Greater Manchester and Eastern Cheshire SCN

Management of Rheumatic and musculoskeletal disorders in pregnancy guideline

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Document Control

Ownership

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Contents

1 Introduction

Pregnancy in women with autoimmune rheumatic and musculoskeletal disorders (RMD) can be associated with maternal and fetal complications. The obstetric management of the pregnant rheumatic patient is largely dictated by the specific disease and the degree to which it is associated with adverse obstetric maternal or fetal outcomes. This guideline will cover the obstetric management of women with systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA) and systemic sclerosis (SSc) and other multisystem RMDs. The main groups of disorders are outlined in table 1.

2 Detail of the guideline

2.1 Joint obstetric rheumatology services across greater Manchester and Eastern Cheshire

The Lupus in pregnancy clinic (LIPS) at St. Mary's Hospital, Oxford Road, Manchester is jointly run by obstetricians with special interest in rheumatology (Dr Clare Tower, Dr Louise Simcox), rheumatology physician (Professor Ian Bruce) and specialist Midwives. This is a tertiary referral service. Referral criteria include any pregnant woman with SLE or other RMD disorder at an early stage following recent diagnosis or with current active disease. For preconception advice, please email or post a formal referral letter to the service.

To refer to this service, contact on 0161 276 6427 or email anna.martin@mft.nhs.uk.

2.2 Types of RMDs and their clinical and immunological criteria

No	RMD	Characteristics
1.	Systemic Lupus Erythematosus (SLE)	Multisystem including musculoskeletal, renal, cardiovascular, neuropsychiatric and pulmonary involvement associated with a wide range of autoantibodies including anti-dsDNA, anti-SSA/B (anti-Ro, anti-La) among others.
2.	Antiphospholipid syndrome (APS)	Autoimmune, thrombophilic condition that is marked by the presence of antibodies that recognize and attack phospholipid-binding proteins. When diagnosed in patients with underlying autoimmune disease (usually SLE), APS is termed secondary APS; in otherwise healthy persons it is termed primary APS.
3.	Sjogren's syndrome (SS)	Associated with dry mouth and eyes, gastrointestinal, urogenital discomfort and disabling fatigue. Secondary SS, in contrast, co-exists with diseases such as RA and SLE. Pregnancy complications due to the occurrence of anti-Ro/SSA and anti-La/SSB autoantibodies are neonatal lupus and congenital heart block (CHB).

No	RMD	Characteristics
4.	Mixed and undifferentiated connective tissue disease (MCTD) /(UCTD)	MCTD clinically presents as an overlap syndrome with features of two or more connective tissue disease, such as SLE, rheumatoid arthritis, or vasculitis.
5.	Systemic vasculitis	Systemic vasculitis is a heterogeneous group of diseases characterized by inflammation and necrosis of small and medium blood vessels.
6.	Adult inflammatory myopathies	Polymyositis (PM) and dermatomyositis (DM) are the most common forms of idiopathic inflammatory myopathy.

2.3 Categorisation of rheumatological conditions in pregnancy and referral criteria

Rheumatological condition	**Next steps**	**Place of Care**
SLE or other RMD disorders in remission, or stable low disease activity, no deep organ involvement.	Medication to be reviewed by local multidisciplinary team and adjusted as necessary.	Care and delivery in local hospital, with escalation if clinical deterioration.
SLE or other RMD disorders at an early stage following recent diagnosis, or active disease.	Delay pregnancy until condition improves or in remission. Review medications and monitor progress.	Shared care between local hospital and LIPS clinic. Refer to tertiary unit to be seen before 16 weeks for management plan.
Impaired organ function and/or pre-existing organ damage. • Lupus flare (including renal flare) within the past 6 months • Previous stroke • Pulmonary arterial hypertension • Any cardiac or respiratory involvement • CKD stage 3 and above • Uncontrolled hypertension • Recurrent thrombosis • SLE with proteinuria (PCR> 50) • Systemic sclerosis • Adult inflammatory myopathies • MCTD on immunosuppression • Large vessel/ANCA vasculitis	Delay pregnancy until condition improves or in remission. High risk of maternal or fetal mortality or morbidity.	Refer to tertiary unit (LIPS clinic at St Mary's Hospital, Manchester).

