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Chapter

Reproductive Environment in Patients with SLE

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Abstract

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder that predominantly affects women in reproductive years. Immunologic and hormonal adaptations during pregnancy focused on creating an ideal environment to achieve a successful pregnancy represent a challenge in SLE women as they can influence on disease activity and outcomes during pregnancy. Several disease-related factors such as the presence of antiphospholipid antibodies and anti-SSA/Ro can also impact in the risk of pregnancy adverse outcomes and neonatal complications. Lupus nephritis and preeclampsia share clinical and laboratory features hindering differentiation between both entities. Contraception constitutes a relevant topic in SLE patients to prevent unplanned pregnancies during periods of disease activity or potentially teratogenic drug exposure, but its potential risk on disease flares and thrombotic events is the main concern. Finally, fertility in patients with SLE can be affected by the use of drugs related to infertility that lead to premature ovarian failure. Recently, assisted reproduction technologies have emerged as a safe option in patients with SLE.

Keywords: systemic lupus erythematosus, pregnancy, pregnancy adverse outcomes, neonatal lupus, contraception, antiphospholipid antibodies, anti-SSA/Ro

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease, with a remitting and relapsing course. It mainly affects young women of reproductive age, so addressing issues such as pregnancy, fertility, and reproductive aspects is an essential part of the comprehensive management of these patients.

In the last decades, diagnostic and therapeutic strategies for SLE and consequently the management of pregnancy have improved. Despite these advances, pregnancies in SLE patients are still considered a high-risk condition due to an increased risk of major obstetrical and neonatal complications.

Pregnancy represents a critical period in women's life due to profound immunological and hormonal changes that mostly occur to tolerate the fetus. The interaction of SLE and immunologic adaptations of pregnancy lead to unique challenges in this setting, as alterations in immune mechanisms can have consequences both for the fetus, including a risk of miscarriage or neonatal lupus, and for the mother, including disease flare.

A close relationship between pregnancy and disease flares has been established. The association of SLE and pregnancy, mainly with active disease and lupus nephritis, has poorer outcomes, with increased frequency of preeclampsia (PE), fetal loss,

preterm birth, and intrauterine growth restriction. On the other hand, pregnancy impacts on maternal disease and can be associated with disease flares requiring immunosuppressive therapy.

This chapter will address the immunological and hormonal adaptations during normal pregnancy and the differences between healthy pregnant women and women with SLE. Later, we will focus on the relationship between lupus activity and pregnancy and the impact of SLE on pregnancy outcomes.

2. Interaction between pregnancy and systemic lupus erythematosus

2.1 Immunologic and neuroendocrine environment in pregnancy

Pregnancy represents a major immunological challenge for the maternal body due to fetal expression of paternal antigens. The maternal immune system has to balance the opposing needs of maintaining robust immune reactivity to protect both the mother and the fetus from invading pathogens while at the same time tolerating highly immunogenic paternal alloantigens to sustain fetal integrity [1].

In order to protect the fetus from an attack of the maternal immune system, pregnancy induces profound immune and neuroendocrine changes in the maternal body [2]. Modulation of the function and composition of the different cellular components and immunomodulatory molecules occur during pregnancy in the mother. Also, immune tolerance to paternal antigens is promoted by migration of fetal cells and cell-free DNA to the maternal circulation during pregnancy, which can remain with the mother for decades [3].

During pregnancy, a shift of cytokine profile toward a T-helper 2 (Th2) response instead of Th1 was considered one of the most important immunological modifications. Suppression of Th CD4+ cells (Th1 response) in uncomplicated human pregnancy and Th1 polarization in patients with reproductive failure has supported the concept of successful pregnancy as a Th2 phenomenon proposed by Wegmann [4]. However, recent extensive research on the physiology of pregnancy has shown that the hypothesis that pregnancy is warranted by Th1/Th2 shift is simplistic [5].

During the different stages of pregnancy, cytokine production at the feto-maternal interface is regulated to create optimal conditions for fetal development. Interferon (IFN)-γ and TNF-α, both cytokines secreted by Th1 cells and major contributors to Th1 immune response, are necessary during early stages of pregnancy for successful implantation and placenta development but later in pregnancy could be detrimental and result in pregnancy loss [2]. Chorionic villous tissue expresses not only Th2-type cytokines but also IL-1 β and TNF-α in the first trimester [6]. On the other hand, high expression of IL-10, a pleiotropic cytokine with both immune stimulatory and immune suppressive functions, is present in the human placenta at term [7].

In line with local cytokine modulation and as a reflection of systemic effects of pregnancy, cytokine secretion in peripheral blood mononuclear cells (PBMC) changes during pregnancy. In vitro assays from whole blood of healthy pregnant women have shown a diminished pro-inflammatory response, with a decrease of TNF-α, IL-1β, and IL-6, while IL-4 and IL-10 remain stable during pregnancy [8]. During the third trimester, a reduction of IL-12 and TNF-α production was detected in monocytes from healthy pregnant women compared to postpartum values [9]. An increase of IL-4-secreting PBMC, but not of IFN-γ-positive cells, was found in the second and third trimesters of pregnancy in healthy women after stimulation with paternal antigens [10]. The same group found significantly higher numbers of IFN-γ- and IL-4-secreting

PBMC in all three trimesters of pregnancy and also postpartum than the nonpregnant controls, indicating a systemic upregulation of both Th1- and Th2-like immune responses during normal pregnancy [11].

Besides cytokines, regulatory molecules that modify cytokine actions such as IL-1Ra and IL-6R have been found to be increased in serum of pregnant women, as well as levels of IL-6 and IL-1. Likewise, levels of soluble TNFR were found significantly increased in the second and third trimesters of pregnancy compared to nonpregnant values [3]. Thereby, both Th1- and Th2-type cytokines are important players of immune adaptation to pregnancy at local and systemic levels. Its production is adjusted to the different stages of pregnancy and, in addition with upregulation of cytokine-regulating molecules, can exert an ideal environment to achieve a successful pregnancy.

