Review



# Modern management of pregnancy in Systemic Lupus Erythematosus: From Prenatal Counselling to Postpartum Support

Anna Gamba , Margherita Zen , Roberto Depascale , Antonia Calligaro , Mariele Gatto , Luca Iaccarino , Andrea Doria *

Posted Date: 17 May 2024

doi: 10.20944/preprints202405.1182.v1

Keywords: systemic lupus erythematosus; preconception management; disease monitoring; adverse pregnancy outcomes; therapeutic strategies

*Review*

# Modern Management of Pregnancy in Systemic Lupus Erythematosus: From Prenatal Counselling to Postpartum Support

**Anna Gamba [1], Margherita Zen [1], Roberto Depascale [1], Antonia Calligaro [1], Mariele Gatto [2], Luca Iaccarino [1] and Andrea Doria [1,*]**

[1] Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Padova, Italy
[2] Academic Rheumatology Centre, Department of Clinical and Biological Sciences, University of Turin, AO Mauriziano di Torino, Turin, Italy
* Correspondence: adoria@unipd.it

**Abstract:** Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that predominantly affects women in the childbearing age. Pregnancy in SLE patients poses unique challenges due to the potential impact on maternal and fetal outcomes. We provide an overview of the management of SLE during pregnancy, including pre-conception risk stratification and counselling, treatment, and disease activity monitoring. These assessments are critical to minimize maternal and fetal adverse events in SLE pregnant patients. Disease flares, preeclampsia, antiphospholipid syndrome complications, and maternal mortality are the major risks for a woman with SLE during gestation. Timely treatment of SLE relapse, differentiation of preeclampsia from lupus nephritis, and tailored management for antiphospholipid syndrome are essential for a successful pregnancy. Fetal outcomes include neonatal lupus (NL), preterm birth, cesarean delivery, fetal growth restriction (FGR), and small for gestational age (SGA) infants. We focused on NL, linked to maternal anti-Ro/SS-A and anti-La/SS-B antibodies, which can lead to various manifestations, particularly cardiac abnormalities in newborns. While there is a common consensus regarding the preventive effect of hydroxychloroquine, the role of echocardiographic monitoring and fluorinated steroid treatment is still debated. Finally, close postpartum monitoring and counseling for subsequent pregnancies are crucial aspects of care.

**Keywords:** systemic lupus erythematosus; preconception management; disease monitoring; adverse pregnancy outcomes; therapeutic strategies

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multiple organ involvements and a relapsing-remitting course. The cause is unknown; however, a number of genetic and environmental factors have been identified[1] Like most autoimmune diseases, it predominantly affects females. The disease generally onsets in early adulthood, which means during fertile age. Historically, pregnancies in these patients were considered high-risk, due to the potential disease flare-ups and unfavorable maternal-fetal outcomes. Over time, more knowledge has been gained, leading to more frequent and safer pregnancies in patients with SLE. Nevertheless, compared to the general population, there are several factors that can negatively influence pregnancy in a woman with SLE, including disease activity, presence of some autoantibodies, pharmacological therapy and comorbidities. Therefore, proper planning and competent management of pregnancy starting from the pre-conceptional period are required.

 doi:10.20944/preprints202405.1182.v1



## 2. Counselling

Appropriate counseling is essential to address the multiple issues related to childbearing age. An integrated approach involving rheumatology and gynecology experts, while challenging to accomplish, can be highly beneficial for patients dealing with fertility and rheumatological issues. Furthermore, it is crucial that the specialist can effectively answer the questions and concerns that patients might have. Several studies [2,3] showed that the number of pregnancies in patients with systemic lupus erythematosus (SLE) is lower than in the general population. This discrepancy is not only due to disease activity and drugs, but it also influenced by personal choices. These decisions often result from patients' concerns about infertility, SLE activity during pregnancy, potential transmission of the disease to offspring, using harmful medications for the fetus and worries that the disease might make them unable to take care of a child. Hence, it is imperative for rheumatologists to engage in counseling to alleviate the psychological stress associated with these issues.

### *2.1. Infertility*

There is no clear evidence that SLE reduces female fertility. Nonetheless, some researches [4] found oophoritis and altered regulation of the hypothalamic-pituitary axis in SLE patients, while hyperprolactinemia is associated with disease flares. Furthermore, SLE women have a reduced ovarian reserve, as indicated by their lower levels of anti-Müllerian hormone (AMH). Antiphospholipid and anti-prothrombin antibodies were reported at higher levels in patients with infertility compared to controls[5]. Additionally, there is a higher incidence of menstrual cycle irregularities, which make it more challenging to initiate pregnancy. Historically, a proportion of patients experienced infertility due to cyclophosphamide (CYC) use, leading to ovarian insufficiency. Over time this risk has significantly decreased due to the combined use of CYC and gonadotropin-releasing hormone analogue (GnRHa), as well as the lower us of CYC due to the introduction of new therapeutic options for managing SLE, including mycophenolate mofetil (MMF). In situations where a woman's fertility window is limited, but the need to postpone pregnancy arises due to high disease activity and/or ongoing teratogenic therapy, the rheumatologist should refer the patient to a gynecologist. Indeed, there are several alternative to natural conception, including oocyte cryopreservation or assisted reproductive techniques.

### *2.2. Contraception*

Since planning a pregnancy is crucial for SLE patients, proper counseling on contraception is equally important. In the past, there was a belief that using combined estrogen-progestin pills (E-P) might trigger disease activity. However, several studies[6–8] have shown the safety profile of contraception with E-P pills and copper intrauterine devices (IUDs) in patients with inactive diseases, while the use of medicated IUDs should only be considered in specific cases where the benefits outweigh the thrombotic risk [8]. Nevertheless, 25% of patients taking teratogenic drug do not use effective contraceptive methods[9]. Therefore, it is essential that rheumatologist reassures patients about the safety of contraceptive methods, emphasizing the need to delay gestation until achieving a disease control with pregnancy-compatible drugs. For patients with antiphospholipid antibodies (aPL), with or without antiphospholipid syndrome (APS) or those with thrombotic risk factors independent from SLE, estrogen-progestin contraception is not recommended. In these cases, progestin-only pills or implants can be considered, carefully weighing the risks and benefits.

### *2.3. Pre-Conception Risk Stratification*

In SLE women, several risk factors can lead to unfavorable pregnancy outcomes. The *2017 European League Against Rheumatism* (*EULAR) recommendations*[8] suggested a helpful checklist of variables to consider during pre-conception counseling, as outlined and further detailed in Table 1. Additionally, factors applicable to the general population should be taken into consideration, including woman's age, diabetes mellitus, arterial hypertension, obesity, thyroid disorders,

 doi:10.20944/preprints202405.1182.v1



smoking/alcohol habits, and vaccination status[10]. Considering all these variables, pregnancy may be recommended, postponed or contraindicated (Table 2).

