Chapter

Challenges in the Delivery Room: Integrated Analysis of Biomarkers Predicting Complications in Lupus Pregnancy

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Abstract

Pregnancy in autoimmune rheumatic diseases remains a real challenge in clinical practice due to complex interplay between disease activity, pregnancy and drugs, and account for potential influence of pregnancy on rheumatic condition and the impact of disease on pregnancy outcomes. Indeed, innovative and successful therapies have dramatically improved the quality of life in immune-mediated rheumatic conditions and, subsequently, allowed more patients of reproductive age to plan a pregnancy/to conceive. The purpose of this chapter is to discuss emerging data about the interaction of pregnancy and systemic erythematosus lupus (SLE) focusing on modulation of the immune system by pregnancy, pregnancy outcomes in women with active lupus, biomarkers of adverse pregnancy outcomes (APO) including predictors of pre-eclampsia, predictors of obstetric complications in SLE, the influence of autoantibodies on fetal health, and, finally, evidence about rheumatologic and obstetric follow-up. There are still unmet needs in this new field of reproductive rheumatology and it becomes crucial that researchers, physicians (rheumatologists, specialists in maternofetal medicine, obstetricians) and midwifes share their knowledge and expertise in counseling women with SLE wishing to conceive, assisting pregnancy and managing different issues related to APO as well as drug optimization in preconception, during pregnancy and postpartum period.

Keywords: midwife, systemic lupus erythematosus, pregnancy

1. Introduction

While documenting the role of midwifery in medical education, it is important to understand how rheumatic diseases respond to pregnancy and to allow continued development of multidisciplinary models in order to facilitate all reasonable steps in reproduction with the best available scientific evidence for health professionals.

In fact, a detailed introspection is pivotal to understand the relationship between the perception of pain, mental stress and/or physical injuries during active labor, midwife confidence and ability to handle labor.

Besides, labor quality cannot be defined by only two or three parameters; therefore, companies should consider knowledge capacities and not price whenever they decide to invest in delivery quality. These comments raise added question: "Is effort better spent at the national level to encourage labor or support for women and their babies during pregnancy?" We are optimistic about Romanian institutions supporting educational efforts that contribute to an adequate quality of labor.

Midwifes are far more important for parturient life providing optimal care based on monitoring of fetal heart, recording delivery data as well as communication with giving birth women [1–4]; also, they will provide our students clear targets for their educational and self-improvement goals.

In fact, it is well known that midwifes give support to the following events: monitor and examine women during pregnancy, breast-feeding and bathing, assist mother during labor, offer advices about still-birth, neonatal abnormality or neonatal death, make referrals to doctors, screening tests in hospital, participate in the training and supervision of youngers colleagues and students [1–4].

Continuous presence of midwifes on bed-side of parturient had positive effects, comprising a decreased risk of hemorrhage and transfusion, a decrease in urinary incontinence, reducing the delivery duration and other complications [1–4].

Pregnancy in women with immune-mediated rheumatic diseases (IMRDs) such as rheumatoid arthritis, connective tissue disorders (lupus and scleroderma), juvenile idiopathic arthritis and spondyloarthropathies is still considered a challenge in routine practice given the complex changes in the maternal immune response and the interferences between disease, pregnancy and medication [4–10].

Systemic lupus erythematosus (SLE) is commonly defined by higher maternal and fetal risk compared with pregnancy in general population, meaning that pregnant lupus patients present worse maternal as well as fetal outcomes including increased the risk of abortion, (pre)-eclampsia and placental complications [4–10].

Recent studies have shown that pregnant women with confirmed diagnosis of SLE are more likely to have hypertension, renal disease, diabetes, cerebrovascular disease, thyroid disorders, ischemic heart disease, pregnancy induced hypertension, preterm delivery, emergent caesarian sections, small for gestational age, congenital anomalies [4–11].

Clinical and/or subclinical inflammation, autoantibodies profile, hormonal dysfunction and immune abnormalities related to lupus may unquestionably contribute to pregnancy complications [5–10].

Furthermore, physiologic changes related to pregnancy are difficult to distinguish not only from disease-related manifestations but also from disease exacerbations, requiring a multidisciplinary approach with close rheumatic, obstetrical, and neonatal monitoring in order to optimize both maternal and fetal outcomes [5–10].

Although several biomarkers predicting complications in early pregnancy have already been investigated, preconception assessment is mandatory to stratify the risk in such patients. In addition to routine pregnancy labs, specific assessments should be reviewed during pregnancy comprising immune profile (total antinuclear antibodies, anti-double stranded DNA antibodies, antiphospholipid antibodies, complement level), inflammatory tests (erythrocyte sedimentation rate, C reactive protein) and proteinuria [5–10].

This review outlines detailed requirements during pre-pregnancy, pregnancy and early motherhood of reproductive-aged women diagnosed with autoimmune rheumatic diseases. We will discuss the major risks associated with pregnancy in SLE as well as management recommendations and we will focus on challenges in the delivery room by integrating the role of biomarkers to predict complications in lupus pregnancy and to foster the responsibility of midwife at parturient bed-side.

2. Healthy pregnancy *vs*. lupus pregnancy

It is critical to mention that pregnancy represents a unique clinical situation, physiologically characterized by a well-documented Th2-cell polarization at both systemic and maternal-fetal interfaces, developed on a background of depressed cellular-mediated immunity, changes in Th1/Th2 cytokine profile, and placental synthesis of complement inhibitors [4, 9, 10]. Also, progressively increased levels of sex hormones - estrogens, progesterone, prolactin, as well as and glucocorticoids are commonly reported during pregnancy [1, 4, 9, 10]. Complex immunological and hormonal adaptive mechanisms are activated to allow the tolerance of fetus classically considered as an immunogenic allograft [4, 9].

A closer look to the pathogenic pathways of autoimmune rheumatic conditions emphasizes specific genetic susceptibility and aberrant immune response driving definite behavior during pregnancy [4, 10]. Rheumatic diseases respond differently to pregnancy, as immune system adjustments may positively or negatively interrelate with underlying autoimmune disease: spontaneous improvement occurs in some of them, while persistent activity or severe flares are seen in others, such as systemic lupus erythematosus [1, 4, 10].

