SYSTEMIC LUPUS ERYTHEMATOSUS IN PREGNANCY

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1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that mainly affects women of child-bearing age. The estimated worldwide prevalence is 20 cases per 100,000 and the incidence is 1 to 10 per 100,000 person-year. It presents a 10-fold higher incidence in women compared to men.

Its clinical pattern is characterised by active periods of the disease, called “flares”, alternated with quiescence periods. Over the last decades, advances in medical treatment have led to improvements in long-term prognosis, and pregnancy has become more achievable for these women.
However, these pregnancies are not exempt from risks, since exacerbations of the disease can occur in up to 60% of cases, especially if lupus is active at the time of conception. Lupus activity can impact the pregnancy, causing a higher rate of complications, especially when the following alterations appear: elevated levels of lupus anticoagulant and anti-dsDNA antibodies, hypocomplementemia, hypertension, lupus nephritis, and thrombocytopenia.

A multidisciplinary approach, consisting of a maternal-fetal specialist and an autoimmune disease specialist, is recommended to optimise pregnancy outcomes.

The PROMISSE study provided a better understanding of the effects of lupus in pregnancy. This is a prospective study for women with an autoimmune disease that observed 385 pregnant patients with SLE and their pregnancy outcomes. Adverse pregnancy outcomes (APOs) appeared in 19% of patients: fetal death occurred in 4%, neonatal death occurred in 1%, preterm delivery (due to placental insufficiency or hypertensive disorders) occurred in 9%, and small for gestational age (SGA) occurred in 10 % of cases. Also, preeclampsia incidence was 5-10% in these patients, which is double the incidence in the general population.

Because these pregnancies present all the aforementioned risks, effective preconception counselling and tailored management run by a specialised team are paramount to improving pregnancy outcomes. Close monitoring of these patients will enable early detection of possible complications that can affect the fetus and the mother.

2. PRECONCEPTION ASSESSMENT AND CARE

All patients affected by SLE are advised to plan for pregnancy in advance. They should get a preconception visit conducted by a multidisciplinary team in order to assess pre-pregnancy risks, design a tailored management, and adjust treatment.

This visit includes:

2.1 Clinical evaluation

Major organ involvement secondary to the disease must be assessed. Chronic renal damage, especially if creatinine is >3 mg/dl, is related to poor blood pressure control during pregnancy, as well as to increased incidence of preeclampsia and gestational loss.

Special attention must be paid to the presence of known adverse outcome predictors, such as positivity to antiphospholipid antibodies and anti-Ro and anti-La antibodies. Additional risk factors involved, such as advanced maternal age and twin pregnancy, must be considered in the risk assessment.

Clinical scenarios associated with high obstetric risks in patients with SLE.

Lupus-related risk factors

Irreversible organ damage

- Chronic kidney disease.
- Heart failure.
- Pulmonary hypertension.
- Interstitial lung disease.

Lupus nephritis.

Active lupus disease.

High-dose corticosteroids treatment at the time of conception.

Presence of antiphospholipid antibodies or antiphospholipid syndrome diagnosis.

Presence of anti- Ro or anti-La antibodies.

Non- lupus-related risk factors

- Previous obstetric complications.
- Maternal age of > 40 years old.

Pregnancy should be discouraged in the following clinical situations:

- Severe pulmonary hypertension (systolic pulmonary artery pressure (sPAP) > 50 mmHg or symptomatic pulmonary hypertension).
- Severe restrictive lung disease (forced vital capacity (FVC) < 1 litre).
- Heart failure.
- Chronic kidney disease (Serum creatinine > 2.8 mg/dl [500 mmol/l]).
- Stroke within the previous six months.
- Severe lupus flare within the previous six months (polyarthritis, lupus nephritis or membranous nephropathy, psychosis, myelitis, thrombocytopenia of < 30 x 10^9/L, myositis, skin rash of >2/3 of the body, serositis).
- Patients with a previous history of severe obstetric complications such as stillbirth, early-onset severe preeclampsia, HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome or severe Intrauterine growth restriction (IUGR) despite preventive therapy with low molecular weight heparin (LMWH) and aspirin. These patients present very high rates of recurrence of adverse pregnancy outcomes in subsequent pregnancies and further therapeutic tools lack strong evidence.