Pregnancy also induces substantial changes in hormone levels, which have powerful effects on blood cells as they can regulate their proliferation, distribution, and function. Estrogens enhance antibody production, Th2-type immune responses, and B-cell immunity [7]. At high concentrations, such as those found in pregnancy, estrogens and gestagens stimulate the secretion of IL-4, IL-10, TGF-β, and IFN-γ while simultaneously suppressing production of TNF-α [3, 12].

Therefore, pregnancy influences the interaction between neuroendocrine and immune systems both locally and systemically with a fine balance that creates optimal, but not uniform conditions at the feto-maternal interface and in the maternal circulation.

2.2 Maternal tolerance to the fetus in normal pregnancy

Although localized mechanisms at the maternal-fetal interface contribute to fetal evasion from an immune attack, several additional mechanisms operate during pregnancy and help the fetus to evade maternal immune response.

In this context, regulatory T (Treg) cells have been shown to play a pivotal role in maternal-fetal tolerance. These Treg cells, a subset of suppressor CD4+ CD25+ cells, play a dominant role in the maintenance of immunological self-tolerance by preventing immune and autoimmune responses against self-antigens. In recent years, it has been observed that Treg cells are essential in promoting fetal survival, avoiding the recognition of paternal semi-allogeneic tissues by maternal immune system, a critical step for successful pregnancy [13, 14].

In healthy pregnant women, CD4+ CD25+ Treg increases rapidly in peripheral blood peaking at midgestation coinciding with the time of maximal trophoblast invasion and decreasing after delivery to prepregnancy levels [15]. Levels of Treg cells within the decidua, which represents the maternal-fetal interface, are elevated compared with those in the peripheral blood. The increase in Treg cells emphasizes the potential role for these cells in the successful development of the placenta by ensuring fetal tolerance [16].

Expansion of Treg cells is not only due to hormonal changes occurring during pregnancy, but can be driven by several other factors like decidual peptides, fetal antigens, and seminal fluid. Indeed, Treg cells act in an antigen-specific manner as they are specifically activated by MHC paternal antigens, but once activated they are able to exert suppressive effects on other local cells in an antigen-independent manner [16, 17].

The exact mechanism by which Treg cells exert their suppressive activity during pregnancy is not completely clear but is likely to be mediated by cell contact-dependent and cell contact-independent manipulations of dendritic cells (DCs) and effector Th cells, as well as direct cytolytic activity on DCs and modulation of the local metabolic environment [1, 17]. Recent data support the capacity of Tregs to block maternal effector T cells, thereby reducing the maternal-fetal pathological responses to paternal antigens [18].

A prospective observational study of 101 women who underwent in vitro fertilization (IVF) showed an increased level of circulating Treg cells in pregnant women. A higher percentage of Treg in peripheral blood was associated with increased rates of pregnancy and live birth [19]. On the other hand, deficit in Treg cell number in the decidua and maternal peripheral blood has been associated with complications such as unexplained infertility, miscarriage, and preeclampsia [1, 13]. These observations support the Need for a substantial increase in Treg cell numbers for a successful pregnancy.

Interestingly, during pregnancy a bidirectional exchange of cells at the maternal-fetal interface occurs, so maternal cells can cross the placenta and engraft in fetal lymph nodes in utero, a phenomenon called maternal microchimerism. Human fetal T cells are responsive against maternal alloantigen, but a pool of fetal Treg cells actively suppresses their function. Maternal microchimerism has been shown to induce development in utero of fetal Treg cells that suppress fetal antimaternal immune response, indicating a mechanism that promotes tolerance toward maternal antigens by the fetus [14, 20].

Besides Th1 and Th2 cells, there is a third subset of CD4+ T-helper cells called Th17 cells, which, like Treg cells, are implicated in pregnancy and maternal immune tolerance to the fetus [14]. These Th17 cells are defined by their ability to produce IL-17, a pro-inflammatory cytokine that promotes development of Th17 cells and interestingly, in the presence of a tolerance milieu, drives differentiation to Treg cells [21]. Both Treg and Th17 cells require transforming growth factor beta (TGF-β) for differentiation, but the copresence of IL-6 favors differentiation of pathogenic Th17 cells as it can inhibit the generation of FoxP3+ in Treg cells induced by TGF-β [22]. Th17 cells promote inflammation and generally have opposing actions to Treg cells so a reciprocal relationship between these two subsets of Th cells has been described [21].

The presence of Th17 cells in human decidua of healthy pregnancies was investigated. The first-trimester human decidua displayed a local expansion of Treg cells, while a low occurrence of Th17 cells was observed, which suggests that the inverse relationship between Treg and Th17 cells seems to be maintained at least in early stages of pregnancy [23].

On the other hand, increased numbers of Th17 have been found in obstetric complications such as preeclampsia and recurrent pregnancy loss (RPL). A significant increase of Treg FoxP3+ to IL-17-expressing CD4+ T cell ratio in peripheral blood at the third trimester of healthy pregnancy was reported, while an absence of a reduction of IL-17 production toward a FoxP3+ expression was observed in preeclamptic pregnancies [24]. In line with these observations, a later study reported an increased prevalence of IL-17-producing circulating T CD4+ and CD8+ cells in preeclampsia, demonstrating a shift in the Th17/Treg balance in this pregnancy complication [25].