Despite significant progress in understanding and treating autoimmune rheumatic conditions, pregnancy in such patients remains a challenge due to complex interplay between pregnancy, disease activity and medication; the main debate focuses on the paradigm "flare without medication" *vs*. "safe drug in pregnancy", emerging the unmet needs for pregnant rheumatic patients [1, 4, 6, 9, 10].

Furthermore, it is widely recognized that the management of reproductive issues in patients with rheumatic diseases commonly differs from general population, requiring a cross-over team with rheumatologists, specialists in the fields of obstetrics-gynecology and maternal-fetal medicine, and, in special cases, reproductive endocrinology and infertility [1–4, 10]. Patients should be counseled about contraception, pregnancy and lactation; additionally, pregnancy in IMRDs needs to be planned and risks assessed in mother and child [1–4, 10, 11]. High-risk pregnancies require careful monitoring and tailored therapy to secure maternal health and positive pregnancy outcomes [4, 10].

Systemic lupus erythematosus is a multi-system autoimmune disease of still unknown etiology, defined by a wide spectrum of organ involvement occurring on a background of fatigue, fever, joint pain and weight changes, and a chronic evolution with exacerbations alternating with quiescent disease [1, 4, 6, 8]. It develops predominantly in women of their reproductive age, making pregnancy a major concern in routine practice; lupus women have higher risk for infertility, miscarriages, and other pregnancy complications due to disease activity, renal involvement, medications (e.g. cyclophosphamide), and presence of certain autoantibodies (anti- Ro/SSA, anti-La/SSB, antiphospholipid antibodies) [4, 10, 12].

The outcomes of lupus pregnancies have dramatically improved over the last decade thanks to advance understanding of disease and its effects in the body, pregnancy planning, multidisciplinary management and close monitoring [1–6]. However, there are clear differences between pregnancy in general population and lupus pregnancy. While a healthy pregnancy is widely defined by specific immunological and hormonal changes, underlying lupus pregnancy is characterized by higher serum pro-inflammatory cytokines, lesser Th2 polarization, lower estrogen and progesterone levels, lower number of T-Reg defective cells, blockade of complement inhibitors by anti-phospholipid antibodies (aPL), increased placental complement component deposition, aberrant activation and, finally, local inflammation. In another words, we talk about an altered physiological response, leading to significant pregnancy morbidity in lupus patients [1–4, 10].

Furthermore, the physiological modulation of the immune system by pregnancy and related hormonal changes may interact with disease activity in autoimmune rheumatic disorders and drive complications (e.g. disease flares); on the other hand, lupus may have a significant impact on pregnancy outcomes [1, 2, 4, 10]. Disease activity, severity of organ damage, antibody profile and drug treatment may promote maternal (e.g. preeclampsia) and fetal complications (pregnancy loss, intra-uterine growth retardation, preterm birth, even neonatal lupus) [1, 4, 9, 10].

Pregnancy in lupus is still considered at increased risk for adverse pregnancy outcomes (APOs) [1–10]. Pregnant SLE-women can develop in 19–57% cases severe obstetric complications including spontaneous abortion (SA), preeclampsia (PE), intrauterine growth restriction (IUGR), small for gestational age (SGA), preterm birth, fetal death in utero and neonatal death. APOs particularly develop if significantly longer disease duration and higher disease activity 6 preconceptual months, during pregnancy and 6 months postpartum period [1, 4, 9, 10, 12, 13]; furthermore, active SLE at the time of conception is a strong predictor of APOs and current recommendations consider disease quiescence for 6 months prior to conception [1, 4, 10, 12, 13].

A detailed look to one of the most important multiethnic cohort of lupus patients in the PROMISSE (*Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus*) prospective study revealed APOs in 19% of pregnancies, with fetal and neonatal death in 4% and 1%, respectively, preterm delivery in 9%, and small-for-gestational-age neonate in 10% suggesting how important is to accurately identify, counsel, and manage lupus patients in order to optimize their pregnancy outcomes [1, 14–17].

3. Biomarkers in lupus pregnancy

A *biomarker* is an indicator of normal biological processes, pathogenic processes or responses to an intervention [16]. Besides their triple diagnostic, prognostic and therapeutic value, biomarkers have major implications in personalized medicine [1, 2, 4, 16].

Specific biomarkers and novel serum or urine biomarkers may represent the best choice to classify stage and treat patients with SLE; an extended list includes complement level, specific antibodies level, CXCL10, Galectin 9, SIGLEC-1, IL-1 family, BAFF family, lymphocyte populations as serum biomarkers, as well as urine biomarkers [16].

In an attempt to identify biomarkers in lupus pregnancy, pivotal studies suggested that active disease, prior nephritis, use of antihypertensive medications, antiphospholipid antibodies (aPL), hypocomplementemia and anti-double stranded DNA (anti-dsDNA) antibodies are highly associated with APOs [1, 4, 9, 10].

We will further focus on different APOs in lupus, emphasizing the role of biomarkers in stratifying risks and, eventually, driving a more personalized approach in lupus pregnancy.

3.1 Impact of pregnancy on SLE

3.1.1 Lupus flares associated with pregnancy

It is well known that 40 to 60% of women with SLE will experience a flare during pregnancy or the first post-partum year; moreover, disease can exacerbate

at any time during pregnancy and postpartum period, without any clear pattern [1, 2, 4–6, 8]. Commonly utilized instruments to asses disease activity in non-pregnant lupus patients have been specifically adapted and validated for the use in pregnant women [5, 6, 8, 18–20]; *SLE Disease Activity Index in Pregnancy* (SLEPDAI), *modified-SLE Activity Measure for Pregnancy* (m-SLAM) and *Lupus Activity Index in Pregnancy* (LAI-P) and are able to detect changes in disease activity in pregnancy, to monitor and to diagnose flares of maternal disease during gravidity, without mistaking signs and symptoms physiologically associated with pregnancy [1, 4, 5, 8, 18, 21].

According to their severity, lupus flares may be classified as *mild flares* (involving skin and joints), with no major impact on pregnancy outcomes, and *severe flares* (in which kidney features, significant hematologic, serositis and severe arthritis may develop) with poor pregnancy outcomes [1, 2, 5, 6, 8].

Most of lupus exacerbations during pregnancy and postpartum period had mucocutaneous, renal and hematological involvement; additionally, postpartum 6-month period appears to have the highest risk for disease exacerbation and up to 50% of flares in postpartum are severe according to a recent analysis [1, 4–8, 10, 13].

