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# Systemic Lupus Erythematosus Pregnancy

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## Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune disease of unknown etiology that often affects women during childbearing age. Pregnant women with SLE are considered high-risk patients, with pregnancy outcomes being complicated by high maternal and fetal mortality and morbidity. Obstetric morbidity includes preterm birth, fetal growth restriction (FGR), and neonatal lupus syndromes. Active SLE during conception is a strong predictor of adverse pregnancy outcomes and exacerbations of disease can occur more frequently during gestation. Therefore, management of maternal SLE should include preventive strategies to minimize disease activity and to reduce adverse pregnancy outcomes. Patients with active disease at time of conception have increased risk of flares, like lupus nephritis, imposing a careful differential diagnosis of pre-eclampsia, keeping in mind that physiological changes of pregnancy may mimic a lupus flare. Major complications arise when anti-phospholipid antibodies are present, like recurrent pregnancy loss, stillbirth, FGR, and thrombosis in the mother. A multidisciplinary approach is hence crucial and should be initiated to all women with SLE at childbearing age with an adequate preconception counseling with assessment of risk factors for adverse maternal and fetal outcomes with a tight pregnancy monitoring plan. Although treatment choices are limited during pregnancy, prophylactic anti-aggregation and anticoagulation agents have proven beneficial in reducing thrombotic events and pre-eclampsia related morbidity. Pharmacological therapy should be tailored, allowing better outcomes for both the mother and the baby. Immunosuppressive and immunomodulators, must be effective in controlling disease activity and safe during pregnancy. Hydroxychloroquine is the main therapy for SLE due to its anti-inflammatory and immunomodulatory effects recommended before and during pregnancy and other immunosuppressive drugs (e.g. azathioprine and calcineurin inhibitors) are used to control disease activity in order to improve obstetrical outcomes. Managing a maternal SLE is a challenging task, but an early approach with multidisciplinary team with close monitoring is essential and can improve maternal and fetal outcomes.

**Keywords:** Systemic Lupus Erythematosus, Pregnancy, Pre-eclampsia, Antiphospholipid Syndrome, Lupus Nephritis, Immunosuppression, Hydroxychloroquine, Neonatal lupus syndrome

## **1. Introduction**

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by production of autoantibodies and polymorphic manifestations of end-organ damage [1, 2]. The disease can manifest itself in many forms and severity, ranging from mild cutaneous and joint involvement, to devastating ocular complications or lethal renal, cardiac and cerebral involvement [3]. SLE is caused by interactions between susceptibility genes and environmental factors, resulting in irreversible loss of immunologic self-tolerance. Its estimated incidence ranges from 0.3 to 23.2 per 100.000 person-years and it mostly affects women, with a female to male ratio as high as 10–15:1 [4, 5]. In women, prevalence varies between 164 to 406/100.000 [6] and most of them are in childbearing age. For these reasons, reproductive health and family planning are issues of utmost importance for physicians managing SLE patients, including internists, rheumatologists, and gynecologists. Even if fertility is not impaired in SLE, pregnancy represents a high-risk period in the disease course, mainly due to serious potential maternal and fetal complications. On the maternal side, risk of flare is increased during pregnancy, and there is risk of pre-eclampsia (PE) and thrombotic complications, especially in women carrying antiphospholipid antibodies (aPL). On the fetal side, fetal growth restriction (FGR) and preterm birth are feared complications, besides the potential harm caused by maternal antibodies, as it is the case of congenital heart block (CHB) and neonatal lupus in women carrying SS-A and SS-B antibodies. Multidisciplinary approach, preconception counseling, pregnancy planning and increased availability of safe drugs in pregnancy and puerperium have contributed to improve both maternal and fetal outcomes.

## **2. Immunopathogenesis**

The immune system is a multidimensional environment with its main role being to protect the host against foreign pathogens and to remove cellular debris without harming the host. The etiology of SLE is multifactorial which leads to a failure to maintain immune tolerance and immune homeostasis manifested by aberrant immune responses against endogenous nuclear and other self-antigens. The pathogenesis of SLE involves various cells and molecules that intervene in apoptosis, innate and adaptive immune responses [7, 8]. This process involves plasma cells migrating to inflamed tissue where they become long-lived plasma cells that make antibodies and contribute to the formation of immune complexes.

### **2.1 Genetic predisposition and epigenetics contributions**

The etiology of SLE still remains unknown, but genetic (e.g. major histocompatibility complex (MHC), interferon regulatory factor 5 (IRF5)) components and environmental factors (e.g. Epstein–Barr Virus (EBV), UV light) play an important role in the pathogenesis of SLE [9].

### **2.2 Coexistence: the interaction of pregnancy and SLE**

The state of pregnancy is a complex and sophisticated one—it requires physiologic adaptations in all maternal systems, including immune and neuroendocrine alterations in the maternal body, in order to adapt and protect the fetus from immunologic attack by the mother [10].

The induction and maintenance of tolerance throughout pregnancy involves many different immunoregulatory cell types, including cells that reside in the decidua, which are recruited to the placenta or proliferate locally in the decidua, as well as cell surface receptors and secreted molecules that orchestrate tolerogenic mechanism [11].

This modulation of the composition and function of the immune-competent cells and immune-modulatory molecules in the maternal system during pregnancy has the ability to enhance and suppress different immune mechanisms to create a balance that protects the fetus, without compromising the mother's defense against infection [10].

In harmony, estrogen cells and regulatory proteins exert their effects on decidual stromal cells and tolerogenic dendritic cells, expand FOXP3<sup>+</sup> T regulatory cells (Treg), calibrate the function of the rapidly increasing number of natural killer (NK) cells and downregulate effector T cells. The fetus promotes tolerance to paternal antigens by migration of fetal cells and cell-free fetal DNA to the maternal circulation during normal pregnancy. The fetus is considered a semi-allogeneic graft and to avoid rejection, a tolerogenic state at the feto-maternal interface has to be induced rapidly [12].

In a simple schematic way, the physiologic immune response to pregnancy occurs by: (1) stimulation of B cells which occurs with production of antibodies; (2) T helper (Th) cells participate as co-stimulatory cells, inducing a shift at the Th 1 and Th 2 helper cell level; (3) leading to a predominance of Th 2 cells during pregnancy which also suppresses the response of cytotoxic T cells; (4) the shift towards the Th 2 response leads to suppression of anti-fetal antigen-mediated immune responses; (5) the hormonal system participates in the suppression of cell-mediated immunity, and thus immune tolerance; and (6) a tight cooperation for preventing a response to fetal antigens occurs between the trophoblast and the maternal immune system [13].

