Management of Gender-Related Problems in Women with Autoimmune Rheumatic Diseases

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ABSTRACT: Autoimmune rheumatic diseases (ARD) affect mainly young women during their reproductive years. Fertility is usually not diminished but the time it takes to conceive is usually longer. Factors related to an ARD or to its treatment are responsible for this effect. In addition, contraception counseling is required to prevent negative fetal outcome and exacerbation of disease symptoms. In recent years, advances in therapies, clarification of risk factors for adverse pregnancy outcomes, and a multidisciplinary approach have vastly improved obstetric management, increasing the possibility of successful pregnancy with a high likelihood of favorable outcome.

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Autoimmune rheumatic diseases (ARD) affect mainly young women during their reproductive years. Therefore, topics such as sexual functioning, fertility, contraception and pregnancy are of major interest for counseling these patients and for disease management.
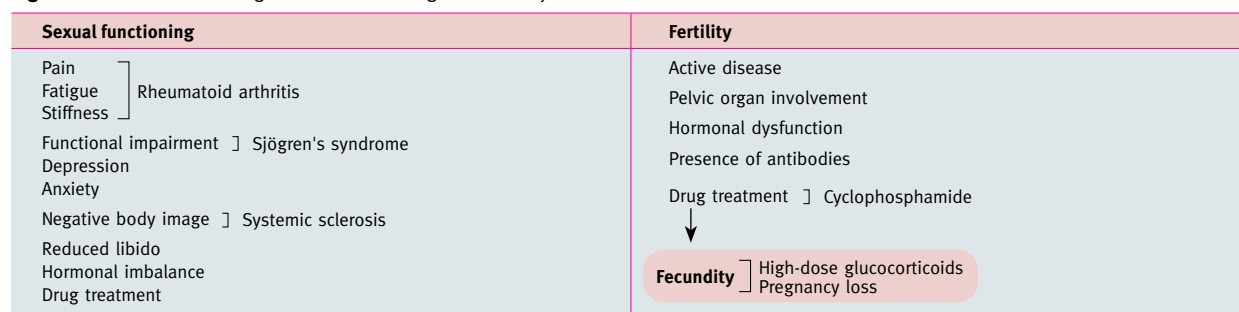
SEXUAL FUNCTIONING

Symptoms and manifestations related to an autoimmune rheumatic disease can impair sexual functioning [1]. Despite its importance as part of health and life quality, this subject is widely neglected in the daily care of patients. Depression, anxiety and low self-esteem related to chronic evolution of ARD contribute to social problems including partnership difficulties. Disease-related disability such as pain and stiffness exacerbate these psychological features [1]. Fatigue and joint symptoms due to active arthritis have been related to sexual difficulties and loss of sexual satisfaction when compared to healthy controls [2]. In women with primary Sjögren´s syndrome, vaginal dryness and other disease-related symptoms increase distress and sexual dysfunction [3]. In fact, patients with systemic lupus erythemathosous (SLE), systemic sclerosis (SS) or rheumatoid arthritis (RA) also show a predisposition to vaginal dryness and dyspareunia [3,4]. Systemic sclerosis-related facial and body changes can predispose patients to low self-esteem behavior. In addition, impaired touch due to Raynaud's phenomena, finger sclerosis and vaginal tightness can have a deleterious effect on foreplay and intercourse [4]. Therefore, different physical and emotional problems were identified as causing loss of sexual interest and diminishing pleasure, with a consequently less active and enjoyable sex life [4] [Figure 1].

FERTILITY

Women with ARD may experience impaired fertility. Amenorrhea due to severe flares, hypofertility related to renal insufficiency, and gonadotoxicity associated with cyclophosphamide or high dose glucocorticoids may be the origin of this condition [5]. Other conditions like luteinized unruptured follicle syndrome after high dose non-steroidal anti-inflammatory drugs

Figure 1. Factors influencing sexual functioning and fertility in women with autoimmune rheumatic disease*

Sexual functioning	Fertility
Pain ⎤ Fatigue ⎬ Rheumatoid arthritis Stiffness ⎦	Active disease
	Pelvic organ involvement
Functional impairment ⎤ Sjögren's syndrome	Hormonal dysfunction
Depression	Presence of antibodies
Anxiety	
Negative body image ⎤ Systemic sclerosis	Drug treatment ⎤ Cyclophosphamide
Reduced libido	↓
Hormonal imbalance	Fecundity ⎤ High-dose glucocorticoids
Drug treatment	⎦ Pregnancy loss

*Modified from Østensen et al. [1]

(NSAIDs) have been described [6]. More often, fecundity (time to achieve pregnancy) is affected. In a population-based study women with rheumatic disease had a lower number of births and fewer women achieved subsequent pregnancy compared to healthy controls. In addition, increased periods of reproduction and inter-pregnancy were also related to rheumatic disease [5,7].

