a control group, and the definition of flare that is being used. In, general flares during pregnancy were observed in 40%-60% of patients in all trimesters and in the puerperium period and they were usually mild. Severe flares may occur in 15%-30% of the cases dependent on disease activity 6 to 12 mo prior to conception[10,11]. Several studies to date provide a consensus: pregnancy outcome is optimal when disease is in complete clinical remission for 6-12 mo[12,13]. Pregnancy should therefore be planned when SLE is in remission.

Disease flare can occur at any time during pregnancy and puerperium without any clear pattern. Minor organ manifestations are common, however major organs manifestations can also occur; the main risk is glomerulonephritis. Some clinical and laboratory features of normal pregnancy can simulate lupus activity (Table 2)[14].

Table 1 Contraindications to pregnancy in women with systemic lupus erythematosus

Severe pulmonary hypertension (estimated systolic PAP > 50 mmHg or symptomatic)
Severe restrictive lung disease (FVC < 1 L)
Heart failure
Chronic renal failure (Cr > 2.8 mg/dL)
Previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin
Stroke within the previous 6 mo
Severe lupus flare within the previous 6 mo

PAP: Pulmonary arterial pressure; FVC: Forced vital capacity.

FLARE INDEXES: WHICH MEASURES OF ACTIVITY ASSESSMENT COULD BE USED?

In the last 2 decades, several lupus activity scales have been adapted for pregnancy: Systemic Lupus Erythematosus in Pregnancy Activity Index (SLEPDAI), Modified Lupus Activity Measurement (m-SLAM) and Lupus Activity Index in Pregnancy (LAI-P). All of them take into account the influence of pregnancy on clinical manifestation and common biochemical tests. LAI-P also accounts for specific manifestations of Antiphospholipid Syndrome in order not to score them as due to SLE activity. SLEPDAI and LAI-P have a sensitivity of 93% and a specificity of 98%. However, daily assessment and management of individual pregnant women with lupus still relies on the clinical skills of attending physicians[15-18].

INFLUENCE OF SLE ON PREGNANCY: ARE OBSTETRIC COMPLICATIONS MORE COMMON IN LUPUS PREGNANCY?

Historically, lupus pregnancy was associated with a high

Table 2 Diferences between lupus flare and normal pregnancy

	Lupus flare	Normal pregnancy
Clinical features	Malar rash	Palmar and facial erythema
	Inflammatory arthritis	Arthralgia/Joint effusions
	Lymphadenopathy	Fatigue
	Fever	Hair loss
	Oral ulcerations	
	Raynaud phenomenon	
Laboratory features	ESR increased	ESR increased
	Leukopenia/lymphopenia	
	Anemia	Anemia due to hemodilution
	Complement levels drop	Complement levels increased
	dsDNA antibodies rising	dsDNA antibodies stable
	Hematuria	
	Proteinuria ⩾ 300 mg/dL	Proteinuria ⩽ 300 mg/dL

ESR: Erythrocyte sedimentation rate.

rate of obstetric and fetal complications. These include spontaneous abortion, late miscarriage, intrauterine growth retardation, preterm delivery and prematurity (Table 3). With the widespread use of careful monitoring and treatment schedules of these patients many improvements in both fetal and maternal pregnancy outcomes have occurred. The rates of fetal loss has declined significantly in pregnancies in patients with SLE, from 43% before 1975 to 17% in recent years, live birth rates of 85%-90% have been reported in recent studies[19].

Predictors of fetal loss include: active disease, lupus nephritis, presence of antiphospholipid antibodies (aPL), thrombocytopenia, proteinuria and hypertension[20]. In our series there were 61 live births, including one twin birth (85%), six still birth (8%) and 5 spontaneous abortions (7%)[21].

Preterm delivery is frequent and the strong predictors of preterm birth are lupus activity, hypertension and corticosteroid use[22].

In this study, forty six percent of 72 pregnancies ended in preterm deliveries. Significantly more women in the preterm delivery group were taking ⩾ 10 mg/d of prednisone compared to the full term delivery group[21].

Intrauterine growth retardation (IUGR) is reported in 10%-30% of pregnancies in patients with SLE. The risk is higher in presence of active disease and lupus nephritis[19].