### *2.2.1 T cell responses in normal pregnancy and in lupus pregnancy*

In the case of pregnancy associated with SLE, the main immune abnormality involves the function of T regulatory (Treg) cells, as these are limited in number and in their functions [14]. The main purpose of the Treg cells during a normal pregnancy is to ensure immune tolerance to the fetus, and in the case of SLE, the immune system is confronted with a weakened response which cannot ensure the right settings of the product of conception.

Therefore, the problem arises with the number of Treg cells. In a normal pregnancy, the number of Treg cells increases and contrarily decreases in cases of pregnancy loss and pre-eclampsia. On one hand, pregnancy benefits from the contribution of Treg cells, which ensure maternal-fetal tolerance. On the other hand, Treg cells are defective in SLE [15]. It is also possible that this impaired immune tolerance results in complications such as miscarriage, preterm birth or pre-eclampsia. However, in cases of pregnancy associated with inactive SLE, Treg cells might ensure maternal-fetal tolerance because functional Treg cells predominate. This is one of the reasons why women should be in remission prior to pregnancy [13].

The Th 17 cell is a subset of the T helper which is regulated by Treg cells. They possess great plasticity and its function is to produce IL-17 and other interleukins such as IL-21, IL-22, and IL-17F [16]. These cells which mainly produce IL-17A and IL-17F can turn into cells that produce interferon gamma [17]. Th 17 cells have a role in inflammatory processes in autoimmune diseases and abnormal changes in the ratio of Th 17 cells to Treg cells may be related to spontaneous abortion and premature birth [17, 18]. Torricelli et al., found that pregnant women with SLE

demonstrated increased levels of IL-17 together with other cytokines, including IL-6, IL-10, and TNF. This may indicate a hyperactive immune system among pregnant women with SLE, and this may be related to the placenta [18].

However, beyond the limited and mal-function of Treg cells, estrogens are also an important part of the immunopathology of SLE, which in pregnancy plays an important part in shaping the immune tolerance.

### *2.2.2 Estrogens and its role in normal pregnancy versus lupus pregnancy*

Estrogens are related to the immune response system and in high concentrations act simultaneously with other reproductive hormones. It is believed to stimulate increased Th2 cytokines during gestation, being a desirable response to normal pregnancy. However, in SLE patient, excessive Th2 responses can lead to increased secretion of IL-17, which may lead to recurrent miscarriages [13, 18]. By promoting Th 2 responses, estrogens in pregnancy tend to worsen Th 2-mediated diseases such as SLE [16, 17]. Torricelli et al., showed high levels of serum IL-17 in pregnant women with SLE [19].

### *2.2.3 B cell response in normal pregnancy versus in SLE*

In SLE, B cells also have an important role in producing antibodies. The B cells participate in maternal immune tolerance to the fetus with secretion of IL-10, which progressively rises during a normal and healthy pregnancy. However, in SLE patients, IL-10 levels are significantly higher at conception and remain elevated throughout pregnancy and postpartum. IL-10 is a pleiotropic cytokine, with both immune stimulatory and immune suppressive functions. Persistent high levels of IL-10 indicate a constitutional overproduction in SLE, resulting in continuous B cell stimulation [12, 13].

## **3. Pregnancy planning and monitoring in SLE**

SLE pregnancies are considered as a high-risk process. The strongest predictor of adverse pregnancy outcomes is an active SLE at time of conception. Patients with active SLE should postpone pregnancy until SLE is under control [20]. In certain cases, pregnancy is contraindicated in patients with severe organ involvement (e.g. severe renal insufficiency or end stage renal disease, congestive heart failure, severe pulmonary fibrosis, and severe pulmonary hypertension) [21]. Women with a past history of thrombotic events have an increased risk for thrombosis during pregnancy and post-partum, and in these cases there should be a switch from warfarin to low molecular weight heparin [22]. Risk stratification should be performed according to the aPL outline, taking into account the type, titer, and persistence of aPL. By doing so, patients can be divided into “high-risk” and “low-risk” profiles and treatment should be given according to each specific case [23]. Women should be started on folic acid preferably 3 months prior to conception; throughout pregnancy, they should be on calcium and vitamin D [24].

Therefore, it is crucial and mandatory the assessment of risk factors for adverse maternal and fetal outcomes in women with SLE who desire to be pregnant – this starts with preconception counseling and implementing appropriate preventive strategies and an individual-tailored monitoring plan before (switch teratogenic medications for non-teratogenic ones, respecting the wash-out of harmful medications, and being in remission for at least 3 to 6 months’ prior conception) and during pregnancy [20].



Once pregnancy is confirmed, a monthly routine need to be ensured and should include: doctor appointments and complete blood analyses, including a complete set of autoantibodies, as well as, specific maternal antibodies such as aPL and anti-Ro/SSA. In the case for patients with current or past renal involvement, blood pressure and 24-h urine proteinuria should be monitored regularly [20, 22].

SLE pregnant should be followed after specific protocols for patients at high-risk of developing hypertensive disorders and/or placental insufficiency. Fetal surveillance should be based on biometric and Doppler findings during the third trimester, and particularly distinguish between early and late FGR, helping to better tailor the time of delivery and reduce perinatal morbidity and mortality. Fetal echocardiography is only indicated if there is suspected fetal dysrhythmia or myocarditis, especially in the context of positive maternal anti-Ro/SSA or anti-La/SSB antibodies [20].

## **4. SLE & other autoimmune diseases**

### **4.1 Presence of antiphospholipid antibodies**

The presence of antiphospholipid antibodies (aPL) during pregnancy is associated with significant risk of maternal and fetal adverse events. The prevalence of aPL in SLE is about 12–44% for anticardiolipin (aCL), 15–34% for lupus anticoagulant (LAC) and 10–19% for anti-beta2 glycoprotein I ( $\beta$ 2GPI) antibodies [25]. These antibodies are responsible for an autoimmune hypercoagulable state, known as antiphospholipid syndrome (APS). Even though aPL are present in about a half of patients with SLE, only a fraction of these patients develops antiphospholipid syndrome (APS), which manifests as thrombotic and/or obstetric adverse events, mediated by persistent circulating aPL detected by means of three tests: LAC, aCL and  $\beta$ 2GPI antibodies, repeated twice with an interval of 12 weeks apart. A different subset of patients, the so-called “aPL carriers”, has been described. These are aPL positive individuals without clinical manifestations, that are at high-risk of prematurity, pre-eclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome. The most severe form of APS is catastrophic antiphospholipid syndrome (CAPS) a potentially fatal and rare condition that women may develop during pregnancy. Its diagnosis is challenging and aggressive treatment is crucial in order to save a patient's life [23].

