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Stratifying management of rheumatic disease for pregnancy and breastfeeding

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Abstract

The management of inflammatory rheumatic diseases during pregnancy and breastfeeding has undergone considerable change in the past few years. Modern therapeutics, including biologic and targeted synthetic DMARDs, have enabled substantial improvements in control of rheumatic diseases, resulting in more patients with severe disease considering pregnancy. Therefore, management of disease for these patients needs to be discussed with clinicians before, during and after pregnancy and patients need to know what complications they might experience before they become pregnant. This Review will summarize the effects pregnancy has on various rheumatic diseases and the effects these diseases have on pregnancy, as well as provide advice regarding the alteration and monitoring of therapy before, during and after pregnancy.

[H1] Introduction

Inflammatory rheumatic diseases, which include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), other inflammatory arthropathies, axial spondyloarthritis, primary Sjögren syndrome, systemic sclerosis (SSc) and primary systemic vasculitis, can affect women of childbearing age (Box 1) [1-5]. In this context, SLE and various inflammatory arthropathies have been studied the most and are associated with an increased burden of adverse pregnancy outcomes (APOs), such as miscarriage, maternal hypertension, intrauterine growth restriction and/or premature delivery. These women often have disease that is being controlled by use of DMARDs and they are, therefore, increasingly considering pregnancy as a possibility [6].

Management of pregnancy in women with rheumatic diseases is affected by various factors. Active disease is associated with APOs [6], hence DMARDs are required during pregnancy to ensure control of maternal disease and satisfactory pregnancy outcomes. However, prescription of many DMARDs is complicated by safety concerns and evidence-based guidelines are unable to provide reliable evidence-based recommendations for all drugs [7-9]. Specific pregnancy concerns exist for various conditions that should be considered when discussing pregnancy planning and disease management with patients.

Conversations between clinicians and patients with rheumatic diseases are vital to ensure the patient understands the potential effects of the timing of conception (with respect to disease activity), of disease upon pregnancy~~,~~ and of pregnancy upon disease, and the potential need for medication alterations ~~that might be required~~ in relation to pregnancy and breastfeeding. **[Au:OK?]**

This Review focuses on pregnancy planning in patients with RA, SLE, psoriatic arthritis (PsA), spondyloarthritis, primary Sjögren syndrome or SSc. Pregnancy in patients with primary systemic vasculitis is rare; advice specific to this disease is beyond the scope of this article but it is managed similarly to SLE.

[H1] Timing of pregnancy

Patients with inflammatory rheumatic diseases should conceive during a period of disease quiescence to reduce the risk of disease flare in pregnancy [6,9,10]. In patients with well-controlled disease that lacks extra-articular manifestations and organ dysfunction, a 3-month period of disease control on stable medications compatible with pregnancy should suffice, but the precise duration of this period of quiescence is a matter of debate. In SLE, the risk of disease flare during pregnancy is increased in patients with~~:~~ active disease within 4–6 months before conception [11,12]~~;~~ in patients with active disease at conception [13,14]~~;~~ and following discontinuation of hydroxychloroquine (even when disease is quiescent) **[Au:OK?]** [15,16]**.** EULAR recommends 6–12 months of disease quiescence is needed prior to conception dependent on various maternal factors, such as degree of residual organ dysfunction [17].

[H1] Effect of disease on pregnancy

[H2] Fertility and parity

Patients with inflammatory rheumatic diseases have fewer children than other women[6,18]Explanations for this phenomenon include physical disability [19], renal failure [20], teratogenic medications [21], depression or fatigue that can lead to reduced libido or sexual dysfunction in women [22], and increasing maternal age associated with reduced ovarian reserves and oocyte quality [23] (reviewed elsewhere [24]). In particular, cyclophosphamide-induced gonadal toxicity **[G]** is a substantial problem for patients with severe rheumatic disease [21,24], and strategies have been developed to safe-guard against fertility loss before treatment with cytotoxic drugs [25]. These strategies include semen cryopreservation, embryo or oocyte cryopreservation, and the use of gonadotropin-releasing hormone analogues or agonists to suppress ovarian function and utero-ovarian blood flow **[Au:OK?]** in order to reduce exposure to gonadotoxic drugs such as cyclophosphamide. However, the use of gonadotropin-releasing hormone analogues is controversial and data from randomised trials of their use in patients receiving chemotherapy for different cancers are inconsistent [25].