Also, the proportion of Th17 cells in peripheral blood and decidua was significantly higher in unexplained RPL patients compared to normal pregnant women. As reported in preeclamptic pregnancies, there was an inverse relationship between Th17 cells and Treg cells in peripheral blood and decidua in unexplained RSA [26]. Another study showed an accumulation of IL-17-producing cells in decidua of inevitable abortion cases compared to normal pregnancies and missed abortions [27]. Therefore, there is evidence suggesting that balance between Th17 cells and Treg cells may be critical to pregnancy outcomes.

2.3 SLE pregnancy vs. normal pregnancy

Differences in sex steroid hormones during pregnancy have been observed in patients with SLE compared to healthy women. In a prospective study, pregnant

lupus patients presented lower levels of estradiol and progesterone in the second and most of the third trimester of pregnancy [28]. The inability to produce high concentrations of these sex hormones during the last two trimesters of pregnancy could be due to placental insufficiency, which in turn can be implicated with the elevated rate of fetal loss in SLE patients [29].

Levels of certain cytokines involved in the humoral immune response have been shown to be modified in the peripheral circulation of pregnant SLE patients. Serum levels of IL-6, a cytokine necessary for T cell help for B cells and proliferation of plasma cells, are lower than expected in the third trimester of gestation. Higher levels of IL-10 before conception through pregnancy and postpartum in lupus patients compared to healthy controls have been observed, suggesting a constitutional overproduction of IL-10 in SLE patients resulting in a continuous B-cell stimulation. Furthermore, levels of soluble TNF receptor I (sTNFR I) and IL-10 are significantly higher during pregnancy and postpartum in pregnant patients with active SLE compared to healthy controls [28].

Cytokine profile of PBMC in SLE and rheumatoid arthritis (RA) pregnant women was investigated in a prospective study by assessing cytokine messenger RNA (mRNA) expression using quantitative PCR. TNF-α was the most abundant cytokine mRNA expressed in PBMC in all three groups studied (healthy pregnant women, RA, and SLE pregnant patients). However, in RA and SLE patients, a general Th2 response reflected by high IL-10 levels was found [30].

Several studies have investigated the phenotype and function of Treg cells in patients with SLE. Most of the studies have shown a decrease in Treg cell numbers in SLE patients and a negative correlation with disease activity [16, 31–33]. In addition to the reduced number of Treg cells, some data suggest an impaired function of Treg in SLE like a reduced migratory ability [34]. Also, a defect in T-cell suppression has been observed in SLE, although this defect seems to be due to effector cell resistance rather than a reduced Treg suppressor capacity [35].

A pilot study have shown that circulating CD4+ CD25+ FOXP3 Treg cell numbers are markedly reduced in nonpregnant women with SLE compared with healthy controls. Treg levels remained depleted in SLE patients when pregnant, while those in healthy individuals raised, peaking at 10–12 weeks of gestation. Lower quantity of Treg cells was evident regardless of disease activity and medication in SLE patients [21]. So, considering the essential role of Treg cells at early stages of pregnancy and its implication for immune tolerance, defective functioning and decreased number of Treg cells could predispose women with SLE to pregnancy complications.

There is little work investigating the presence of Th17 cells in pregnant SLE patients, although a study supports an imbalance between Treg and numbers of Th17 cells in active SLE. An inverse correlation between Treg/Th17 ratio with severity of active SLE and anti-DNA antibody levels was reported [36]. Disease flares and severe complications of SLE, such a lupus nephritis, seem to be associated with a decrease in FoxP3+ Treg cells and an increase in Th17 cells [37, 38]. In a longitudinal study that evaluated the changes of serum IL-17 and other cytokines in SLE pregnant woman during pregnancy, serum IL-17 concentrations were higher in SLE than in controls with no changes during pregnancy [36].

As discussed previously, TGF-β is essential for the differentiation of both Treg cells and Th17 cells. In a large cohort study, reduced levels of TGF-β were associated with increased SLE activity [39]. Although TGF-β influence in reproduction and complications in pregnancy is not clear, a possible role in trophoblast invasion has been proposed as low levels of TGF-β in the second trimester of pregnant woman have been associated with an increased risk of developing preeclampsia [16]. Clearly, more studies are needed to understand the role of Treg/Th17 imbalance

in SLE pregnancies and its possible implications in the risk of maternal-fetal complications.

As mentioned above, pregnancy induces important hormonal changes. Prolactin (PRL) levels increase progressively during pregnancy and lactation in order to stimulate the synthesis of milk in the mammary glands [42]. Elevated levels of PRL have been found in almost one third of SLE patients, and higher levels during the second and third trimesters have been associated with clinical activity and poor maternal and fetal outcome [40, 41]. On the other hand, the presence of anti-PRL autoantibodies in 13.1% of pregnant patients with SLE has been reported. Likewise, a lower frequency of maternal and fetal complications in SLE patients than those without these antibodies was reported [41].

Therapeutic blockade of PRL with bromocriptine (BRC), a dopamine analog that suppresses PRL secretion, has been evaluated to prevent lupus relapses during pregnancy and postpartum. A pilot study explored the use of BRC between 25 and 35 weeks of gestation in two groups of ten pregnant SLE patients each. No patient in BRC group had disease flares, and there were lower adverse maternal and fetal outcomes in the treatment group than the group that did not receive BRC during pregnancy [42]. More recently, a randomized clinical trial evaluated the use of BRC in the postpartum of 76 SLE pregnant women. BRC administration for 2 weeks after delivery reduced the disease relapse rate of the treatment group [43].

So, results from clinical studies support the contribution of PRL to complications in pregnant SLE women and a possible role of BRC in the prevention of disease relapses during pregnancy and postpartum.

3. Influence of pregnancy in SLE outcomes

The critical immunologic adaptations during pregnancy and postpartum can impact maternal autoimmune diseases in several ways. One is triggering the onset of an autoimmune disease in postpartum or influencing disease activity of an established disease. In this manner, disease response to complex pregnancy changes depends on its pathophysiology [2].