SLE flares critically depend on disease activity 6 to 12 months prior to the conception suggesting that pregnancy outcomes are optimal when disease is in complete clinical remission for 6–12 months before conception; besides, there is a 2 to 4 times risk of flare if active lupus before pregnancy, and a SLEDAI≥4 points 6 months before pregnancy and lupus nephritis are main predictors of adverse maternal outcomes [1, 4–8].

Several factors should be considered for risk stratification in SLE women in preconception [1, 4–10] (**Table 1**).

Biomarkers predicting lupus flare in pregnancy may be classified in three main categories, as follows [1, 4–8, 10]:

- *predictors of poor pregnancy outcomes,* including active maternal disease, any prior or current renal involvement, specific autoantibody subsets and advanced organ damage;

- *predictors for SLE flares during pregnancy,* such as increased SLE activity in the 3 to 6 months before conception, discontinuation of specific medication (hydroxychloroquine) during pregnancy, history of frequent and significant flares, low C4 levels at preconception visit; and

- *predictors of renal flare during pregnancy,* including serum creatinine>1.2 mg/dL, proteinuria>500 mg/24 hours at the time of conception and low C4 serum levels, but not low C3 or dsDNA levels.

Although it is widely recognized that low C3 and C4 levels are associated with active SLE, it seems that low complement occurring during SLE pregnancy may predict APOs [1, 4, 6–8, 22]. Recent data confirm that low C4 at preconception predict flares during pregnancy and suggest that complement evaluation during pregnancy is suitable to detect the high-risk patients that require a more vigilant SLE monitoring and management [23]. Surprisingly, the same study failed to demonstrate any statistical correlation between lupus flare and anti-dsDNA positivity, disease activity (SLEDAI at preconception visit and SLEPDAI during pregnancy), antiphospholipid antibodies positivity as well as clinical SLE manifestations [1, 4–8, 18, 24].

SLE specific risk factors	General risk factors
• active SLE	• maternal age,
• serological activity	• arterial hypertension
• lupus nephritis	• diabetes mellitus
• anti-Ro/SSA and anti-La/SSB antibodies	• overweight/obesity
• anti-phospholipid antibodies	• smoking
• antiphospholipid syndrome	• alcohol use
• organ damage	• thyroid disease

Table 1.
Risk stratification of SLE in preconception period.

	Lupus flare/ activity	Normal pregnancy that can mimic a lupus flare
Clinical	Active malar rash	Palmar and facial erythema
	Oral/nasal ulcers	Arthralgia/ joint effusion
	Inflammatory arthritis	Fatigue
	Lymphadenopathy	Hair loss
	Fever >38 without infection	Mild edema
	Serositis	Mild dyspnea
Labs	Increased ESR	Increased ESR
	Anemia (<10.5 g/dl)	Anemia due to hemodilution
	Thrombocytopenia, leukopenia, lymphopenia	Mild thrombocytopenia
	≥ 25% complement drop	Increase in complement
	dsDNA rising	dsDNA stable
	Hematuria or cellular casts	Rare hematuria
	Proteinuria ≥300 mg/dL	Proteinuria <300 mg/dL

ESR, Erythrocyte sedimentation rate; dsDNA, double stranded DNA.

Table 2.
Differences between lupus flare and physiological pregnancy changes.

On the other hand, many authors reported that disease activity during pregnancy increases the risk of APO, while patients with sustained low lupus disease activity scores have significantly lower APO rates [8, 13, 18].

Recognizing a lupus flare can be difficult given that normal changes related to pregnancy can mimic lupus activity [1, 4, 10]. Main clinical and lab assessment in lupus flare and normal pregnancy are summarized in table above (**Table 2**).

Serological biomarkers are suitable for monitoring lupus activity, but serological activity that develops during pregnancy, especially in the context of clinical activity, may be associated with increased risk for pregnancy loss, intrauterine growth restriction and preterm birth [1, 4–10].

Finally, the so-called *'critical' clinical and serological lupus phenotypes* define patients at increased risk for pregnancy complications; such phenotypes require a special monitoring during pregnancy and encompass for past or present history of lupus nephritis, anti-Ro/SSA and/or La/SSB positivity and aPL positivity or SLE associated with APS [1, 4–10].

3.1.2 Lupus nephritis and pregnancy

It is basically recognized that renal activity may be associated with APOs, requiring a strict follow-up based on urine protein excretion, urine sediment analysis (haematuria, urinary casts) as well as serum creatinine level and glomerular

filtration rate [1, 2, 4–9]. Moreover, urinary levels of CXCL10, and CXCL16 are highly increased in lupus nephritis, TCD4 cells may be an indicator of all treatment response and CCL2 sensitive indicator of renal flare [16].

Recommendations for the approach of pregnancy in the context of lupus nephritis have been released by *European League Against Rheumatism* (EULAR) in 2017. Severe renal flares during pregnancy not responding to drugs with an acceptable safety profile (azathioprine, antimalarials) warrant for a complex, multidisciplinary management, with potential early termination of pregnancy and/or use of embryotoxic drugs if required. [4, 6–8, 25–28].

Several practical points should be emphasized as follows:

- high SLE activity has critical, unfavorable effect on pregnancy;
- a high activity score SLEDAI≥4 out of 105 in the 6 months before conception raises the flare rate;
- renal flares usually occur if pre-existing renal involvement, particularly if remission was not achieved before pregnancy;
- the timing of flare is unpredictable, regular monitoring being indicated during pregnancy and postpartum;
- antimalarials should not be discontinued during pregnancy even in lupus remission [1, 4, 6, 8, 10].

3.2 Impact of SLE on pregnancy

3.2.1 Pre-eclampsia (PE)

Considered as a syndrome unique to pregnancy, preeclampsia remains a significant maternal complication in lupus pregnancy [1, 4–10] and a challenge in clinical practice. Key parameters that allow us to distinguish between PE and SLE activity are listed below (**Table 3**) [1, 4–8, 10, 22, 29]. Interestingly, serologic biomarkers can also distinguish between SLE flare (decreased serum C3 and C4 levels associated with increased anti-dsDNA concentrations) and pre-eclampsia. [4, 7, 8, 22, 24].