[H2] Risk of adverse pregnancy outcomes

An increased burden of APOs has been reported in various inflammatory rheumatic diseases, described below and in Table 1. Various retrospective studies have shown that women with RA have an increased risk of hypertensive disorders of pregnancy (gestational hypertension **[G]** and preeclampsia **[G]**), intrauterine growth restriction **[G]** (IUGR), premature delivery, caesarean

delivery and increased length of hospital stay for pregnancy in population studies that included >3,500 patients with RA [26-29]. Although a smaller retrospective cohort study (243 women with RA **[Au:OK?]**) also confirmed an increased risk of~~for~~ prematurity and caesarean section, an approximately 50% increased risk of hypertensive disorders of pregnancy and reduced fetal growth in patients with RA was not statistically significant as compared with population controls ~~in one study~~ [30]. In other small (up to 150 patients) prospective studies of pregnancy in patients with RA, the risk of hypertensive disorders was increased in one study [31], but not in two others [10,32]. Overall, given the consistent finding of an increased risk of hypertensive disorders in RA pregnancy from large population studies it would seem prudent to counsel women with RA about this risk.

In SLE, several large (mostly retrospective) population-based studies of a total >15,000 pregnancies in patients with SLE have identified an increased risk of hypertensive disorders of pregnancy, pre-term labour and IUGR [14,33-36]. In addition, a meta-analysis including studies published 2001–2016 (including 3,395 patients with SLE) confirmed an increased risk of a range of maternal and fetal APOs, including hypertension (relative risk (RR) 1.99), preeclampsia ((RR 1.91), pre-term labour (RR 3.05), IUGR (RR 4.44) and small for gestational age **[G]** (RR 1.69) [37].

High disease activity immediately prior to and during pregnancy is clearly linked with APOs in RA and SLE [10,38,39]. A cohort study of pregnancy in patients with axial spondyloarthritis found an increased risk of APOs in these patients compared with healthy individuals **[Au:OK?]** as well as an association between active disease and preterm delivery [31].

The effect of other inflammatory rheumatic diseases on pregnancy outcome is not well characterised. Pregnancy in PsA does not seem to be associated with APOs [40,41]. Case–control studies have shown an increase in the rates of spontaneous abortion, preterm deliveries and caesarean section in pregnancies in women with primary Sjögren syndrome ~~pregnancies~~ compared with those in healthy individuals [42]. A high frequency of pre-term births and small full-term infants has been shown to occur in patients with SSc, with no difference in the frequency of miscarriage and neonatal survival compared with healthy individuals [43].

[H1] Effect of pregnancy on disease

[H2] Remission and relapse in pregnancy

Reports of ~~reduced~~ improvement in disease activity in as many as 90% of RA pregnancies come mostly from retrospective studies that do not reflect current practice, ~~in~~ as the use of biologic therapies ~~that~~ now enables many women with severe disease to become pregnant **[Au: wording OK?]** [6,44]. Studies using validated measures of disease activity, such as the 28-joint Disease Activity Score for RA, found less convincing evidence that pregnancy reduces disease activity, with only 48–60% of women with active RA showing signs of reduced disease activity during pregnancy and 39–50% having a disease flare within 6 months post-partum [45].

The effect of pregnancy on SLE disease activity is unclear as some studies have reported no increased risk of SLE flares during pregnancy, compared with non-pregnant patients with SLE [13,46,47], whereas other studies show pregnancy is associated with an increased SLE flare rate [48-50]. These results are conflicting, possibly because of small cohort sizes and the use of varying methodologies

to assess disease activity and define disease flares, but a systematic review calculated an overall flare rate (mostly mild flare) of ~25% and a severe flare rate of ~5% [51]. These flare rates were obtained from a meta-analysis of 1,842 patients with SLE with 2,751 pregnancies between them, including patients with lupus nephritis [35] and the prospective PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study of 385 SLE pregnancies [34]. In the PROMISSE study, 12.7% had a mild or moderate flare and 2.5% had a severe flare at 20 to 23 weeks, plus 9.6% had a mild or moderate flare and 3.0% had a severe flare at 32 to 35 weeks [34]. A single-centre observational study [52], which was not included in the meta-analysis [35], of 398 pregnancies in 304 patients with SLE and 1,045 non-pregnant patients with SLE reported an increased flare rate in pregnancy (hazard ratio (HR) 1.59; 95% CI 1.27–1.96) that was reduced by hydroxychloroquine therapy (HR 1.26 (95% CI 0.88–1.69) in hydroxychloroquine-treated patients, compared with HR 1.83 (95% CI 1.34–2.45) in those who were not treated with hydroxychloroquine).