ARE HYPERTENSIVE PREGNANCY COMPLICATIONS FREQUENT IN LUPUS PATIENTS?

Lupus pregnancy is associated with an increased risk of pre-eclampsia especially in the setting of lupus nephritis. Pre-eclampsia and eclampsia can both mimic lupus by presenting as edema, thrombocytopenia, hyperuricemia, anemia, hypertension, proteinuria, hematuria and seizures in eclampsia[23].

Table 3 Obstetric complications of systemic lupus erythematosus

Spontaneous abortion
Late miscarriage
Intrauterine growth retardation
Preterm delivery
Prematurity

Table 4 Differences between preeclampsia and active lupus nephritis

	Pre eclampsia	Lupus nephritis
Backgrounds	Chronic hypertension, antiphospholipid syndrome, diabetes mellitus, past preeclampsia	
Hypertension	Onset after 20 wk	Onset before 20 wk
Proteinuria	++	++
Urinary sediment	Inactive	Active (red cells, white cells and cellular casts)
Complement levels	Normal	↓↓
Anti DNA antibodies	Stable	↑↑
Uric acid levels	↑	
Urinary calcium excretion	↓	
Extrarenal manifestations		Present

Pre-eclampsia is more common in patients with antiphospholipid syndrome, lupus nephritis, diabetes mellitus or past pre-eclampsia[24].

Investigations of serum complements C3, anti DNA antibodies and urinary sediment can help to differentiate between both diseases (Table 4). In our study we have seen gestational hypertension in 15 pregnancies (21%) and preeclampsia in 8 pregnancies (11%). No eclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) occurred[21].

LUPUS NEPHRITIS: HOW DOES LUPUS NEPHRITIS INFLUENCE PREGNANCY?

Approximately 50% of SLE patients will develop renal compromise[25] that may carry complication to the mother and/or fetus. High rates of pre-eclampsia are common in women with lupus nephritis ranging from 9% to 35%, specially in women diagnosed with lupus nephritis during pregnancy, unplanned pregnancies or with active disease before pregnancy[5]. Furthermore, the activity of lupus nephritis (LN) at conception has a high impact on premature birth[26] and fetal losses, which range between 25%-57% in women with active LN *vs* 8%-12.5% in those with stable renal disease[24]. Others potential pregnancy complications in patients with renal involvement are pre term delivery[27,28] and intrauterine growth retardation[26].

Table 5 Pregnancy morbidity of antiphospholipid syndrome

Classification criteria of APS in pregnancy
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (1) eclampsia or severe preeclampsia defined according to standard definitions[11], or (2) recognized features of placental insufficiency-, or (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Others obstetric manifestations of APS
Increased risks of intrauterine growth retardation
HELLP syndrome
Utero-placental insufficiency
Preeclampsia
Risk of thrombosis in the mother

APS: Antiphospholipid syndrome.

ANTIPHOSPHOLIPID SYNDROME: HOW CAN ANTIPHOSPHOLIPID SYNDROME COMPLICATE LUPUS PREGNANCY?

The antiphospholipid syndrome (APS) is defined by the presence of thrombosis and/or pregnancy morbidity in combination with the persistent presence of circulating aPL: lupus anticoagulant (LA), anticardiolipin antibodies (ACL) and/or anti-B2 glycoprotein I antibodies (anti-B2 GPI) in medium to high titers[29].

Several pregnancies morbidity are related to APS[30] (Table 5).

The treatment of pregnancies in women who are positive for aPL, depends on the presence of concomitant risk factors. In women positive for aPL but with no prior thrombotic event or pregnancy loss, low dose aspirin is recommended throughout the pregnancy. In those with aPL positivity and with recurrent early losses or one or more late fetal loss, without history of systemic thrombosis, aspirin in combination with prophylactic doses of heparin is indicated during pregnancy. Patients with prior systemic thrombosis in the presence of aPL should receive full therapeutic doses of heparin during pregnancy.