The outcomes of pregnancies in patients with aPL have significantly improved and live birth rates over 80% are achieved nowadays. The management is based on the risk of profile of aPL and/or previous thrombotic and/or obstetric complications.

### **4.2 Presence of anti-Ro antibodies**

Anti-Ro/SSA and/or anti-La/SSB autoantibodies are detected in approximately 40% of patients with SLE. The transplacental passage of maternal IgG antibodies (anti-Ro/SSA and anti-La/SSB) may lead to neonatal lupus in 1–2% of all pregnancies affected by SLE [26].

Congenital Heart Block (CHB) is the most severe manifestation, affecting 2% of pregnancies with positive antibodies (especially anti-Ro/SSA) and without a previous history of complicated pregnancies. This usually manifests between the 18th and 24th weeks of gestation. The risk increases significantly 10 to 15% in patients who have a prior history of another neonate affected with cutaneous lupus and up to 15–20% in those with a prior neonate affected with CHB [27].

5. Pregnancy: physiological changes versus SLE activity

It is crucial to differentiate physiological changes that occur during a normal pregnancy versus pathological conditions, since both situations can have clinical and/or laboratory changes.

In a healthy pregnancy, many clinical manifestations can overlap those of an active SLE – see **Table 1**. Sex hormone levels vary throughout pregnancy, which affect the immune system and can lead to a SLE flare [28]. The hormonal system has receptors for cytokines, immune cells, and lymphatic tissues. In a pregnancy with SLE, the serum levels of gonadotropins and sex steroids differ from the healthy individuals; as there is a decrease of estradiol, cortisol, testosterone, dehydro-epiandrosterone and progesterone. Estrogen stimulates, by itself, the maturation of peripheral immune cells, especially Treg cells, that will further promote the immune system tolerance or suppression. In a healthy pregnancy, as explained in point 2.2.1, Treg cells numbers can increase, providing a higher level of fetal tolerance [15, 28]. However, in SLE pregnancy, a reduced number and function of Treg cells has been detected, which can lead to a worse outcome.

It is also known that pregnancy stimulates an increase in blood volume, involving an increase in plasma volume, raising both red-blood cell and white-blood cell volumes [29]. The discrepancy between plasma volume expansion and red-blood cell augmentation will provoke a hemodilution and cause the so-called, “physiological anemia of pregnancy” (normal hemoglobin of >11 g/dL and hematocrit >33% in the 1st and 3rd trimester). This may be caused by an increase in sodium retention, mediated by mineralocorticoid stimulation, that will lead to fluid retention and, subsequently, vasodilatation. During labor, blood volume will increase even further, due to uterine contractions, squeezing blood out of the intervillous space into the main circulation. So, after delivery, retraction of uterus and interruption of placental circulation will raise about 500 mL of blood, acting like an auto-transfusion.

	Pregnancy changes	SLE activity
Clinical Features	Facial flush	Photosensitivity
	Hyperpigmentation	Vespertilio
	Palmar erythema	Oral or nasal ulcers
	Friable mucous membranes	
	Arthralgia	Inflammatory arthritis
	Fatigue	Fatigue Lethargy
	Mild peripheral edema	Moderate to severe edema
Laboratory features	Mild resting dyspnea	Pleuritis Pericarditis
	Mild anemia	Immune hemolytic anemia
	Mild thrombocytopenia	Thrombocytopenia Leukopenia Lymphopenia
	Mild ↑ ESR	↑ inflammatory marker levels
	Physiologic proteinuria	Proteinuria >300 mg/day
		Active urinary sediment

Abbreviation: ESR - erythrocyte sedimentation rate.

**Table 1.**  
Overlapping features of pregnancy and systemic lupus erythematosus (SLE).

Levels of clotting factors, fibrinogen, platelet production, aggregation and destruction will also be elevated, causing a hypercoagulable state [29]. Endogenous anticoagulants, such as protein S, are also diminished and there is an acquired resistance to activated protein C. Fibrinolysis is also impaired due to placental production of plasminogen activator inhibitor. Overall, these imbalances will also promote a prothrombotic and procoagulant status. This process of enhanced coagulation and increased blood volume guarantees important functions: supplying an increase uterus, a placenta and a growing fetus, and protecting the mother from a massive bleeding during labor [29].

Following delivery, blood volume will then be restored to its normal levels about 8 weeks' post-partum. Moreover, it is known that the increase in blood volume leads to an increase in glomerular filtration, which in turn will stress the renal function [28]. This aggravation will be more pronounced in patients with underlying kidney disease. In a healthy pregnancy, glomerular filtration rate can increase up to 50% and creatinine clearance by 30%. Tubular reabsorption of sodium is then enhanced, but glucose and amino acids may not be absorbed in the same proportion, leading to glycosuria and aminoaciduria in healthy pregnancies [29]. Renal failure before pregnancy, as it may occur in SLE, is related to poor fetal outcome and early delivery [28]. When serum creatinine is higher than 140 mmol/L, there's a 50% chance of miscarriage; this probability raises up to 80% when creatinine is over 400 mmol/L. Nephrotic syndrome will further worsen the prognosis, as it relates to another increased risk of thrombosis.

Cardiac output will increase, reaching a plateau at 28–32 weeks' gestation [29]. Stroke volume will increase ejection fraction and maternal heart rate is also accelerated [30]. However, the distended uterus compresses aortocaval circulation, reducing cardiac filling while in supine position. Filling pressure will not change, due to myocardial remodeling that occurs during pregnancy. Peripheral and systemic vascular resistance is reduced, due to vasodilation. Altogether, these changes will contribute for blood pressure stabilization in a healthy pregnancy. This equilibrium will be imbalanced in nephrotic syndrome and PE situations, as cardiac output and blood pressure are elevated.

The enlarged gravid uterus displaces the heart to the left and upward, so the electrocardiogram may present sinus tachycardia, benign dysrhythmias, depressed ST segments or flattened T waves, left axis deviation and left ventricular hypertrophy [29]. Diaphragm will also be displaced, progressively decreasing functional residual capacity (FRC), expiratory reserve volume and residual volume. Tidal volume and inspiratory reserve volume will increase, so that vital capacity will remain unchanged. Reduction of FRC combined with an increase of oxygen consumption can provoke a rapid development of maternal hypoxemia during apnea.

Heartburn progressively increases, as the uterus displaces and disrupts the lower esophageal sphincter, intensified by progesterone induced relaxation [29]. Although gastric pressure increases, gastric emptying is normal. Obstipation is frequent, due to an increased intestinal transit time. Liver enzymes are normal, but placental production of alkaline phosphatases can increase up to 2–4-fold of its normal range. Gallstone formation can be induced by impaired emptying of gallbladder.