**Table 1.** EULAR Checklist for Pre-Conception Risk Stratification in Women With SLE.

| **Relative Contraindications:** |
|---|
| • Active disease in the 6 months before conception<br>• Active lupus nephritis, especially if requiring teratogenic therapy<br>• Stroke or major thrombotic event in the previous 6 months<br>• Medications contraindicated during pregnancy<br>• Vaccination status: recommended vaccines not administered |
| **Absolute Contraindications:** |
| • Severe pulmonary hypertension<br>• Severe restrictive lung disease<br>• Severe renal insufficiency (eGFR <30 mL/min/1.73 m2)<br>• Advanced heart failure<br>• Previous PE or HELLP syndrome despite appropriate treatment |

**Table 2.** Guiding Factors for Delaying or Contraindicating Pregnancy.

| **Risk Factors Related to SLE:** |
|---|
| • Disease activity in the 6-12 months before conception<br>• Lupus nephritis (active or historical)<br>• Serological activity (complement consumption, positive anti-ds DNA)<br>• End-stage organ damage |
| **Risk Factors Associated with SLE:** |
| • Antiphospholipid antibodies<br>• Anti-SSA Ro/SSB antibodies<br>• Previous negative pregnancy outcomes<br>• Previous thrombotic events |

Legend: PE: pre-eclampsia; HELLP syndrome: hemolysis, elevated liver enzymes, and.

Inactive disease for a minimum of 6-12 months before conception is essential to reduce the risk of adverse outcomes. The risk of a SLE flare during pregnancy [11,12] is two-fold increased in patients with active disease prior to conception, compared to those with inactive disease [11,12]. Relapse, in turn, increases the risk of fetal loss, preterm birth, preeclampsia (PE), and intrauterine growth restriction (IUGR). Most of flares occur in musculoskeletal, cutaneous, hematological, and renal systems. Notably, most of disease flares during pregnancy affect the same organs involved before pregnancy[10,13]. For instance, if the disease was previously active in the skin, a recurrence of cutaneous manifestations is likely to occur, more than other manifestations. Only renal involvement is a risk factor for both renal and non-renal flares.

 doi:10.20944/preprints202405.1182.v1



*2.4. Allowed Therapies during Pregnancy*

In the pre-conception assessment, pharmacological therapy plays a pivotal role (Table 2). A number of studies and guidelines[13–18] advocate for the continuation or initiation of hydroxychloroquine (HCQ) during pregnancy. Indeed, it can contribute in maintaining disease control and its discontinuation has been linked to an increased risk of flares during pregnancy.[8] The recommended dose is ≤400 mg/day, as a greater risk of fetal malformations above this dosage has been reported[19]. Other drugs with a favorable safety profile during pregnancy are oral glucocorticoids (OGC), azathioprine (AZA), cyclosporine (CsA), and tacrolimus (TAK). These medications should be administered at the minimum effective dose, carefully considering the risk/benefit ratio associated with their use. Regarding OGC, a study by Desai R. *et al*.[20] showed that high doses of OGC (prednisone, PDN, >10 mg/day) are an independent risk factor for severe infections (defined as bacterial or opportunistic infections requiring hospitalization) in pregnant women with systemic inflammatory diseases, including SLE. OGC are also associated with gestational hypertension, gestational diabetes, premature rupture of membranes, and small for gestational age (SGA) newborns. Despite no evidence of a teratogenic effect, Belimumab (BEL) and Rituximab (RTX) are generally discontinued upon conception due to a lack of sufficient data regarding their safety profile during pregnancy. However, they may be continued in cases of severe disease despite the use of drugs which are considered safe during pregnancy. For the treatment of ongoing flares during pregnancy, the following treatment can be used, weighing risks and benefits: intravenous GC, intravenous immunoglobulins (IVIG), and plasma exchange. CYC can only be used in cases of severe organ failure or risk of maternal-fetal death. Use of antiplatelet and anticoagulant medications will be discussed later.

**Table 3.** Therapy management for SLE during pregnancy.

| **Rheumatologic Medications Safe Throughout Pregnancy:** | **Rheumatologic Medications Usable in Pregnancy in Exceptional Circumstances:** | **Rheumatologic Medications Contraindicated in Pregnancy:** |
|---|---|---|
| • Hydroxychloroquine (HCQ)<br>• Azathioprine (AZA)<br>• Prednisone (PDN) <7.5 mg/day<br>• Cyclosporine (CsA)<br>• Tacrolimus (TAC) | • Cyclophosphamide (CYC)<br>• Belimumab<br>• Rituximab (RTX) | • Methotrexate (MTX)<br>• Mycophenolate Mofetil (MMF)<br>• Leflunomide (LEF) |

*2.5. Medications to Discontinue before Pregnancy*

Drugs with demonstrated teratogenic effects should be discontinued before conception and replaced with pregnancy-safe alternatives. The effectiveness of not-harmful treatments in maintaining disease control should be assessed for at least 3-6 months before conception.[2,8,21] Timing of discontinuing medications depends on their half-life. Methotrexate should be stopped at least one month before conception, mycophenolate at least 6 weeks before conception and leflunomide should be halted when has planned with washout period using cholestyramine. Beside immunosuppressants, some medications used in various SLE manifestations are contraindicated during pregnancy. ACE inhibitors/angiotensin receptor blockers (ARBs), prescribed for lupus nephritis as antihypertensive and antiproteinuric agents, should be discontinued due to the associated risk of fetal complications, including IUGR, cardiac and renal abnormalities, limb malformations and oligohydramnios[22]. If necessary, alternative antihypertensive medications such as methyldopa, labetalol, and nifedipine can be administered. In APS patients on anticoagulant

 doi:10.20944/preprints202405.1182.v1



therapy, warfarin, due to its teratogenic effect, is replaced with low-molecular-weight heparin (LMWH) at therapeutic dosage. In managing arthritis and joint pain, NSAIDs can be used at the lowest effective dose until the 30$^{th}$ gestational week (GW), after which they are associated with an increased risk of ductus arteriosus constriction.

*2.6. Supportive Therapies during Pregnancy*

Many studies[23–27] support vitamin D supplementation in pregnant SLE women, emphasizing its anti-inflammatory and immunomodulatory effects. Additionally, a correlation has been observed between vitamin D deficiency and conditions such as PE and miscarriages. Moreover, vitamin D appears to play a protective role even in patients with aPL. In vitro studies demonstrated a reduced expression of coagulation cascade activation molecules in endothelial cells exposed to anti-beta2-glycoproteinI antibodies (anti-β2GPI). Furthermore, an increase number of thrombotic events has been noted in cases of vitamin D deficiency. Its usage is crucial, especially in patients undergoing treatment with steroids or LMWH, considering their potential impact on reducing bone mass.[8] However, despite these evidences, not all pregnant patients routinely take vitamin D in clinical practice.

