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Review

# Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation

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ABSTRACT

The crucial issue for a better pregnancy outcome in women with autoimmune rheumatic diseases is appropriate planning, with counseling of the ideal timing and treatment adaptation. Drugs used to treat rheumatic diseases may interfere with fertility or increase the risk of miscarriages and congenital abnormalities. MTX use post-conception is clearly linked to abortions as well as major birth defects, so it should be stopped 3 months before conception. Leflunomide causes abnormalities in animals even in low doses. Although in humans, it does not seem to be as harmful as MTX, when pregnancy is detected in a patient on leflunomide, cholestyramine is given for washout. Sulfasalazine can be used safely and is an option for those patients who were on MTX or leflunomide. Azathioprine is generally the immunosuppressive of choice in many high-risk pregnancy centers because of the safety profile and its steroid-sparing property. Cyclosporine and tacrolimus can also be used as steroid-sparing agents, but experience is smaller. Although prednisone and prednisolone are inactivated in the placenta, we try to limit the dose to the minimal effective one, to prevent side effects. Antimalarials have been broadly studied and are safe during pregnancy and breastfeeding. Among biologic disease modifying anti-rheumatic agents (bDMARD), the anti-TNFs that have been used for longer are the ones with greater experience. The large monoclonal antibodies do not cross the placenta in the first trimester, and after conception, the decision to continue medication should be taken individually. The experience is larger in women with inflammatory bowel diseases, where anti-TNF is generally maintained at least until 30 weeks to reduce fetal exposure. Live vaccines should not be administrated to the infant in the first 6 months of life. Pregnancy data for rituximab, abatacept, anakinra, tocilizumab, ustekinumab, belimumab, and tofacitinib are limited and their use in pregnancy cannot currently be recommended.



**Contents**



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## 1. Introduction

Autoimmune diseases (AID) affect mostly women and many peaks in fertile age. As a rule, fertility is normal or near normal, despite the use of many cytotoxic agents, so that pregnancy becomes relatively common among these patients. In previous decades, gestation was not only discouraged but even prohibited for patients with AID like systemic lupus erythematosus (SLE) as maternal mortality happened to be up to 20-fold higher [1]; however, recent data show a much better prognosis, as well as, for SLE in general.

Pregnancy in patients with AID should always be considered as a high-risk situation that requires a special attention and care, notwithstanding the current good results for most patients. Specific clinical presentations should require more focused attention from the rheumatologist and obstetrician as they increase the rates of fetal and maternal complications. Ideally, all patients should be carefully evaluated before conception not only to confirm disease quiescence but also to identify possible risk factors for maternal and fetal complications. In general, the only absolute contraindication for pregnancy is the presence of pulmonary hypertension, a clinical condition described more frequently in systemic sclerosis but also found among SLE, mixed connective tissue disease, rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome, which carries a risk up to 50% of mortality during gestation [2].

Some clinical phenotypes and status of disease, despite not prohibiting pregnancy, impose further risks for maternal and fetal outcome. This is the case of lupus nephritis (LN) that is associated with a higher frequency of abortions, intrauterine growth restriction (IUGR), prematurity and pre-eclampsia (PE), and reactivation of disease (SLE) [3]. The patients at higher risk are those who present active glomerulonephritis at conception, hypertension, reduced glomerular filtration rate, thrombocytopenia, antiphospholipid syndrome (APS), or the presence of antiphospholipid antibodies (aPL) [4]. Reactivation of SLE can occur in up to 50% of patients [5] and renal flare during pregnancy is more common in those women with a previous diagnosis of LN, contributing for progressive renal dysfunction in up to a quarter of the patients [6].

On the other hand, patients with active RA and those negative for anti-cyclic citrullinated peptide and rheumatoid factor are more likely to improve during pregnancy [7]. In an Italian multi-center study including women with systemic sclerosis, most of patients did not have progression of disease during pregnancy, but preterm delivery and fetal growth restriction were more frequent than general population [8]. Rare diseases, such as vasculitidities, have limited data during pregnancy [7].

Pre-eclampsia (PE), the major complication exclusively related to pregnancy, tends to be more frequent in patients with AID, mainly SLE and APS, and it presents a challenge in clinical practice as many of their manifestations are very similar (edema, proteinuria, hypertension, and renal failure). Careful interpretation of clinical and laboratorial biomarkers of lupus glomerulonephritis (anti-DNA, hypocomplementemia, and dysmorphic hematuria) or PE (serum levels of angiogenic [VEGF, PlGF] and antiangiogenic [sFlt-1] cytokines and changes in Doppler-fluxometry) may allow their differentiation despite the possible superposition of both conditions [9].

### 1.1. Fertility

Reproduction of women with AID has attracted the attention of clinicians and researchers concerned to clarify the factors involved in this process. Women with AID have fewer children than planned when compared with matched controls from the general population. Sub- or infertility is a multifactorial condition that can be related to immunological mechanisms, to pregnancy loss, to increase in disease burden, to therapy, and to choices concerning family size [7]. Psychosocial factors and pain symptoms related to the disease activity may lower fecundity and could be associated with apparent infertility [10]. In a report with structured interviews of 411 married women with RA, almost all women (91.2%) reported at least one pregnancy. Nearly 20% replied that RA influenced childbearing decisions, and especially this was more marked in women diagnosed at a young age [11]. Clowse et al. applied a reproductive history questionnaire to women with RA and SLE. More than 60% of those in the group were no longer interested in having children. Of those interested in having children, 55% with RA and 64% with SLE had fewer children than originally planned. Analyzing the questionnaire, they concluded that while patient choice plays a role, the fewer babies are related to infertility in RA patients and miscarriage in SLE patients [12]. A prospective study conducted in the Netherlands evaluated patients with RA and founded a time to pregnancy (TTP) greater than 12 months in 42% of 245 patients. TTP was longer if patients were older or nulliparous, had higher disease activity, used NSAID or prednisone >7.5 mg daily [13].

Some conditions may contribute to the impairment of fertility [10], like presence of chronic renal failure [14] and use of cyclophosphamide (CYC). The risk of infertility is related to the cumulative dose of the drug and the patient's age [15], with older women having a lower ovarian reserve at higher risk for premature ovarian failure. The anti-Müllerian hormone (AMH), secreted from granulosa cells of growing ovarian follicles, appears to be the best endocrine marker capable of estimating the