Today, older age at the time of conception is common. Postponing pregnancy is a modern trend and can be associated with disease factors. Decreasing oocyte reserve sustains the inverse relationship between aging and fecundity. A decreased oocyte reserve was also demonstrated in women with ARD in comparison to age-matched controls [8]. Psychosocial factors and their negative impact on childbearing decisions also affect fecundity. Among women with chronic disease the fear of genetic transmission or parenting disability is still common. In summary, immunological mechanisms, pregnancy loss, disease disability, treatment, or the decision to limit family size contribute to impaired fertility/fecundity in women with ARD [7].

CONTRACEPTION

Advice on contraception is fundamental to avoid pregnancy in women taking teratogenic drugs and/or who have active disease. This means that many women will need to use contraception during periods of moderate to highly active disease. Regardless of its importance, contraception counseling is not systematically practiced. Interestingly, even in a group of patients who received detailed information on the treatment, one-third of women taking teratogenic drugs did not practice any birth control [9]. To improve this situation, different options of contraception should be considered for each patient individually.

The assumption of exogenous estrogens as triggers to autoimmune mechanisms contributed for many years to the exclusion of oral contraception in women with ARD. A systematic literature review concluded that hormonal contraceptives were unlikely to adversely impact RA disease activity and progression [10]. RA patients have no disease-related restrictions with regard to contraception but need to be counseled on safe birth control, particularly during treatment with potentially teratogenic drugs. Similar conclusions are applicable to most patients with different chronic arthritis [11]. Specific considerations must be taken into account regarding contraception counseling in women with SLE and antiphospholipid syndrome (APS). Increased number of flares was not found in women with inactive or stable SLE randomized to a low estrogen oral contraceptive [12]. In addition, oral contraceptives are recommended for management of ovarian cysts and endometriosis. Ovarian cysts are often related to SLE. Patients with glucocorticoid-induced osteoporosis may also benefit from their use [13]. However, it is essential to highlight that estrogen contraception in SLE women with active lupus nephritis, high disease activity or antiphospholipid positivity has not been studied. Therefore, avoidance in these groups is recommended [14]. Estrogen-containing contracep-

tives raise the risk of clotting so their use in high risk groups for thrombosis, e.g., APS patients, is not advised. Given the additive effects of different risk factors, a tailored assessment of smoking habits, weight and blood pressure is part of effective counseling. A plausible alternative to estrogens are the progesterone-only contraceptives (as oral or subcutaneous implant). No adverse effects on SLE activity were reported [15]. However, even if they represent a lower risk factor for thrombosis, this risk is still present and their use should be evaluated case by case. Intrauterine devices can be a useful option.

New-generation devices are no longer incompatible with immunosuppressive drugs. Copper intrauterine devices (IUDs) are considered safe in APS patients since no association with thrombotic events was found. On the other hand, levonogestrel IUD can be advantageous in APS patients with anticoagulant-induced metrorrhagia [16].

Similar considerations can be applied to hormonal replacement therapy during menopause. Individual patient assessment concerning the presence of important symptoms and co-morbidities must be performed. Evaluation of antiphospholipid antibodies and thrombotic risk factors should be included when considering estrogen-containing preparations [5].

PRECONCEPTION COUNSELING AND DRUGS

Pregnancy and reproductive counseling should always be offered to the patient even if she is not considering pregnancy. If she does wish to become pregnant it is well established that conception in a stage of quiescent or well-controlled disease is essential for good maternal and fetal outcome [17]. Postponing pregnancy until remission or stable disease, ideally for more than 6 months, remains the best decision in most cases [17]. Individual risk assessment is also fundamental in preconception counseling.