As seen before, steroid hormones and cytokine profiles differ in SLE patients compared with healthy women during pregnancy leading to a dysregulation of the balance between cell-mediated and humoral immune responses, which could explain the variability of the SLE course during gestation [44]. Since SLE is considered mainly a Th2-mediated disease, pregnancy-related changes could trigger disease onset or increase the risk of disease exacerbations during this period [45]. Also, hormones such as estrogen and prolactin could play a role in amplifying the inflammatory effect that characterizes lupus relapses. In murine models, increasing doses of estrogen, like those seen in pregnancy, promotes physiological and immunological changes associated with increased lupus activity [46].

3.1 Lupus activity and its relationship with pregnancy

Whether SLE activity increases during pregnancy or not has been previously debated in the literature. The majority of prospective studies in SLE pregnancies have shown that the risk of disease flare is higher during pregnancy, although some discrepancies exist due to heterogeneity of lupus flare definition and tools used to assess lupus activity [2]. Newer studies using validated instruments for disease activity assessment have found a two–threefold increase in SLE activity during pregnancy [47, 48]. Even though SLE flares occur at any time during pregnancy,

most of these flares are considered mild to moderate in severity and may include renal, hematological, and musculoskeletal systems. Likewise, previous organ involvement predicts the same type of condition during pregnancy, particularly in the case of renal, hematological, and cutaneous activity [36].

Disease activity at conception and in the previous 6 months, both clinical and serological, is a key predictor not only for obstetrical complications but also of SLE flares during pregnancy. Prospective studies of pregnant lupus patients have reported some risk factors for SLE activity during pregnancy: a high number of relapses prior to pregnancy, high SLEDAI index before pregnancy, and preconception SLE activity [46, 49]. In fact, the risk of severe lupus flare is increased about seven times in patients with active SLE at conception [50]. Moreover, SLE disease activity immediately prior to pregnancy also impacts on damage accrual after pregnancy [51].

Besides disease activity at and before conception, several predictors for flares in pregnant patients have been described. A prospective evaluation of 254 patients found that discontinuation of hydroxychloroquine (HCQ) was associated with a higher degree of lupus activity (measured by SLEDAI) during pregnancy as well as an increased rate of flare during this period. On the contrary, women who continued taking HCQ required lower average dose of prednisone during pregnancy [52].

In addition, primigravity seems to influence the risk of lupus flares during pregnancy. A retrospective analysis of 124 pregnancies found that the first pregnancy in SLE women was associated with an increased risk of relapse at any level, particularly in the kidney [53].

On the other side, SLE activity during or prior to pregnancy is associated with several maternal and fetal complications such as fetal loss, preterm birth, intrauterine growth retardation (IUGR), and hypertensive complications. Previous renal disease is also a risk factor for obstetric complications like PE, fetal loss, IUGR, and premature birth. Therefore, early identification and prompt treatment in pregnant women with lupus activity are essential to improve pregnancy outcomes [49]. However, recognition and management of disease flares during pregnancy can be challenging due to the physiological changes that occur during this period, which can overlap with clinical and laboratory features of active SLE [46]. For this reason, clinical data and laboratory findings in pregnant patients with SLE should be interpreted with caution. Thrombocytopenia, mild anemia, and increased erythrocyte sedimentation rate (ESR) often occur during normal pregnancy. In addition, complement levels are less reliable to identify or support the suspicion of disease activity due to its physiological increase during pregnancy, although a decrease in C3 and C4 titers as well as an increase in anti-DNA antibodies may be useful to differentiate complications such as preeclampsia and SLE activity.

3.2 Lupus nephritis, pregnancy, and hypertensive complications

Lupus nephritis is among the findings that most often induces increased morbidity and mortality during pregnancy. Indeed, lupus nephritis, especially active at the time of conception, has been associated with an increased risk of relapse during pregnancy. A higher risk of SLE activity has been reported, particularly renal flares, in pregnant patients with previous nephritis compared to those patients without history of renal involvement [54]. However, a recent prospective multicenter study did not find an increased risk of renal flares during pregnancy in patients with a history of previous renal activity and clinically active lupus nephritis at conception. Instead, history of renal flares before pregnancy predicted hypertensive

Features	Preeclampsia	Lupus nephritis
Timing in pregnancy	>20 weeks of gestation	Throughout gestation and postpartum
Physical findings		
- Hypertension (BP >140/90)	Present	Present
- Edema	Present	Present
- RUQ tenderness	May be present	Absent
- Visual symptoms/seizures	Present with severe features	Absent
Lupus activity		
- Fever	Absent	Present/absent
- Malar rash	Absent	Present/absent
- Arthralgias/arthritis	Absent	Present/absent
- Oral ulcers	Absent	Present/absent
Laboratory findings		
- Proteinuria	Present >20 weeks	Present <20 weeks
- Active urinary sediment	Absent	Present
- Increased creatinine	Usually normal	May be increased
- Complement	Normal/increased	Normal/decreased
- Anti-dsDNA	Absent	May be increased
- aPL antibodies	Absent	May be present
- Abnormal LFTs	Present with severe features	Absent
Renal biopsy findings	Endothelial cell swelling, loss of fenestrations, occluded capillary lumen, rare thrombi	WHO class II to class VI lupus nephritis Thrombi and vascular changes with aPL

Data from [60, 61]. BP, blood pressure; RUQ, right upper quadrant; anti-dsDNA, anti-double-stranded DNA; aPL, antiphospholipids; LFTs, liver function tests

Table 1.
Clinical, laboratory, and renal biopsy findings in preeclampsia and lupus nephritis during pregnancy.

complications such as preeclampsia (PE) [55]. A meta-analysis of 37 studies reported lupus nephritis flare in 16% of pregnant lupus patients and confirmed the association of lupus nephritis at conception with an increased risk of hypertension during gestation. Adverse outcomes in pregnant patients with lupus nephritis were also related to hypertension and presence of antiphospholipid antibodies [56]. Moreover, the onset of PE seems to occur at earlier weeks of gestation in lupus nephritis patients compared to SLE patients without renal involvement [57].

