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Safety issues and recommendations for successful pregnancy outcome in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) primarily affects women of childbearing age. One of the major changes in SLE focuses on the timing of a successful pregnancy. In the past, pregnancy was strongly discouraged in SLE, especially in the presence of risk factors such as nephritis, use of immunosuppressive therapies, or positivity of specific autoantibodies such as anti-phospholipids and anti-Ro/SSA, La/SSBA. Thanks to our better knowledge on the disease and management, pregnancy success rates in SLE patients have significantly improved care by the a multidisciplinary team which fosters a successful pregnancy with minimal complications for the mother and fetus when the disease is inactive or in remission. This approach is based on a counseling phase before pregnancy, to assess SLE activity phase, specific medications, risk factors, and continues through pregnancy and lactation with significantly improved pregnancy outcomes. Further, we can now better define the risk of disease flares during pregnancy based on a better understanding of the changes in maternal immunity and its relationship with SLE-associated autoimmunity and chronic inflammation. There is wide consensus that women with SLE can have successful pregnancies as long as conception is planned in a phase of inactive disease, and when the patient is closely managed by a rheumatologist, high-risk OB/GYN, neonatologist, and other medical specialists as indicated. Preconception counseling is essential to assess the risk of both fetal and maternal complications as well as identify life-threatening contraindications. Particular attention should be used in those SLE cases that have nephritis, APS or positivity for aPL, pulmonary hypertension, and positive anti-Ro/SSA or anti-La/SSB antibodies. In conclusion, the use of specific guidelines on the management of SLE before and during pregnancy and lactation, and a better understanding of the use of immunosuppressive therapies have significantly increased pregnancy success.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease that can manifest a wide clinical spectrum, ranging from mild to life-threatening features, i.e. lupus nephritis and neurological signs [1,2]. As SLE effects predominantly women, and particularly those of child-bearing age, pregnancy and family planning are topics of key interest both in research and in clinical practice. Women with SLE typically have normal fertility but they may have complicated pregnancies and, in the past, pregnancy was discouraged due to risk of flares and poor obstetric and maternal outcomes [3]. However, this has changed due to advances in our knowledge and treatment options [4]. However, disease flares, pre-term birth, pre-eclampsia and pregnancy loss remain well-known risks during pregnancy in women with SLE, and several risk factors for these adverse outcomes during pregnancy have been identified. For this reason, pre-conception counseling, risk stratification, and appropriate surveillance using a multi-disciplinary approach are essential [5,6].

The management of SLE is challenging during pregnancy due to the impact of physiological and immunological changes on the patient and the fetus. Pregnancy-related complications can mimic disease flares making earlier identification more challenging. Complications during pregnancy can be firstly divided into maternal factors, such as lupus flares, worsening of renal function, onset or worsening of arterial hypertension, preeclampsia, and/or venous thromboembolism, and secondarily fetal-neonatal complications, i.e. miscarriage, intrauterine growth retardation, preterm delivery, and/or neonatal lupus syndrome [7], congenital heart block or neonatal cutaneous lupus erythema)

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[8,9]. In this review, we will critically discuss guidelines on counseling, potential maternal and fetal complications, and proper use and safety of rheumatic medications during pregnancy.

2. Physiological and SLE-related changes during pregnancy

A healthy pregnancy induces changes in intravascular volume, thrombotic state, and cell-mediated immunity, and these can be challenging in patients with underlying autoimmune diseases such as SLE, which may exacerbate during pregnancy [9,10]. Differentiating SLE manifestations from these physiologic changes can also be difficult, particularly for symptoms such as fatigue, arthralgia, hair loss, dyspnea, headache, peripheral edema, anemia, and even thrombocytopenia which can be a manifestation during pregnancy and possibly mistaken for manifestations of lupus flare [11]. Increases in weight can also contribute to joint pain [5,8], and an increase of the intravascular volume by 30–50% in normal pregnancy can be troublesome for patients with heart and renal involvement. Pregnancy also causes a prothrombotic state which can increase the risk of thromboembolism by 5-fold and this risk is concerning especially in patients with serum antiphospholipid antibodies (aPL) or with clinical manifestations of antiphospholipid syndrome [12]. The major physiological and SLE-related changes observed during pregnancy are summarized in Table 1.

Laboratory findings in pregnancy can also mimic SLE disease flares, as pregnant women can become anemic during the third trimester due to a hemodilution effect, and inflammatory markers can become elevated due to increased fibrinogen production in the liver; therefore these alterations should be clinically evaluated in assessing SLE disease flares. Similarly, thrombocytopenia is observed in approximately 7–10% of normal, uncomplicated pregnancies [13].