2.2 Laboratory testing

2.2.1. Blood test

- Complete blood count

- Acute phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein)
- Biochemistry test (measure glucose, creatinine, creatine phosphokinase (CPK), total protein, albumin, sodium, and potassium).
- Coagulation tests (prothrombin time test, activated partial thromboplastin time (aPTT)).

2.2.2 Urine tests
- Urinalysis.
- Measure urine protein/creatinine ratio. Consider 24-hour urinary protein in patients with a history of lupus nephritis.

2.2.3 Tests for autoimmunity
- Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies.
- Complement levels (C3, C4, CH50).
- Anti-Ro and anti-La antibodies. If previous determinations were negative, a new test must be run prior to conception, especially if they were not measured within the last year.
- Antiphospholipid antibodies: lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and IgG and IgM anti-beta-2-glycoprotein I antibodies [aβ2GPI]).
- Consider measuring "non-criteria" antiphospholipid antibodies (anti-phosphatidylserine and antiprothrombin antibodies [anti PS/PT]), when "classical" antiphospholipids were negative but clinical history strongly suggests an antiphospholipid syndrome (APS).

2.3 Preconceptional treatment assessment
A review of patient treatment is essential in order to discontinue possible teratogenic drugs and change them to the safest options. Patients under treatment with methotrexate or mycophenolate should be advised to change to azathioprine and postpone pregnancy for 6 months. Pregnancy can be encouraged if, after this period of time, the disease is in remission.
- All patients should start a preconception treatment with hydroxychloroquine at a dose of 5 mg/kg/day and maintain it throughout pregnancy.
- If there is an APS associated with SLE, preconceptional low dose aspirin (100 mg) should be started.

2.4 Treatment after conception

- Hydroxychloroquine treatment should be continued at a dose of 5 mg/kg/day.
- The corticosteroids dose should not be increased in order to prevent lupus flares when disease is not active.
- Aspirin dose should be increased to 150 mg/day (taken before bed) if preeclampsia screening result is positive or if there is a previous history of lupus nephritis.
- Prophylactic LMWH should be started when there is an associated APS.

3. PRENATAL CARE /MATERNAL FETAL MONITORING

Prenatal care of pregnant women with SLE should involve close collaboration between an obstetrician, haematologist, neonatologist, and an autoimmune disease specialist, for early detection and management of complications.

3.1 Frequency of visits
The frequency of follow-up visits is not well established and will be adjusted depending on the presence of risk factors or poor prognosis factors.

In general terms, it involves monthly check-ups from the beginning of pregnancy until 36 weeks, and every two weeks thereafter. Delivery should be scheduled around 39-40 weeks in women with stable SLE, unless complications arise. Women should be interrogated about symptoms and manifestations of the disease to identify possible flares. During visits, special attention must be paid to high blood pressure and the presence of proteinuria, in order to prevent kidney damage. Routine lupus activity blood markers should not be checked unless clinical situation suggests a lupus flare. A general approach to monitoring pregnant women with stable SLE during pregnancy is presented below:

3.1.1 Early first trimester visit (6-8 weeks): if there was no preconceptional visit, it should take place during this appointment. Gestational viability must be confirmed. Laboratory tests and first trimester ultrasounds should be scheduled and treatment should be reviewed and modified if necessary.

3.2 Blood and urine tests

3.2.1 First trimester tests

- Routine first trimester blood test (complete blood count, blood type and Rh factor, Coombs test, and serologic testing for HIV, hepatitis B, hepatitis C, and syphilis) and maternal serum screening for aneuploidy.
- Kidney function test, including creatinine, glomerular filtration rate, blood urea nitrogen (BUN), uric acid, and urinary sediment.
- Liver function test.
- Thyroid function test (T4, thyrotropin).
- Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies and complement levels (C3, C4, CH50).
- Anti-Ro, anti-La, and antiphospholipid antibodies (aPL) if they were not checked preconceptionally.
- Anti PS/PT antibodies in case they were not checked in the first appointment (when “classical” antiphospholipids were negative but clinical history strongly suggests an APS).