## 3. Pregnancy Follow-up

As observed, the prognosis of pregnancy largely depends on the disease activity, as flares are major risk factors for unfavorable maternal-fetal outcomes. Assessing disease activity during pregnancy can be challenging for rheumatologists, as there are clinical and laboratory changes in gestational period that can mimic manifestations of SLE.[28] Indeed, pregnant women may present cutaneous features (facial rash, palmar rash, melasma), arthralgia, mild joint swelling, and postpartum alopecia. In order to ensure adequate blood flow to the placenta, there is a general vasodilation, resulting in increased hemodynamic load. This leads to hemodilution, causing mild anemia, mild thrombocytopenia, increased erythrocyte sedimentation rate (ESR) and an elevation in glomerular filtration rate (GFR). Therefore, it is important to bear in mind that there could be a reduction in renal function with eGFR still within normal limits. As filtration increases, also the excretion of proteins in urine rises. Therefore, gestational proteinuria is considered within the normal range up to 500 mg/24 hours. Pregnancy also triggers a prothrombotic condition linked to elevated coagulation factors I, VIII, IX, X, and reduced concentrations of anticoagulants like protein S and antithrombin. Normally active SLE involves complement consumption. During pregnancy, there is an increase in complement values, especially the C3 fraction, which synthesis is stimulated by estrogen. In the PROMISSE study (Predictors of pRegnancy Outcome: bioMarker In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus)[29], Buyon *et al*. analyzed 385 pregnancies in SLE patients. They found that a smaller increase in C3 in the second and third trimesters correlated with a higher risk of adverse pregnancy outcomes, defined as fetal death, neonatal death, preterm delivery due to hypertension, PE, placental insufficiency (PI), and SGA. Ideally, pregnancy in SLE women should be managed by a multidisciplinary team, including a rheumatologist, gynecologist, obstetrician, and neonatologist. Regular assessments by the rheumatologist are crucial, involving close clinical and laboratory monitoring every 4-6 weeks to early detect signs of disease activity. Visits should include a physical examination, blood pressure assessment, hematological and biochemical biomarkers evaluation (complete blood count, liver enzymes, creatinine, urine analysis, complement, anti-dsDNA titers), and disease activity indices. Over time, various clinimetric indices have been proposed for assessing disease during pregnancy such as SLE-Pregnancy Disease Activity Index (SLEPDAI), the Lupus Activity Index (LAI) in Pregnancy (LAI-P), modified SLAM (m-SLAM)[30], modified-European consensus lupus activity measurement (m-ECLAM)[31,32], and the British Isles Lupus Assessment Group-2004 for pregnancy (BILAG2004-P)[33]. These indices have been modified from their original versions, excluding confounding factors between SLE and pregnancy[28]. Only LAI-P has been validated[34]. The characteristics of various clinimetric indices are provided in Table 4. In addition, the potential onset of gestational diabetes, especially in patients receiving steroid therapy should be considered and glucose tolerance tests in agreement with local gynecological

 doi:10.20944/preprints202405.1182.v1



guidelines, should be performed. It is important to consider that a diabetogenic state commonly emerges especially as the pregnancy progresses into the third trimester. Monitoring patients with anti-SSA and anti-SSB antibodies will be addressed later.

**Table 4.** Clinimetric indices of SLE activity during pregnancy 28.

| Clinimetric index | Difference from the original version | Assessment time | Final score | Flare definition |
|---|---|---|---|---|
| **LAI-P** | • Excluded: PGA, fatigue<br>• Added: fever, vasculitis, myositis<br>• CVA or TP: not scored in aPL+ pt<br>• Proteinuria: >500mg/day or doubling if previous LN, with ↓ C′ o ↑ Anti ds DNA; rule out PE | 2 weeks | 0-2.6 | Increase of 0.25 from the last evaluation |
| **SLEPDAI** | • Rule out: PE, HELLP, E, infection, Belly palsy, placental problems, pregnancy TP<br>• Consider physiological during pregnancy: ↑ C′, bland knee effusions, ↑ lymphocytes, palmar erythema, hyperventilation due to progesterone and dyspnea due to enlarging uterus, post-partum alopecia | 10 days | 0-105 | 4-11: moderate activity;<br>> 12: severe activity |
| **m-SLAM** | • Excluded: Weight loss, ESR, and scale for miscellaneous disease manifestations<br>• Rule out: PE, E, FM, placental problems, chloasma<br>• Consider physiological during pregnancy:<br>bland knee effusions, ↑ lymphocytes, palmar erythema, hemodilution, ↓ serum creatinine, hyperventilation due to | 1 months | 0-81 | ≥7: active disease |

 doi:10.20944/preprints202405.1182.v1



| | | | | |
|---|---|---|---|---|
| | progesterone and dyspnea due to enlarging uterus, post-partum alopecia | | | |
| **m-ECLAM** | • Proteinuria pathological if >500 mg/day after excluding PE<br>• Non-hemolytic anemia not considered<br>• ESR not considered | 1-3 months | 0-17.5 | ≥2: active disease |
| **BILAG2004-P** | • Rule out: bland knee effusion, peripheral edema of pregnancy and mechanical pain, PE, E, HELLP, APS, melasma, chloasma<br>• Physiological during pregnancy: ↑ lymphocytes and neutrophils, ↓ serum creatinine, hemodilution, post-partum alopecia<br>• For DD LN-PE: Added C' levels and anti-dsDNA added; excluded hypertension | 4 weeks | A-E | A: severe;<br>B: moderate; C: mild stable disease;<br>D: no disease activity;<br>E: no current or previous disease activity |

**Legend**: ↑: Increase; ↓: reduction; aPL: antiphospholipid antibody; APS: antiphospholipid syndrome; C': complement; CVA: cardio-vascular accident; DD: differential diagnosis E: eclampsia; ESR: erythrocyte sedimentation rate; FM: fibromyalgia; HELLP: hemolysis, elevated liver enzymes, and low platelets; LN: lupus nephritis; PE: pre-eclampsia; PGA: physician global assessment; Pt: patient; TP: thrombocytopenia.

### 4. Adverse Pregnancy Outcomes

A cross-sectional study compared pregnancy outcomes in 93,820 women diagnosed with SLE and 78,045,054 women without SLE admitted to hospitals in the United States between 1998 and 2015 [35]. Adverse events which were studied were maternal mortality, fetal mortality, PE, eclampsia, cesarean deliveries, non-delivery-related hospitalizations, and the duration of hospital stays. Over the 18-year study period, a declining trend in adverse events was observed in both groups, although it remained greater in the SLE group. Early fetal losses in the first trimester may be linked to common factors shared with the general population, such as chromosomal abnormalities, hormonal imbalances and advanced maternal age. However, women with SLE face additional risk factors, including aPL/APS, disease activity (especially lupus nephritis), arterial hypertension, and organ damage. Beyond early adverse outcomes, the study identified a series of adverse pregnancy outcomes (APOs) occurring in second and third trimesters, such as PE, eclampsia, IUGR, preterm birth, and SGA neonates.

 doi:10.20944/preprints202405.1182.v1



*4.1. Maternal Outcomes*

4.1.1. Disease Flares and Renal Flares

One of the major risk factors for APO is the reactivation of SLE. Disease flares are, in turn, influenced by the control of SLE activity in the pre-conception period. The percentage of flares varies, ranging from 7-20% in women with inactive disease in the six months before pregnancy to 20-60% in those with active disease[36]. Smyth et al. conducted a meta-analysis of 37 studies, encompassing a total of 2751 pregnancies in SLE, including 1000 with LN. From this analysis, the most frequent maternal complications were disease flares, observed in a quarter of pregnancies, and active lupus nephritis, occurring in one out of six pregnancies. [37] Renal flares not only increase the risk of maternal complications, such as hypertension and PE (57% vs. 11%), but also elevate the likelihood of fetal complications, including preterm birth and fetal deaths (35% vs. 9%).[38,39]

Therefore, disease relapses, particularly renal ones, should be timely treated with aggressive immunosuppressive therapy. This may involve pulse intravenous non-fluorinated GC (which do not cross the placenta), AZA, CNI, plasma exchange, and IVIG. As the pregnancy progresses into the second trimester, careful consideration may be given to the use of cyclophosphamide, sharing with the patient the potential risks and benefits associated with this drug[40].