Neuropsychiatric symptoms represent a clinical challenge, as they can result from the pregnancy itself or postpartum period, but also from preeclampsia, eclampsia, or even electrolyte imbalance, infection, renal failure, and drug toxicity [31]. For example, headaches can result from hormonal and postural changes, insomnia, anxiety, preeclampsia, but can also be a symptom of neurolupus [32]. An accurate clinical history and examination is hence always mandatory.

Laboratory tests may reveal different values from the normal range that are considered acceptable in pregnancy, which makes them less reliable. Pregnant women



frequently present mild anemia and thrombocytopenia, elevated erythrocyte sedimentation rate, proteinuria (up to 300 mg/day) and increased levels of complement [31]. So, it is essential that a proper evaluation of disease activity is done. Also, complement levels can be falsely increased, so it will not serve as a strong biomarker. On the other hand, anti-DNA antibodies can still be related to disease activity. The scales of pregnancy SLE, as mentioned above, SLEPDAI, LAI-P, and BILAG2004-Pregnancy index, can also be a useful tool, combined with clinical judgment and laboratory parameters.

## **6. Disease activity assessment during pregnancy**

As mentioned above, a strict assessment and control of disease activity before and throughout pregnancy is fundamental. Physiological changes in pregnancy may mimic a lupus flare (e.g. constitutional symptoms, non-inflammatory joint pain, skin rash, alopecia), as well as, laboratory changes (e.g. anemia, thrombocytopenia, proteinuria, increase of ESR and complement levels).

In order to reduce confounding features from physiological pregnancy and SLE exacerbations, three scores were modified in order to adapt to these changes: the SLE-Pregnancy Disease Activity Index (SLEPDAI), the LAI (Lupus Activity Index) in Pregnancy (LAI-P), and the modified SLAM (Systemic Lupus Activity Measure) (m-SLAM). Two other pregnancy-adapted scores have been introduced more recently, the modified-European consensus lupus activity measurement (m-ECLAM) and the British Isles Lupus Assessment Group-2004 for pregnancy (BILAG2004-P).

In all the above-mentioned indices, modifications were made to address influential items: some were eliminated (e.g. ESR, asthenia) and others were adapted to physiological pregnancy changes (e.g. proteinuria levels), emphasizing the need to differentiate those changes from pregnancy comorbidities (e.g. PE/E). The scoring of each index is calculated in the same way as the original version, except for the LAI-P, in which the weighted score given to each item has been modified. Although many attempts have been made to have a reliable tool, the clinical judgment of an experienced physician remains the gold standard in the management of pregnant women with SLE. As recently recommended, these women should be frequently monitored (every 2 to 8 weeks). During each visit, prostaglandin A (PGA) in conjunction with at least one of the activity tools and pregnancy-specific SLE activity indices (such as SLEPDAI, LAI-P, BILAG 2004- P) should be applied [20].

## **7. Maternal and fetal complications during lupus pregnancy**

Maternal and fetal complications are more frequent in lupus pregnancy than in healthy ones. So, even if new treatment strategies have been incorporated in guidelines for managing this complex situation, SLE is still a severe risk factor for pregnancy.

As discussed, SLE pregnancy is related to an increased risk of miscarriage, stillbirth, neonatal death, premature delivery and FGR [33, 34]. Cesarean section due to pregnancy complications is also more prevalent in lupus patients. A large nationwide study revealed that maternal mortality rate in SLE patients reaches 325/100,000 live births, meaning more than 20-fold higher than in non-SLE population [35]. The risk for other maternal complications includes thrombosis, hypertension, infection, thrombocytopenia, and transfusion, being each 3- to 7-fold

higher in SLE population. Gestational hypertension, apart from pre-eclampsia, may provoke long-term complications related to cardiovascular and peripheral artery disease [34].

The risk of gestational diabetes is also increased in SLE pregnancy [22, 36]. It is mainly related to glucocorticoid therapy during pregnancy. About 10% of gestational diabetes result from autoimmune activity (GADA, IA2A, IAA and ZnT8-A antibodies) [37]. Nevertheless, the prevalence of SLE and autoimmune gestational diabetes, and the relationship between them, needs further research.

## 7.1 Lupus flare

During lupus pregnancies, there is an increased risk of maternal and fetal morbidity and mortality, but a stable disease prior to conception can act as predictor of a good outcome [38]. The onset of new symptoms or signs as arthritis, discoid or subacute cutaneous lupus lesions, oral ulcers, vasculitis, polyserositis, lymphadenopathy, positive direct Coombs, myocarditis, pneumonitis, proteinuria, leucopenia, thrombocytopenia, complement consumption or raised anti-DNA antibody expression must arise the suspicion about an ongoing lupus flare [12, 38].

During a healthy pregnancy, complement levels are usually raised, as it acts as acute phase reactant [31]. So, normal or lower range of complement suggests serum consumption due inflammatory process [38]. The coexistence of hypocomplementemia and high SLE activity usually predicts a poor pregnancy outcome. Proteinuria and leukopenia are also associated to a worse prognosis [31, 38].

Recently, the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study revealed that up to 20.8% lupus pregnancies experience mild to moderate flares but only 6.25% have severe ones [39]. Patients at risk were the ones with younger age, low C4 and higher physician global assessment at baseline as independent risk factors for having at least one flare during pregnancy. This study is remarkable and unique in that it has a multicenter, multiethnic and multiracial sample included. Hence, non-white race was also identified as a risk factor for lupus flare. According to the authors, there were no medications associated with flare, including hydroxychloroquine, in contrast to other studies.

SLE patients with central nervous system (CNS) involvement during pregnancy have higher risk for maternal and fetal complications and poor prognosis [40]. Preterm birth incidence can be 60% higher than in other lupus pregnancies and extreme prematurity can reach 40% of the newborns. CNS lupus pregnancies have higher risk for complications, whether neurological symptoms are present or not.

In contrast, in cutaneous lupus erythematosus the pregnancy outcomes are comparable to those of healthy populations [41].

As mentioned on Section 5.1, lupus patients can also have APS. Although rare, catastrophic APS (CAPS) can occur in up to 1% of patients and mortality reaches 50% [31].

## 7.2 Pre-eclampsia and lupus nephritis

Lupus nephritis (LN) is severe and independent risk factor for both maternal and fetal outcomes. It is related to preterm birth, hypertension and pre-eclampsia [42]. Pre-eclampsia have an increased risk in SLE pregnancy and can appear in up to 25% of SLE patients [31, 33]. Active LN at the time of conception has been pointed as the major risk factor for pre-eclampsia in SLE pregnancies [43]. LN activates in 4–30% of patients; those who had previous recurrence of LN are at a higher risk 20–30% [44].