Low-molecular weight heparin (LMWH) has similar efficacy to unfractionated heparin with less adverse effects and easy monitoring. It requires more frequent dosing and twice-daily administration for all doses and it should be transitioned to unfractionated heparin near term to ensure fast reversal of anticoagulation at the time of delivery. Heparin treatment should be continued for 6 wk after delivery[31]. Corticosteroids, in combination with aspirin, were shown to have similar efficacy to heparin, but with higher maternal morbidity. IVIg was evaluated in two randomized trials and it was less efficient than the aspirin and heparin combination treatment in prevention of recurrent loss. Some women are refractory to aspirin and heparin combination and continue to have recurrent losses despite treatment. No consensus exists for the management of this group of patients. The addition of corticosteroids, IVIg, and plasmapheresis has been tried, but data are limited[19].

NEONATAL LUPUS ERYTHEMATOSUS: WHAT'S THE FREQUENCY OF NEONATAL LUPUS?

Neonatal lupus erythematosus (NLE) is a condition represented by cutaneous, cardiac, hepatic, hematologic, neurologic and splenic abnormalities, observed in newborn infants whose mothers have autoantibodies against Ro/SSA, La/SSB and, less frequently, U1-RNP[32].

These autoantibodies cross the placenta and cause neonatal lupus in 1% of newborns, and subsequent children have a 25% risk if the mother has had a previously affected baby[33].

All lupus patients contemplating pregnancy should have an anti-Ro/SSA, anti-La/SSB status determined, these antibodies are present in 30%-50% of SLE patients. The majority of the affected babies suffer a transient and often mild lupoid rash characterized as annular erythematous or polycystic plaques on the scalp, neck or face, typically periorbital; they resemble the lesions of subacute cutaneous lupus erythematosus. These lesions last for weeks or months and then resolve spontaneously consequent to the disappearance of maternal antibodies in the neonatal circulation[34].

Hepatobiliary involvement in NLE includes elevation of liver enzymes and/or conjugated hyperbilirubinemia. Some babies may have hepato-splenomegaly and less frequently, cholestatic hepatitis and hepatic failure.

Hemolytic anemia, thrombocytopenia and neutropenia may occur in the first 2 wk of life and they usually are asymptomatic. Hematologic symptoms disappear by the end of the second month. Other abnormalities like aseptic meningitis, myelopathy, hydrocephalus and macrocephaly have rarely been described[35].

The most common and well recognized cardiac manifestation of NLE is congenital heart block (CHB) that occurs in only 2% of infants born to mothers with anti-Ro/SSA or anti-La/SSB antibodies. The risk of CHB increases in infants born to mothers with a previous child having CHB and occurs in nearly 20% of the subsequent pregnancies.

This cardiac manifestation is irreversible and has significant mortality (approximately 20% in the neonatal period), and morbidity with more than 60% of the cases requiring permanent pacemakers and 10% developing severe cardiomyopathy[33].

The first fetal echocardiogram should be performed at 16 wk of gestation and then weekly for high risk infants (prior fetus with CHB) or every 2 wk in lower risk settings[23].

The goal of this monitoring would be to identify a biomarker of reversible injury such as PR interval prolongation > 150 ms, moderate/severe tricuspid regurgita-

Table 6 Medications use during systemic lupus erythematosus pregnancy

Medication	Permitted	Not allowed
Corticosteroids	Prednisolone, Dexamethasone, Betamethasone, Pulses methylprednisolone	
Antimalarials	Hydroxychloroquine	
Immunosuppressives	Cyclosporine Azathioprine Tacrolimus	Cyclophosphamide Methotrexate Leflunomide Mycophenolate mofetil
Anticoagulants	Unfractionated heparin Low-molecular-weight heparin	Warfarin Acenocumarol
Antiplatelets	Aspirin	Clopidogrel Ticlopidine
Non-steroidal anti-inflammatory drugs and analgesics	NSAIDs (until week 32) Acetaminophen	COX-2 inhibitors
Biologics		Rituximab Belimumab
Miscellaneous	Intravenous immunoglobulin	

NSAID: Non-steroidal non steroidal antiinflammatory drugs.

tion, and/or atrial echodensity[36].

Prenatal maintenance therapy with betamethasone or dexamethasone given to the mother starting early in pregnancy (before 16 wk' gestation), might reduce the risk of developing antibody-mediated congenital heart block in the offspring[37].

In contrast, recent data confirm the irreversibility of third degree block and progression of second to third degree block despite the use of dexamethasone. A potential benefit of this drug in reversing first or second degree block was observed in rare cases[38].