4.1.2. Preeclampsia

Between 20% and 30% of SLE pregnancies are at risk of developing PE[41–43]. PE is defined as an elevation in blood pressure (>140/90 mmHg, measured on at least two occasions) accompanied by increased proteinuria. HELLP syndrome, characterized by thrombocytopenia, elevated liver enzymes, and hemolytic anemia, is a condition associated with PE. In cases where central nervous system manifestations, such as seizures, occurs, it is referred to as eclampsia. Factors such as placental malformations, including altered remodeling of spiral arteries, genetic factors, and proinflammatory factors, especially dysregulation of the complement system, seem to contribute to its development. One of the significant challenges during pregnancy is distinguishing between a flare of LN and PE. Overall, disease activity is a risk factor for PE. Differential diagnosis is further complicated by the fact that LN itself is a risk factor for PE. Furthermore, a study has demonstrated that the use of PDN in the third trimester is associated with the development of PE[44]. The distinction is paramount because the treatment differs; LN is managed with immunosuppressants, whereas PE requires the delivery. Table 5 outlines the key biomarkers that, when considered together, contribute to an accurate differential diagnosis. From a clinical perspective, unlike PE, LN may present with signs of disease activity in other organs, such as skin, serous membranes, and musculoskeletal system.

**Table 5.** Differential diagnosis NL-PE.

| **Biomarker** | **Lupus nephirtis** | **Preeclampsia** |
|---|---|---|
| Blood pressure | Normal or ↑ | ↑↑ |
| Onset | At any time | >20$^{th}$ GW |
| Renal Biopsy | May show signs of active nephritis | - |
| Serologic Markers | ↑ Anti-dsDNA antibodies<br>↓ Complement levels<br>Normal uric acid<br>Normal or ↓ PLT | Not specific, may include:<br>↑ Liver enzymes<br>↑ Uric acid<br>↓ PLT |

 doi:10.20944/preprints202405.1182.v1



| | | |
|---|---|---|
| Urine analysis | Proteinuria ↑<br>Active sediment | Proteinuria ↑↑↑<br>Not active sediment |
| SLE nor renal symptoms | Could be present and increasing | Stable |
| Angiogenic Factors | ↓ (e.g. angiopoietin-2) | ↑ (e.g. soluble fms-like tyrosine kinase-1) |
| Anti-angiogenic Factors | ↑ (e.g. soluble endoglin) | - |

Legend: ↑: Increase; ↓: reduction, GW: gestatonal week; PLT: platelets;.

Maynard *et al.*[45] advocate for the performance of renal biopsies in cases where the differential diagnosis poses a challenge. They reference two studies, one from 2013 involving 197 pregnancy-related biopsies[46] and another from 2015 covering 11 pregnancies[47]. In the first cohort, significant complications (bleeding, fetal loss, infections, PI) occurred in only 3% of cases, while there were no major complications in the second cohort. Furthermore, in the second study, therapeutic decisions completely changed in 10 out of 11 cases based on the histological results of the biopsy. According to Maynard *et al.*, the decision to perform a biopsy should be influenced by gestational age. Complications related to the procedure are minimal in the first trimester, but in the third trimester it is more prudent to consider delaying the biopsy until post-partum, due to the risk of an emergency preterm delivery. The greatest challenge is the second trimester, when first line approach might involve a personalized lupus therapy tailored to the patient's characteristics, allowing pregnancy progression until a permissive gestational age for induced-delivery.

Several studies showed that the early administration of Low-Dose Aspirin (LDA) during pregnancy reduces the risk of PE. This drug is particularly recommended for patients with PE risk factors, including extreme age, primigravida status, arterial hypertension, pre-existing renal conditions, and aPL[48]. As demonstrated in the ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial [49], initiating 150mg/day of LDA before the 16th GW reduces the risk of PE in high-risk women. The use of LDA is recommended by the EULAR group[8] and the American College of Obstetrics and Gynecology (ACOG)[50]. In both SLE and PE, tissue damage seems to be due to reactive oxygen species. Multiple studies[51–53] have indicated that HCQ reduces the synthesis of reactive oxygen species (ROS) and, consequently, their associated damage.

#### 4.1.3. Antiphospholipid Syndrome

The prevalence of aPL in patients with SLE is 12-44% for anticardiolipin antibodies (aCL), 15-34% for lupus anticoagulant (LAC), and 10-19% for *anti*-β2GPI.[54]

The presence of these antibodies is an independent risk factor for APO, including early (<10$^{th}$ GW) and late fetal deaths, thrombotic events, and PI. A number of *in vitro* and in vivo studies[55,56] have demonstrated the pathogenicity of these antibodies, which seem to target β2GPI, expressed by trophoblast cells, leading to tissue damage. However, the presence of aPLs alone is not sufficient for diagnosing APS. In 2023, ACR/EULAR[57] criteria for APS were established. These criteria require the concomitance of both clinical events and laboratory positivity for aPL. APS is categorized into two main groups: thrombotic and obstetric APS. The former is characterized by macrovascular (arterial or venous), microvascular, cardiac valve, hematological (thrombocytopenia) involvement. The latter is defined by the anamnestic presence of: ≥3 pre-fetal deaths before the 10th GW; or ≥3 early fetal deaths between 10th-15th GW; or ≥1 fetal deaths (16th-33rd GW) without severe PE or severe PI; or severe PE and/or PI, associated or not with fetal death. Laboratory criteria require the positivity of one or more aPLs, confirmed on at least one occasion at a minimum of 12 weeks apart from the first detection, within 3 years of a clinical event. It is important to point out that these are classification

 doi:10.20944/preprints202405.1182.v1



and not diagnostic criteria. When APS is diagnosed in the context of an SLE diagnosis, it is termed secondary; otherwise, it is considered primary (PAPS). Additionally, there are autoantibody profiles defined as "high-risk": the presence of elevated LAC and triple positivity (LAC, aCL, and anti-β2GPI), associated with worse outcomes. Addressing treatment, three situations should be distinguished: patients with aPL without a history of clinical events, patients with thrombotic APS, and patients with obstetric APS. According to the 2019 EULAR recommendations[58], pregnant patients with SLE and a high-risk aPL profile, without previous thrombotic or pregnancy episodes, should be treated with LDA (75-100 mg/day) during pregnancy. In pregnant patients with obstetric APS and SLE, LDA should be used from the preconception period, with the addition of prophylactic LMWH upon pregnancy confirmation. If the obstetric clinical event was a fetal death from the 10$^{th}$ to the 34$^{th}$ GW, the use of LMWH should be evaluated depending on the patient's risk profile. Additionally, in patients with clinical events not sufficient to define obstetric APS, the use of LDA alone or in combination with LMWH should be taken into consideration. In patients with obstetric APS experiencing recurrent pregnancy complications despite prophylactic therapy with LDA and LMWH, escalation to therapeutic LMWH dosage or the addition of HCQ or low-dose PDN from the first trimester may be considered. In highly selective cases where conventional treatments have failed, IVIG may be an option.

Pregnant women with SLE and thrombotic APS should be treated with a combination of LDA and therapeutic LMWH. LMWH should be maintained until 12 hours before delivery and reintroduced 4-6 hours after cesarean section or epidural catheter removal. If the patient has a high thromboembolic risk, LMWH can be converted to unfractionated heparin before delivery, as its effect is more rapidly reversible. LDA is discontinued near delivery, always considering the pregnant woman's risk, and resumed within a week after delivery, continuing for up to 6 weeks postpartum due to the elevated thrombotic risk during the puerperium. In women at high risk, the LDA-LMWH combination can be continued until the onset of uterine contractions. Women who were on warfarin therapy before pregnancy can be transitioned to oral anticoagulants usually 5-7 days after delivery, in the absence of bleeding complications. Breastfeeding is compatible with both warfarin and LDA and LMWH.