Information on disease activity and pregnancy outcomes in women with other inflammatory rheumatic diseases is limited. Some studies show that disease course and severity are not altered by pregnancy in axial spondyloarthritis [53,54] and similar data are conflicting for PsA [40,41,55].

[H2] Presence of autoantibodies

Anti-SSA/Ro and anti-SSB/La antibodies are usually detected in patients with SLE and primary Sjögren syndrome, are uncommon in RA and are sometimes detected incidentally in patients who lack other features of autoimmune disease [56]. Around 16 weeks gestation, these antibodies cross the placental barrier by active transplacental transfer (Figure 1). This process involves engagement of the Fc region with neonatal Fc receptors on syncytiotrophoblast cells [57] and has a number of implications for the fetus and newborn. The most important risk is that of atrioventricular block (AVB), with congenital complete heart block occurring in 1–2% of babies born to anti-SSA/Ro positive mothers with no previously affected pregnancies, known as neonatal lupus syndrome. This risk **[Au: do you mean risk of CHB? Or of AVB?]** increases to ~17% if previous pregnancies have resulted in AVB [58]. Less common **[Au: less common than CHB? or than AVB?]** in children born to mothers who are positive for anti-SSA/Ro antibodies is late-onset cardiomyopathy leading to congestive cardiac failure[58]. In three case reports anti-SSA/Ro positivity and anti-SSB/La positivity have also been associated with endocardial fibroelastosis **[G]** , which has a poor cardiac prognosis including end-stage heart failure and death and can occur in the absence of AVB [59] . Other features of neonatal lupus syndrome include a transient subacute cutaneous lupus rash exacerbated by UV exposure after birth, haematological manifestations (such as cytopenias) and hepatobiliary disease [60]. Most of these manifestations resolve in the first 6–9 months of life as maternal anti-SSA/Ro antibodies are cleared from the baby's circulation [60] .

Persistent positivity for anti-phospholipid antibodies (aPL) identifies individuals at risk of various specific APOs (one or more unexplained deaths of a morphologically normal fetus at ≥10 weeks gestation; one or more premature births of a morphologically normal neonate before 34 weeks gestation because of eclampsia, preeclampsia, or placental insufficiency **[G]** ; or three or more consecutive spontaneous pregnancy losses at <10 weeks gestation, unexplained by chromosomal abnormalities or by maternal anatomical or hormonal causes) and maternal thrombosis that characterise antiphospholipid syndrome (APS) [61,62]. Common aPL are detected by lupus anticoagulant, anti-cardiolipin and anti-β2 glycoprotein 1 assays. Lupus anticoagulant positivity

seems to be the strongest predictor of APOs in APS [34,63] and triple positivity for all three tests indicates an especially high risk of pregnancy complications and thrombosis [64,65] . The presence of aPL increases the risk of venous thromboembolism in patients with SLE two-fold for anticardiolipin positivity and six-fold for lupus anticoagulant positivity, compared with normal populations **[Au: Do you mean 'healthy individuals'? or patients with SLE negative for aPL?]** [66]. In patients without an underlying autoimmune disease, venous thrombotic risk is increased 1.5-fold for anticardiolipin positivity and up to 10-fold for lupus anticoagulant positivity [67,68], whereas arterial thrombosis is increased three-fold and four-fold, respectively [68]. However, these estimates, derived from meta-analyses, are limited by a lack of prospective data, small cohort size, lack of controls and variable aPL assay methodology amongst the source studies. Patients with a history of thrombotic APS have a lower live birth rate than those without thrombosis [65]. A 2019 survey of data from the European Registry on Obstetric Antiphospholipid Syndrome [69], which studied 1,000 women with obstetric APS as defined by the 2006 Sydney classification criteria [61], has shown that the live-birth rate is only 49.6% without treatment but rises to 85% with the recommended treatment regimen and to 72.4% with other regimens including low-dose aspirin or low-molecular-weight heparin (LMWH) but not on the recommended schedule. Recurrent miscarriages were observed before 10 weeks gestation in 27%, fetal loss in 17% and stillbirth in 18.5% of this cohort of patients with obstetric APS. The survey also reported early preeclampsia (before 34 weeks gestation) in 18.1% and early IUGR (before 34 weeks gestation) in 16.1% of the cases studied [69].