Moreover, in regard to the role of Toll- like receptors in the pathogenesis of cardiac-NLE, two studies, a case -control study and a multinational historical cohort study, suggest that hydroxychloroquine use in a mother with anti-SSA/Ro antibodies and a previous child with cardiac-NLE may reduce the risk of cardiac NLE recurrence in a subsequent pregnancy[39,40].

In our study, there was only one infant with CHB in an anti-Ro/SSA positive mother. Although intrauterine dexamethasone was administered, the infant did not survive[21].

WHICH DRUGS ARE ALLOWED IN LUPUS PREGNANCY?

SLE in women in their reproductive years may need potentially teratogenic drugs during pregnancy, puerperium and in the breastfeeding period, to control maternal disease and to ensure successful pregnancy outcome.

Because only those drugs considered safe can be studied in pregnant or lactating women, the number of controlled studies is small. Information on the safety of these drugs during these periods is derived only from experimental and preclinical studies (Table 6).

Non steroidal antiinflammatory drugs

Cox-1 and Cox-2 are involved in ovulation and implantation. Several case reports and small series have described transient infertility after treatment with suppress duplicate non steroidal antiinflammatory drugs (NSAID), such as indomethacin, diclofenac, piroxicam and naproxen. Also, some studies in animals and humans have shown that these drugs can inhibit the rupture of the luteinized follicle.

Non-selective Cox inhibitors are not teratogenic and can be continued during the first and second trimesters, but all NSAID (except aspirin add at less than 100 mg/d) after the 20th gestational week can cause constriction of the ductus arteriosus and impair fetal renal function. Consequently, they should be withdrawn at gestational week 32.

In relation to low dose aspirin (LDA) there is no consensus on when to stop it before delivery. Some advice cessation of the treatment one week before a planned delivery with epidural anesthesi. Other experts do not stop LDA in patients with APS.

Most NSAID are excreted in very small quantities into breast milk. The American Academy of Pediatrics considers ibuprofen, indomethacin, diclofenac, piroxicam, naproxen, mefenamic acid, tolmetin, and flufenamic acid to be compatible with breastfeeding.

At present there are no reliable data on selective Cox-2 inhibitors so they should be avoided in pregnancy[41].

Corticosteroids

11-β hydroxi steroid dehydrogenase in the placenta deactivates prednisone and prednisolone[42]. On the other hand fluorinated corticosteroids (betamethasone and dexamethasone), are less well metabolized by the placenta and should be avoided unless there is a need to induce fetal lung maturation or in an effort to treat in utero fetal heart block[36].

All corticosteroids increase the risk of premature rupture of membranes, hypertension, pre-eclampsia, diabetes mellitus and infection. Ideally, treatment should not exceed the recommended maximum dose of 15 mg a day[10].

An increased risk for clef palate has been associated with corticosteroid use during first trimester, although the risk is low[11].

Due to the side effects, prophylactic use of corticosteroids during pregnancy is not recommended[42].

Stress doses of hydrocortisone at delivery are recommended in patients on corticosteroids long term therapy.

Breast feeding is allowed with low to moderate doses of corticosteroids.

Antimalarial drugs

Hydroxychloroquine (HCQ) crosses the placenta with no significant difference in the mean concentration in maternal and cord blood. Discontinuation of this drug leads to increased risk of disease activity. The half-life of HCQ is approximately 2-3 mo, therefore pregnancies in which

this drug was stopped just prior to or after conception will still have exposure to it[42].

Other articles did not find an increase in congenital malformations or cardiac conduction disturbances in children exposed antenatally to this drug.

A recent multinational study showed that HCQ use in mothers with positive anti-SSA/Ro antibodies and a previous child with cardiac neonatal lupus may reduce the risk of cardiac neonatal lupus in a new pregnancy[40].

Breastfeeding is permitted with this drug.

Methotrexate

Methotrexate is contraindicated during pregnancy and in the breastfeeding period. There are known risks of fetal abnormalities in humans associated with methotrexate use. Therefore, all women of childbearing potential should be strongly counseled and advised to use reliable forms of contraception while taking methotrexate. If a woman inadvertently becomes pregnant, she should discontinue the medication immediately and be counseled concerning the risks of congenital abnormalities. Reports based on human cases describe a methotrexate embryopathy that includes growth deficiency, abnormalities in central nervous system, microcephaly, hypoplasia of skull bones, craniosynostosis, short limbs, hypodactyly, and syndactyly.