Preeclampsia is a syndrome unique to pregnancy that manifests with hypertension and proteinuria and resolves following delivery. Besides classical risk factors in general population, diseases that promote endothelial dysfunction including SLE increase the risk of preeclampsia. Among lupus pregnancy cohorts, the rate of preeclampsia ranges varies widely. Whereas a meta-analysis of lupus pregnancies reports a preeclampsia rate of 7.8%, other studies suggest that it can be twice as high, particularly in women with nephritis [29, 56]. Dysfunctional angiogenesis leading to an impair in placental development has been implicated in pathogenesis of preeclampsia. Several markers in maternal serum like VEGF, placental growth factor (PlGF), and soluble fms-like tyrosine kinase (sFlt-1) have been found to be predictive of preeclampsia in lupus patients. Lower than expected levels of

proangiogenic factors VEGF and PlGF and high levels of antiangiogenic factor sFlt-1 seem to reflect poor placental perfusion and impaired angiogenesis in the rapidly growing placenta [29].

Similar to what happens in lupus flares during pregnancy, distinguish clinical indicators of lupus nephritis from pregnancy physiological features, and those related preeclampsia can be a complex task. In the first trimester of pregnancy, maternal systemic circulation suffers remarkable physiological vasodilation conditioned by relaxin, a hormone produced by the corpus luteum. As a result of systemic vasodilation, glomerular filtration rate (GFR) elevates, and serum creatinine consequently diminishes making it more difficult to identify a renal compromise in a timely manner [58]. Urine protein excretion is also increased during pregnancy, so isolated elevation of proteinuria is not necessarily indicative of active nephritis [7].

Besides physiological changes induced by pregnancy, PE and LN share some clinical and laboratory features like hypertension, proteinuria, and edema, making it difficult to distinguish between the two entities. This distinction is critical since management differs significantly; while LN requires immunosuppressive treatment, in severe PE delivery may be indicated. A detailed evaluation of biomarkers of SLE activity as anti-dsDNA, the low level of complement, active urine sediment (red cells, white cells, and cellular casts), and the presence of extrarenal SLE manifestations may be helpful in the differential diagnosis. In contrast, in pregnant women with a gestational age greater than 22 weeks and absence of sign of SLE activity, the diagnosis of PE is very likely [59].

Clinical, laboratory, and renal biopsy features present in PE and LN are shown in **Table 1**.

4. Impact of SLE on pregnancy outcomes

Despite diagnostic and therapeutic advances, pregnancies in SLE patients are still considered a high-risk condition due to an elevated risk of major obstetric and neonatal complications. A population-based study from 2000 to 2003 found that maternal mortality was 20-fold higher among women with SLE. The risk for serious medical and pregnancy complications during pregnancy was also three- to seven-fold higher for SLE women than the general population [62].

In recent years, outcomes during pregnancy in patients with SLE related to preconceptional counseling, close monitoring during pregnancy, and postpartum and multidisciplinary management have improved [63]. However, according to a recent meta-analysis comparing maternal and fetal outcomes of women with and without SLE, adverse outcomes such as spontaneous abortion (RR, 1.51), PE (RR, 1.91), thromboembolic disease (RR, 11.29), and preterm birth (RR, 3.05) are still more frequent in pregnancies of women with SLE [64]. Additionally, it has been estimated that women with SLE have fewer live births than the general population [65].

In the last two decades, the rate of fetal losses has declined from 43% in the years 1960–1965 to 17% in the period 2000-2003 [66]. Most recent studies reported a pregnancy loss rate of 10–25% in women with SLE [67]. In addition to risk factors associated with pregnancy losses in the general population, such as chromosomal and anatomical abnormalities, specific factors associated with SLE have to be Considered, including thrombocytopenia, antiphospholipid antibody (aPL) positivity or antiphospholipid syndrome (APS), lupus nephritis, and high SLE disease activity [68]. Both low complement and presence of anti-DNA in the second trimester, regardless of clinical activity, have also been associated with a higher rate of fetal loss and preterm delivery [69].

4.1 Antiphospholipid antibodies and pregnancy

The presence of antiphospholipid syndrome (APS) is one of the most important causes for pregnancy loss in women with SLE, manifesting a recurrent pregnancy loss, fetal loss, or stillbirth (pregnancy loss after 20 weeks of gestation) [29]. In addition to recurrent pregnancy loss, APS predisposes pregnant women to late gestational complications associated with impaired placental function, such as PE and fetal growth restriction. Serious complications have been reported in up to 12% of pregnancies in lupus patients. Interestingly, adverse outcomes in pregnancies of SLE women with aPL antibodies can present even during disease remission or mild activity [50].

Antiphospholipid antibodies target the placenta by binding β2 glycoprotein I (β2GPI) constitutively expressed on trophoblast cell surface, perturbing the secretion of trophoblast angiogenic factors in the first trimester of gestation and favoring adverse outcomes [70].

The prevalence of aPL antibodies in patients with SLE is variable and depends on the type of antibodies and isotype. A prevalence of 12–44% of anticardiolipin antibodies (aCL), 15–34% for lupus anticoagulant (LA), and 10–19% for anti-β2 glycoprotein I (aβ2GPI) has been reported [71], although prevalence of aPL could be underestimated due to immunosuppressive treatment. A higher frequency of thrombosis and pregnancy loss in SLE-associated APS (secondary APS) than in primary APS has been reported. Moreover, in the Hopkins lupus cohort, the diagnosis of secondary APS led to a threefold increase in pregnancy loss, especially after 20 weeks of gestation and was an independent risk factor for further pregnancy losses [68].