[H2] Presence of organ dysfunction

The presence of organ dysfunction as a complication of an inflammatory rheumatic disease greatly increases the prospect of maternal and fetal morbidity and mortality and should therefore be discussed during pregnancy planning. Conception should be delayed if a patient has active disease and organ dysfunction, until a period of disease quiescence and improvement or normalisation of organ function is achieved. For example, the presence (or even history) of active lupus nephritis at conception is a strong predictor of poor maternal and fetal outcomes [35,71]. However, the risk associated with renal disease is not specific to patients with rheumatic disease and prospective studies involving women with chronic kidney disease of various aetiologies have demonstrated increased risks of pre-eclampsia, preterm delivery, small size for gestational age and increased infant and perinatal mortality rates [72-74]. Furthermore, women with advanced chronic kidney disease (stage 4–5) prior to pregnancy have an increased risk of an accelerated decline in renal function, potentially leading to end-stage disease and the need for renal replacement therapy either in pregnancy or shortly after [75]. Other relative contraindications to pregnancy in patients with inflammatory rheumatic diseases that require multidisciplinary consultation and management include pulmonary hypertension [76], severe interstitial lung disease [77], advanced heart failure [78] and previous severe gestational hypertensive disorders despite therapy [79].

[H1] Medication

Predictive tests to stratify patients at risk of disease relapse and thus requiring intensification rather than withdrawal of therapy in pregnancy are lacking. Therefore, treatment decisions are made on the basis of the pattern of disease activity and manifestations and using standard laboratory markers of disease activity. Medications that are compatible with pregnancy therapy should be continued and intensified appropriately during pregnancy to ensure maintenance of disease control and reduce the risk of APOs (Figure 2). The British Society for Rheumatology (BSR) and EULAR have published guidance regarding the use of various anti-rheumatic drugs in pregnancy and breastfeeding [7-9]. Evidence-based recommendations are summarised here and in Table 2.

[H2] Glucocorticoids

Glucocoticoids can be divided into non-fluorinated (such as prednisone, prednisolone, hydrocortisone and methylprednisolone) and fluorinated (such as dexamethasone and betamethasone) formulations. Non-fluorinated glucocorticoids are safe in pregnancy and breastfeeding as they are metabolised in the placenta with less than 10% of the active drug reaching the fetus [80]. Titration to the minimum tolerable dose **[G]** of corticosteroid is required to reduce complications such as steroid-induced diabetes mellitus, hypertension and infections in the mother [81]. Glucocorticoids are associated with an increased risk of premature birth and some reports have suggested that this increased risk is independent of disease activity [10,82]. Some studies in SLE have detected an association between these drugs and premature rupture of the amniotic sac (known as rupture of membranes) surrounding the baby [83], but other studies did not detect this association [84-86]. Fluorinated corticosteroids are not metabolised by the placenta and cross the placental barrier[87], so these drugs should be used for fetal indications only. Dexamethasone has been suggested to cause developmental problems, such as delayed neuropsychiatric development [83], but this conclusion was not confirmed in two other cohorts of children born to anti-Ro/SSA antibody positive mothers[88,89]. In pregnancy, non-fluorinated corticosteroids are generally administered orally (prednisolone), whereas intravenous administration (for example, with methylprednisolone) is generally used as rescue therapy **[G]** for severe disease. Compared with prednisolone, parenterally administered methylprednisolone has a prolonged duration of action, with equivalent glucocorticoid (anti-inflammatory) effects at a lower dose (80% of prednisolone dose) and similar rates of trans-placental transfer [7].

[H2] Synthetic DMARDs

A number of conventional synthetic DMARDs should be stopped prior to conception. Methotrexate is teratogenic and should be stopped 3 months before conception [7,9]. Given that leflunomide was teratogenic in animal studies and has a long half-life, a cholestyramine washout to eliminate the drug from the body should be completed pre-conception, despite reassuring data from accidental exposures in human pregnancies[90] . Mycophenolate mofetil is teratogenic and should be stopped 6 weeks before conception [91]. Cyclophosphamide is teratogenic and should be stopped at least 3 months before conception [92] .

Conventional DMARDs that can be continued during pregnancy include hydroxychloroquine, sulfasalazine, azathioprine and the calcineurin inhibitors ciclosporin and tacrolimus [7,9]. Women who have conceived while being treated with leflunomide and then stopped this drug and undergone cholestyramine washout in the first trimester [90,93], or who have been exposed to leflunomide at various stages of pregnancy without washout [94,95], do not have an increased risk of APOs. Although leflunomide does not seem to be a major human teratogen, more data are required before its use during pregnancy can be safely advised.

Targeted synthetic DMARDs (such as apremilast, tofacitinib and baricitinib) are small-molecule inhibitors that are increasingly being used to treat inflammatory rheumatic diseases [96-98]. These drugs should be avoided during pregnancy until data are gathered on the risks associated with their use. The precise timing of when to stop these drugs before pregnancy is unclear, but given their short half-lives (3–12 hours [96-98]), stopping each drug 1 month before conception should be sufficient.