Therefore, this drug must be withdrawn three months before a planned pregnancy. Although the amount of methotrexate excreted in breast milk is low, it is unknown how this may affect a young infant and, therefore, methotrexate is considered to be unsafe during lactation[43,44].

Cyclophosphamide

Cyclophosphamide (CYC) is gonadotoxic in both women and men. Cryopreservation of sperm and sperm banking is the method of choice in men. Preservation of gonadal function in women is best done with a gonadotrophin-releasing hormone agonist. Its use in the first trimester of pregnancy is associated with fetal malformations and growth retardation, and suppression of fetal hematopoiesis if it is used during the second and third trimester[45].

This drug is excreted into breast milk. Suppression of hematopoiesis in breastfed infants has been reported, so it is contraindicated during breast feeding period. As MTX, it must be withdrawn 3 mo before a planned pregnancy[41].

Azathioprine

Azathioprine (AZA) does not adversely affect the fertility of both women and men. It can be used during pregnancy at a daily dose not exceeding 2 mg/kg per day because higher doses have risk of depressed hematopoiesis in infants.

Nursing is not recommended by the American Academy of Pediatrics[10].

Cyclosporin A

Successful use of Cyclosporin A (CsA) in pregnancy has been reported mainly in transplant recipients. It can be used in pregnancy at the lowest effective dose, with close control of maternal blood pressure and renal function during therapy. Breastfeeding is not recommend because small amounts of CsA are excreted in breast milk[41].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is contraindicated during pregnancy. It is associated with craniofacial malformations, ocular anomalies, limbs abnormalities and renal, cardiovascular and nervous system malformations. The drug should be stopped at least 12 wk before a planned pregnancy. Breastfeeding is not allowed[10].

Leflunomide

Leflunomide is contraindicated during pregnancy and breastfeeding. It should be discontinued 2 years before conception or a washout procedure with cholestyramine should be used[10].

Tacrolimus

There is an increased risk of gestational diabetes and hypertension in women taking tacrolimus. It may be maintained during pregnancy at the lowest possible dose. Nursing is possible[5].

Intravenous immunoglobulin

It can be used in pregnancy and in the breastfeeding period, no fetal adverse effects have been reported[20].

Rituximab

Rituximab crosses the placenta. It is not clear whether preconceptional or first trimester exposure to rituximab would expose the fetus to any risk. However, second and third trimester exposure causes B-cell depletion in the fetus with unknown long-term effects in the child. With a maximal elimination half-life of 36 d, discontinuation of rituximab for a period five times the half-life (6 mo) before conception may be adequate to not expose the baby to deleterious effects[46].

Belimumab

At present there are no data about the safety of Belimumab use during pregnancy.

Thromboprophylaxis

Low-molecular-weight heparin (LMWH) and unfractionated heparin are safe in pregnancy and are considered in pregnant patients with lupus nephritis with serum albumin $\leqslant$ 30 g/L or with proteinuria $\geqslant$ 3g/24 h[5].

ANTIHYPERTENSIVE DRUG

Arterial hypertension can develop during pregnancy, or a known history of hypertension pre-pregnancy can be present in a SLE patient with renal involvement.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are popular for the

treatment of hypertension in SLE patients and are widely used because they antiproteinuric effects. However, ACE inhibitors and ARBs should be stopped immediately after pregnancy is confirmed because these medications are associated with renal agenesis and fetal demise.

All antihypertensive agents cross the placental barrier and are present in varying concentrations in the fetal circulation.

Methyldopa is the first line agent for treating hypertension in pregnancy. It has been the most frequently assessed antihypertensive in randomized trials and has the longest safety track record.

Beta Adrenergic Blockers, as Labetalol or Metoprolol, should be used when monotherapy with Methyldopa is insufficient or when women are unable to tolerate Methyldopa.

Calcium channel blockers, such as nifedipine or isradipine are second line agents; they can be administered in hypertensive emergencies or in hypertension caused by pre-eclampsia.

Besides, nifedipine may be considered in patients with severe Raynaud phenomenon.

Diuretics should be avoided for treatment of hypertension because they may decrease placental blood flow.