The association of aPL with adverse pregnancy outcomes (APOs) is variable between different aPL antibodies. Particular serological profiles have been defined as "high-risk profiles" because of its stronger association with APOs. Lupus anticoagulant rather than aCL has been identified as the primary predictor of APOs [72]. In the PROMISSE study, a large-scale multicenter prospective study of pregnant women with aPL and/or underlying stable SLE, a higher rate of APOs in pregnant patients with aPL (43.8%) compared to 15.4% of patients without aPL was observed, while poor pregnancy outcome was observed mainly in LA-positive patients. The presence of LA was identified as a baseline independent predictor of APOs (OR 8.32), while no other aPL antibody independently predicted APO [73]. The EUROAPS registry also reported that the presence of LA, isolated or in combination with aCL and/or aβ2GPI, was the strongest marker related to poor obstetric outcomes [74].

Regarding treatment, there is no current evidence that the management of pregnancy should be different in SLE-associated APS than in primary APS. Actually, treatment of pregnant patients with aPL will depend on the risk profile and history of adverse obstetric events or previous thrombosis. According to this risk, they can be classified into three groups: (a) presence of aPL antibodies in the absence of obstetric or thrombotic events, (b) high-risk profile (LA or triple positivity) or adverse obstetric events, and (c) aPL antibodies and previous thrombosis.

Although increased lupus activity does seem to not increase the risk for miscarriage, stillbirth rate is threefold higher [53]. Additionally, the timing of lupus activity seems to impact the pregnancy loss rate, with activity early in pregnancy being the most dangerous [68].

4.2 Antibodies anti-SSA/Ro and anti-SSB/La and neonatal lupus

Pregnancies exposed to anti-SSA/Ro and anti-SSB/La have an increased risk of developing neonatal lupus (NL), a passively acquired autoimmune disease

mediated by maternal antibodies. There are two main forms of NL: NL erythematosus (NLE) and congenital heart block (CHB). Other less frequent forms include hepatic and hematologic. NLE occurs in 5% of children born to women with anti-Ro/SSA or anti-La antibodies. It usually presents within the first 2 weeks of life as erythematous geographical lesions in light-exposed areas, resembling subacute cutaneous lupus. Rash resolves within 6–8 months of life as the maternal antibodies are cleared, without leaving residual scarring [75]. CHB is a more serious form of NL, affecting 1–2% of newborns of anti-Ro-positive women and a recurrence rate in subsequent pregnancies up to 16–20%. Incomplete forms of CHB have been described, including first-degree heart block that can progress during childhood. Permanent pacemaker will be needed in most children with CHB, and up to 20% may die in the perinatal period [76].

Starting from the second trimester, maternal IgG antibodies are actively transferred via the placental FcRn receptor to the fetus. Although the precise mechanism of injury is not fully known, one hypothesis considers a direct effect of anti-SSA/Ro and/or anti-SSB/La antibodies by binding to fetal cardiac tissue and altering cardiocyte function. In the case of anti-SSA/Ro antibodies, they can bind cross-reactive epitopes on calcium-regulating molecules such as ion channels, inducing disturbances in calcium homeostasis and signal electrogenesis at the atrioventricular node. A demonstration that anti-SSA/Ro antibodies are arrhythmogenic and inhibit inward calcium fluxes across cell membranes supports this hypothesis [77].

Another hypothesis raise that intracellular anti-SSA/Ro and SSB/La antigens translocate to the surface of cardiomyocytes undergoing apoptosis during physiological remodeling and thus become accessible to extracellular antibody. This allows the formation of pathogenic antibody-apoptotic cell immune complexes that promote a pro-inflammatory and profibrotic response [78]. In vitro studies support a protective role of β2GPI by preventing opsonization of apoptotic cardiomyocytes by maternal anti-Ro60 IgG [79].

CHB is usually preceded by lesser degrees of conduction delays which may be reversed with early treatment. Given that the majority of conduction abnormalities develop between 18 and 24 weeks of gestation, several tools for early detection of lesser degrees of heart block are available, including fetal Doppler echocardiography, fetal kinetocardiogram, and transabdominal fetal echocardiography. Close monitoring of anti-SSA/Ro-positive pregnant women with weekly fetal Doppler echocardiography between 16 and 26 weeks of gestation and biweekly thereafter is highly recommended [61]. This enables assessment of atrial and ventricular rates, cardiac anatomy and function, and the presence or absence of hydrops. Urgent referral to a fetal medicine unit or fetal cardiology service is advised if a low fetal heart rate (<110 bpm) is detected. An increased risk of hydrops and death is present if the rate is <55 bpm [76].

Although fetal echocardiogram is the most commonly used modality, it may underestimate pathological findings of NL, so recently other biomarkers for early detection of heart disease and to monitor severity and progression of cardiac LN have been suggested, such as NT-proBNP in amniotic fluid [80].

Different strategies have been evaluated for CHB associated with anti-Ro and/or anti-La antibodies. Prenatal therapy with fluorinated steroids like dexamethasone in mothers of fetuses with incomplete heart block is currently used; however, its role has been questioned since published data are discordant regarding its efficacy. A multiracial/ethnic US-based registry of cardiac neonatal lupus demonstrated that fluorinated steroids do not prevent heart block progression or death in cases with isolated heart block and without evidence of extranodal disease [81]. In a more recent study, the use of fluorinated steroids was not associated with

complete heart block regression or an increase in survival [82]. Therefore, the decision to administer this type of steroid, usually at high doses (at least dexamethasone 4 mg daily), should be weighed against the potential risk of adverse effects on the fetus and the mother [78].

