MANAGEMENT OF COMMON RHEUMATIC DISEASES DURING PREGNANCY

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“A baby is something you carry inside you for nine months, in your arms for three years, and in your heart until the day you die.” – Mary Mason

Introduction

- Most women with inflammatory rheumatic diseases can contemplate pregnancy
- All women with rheumatic diseases of childbearing age should receive pre-pregnancy counseling
- Effective disease control in the mother and safety of the fetus both should be ensured
- Multidisciplinary care and evidence-based antirheumatic therapy can reduce maternal and fetal morbidity and mortality

Fertility in rheumatic diseases

- Fertility in women with rheumatic diseases is generally not affected except in
- CKD stage 3-5
- Cyclophosphamide induced damage to ovarian primordial follicles

Ilva CA, Bonfa E, Ostensen M. Maintenance of fertility in patients with rheumatic diseases needing anti-inflammatory and immunosuppressive drugs. Arthritis Care Res.62,1682–1690 (2010).

Fertility in rheumatic diseases

Women with RA, scleroderma and other arthritides have lower birth rates compared with the general population probably because of

a) diminished sexual relationships as a result of -

- joint pains
- fatigue
- depression
- dyspareunia
- reduced libido

b) Diminished or delayed ovulation due to NSAID use

Wallenius M, Skomsvoll JF, Irgens LM et al. Fertility in women with chronic inflammatory arthritides. Rheumatology (Oxford)50,1162–1167 (2011).

Rheumatoid arthritis in pregnancy

- The level of disease activity in in 50% of RA patients will improve during pregnancy
- 20% to 40% achieve remission by the third trimester
- Nearly 20% will have worse or moderate-to-high disease activity during pregnancy.
- 49-62% of women experience postpartum flares.

Areskoug-Josefsson K, Oberg U. A literature review of the sexual health of women with rheumatoid arthritis. Musculoeskeletal Care7,219–226 (2009).

Ostensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic disease. Autoimmun Rev 2012;11:A437–46.

Pregnancy outcomes in patients with RA

- Delivery by cesarean section has been demonstrated to be more common among women with RA
- There is an increased risk of preterm births
- There is NO increased risk of congenital abnormalities among offsprings of women with RA.

Nørgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, Ekbom A, Sørensen HT, Stephansson O. J Intern Med. 2010 Oct; 268(4):329-37.

Preferred medications to manage RA in pregnancy

- Sulfasalazine (FDA category B)- may reduce fertility in male
- Hydroxychloroquine (C)
- Prednisolone, methylprednisolone (B)
- NSAID's (B) -must be avoided after 32 weeks

Krause ML, Makol A. Management of rheumatoid arthritis during pregnancy: challenges and solutions. Open Access Rheumatol. 2016;8:23–36.

Medications relatively safe to use in pregnancy with RA

- TNFα inhibitors (FDA category B)
- Azathioprine (D)
- Etanarcept and certolizumab can be used in all trimester due to low transplacental passage.
- Infliximab should be stopped at 16 weeks
- Adalimumab should not be used in third trimester.
- No data for golimumab.

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et alThe EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases 2016;75:795-810.

Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7

Contraindicated medications in pregnancy with RA

- Methotrexate (FDA category X)- female patients must stop MTX 3 months before conception.
- Leflunomide (X)- Cholestyramine washout needed before planning pregnancy

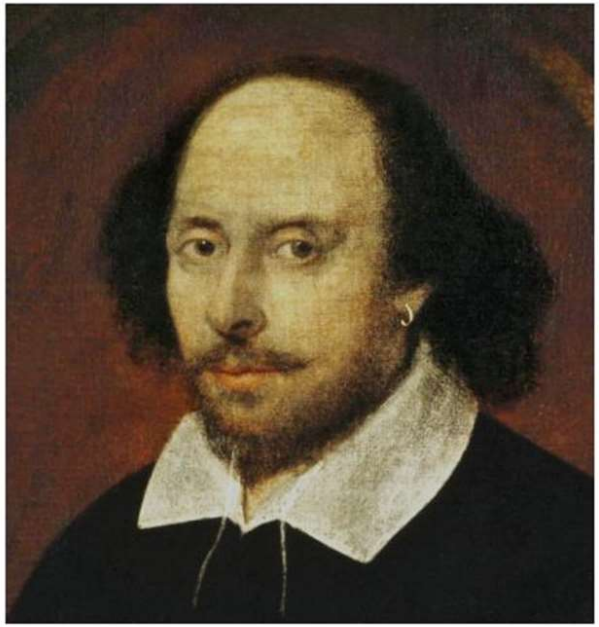
Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7

