Pregnancy in Patients with Inflammatory Rheumatic Diseases

A Focus on Rheumatoid Arthritis and Systemic Lupus Erythematosus

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Autoimmune rheumatic diseases are common in women in their childbearing years, making contraception, preconception counselling, management of the pregnant patient with immunosuppression and subsequent post-partum management a crucial part of modern rheumatology. The symptoms of some rheumatic diseases, such as rheumatoid arthritis (RA) can commonly improve in pregnancy, whilst other disorders, such as systemic lupus erythematosus (SLE) frequently flare, in particular with renal and thrombotic complications occurring in this population. It is important that pregnancy is planned so that medications can be optimised and specific issues relating to pregnancy discussed. Disease control, assessment of antibodies which can contribute to pregnancy outcomes and appropriate immunosuppression and anticoagulation should be addressed. These patients commonly require a multidisciplinary team approach with rheumatology, obstetrics (frequently fetal and maternal subspecialists), nephrology and haematology all contributing to their care. Pregnancy outcomes are determined by the diagnosis, disease activity, medication and presence of specific autoantibodies, such as Ro(SSa) and the antiphospholipid antibodies. Poorly controlled systemic inflammatory disease, thrombotic disease and some antirheumatic medications, such as methotrexate and mycophenolate mofetil, known teratogens, and corticosteroids can result in adverse outcomes. Therefore, pre-pregnancy counselling including contraception where needed is crucial. Here we focus on RA and SLE. A full guidance on pregnancy management in rheumatic diseases is published by the American and European rheumatology associations3,4.

Pregnancy Planning: General Measures

Family planning should be discussed with all women with rheumatic diseases in their reproductive years to ensure disease control and medications are optimised pre conception. Most women can have successful pregnancies and measures can be taken to reduce the risks of adverse maternal or fetal outcomes. Pregnancy risk stratification includes assessment of disease activity, autoantibody profile evaluation, previous vascular and pregnancy morbidity, hypertension and the use of certain medicines. In those wanting to conceive, teratogenic medications should be discontinued and alternatives, which are pregnancy compatible, substituted where needed.

Teratogenic medication such as methotrexate, mycophenolate mofetil, cyclophosphamide and thalidomide should be discontinued a minimum of 3 months prior to conception. Cholestyramine washout should be provided for women treated with leflunomide if there are detectable serum levels of metabolite. In SLE, and in those with Ro antibodies, hydroxychloroquine appears to have significant pregnancy benefits and should be considered for those not already taking it. Patients with antiphospholipid antibodies with and without a diagnosis of antiphospholipid syndrome, consideration should be assessed as to whether anticoagulation and antplatelets are needed. Non steroids should be stopped where possible and prednisolone doses minimized. Breast feeding rates are low for women with rheumatic diseases. It is important that postpartum management is also discussed during pregnancy; medication, flare management and breast feeding. Post-partum women with RMD may experience disease flare and would require appropriate therapy. Most antirheumatic medication is lactation-compatible with the exception of cyclophosphamide, leflunomide, mycophenolate mofetil, thalidomide and methotrexate.

Contraception

Effective contraception in women with autoimmune rheumatic disease is important to prevent unplanned pregnancy which may threaten maternal health and result in poor pregnancy outcomes and teratogenicity.

Reproductive-age women including patients with systemic lupus erythematosus (SLE) with stable or low disease activity who are not positive for antiphospholipid antibodies should use effective contraceptives such as hormonal contraceptives, the combined oral contraceptive pill, intrauterine device (IUD) or subdermal progesterone implant. Levonorgestrel can be used as an emergency contraception where needed.

For SLE patients with moderate or severe disease activity including lupus nephritis and those with positive antiphospholipid antibodies, oestrogen should be avoided. Depot medroxyprogesterone acetate has been shown to decrease bone mineral density by up to 7.5% over 2 years and is not suitable for women considered to be at an increased risk of osteoporosis. For patients taking mycophenolate mofetil, effective contraception is crucial and an IUD is recommended, often in addition to a barrier method of contraception.

Rheumatoid Arthritis

RA is common, the prevalence worldwide is believed to range from 0.4% to 1.3%, the estimated prevalence in women of child bearing potential is 120/100,000. Several studies have demonstrated that women with RA have fewer children1-3 and commonly experience difficulties in conceiving. Factors associated with increased time to pregnancy in this population include advanced age, nulliparity, disease activity, use of non-steroidal anti-inflammatory drugs and prednisone >7.5 mg daily4.

Disease activity in pregnant women with RA has been shown to improve in 60% and flares in half postpartum. Seropositivity, (rheumatoid factor or CCP positivity) has been associated with active disease in pregnancy5.
whilst flares occur in a similar proportion of those who are seronegative and seropositive. Active disease and elevated CRP in early pregnancy along with discontinuation of tumour necrosis factor inhibitor in the first trimester have been identified as risk factors for disease activity in pregnancy.