Preventive management of anti-SSA/Ro- and/or anti-La/SSB-positive pregnant women is under investigation. Hydroxychloroquine administration during pregnancy has been associated with a decrease of recurrent NL [83]. On the other hand, recent studies failed to demonstrate efficacy of monotherapy with intravenous immunoglobulin or plasma exchange in reducing the incidence of cardiac NL [84, 85].

5. Contraception, fertility, and assisted reproduction in SLE

Contraception is a complex issue and of particular interest in SLE patients to prevent unplanned pregnancies during periods of disease activity or potentially teratogenic drug exposure. The main concerns about hormonal contraceptive methods are disease flares and risk of thromboembolism [86]. The risk of complications associated with the use of hormonal contraceptives has been evaluated by two randomized clinical trials. A first study compared a combined three-phase oral contraceptive with placebo in 183 patients with SLE. No significant differences in the number of disease flares between both groups were observed [87]. A second study compared a combined oral contraceptive, a progestogen, and non-medicated intrauterine device. Disease activity remained stable during follow-up, and only four thrombosis episodes were recorded, two episodes per hormone treatment group [88]. However, both studies excluded patients with severely active SLE, history of previous thrombosis, malignant gynecological neoplasm, acute myocardial infarction, and previous hepatopathies and patients actively smoking. Regarding aPL antibodies, patients with positivity for these antibodies were excluded in the first study, but not in the second trial. According to both studies, combined hormonal contraceptives (estrogens plus progestogens or progestins alone) are safe in patients with stable SLE in the absence of aPL, without increasing the risk of disease flares of thrombotic events.

Fertility is a relevant topic in SLE patients due to predominance of female gender and reproductive age. The reproductive issue in SLE women does not result from an increase in primary fertility rate but from an increase in the number of fetal losses and use of drugs related to infertility. Cyclophosphamide (CYC) has been associated with ovarian reserve depletion by inducing apoptosis of oocytes and granulosa somatic cells, with the consequent premature ovarian failure in a dose- and age-dependent manner. Although the exact incidence of secondary ovarian failure due to CYC is not clear, it may vary between 11 and 59%, and a higher risk is observed in women older than 30 years [89]. Simultaneous administration of GnRH agonist has been suggested to minimize the gonadotoxic effect of CYC. Other disease-modifying rheumatic drugs (DMARDs) such as mycophenolate mofetil, cyclosporine, or tacrolimus have not been associated with infertility in lupus patients [90].

On the other hand, it has recently been suggested that SLE per se has a negative effect on ovarian function and reserve, regardless of the disease activity and use of gonadotoxic immunosuppressive therapies. A study that measured levels of anti-Müllerian hormone (AMH), a marker of ovarian reserve, in lupus patients and healthy controls found lower levels of AMH in the first group, with no correlation between disease activity and duration [91].

The role of aPL antibodies as a cause of infertility is controversial, as previous retrospective studies have suggested an association between aPL antibodies and infertility. However, two recent studies have not demonstrated a higher prevalence of these antibodies in women with infertility or a correlation with the type of infertility [92, 93].

A strategy to overcome the difficulties of achieving a successful pregnancy is the use of assisted reproduction technologies (ARTs), which includes ovarian stimulation, oocyte retrieval, in vitro fertilization (IVF), and transfer of the embryo to the uterus [94]. Many stimulation protocols are available, but ovarian stimulation with human chorionic gonadotropin (hCG) is the most frequently applied. These hormones determine an estrogenic peak in order to stimulate the growth of multiple follicles, which may increase the risk of multiple pregnancy, preterm birth, and ovarian hyperstimulation syndrome, but the main concern rises around the risk of disease exacerbation or maternal complications. Although the hormonal stimulation could theoretically trigger a disease flare or the onset of thrombosis in patients with aPL antibodies, recent studies have shown that they can be safe and have a low probability of SLE flare [94, 95].

A relevant issue with the use of ARTs is the incidence of thrombotic events. During ovarian stimulation, several changes in coagulation have been described including an increase in fibrinogen, von Willebrand factor, and platelets and decrease in antithrombin III and fibrinolytic activity. These changes may induce a state of relative hypercoagulability. However, the absolute risk of thrombosis during ovarian stimulation is low due to the predominant use of estradiol (E2) and short time of stimulation. The observed incidence is quite low and related to ovarian hyperstimulation syndrome. A systematic review identified as risk factors for thromboembolic complications advanced age (>35 years) and hereditary thrombophilias, while SLE and APS were not independent risk factors [96].

Regarding the efficacy of ART, the success rate varies from 16 to 31% in women with SLE, similar to the general population [48]. The role of aPL has been examined by previous retrospective studies that suggested a relationship between aPL positivity, infertility, and multiple failures of ART procedures. However, recent evidence does not support this since the presence of aPL antibodies has not been identified as a predictor of failure during the use of ART [97]. In a prospective study of 101 infertile women with at least three unsuccessful IVF attempts, no association was found between aPL positivity and success rate [98].

Despite the lack of studies evaluating the risks and benefits of different ovarian stimulation protocols, it is suggested to avoid high serum concentration of estradiol. In the case of anovulation, ovarian induction with clomiphene citrate represents the first choice. In treatment failure, pulsatile administration of GnRH over the use of gonadotropins is preferred since the latter does not confer the risk of ovarian hyperstimulation syndrome [91].

The period of the highest risk is not ovarian stimulation but pregnancy due to elevated rates of fetal and maternal complication, so the main reason for rejecting ART in women with SLE is foremost the risk of obstetric and maternal adverse outcomes. ART is safe in patients with stable SLE; however, its use is not recommended in patients with active SLE, uncontrolled hypertension, chronic kidney disease, severe valve disease, or severe thromboembolic events [48].