Inadequate data to support safety in pregnancy with RA (hence should be avoided)

- Anakinra
- Abatacept
- Tocilizumab-stop 3 months before pregnancy
- Tofacitinib
- Rituximab- RTX should be stopped 6 months before conception.
- Belimumab
- Selective COX II inhibitors

Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7

SLE & pregnancy



“ The web of our life is of a mingled yarn, good and ill together. ”

William Shakespeare (All's Well That Ends Well)

SLE & pregnancy

Lupus patients are at risk of developing following complications-

- maternal (lupus flares, worsening renal impairment, onset of or worsening hypertension, development of preeclampsia, or venous thromboembolism
- fetal–neonatal (miscarriage, intrauterine growth restriction, preterm delivery, neonatal lupus syndrome)

Prepregnancy evaluation of lupus patients

- Past and current disease activity (especially 6 months before conception)
- Preexisting organ damage (especially lupus nephritis)
- Serological profile (anti-dsDNA, anti-Ro/La antibodies, antiphospholipid antibodies, complement)
- Medication history
- Additional medical disorders
- Past obstetric history (miscarriage, stillbirth, preterm birth, neonatal CHB, small for gestational age etc)
- Baseline blood pressure, urinalysis

Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol 2011;38:1906–13.

Relative contraindications to pregnancy in SLE

- Severe lupus flare (including renal flare) within the past 6 months
- Stroke within the past 6 months
- Pulmonary hypertension
- Moderate-to-severe heart failure
- Severe valvulopathy
- Severe restrictive lung disease
- Chronic kidney disease stage 4–5
- Uncontrolled hypertension
- Previous severe early-onset (<28 weeks) preeclampsia or HELLP syndrome despite therapy with aspirin plus heparin

Knight CL, Piercy CN. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatol. 2017; 9: 37–53.

Factors affecting pregnancy outcomes in SLE

- Disease activity
- Lupus nephritis (both in terms of hypertension and renal impairment)
- Anti-Ro/anti-La antibodies
- Antiphospholipid syndrome
- Cardiac/lung involvement

Doria A, Tincani A, Lockshin M. Challenges of lupus pregnancies. Rheumatology (Oxford).2008 Jun;47 Suppl 3:iii9-12.

Fetal and maternal morbidity in SLE with pregnancy

Fetal complications (%)		Maternal complications (%)	
Unsuccessful pregnancy	(23.4%)	Lupus flare	(25.6%)
Premature birth <37/40	(39.4%)	Hypertension	(16.3%)
Still birth	(3.6%)	Nephritis	(16.1%)
Neonatal death	(2.5%)	Pre-eclampsia	(7.6%)
Foetal growth retardation	(12.7%)	Eclampsia, stroke and death (<1%)	

*Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol 2010 ; **5** : 2060-8.*

Lupus flare during pregnancy

- Lupus flares during pregnancy and postpartum are generally nonsevere, characterized by articular, dermatological and mild hematological involvement and are usually well controlled with short-term introduction or increase of oral steroids.
- But, severe flares with major organ involvement may occur.

Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy: the Hopkins lupus pregnancy center experience. Arthritis Rheum. 34, 1538–1545 (1991).

Follow up

- Pregnant women with active SLE, APS, lups nephritis, anti Ro/La antibody should be considered as a higher risk group and managed by the multidisciplinary expert team.
- Four weekly review of disease activity, BP, proteinuria, assessments of fetal growth.
- Screen for GDM

How to differentiate lupus nephritis flare from preeclampsia?

Features suggestive of preeclampsia	Features suggestive of lupus flare	Features that may be common to both
Severe headache	Onset <20 weeks (more suggestive of SLE)	Hypertension
Visual symptoms (including flashing lights)	Active urinary sediment/cellular casts	Worsening proteinuria
Epigastric or right upper quadrant tenderness	Hematuria	Oedema
Rising uric acid level	Low/falling complement levels	Renal impairment
Abnormal LFTs	High/increasing anti-dsDNA antibodies	Thrombocytopenia
Signs of hemolysis	Evidence of flare involving other organs	
Clonus (>2 beats)		

Knight CL, Piercy CN. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatol. 2017; 9: 37–53.