**Table 6.** ACR/EULAR definition of Obstetric APS criteria.

| **Clinical domains** | **Weight** | **Laboratory domains** | **Weight** |
|---|---|---|---|
| ≥3 Consecutive pre-fetal deaths (<10$^{th}$ GW) and/or ≥3 Early fetal deaths (10th-16th GW) | 1 | Positive LAC (single, one time) | 1 |
| ≥1 Fetal death (16$^{th}$-33$^{rd}$ GW) without severe PE or severe PI | 1 | Positive LAC (persistent) | 5 |
| Severe PE **or** PI with or without fetal death (<34$^{th}$ GW) | 3 | Moderate or high positive IgM aCL and/or aβ2GP | 1 |
| Severe PE **and** PI with or without fetal death (<34$^{th}$ GW) | 4 | Moderate positive IgG aCL and/or aβ2GP | 4 |
| | | High positive IgG aCL **or** aβ2GP | 5 |
| | | High positive IgG aCL **and** aβ2GP | 7 |

Legend: a-β2GPI: anti-beta2-glycoprotein I antibodies; aCL: anticardiolipin antibodies GW: gestational week; LAC: ; lupus anticoagulant PE: preeclampsia; PI: placenta insufficiency.

 doi:10.20944/preprints202405.1182.v1



4.1.4. Maternal Mortality

There are not many recent data on maternal mortality. In a US national study of 13,555 SLE pregnancies from 2000 to 2003, Clowse *et al.*[59], found that the risk of maternal death (325/100,000 live births) was more than 20-fold higher than the non-SLE population. A review by Ritchie J. et al.,[60] reported 17 cases of maternal death. In all of them there was active disease, and the most frequent causes were infection and flare of disease (40% and 30%, respectively). Other rarer causes were pulmonary embolus, pregnancy-associated cardiomyopathy and adrenal failure due to abrupt glucocorticoids withdrawal**.**

*4.2. Fetal Outcomes*

4.2.1. Neonatal Lupus

**NL is an autoimmune condition acquired passively by the newborn from mothers with anti-**Ro/SS-A and anti-La/SS-B antibodies. Anti-SSA antibodies target the antigenic subunit of molecular weight 52kD or 60kD, known as anti-Ro52 and anti-Ro60, respectively. The former is more commonly found in cases of cardiac manifestations. Cardiac NL rarely occurs in offspring of women exclusively positive for anti-La/SS-B[61]. However, when both anti-Ro/SS-A and anti-La/SS-B antibodies are present, the likelihood of NL increases[62]. Buyon J. in 1993[63]and Jaeggi E. in 2010[64] showed that the lower the antibody titer, the lower the risk of newborn lupus. Overall, 40% of SLE patients have these antibodies, which are also found in other rheumatological conditions such as Sjogren's syndrome, undifferentiated connective tissue diseases[65], rheumatoid arthritis, as well as in the general population[66]. Notably, 50% of mothers of infants born with NL will develop the autoimmune disease after pregnancy[67]. Cutaneous manifestations of NL have also been identified in offspring of mothers who have only anti-U1RNP antibodies[68]. The precise pathogenetic mechanism of NL remains elusive. A cross-reaction between maternal autoantibodies and various embryonic tissues has been hypothesized. In fact, being IgG, mother's autoantibodies are able to cross the placenta from the second trimester. In *vitro* studies have demonstrated that anti-Ro/SS-A and anti-La/SS-B bind calcium-regulating molecules such as calcium channels T and L, which are present in cardiac conduction tissue. This binding would likely promote a local inflammatory response, leading to tissue damage. However, only 2% of offspring born to mothers carrying anti-SSA and anti-SSB antibodies develop manifestations of NL. Probably a genetic predisposition promotes progression to fibrosis or disrupts the inflammatory process. Some studies have indicated an increase in biomarkers of inflammation and cardiac distress (C reactive protein, metalloproteinases, NT-ProBNP) in the umbilical cord blood of neonates with cardiac manifestations compared to those without such manifestations[69]. A type of macrophage expresses high levels of sialic acid-binding Ig-like lecithin 1 (SIGLEC-1). It is a pro-inflammatory cell, upregulated by type I interferon (IFN). These macrophages were found in the cardiac tissue of fetuses with CHB[70]. A study conducted by Lisney et al. demonstrated a correlation where mothers of children with congenital heart block (CHB) exhibited significantly higher expression levels of SIGLEC-1 and IFN-$\alpha$ compared to mothers with healthy children[71]. The term "neonatal lupus" refers to a range of manifestations that can vary both in severity and duration. These manifestations include transient skin involvement, characterized by the appearance of annular erythematous lesions. Manifestations typically affect face, scalp and neck. These lesions may be present from birth or emerge between 4 and 6 weeks of life, usually auto-resolving in 17 weeks, when mother’s autoantibodies disappear from neonatal blood. Additionally, there may be transient and asymptomatic liver involvement, marked by a mild elevation of transaminases, as well as mild hepatosplenomegaly that can progress to cholestasis and hepatitis. Varying degrees of cytopenia can occur, occasionally progressing to aplastic anemia. Neurological involvement, often transient, may present with subtle symptoms and nonspecific neuroradiological signs, or with macrocephaly and hydrocephalus. However, the association with NL is not universally supported by all researchers. The most severe complication, but also the least frequent, involves cardiac involvement [68]. Cardiac NL occurs between 18$^{th}$ and 26$^{th}$ GW, corresponding to the embryonic development period of cardiac tissue. About 2% of the newborns from mothers with anti-

 doi:10.20944/preprints202405.1182.v1



Ro/SS-A and anti-La/SS-B antibodies develop cardiac NL. The recurrence risk of cardiac NL in a subsequent pregnancy is 12-17%, whereas if the woman has already given birth to a child with non-cardiac NL manifestations, the likelihood is similar to that of patients with only anti-SSA and anti-SSB. Typically, it manifests without structural cardiac anomalies but with rhythm disturbances, notably atrioventricular congenital heart block (CHB) of first, second, or third degree (Complete CHB, CCHB). In the latter case, mortality reaches 17% by the 30$^{th}$ GW. Other potential cardiac complications include endocardial fibroelastosis and consequent dilatated cardiomyopathy, congestive heart failure, sinus bradycardia, valvular alterations, and myocarditis. Current recommendations suggest a close echocardiographic monitoring of the fetal heartbeat between 18$^{th}$ and 26$^{th}$ GW. However, some studies[72] are questioning the usefulness of this approach, since only rarely standard fetal heart rate surveillance has detected CHB in time for effective treatment. Evers *et al.*[73], suggested that utilizing antibody levels to categorize this population can enhance surveillance for CHB. Standard (weekly) screening is not cost-effective and leads to excessive resource utilization.

In the past, it was evenly recommended the administration of fluorinated GC, such as dexamethasone and betamethasone. The rationale for their use was based on the idea that, by crossing the placenta, they could act on the inflammatory component of cardiac damage. However, multiple studies[74,75] show that first-degree block does not worsen in fetuses of untreated mothers. Second-degree BAVs tend to regress or progress whether treated or untreated, whereas third-degree blocks never regress with steroid therapy[75]. A metanalysis of 9 studies, conducted by Hoxha et.al, analyzed 747 pregnancies in which fluorinated steroids do not demonstrate superiority over other treatments for patients with CHB[72]. In this study the outcomes were: live birth, prevention of incomplete CHB progression, pacemaker implantation, and extra-nodal disease.