Post partum hypertension is common. Blood pressure typically rises after delivery over the first five days. Most antihypertensive agents used in routine practice are compatible with breastfeeding, but safety data for doxazosin, amlodipine, and ARBs are lacking.

Methyldopa should be avoided post partum because of the risk of postnatal depression.

The first line agent is labetalol, plus nifedipine or an ACE inhibitor if another agent is required. Diuretics are usually avoided if the woman wishes to breastfeed because of increased thirst[47,48].

CONCLUSION

Pregnancy in a lupus patient continues to be a mayor challenge for the physician and it should be considered as a high-risk situation. However, if it is planned when the disease is stable and under close supervision by a multidisciplinary team, we could expect a good outcome for the mother and her baby.

REFERENCES

1 **Lockshin MD**. Pregnancy does not cause systemic lupus erythematosus to worsen. *Arthritis Rheum* 1989; **32**: 665-670 [PMID: 2638570 DOI: 10.1002/anr.1780320602]

2 **Nossent HC**, Swaak TJ. Systemic lupus erythematosus. VI. Analysis of the interrelationship with pregnancy. *J Rheumatol* 1990; **17**: 771-776 [PMID: 2388198]

3 **Petri M**. The Hopkins Lupus Pregnancy Center: ten key issues in management. *Rheum Dis Clin North Am* 2007; **33**: 227-235, v [PMID: 17499704 DOI: 10.1016/j.rdc.2007.01.003]

4 **Petri M**. Treatment of systemic lupus erythematosus: an update. *Am Fam Physician* 1998; **57**: 2753-2760 [PMID: 9636338]

5 **Bramham K**, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. *Lupus* 2012; **21**: 1271-1283 [PMID: 22878255 DOI: 10.1177/0961203312456893]

6 **Cavallasca JA**, Maliandi M del R. Pregnancy a challenge in patients with systemic lupus erythematosus. In Seward TI. Progress in Systemic Lupus Erythematosus Research. New York : Nova Science Publishers, 2007: 9-15

7 **Ruiz-Irastorza G**, Khamashta MA. Lupus and pregnancy: integrating clues from the bench and bedside. *Eur J Clin Invest* 2011; **41**: 672-678 [PMID: 21158850 DOI: 10.1111/j.1365-2362.2010.02443.x]

8 **Petri M**, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, Lockshin M, Merrill JT, Belmont HM, Askanase AD, McCune WJ, Hearth-Holmes M, Dooley MA, Von Feldt J, Friedman A, Tan M, Davis J, Cronin M, Diamond B, Mackay M, Sigler L, Fillius M, Rupel A, Licciardi F, Buyon JP. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353**: 2550-2558 [PMID: 16354891 DOI: 10.1056/NEJMoa051135]

9 **Yazdany J**, Trupin L, Kaiser R, Schmajuk G, Gillis JZ, Chakravarty E, Schwarz EB. Contraceptive counseling and use among women with systemic lupus erythematosus: a gap in health care quality? *Arthritis Care Res* (Hoboken) 2011; **63**: 358-365 [PMID: 21080446 DOI: 10.1002/acr.20402]

10 **Jain V**, Gordon C. Managing pregnancy in inflammatory rheumatological diseases. *Arthritis Res Ther* 2011; **13**: 206 [PMID: 21371350 DOI: 10.1186/ar3227]

11 **Stojan G**, Baer AN. Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management. *Expert Rev Clin Immunol* 2012; **8**: 439-453 [PMID: 22882219 DOI: 10.1586/eci.12.36]

12 **Petri M**, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. *Arthritis Rheum* 1991; **34**: 1538-1545 [PMID: 1670196]

13 **Urowitz MB**, Gladman DD, Farewell VT, Stewart J, McDonald J. Lupus and pregnancy studies. *Arthritis Rheum* 1993; **36**: 1392-1397 [PMID: 8216399 DOI: 10.1002/art.1780361011]

14 **Doria A**, Tincani A, Lockshin M. Challenges of lupus pregnancies. *Rheumatology* (Oxford) 2008; **47** Suppl 3: iii9-ii12 [PMID: 18504287]

15 **Doria A**, Cutolo M, Ghirardello A, Zampieri S, Vescovi F, Sulli A, Giusti M, Piccoli A, Grella P, Gambari PF. Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. *Arthritis Rheum* 2002; **47**: 202-209 [PMID: 11954015 DOI: 10.1002/art.10248]