Drugs safe to use in SLE with pregnancy

- HCQ- unless contraindicated, all lupus patients should remain on hydroxychloroquine throughout and after pregnancy.
- Prednisolone, methylprednisolone
- Azathioprine
- Cyclosporine
- Tacrolimus
- Aspirin

Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7

Knight CL, Piercy CN. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatol. 2017; 9: 37–53.

Prednisolone in pregnancy

- Lowest possible dose should be used
- It may increase the risk of PROM, IUGR, HTN, GDM and infection.
- High dose should be used when benefit outweighs risk.

Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006; 8:209.

Drugs that should be avoided or used in special situations only in SLE with pregnancy

- Mycophenolate mofetil- should be stopped at least 6 weeks before a planned pregnancy
- Cyclophosphamide is teratogenic and gonadotoxic, therefore it should only be considered in pregnancy in life-/ organ-threatening maternal disease.
  (*Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7)*
- In severe, refractory maternal disease during pregnancy, second or third trimester use of cyclophosphamide should be considered. (Grade of recommendation D-opinions of respected authorities)

(*Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases 2016;75:795-810)*

Treatment of pregnant women with SLE & APS

- In patients with SLE and no history of thrombosis or pregnancy complications: With high or low risk aPL profile, prophylactic treatment with low dose aspirin (LDA) is recommended .
- In women with prior obstetric APS, combination treatment with low dose aspirin and prophylactic dosage heparin during pregnancy is recommended.
- With a history of delivery < 34 th week of gestation due to eclampsia or severe pre-eclampsia or due to recognised features of placental insufficiency, treatment with LDA or LDA and heparin at prophylactic dosage is recommended.

Tektonidou MG, Andreoli L, Limper M, et al.EULAR recommendations for the management of antiphospholipid syndrome in adults. Annals of the Rheumatic Diseases 2019;78:1296-1304.

Treatment of pregnant women with SLE & APS

- With obstetric APS treated with prophylactic dose heparin during pregnancy, continuation of heparin at prophylactic dose for 6 weeks after delivery should be considered.
- In women with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose or addition of HCQ or low - dose prednisolone in the first trimester may be considered.

Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Annals of the Rheumatic Diseases 2019;78:1296-1304.

Pregnancy with SLE with anti SS-A/ SS-B antibodies

- Are at risk of developing fetal complete congenital heart block (CHB), that usually appears between week 16 and 24 of pregnancy
- 2 weekly fetal echocardiogram should be done from 16th week onwards
- Early fetal heart abnormalities may justify treatment with dexamethasone
- HCQ reduces the chance of development of CHB

Martínez-Sánchez N, Pérez-Pinto S. Obstetric and perinatal outcome in anti-Ro/SSA-positive pregnant women: a prospective cohort study. Immunol Res. 2017 Apr;65(2):487-494

Systemic sclerosis with pregnancy

- Pregnancy does not affect disease activity in two thirds of cases
- In remaining one third, SSc will either improve or worsen during pregnancy
- Patients with cardiomyopathy, severe restrictive lung disease, pulmonary hypertension, malabsorption or severe renal insufficiency should be discouraged from becoming pregnant
- Raynaud's phenomenon generally improves
- There is increases risk of preeclampsisa and scleroderma renal crisis
- In renal crisis, treatment should be ACEI. Despite the fetal risk, ACEI should be used as it is lifesaving for the mother.

Steen VD. Pregnancy in scleroderma. Rheum Dis Clin North Am. 33, 345–358 (2007).

Axial SPA in pregnancy

- Patients with ankylosing spondylitis have normal fertility rate
- In contrast to RA, pregnancy does not improve the symptoms of AS
- Disease activity remains high until early in the second trimester and decreases in the third trimester.
- 50% to 80% of patients with AS experience aggravation of symptoms 4–12 weeks after delivery
- The rate of miscarriage, foetal death, prematurity and infants SGA is not increased

Ostensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic diseases. Autoimmunity Reviews 2012;11:437 446

Lui NL, Haroon N, Carty A, et al. Effect of pregnancy on ankylosing spondylitis: a case-control study. J Rheumatol 2011;38:2442–4.