Thus, whereas of minimal benefits, GC can lead to a series of both fetal and maternal complications, including infections, osteoporosis, osteonecrosis, diabetes, IUGR, and oligohydramnios. It has also been noted that their preventive use has no impact on NL development. There have been no controlled studies assessing the effectiveness of plasmapheresis in cardiac NL. IVIG was not demonstrated to prevent cardiac NL at a dose of 400 mg/kg.[76] In contrast, several studies[77–79] have demonstrated that the use of HCQ from the early GW reduces the risk of NL, even in cases of NL in previous pregnancies. Considering the potential benefits, HCQ should be initiated before conception or as early as possible during the first trimester in women positive for anti-SSA/-SSB antibodies, particularly in those with a history of CHB. With no therapies proven effective for occurred CHB, close monitoring is recommended. In cases of fetal distress, early delivery is indicated. It has also been observed that 2% of AV blocks may appear up to 1 month after birth; hence, these children should be monitored by an expert pediatrician in the early weeks of life. The only procedure that increases the survival of these infants is the implantation of a pacemaker. Indeed, 70% have undergone pacing by the age of 10 years[76].

#### 4.2.2. Preterm Birth and Cesarean Delivery

It is defined preterm birth when delivery occurs before the 37$^{th}$ GW. Lupus patients have a higher likelihood of experiencing preterm birth compared to the general population. In the United States, for instance, the percentage varies from 33% in SLE pregnant women to 12% in the National average[80]. Several factors contribute to an increased risk of this complication. Inflammation, both local and systemic, leads to the release of cytokines, prostaglandins, and complement consumption[81]. Indeed, SLE patients often exhibit reduced levels of estradiol, which are directly proportional to placental health[31]. Risk is also related to administration of oral PDN[82,83] and dysfunctions in the maternal or fetal hypothalamic-pituitary axis, which result in elevated placental corticotropin-releasing hormone, leading to increased synthesis of cortisol and prostaglandins[84]. The risk is amplified by disease activity and the occurrence of PE. Moroni *et al.*[85], identified risk predictors for preterm delivery which include: SLEDAI, active nephritis, proteinuria (g/day), arterial hypertension, previous renal flares, quarterly change of a single unit in SLEDAI, and quarterly increase of daily proteinuria >1 g during pregnancy.

 doi:10.20944/preprints202405.1182.v1



Indications for cesarean sections in lupus pregnancies are not different from those in the general population. Nevertheless, due to a higher incidence of complications such as PE or fetal distress in SLE patients compared to those in healthy women, cesarean sections are performed in 33% of SLE pregnancies. Nevertheless, a woman with lupus experiencing an uncomplicated pregnancy is not prevented from opting for a standard vaginal delivery.

4.2.3. Fetal growth Restriction and Small for Gestational Age Infants

Fetal growth restriction (FGR) is defined as an estimated fetal weight or abdominal circumference <10$^{th}$ percentile for gestational age. It is a rare complication in healthy pregnancies; the risk increases in smokers or those with gestational hypertension. Several studies have compared birth weights between offspring of SLE and healthy women, matched for age and risk factors, revealing a higher risk of FGR and SGA infants (<5$^{th}$ percentile) in SLE pregnancies. The risk increased in cases of active disease or renal flares[37,86,87]. Furthermore, in APS, placental infarction leads to reduced nutritional supply to the fetus and consequent growth delay. A meta-analysis involving over 20,000 pregnant women revealed that when LDA was given before 16 weeks, there were significant dose-dependent reductions in the rates of FGR[88]. The likelihood of having a baby classified as SGA was reduced by 85% in patients who received HCQ during pregnancy[85].

## 5. Post-Partum

Women with active disease in the six months before conception or during pregnancy are at a higher risk of experiencing a flare during the post-partum period (defined as six to eight weeks after birth). Therefore, close monitoring is recommended. Breastfeeding is possible, as almost all the treatments administered during pregnancy are compatible with lactation. In women with anti-Ro/SS-A and anti-La/SS-B antibodies, it is essential to provide counseling regarding subsequent pregnancies, especially about the use of preventive HCQ in future pregnancies. Additionally, it is important to remember that the prevalence of post-partum depression in Europe is estimated to be around 10%[89]. This condition should be considered in the differential diagnosis with neuropsychiatric SLE[90]

## Conclusion

Managing SLE during pregnancy requires a critical approach that balances maternal with fetal health. Preconception counseling, achieving disease control before pregnancy, vigilant disease monitoring, scrupulous medication assessment, and proactive management of potential complications are crucial. Nevertheless, despite advancements in medical care and a greater understanding of the pathophysiology of SLE pregnancy, adverse gestational events are still more frequent in women with SLE than in the general population. Therefore, ongoing and future studies are essential to further refine our understanding and management of SLE in pregnancy. By focusing on education, research, and multidisciplinary care, the impact of SLE on pregnancy can be reduced, leading to an improvement in the quality of life of affected women and their offspring.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References

1. Sarzi-Puttini P, Atzeni F, Iaccarino L, Doria A (2005) Environment and systemic lupus erythematosus: An overview. Autoimmunity 38:465–472
2. Sammaritano LR, Bermas BL, Chakravarty EE, et al. (2020) 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis & Rheumatology 72:529–556
3. Clowse MEB, Chakravarty E, Costenbader KH, Chambers C, Michaud K (2012) Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 64:668–674