6. Algorithm in women with SLE

An algorithm proposal to approach women with SLE of childbearing age is presented in **Figure 1**.

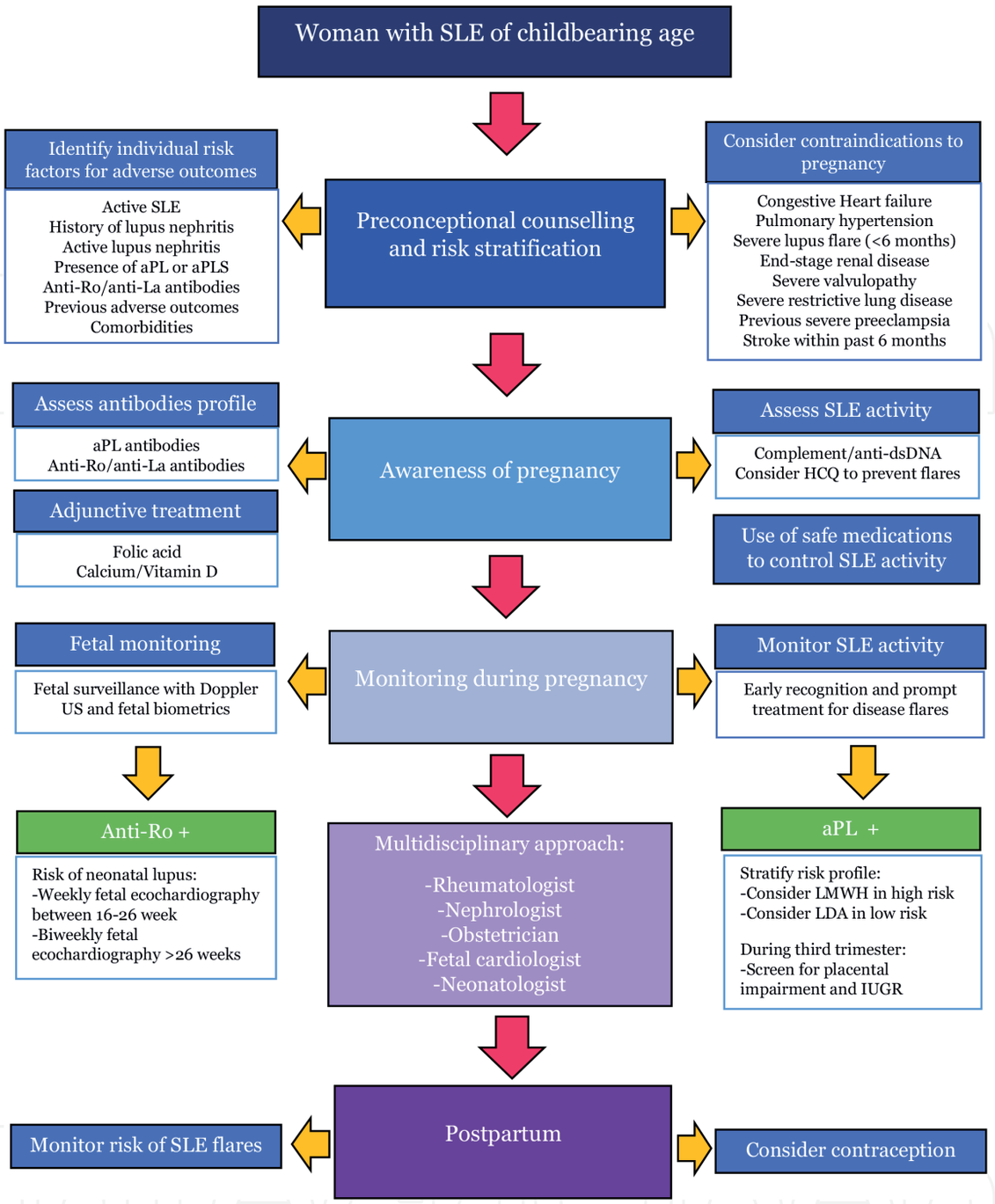

Figure 1.
Approach to pregnant woman with SLE. Data from [76, 99]. aPL, antiphospholipid; LMWH, low-molecular-weight heparin; LDA, low-dose aspirin; IUGR, intrauterine growth restriction.

7. Conclusions

Pregnancy induces immunologic and hormonal adaptations on a pregnant woman to permit maternal tolerance to the fetus. The balance between Th17 cells and Treg cells seems critical to pregnancy outcomes, although its possible implication in maternal-fetal complications in SLE woman is not completely understood.

The relationship between SLE and pregnancy is close and bidirectional; active disease is associated with the increased risk of adverse pregnancy outcomes and pregnancy changes which impact on maternal disease triggering flares during this period.

Besides disease activity, immunologic factors related to SLE such as aPL and anti-SSA/Ro antibodies can also influence obstetric and neonatal outcomes. The

presence of aPL antibodies is one of the most important risk factors for pregnancy loss and late gestational complications in women with SLE. Treatment of pregnant patients with aPL will depend on the risk profile and history of obstetric or thrombotic events. Anti-SSA/Ro antibodies are related to neonatal lupus due to active transplacental transfer of these antibodies possibly causing direct injury to the cardiac conduction system manifesting as congenital heart block. Fetal Doppler echocardiographic monitoring between 16 and 26 weeks of gestation is highly recommended in pregnant women with anti-SSA/Ro for early detection of heart conduction delays.

Combined hormonal contraceptives are safe in women with stable SLE in the absence of aPL, without an increasing risk of disease flares or thrombotic events. Fertility in women with lupus can be affected not only by exposure to drugs related to infertility but also by SLE per se.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this chapter.

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