16 **Ruiz-Irastorza G**, Khamashta MA. Evaluation of systemic lupus erythematosus activity during pregnancy. *Lupus* 2004; **13**: 679-682 [PMID: 15485102]

17 **Ruiz-Irastorza G**, Khamashta MA, Gordon C, Lockshin MD, Johns KR, Sammaritano L, Hughes GR. Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. *Arthritis Rheum* 2004; **51**: 78-82 [PMID: 14872459]

18 **Buyon JP**, Kalunian KC, Ramsey-Goldman R, Petri MA, Lockshin MD, Ruiz-Irastorza G, Khamashta M. Assessing disease activity in SLE patients during pregnancy. *Lupus* 1999; **8**: 677-684 [PMID: 10568906]

19 **Lateef A**, Petri M. Management of pregnancy in systemic lupus erythematosus. *Nat Rev Rheumatol* 2012; **8**: 710-718 [PMID: 22907290 DOI: 10.1038/nrrheum.2012.133]

20 **Meyer O**. Making pregnancy safer for patients with lupus. *Joint Bone Spine* 2004; **71**: 178-182 [PMID: 15182787 DOI: 10.1016/S1297-319X(03)00155-6]

21 **Cavallasca JA**, Laborde HA, Ruda-Vega H, Nasswetter GG. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). *Clin Rheumatol* 2008; **27**: 41-46 [PMID: 17516127]

22 **Chakravarty EF**, Colón I, Langen ES, Nix DA, El-Sayed YY, Genovese MC, Druzin ML. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *Am J Obstet Gynecol* 2005; **192**: 1897-1904 [PMID: 15970846 DOI: 10.1016/j.ajog.2005.02.063]

23 **Dhar JP**, Sokol RJ. Lupus and pregnancy: complex yet manageable. *Clin Med Res* 2006; **4**: 310-321 [PMID: 17210979 DOI: 10.3121/cmr.4.4.310]

24 **Kong NC**. Pregnancy of a lupus patient--a challenge to the nephrologist. *Nephrol Dial Transplant* 2006; **21**: 268-272 [PMID: 16339162 DOI: 10.1093/ndt/gfi329]

25 **Bertsias GK**, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, Boletis J, Cervera R, Dörner T, Doria A, Ferrario F, Floege J, Houssiau FA, Ioannidis JP, Isenberg DA, Kallenberg CG, Lightstone L, Marks SD, Martini A, Moroni G, Neumann I, Praga M, Schneider M, Starra A, Tesar V, Vasconcelos C, van Vollenhoven RF, Zakharova H, Haubitz M, Gordon C, Jayne D, Boumpas DT. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; **71**: 1771-1782 [PMID: 22851469 DOI: 10.1136/annrheumdis-2012-201940]

26 **Smyth A**, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010; **5**: 2060-2068 [PMID: 20688887 DOI: 10.2215/CJN.00240110]

27 **Moroni G**, Quaglini S, Banfi G, Caloni M, Finazzi S, Ambroso G, Como G, Ponticelli C. Pregnancy in lupus nephritis. *Am J Kidney Dis* 2002; **40**: 713-720 [PMID: 12324905 DOI: 10.1053/ajkd.2002.35678]

28 **Gladman DD**, Tandon A, Ibañez D, Urowitz MB. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *J Rheumatol* 2010; **37**: 754-758 [PMID: 20231194 DOI: 10.3899/jrheum.090872]

29 **Ruiz-Irastorza G**, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, Erkan D, Krilis S, Machin S, Pengo V, Pierangeli S, Tektonidou M, Khamashta M. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. *Lupus* 2011; **20**: 206-218 [PMID: 21303837 DOI: 10.1177/0961203310395803]

30 **Giannakopoulos B**, Krilis SA. The pathogenesis of the antiphospholipid syndrome. *N Engl J Med* 2013; **368**: 1033-1044 [PMID: 23484830 DOI: 10.1056/NEJMra1112830]

31 **Bates SM**, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 844S-886S [PMID: 18574280 DOI: 10.1378/chest.08-0761]

32 **Hon KL**, Leung AK. Neonatal lupus erythematosus. *Autoimmune Dis* 2012; **2012**: 301274 [PMID: 22973504 DOI: 10.1155/2012/301274]

