Pregnancy and Rheumatic Disease

This document is a summary of guidelines of EULAR, ACR and BSR along with the inputs from a literature search. It is designed to be brief and in simple language understandable both to the patient and the specialist. However patients are strongly advised not to interpret the drug advisory on their own without consulting their treating physicians.

A. A successful pregnancy is possible in almost all rheumatic diseases provided disease is well-controlled, and there is no permanent organ damage.
   1. Pregnancies are more likely to be successful when they are planned, with adequate discussion among the patient, the rheumatologist and the obstetrician.
   2. Successful, however, does not mean uneventful. Doctors and patients must be prepared to deal with possible complications for both mother and child.
   3. Diseases with the potential to affect the kidneys, or lung (including increasing pressure of the pulmonary arteries) like lupus, antiphospholipid syndrome, inflammatory myositis, systemic sclerosis and overlap syndromes are more likely to affect pregnancy outcome than others.
   4. Persistently raised creatinine (end-stage renal disease) or high pulmonary arterial pressures may hinder successful pregnancies. In fact in these conditions, pregnancy may worsen the health condition of the mother.
   5. Any rheumatic disease must be under optimal control for 6 months before pregnancy is planned.

B. Effects of rheumatic diseases on pregnancies:
   1. In the absence of permanent organ damage, the fertility of patients is not altered due to rheumatic diseases. Diseases like systemic sclerosis or Sjogren syndrome may lead to dyspareunia.
   2. Uncontrolled rheumatic diseases have a lot of inflammation and may lead to pregnancy loss especially in the 1st trimester.
   3. In the later phase there are more chances of pregnancy induced hypertension and foetal growth retardation. Patients who have or have had kidney disease, due to vasculitis, scleroderma, or lupus, generally have an increased risk of severe hypertension and pre-eclampsia..
   4. Pulmonary arterial hypertension worsens in the post-partum period. Patients with high pulmonary artery pressures are advised not to get pregnant.
   5. APS probably has the greatest impact on pregnancy. It causes both early and late miscarriage. Other complications include premature birth, low-weight babies, thrombosis (condition where blood clots form in the blood vessels) and pre-eclampsia. Thus, pregnancy with APS should always be considered as high risk and require close medical and obstetric monitoring. Treatment is based on low-dose aspirin and heparin.
   6. Babies of mothers having anti-Ro antibodies (in Sjogren or lupus) are at higher risk of developing congenital heart blocks. The anti-Ro antibodies may interfere with the development of the electric conduction system of the heart. Thus mother with anti-Ro

antibodies needs foetal heart monitoring with foetal echocardiography (ultrasound of foetalheart) during 2nd trimester.

7. It is important to discuss the possible effects of various anti-rheumatic drugs on pregnancy. There should be expert assessment of risk-benefit to determine the drugs to be continued during pregnancy starting from the pre-conception stage.

C. Effect of pregnancies on rheumatic diseases:
   1. The earlier paradigm was that diseases like rheumatoid arthritis tend to go into quiescence (2/3rd of RA) while diseases like lupus would invariably flare (50% of SLE flare with 20% being major organ flares) during pregnancy.
   2. With newer treatment strategies and better disease control, studies have shown that only a minority (~10%) of RA have improved disease activity while lupus patients (in remission for at least 6 months, and on hydroxychloroquine) do not have increased flare rates.
   3. It is very important to report any new symptoms and any worsening to both your rheumatologist and obstetrician.

D. Drugs permissible in pregnancy:
   1. Previously drugs were prescribed following USFDA pregnancy categories: A, B, C, D, and X. However these are not water-tight compartments and this has lead the FDA to abandon this approach. Thus, risk-benefit of each drugs should be discussed in context of the patient, the disease and the age of gestation.
   2. As overarching guidelines, we endorse the ACR recommendation that currently stand as: (please also see the BSR guidelines: table 2)

	Pregnancy	**Lactation**
NSAID	Yes (avoid after 32 weeks)	Yes
Sulfasalazine	Yes	Yes
Antimalarials	Yes	Yes
Corticosteroids	Yes	Yes
Cyclosporine/Tacrolimus	Yes	Probably yes
Azathioprine	Yes	Probably yes
Mycophenolate	No	No
Methotrexate	No	No
Cyclophosphamide	No	No
Anti-tumor necrosis factor (TNF)	Yes	Yes
Rituximab	No	No
Warfarin	No (with caution, only after first trimester)	Yes

	Pregnancy	Lactation
Heparin	Yes	Yes

Table 1: Acceptable medications during pregnancy and lactation

4. There is strong evidence that hydroxychloroquine must be continued in lupus and APS during pregnancy and it is our personal opinion that it should be continued in RA during pregnancy as well.
5. Captopril and enalapril are to be avoided in pregnancy but are safe drugs during breastfeeding.
6. Other drugs:

Tocilizumab

- Tocilizumab (TCZ) should be stopped at least 3 months before conception, but unintentional exposure early in the first trimester is unlikely to be harmful
- There are no data upon TCZ use in breastfeeding

Abatacept

- There are insufficient data to recommend abatacept (ABA) in pregnancy. Unintentional exposure early in the first trimester is unlikely to be harmful
- There are no data upon ABA use in breastfeeding

Secukinumab

- There are insufficient data to recommend Secukinumab(SEK) in pregnancy.
- There are no data upon SEK use in breastfeeding

E. Preconception planning for males:

1. Limited data is available but it has shown that Methotrexate is unlikely to affect male fertility (table 2). Currently there are no recommendations to stop it during pre-conception stage.
2. For sulfasalazine, conception rates may be enhanced by stopping sulfasalazine for 3 months prior to conception
3. Thalidomide should be stopped at least 3 months in advance prior to planned conception (as it is present in spermatozoa).

Summary::

- The likelihood of a successful and healthy pregnancy is highest if kidney and heart function, and blood pressure are normal.
- The disease is inactive for at least 6 months prior to conception.
- Drugs should be used after patient tailored risk-benefit assessment.

Table 2: BSR guideline for drugs used in rheumatology during pregnancy:

Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
CORTICOSTEROIDS					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
ANTIMALARIALS					
Hydroxychloroquine	Yes	Yes	Yes	Yes	Yes*
DMARDS					
Methotrexate <20mg/week	Stop 3 months in advance	No	No	No	Yes*
Sulfasalazine (with 5mg folic acid)	Yes	Yes	Yes	Yes†	Yes‡
Leflunomide	Cholestyramine washout, no	No	No	No data	Yes*
Azathioprine <2mg/kg/day	Yes	Yes	Yes	Yes	Yes
Ciclosporin	Yes	Yes§	Yes§	Yes*	Yes*
Tacrolimus	Yes	Yes§	Yes§	Yes*	Yes*
Cyclophosphamide	No	No‖	No‖	No	No
Mycophenolate mofetil	Stop 6 weeks in advance	No	No	No	Yes*
Intravenous immunoglobulin	Yes	Yes	Yes	Yes	Yes*

Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
ANTI-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes*	Yes*
Etanercept	Yes	Yes	Second but not third	Yes*	Yes*
Adalimumab	Yes	Yes	Second but not third	Yes*	Yes*
Certolizumab	Yes	Yes	Yes*	Yes*	No data
Golimumab	No data	No data	No data	No data	No data
OTHER BIOLOGICS					
Rituximab	Stop 6 months in advance	No¶	No	No data	Yes*
Tocilizumab	Stop 3 months in advance	No¶	No	No data	No data**
Anakinra	No	No¶	No	No data	No data**
Abatacept	No	No¶	No	No data	No data**
Belimumab	No	No¶	No	No data	No data**
CONVENTIONAL PAINKILLERS					
Paracetamol	Yes	Yes††	Yes††	Yes	Yes‡‡
Codeine	Yes	Yes	Yes	Caution	Yes‡‡
Tramadol	Yes	Yes	Yes	Yes§§	Yes‡‡
OTHER CHRONIC PAIN TREATMENTS					
Amitriptyline	Yes	Yes	Yes	Yes	Yes‡‡

Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Gabapentin	No	Insufficient data‖	Insufficient data‖	Insufficient data	No data
Pregabalin	No data	No data	No data	No data	No data
Venlafaxine	Yes	Yes	Yes	Insufficient data‖	Yes‡‡
Fluoxetine	Yes	Yes	Yes	Caution‖	Yes‡‡
Paroxetine	Yes	Yes	Yes	Caution‖	Yes‡‡
Sertraline	Yes	Yes	Yes	Caution‖	Yes‡‡
NSAIDS					
NSAIDs	Yes	Caution¶¶	Stop by week 32	Yes	Yes
COX-2 inhibitors	No	No	No	No	No data
Low-dose aspirin	Yes	Yes	Yes	Yes***	Yes‡‡
ANTICOAGULANTS					
Warfarin	No	No	No/Caution	Yes	No data
Low-molecular-weight heparin	Yes	Yes	Yes	Yes***	Yes‡‡
Rivaroxaban	No data	No data	No data	No data	No data
Dabigatran	No data	No data	No data	No data	No data
BISPHOSPHONATES					
Bisphosphonates	Stop 6 months in advance	No	No	No data	No data
ANTIHYPERTENSIVES					

Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Angiotensin-converting-enzyme inhibitor	Stop when pregnancy confirmed		No	Yes[§§]	No data
Nifedipine	Yes	Yes<60mg/day	Yes<60mg/day	Yes	Yes[‡‡]
Amlodipine	No data	No data	No data	No data	Yes[***]
PULMONARY VASODILATORS					
Sildenafil	No data	No data	No data	No data	No data
Bosentan	No data	No data	No data	No data	No data
Prostacyclin	No data	No data	No data	No data	No data

NSAIDS=non-steroidal anti-inflammatory drugs; COX-2=cyclooxygenase-2; MDT=multidisciplinary team.
[*] Data are limited
[†] In healthy full-term infants only
[‡] Conception may be enhanced by stopping sulfasalazine for 3 months prior to conception
[§] Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels
[‖] Only consider in severe or life-/organ-threatening maternal disease
[¶] Unintentional first trimester exposure is unlikely to be harmful
[**] Unlikely to be harmful
[††] Intermittent use advised, see full guideline for details
[‡‡] No studies identified, but unlikely to be harmful due to maternal compatibility
[§§] Limited evidence, but unlikely to be harmful
[‖‖] Insufficient evidence regarding use for treatment of chronic pain in pregnancy
[¶¶] Possible association with miscarriage and malformation
[***] No studies identified, but unlikely to be harmful.

Table 3 The impact of rheumatic disease on pregnancy and vice-versa.

Rheumatic Diseases	Impact of pregnancy on rheumatic disease	Pregnancy outcome				Fertility
		IUGR/premature /SGA	Foetal Loss	Other complications	Postpartum	
RA	Decreased disease activity (found in only a minority of recent studies under T2T regimens)	Patients on glucocorticoids maybe at risk for small for gestational age and for preterm delivery	not been convincingly shown to be associated with an increase in foetal morbidity or foetal losses	pregnancy outcomes in women with well-controlled RA are comparable to those in the general population	Flares in up to 90%. Usually not in well controlled disease.	Preserved.
SLE	Increased flare rates. Patients on HCQ have similar flare rates as non-pregnant counterparts	extremely variable rate of induced abortions reported. Possibility of CHB if anti-Ro present in mother. Concomitant APS increases risk	~5%	two- to fourfold increased rate of obstetric complications including preterm labour, unplanned caesarean delivery, foetal growth restriction, preeclampsia, and eclampsia. Patients with SLE also have significantly higher risk of thrombosis, infection, thrombocytopenia, and transfusion	Flares. Usually not in well controlled disease.	Preserved in well controlled lupus without organ damage. High dose CYC is a risk factor for reduced fertility. Apparent infertility is common due to effects on their own self-esteem and mental well-being, and stress with partner.
APS	Potentially increased risks of thrombosis especially in post-	Up to 50% of treated cases have PIH and related foetal complications	up to 80% risk of current pregnancy loss without treatmen	Operative deliveries are commoner; increased risk of PIH, placental insufficiency and abruption,	Increased risk of thrombosis	Much lowered.

	partum period		t. 20% with treatment	HELLP syndrome and pre-term labour. Rarely foetal thrombosis		
SSc	Less data available. May exacerbate vasculopathy like PAH, raynaud, or risk for renal crisis	Limited data: possibly more premature births and more infants small for gestational age	Multiple studies (but not all) suggest increased risk of abortion; but most have small numbers	increased frequency of preterm delivery, intrauterine growth restriction, and low-birthweight baby		Data is less but apparently fertility is maintained. Dyspareunia can be an issue
Sjogren	Like lupus: likely to worsen during pregnancy and more so in the postpartum period, especially in presence of PAH	Increased risk of foetal growth restriction.	variable rate of induced abortions	prevalence of CHB is 1-2%. Recurrence rates are 10-20%. Neonatal lupus risk is ~2%	Flares. Flares expected to be less in well controlled disease	Data is less but apparently fertility is maintained in absence of organ damage. Dyspareunia can be an issue
Takayasu	Unknown; theoretically possible to increase long term morbidity	~25% have growth retardation;	25%	Operative deliveries are commoner (~40%); increased risk of PIH and pre-term labour	Unknown	Data is less. Major determinants of fertility are hypertension, cardiac involvement and renal (artery) involvement
ANCA associated vasculitis	Data is very limited but around 20% flare during pregnancy	Limited data	10% of cases in GPA, up to 20% in EGPA (under optimal conditions)	20% preterm	Unknown	Decreased

T2T: treat to target strategy; PAH: pulmonary arterial hypertension; HCQ: hydroxychloroquine; ANCA: anti-neutrophil cytoplasmic antibodies; CHB: complete heart block