Mild PE refers to the new onset of hypertension (≥140/90 mmHg) associated with proteinuria (≥300 mg/24 h urine specimen) after 20 weeks of gestation in a previously normotensive women, while *severe PE* account for new onset proteinuric hypertension and at least one of the following: thrombocytopenia (less than 100.000 platelets/mm^3), symptoms of central nervous system dysfunction, proteinuria ≥5 g/24 h and oliguria, liver involvement (serum transaminase at least twice normal), severe blood pressure elevation (≥160/110 mmHg). It is undoubtedly associated with high risk for stroke, preterm birth, death and eclampsia [1, 4, 10].

Furthermore, preeclampsia should also be differentiated by active lupus nephritis and there are several clinical and lab parameters that help to correctly assess the patient and recognize the renal involvement or pregnancy complication (**Table 4**) [1, 4, 10].

Finally, biomarkers predicting preeclampsia in lupus are already documented, as follows [4, 8, 22, 29, 30]:

- *SLE-specific factors* - active lupus nephritis (especially class III or IV), renal failure at the time of conception, sustained use of prednisone (≥ 20 mg/day during pregnancy), thrombocytopenia, active SLE at conception, low C4, anti-RNP positivity, presence of aPL antibodies; and

- *Maternal factors* - age ≥ 40 years, previous personal or family history of preeclampsia, pre-existing hypertension or diabetes, multiple pregnancies, obesity, low pro-angiogenic factors (VEGF, PIGF1), high anti-angiogenic factors (sFlt-1, soluble endoglin), increased vascular resistance in uterine artery with deficient spiral artery remodeling.

The use of vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and FMS–like tyrosine kinase-1(sFlt-1) are useful for the differential diagnosis between nephritis and preeclampsia [1, 4, 10].

Asymptomatic aPL-positive patients (without any pregnancy complications or history of thrombosis) are not generally treated with prophylactic therapy to prevent pregnancy loss. However, presence of aPL regardless of clinical history is considered a risk factor for development of preeclampsia [4, 5, 8, 10, 22, 29].

Although the outcomes of lupus pregnancy have dramatically improved, *pregnancy loss, preterm birth, low birth weight and cesarean section* are still reported in such patient population [1, 4, 9, 10].

3.2.2 Pregnancy loss (PL)

Pregnancy loss has decreased from 45% in the '60s to a 20–33% nowadays, but we can still talk about fewer than expected children in SLE due to recurrent miscarriage, fetal loss, stillbirth and increased perinatal death [1, 4, 10].

Main causes for pregnancy loss are increased complement activation and placental inflammation (C5a), secondary antiphospholipid syndrome (APS) with specific aPL antibodies, complete atrio-ventricular block (CHB) secondary to anti-Ro/SSA and La/SSB antibodies (diagnosis before gestational week 20 increases four times the intrauterine mortality rate), ventricular rate 50–59 bpm (with a five times higher mortality rate if under 50 pm) [1, 4, 10].

	Preeclampsia	**SLE activity**
Risk factors		
1st pregnancy	Increased risk	No impact
Preeclampsia in prior pregnancy	Increased risk	No impact
Multifetal pregnancy	Increased risk	Unknown impact
History of LN	Increased risk	Increased risk
Timing in pregnancy	Always >20 weeks, usually >30 weeks	Any time in pregnancy
Laboratory findings		
Active urine sediment	Usually, negative	Positive
Coombs test	Usually, negative	May be positive
Anti-platelet antibody	Usually, negative	May be positive
C3 and C4	Usually, normal	Decreased
Anti-dsDNA ab	Normal or stable	High
Serum uric acid	>5.5 mg/dL	No change
Urine calcium	Low	Normal
Proteinuria	High, even>5 g/24 h	Present ++
Serum creatinine	High	Normal or high
Physical findings		
Dermatologic disease*	Not present	Present
Arthritis	Not present	Present
Serositis	Not present	Present
Blood pressure	High ≥160/110 mmHg	Normal or high

**Vasculitis, Discoid rash, Mouth ulcers, Alopecia.*

Table 3.
Differences between preeclampsia and SLE activity.

Clinical & labs	Active lupus nephritis	Preeclampsia
Hypertension	Onset before 20 weeks	Onset after 20 weeks
24 h Proteinuria	Usually high (≥ 300 mg/day)	Usually high (≥ 300 mg/day)
Urinary sediment	Active	Inactive
Uric acid	Usually≤5.5 mg/dL, but may be increased	Usually hyperuricemia (> 5.5 mg/dL)
DNA antibody level	Usually positive or rising	Stable or negative
24 h urine calcium	≥ 195 mg/day	< 195 mg/day
Complement levels	Usually low or decreasing (≥ 25% drop)	Usually high or stable (normal)
Clinical lupus symptoms (arthritis, rash, fever)	Often present	Usually absent

Table 4.
Differentiation of active lupus nephritis from preeclampsia (adapted [10]).

Four main types of pregnancy loss predictors have been so far identified, as follows:

- *disease activity,* meaning active SLE 6 months prior to conception and active SLE during pregnancy;

- *secondary APS,* with either single, dual or multiple positivity for aPL; triple positivity is not better than lupus anticoagulant alone in predicting adverse pregnancy outcomes;

- *organ involvement - nephritis,* comprising preexisting lupus nephritis and first trimester proteinuria (active lupus nephritis particularly class III and IV), thrombocytopenia, chronic hypertension and prior pregnancy loss; and

- *lupus serology* with low C3 and C4 serum levels and anti-dsDNA antibodies [1, 2, 4–6, 10].

3.2.3 Preterm birth (PTB)

Preterm birth meaning pregnancy termination under 37 weeks of gestation is still reported in up to 40% of lupus pregnancies; even women with quiescent lupus prior to and during pregnancy have a higher rate of preterm delivery, with delayed development and lung immaturity, poor long-term outcomes and prolonged hospitalization (if PTB under 30 weeks) as main consequences [1, 2, 4–6, 9, 10].

Spontaneous or lupus-related PTB reflects hormonal dysfunction as well as clinical and subclinical inflammation: activation of maternal or fetal hypo-thalamus pituitary axis with cortisol and prostaglandin production, poor placental development with lower estradiol levels, inflammation with CK, prostaglandin and complement activation.