The definition of pre-eclampsia by the International Society for the Study of Hypertension in Pregnancy Society (ISSHP) has recently been considered as being more sensitive than the definition made by the American College of Obstetricians and Gynecologists [45]. Pre-eclampsia is defined by the ISSHP as gestational hypertension, accompanied by at least one of the following conditions, at/or after 20 weeks' of gestation:

1. Proteinuria
2. Other maternal organ dysfunction, such as:
  - a. Acute kidney injury (creatinine greater than 1 mg/dL)
  - b. Liver involvement (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 40 IU/L)
  - c. Neurologic complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotoma)
  - d. Hematological complications (thrombocytopenia less than 150000/ $\mu$ L, disseminated intravascular coagulation, hemolysis)
3. Uteroplacental dysfunction – including fetal growth restriction, abnormal umbilical artery Doppler wave form analysis or stillbirth [46].

Therefore, after 20 weeks of gestation, the distinction between a lupus flare and pre-eclampsia can represent a diagnostic dilemma, since both can have similar characteristics – increased proteinuria, hypertension, thrombocytopenia, kidney dysfunction and generalized symptoms [31]. A thorough clinical history and biochemical investigation are always required. In a normal pregnancy, the complement is expected to be normal or high, since it acts as an acute phase reactant. If a normal or decreased range is detected, immune complexes are probably being formed and a lupus flare is ongoing. An increase of anti-DNA antibody levels is also related to lupus activity [31]. The onset of unexpected significant proteinuria should raise suspicion, especially if it occurs in the first trimester or part of the second trimester. In these cases, a proper clinical and laboratory approach is mandatory. In discordant results, renal biopsy can be considered. However, if aPL are present, the risk of thromboembolism should prompt to anticoagulation treatment, which would, in turn, raise the risk of major bleeding after biopsy. Other procoagulant factor include pregnancy itself, nephropathy, and SLE activity, so the need to a biopsy must be carefully outweighed [31].

If a patient develops only pre-eclampsia, it is not expected to find hematuria, urinary casts, complement consumption or increased anti-DNA antibodies [31]. On the other hand, LN can also induce pre-eclampsia, so, once again, the distinction of these two entities can be problematic. The correct diagnosis must be accurate, as the treatment approach will be totally different: in pre-eclampsia, the delivery should be anticipated; in LN, immunosuppressive treatment should be immediately started.

HELLP (Hemolysis with elevated liver enzymes and thrombocytopenia) syndrome is the worst manifestation of pre-eclampsia [22]. It is usually associated with aPL, but evidence has shown that it consists of a complementopathy, either due to an inherited defect in a complement regulatory protein or an acquired autoantibody [47]. *In vitro* experiments, using serum from HELLP patients in modified Ham test,

disclosed activation of the alternative pathway of complement cascade (C5b-9). This dysregulation of complement system would be similar to that occurring in hemolytic uremic syndrome.

Although pre-eclampsia and LN exhibit different clinical manifestations, clear discrimination in the set of a new-onset SLE during pregnancy can be challenging – see **Table 2**. Soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PIGF) ratio can be useful in discriminating these two entities: women with SLE and APS who develop pre-eclampsia have a significantly higher sFlt-1/PIGF ratio compared with women with SLE and APS, but without pre-eclampsia [31, 48]. These variances increase during pregnancy.

### 7.3 Impact on fetal development and monitoring of fetal development during lupus pregnancy

As mentioned above, fetal risks of lupus pregnancy include pregnancy loss, preterm birth, premature rupture of membranes and FGR. Preterm birth is more frequent than pregnancy loss, and even if its relation to pre-eclampsia and disease activity is established, a causative factor may not be identified [22]. Other fetal complications associated with SLE include infants small for gestational age and infants with low birth weight [33]. Neonatal intensive care unit admissions are also more prevalent in these newborns.

Zhan Z et al., in a retrospective study identified that the best method to monitor adverse pregnancy complications during third trimester of pregnancy is by doing an umbilical artery Doppler. Nevertheless, the umbilical artery Doppler can be initiated in the second trimester in monitoring for neonatal heart block for possible earlier intervention [49]. The use of hydroxychloroquine (HCQ) is associated with

Clinical measure	Preeclampsia	Lupus nephritis
Hypertension	After 20 weeks gestation	Any time during pregnancy
Urine active sediment	Rare	Common
Onset of proteinuria	Abrupt, after 20 weeks	Abrupt or gradual, anytime
Creatinine	Normal to raised	Normal to raised
Uric acid	Raised	Normal
C3 and C4	Usually normal	Usually low or decreasing
Complement products	Normal-low	Rising titres
Anti-DNA	Absent or unchanged	Normal to increased
Lupus activity	No	Yes
24 hour Urine calcium	<195 mg/day	>195 mg/day
Thrombocytopenia	Yes (HELLP)	20% of SLE
Other organ involvement	Occasionally CNS or HELLP	Evidence of active nonrenal SLE
Liver function test	May be elevated (HELLP)	Usually normal
Kidney biopsy	Glomeruloendotheliosis	SLE nephritis
sFlt-1/PIG ratio	Higher	Normal
Response to steroids	No	Yes

Abbreviations: HELLP - hemolysis, elevated liver enzymes, low platelets; SLE – systemic lupus erythematosus; sFlt-1 – soluble fms-like tyrosine kinase; PIGF – placental growth factor.

**Table 2.**  
*Differentiation of preeclampsia from lupus nephritis flare in pregnancy.*



a lower incidence of FGR the risk of preterm delivery, whether spontaneous or induced, in lupus pregnancy [50, 51]. As prematurity decreases, there will also be a reduced risk of neonate complications, as respiratory distress syndrome, intra-ventricular hemorrhage, sepsis, hypoglycemia, jaundice requiring phototherapy, enterocolitis, among others [50]. Among the different studies done so far, it should be noted that children with in utero exposure to HCQ did not develop visual, auditory, developmental or growth abnormalities.

## **7.4 Delivery**

The objective in a pregnant lupus patient would be a vaginal spontaneous delivery at term, data reveals that these women have a high prevalence of cesarean section. This procedure should be restricted to obstetric indications, once it represents an additional risk factor for venous thromboembolism, hemorrhage, infection and repercussion in future pregnancies. During labor, women exposed to long-term oral steroids may need intravenous hydrocortisone to overcome the physiologic stress of labor and delivery. Prophylactic or therapeutic anticoagulation should be interrupted as spontaneous delivery starts or, if induced labor or cesarean section is scheduled, it should be discontinued 12 or 24 hours before. Epidural or spinal anesthesia can be safely administered until 12 hours after the last dose of anticoagulant.