- sFlt-1/PlGF ratio.

3.2.2 Second and third trimester tests

- Routine second or third trimester blood test (complete blood count and O’Sullivan test in second trimester and complete blood count, HIV serology, and coagulation tests in the third trimester).
- Kidney function test, including creatinine, glomerular filtration rate, BUN, uric acid, and urinary sediment.
- Liver function
- Thyroid function (T4, thyrotropin)
- Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies and complement levels (C3, C4, CH50).
- Soluble fms-Like Tyrosine Kinase 1/ Placental Growth Factor (sFlt-1/PlGF ratio).

If qualitative tests for urinary protein are positive or hypertension appears, urinary sediment and 24-hour proteinuria should be obtained.
If lupus flares and fetal or maternal complications occur, further and more frequent blood tests might be needed.

3.3 Fetal ultrasound monitoring

- First trimester scan (11-14 weeks) that must include uterine artery Doppler measurement.

- Second trimester scan (20-23 weeks) also including uterine artery Doppler measurement.
- Early growth second trimester scan (24-26 weeks) when second trimester scan shows a second-trimester growth percentile <10 or mean pulsatility index of uterine arteries (PIUtA) is > 95th percentile for gestational age.
- Growth third trimester scans (at 28, 32, and 36 weeks), also including uterine arteries Doppler measurement.
- Nonstress test monitoring is recommended from 38 weeks and onwards.
- Further scans could be necessary if fetal or maternal complications occur. If intrauterine growth restriction develops, fetal monitoring should be scheduled according to specific guidelines for this condition.

3.4 Preeclampsia screening

- This should be performed between 11-13 weeks. Special attention must be paid to the presence of pre-pregnancy or current pregnancy risk factors.
- Primary prevention starting before 16 weeks with 150 mg aspirin taken orally every night should be prescribed to patients at high risk of developing early onset preeclampsia.
- If the patient presents a previous history of lupus nephritis, preeclampsia prevention should be started with 150 mg of aspirin, without undergoing preeclampsia screening.
- Inactive SLE without a history of lupus nephritis should not be considered a risk factor to be included in the preeclampsia screening algorithm.

4. SPECIAL SITUATIONS

4.1 Anti-Ro and/or anti-La antibodies positivity:

Positivity to Anti-Ro or anti-La increases the risk of:

- Congenital heart block (CHB): anti-Ro/SSA and La/SSB autoantibodies (which are part of the conduction system in myocardial cells) can potentially cause a CHB. These autoantibodies can cross the placental barrier and be detected in fetal circulation after 16 weeks of pregnancy. The risk of developing a fetal congenital heart block when the mother is a carrier is 1.5-2%. However, this risk can increase to up to 15% if a previous child was born with neonatal lupus, and up to 20% if a previous child developed a CHB (40-50% risk of recurrence if 2 previous children were affected). The most severe expression of the disease is a complete atrioventricular block (AVB), which can be associated to myocardiopathy. It can eventually cause hydrops in 40-60% of cases. More than 80% of newborns with an AVB will need a pacemaker and estimated perinatal mortality is 45-50%.