Kishore et al evaluated approximately 42 millions deliveries, as part of the Nationwide Inpatient Sample and corroborated previous research findings; the maternal RA population had higher prevalence of hypertension, premature rupture of membranes, antepartum hemorrhage, preterm delivery, intrauterine growth restriction and Cesarean delivery. These adverse outcomes are reported more commonly in those with active RA making disease control pre conception and in pregnancy an important part of antenatal care. Women with well controlled disease have similar outcomes to the general population.

Regarding non-teratogenic medicines in RA, patients are frequently prescribed sulfasalazine, hydroxychloroquine and TNF alpha inhibitors, which are sometimes continued to full term, although many advocate for a preconception switch to Certolizumab as it does not contain the Fc chain and has minimal placentation transfer. Other tumour necrosis factor inhibitors that include an Fc IgG1 do cross into the fetal circulation during second trimester, and are commonly held in the third trimester (preconception time of cessation depending on the half-life). These may be continued if patient’s disease is very active. Other small molecules such as the JAK inhibitors are not recommended in pregnancy. Rituximab is reserved in pregnancy for life or organ threatening disease and is thus uncommonly used for RA.

Systemic lupus erythematosus

SLE affects 80/100,000 women in their childbearing years. The largest study to evaluate pregnancy complications associated with SLE included 13,555 pregnancies and demonstrated a two- to fourfold increased rate of obstetric complications including preterm birth, cesarean delivery, fetal growth restriction, preeclampsia and eclampsia, they also demonstrated an increased risk of thrombosis, infection, thrombocytopenia, and transfusion.

Pregnancies in SLE patients during periods of high disease activity (particularly nephritis) or with a significant burden of disease-related damage are associated with maternal morbidity and mortality and poor fetal outcomes. Active SLE at the time of conception is a strong predictor of adverse maternal and obstetrical outcomes, as is the presence of nephritis, antiphospholipid syndrome (APS) and hypertension. A study of 267 pregnancies in a multi-ethnic lupus cohort found that women with high disease activity compared with low disease activity in the first and second trimesters showed a threefold increase in pregnancy loss (miscarriages and stillbirth), again making disease control a corner stone of pregnancy planning in women with SLE.

Furthermore, similar to RA, many of the medications used for the management of SLE and antiphospholipid syndrome, such as mycophenolate mofetil, cyclophosphamide, methotrexate, and warfarin, are contraindicated in pregnancy, making preconception counselling and planning crucial. Despite all of this, the largest observational study, including 385 pregnant lupus patients with inactive or mild or moderate disease at conception, found 81 percent of subjects had uncomplicated pregnancies.

Our approach to pregnancy planning and management in SLE is consistent with recommendations developed by the European and American rheumatology associations.

Preconception evaluation in women with SLE includes disease activity and major organ involvement, as well as hypercoagulability. Previous obstetric outcomes should be reviewed, intrauterine growth restriction, preeclampsia, stillbirth, miscarriage, and preterm birth. Patients with evidence of active SLE, especially nephritis, should be advised to defer pregnancy until the disease is well controlled for a minimum of six months. For those with chronic kidney disease, counselling should include an assessment of the risk of temporary or permanent decline in renal function, women with stroke history, pulmonary hypertension and interstitial lung disease, amongst other end organ complications, should be carefully counselled with maternal medicine and in some cases the risk of pregnancy is too high.

Antibodies to Ro/SSA, La/SSB, double stranded DNA and phospholipids, should be assessed prior to pregnancy. A baseline complement (CH50, C3 and C4) should be checked along with renal function including a spot urine/creatinine ratio and a full blood count and liver profile.

Unless a contraindication exists hydroxychloroquine should be started for those not taking it, and in those taking it, it should be continued in pregnancy as it minimises prednisone use and improves pregnancy outcomes. A large prospective study with 257 pregnancies in 197 women also found that discontinuation of hydroxychloroquine during pregnancy was associated with a higher rate of flare compared with women who either continued it during pregnancy or never took it. There is also a decrease in occurrence of congenital heart block in at-risk fetuses of mothers with anti-Ro/SSA and anti-La/SSB antibodies exposed to hydroxychloroquine. Low dose aspirin is recommended after 12 weeks, provided no contraindication exists. Azathioprine is compatible with pregnancy, but doses should not exceed 2 mg/kg/day. Tacrolimus can also be used in pregnancy for nephritis in particular. Proton pump use should be minimised where possible and stress doses need to be considered for those taking chronic corticosteroids and delivery and with intermittent illness. Multidisciplinary care and close monitoring of disease activity in patients with SLE is indicated at least once every trimester. The management of thrombotic disease and antiphospholipid associated disease is dealt with in the guidelines.

Conclusion

The management of maternal-fetal health in patients with rheumatic diseases is an important component of patient care as improved disease control in turn improves pregnancy outcomes. Pre conception counselling is crucial as it is a combined care approach. Here we have discussed RA and SLE, there are similar management paradigms and considerations for patients with psoriatic arthritis, scleroderma, ankylosing spondylitis amongst others which are outlined in the guidelines.

References available on request