 doi:10.20944/preprints202405.1182.v1




4. Pasoto SG, Mendonça BB, Bonfá E (2002) Menstrual disturbances in patients with systemic lupus erythematosus without alkylating therapy: clinical, hormonal and therapeutic associations. Lupus 11:175–180
5. Shoenfeld Y, Carp HJA, Molina V, et al. (2006) Autoantibodies and Prediction of Reproductive Failure. American Journal of Reproductive Immunology 56:337–344
6. Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, Cravioto M-C (2005) A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus. New England Journal of Medicine 353:2539–2549
7. Petri M, Kim MY, Kalunian KC, et al. (2005) Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus. New England Journal of Medicine 353:2550–2558
8. Andreoli L, Bertsias GK, Agmon-Levin N, et al. (2017) EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 76:476–485
9. Sammaritano LR (2020) Contraception and preconception counseling in women with autoimmune disease. Best Pract Res Clin Obstet Gynaecol 64:11–23
10. Borella E, Lojacono A, Gatto M, Andreoli L, Taglietti M, Iaccarino L, Casiglia E, Punzi L, Tincani A, Doria A (2014) Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunol Res 60:170–176
11. Kwok L-W, Tam L-S, Zhu T, Leung Y-Y, Li E (2011) Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. Lupus 20:829–836
12. Buyon JP, Kim MY, Guerra MM, et al. (2015) Predictors of Pregnancy Outcomes in Patients With Lupus. Ann Intern Med 163:153–163
13. Russell MD, Dey M, Flint J, et al. (2023) British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology 62:e48–e88
14. Costedoat-Chalumeau N, Amoura Z, Le Thi Huong D, Wechsler B, Piette J-C (2005) [Pleading to maintain hydroxychloroquine throughout Lupus pregnancies]. Rev Med Interne 26:467–9
15. Clowse MEB, Magder L, Witter F, Petri M (2006) Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 54:3640–7
16. Levy RA, Vilela VS, Cataldo MJ, Ramos RC, Duarte JL, Tura BR, Albuquerque EM, Jesús NR (2001) Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 10:401–404
17. Barsalou J, Jaeggi E, Laskin CA, Brown P, Tian SY, Hamilton RM, Silverman ED (2017) Prenatal exposure to antimalarials decreases the risk of cardiac but not non-cardiac neonatal lupus: a single-centre cohort study. Rheumatology 56:1552–1559
18. Andersson NW, Skov L, Andersen JT (2021) Fetal safety of chloroquine and hydroxychloroquine use during pregnancy: a nationwide cohort study. Rheumatology 60:2317–2326
19. Huybrechts KF, Bateman BT, Zhu Y, Straub L, Mogun H, Kim SC, Desai RJ, Hernandez-Diaz S (2021) Hydroxychloroquine early in pregnancy and risk of birth defects. Am J Obstet Gynecol 224:290.e1-290.e22
20. Desai RJ, Bateman BT, Huybrechts KF, Patorno E, Hernandez-Diaz S, Park Y, Dejene SZ, Cohen J, Mogun H, Kim SC (2017) Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions: cohort study. BMJ j895
21. Keeling SO, Alabdurubalnabi Z, Avina-Zubieta A, et al. (2018) Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus. J Rheumatol 45:1426–1439
22. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD (2012) Pregnancy Outcome Following Exposure to Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists. Hypertension 60:444–450
23. LINDQVIST PG, EPSTEIN E, OLSSON H (2009) Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis. Journal of Thrombosis and Haemostasis 7:605–610
24. Agmon-Levin N, Blank M, Zandman-Goddard G, et al. (2011) Vitamin D: an instrumental factor in the anti-phospholipid syndrome by inhibition of tissue factor expression. Ann Rheum Dis 70:145–150
25. Breslin LC, Ball E, Armstrong D, Bell A, Magee P, Laird E, Wallace J, McSorley E (2013) AB0409 An observational study of vitamin d in systemic lupus erythematosus patients: associations among vitamin d status, fatigue, quality of life and disease activity. Ann Rheum Dis 72:A912.4-A913
26. Statache G, Brown S (2022) Vitamin D in Lupus Patients of Childbearing Age: Are We Doing Enough? Frontiers in Reproductive Health. https://doi.org/10.3389/frph.2022.936810
27. Lomarat W, Rattapol Pakchotanon R, Chaiamnuay S, Narongroeknawin P, Asavatanabodee P (2016) OP0283 A Randomized Double-Blind Comparative Clinical Trials To Evaluate Efficacy of Vitamin D in Systemic Lupus Erythematosus (SLE) Patients. Ann Rheum Dis 75:165.2-165

 doi:10.20944/preprints202405.1182.v1




28. Andreoli L, Gerardi MC, Fernandes M, et al. (2019) Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. Autoimmun Rev 18:164–176
29. Buyon JP, Kim MY, Guerra MM, et al. (2015) Predictors of Pregnancy Outcomes in Patients With Lupus. Ann Intern Med 163:153–163
30. Buyon JP, Kalunian KC, Ramsey-Goldman R, Petri MA, Lockshin MD, Ruiz-Irastorza G, Khamashta M (1999) Assessing disease activity in SLE patients during pregnancy. Lupus 8:677–684
31. Doria A, Cutolo M, Ghirardello A, Zampieri S, Vescovi F, Sulli A, Giusti M, Piccoli A, Grella P, Gambari PF (2002) Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 47:202–209
32. Doria A, Ghirardello A, Iaccarino L, et al. (2004) Pregnancy, cytokines, and disease activity in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 51:989–995
33. Yee C-S, Akil M, Khamashta M, Bessant R, Kilding R, Giles I, Farewell VT, Gordon C (2012) The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. Rheumatology 51:1877–1880
34. Zuppa AA, Riccardi R, Frezza S, Gallini F, Luciano RMP, Alighieri G, Romagnoli C, De Carolis S (2017) Neonatal lupus: Follow-up in infants with anti -SSA/Ro antibodies and review of the literature. Autoimmun Rev 16:427–432
35. Mehta B, Luo Y, Xu J, Sammaritano L, Salmon J, Lockshin M, Goodman S, Ibrahim S (2019) Trends in Maternal and Fetal Outcomes Among Pregnant Women With Systemic Lupus Erythematosus in the United States. Ann Intern Med 171:164–171
36. Fernández-Buhigas I (2022) Obstetric management of the most common autoimmune diseases: A narrative review. Front Glob Womens Health. https://doi.org/10.3389/fgwh.2022.1031190
37. Smyth A, Oliveira GHM, Lahr BD, Bailey KR, Norby SM, Garovic VD (2010) A Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus and Lupus Nephritis. Clinical Journal of the American Society of Nephrology 5:2060–2068
38. Skorpen CG, Lydersen S, Gilboe I-M, Skomsvoll JF, Salvesen KÅ, Palm Ø, Svean Koksvik HS, Jakobsen B, Wallenius M (2018) Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study. Ann Rheum Dis 77:264–269
39. Wagner S, Craici I, Reed D, et al. (2009) Maternal and foetal outcomes in pregnant patients with active lupus nephritis. Lupus 18:342–347
40. Moroni G, Doria A, Giglio E, et al. (2016) Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. J Autoimmun 74:194–200
41. Mehta B, Luo Y, Xu J, Sammaritano L, Salmon J, Lockshin M, Goodman S, Ibrahim S (2019) Trends in Maternal and Fetal Outcomes Among Pregnant Women With Systemic Lupus Erythematosus in the United States. Ann Intern Med 171:164–171
42. Ananth C V., Keyes KM, Wapner RJ (2013) Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ 347:f6564–f6564
43. Chakravarty EF, Colón I, Langen ES, Nix DA, El-Sayed YY, Genovese MC, Druzin ML (2005) Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. Am J Obstet Gynecol 192:1897–1904
44. Skorpen CG, Lydersen S, Gilboe I-M, Skomsvoll JF, Salvesen KÅ, Palm Ø, Svean Koksvik HS, Jakobsen B, Wallenius M (2018) Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study. Ann Rheum Dis 77:264–269
45. Maynard S, Guerrier G, Duffy M (2019) Pregnancy in Women With Systemic Lupus and Lupus Nephritis. Adv Chronic Kidney Dis 26:330–337
46. Piccoli G, Daidola G, Attini R, et al. (2013) Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. BJOG 120:412–427
47. Chen TK, Gelber AC, Witter FR, Petri M, Fine DM (2015) Renal biopsy in the management of lupus nephritis during pregnancy. Lupus 24:147–154
48. Dao KH, Bermas BL (2022) Systemic Lupus Erythematosus Management in Pregnancy. Int J Womens Health Volume 14:199–211
49. Poon LC, Wright D, Rolnik DL, et al. (2017) Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. Am J Obstet Gynecol 217:585.e1-585.e5
50. Petri M (2020) Systemic Lupus Erythematosus. Obstetrics & Gynecology 136:226–226
51. Miyachi Y, Yoshioka A, Imamura S, Niwa Y (1986) Antioxidant action of antimalarials. Ann Rheum Dis 45:244–248
52. Abd Rahman R, DeKoninck P, Murthi P, Wallace EM (2018) Treatment of preeclampsia with hydroxychloroquine: a review. The Journal of Maternal-Fetal & Neonatal Medicine 31:525–529