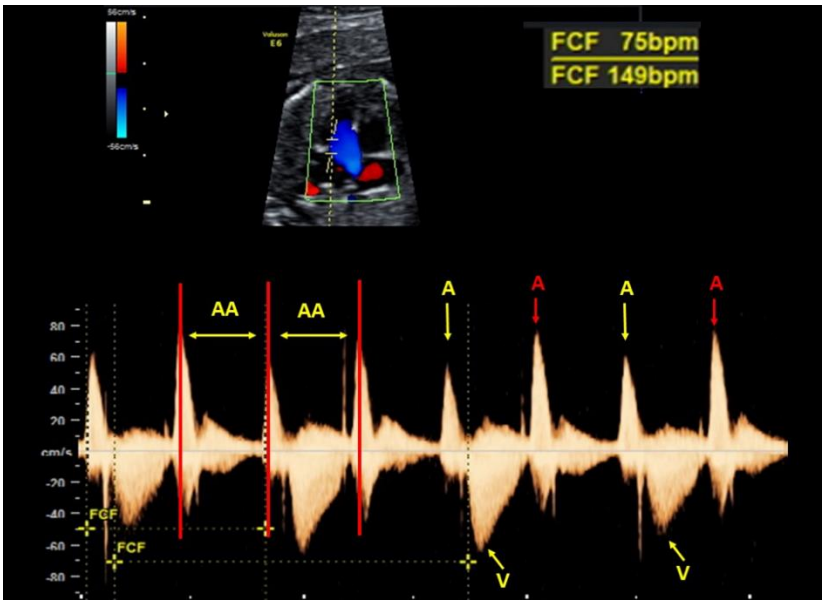


Figure 1. Second-degree AVB. Mitral and aortic pulsed Doppler shows a regular atrial rhythm (atrial to atrial interval is preserved). However, only one out of two atrial impulses reach the ventricle (AV relation 2:1). Ventricular frequency corresponds with one-half of the atrial frequency.

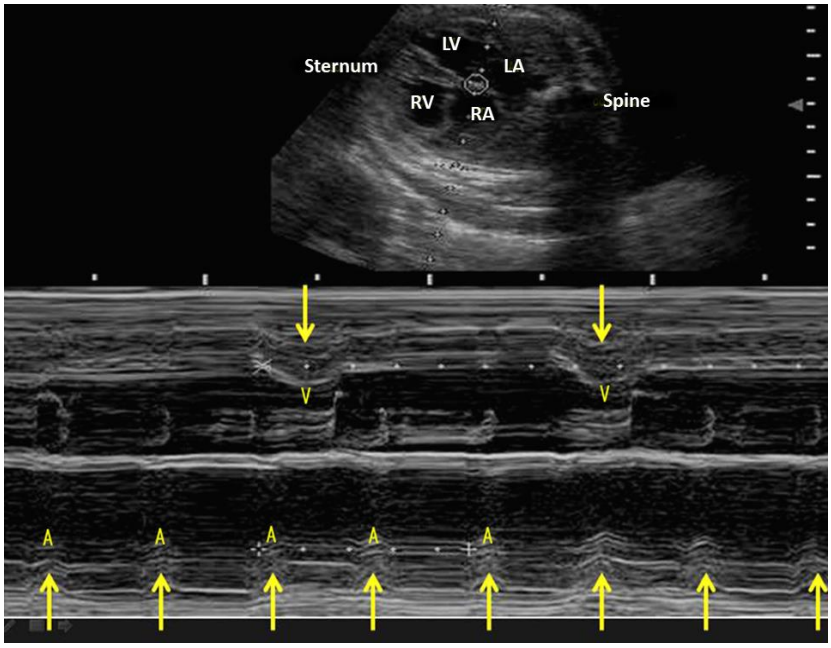


Figure 2. Complete AVB. Image is displayed in M mode (motion mode). Ultrasounds pass through the lateral wall of left ventricle and right atrium simultaneously. Ventricular frequency is much slower than atrial frequency and atrioventricular dissociation is observed.

-Neonatal lupus: the most common symptom is a ring-like skin rash, although thrombocytopenia, leukopenia, anaemia and liver disorder may appear too. Neonatal lupus incidence is 3-5%.