Serum C3 and C4 levels rise in pregnancy due to increased hepatic production, therefore when assessing a lupus flare in a pregnant patient, it is important to compare with baseline values as absolute values may remain within the normal range for pregnant patients with active SLE; for example, a decrease exceeding 25% in serum complement levels during pregnancy can suggest a disease flare [14]. Proteinuria may also increase during pregnancy due to increased renal blood flow without evidence of active lupus nephritis [5,8]. Pre-eclampsia, eclampsia, and the HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome all mimic SLE flares [15], particularly lupus nephritis, and these conditions can be seen more frequently in SLE (13–35%) vs normal pregnancies (5–8%) [16,17]. Both pre-eclampsia and SLE cause increased proteinuria, arterial hypertension, lower extremity edema, thrombocytopenia, and elevated creatinine [12,18], but understanding when SLE is responsible for these alterations is crucial given the different treatments. Clinical features that can help to distinguish preeclampsia, HELLP syndrome, and eclampsia from SLE/lupus nephritis are illustrated in Table 2.

New biomarkers, including angiogenic factors such as placental growth factor, may become important in the challenging situation of identifying superimposed preeclampsia to SLE. A recent study demonstrated that between 20 and 42 weeks of gestation, lower maternal placental growth factor concentrations have high diagnostic accuracy for preeclampsia requiring delivery within 14 days [19].

Table 2
Different features that characterize active lupus nephritis, pre-eclampsia and the HELLP syndrome.

	Active lupus nephritis	Pre-eclampsia	HELLP syndrome
Gestational age	Any gestational age, including post-partum	> 20 weeks	> 34 weeks
Elevated Creatinine	Common	Typically absent	Rare
Thrombocytopenia	Present	Absent	Present
Neutropenia	Present	Absent	Absent
Complement levels	Typically decreased	Normal	Normal
Active urinary sediment	Common	Absent	Absent
Elevated liver enzymes	Absent	Absent	Present
Serum uric acid levels	Normal	Elevated	Present

3. Immunological changes during pregnancy

Immune modulation is necessary to maintain a healthy pregnancy, specifically to prevent the fetus from being rejected by the maternal immune system. Cross-talk between the fetus and the maternal immune system is essential and part of the growth and development of the maternal uterus. The most significant known immunologic changes during pregnancy are a shift towards T helper type 2 (Th2) anti-inflammatory cytokines. The over-expression of Th2 cytokines, in particular IL-10 may play a central role in the pathogenesis of SLE [12,20]. Moreover, estrogens enhance antibody production and B-cell immunity, and at pregnancy-related high concentrations, estrogens stimulate the secretion of interleukin (IL)-4, IL- 10, TGF-β and interferon gamma (IFNγ), while suppressing production of tumor necrosis factor α (TNFα) [21].

In 1993, Wegmann proposed the concept of a successful pregnancy as a Th2 phenomenon suppressing $CD4^+$ Th1 cells [22,23], characterized by the production of IFN γ, IL-12, TNFα and IL-2 and involved in cell mediated immunity. A suppression of the Th1 response has been shown in T cells of uncomplicated human pregnancy whereas reproductive failure demonstrates a Th1 polarization with IFN-γ, and TNF-α expressing T cells [24]. The Th2 subset mainly produces IL-4, IL-10 and IL-13, and enhances humoral immunity [22] with IL-10 down-regulating the production of pro-inflammatory cytokines by Th1 cells and macrophages, and this has been demonstrated also during SLE pregnancy [24]. It has been noted that cytokine production is adjusted at different stages of pregnancy: while Th1 cells producing IFNγ and TNFα are necessary during the early stages of pregnancy for successful implantation and placenta development, these may be detrimental at later stages of pregnancy and result in pregnancy loss [24]. In contrast, the presence of high levels of Th17 cells, a third set of $CD4^+$ T helper cells, are found in preeclampsia and recurrent pregnancy loss [25].

Table 1
Physiological and pathological SLE-related symptoms during pregnancy [27].

Manifestation	Pregnancy Changes	SLE Activity
Mucocutaneous	Facial flush, palmar erythema, postpartum hair loss	Oral or nasal ulcers, photosensitive skin rash
Hematologic	Mild anemia and thrombocytopenia (due increased plasma volume)	Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
Musculoskeletal	Arthralgia and myalgia, loosening of the sacroiliac joint, widening of pubic symphysis and lumbar lordosis	Inflammatory arthritis involving peripheral joints
Renal	Increased GFR and decreased tubular protein resorption, with low level proteinuria (< 200 mg/day in the 2nd and 3rd trimester)	Proteinuria > 300 mg/day, active urinary sediment, associated with increased anti-dsDNA antibody and reduced complement levels
Hepatic	Increased complement, fibrinogen, and inflammatory parameters levels	Decline in complement factors
Cardiopulmonary	Increased blood volume and heart rate, mild resting dyspnea	Serositis (pleuritis, pericarditis)