 doi:10.20944/preprints202405.1182.v1




53. Gómez-Guzmán M, Jiménez R, Romero M, et al. (2014) Chronic Hydroxychloroquine Improves Endothelial Dysfunction and Protects Kidney in a Mouse Model of Systemic Lupus Erythematosus. Hypertension 64:330–337
54. Biggioggero M, Meroni PL (2010) The geoepidemiology of the antiphospholipid antibody syndrome. Autoimmun Rev 9:A299–A304
55. Carroll TY, Mulla MJ, Han CS, et al. (2011) Modulation of Trophoblast Angiogenic Factor Secretion by Antiphospholipid Antibodies is Not Reversed by Heparin. American Journal of Reproductive Immunology 66:286–296
56. Meroni P-L, Chighizola C (2012) Pathophysiology of the antiphospholipid syndrome (APS). Rev Med Interne 33:A2–A4
57. Barbhaiya M, Zuily S, Naden R, et al. (2023) 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis 82:1258–1270
58. Tektonidou MG, Andreoli L, Limper M, et al. (2019) EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 78:1296–1304
59. Clowse MEB, Jamison M, Myers E, James AH (2008) A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol 199:127.e1-127.e6
60. Ritchie J, Smyth A, Tower C, Helbert M, Venning M, Garovic V (2012) Maternal deaths in women with lupus nephritis: a review of published evidence. Lupus 21:534–541
61. Salomonsson S, Dzikaite V, Zeffer E, et al. (2011) A Population-based Investigation of the Autoantibody Profile in Mothers of Children with Atrioventricular Block. Scand J Immunol 74:511–517
62. Brito-Zerón P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA (2015) The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol 11:301–312
63. Buyon JP, Winchester RJ, Slade SG, Arnett F, Copel J, Friedman D, Lockshin MD (1993) Identification of mothers at risk for congenital heart block and other neonatal lupus syndromes in their children. comparison of enzyme-linked immunosorbent assay and immunoblot for measurement of anti–ss-a/ro and anti–ss-b/la antibodies. Arthritis Rheum 36:1263–1273
64. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E (2010) The Importance of the Level of Maternal Anti-Ro/SSA Antibodies as a Prognostic Marker of the Development of Cardiac Neonatal Lupus Erythematosus. J Am Coll Cardiol 55:2778–2784
65. Doria A, Mosca M, Gambari PF, Bombardieri S (2005) Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? J Rheumatol 32:213–5
66. Fredi M, Cavazzana I, Quinzanini M, Taraborelli M, Cartella S, Tincani A, Franceschini F (2014) Rare autoantibodies to cellular antigens in systemic lupus erythematosus. Lupus 23:672–677
67. Rivera TL, Izmirly PM, Birnbaum BK, Byrne P, Brauth JB, Katholi M, Kim MY, Fischer J, Clancy RM, Buyon JP (2009) Disease progression in mothers of children enrolled in the Research Registry for Neonatal Lupus. Ann Rheum Dis 68:828–835
68. Gryka-Marton M, Szukiewicz D, Teliga-Czajkowska J, Olesinska M (2021) An Overview of Neonatal Lupus with Anti-Ro Characteristics. Int J Mol Sci 22:9281
69. Izmirly P, Saxena A, Buyon JP (2017) Progress in the pathogenesis and treatment of cardiac manifestations of neonatal lupus. Curr Opin Rheumatol 29:467–472
70. Clancy RM, Halushka M, Rasmussen SE, Lhakhang T, Chang M, Buyon JP (2019) Siglec-1 Macrophages and the Contribution of IFN to the Development of Autoimmune Congenital Heart Block. The Journal of Immunology 202:48–55
71. Lisney AR, Szelinski F, Reiter K, Burmester GR, Rose T, Dörner T (2017) High maternal expression of SIGLEC1 on monocytes as a surrogate marker of a type I interferon signature is a risk factor for the development of autoimmune congenital heart block. Ann Rheum Dis 76:1476–1480
72. Cuneo BF, Sonesson S-E, Levasseur S, et al. (2018) Home Monitoring for Fetal Heart Rhythm During Anti-Ro Pregnancies. J Am Coll Cardiol 72:1940–1951
73. Evers PD, Alsaied T, Anderson JB, Cnota JF, Divanovic AA (2019) Prenatal heart block screening in mothers with SSA/SSB autoantibodies: Targeted screening protocol is a cost-effective strategy. Congenit Heart Dis 14:221–229
74. Levesque K, Morel N, Maltret A, et al. (2015) Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. Autoimmun Rev 14:1154–1160
75. Michael A, Radwan AA, Ali AK, Abd-Elkariem AY, Shazly SA (2019) Use of antenatal fluorinated corticosteroids in management of congenital heart block: Systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol X 4:100072
76. Fischer-Betz R, Specker C (2017) Pregnancy in systemic lupus erythematosus and antiphospholipid syndrome. Best Pract Res Clin Rheumatol 31:397–414
77. Barsalou J, Costedoat-Chalumeau N, Berhanu A, et al. (2018) Effect of in utero hydroxychloroquine exposure on the development of cutaneous neonatal lupus erythematosus. Ann Rheum Dis 77:1742–1749

 doi:10.20944/preprints202405.1182.v1



78. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, Friedman D, Llanos C, Piette J-C, Buyon JP (2012) Maternal Use of Hydroxychloroquine Is Associated With a Reduced Risk of Recurrent Anti-SSA/Ro-Antibody–Associated Cardiac Manifestations of Neonatal Lupus. Circulation 126:76–82
79. Izmirly P, Kim M, Friedman DM, et al. (2020) Hydroxychloroquine to Prevent Recurrent Congenital Heart Block in Fetuses of Anti-SSA/Ro-Positive Mothers. J Am Coll Cardiol 76:292–302
80. Clark CA, Spitzer KA, Nadler JN, Laskin CA (2003) Preterm deliveries in women with systemic lupus erythematosus. J Rheumatol 30:2127–32
81. Park JS, Park CW, Lockwood CJ, Norwitz ER (2005) Role of cytokines in preterm labor and birth. Minerva Ginecol 57:349–66
82. Wei S, Lai K, Yang Z, Zeng K (2017) Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies. Lupus 26:563–571
83. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M (2013) Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. European Respiratory Journal 41:1082–1090
84. Voltolini C, Torricelli M, Conti N, Vellucci FL, Severi FM, Petraglia F (2013) Understanding Spontaneous Preterm Birth: From Underlying Mechanisms to Predictive and Preventive Interventions. Reproductive Sciences 20:1274–1292
85. Moroni G, Doria A, Giglio E, et al. (2016) Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. J Autoimmun 74:6–12
86. Kim S-Y, Lee J-H (2008) Prognosis of Neonates in Pregnant Women with Systemic Lupus Erythematosus. Yonsei Med J 49:515
87. GLADMAN DD, TANDON A, IBAÑEZ D, UROWITZ MB (2010) The Effect of Lupus Nephritis on Pregnancy Outcome and Fetal and Maternal Complications. J Rheumatol 37:754–758
88. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E (2017) The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol 216:110-120.e6
89. O'Hara MW, Wisner KL (2014) Perinatal mental illness: Definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 28:3–12
90. Govoni M, Bombardieri S, Bortoluzzi A, et al. (2012) Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. Rheumatology (Oxford) 51:157–68