Treatment and management of immunological congenital heart block (Figure 3):

1. **Fetal echocardiographic follow-up:**
   Currently, there are no prognosis markers available that can predict the development of a CHB in fetuses whose mothers are positive for Anti-Ro or Anti-La. Increased ultrasound surveillance measuring atrioventricular (AV) interval has not shown a significant impact on the long-term prognosis. Most cases of CHB appear at 18-24 weeks of pregnancy. For these reasons, we recommend a close follow-up consisting of monitoring fetal heart frequency alternated with fetal echocardiographies according to the following plan:

   -Patients with no previous child affected by a CHB: Fetal heart rate monitoring in outpatient visits at 16, 20 (second trimester ultrasound appointment), 24, 28 (third trimester growth scan) weeks, and fetal echocardiography including a measure of AV interval at 18 and 22 weeks.

   -Patients with a previous child affected by a CHB (risk of recurrence of 15-20%): weekly fetal echocardiography between 16-24 weeks. Consider extending the cardiac surveillance until weeks 28-32 depending on the time of CHB onset in the previous fetus.

   -All newborns whose mothers are positive for Anti-Ro/La must undergo routine echocardiography after birth.

2. **Congenital heart block prevention**
   Although evidence is limited, some studies have shown that treatment with hydroxychloroquine during pregnancy can reduce the probability of developing a CHB and also reduce the rate of recurrence if the previous fetus was affected by a CHB. Recommended dosage is 5 mg/kg/day and should be started 1-2 months preconceptionally and throughout pregnancy in all patients positive to anti-Ro/anti-La autoantibodies, regardless of their previous history of pregnancies. Hydroxychloroquine is safe during pregnancy and numerous studies have reported benefits in lupus (in pregnant and non-pregnant patients).

3. **Congenital heart block treatment**
   CHB is a rare complication and there are no available data from randomised controlled trials to evaluate the efficacy of different proposed treatments in order to prevent an AVB progression or to reverse it once it appears. When a CHB is diagnosed, we recommend the following:

- Consider anti-inflammatory treatment with dexamethasone (4-6 mg/day) in the following clinical scenarios:
  1. Incomplete AVB: this includes persistent first-degree atrioventricular (AV) block (found in consecutive ultrasounds during 48-72 hours with an atrioventricular interval > 150 ms) or second-degree AV block. The objective of the treatment is to avoid progression to complete AVB. If this occurs, corticosteroid therapy must be discontinued.
  2. Fetal myocardial injury signs: consisting of pericardial effusion, endocardial fibroelastosis, and/or dilated myocardiopathy. Treatment with dexamethasone

should be maintained until delivery regardless of the grade of AVB, since the objective of treatment is to avoid the progression to myocardiopathy associated to AVB.

It is advised to withdraw dexamethasone at a rate of 2 mg every 15 days, until a 2 mg /day dose is reached, which should be maintained during pregnancy. Dexamethasone can be changed to prednisone (10 mg/day) after delivery, and then gradually discontinued.

- If a complete AVB with a high risk of heart failure and hydrops (ventricular fetal heart rate < 50-55 bpm) appears, we should consider treatment with beta-adrenergic blocking agents (salbutamol, 2-8 mg/6-8 hours, maximum: 40 mg/day; terbutaline, 2.5-7.5 mg/6-8 hours, maximum: 30 mg/ day). This therapy can increase fetal ventricular heart rate by 5-10 beats per minute and reduce the risk of heart failure.