Conversely *induced PTB* mirrors high rates medical complications in women with lupus and may be related to disease activity, prior and current lupus nephritis, renal failure, maternal hypertension, lupus anticoagulant and corticosteroids use [1, 4, 6, 9, 10].

Several predictors of preterm birth in lupus pregnancy have already been reported, including:

- *predictors for spontaneous PTB,* such as low estradiol at mid-gestation (marker of poor placenta function), high ferritin at mid gestation (marker of inflammation), high uric acid at mid gestation (marker of poor kidney function), oral prednisone, elevated anti-dsDNA, low complement; and

- *predictors for induced PTB*, such as lupus activity during pregnancy, prior lupus nephritis, active lupus nephritis during the first trimester, renal insufficiency, lupus anticoagulant, hypertension, as well as glucocorticoids [1, 4, 10].

3.2.4 Intrauterine growth restriction (IUGR)

Defined as a condition in which the fetus is smaller than expected for the number of weeks of pregnancy, the three different types of IUGR (*type I symmetric or primary,* 20–25% of cases*; type II asymmetric or secondary; type III or intermediate IUGR*) may depend on poor placentation and endothelial dysfunction, persistent inflammation (clinical, subclinical), high autoantibodies levels and medication (excess glucocorticoids have impact on placenta vascular resistance and fetal growth).

IUGR is significantly increased in SLE pregnancy (about 30%) and is typically associated with increased risk of perinatal morbidity and mortality as well as short and long-term neurological complications [1, 2, 4, 9, 10].

Predictors of IUGR include changes in cerebral brain blood perfusion (Doppler), increase in circulating mitochondrial DNA content, maternal hypertension, APS and active lupus [1, 2, 4, 10].

Interesting data are reported during the PROMISSE study - *Predictors of Pregnancy Outcome: Bio-Markers In antiphospholipid antibody Syndrome and Systemic Lupus Erythematosus*: up to 80% of lupus patients had a favorable pregnancy outcome. *Poor outcome predictors* recognized in PROMISE study are increase in lupus activity during pregnancy (SLEPDAI) ≥4 at baseline increase over baseline in SLEPDAI ≥3 at 20 or 32 weeks, high titer of aPL and high median uric acid levels at baseline, high prolactin levels related to disease activity and poor fetal outcome; SLE patients without anti-PRL antibodies had a significantly higher frequency of maternal and fetal complications, as premature deliveries or IUGR [1, 4, 5, 14–18].

3.2.5 Neonatal lupus (NLE)

Considered as fetal manifestation of passively acquired autoimmunity, neonatal lupus is caused by or associated with maternal anti-Ro/SSA (52 or 60KDa) and/or, rarely, anti-La/SSB (48KDa) positivity; around 10% cases present with skin rash, 20% with transient cytopenia, and up to one third with mild transient high levels of transaminases; all of these complications are usually short-lived and spontaneously resolves as the child's maternal antibodies disappear [1, 2, 4, 10]. More severe is the complete (third-degree) heart block (CBH) that occurs rarely, in about 2% of pregnancies of women with anti-Ro/La positivity who had never a prior infant with NLE; however, the rate increases up to 18% if a history of prior infant who had either cutaneous or cardiac NLE [1, 2, 4, 10].

The impact of autoantibodies on fetal health was analyzed in different cohorts, suggesting their role as predictors for NLE and CBH [1, 2, 4, 10]. High titers of antibodies carry on a specific risk for CBH. Regarded as a major and irreversible complication, CBH may associate with fatal outcome in one out of five cases (*in utero* or death first year of life), while more than half require a pacemaker [1, 4, 10].

Absolute contraindications	Relative contraindications
Severe organ damage • severe pulmonary hypertension (systolic PAP > 50 mmHg or symptomatic) • severe restrictive lung disease (forced vital capacity FVC < 1 L) • advanced heart failure • previous severe preeclampsia • HELLP syndrome despite therapy • advanced renal failure (creatinine>2.8 mg/dL)	• severe lupus flare within the past 6 months • active lupus nephritis within the past 6 months • stroke within the previous 6 months • teratogenic drugs 6 months prior to the current pregnancy

Table 5.
Contraindication for pregnancy in SLE.

3.3 Contraindications for pregnancy in SLE

Absolute pregnancy and relative contraindications in SLE are listed above (**Table 5**) [1, 4, 9, 10].

3.4 Predicting outcomes in lupus pregnancy

Since SLE is highly associated with poor obstetric outcomes, predicting the risks is critical for optimizing pregnancy success [4, 10]. The risk of undesirable fetal outcomes estimation in the early first trimester of pregnancy by rheumatologists may guarantee a desirable pregnancy outcome [4, 10, 31].

An clinical decision support system has already been developed in SLE pregnant women based on the artificial neural network (multi-layer perceptron machine-learning algorithm, MPL) by Khadijeh and colab. (2017) helping physician to predict the pregnancy outcomes in women with SLE based on 16 different features (https://pubmed.ncbi.nlm.nih.gov/27919382/) [31].

Cumulative clinical, laboratory and serological parameters have been tested and classified as qualitative and quantitative factors [31].

Distribution of *qualitative features* predicting SLE-pregnancy outcomes and their influence on spontaneous abortion and live births focus on *flare-up* (yes/ no), *anemia and leukopenia before pregnancy* (positive/ negative), *APS* (positive/ negative), *anticardiolipin antibodies IgG in the first trimester of pregnancy* (positive/ negative), *anti-dsDNA in the first trimester of pregnancy* (positive/ negative), C-*reactive protein before pregnancy* (positive/ negative), *azathioprine before or in the first trimester* (use/ non-use) *and aspirin in the first trimester of pregnancy* (use/non-use) [31].

On the other hand, *quantitative features* predicting pregnancy outcome in SLE include *platelets count before and during pregnancy, hematuria during pregnancy, proteinuria before and during pregnancy, C3 complement level before and during pregnancy, and hydroxychloroquine dose before pregnancy* [31].

The use of the above-mentioned factors can help the rheumatologist to predict spontaneous abortion or live birth, allowing the optimal anti-rheumatic treatment [31].

4. Guidelines for the management of pregnant lupus women

Guidelines recommend addressing family planning in women with chronic rheumatic diseases focusing on medication, disease control and reproductive health outcomes [1–8].