33 **Buyon JP**, Clancy RM. Neonatal lupus: review of proposed pathogenesis and clinical data from the US-based Research Registry for Neonatal Lupus. *Autoimmunity* 2003; **36**: 41-50 [PMID: 12765470 DOI: 10.1080/0891693031000067340]

34 **Lee LA**. Cutaneous lupus in infancy and childhood. *Lupus* 2010; **19**: 1112-1117 [PMID: 20693205 DOI: 10.1177/0961203310370347]

35 **Silverman E**, Jaeggi E. Non-cardiac manifestations of neonatal lupus erythematosus. *Scand J Immunol* 2010; **72**: 223-225 [PMID: 20696019 DOI: 10.1111/j.1365-3083.2010.02443.x]

36 **Friedman DM**, Kim MY, Copel JA, Davis C, Phoon CK, Glickstein JS, Buyon JP. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation* 2008; **117**: 485-493 [PMID: 18195175 DOI: 10.1161/CIRCULATIONAHA.107.707661]

37 **Shinohara K**, Miyagawa S, Fujita T, Aono T, Kidoguchi K. Neonatal lupus erythematosus: results of maternal corticosteroid therapy. *Obstet Gynecol* 1999; **93**: 952-957 [PMID: 10362161 DOI: 10.1016/S0029-7844(99)00006-X]

38 **Friedman DM**, Kim MY, Copel JA, Llanos C, Davis C, Buyon JP. Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study. *Am J Cardiol* 2009; **103**: 1102-1106 [PMID: 19361597 DOI: 10.1016/j.amjcard.2008.12.027]

39 **Izmirly PM**, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, Salmon JE, Buyon JP. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis* 2010; **69**: 1827-1830 [PMID: 20447951 DOI: 10.1136/ard.2009.119263]

40 **Izmirly PM**, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, Friedman D, Llanos C, Piette JC, Buyon JP. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012; **126**: 76-82 [PMID: 22626746 DOI: 10.1161/CIRCULATIONAHA.111.089268]

41 **Østensen M**, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, Doria A, Rai R, Meroni P, Cetin I, Derksen R, Branch W, Motta M, Gordon C, Ruiz-Irastorza G, Spinillo A, Friedman D, Cimaz R, Czeizel A, Piette JC, Cervera R, Levy RA, Clementi M, De Carolis S, Petri M, Shoenfeld Y, Faden D, Valesini G, Tincani A. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006; **8**: 209 [PMID: 16712713 DOI: 10.1186/ar1957]

42 **Clowse MEB**, Petri M. Pregnancy. In: Tsokos GC, Gordon C, Smolen JS. Systemic Lupus Erythematosus. A companion to Rheumatology. New York: Mosby, 2007: 449-459 [DOI: 10.1016/B978-0-323-04434-9.50051-8]

43 **Elliott AB**, Chakravarty EF. Immunosuppressive medications during pregnancy and lactation in women with autoimmune diseases. *Womens Health* (Lond Engl) 2010; **6**: 431-440; quiz 441-442 [PMID: 20426608]

44 **Hyoun SC**, Običan SG, Scialli AR. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol* 2012; **94**: 187-207 [PMID: 22434686 DOI: 10.1002/bdra.23003]

45 **Clowse ME**, Magder L, Petri M. Cyclophosphamide for lupus during pregnancy. *Lupus* 2005; **14**: 593-597 [PMID: 16175930 DOI: 10.1191/0961203305lu2169oa]

46 **Ostensen M**, Förger F. Treatment with biologics of pregnant patients with rheumatic diseases. *Curr Opin Rheumatol* 2011; **23**: 293-298 [PMID: 21346578 DOI: 10.1097/BOR.0b013e328344a732]

47 **Yoder SR**, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. *Am J Med* 2009; **122**: 890-895 [PMID: 19786154 DOI: 10.1016/j.amjmed.2009.03.036]

48 **Regitz-Zagrosek V**, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**: 3147-3197 [PMID: 21873418 DOI: 10.1093/eurheartj/ehr218]

P- Reviewers: Andonopoulos AP, Tanaka H **S- Editor:** Song XX
L- Editor: A **E- Editor:** Ma S

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com