3 Pre-pregnancy counselling and support

The need for effective pre-pregnancy counselling is highlighted in the recent MBRRACE report. The pre-pregnancy consultation should gather detailed information about:

- Disease activity.
- Pre-existing organ damage (particularly cardiac, lung, and/or renal).
- Serological profile relevant to the disorder which may include anti-dsDNA, anti-Ro/La antibodies (anti SSA-SSB, ENA), antiphospholipid antibodies (anticardiolipins, anti-β2 glycoprotein, lupus anticoagulant), anti-RNP, complement.
- Presence of co-existing medical disorders such as hypertension, diabetes, renal disease and thrombosis.
- Medications.
- Past obstetric history (gestation and outcome of all pregnancies, complications such as preeclampsia, preterm delivery, fetal/neonatal complications).
- Baseline blood pressure and urinalysis.
- Baseline blood tests (full blood count [FBC], urea and electrolytes [U&E], creatinine, liver function tests [LFTs]. Consider thyroid function tests. Additional organ-specific tests (cardiac echo, lung function tests) may be helpful in assessing function where clinically indicated.
- Baseline urine protein:creatinine ratio.
- General preconception advice including smoking cessation, stopping/reducing alcohol intake, optimising BMI if overweight, checking rubella immunity/ MMR vaccination should be given.
- Any woman planning to conceive should take 400 micrograms folic acid daily to reduce the risk of neural tube defects, ideally for 3 months prior to conception and the first 3 months of pregnancy.
- If the woman has had methotrexate in the previous 3 months or diabetes, obesity, or any history (or family history) of neural tube defects, then she should be prescribed high dose (5 milligrams) folic acid.
- All women should also take 10 micrograms (400 units) of vitamin D daily for bone and teeth health and development. Women at increased risk of vitamin D deficiency (including those with previous vitamin D deficiency) should have levels checked as they may require a higher dose. Calcium therapy is also recommended.
- Women who are not currently interested in pursuing pregnancy but desire to conceive in the future should be appropriately counselled about the potential safety and risks or teratogenicity of medications. Contraception counselling should be individualised.

3.1 Optimisation

- All women with active disease or impairment of organ function secondary to SLE ideally must have a pre-conception appointment with clinicians that have experience of managing pregnant women with this disorder prior to getting pregnant.
- Disease optimisation is important to reduce incidence of lupus flares which has a two- to three-fold increase in lupus disease activity during pregnancy. Women with active disease should be advised to postpone pregnancy and use effective contraception until stable for 6

months particularly following a change in medication. Women with impairment of organ function should be informed of the risks to their health and pregnancy related risks.

- Women with antiphospholipid syndrome (APS) are at an increased risk of VTE and pregnancy loss and require aspirin and/or low-molecular weight heparin (LMWH) during pregnancy.
- Women with anti-Ro and/or anti-La antibodies should be counselled about the risks of fetal/neonatal congenital heart block (1-2%) and/or neonatal lupus erythematosus (NLE) (2-5%). The risk of recurrence (up to 15%) is present if there is one previously affected baby.
- In cases of SLE with renal impairment, communication with the renal team including discussion about any alteration of medication. Optimisation of hypertension is essential.
- All information should be summarised in a letter to the woman and the team of professionals who care for her. This should include any instructions for when she becomes pregnant. Clear information on how to access antenatal services rapidly should she get pregnant as often these women need to be seen before a GP/MW referral is received.

4 Medications

Active disease is associated with worse pregnancy outcomes. The aim should be stability and women should be reassured about those medications known to be safe in pregnancy.

The British Society for Rheumatology and British Health Professionals in Rheumatology produced evidence-based guidelines in 2016 on drug compatibility in pregnancy and breastfeeding. See appendix 1 for full details.