The preconception counseling should address several aspects regarding fertility and pregnancy issue in women with SLE especially the impact of pregnancy on disease outcomes and vice-versa the impact of disease and SLE-related medication on maternal and fetal outcomes, factor that can influence the pregnancy course (e.g., maternal age, medication, previous pregnancies) and, finally, the attitude face to an unplanned pregnancy (**Table 6**).

Pregnancy may be responsible for exacerbation of SLE clinical activity and, in turn, active disease may challenge pregnancy course [4]. Since the outcomes of SLE pregnancies and the complication rates are linked to diseases activity, achievement of remission or stable disease is recommended before pregnancy to reduce maternal-fetal problems [1, 4, 10].

Adequate **preconception assessment** should be advanced including a complete obstetric-gynecological history, comorbidities, contraindications and risks of pregnancies based on individual evaluation of clinical SLE activity at the time of conception, antibody panel and medication (**Table 7**).

Apart from this plan before pregnancy, another check list including **risk factors for maternal and fetal complications in SLE pregnancy** should be included in patient's file and updated during pregnancy according to individual data (**Table 8**).

Women with SLE require additional care and will qualify as high-risk pregnancies; they should be informed about specific risks such as IUGR, pregnancy loss, preterm birth and neonatal lupus [4, 10]. High risk lupus pregnancy factors comprise active lupus, medication that can cause birth defects and untreated antiphospholipid syndrome.

Gestational planning and the follow-up should be performed by a multidisciplinary team including at least an experienced in high-risk pregnancy obstetrician and treating rheumatologist with broad experience in planning and control pregnancy in SLE; accurate obstetric visits as well as strict control of the underlying lupus are essential, but the schedule of follow-ups will depend on both obstetric evaluation and disease activity [1, 4–6, 10].

Thus, we can identify at least three situations [4]:

- *pregnant SLE in remission or low disease activity*, *with a clinically stable disease;* in such patients, follow-up visits will be planned every 4 to 6 weeks during the first two trimesters and on a basis of 2 weeks between 32 weeks of gestation to the end of pregnancy;

- *pregnant SLE women with SLE exacerbation and/or developing obstetric complications*; follow-ups will be scheduled every 4 weeks by the obstetrician and every 4 to 6 weeks by the rheumatologist until the 20th week of gestation, every 2 weeks between 21st and 28th week, and weekly until the end of pregnancy;

- *pregnant SLE with anti-Ro/La positivity* will undergo weekly fetal echocardiography (PR interval, fetal heart rate) between 16th and 26th week of gestation.

Check-ups visits include preplanned evaluation tests [4]:

- *at each visit* - monitoring blood pressure, body weight and basic physical examination, urinalysis as well as complement and anti-dsDNA antibodies;

- *at 8–12 weeks*: complete blood count, erythrocyte sedimentation rate, C reactive protein, routine glucose, renal and liver function; in the case of a SLE flare, blood samples should be performed more frequently;

Preconception issue
Impact of SLE on fertility **Impact of SLE on pregnancy** **Impact of pregnancy on SLE** **Planning the pregnancy:** disease activity prior conception, drug modification prior to conception, calendar for visits, pre-pregnancy tests **Measures required during pregnancy and breastfeeding** **Risks in newborn**: risks to develop maternal disease, sequelae related to medication used during pregnancy, special care **Unforeseen management of pregnancy**

Table 6.
Preconception counseling in SLE women (adapted [4]).

Preconception steps
1. Make a complete obstetric-gynecological history • Fertility issues • Data about previous pregnancies: parity, term delivery, type of delivery (vaginal/ caesarian section), abortions, fetal loss • Complications: preeclampsia, HELLP, hypertension, thrombosis • IUGR, low birth weight 2. Make a list of relevant comorbidities • Hypertension, diabetes 3. Assess SLE activity, organ damage, history of flares • Activity scores (SLEDAI, SLAM, LAI), damage scores (SLICC/ ACR) • Last flare (time, duration, medication) • Remission/ sustained remission; low disease activity/ high disease activity; stable disease 4. Evaluate treatment plan and reevaluate therapeutic options • Glucocorticoids, antimalarials, immunosuppressives, biological agents during the last 6–12 months • Contraindicated drugs in pregnancy and time to last administration • Adapt medication according to disease activity 5. Identify contraindications for pregnancy (absolute and relative contraindications that require postponed pregnancy) 6. Estimate maternal and fetal risk during pregnancy • Complication in previous pregnancies • Age, disease activity, medication, serology 7. Basic lab tests • Standard analysis • SLE-related: complement, ANA, anti-dsDNA, aPL (lupus anticoagulant, anti-β2 glycoprotein, anticardiolipin), anti-Ro/ La
Conclude on risks, complications, follow-up
• Disease activity • Medication • Risk factor for adverse pregnancy outcomes • Plan of action if maternal or fetal complications

Table 7.
Algorithm for pregnancy planning in SLE women (adapted [4]).

Risk factors
1. Previous adverse obstetric outcomes
• Preeclampsia/ severe preeclampsia
• HELLP syndrome
2. Previous thrombotic events
• Thrombosis 6 months prior to pregnancy
3. Chronic kidney disease
• Creatinine >2.8 mg/dL
4. Risk factors for preeclampsia
• Age > 40
• Family or personal history of preeclampsia
• Multiple pregnancies
• Nulliparity
• Diabetes
• Obesity or hypertension before pregnancy
• Active SLE
• History of lupus nephritis class III or IV
• aPL positivity
5. SLE
• high risk for flare
• history of abortion, neonatal deaths, premature delivery, low birth weights infants
• avoid pregnancy in severe pulmonary hypertension, interstitial lung disease, heart failure, stroke
• avoid pregnancy if severe flare the last 6 months
6. Evidence of APS
• history of abortion, neonatal deaths, premature delivery, low birth weights infants
• avoid pregnancy in severe pulmonary hypertension or thrombosis within the last 6 months

Table 8.
Check list: risk factors for maternal and fetal complication in SLE pregnancy (adapted [4]).

Disease activity should be assessed using indexes adapted for the use during pregnancy (e.g. SLEPDAI), as gravidity may influence certain variables used in the evaluation of activity scores.

Two main recommendations are on the so-called "To do list" for pregnant SLE-women [1–4]:

- see your rheumatologist at least once every trimester;

- see your obstetrician and perinatologist regularly, frequently and tell them about anything new or abnormal in your health.