Postpartum care must focus on a possible lupus flare or coexisting pre-eclampsia [31]. Women who underwent anticoagulation should continue it for at least 6 weeks after delivery in a prophylactic dose. Safe contraception should be offered and progestogens can be an appropriate option.

## **8. Treatment & prevention of complications during pregnancy**

Therapeutic management in SLE patients is one of the most important aspects when planning a pregnancy. The main goal is to assure the most effective treatment to maintain disease remission, while keeping the ability to treat disease flares and guaranteeing maximum safety for the fetus. As mentioned in Section 3, disease activity should be under control (3 to 6 months) prior to pregnancy.

In order to decrease maternal and fetal complications, the the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [20, 52] developed general recommendations describing which drugs are safe during pregnancy and which ones should be avoided. Also, the United States Food and Drug Administration (FDA) has changed the way of labelling medication safety during pregnancy and lactation. Previously, it was based on letters, which classified drugs from A to D, according to its increased risk for the fetus. Drugs classified as had not enough evidence or information available. Nowadays, this classification reflects more the quantity and quality of the data known for each drug. For practical purposes, the current drug options available to treat SLE pregnancy has been divided into 4 main categories:

### **8.1 Drugs recommended during SLE pregnancy**

#### **8.1.1 Hydroxychloroquine**

Hydroxychloroquine (HCQ) is an antimalarial agent used for its immunomodulatory effects. Although HCQ crosses the placenta, it does not seem to have toxic effects on the fetus [53]. On the contrary, this drug is recommended to all women with SLE, whether they are pregnant or not, as it decreases the

risk of flares, reduces the risk of pre-eclampsia and preterm birth [54]. Various studies have also shown positive effects of HCQ in pregnant women with APS (higher birth rates and fewer pregnancy complications) versus untreated patients, concluding that SLE pregnant women that have aPL, also known as “aPL carriers” also benefit from HCQ. Furthermore, some studies suggest that HCQ decreases the occurrence of CHB and cutaneous involvement in neonatal lupus, in fetuses whose mothers are carriers of anti-Ro/SSA and anti-La/SSB antibodies [55].

### 8.1.2 Low-dose acetylsalicylic acid

Low dose acetylsalicylic acid, as known as, “low dose aspirin” (LDA) is recommended in all women with SLE during pregnancy, it should be started during pre-conception period in case of a planned pregnancy and no later than 16 weeks. LDA (75-150 mg/day) has proved to reduce the risk of pre-eclampsia and its complications, regardless the presence of aPLs [56].

## 8.2 Drugs with a safe profile during pregnancy

The following drugs have an acceptable safety profile, but should be used selectively, if needed, to control SLE manifestations during pregnancy.

### 8.2.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to control symptoms in patients with rheumatic diseases. However, these drugs should be prudently used during pre-conception period and during pregnancy, as they can provoke oligohydramnios, due to reduced fetal glomerular filtration rate. In case of absolute necessity, amniotic fluid monitoring is necessary [57].

Discordant findings from large retrospective studies have shown an increased risk of miscarriage in the first trimester with the use of NSAIDs [52]. These drugs should be avoided after 32 weeks of gestation, because of the risk of premature closure of the *ductus arteriosus*, with the exception of aspirin. Indomethacin and ibuprofen appear to have much stronger ductal effects than LDA [57].

Some studies suggest that high doses of aspirin may increase the risk of fetal or neonatal bleeding or bruising in the 3rd trimester. However, these data is not robust enough to warrant conclusions. The use of selective cyclooxygenase (COX)-2 inhibitors is not recommended in pregnancy, due to the lack of safety data [52, 58].

### 8.2.2 Glucocorticoids

Glucocorticoids (GC) have a remarkable path in the treatment of autoimmune diseases, such as SLE. Yet, its chronic use is associated with multiple side-effects and organ damage [59]. Prednisone and prednisolone are glucocorticoids recommended during pregnancy due to its pharmacokinetics and its shorter duration of action, since they are metabolized by placental enzymes the fetus is basically unexposed. The recommended daily dose should be  $\leq 7.5$  mg of prednisone. Doses superior to 10 mg/day are associated with preterm delivery, premature rupture of membranes and FGR. Higher doses should be reserved for organ-threatening situations, when the benefits outweigh the risks [60]. For hypothalamic–pituitary–adrenal axis suppression, for example, we use doses superior to 5 mg/day for at least 3 weeks, after the first trimester, so that labor and delivery can be managed accordingly.

Methylprednisolone has similar rates of placental transfer to prednisone so it is expected to be safe and compatible with pregnancy [20].

### *8.2.3 Azathioprine (AZA)*

Azathioprine is especially used in SLE patients with hematological manifestations, but it can also be used in LN, as a maintenance drug [60]. This drug is compatible with pregnancy, since fetal liver lacks the enzyme to convert AZA to its active form [61]. Therefore, AZA is considered a safe drug, but doses should not exceed 2 mg/Kg/day.

### *8.2.4 Intravenous immunoglobulin*

Intravenous immunoglobulin (IVIG) is an immunomodulator that regulates the inflammatory processes through anti-idiotypic mechanisms. Although it crosses the placenta after the 2nd trimester and in a more significant way after the 3rd trimester, no fetal malformations have been reported. Hence, it is considered a drug compatible with pregnancy [62].

### *8.2.5 Cyclosporine and tacrolimus*

Both cyclosporine (CSA) and tacrolimus are calcineurin inhibitors used as maintenance drugs and steroid-sparing agents, in patients with moderate to severe SLE [60]. CSA is considered safe in pregnancy, but blood pressure and renal function should be closely monitored [20]. It is recommended that CSA and tacrolimus should only be used when maternal benefit outweighs fetal risk, and preferably at minimum doses [63].

### *8.2.6 Antihypertensive medications*

Metildopa, labetalol and hydralazine are frequently used during pregnancy with efficacy and no harm. Nifedipine is also compatible at doses up to 60 mg/day. By contrast, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are contraindicated throughout gestation and should be stopped as soon as possible, once pregnancy is confirmed. Diuretics can be used with caution and should be used as a last resource to control a severe and refractory hypertension, in an emergency setting and for a short period of time [20].

## **8.3 Drugs to be used with caution during pregnancy**

### *8.3.1 Biologic agents*

There is no sufficient data regarding biologic agents during pregnancy, so their use cannot be encouraged. Rituximab (RTX) is a B-cell depleting chimeric monoclonal antibody and is recommended to be stopped 6 months before conception. However, it has not been shown to be teratogenic [60, 64].

Belimumab (BEL) is BAFF inhibitor human monoclonal antibody and there is no sufficient data to recommend it during pregnancy. Until 12th week, IgG does not cross placenta in significant amounts; so, accidental exposure to RTX or BEL during the first trimester is unlikely to be harmful. On the other hand, second/third trimester exposure will be associated with neonatal B-cell depletion [65].