- Prednisolone is compatible with each trimester of pregnancy and breastfeeding.
- Hydroxychloroquine is the antimalarial of choice and can be continued in pregnancy and breastfeeding.
- Methotrexate at any dose should be avoided and stopped at least 3 months prior to conception. High dose folic acid 5mg daily should be given throughout pregnancy in women who have been on methotrexate within 3 months prior to conception. If accidental pregnancy occurs during methotrexate treatment, stop immediately and commence folic acid 5mg daily. Refer to local fetal medicine specialist.
- Sulfasalazine is compatible in pregnancy (with folic acid 5mg daily) and breastfeeding.
- Leflunomide is not recommended currently in women planning a pregnancy. If women are taking leflunomide and planning pregnancy, they need a cholestyramine washout and to be changed to an alternative.
- Azathioprine is compatible in pregnancy and breastfeeding.
- Ciclosporin is compatible throughout pregnancy at the lowest effective dose and mothers can breastfeed.
- Tacrolimus is compatible throughout pregnancy at the lowest effective dose and mothers can breastfeed.
- Mycophenolate mofetil and cyclophosphamide need to be stopped and changed to an alternative (such as hydroxychloroquine or azathioprine) at least 6 weeks prior to trying for a pregnancy. Breastfeeding is not recommended.
- Intravenous immunoglobulin is compatible with pregnancy and breastfeeding.

- Anti-TNF medications such as infliximab may be continued up to 16 weeks. Etanercept and adalimumab may be continued until the end of the second trimester. There is little information on breastfeeding but current knowledge indicates that women should not be discouraged from breastfeeding. Rituximab should be stopped 6 months prior to conception. Toclizumab should be stopped 3 months prior to conception. There is limited evidence on Anakinra, Abatacept and Belimumab.
- ACE inhibitors should be stopped or changed to an alternative antihypertensive when a pregnancy is confirmed by a positive pregnancy test.
- Warfarin needs to be changed to heparin at a treatment dose (including antiXa monitoring as required) from a positive pregnancy test (but can be safely recommenced post-partum even if breastfeeding).
- Calcium and vitamin D3 are to be encouraged before and during pregnancy.
- Bisphosphonates - There is no evidence of harm from limited reports in pregnancy but insufficient data to recommend specific time to be stopped pre-conception. A pragmatic recommendation is that they should be stopped 3 months before pregnancy.

5 Pregnancy care management plan

5.1 Antenatal care

- Overall, the risk of flare (antenatal or postpartum) appears to be dependent on disease activity 6–12 months prior to conception.
- Women with quiescent SLE over this period have less risk of flare during pregnancy, whereas women with active SLE have a higher of flare.
- Most flares are non-severe with articular, dermatological, and/or mild haematological involvement. These are usually well controlled with short term introduction or increase of oral steroids.
- Lupus nephritis at conception confers a higher risk of flare during pregnancy, even in women in remission.
- Other complications include a worsening of hypertension, or onset of new hypertension and/or preeclampsia. The risk of preeclampsia is 28 % in the presence of nephritis compared to 16% with only a background of SLE. The risk of VTE is also increased. Low-dose aspirin (150 mg) taken at night is recommended until 36 weeks gestation to reduce the risk of placental disease.
- All women with lupus should be encouraged to continue hydroxychloroquine in pregnancy to improve neonatal outcomes unless contraindicated.
- Baseline bloods (FBC, U&E, creatinine, LFTs, serological profile) and urinalysis with proteinuria quantification (PCR/ACR) should ideally be obtained in early pregnancy to help to monitor disease status and identify flares.
- Lupus flares may occur during pregnancy or in the immediate postpartum period; the most common organs involved are renal (presence of haematuria or cellular casts in lupus and significant proteinuria (PCR > 50) and followed by the skin and joints.
- A glucose tolerance test (GTT) at 24-28 weeks should be offered to all women prescribed steroids or calcineurin inhibitors (e.g. tacrolimus) or with risk factors for GDM (see NICE

guidelines). Consider an earlier GTT at 16 weeks, or blood glucose monitoring if on Prednisolone 20 mg or higher dose or if other risk factors present.