Axial SPA in pregnancy

- Inflammation or ankylosis of the sacroiliac joints, hip disease or total hip replacements are not a mechanical hindrance to the progression of parturition, so normal delivery can be done.
- Caesarean section is more commonly done in patients with AS.
- NSAIDs (before 32 weeks), and TNF inhibitors can be used to treat SPA in pregnancy

Lui NL, Haroon N, Carty A, et al. Effect of pregnancy on ankylosing spondylitis: a case-control study. J Rheumatol 2011;38:2442–4.

Drugs that can be safely used during breastfeeding

- Prednisolone/methylprednisolone- Consider a 4 h delay before breast feeding after prednisone dose >50 mg (EULAR guideline)
- HCQ
- Low dose aspirin
- Ibuprofen
- Sulfasalzine
- Azathioprine
- Infliximab, etanarcept, adalimumab, certolizumab (no data for golimumab)
- Warfarin
- Cyclosporine, tacrolimus

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et alThe EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases 2016;75:795-810

Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7

Drugs that should be avoided during breastfeeding

- MTX
- Cyclophosphamide
- Tofacitinib
- MMF
- Leflunomide
- COX 2 inhibitors except celecoxib

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et alThe EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases 2016;75:795-810

Vaccines in pregnancy

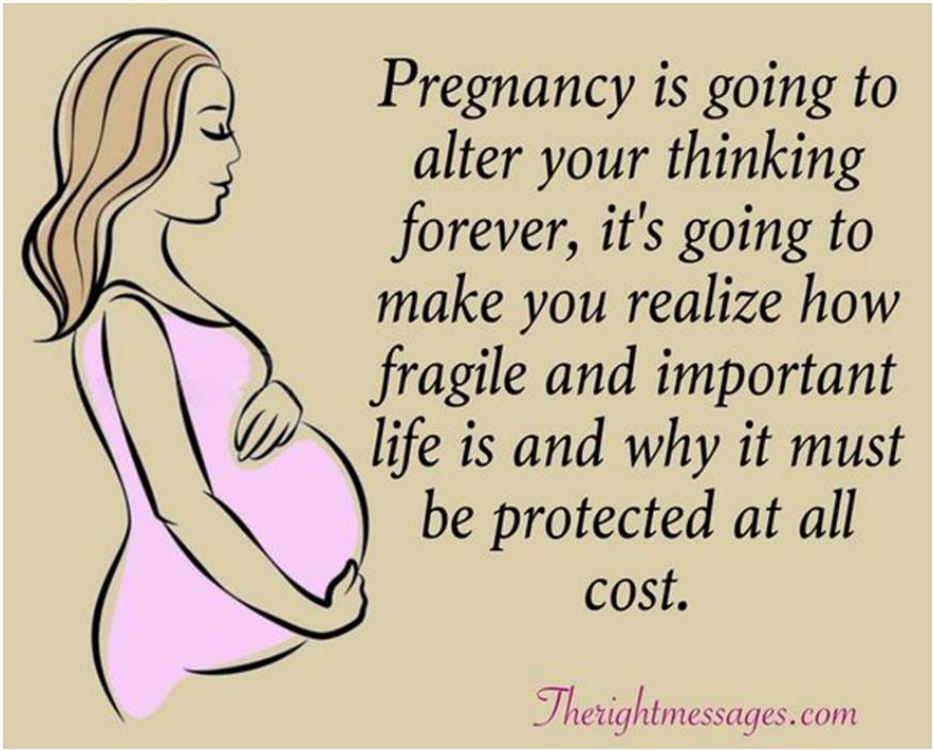
- Live attenuated vaccines are contraindicated during pregnancy and/or when patients receive immunosuppressive agents, biological therapy or corticosteroid up to10 mg per day for more than 2 weeks.

United States Centers for Disease Control. ACIP: Guidance for Vaccine Recommendations in Pregnant and Breastfeeding Women, 2016

Conclusion

- Most of the women with chronic rheumatic disease wants to be a mother.
- Most of the women with chronic rheumatic disease can be a mother, when they are efficiently managed.
- Multidisciplinary care, prepregnancy counseling & disease control, close follow up during pregnancy & postpartum period and early detection & management of complications are prerequisites for successful pregnancy outcome.

Thank you


Pregnancy is going to alter your thinking forever, it's going to make you realize how fragile and important life is and why it must be protected at all cost.
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