A multidisciplinary approach including medical and obstetric care increases the likelihood of successful planning and favorable outcome [18]. Obstetric anamnesis, focusing on a history of pregnancy loss, preeclampsia and past thrombotic events, should be systematically included. Assessment of general risk factors for pregnancy complications, such as age over 40 years, multiparity, hypertension, diabetes and cigarette smoking, is also required. In fact, most of these factors account also as risk factors for thrombotic events. Vaccination should be checked and updated if necessary. A complete immunological profile including autoantibodies related to poor pregnancy outcome must be available for pregnancy planning [19,20]. A complete antiphospholipid profile including functional lupus anticoagulant (LAC), anticardiolipin (aCL) and anti-beta2-glycoprotein I (anti-β2GPI) should be included. Particular attention should be given to high risk profiles such as triple positivity, high titers and LAC presence [19]. Women with anti-Ro/SSA and anti-La/SSB should be informed about neonatal lupus risk including congenital heart block (CHB) [20].

Complete clinical and laboratory assessments allow identification of risk factors and further stratification into a risk profile [Figure 2]. Based on that, a planned workup including visit frequency and monitoring exams should be scheduled. Another important part of global comprehensive counseling is treatment. Misconceptions about fetal harm related to ongoing treatment during pregnancy can lead to lack of compliance [21]. Therefore, it is imperative that the patient be instructed about compatible pregnancy medication – namely, hydroxychloroquine, cyclosporine, azathioprine, glucocorticoids and salazopyrin. Even more relevant is to emphasize the need for disease control to achieve a successful pregnancy [18]. Medication counseling should focus on high risk drugs. Methotrexate, leflunomide, mycophenolate mofetil and cyclophosphamide should be switched before conception, sometimes mandating several months for washout. To avoid the risk of relapse, frequent controls and alternative therapy are required during preconception time. Treatment with anti-tumor necrosis factor alpha (anti-TNFα) antibodies, not considered teratogenic, is often interrupted following positive pregnancy test. However, their use during the first part of pregnancy is not excluded; certolizumab and etanercept are preferred due to their low rate of transplacental passage [7]. Low dose aspirin before conception and heparin after positive pregnancy test increase the probability of good outcome, particularly in cases of APS pregnancies. Adequate calcium and vitamin D supplementation especially in women receiving glucocorticoids and heparin is recommended [7] [Figure 3].

Today, contraindications to pregnancy are unusual and generally transient. Active disease and recent flares, especially in SLE, are the most paradigmatic examples [17]. Nevertheless, a history of severe complications during pregnancy despite treatment and severe organ damage (severe restrictive pulmonary disease, symptomatic pulmonary hypertension, heart failure, severe chronic renal failure) is a true contraindication to pregnancy [5].

PREGNANCY OUTCOME
• Immunology of pregnancy
Maternal neuroendocrine changes occurring during pregnancy are a dominant stimulus for placental-fetal development. Cortisol, estrogens and progesterone rise progressively during pregnancy. In response, placental immunomodulation factors are actively produced. These changes favor a switch toward Th2 suppressing maternal autoimmune responses. Successful pregnancies seem related to the Th2 profile. This mechanism can at least partially explain different effects of pregnancy on ARD activity [22].

• Rheumatoid arthritis
The duration of pregnancy in women with rheumatoid arthritis is historically associated with disease amelioration. Although these results could be associated with design bias, recent studies support this finding. In a large prospective study, improvement was noted in at least 48% of patients during pregnancy. However,

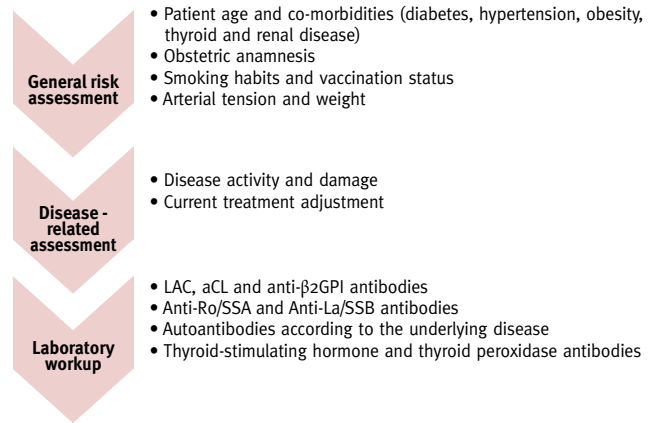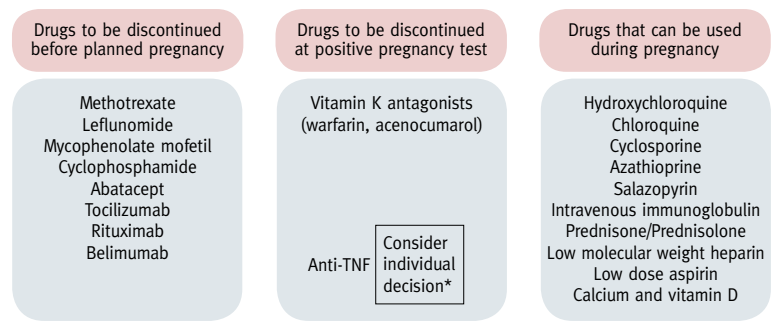**Figure 2.** Counseling and pregnancy planning for patients with autoimmune rheumatic diseases