- Serum C3 and C4 levels and ESR rise in pregnancy so they may remain within normal range even in women with active disease.
- A fall of ≥25% in serum complement levels during pregnancy may be suggestive of an impending lupus flare.
- Distinguishing pregnancy-associated signs and symptoms from those of SLE related flares may be difficult. Fatigue, mild arthralgia, hair loss, dyspnoea, headaches, malar and palmar erythema, oedema, anaemia, and thrombocytopenia need careful clinical assessment by rheumatology physicians VTE risk must be carefully assessed. Mild stable lupus is not an indication in isolation to start LMWH. Women with active disease or significant proteinuria should be offered LMWH prophylaxis.
- In patients with persistent proteinuria due to previous lupus nephritis, proteinuria may increase during pregnancy due to increased renal blood flow, so careful MDT assessment of disease activity and blood pressure control is needed. Women should be counselled that with lupus nephritis there is preterm delivery rate, spontaneous and iatrogenic, of 30–40% with an increased fetal loss rate of 17%.
- Thromboprophylaxis with LMWH may be required if there is persistent significant proteinuria (PCR > 100). Monitoring of antifactor Xa levels if PCR > 300 is recommended.
- Those with SLE in remission without major organ involvement, or those with cutaneous lupus erythematosus only, are likely to have a normal pregnancy with pregnancy outcomes comparable to those of the healthy population.
- The risk of preeclampsia is noticeably increased in women with SLE especially if they have had a history of APS, lupus nephritis, previous preeclampsia, chronic kidney disease, on high dose steroids or pre-existing hypertension.
- Angiogenic factors such as placental growth factor (PLGF) or sFLT: PLGF ratio may help to diagnose preeclampsia and may be particularly important in the challenging situation of identifying superimposed preeclampsia in patients, including those with SLE and those who have underlying hypertension and/or renal disease.

Fetal Monitoring

- SLE carries increased risks of SGA and/or IUGR (6%–35%). Monitoring fetal growth with serial ultrasound scans is important in women with SLE who have risk factors for poor pregnancy outcome.
- Congenital heart block (CHB) is a rare complication affecting 2% of babies born to mothers with anti-Ro/La antibodies regardless of background disease. These antibodies are actively transported across the placenta from 18 to 30 weeks of gestation. There is no good evidence to support fetal echocardiography in all women with these antibodies. All women with anti-Ro/La (anti SSA/SSB antibodies) required auscultation of fetal heart rate every 1–2 weeks from 18 – 30 weeks. This can be done in the community with urgent referral to a fetal medicine unit if a low fetal heart rate (<110 bpm) is detected. There is an increased risk of hydrops and fetal death if the rate is <55 bpm. Women with a previously affected baby with congenital heart block due to anti SSA/SSB antibodies must be referred for pre-conception counselling and antenatal care to the LIPS clinic. These women will require fetal echocardiography during pregnancy.

5.2 Planning birth

- Timing/mode of birth should be guided by individual obstetric factors in women with stable disease in the presence of associated hypertension, birth should be offered by 39 weeks. Earlier induction is not usually required in women with stable superficial disease.
- In pregnancies complicated by small for gestational age babies, gestational hypertension or pre-eclampsia, timing/mode of birth should be based on clinical judgement (refer to the relevant local guideline for small for gestational age babies / hypertensive disorders in pregnancy).
- A care plan should be documented prior to 36 weeks in women where there are special considerations likely to affect birth/post-partum management. These include:
  - Anaesthetic considerations
  - Care plan for the management of LMWH
  - Plan for IV hydrocortisone where indicated
  - Additional considerations in women with renal impairment who are at risk of volume depletion or volume overload.
  - A plan for medications in the immediate postnatal period.

5.3 Intrapartum management

- Vaginal birth should be the mode of choice. Lower segment caesarean section should be performed for obstetric reasons.
- There is no contraindication to the use of labour analgesia including epidural analgesia. For women prescribed LMWH, a haematology care plan should be documented by 36 weeks.
- A specific assessment of the increased risk of pulmonary oedema should be undertaken in women with CKD and pre-eclampsia.
- In women taking >7.5mg of prednisolone daily then intravenous hydrocortisone 100mg should be given in labour 6 hourly until oral medication can be recommenced.

5.4 Postnatal care

- Methyldopa is contraindicated in all postnatal women because of the risk of depression.
- LMWH should be continued for 6 weeks postpartum in women with significant risk factors for VTE or where antenatal VTE prophylaxis was recommended.
- Non-steroidal anti-inflammatories should not be given to women with renal impairment.
- Women should continue their long term care with the rheumatology team.
- Women should be informed about the risks in future pregnancies and the importance of pre-conception care when planning future pregnancies.