## 8.4 Drugs contraindicated during pregnancy

### 8.4.1 Cyclophosphamide (CYC)

Cyclophosphamide (CYC) is an alkylating drug used in SLE, to treat severe organ or life-threatening manifestations [60]. Due to its teratogenic effects, its use in pregnancy is contraindicated, especially during the first trimester, when the fetus is more susceptible to congenital malformations. Nevertheless, it can be considered in exceptional circumstances, when mother faces an organ- or life-threatening disease complication. Embryotoxicity varies according to the stage of gestation. The use of this drug in fertile women should always be carefully evaluated and counseling about fertility preservation strategies should be advised prior to its use [66].

### 8.4.2 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an inhibitor of purine biosynthesis, commonly used in LN, as both in induction and maintenance therapy, and is also used in severe to refractory non-renal manifestations, with the exception of neuropsychiatric lupus [60]. Due to its teratogenic effects, its use in pregnancy is contraindicated. MMF exposure can cause lip and cleft palate, abnormalities of distal limbs and malformations of multiple internal organs, such as heart, esophagus and kidneys [67]. For these reasons, it should be avoided. Alternative options are azathioprine, tacrolimus or low dose of glucocorticoids, which can be used to control disease activity. They should be started, ideally, 6 months prior conception.

### 8.4.3 Methotrexate

Methotrexate (MTX) is a folate antagonist – it inhibits the enzyme dihydrofolate reductase which impairs purine and pyrimidine synthesis. It is contraindicated during pregnancy, due to its teratogenic effects. MTX exposure *in utero* can induce multiple congenital abnormalities, such as cleft palate, hydrocephalus, anencephaly and meningoencephalocele, delayed ossification and multiple facial deformities. It is strongly advised contraceptive use in patients taking MTX. This medication should be discontinued 3 months before attempting to conceive. If a woman is being treated with a low dose of MTX within 3 months prior to conception, or an accidental pregnancy occurs, the drug should be stopped immediately and the mother should continue to take folate supplementation (5 mg daily) throughout pregnancy. In the last case, a careful evaluation of fetal risk at an experienced center must take place [67].

### 8.4.4 Leflunomide

Leflunomide (LEF) is another drug that, although it may not be teratogenic, it is strongly advised to be avoided during pregnancy [68, 69]. It's an antimetabolite that inhibits dihydroorotate dehydrogenase, the catalyst enzyme responsible for the limiting step in pyrimidine biosynthesis. Despite its short half-life (approximately 15 days), its major metabolite follows a long path through enterohepatic circulation remaining detectable for more than 2 years. It is essential to complete its washout until undetectable levels before switching to alternative medication compatible with pregnancy and trying to conceive. For accelerate elimination of this drug, for example if an accidental pregnancy occurs, it is used cholestyramine (8 g orally, 3 times a day, for 11 days).



## **8.5 Management of maternal antiphospholipid syndrome**

APL carriers or APS pregnancy represent a great challenge and require an additional monitoring and therapy to prevent maternal and/or fetal complications. Below is the clinical management according to the different clinical situations: [23, 52]

### *8.5.1 Asymptomatic aPL-positive patients “aPL carriers”*

In SLE *aPL carriers* prophylaxis with LDA daily, is recommended during pregnancy. Combination therapy with prophylactic-dose heparin and LDA, even for those pregnant with triple-positive aPL or high LAC concentration, is not recommended [23, 52]. These women should be treated with prophylactic-dose low molecular weight heparin (LMWH) until, at least, 6 weeks after delivery.

### *8.5.2 Obstetric APS*

In SLE women with history of obstetric complications prophylactic or therapeutic-dose heparin (usually LMWH) and LDA during gestation is recommended. Prophylactic or therapeutic-dose LMWH should continue until 6 weeks after delivery [23, 52].

### *8.5.3 Thrombotic APS*

Women with previous thrombosis have a high risk of recurrent thrombotic event during pregnancy. Therefore, as soon as pregnancy is confirmed, vitamin K antagonists should be stopped, due to the fetotoxicity, and should be switched to therapeutic LMWH and LDA). LMWH and LDA should be stopped before delivery. Women with thrombotic APS are at very high risk of recurrent venous thromboembolism during post-partum. Therapeutic LMWH dose is recommended. Other possible option is to return to warfarin, which is safe during breastfeeding [23].

### *8.5.4 Refractory obstetric APS*

Refractory Obstetric APS is a delicate and challenging situation, as there is no response to standard therapy. Some alternatives can be tried such as increased-dose of heparin (LMWH), low-dose prednisone (10 mg/day in the 1st trimester), IVIG, plasmapheresis, HCQ (5-6 mg/Kg/day). In 25% of obstetric APS, despite treatment, pregnancy loss can occur [23].

## **8.6 Management of SLE treatment and APS/aPLs positive patients in breastfeeding**

Breastfeeding should be encouraged for all women and SLE patients are not an exception. However, some medications are transferred into the breast milk and can be harmful for the infant. Additionally, premature or ill infants are more susceptible to some medication's exposure [63, 69].

### *8.6.1 Drugs that are compatible with breastfeeding*

Hydroxychloroquine is transferred to human breast milk, but only in an insignificant amount, about 2%, which is considered safe. Glucocorticoids, as prednisone or methylprednisolone, are considered compatible with breastfeeding,

since they are excreted in the breast milk in very low quantities. It is accepted by the American Academy of Pediatrics and the British Society of Rheumatologists. Lactation is recommended to be avoided in the first 4 hours after ingestion of  $\geq 20$  mg of prednisone, as the peak concentration in breast milk is achieved 2 hours after maternal ingestion [63, 64].

Azathioprine, cyclosporine and tacrolimus, IVIG, heparin and warfarin are compatible with nursing, since the evidence shows that the excretion in breast milk is very low [63, 64].

Antihypertensive medications are commonly used, though evidence about the use of ACEIs and breastfeeding are lacking. Some data point out that captopril and/or enalapril seems to be selectively barred from blood to breast milk, so it is unlikely to cause adverse effects in nursing newborns. Nifedipine is considered safe during lactation [63, 70].

#### 8.6.2 *Drugs that are not compatible or should be avoided when breastfeeding*

NSAIDs are not recommended, since there is not enough information about the safety of these drugs. Ibuprofen is the preferred drug, but only because it appears to be excreted in very small amounts in breast milk. Once more, LDA seems to be the exception, but there is no robust data about LDA and nursing.

Methotrexate is excreted in low concentrations into breast milk, but it can accumulate in neonatal tissues, so guidelines strongly advise to avoid MTX in breastfeeding mothers.