All the above-mentioned specialists play specific roles in managing the disease and may result in decreased hospital stay and/or serious morbidity and mortality. This can be also largely attributed to the excellent work of midwifes and inter-disciplinary approach on Public Health. Doctors and midwifes collaborate with researches in creating a research group of professionals in order to monitor and evaluate the safety of women giving birth [1–3].

These demonstrated that midwifes support is indispensable for the wellbeing of childbearing women and their infants before and after delivery.

4.1 ACR recommendations for reproductive health-care in SLE

In 2020, *American College of Rheumatology* (ACR) releases an updated guideline with recommendations for reproductive health-care in rheumatic diseases, particularly SLE with and without anti-Ro/La and aPL antibodies [6].

Hereby we summarized the most important statements regarding pregnancy counseling, assessment and monitoring to improve maternal and fetal outcomes in SLE women (**Figure 1**) [6]**:**

- ACR strongly suggests as standard good practice counseling SLE women who are considering pregnancy and proposing pregnancy in quiescent/low disease activity. Besides, ACR advise maintaining parallel care with specialists in obstetrics-gynecology, maternal-fetal medicine, neonatology [6];

- if lupus woman wishing to conceive is currently on drugs incompatible with pregnancy, ACR strongly recommend switching to a pregnancy-compatible one and observing for sufficient time to assess efficacy and tolerability of the new medication [6];

- moreover, if active lupus that requires medication during pregnancy, ACR strongly recommend initiating or continuing a pregnancy-compatible steroid-sparing medication, as both active disease and continuous high-dose glucocorticoid treatment may account for maternal and fetal harm [6, 31];

- all SLE-women require antimalarials - hydroxychloroquine (HCQ) during pregnancy if possible; if a patient is already taking HCQ, ACR strongly recommend continuing it during pregnancy, but in cases not on HCQ, it is conditionally recommended if no contraindication [6, 31];

- *monitoring SLE activity* with clinical history, examination, and laboratory tests *at least once per trimester* is strongly indicated because active disease may affect both maternal and pregnancy outcomes; thus, although testing for anti-Ro/La once before or early in pregnancy is strongly recommended, given the relative

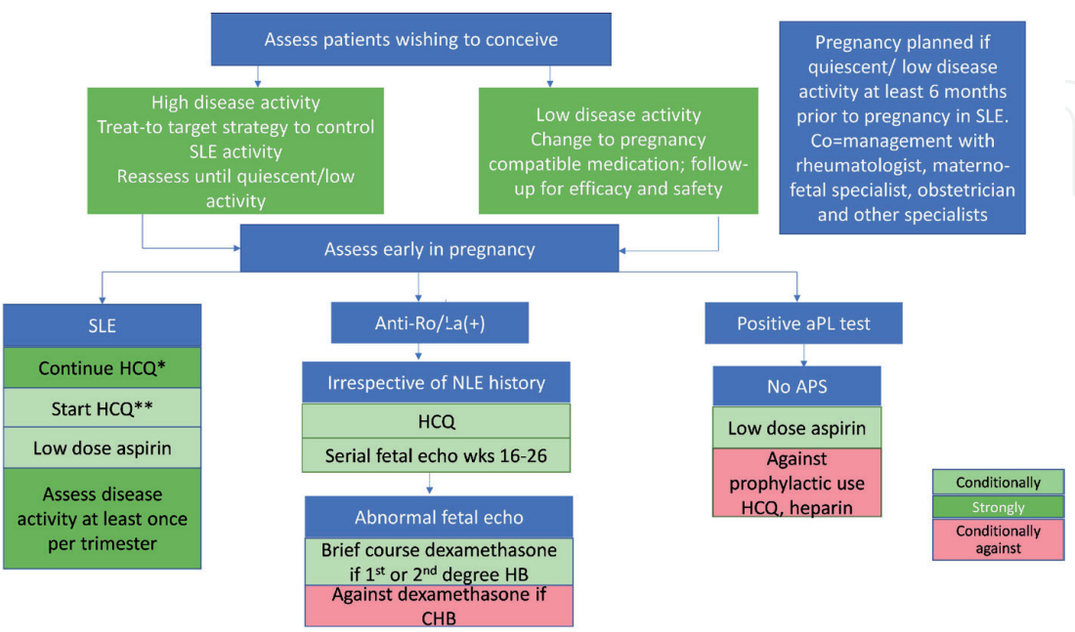

Figure 1.
*Pregnancy counseling, assessment and management in woman with SLE (ACR2020 adapted) [6]. *If on; **if not a contraindication; NLE, neonatal lupus; HB, heart block; CBH, complete heart block.*

persistence of unchanged titers of these antibodies, ACR strongly recommend *against* repeating the test during pregnancy. Besides, it is also strongly recommend testing for aPL before or early in pregnancy, while repeating these tests during pregnancy is not necessary [6];

- in pregnant anti-Ro/LA patient with no history of infants with NLE or CBH, ACR conditionally recommend serial fetal echocardiography (eventually less frequent than weekly, but no interval specified) between 16 to 26 weeks; if a prior infant with NLE or CHB, ACR conditionally recommends strict follow-up using fetal echocardiography weekly, between 16 to 26 weeks [6];

- moreover, all women who are positive for anti-Ro/SSA and/or anti-La/SSB positivity conditionally require with HCQ during pregnancy as there is a lower risk of the current fetus developing CHB under HCQ [6, 32];

- low-dose aspirin (81 or 100, but not more than 150 mg daily) is conditionally recommended in the first trimester; in addition, in pregnant women with positive aPL who do not meet criteria for obstetric or thrombotic APS, ACR conditionally recommend treating with prophylactic aspirin during pregnancy as preeclampsia prophylaxis, beginning early in pregnancy (before 16 weeks) and continuing through delivery [6, 32];

- for pregnant anti-Ro/SSA and/or anti-La/SSB positive patients and fetal first- or second-degree heart block shown on echocardiography, ACR conditionally recommend treatment with oral dexamethasone 4 mg daily; nevertheless, if CHB (without other cardiac inflammation) develop, ACR is conditionally *against* dexamethasone [6, 32].

4.2 EULAR 2020 consensus-based core set data for pregnancy in SLE

In an effort to increase knowledge about pregnancy course and safety of treatment in women with immune mediated rheumatic disorders, *European League Against Rheumatology* published in 2020 its first consensus-based core data set for prospective pregnancy registries in rheumatology [5].