General risk assessment
- Patient age and co-morbidities (diabetes, hypertension, obesity, thyroid and renal disease)
- Obstetric anamnesis
- Smoking habits and vaccination status
- Arterial tension and weight

Disease-related assessment
- Disease activity and damage
- Current treatment adjustment

Laboratory workup
- LAC, aCL and anti-β2GPI antibodies
- Anti-Ro/SSA and Anti-La/SSB antibodies
- Autoantibodies according to the underlying disease
- Thyroid-stimulating hormone and thyroid peroxidase antibodies

Figure 3. Therapeutic approach during preconception and pregnancy (*not teratogenic)

Drugs to be discontinued before planned pregnancy
Methotrexate
Leflunomide
Mycophenolate mofetil
Cyclophosphamide
Abatacept
Tocilizumab
Rituximab
Belimumab

Drugs to be discontinued at positive pregnancy test
Vitamin K antagonists (warfarin, acenocumarol)

Anti-TNF | Consider individual decision*

Drugs that can be used during pregnancy
Hydroxychloroquine
Chloroquine
Cyclosporine
Azathioprine
Salazopyrin
Intravenous immunoglobulin
Prednisone/Prednisolone
Low molecular weight heparin
Low dose aspirin
Calcium and vitamin D

after delivery 39% of the patients had at least a moderate flare [23]. Another study demonstrated that women negative for both anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) were more likely to exhibit a decrease in disease activity assessed by the Disease Activity Score in 28 joints compared to those positive for ACPA and RF [24]. Maternal rheumatoid arthritis is also associated with obstetric and fetal complications, shown in 7.8–13.6% of pregnancies [5]. Fetal death, intrauterine growth restriction, small for gestational age infants, preeclampsia, and preterm delivery seem to be increased in comparison to the healthy population. Unstable disease is also a predictor of worst outcome [23].

• Systemic lupus erythematosus
Increased risk of flare is an important aspect of pregnancies in lupus patients. The incidence or time of relapse is significantly different across studies due to different definitions of flare and types of patients enrolled [25,26]. Consistently reported is the influence of prior 6–12 months disease activity on relapse risk [26]. Increased risk of flare is linked to history of lupus nephritis and discontinuation of therapeutics like hydroxychloroquine [27,28]. In a study of 132 prospectively followed pregnancies

in SLE women, the previous number of flares, hematologic abnormalities and low complement predicted the occurrence of relapse. A tendency to repeat previous manifestations during flare was also described [29].

A particular challenge in SLE pregnancies is to differentiate between physiological pregnancy modifications and pregnancy complications such as eclampsia, and renal or hematological flare. Associated with high mortality, the pregnancy complications require prompt and multidisciplinary management to improve outcome [30]. A high risk of obstetric and neonatal complications is a well-known feature of SLE pregnancies. Adverse obstetric outcomes include fetal loss (spontaneous abortion and intrauterine fetal death), intrauterine growth restriction, premature birth, premature rupture of membranes, and perinatal mortality. The number of flares, past glomerulonephritis, and central nervous system or kidney involvement are predictive of these complications [29]. In other prospective cohorts, LAC, hypertension and low platelet count were also recognized as predictors of poor outcome in women with stable SLE at conception [17].