  Women should be given advice about contraception and how to access services rapidly if they become pregnant again.

6 Contraception

6.1 Contraception safety in RMD conditions

Type of contraception	Safety in RMD disorders
LNG-IUS	Safe
Depo-Provera	Safe
Progesterone subdermal implants	Safe
Depot progestogens	Variable interaction with tacrolimus and cyclosporine
Progesterone only methods	Safe
IUCD (copper coil)	Safe Can increase menstrual bleeding, so it may not be suitable for women on long-term warfarin or LMWH.
Oestrogen-containing	Contraindicated in women with aPL or APS, active SLE (including lupus nephritis) as increases VTE risk.

7 Resources

https://www.lupusuk.org.uk/wp-content/uploads/2015/09/LUPUS-A-Guide-to-Pregnancy-V1.pdf

8 References

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Appendix 1 - Drug compatibility in pregnancy and breastfeeding

Taken from BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding. See references for full articles.

Corticosteroids

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes

Antimalarials

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Hydroxycholorquine	Yes	Yes	Yes	Yes	Yes

DMARDs

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Methotrexate (<20mg/week)	Stop 3 months prior to conception	No	No	No	Yes
Sulfasalazine (with 5mg folic acid)	Yes	Yes	Yes	Yes (healthy full term babies only)	Yes
Lefunomide	Cholestyramine washout, no	No	No	No data	Yes
Azathioprine (<2 mg/kg/day)	Yes	Yes	Yes	Yes	Yes
Ciclosporin	Yes	Yes	Yes	Yes (limited data available)	Yes
Tacrolimus	Yes	Yes	Yes	Yes (limited data available)	Yes
Cyclophosphamide	No	No	No	No	No
Mycophenolate mofetil	Stop 6 weeks in advance	No	No	No	Yes
Intravenous immunoglobulin	Yes	Yes	Yes	Yes (limited data available)	Yes

Anti-TNF

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Infliximab	Yes	Yes	Stop at 16 weeks	Yes (limited data available)	Yes
Etanercept	Yes	Yes	Second only	Yes (limited data available)	Yes
Adalimumab	Yes	Yes	Second only	Yes (limited data available)	Yes
Certolizumab	Yes	Yes	Yes (limited data available)	Yes (limited data available)	No data
Golimumab	No data	No data	No data	No data	No data

Other biologics

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
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

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Paracetamol	Yes	Yes (Intermittent use)	Yes (Intermittent use)	Yes	Yes
Codeine	Yes	Yes	Yes	Caution – risk of CNS depression	Yes
Tramadol	Yes	Yes	Yes	Yes	Yes

Other chronic pain treatments

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Amitriptyine	Yes	Yes	Yes	Yes	Yes
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 (Insufficient evidence in use for use in chronic pain)	Yes
Paroxetine	Yes	Yes	Yes	Caution (Insufficient evidence in use for use in chronic pain)	Yes
Sertraline	Yes	Yes	Yes	Caution (Insufficient evidence in use for use in chronic pain)	Yes

NSAIDS

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
NSAIDS	Yes	Caution (Possible association pregnancy loss and malformation)	Stop by week 32	Yes	Yes
Aspirin	Yes	Yes	Yes	Yes	Yes
COX-2 inhibitors	No	No	No	No	No data

Anticoagulants

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Warfarin	No	No	No	Yes	No data
LMWH	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

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Bisphosphonates	Stop 3 - 6 months in advance	No	No	No data	No data

Antihypertensives

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
ACE Inhibitors	Stop once pregnancy confirmed	Stop once pregnancy confirmed	No	Yes	No data
Nifedepine	Yes	Yes <60mg/day	Yes <60mg/day	Yes	Yes
Amlodipine	No data	No data	No data	No data	Yes

Pulmonary vasodilators

Drug	Compatible pre conception	Compatible first trimester	Compatible second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Sildenafil	MDT assessment	MDT assessment	MDT assessment	No data	No data
Bosentan	MDT assessment	MDT assessment	MDT assessment	No data	No data
Prostacyclines	MDT assessment	MDT assessment		No data	No data