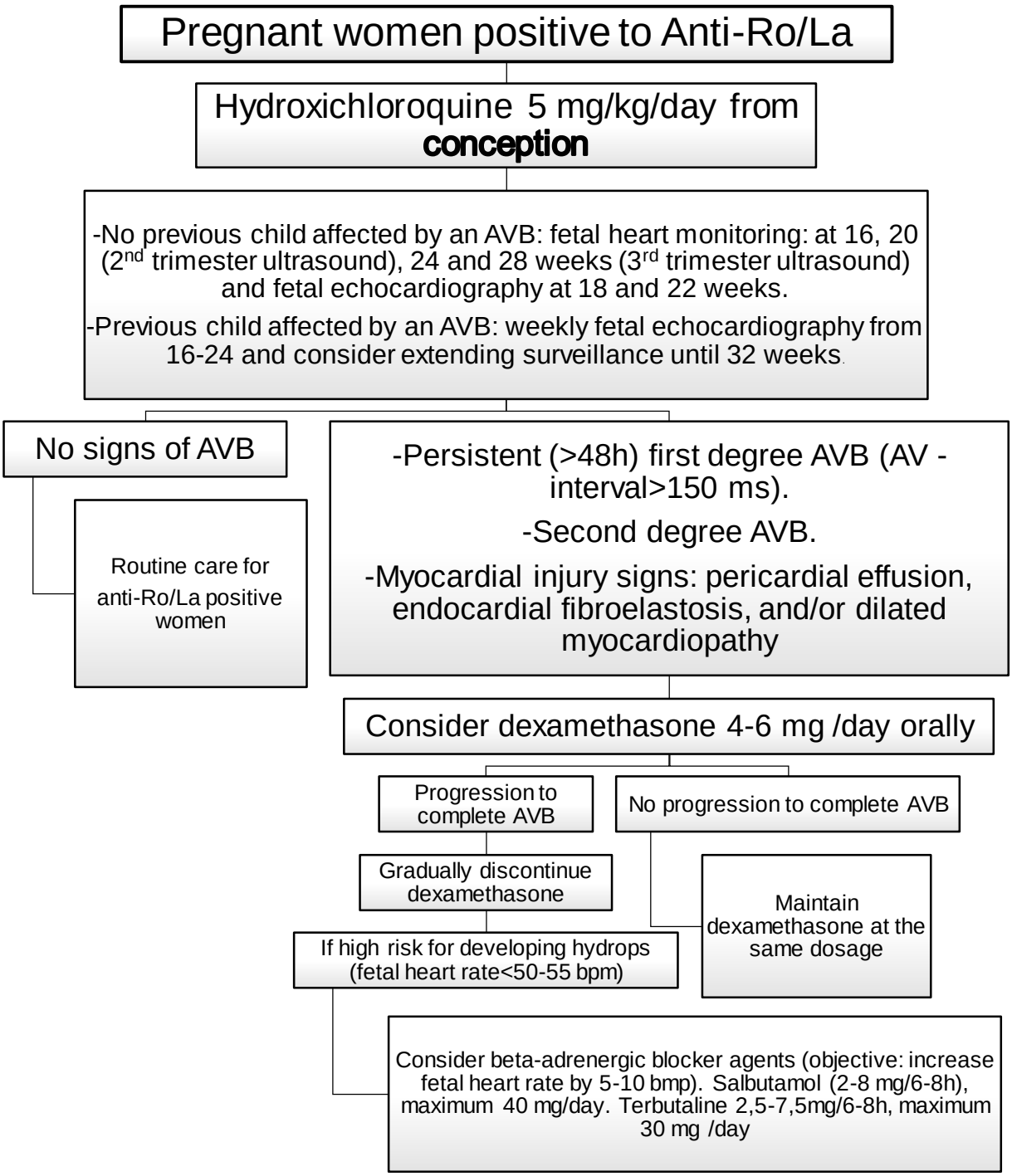
- Maintain treatment with hydroxychloroquine in the same dose if an AVB of any grade develops.

- In selected cases, a combined therapy consisting on plasmapheresis and intravenous immunoglobulins (IVIG) might be considered. Evidence about its efficacy is very limited. The treatment regimen is detailed in Annex 1.

Fetal follow-up requires frequent echocardiography assessment. Delivery should be at term if there are no hydrops or heart failure. If these complications appear, time of delivery should be discussed in a multidisciplinary team and individualised according to the clinical situation.

Delivery should be scheduled in a third-level maternity hospital via caesarean section and coordinated with neonatology and paediatric cardiology teams.

Figure 3. Recommended management in women positive to anti-Ro/La antibodies.