• Neonatal lupus syndromes

Maternal anti-Ro/SSA and anti-La/SSB autoantibodies cross the placenta and are associated with neonatal lupus syndromes (NLS) in the offspring. Women with connective tissue disease like SLE and Sjögren's syndrome are more frequently positive to these autoantibodies. However, they can also appear in association with other ARD and in asymptomatic women. The most permanent and life-threatening condition associated with these autoantibodies is congenital heart block (CHB). Congenital heart block risk is estimated in 2% of babies, although the recurrence rate rose to 18% when previous siblings were affected with cardiac or cutaneous NLS [31]. A fetal echocardiogram at least every 2 weeks should be performed in the period between the 16th and 25th gestational weeks in order to diagnose this condition [20]. Hydroxychloroquine use during pregnancy is associated with significant risk reduction in women with SLE and anti-Ro/anti-La positivity. In contrast, synchronous untreated hypothyroidism increases the risk for cardiac NLS ninefold. Fluorinated glucocorticoids (betamethasone, dexamethasone) have been used in CHB treatment but with limited benefit [20]. More frequent and benign is the cutaneous form of NLS. This condition can be present in 15–25% of affected children. It is characterized by a photosensitive rash that usually disappears around 6–8 months of life, the time required for clearance of the maternal antibodies [31].

• Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder defined by thrombotic events and/or pregnancy morbidity in the presence of antiphospholipid antibodies. APS can be associated with other ARD, mainly SLE, or occurs as a primary syndrome in the absence of related diseases. Antiphospholipid antibodies (aPL) can also be present in asymptomatic carriers or in association with different conditions. In fact, aPL are recognized as an independent acquired risk for thrombophilia and poor pregnancy outcome [32]. Thrombophilic and direct effects of aPL on trophoblast differentiation are well-known damage mechanisms. The multifactorial influence of aPL emphasizes the importance of APS as a frequent cause of pregnancy morbidity. APS is frequently recognized during investigation of pregnancy loss. Early miscarriages are common in the obstetric population (10–15%). The association between aPL autoantibodies injury and loss before the 10th week of gestation implies exclusion of genetic and other frequent abnormalities. After the 10th week of gestation the probability of aPL having a negative influence on pregnancy outcome increases [32]. Another critical issue associated with APS pregnancy is placental insufficiency and related complications. A high incidence of early-onset preeclampsia, intrauterine growth restriction and premature delivery was recognized in different studies [19,30]. Preeclampsia and HELLP syndrome have been reported to be increased in patients with APS, usually with early and severe onset. The real prevalence of these outcomes remains uncertain although disease subsets were identified as having higher risk for obstetric complications. Past thrombotic complications, lupus anticoagulant presence, or triple positivity were related to poorer outcome [33].

• Systemic sclerosis

Reports from large retrospective studies identified pregnancy as a non-exacerbation event in stable systemic sclerosis. A transient improvement and cutaneous disease stability were also described in patients with Raynaud's phenomenon and digital ulcers. Increased intraabdominal pressure associated with enlarging gravid uterus was associated with gastroesophageal reflux and dyspnea exacerbation [34]. Special attention should be paid to the presence of severe cardiomyopathy (left ventricle ejection fraction < 30%), moderate-to-severe pulmonary arterial hypertension (stage III), reduced lung volume (forced vital capacity < 50%), and renal insufficiency (serum creatinine > 2.9 mg/dl). Since these are well-established predictors of poor prognosis, their presence supports advising against pregnancy [5]. With regard to obstetric outcomes, an Italian multicenter retrospective study reported increased risk for preterm delivery (odds ratio 2.5), severe preterm delivery (2.2), intrauterine growth restriction (4.4), and very low birth weight (4.9) [35].

• Systemic vasculitis

The literature on systemic vasculitis in pregnancy is limited. Low incidence, male preponderance, and common onset after childbearing age explain this paucity. Takayasu arteritis is an exception, as women in reproductive age are mainly affected. Data from prospective observational studies reported a satisfactory course during pregnancy, with stable disease activity score and vasculitis damage index [36]. Despite reports from sparse and low quality studies, unchanged disease activity was suggested in other pri-

mary vasculitides. Increased rates of premature birth have been described. These findings were recently confirmed by a large multicenter cohort focusing on 65 systemic vasculitis pregnancies followed prospectively. The description of three transient ischemic attacks during pregnancy and puerperium suggested an increased risk of thrombotic complications. Consequently, particular caution should be given to antithrombotic prophylaxis [37].

CONCLUSIONS

Autoimmune rheumatic diseases touch all aspects of life quality, including sexual functioning and reproduction. Different disease-related symptoms can negatively influence these aspects. These topics are not routinely addressed by physicians or health professionals even if this could be the first step to comprehensive counseling. Advice on contraception and multidisciplinary pregnancy planning represent further key points in preventing complications and improving outcomes. Structured and comprehensive counseling represents a crucial path for successful management of women with ARD.

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