There is no sufficient data on the transmission of mycophenolate mofetil, leflunomide, RTX, BEL and in cyclophosphamide into breast milk, so these drugs should be avoided during lactation [58, 63, 70].

## 9. Postpartum and neonate complications

Maternal and fetal complications after pregnancy can result not only from SLE (disease), but also from other factors frequently associated with SLE. Maternal flares can occur in any trimester of pregnancy or after delivery, but it seems to be more prevalent in the 3rd trimester and until one year after delivery. Thus, the importance of maternal (and newborn) monitoring in the first year after delivery is of extreme importance [71–74].

### 9.1 Maternal complications of postpartum SLE

In a healthy SLE pregnancy, the woman should be offered the chance to a spontaneous labor, at term, with vaginal delivery [75]. Maternal medication may need a special adjustment for labor: intravenous hydrocortisone to overcome its physiological stress, discontinuation of LMWH, for which the timing will condition regional anesthesia.

As mentioned, SLE is associated with a higher incidence of maternal complications, both during pregnancy and in the postpartum period. Pregnant women with SLE are more likely to have a cesarean section (unplanned), high blood pressure, pre-eclampsia, spontaneous abortion, thromboembolic events, and infections [20]. In patients under corticosteroids at immunosuppressive dose ( $\geq 1$  mg/Kg), prophylactic antibiotics is recommended, due to the risk of infections and sepsis [75].

HELLP syndrome (characterized by hemolysis, elevated liver enzymes and a low platelet count in the context of pregnancy) can, by definition, occur in the postpartum period. This occurs in one third of the cases, being more prevalent in

women with severe pre-eclampsia [43]. Catastrophic antiphospholipid syndrome (CAPS), characterized by acute thrombotic micro-angiopathy, was also recorded in the postpartum period [76]. These syndromes are more frequent in patients with SLE, thus increasing the risk of complications in this population.

The postpartum period demands a rigorous monitoring for maternal complications, as SLE flare [75]. Although no increased risk of lupus flares between 2 and 6 months postpartum, compared to during pregnancy, was found, which rate is about 24%, flares can reach almost every patient in the first 6 months after delivery [39]. The treatment for these situations is similar for non-pregnant SLE patients, but the risks of breastfeeding under aggressive therapy should be outweighed. LMHW should be continued for 6 weeks after delivery, due to the increased risk of venous thromboembolism (VTE) during puerperium. Contraception should be encouraged, but estrogen-containing pills must not be used by women with aPL antibodies or APS, moderate to severe SLE and other conditions, as previous VTE, hypertension, obesity or smoking.

## **9.2 Newborn complications of SLE**

In general, SLE in pregnancy is associated with a higher incidence of stillbirths, a greater occurrence of great premature babies, with a greater number of newborns admitted to neonatal intensive care units, an APGAR score below 7 within 1 and 5 minutes and a significantly higher number of birth defects [33, 77, 78].

Neonatal SLE (0 to 27 days after delivery) is an autoimmune disease that results from passive transfer of autoantibodies from a mother with SLE to the fetus, resulting in fetal and neo-natal disease. It occurs in about 3.5–8% of these pregnancies and is associated with the presence of maternal anti-Ro/SSA and anti-La/SSB autoantibodies [20, 79]. Main manifestations involve cutaneous and cardiac systems, but it can affect and cause other organ dysfunctions (including thrombocytopenia, hepatitis, and myocarditis) [71]. The presence of anti-Ro/SSA antibodies may be associated with clinical manifestations, but does not appear to have a negative impact on other SLE-related events during pregnancy [80].

The most frequent manifestation of SLE in the neonate, with a prevalence of 10 to 20%, is a transient cutaneous rash with annular or elliptical erythematous plaques, which develops in the weeks following delivery [80]. It involves predominantly the face and scalp, is generally photosensitive and resolves spontaneously in the first 6 to 8 months of life, which coincides with the clearance of maternal autoantibodies from the circulation [71].

The most serious complication of neonatal SLE is a CHB, which can be diagnosed in-utero, on the date of birth or in the neonatal period. This occurs in about 2% of the fetuses of women with anti-Ro/SSA antibodies with a recurrence rate of 20% in the following pregnancies [76, 81, 82]. CHB can be of any degree and can be accompanied by extra-nodal disease, with valve involvement, endocardial (endocardial fibroelastosis) or structural changes, including dilated cardiomyopathy. About 60% of CHB babies will require a pacemaker; 10% of those will develop cardiomyopathy after birth [12]. The 10-year mortality rate ranges 20–35%. The use of HCQ during pregnancy seems to reduce in 65% the risk of cardiac manifestations of neonatal lupus in women with anti-Ro/SSA and anti-La/SSB autoantibodies [83, 84]. Despite immunoglobulin can reduce transplacental transfer of anti-Ro/SSA antibodies, a clinical trial failed to prove its efficacy [22].

Management of SLE pregnancy includes serial fetal echocardiography surveillance between 16 and 28 weeks of gestation [22]. If CHB is detected, it is usually no longer reversible. However, corticosteroids that are transplacental, as dexamethasone, can be administrated in order to reduce the resultant cardiomyopathy.

Prognostic factors related to poor outcomes of neonatal CHB include: detection of CHB at gestational age < 20 weeks, ventricular rate < 50 bpm, fetal hydrops, carditis, changes in fetal echocardiogram, endocardial fibroelastosis, impaired left ventricular function, and a maternal diagnosis of SLE or Sjögren's syndrome [12].

## 10. Conclusion

The improvement in disease management and pregnancy monitoring have resulted in a significant decrease in maternal and fetal complications in the last few decades. This has been mainly contributed by 3 pillars: 1) new technologies – which have permitted a better understanding of the immunopathogenesis of the disease, enabling substantial data on SLE patients and focusing on the area of genetics, such as genetic predisposition, epigenetics contribution and how these contribute in developing irreversible loss of immunologic self-tolerance; 2) access to healthcare – has permitted SLE patients to better hospital care through the course of their disease; and most importantly: 3) multidisciplinary management – this is essential to achieve successful maternal and fetal outcomes. This is made by a multidisciplinary team of experienced and dedicated physicians that define a strategic plan, such as preconception counseling, pregnancy planning and increased availability of safe drugs in pregnancy and puerperium, to improve both maternal and fetal outcomes. It is crucial to make the correct choice of therapy for women with SLE preconceptionally, during pregnancy and lactation. Medications must be reviewed and adjusted to minimize the effect on the fetus, while maintaining the disease under control.

In this way, even if SLE keeps being a severe risk factor for pregnancy, a healthy outcome for both mother and child has become a more frequent reality.

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