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4.2 Positivity for antiphospholipid antibodies

Patients with SLE who present with antiphospholipid (aPL) antibodies are at a higher risk of miscarriage and fetal loss compared to aPL-negative patients. Patients with aPL antibodies should be advised to follow a preventive treatment with 100 mg of aspirin preconceptionally and continue it throughout the pregnancy. Patients diagnosed with APS should be managed and treated according to the specific guidelines for this disease.

4.3 Systemic lupus erythematosus flare

The risk of exacerbation of the disease during pregnancy is directly related to lupus activity at the time of conception. Lupus flare incidence oscillates between 7 to 30% in patients who were in remission for a least 6 months before pregnancy, and can rise up to 60% in patients with active disease at the time of conception.

Patients should be closely monitored and asked in every visit about possible lupus flare symptoms (such as arthritis, skin rash, fever, chest pain, lower limbs oedema, oral thrush, etc.). Diagnosis of SLE exacerbation during pregnancy is challenging, as many physiological changes in normal pregnancy and obstetric complications may mimic SLE symptoms.

Levels of anti-DNAds are useful for monitoring disease activity and should be checked when an SLE exacerbation is suspected. We should be cautious when using complement levels to monitor disease activity during pregnancy, since these are physiologically slightly increased.

4.3.1 Mild lupus flare (fatigue, arthritis, skin rash, myalgia)

The recommended treatment plan is:

- Relative rest
- Maintain hydroxychloroquine treatment at the same dosage.
- Topical corticosteroids for skin lesions
- Paracetamol to relieve pain caused by joint inflammation or as an antipyretic for fever.
- If there is no improvement with the aforementioned conservative measures, prednisone can be added at the lowest possible dose (5-7.5 mg/day and maximum 20 mg/day) and de-escalated as soon as possible.
- A weekly maternal follow-up appointment is advised, with no need to increase frequency of ultrasounds on the fetal side.

4.3.2 Moderate-severe lupus flare (serositis, thrombocytopenia, autoimmune haemolytic anaemia, neuropsychiatric lupus)

To the previously described treatment, we should add corticosteroids at a high dose (maximum 30 mg/day). Exceptionally, intravenous pulses of methylprednisolone can be administered (250-500 mg/day for 3 days) in order to reduce the duration of treatment with high-dose corticosteroids. Moderate or severe lupus flares require hospital admission and close maternal and fetal monitoring.

4.3.3 Differential diagnosis between lupus nephritis and preeclampsia

One of the biggest challenges for clinicians involved in the care of pregnant patients with SLE is to differentiate between lupus nephritis and preeclampsia.

Both conditions share clinical features and, moreover, the two conditions may coexist.
The incidence of preeclampsia is increased among women with lupus, and it oscillates between 11-35% (compared to the 5% preeclampsia incidence in healthy pregnant women).

It is essential to identify any risk factors for preeclampsia developing in the preconception assessment, such as a history of lupus nephritis, positivity for antiphospholipid antibodies, chronic hypertension, and a previous history of preeclampsia.

Some laboratory tests can help to differentiate preeclampsia and renal flare:

- Anti-dsDNA, urinalysis, and complement levels, especially when lupus nephritis is suspected.
- sFlt-1/PIGF ratio, especially when preeclampsia is suspected. Mean uterine artery pulsatility index based on Doppler measurements can also help to differentiate both conditions. The PROMISSE study shows that these angiogenesis markers measured from week 12 of pregnancy could predict adverse pregnancy outcomes such as preeclampsia, fetal loss, and IUGR in women affected by SLE and APS.

Some key points to differentiate preeclampsia and renal flare are listed in **Table 4**.