The *EULAR Task Force* recommended disease-specific items, autoantibodies/laboratory markers and disease activity measurements relevant for different IMRDs including SLE. aPL antibodies, particularly anti-cardiolipin, and anti-beta-2-glycoprotein-I antibodies as well as lupus anticoagulant; antinuclear and anti-dsDNA

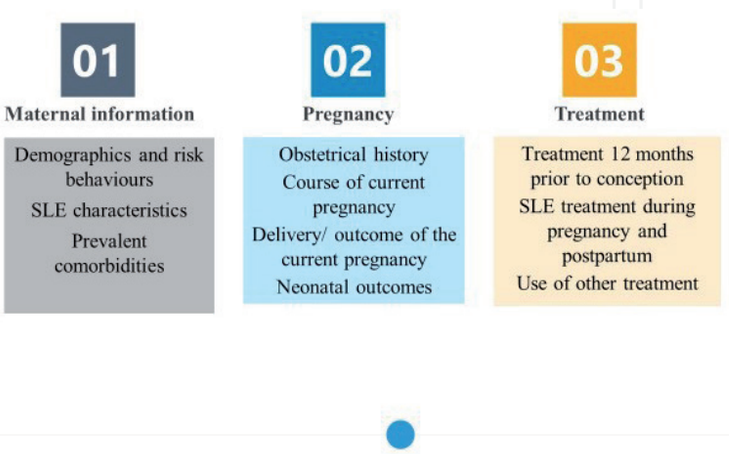

Figure 2.
EULAR core set data for pregnancy in rheumatology (adapted [5]).

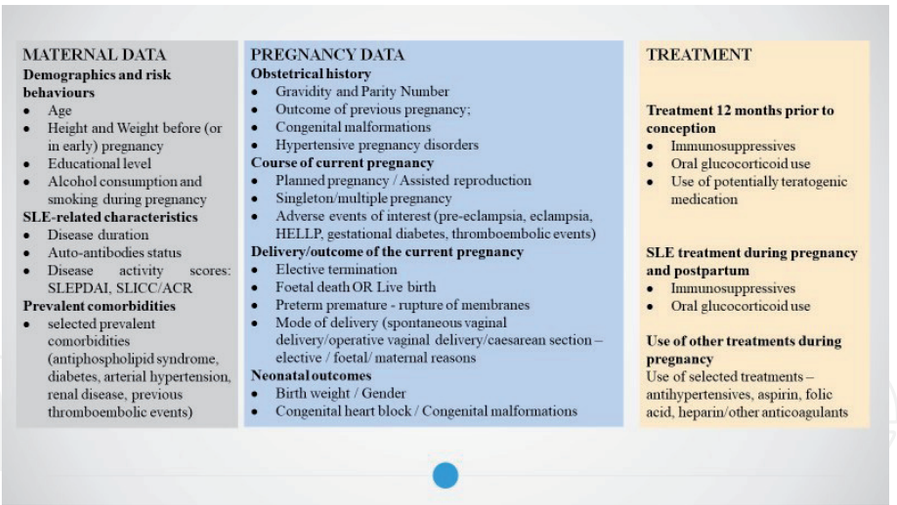

Figure 3.
Proposed core-set data for the midwifery room (adapted from EULAR 2020) [5].

antibodies, extractable nuclear antigen antibodies such as anti-Ro/La, anti-Sm and anti-U1-ribonucleoprotein, but also serum C3 and C4 levels should be collected as recommended by EULAR, while follow-up indexes include SLEPDAI and SLICC/ACR damage index [4, 5, 18].

EULAR endorsed three core set data on clinically relevant parameters - maternal information, pregnancy and treatment [1–3, 5, 21] (**Figure 2**); *maternal information* refers to demographics and risk behaviors, disease characteristics of the underlying SLE and prevalent comorbidities; *pregnancy* data covers obstetrical history, the course, outcomes and delivery of previous and current pregnancy and outcomes of the neonate, while *treatment* domain encompasses for medical treatment within 12 months prior to conception, SLE treatment during pregnancy and postpartum [1–5, 21].

A comprehensive/extensive list of items were considered the most relevant items regarding maternal information and the rheumatic disease as well as pregnancy and neonatal outcomes (**Figure 3**) and should be collected uniformly [1, 3–5, 21].

EULAR endorsed recommendations focused on the time of pregnancy and the 28-day postpartum period (neonatal phase); as the core set represents clinically relevant and feasible parameters, it should be collected once every trimester for the maternal and new-born health evaluation [1, 3, 5, 21].

Besides, as addressing the most important information needed to answer questions about disease activity, medication use and pregnancy outcome, EULAR parameters should be extrapolated, at least in part, for the assessment in daily practice; this will clearly be of help in the midwifery room [1, 3, 5, 21].

5. Conclusion

Reproductive health in SLE remains an important topic as maternal complications and adverse fetal outcomes in lupus still exceed the rate of pregnancy complications in general population. Clinical or subclinical inflammation, autoantibodies, hormonal dysfunction and specific immune alterations of lupus may contribute to pregnancy complications.

Thus, SLE and pregnancy is definitely associated with an increased need for investigations (repeated ultrasound, tests for fetal well-being, predictive biomarkers for pregnancy outcomes) as well as prolonged hospitalization, promoting high prenatal and neonatal burden.

Several biomarkers have been already investigated in early pregnancy and we are now able to predict complications in SLE suggesting that both preconception and follow-up assessments are mandatory to risk-stratify patients and to identity predictors for adverse pregnancy outcomes.

Although pivotal studies have demonstrated a greater rate of caesarian section among lupus pregnancy than in general population, vaginal delivery still remains an option and adequate pelvic assessment should always be performed by midwifes in order to ensure best delivery outcomes.

Moreover, midwifes help our researchers to discover valuable information in an effort of better understand the mechanisms involved in the disease. On the other hand, there is a lack of full understanding of what the researchers in our hospitals are doing, as every researcher and midwife should be allowed to examine patients for any possible medical signs and symptoms and to determine the general status during pregnancy.

This chapter is intended to be a state-of-the-art manuscript focused on improving health-care for pregnant women with SLE.

Conflict of interest

"The authors declare no conflict of interest." or delete this entire section.

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