	Preeclampsia/HELLP syndrome	**Lupus nephritis**
Onset	From 20 weeks and onwards	In any stage of pregnancy
Physical examination		
Hypertension	+	+
Oedema	+	+
Pain in the right upper quadrant	+	-
Seizures/neurologic symptoms	+	+/-
Fever	-	+/-
Erythema, arthritis, oral thrush, lymphadenopathies.	-	+/-
Laboratory tests		
Pathological urinary sediment	-	+
Proteinuria	+ (when >20 weeks)	+ (at any stage of pregnancy)
Anaemia	+/-	+

Thrombocytopenia	+ (in severe forms of the disease)	+/-
Hypocomplementaemia	-	+
Anti-dsDNA	-	+
aPL antibodies	-	+/-
Uric acid	Increased	Normal/Increased in kidney failure
Altered Liver function tests	+ (in severe forms of the disease)	-
Serum creatinine	Normal	+/-
Angiogenesis markers		
Soluble endoglin	Increased	Normal
sFlt-1/PIGF ratio	Increased	Normal
mUtA-PI	Pathological	Normal
Histopathology	Glomerular endotheliosis, fenestration loss in liver cells, capillary occlusion.	Histopathology depends on International Society of Nephrology/Renal Pathology Society (ISN/RPS classification)
Response to corticosteroids	No	Yes

4. DELIVERY AND POSTPARTUM

Expectant management and spontaneous onset of labour are recommended in most women affected by SLE. Induction of labour is more frequently scheduled in these patients since they are at a higher risk for maternal and fetal adverse outcomes. Clinicians should advise an elective induction of labour if any complications arise in term pregnancy. Preterm induction of labour could be considered if severe pregnancy complications (such as severe preeclampsia or severe IUGR) develop.
Pregnancy, childbirth, and postpartum are associated with an increased risk of SLE disease flare and thrombotic events. Women with a history of active lupus around the time of conception are at highest risk of flare.

A summary of recommended postpartum management is presented below:

5.1 Thromboprophylaxis

- In patients with SLE without APS: thromboprophylaxis with LMWH until 7 days postpartum is recommended in women who present one or more risk factors for thrombosis (35 years or older, obesity, smoking, varicose veins, thrombophilia, twin pregnancy, caesarean section delivery or preeclampsia).

- In patients with SLE and APS: thromboprophylaxis with LMWH should be administered during 6 weeks postpartum.

5.2 Treatment during postpartum

Treatment for postpartum women is similar to that for nonpregnant women.

- Hydroxychloroquine: is compatible with breastfeeding and should be continued in the same dose as in pregnancy.
- Corticosteroids: a dosage under 20 mg/day is considered safe for breastfeeding. If a higher dosage is needed, breast milk produced within the first four hours after drug intake should be discarded.
- Immunosuppressants: women should be informed about risks and benefits of continuing breastfeeding when taking these drugs since there is limited evidence on safety. Tacrolimus, azathioprine, and cyclosporine are considered compatible with breastfeeding.
- Antihypertensive drugs: this group presents an excellent safety profile for lactation. Angiotensin Converting Enzyme (ACE) inhibitors should be avoided when breastfeeding a premature baby of < 32 weeks.

5.3 Postpartum visit

The postpartum visit takes place 4 to 6 weeks following delivery and must involve an assessment of disease activity and laboratory tests, including:

- Total blood count, urinalysis, urine protein/urine creatinine ratio.
- Kidney and liver function test.
- Anti-dsDNA
- Complement (CH50, C3 and C4)

5.4 Contraception

Hormonal contraception should be used with caution, since oestrogens have been related to lupus disease flares. In the presence of APS, hormonal contraception containing oestrogens is strongly contraindicated.

ANNEX 1.

Plasmapheresis treatment regimen for autoimmune AVB

- Indication for plasmapheresis should always be discussed by a multidisciplinary team led by a Haematologist.
- A peripheral intravenous catheter is required for all patients undergoing this treatment.
- Plasma volume exchange per session is 1.2 litres.
- Intravenous 5% albumin infusion must be administered after plasmapheresis.
- Citrate anticoagulation (infusion rate 1.2 mL/min/L)
- Treatment can be repeated every 21 days.

DAY 1: plasmapheresis.
DAY 3: plasmapheresis.
DAY 5: plasmapheresis.
DAYS 6 and 7: Administer intravenous immunoglobulins (IVIG) at 1 g/kg.