[H2] Biologic DMARDs

Biologic DMARDs are recombinant proteins, usually either monoclonal IgG1 antibodies or fusion proteins containing the Fc portion of IgG1 joined to receptor-blocking proteins. These drugs share similar structure with maternal IgG, which are large proteins (~150 kDa) that are unable to diffuse across the placenta [99]. Active trans-placental transfer of maternal IgG takes place via neonatal Fc receptors on syncytiotrophoblast [100-102] and occurs rapidly from 16 weeks of pregnancy onwards [100-012] (Figure 1). Some biologic DMARDs are fusion proteins containing part or none of the IgG structure , principally etanercept and abatacept. Etanercept is a fusion protein of the soluble TNF receptor 2 and the Fc region of IgG1a and despite the presence of the Fc region has low rates of trans-placental transfer [103,104]. Anakinra is a recombinant human IL-1 receptor antagonist that does not contain any immunoglobulin structure, hence it lacks the Fc region, and has not been found to cross full-term human placenta [105]. Abatacept contains the Fc region of IgG1 fused to the extracellular domain of CTLA-4 and has not yet been associated with any specific pattern of risk [106]. Therefore, it is important to consider carefully both the structure and timing of biologic DMARD exposure during pregnancy.

Current guidelines recommend that patients treated with TNF inhibitors should continue with these drugs through to the second or third trimester (depending on drug bioavailability based on the half-life of the drug in the circulation, and on transplacental passage based on the structure of the TNF inhibitor). Administration of the TNF inhibitors is usually stopped at appropriate times in pregnancy (Table 3) to ensure that there is no TNF inhibitor in the maternal circulation at the time of birth as it would also be present in the baby and persist in the neonatal circulation, possibly putting the baby at risk of infection after administration of live vaccines [7,9]. If there is a concern that an inflammatory rheumatic disease will flare, TNF inhibitors should be continued throughout pregnancy but live vaccines, such as rotavirus and tuberculosis, should be avoided in the exposed infant until 6 months of age. This advice is based on a case of fatal tuberculosis-like disease reported post-BCG vaccination in an infant who was not breastfed but was exposed throughout pregnancy to infliximab, a TNF-inhibitor with a long half-life in infants [107]. Certolizumab pegol, a PEGylated Fab' that is specific for TNF, has minimal levels of transfer across the placenta [108] and into breastmilk [109], and is therefore licenced by the European Medicines Agency and Food and Drug Administration for use during pregnancy and breastfeeding.

Current British and European guidelines recommend that other biologic DMARDs (such as rituximab, belimumab, anakinra, and tocilizumab) are stopped in advance of pregnancy owing to limited data [7,9]. However, some of these drugs (anakinra and tocilizumab) have been recommended for use during pregnancy if other treatment options are limited and the benefits of maintaining disease suppression with these biologic agents outweigh the risks [110,111].

Increasingly, biosimilars are replacing existing originator biologic DMARDs. To date, published evidence on the use of biosimilars in pregnancy is very limited. Given their similarity to originator compounds in terms of identical molecular target and antibody structure with variation only in post-translational modifications (as exists between different batches of existing originator biologic DMARDs), it seems reasonable to counsel patients regarding the use of biosimilars in pregnancy on the basis of the existing evidence for each originator compound.

[H2] Analgesics

Conventional NSAIDs are generally safe, but should be avoided in the third trimester owing to their effects upon the ductus arteriosus **[G]**, namely the premature closure of this vessel leading to progressive right heart dysfunction, congestive heart failure and intrauterine death, ~~and should~~but can be used with caution **[Au:OK?]** in the first trimester owing to a low risk of miscarriage [8]. However, cyclooxygenase-2-selective NSAIDs are not recommended because of a lack of data and the theoretical risks that these drugs could impair fertilisation, implantation and maintenance of pregnancy [112] .

Codeine is compatible with pregnancy and during peri-conception for acute pain [8]. British Society for Rheumatology guidelines state that no consistent evidence exists to recommend dose-reduction before delivery, but neonatologists should be aware of maternal use of codeine during breastfeeding, owing to the risk of central nervous system depression resulting from unpredictable metabolism of codeine to morphine[8].

Amitriptyline, gabapentin and pregabalin are commonly used to treat chronic pain. Amitriptyline is safe to use during pregnancy, but gabapentin or pregabalin are not recommended [8].

[H2] Co-morbidity medications

A review of the entire drug list prescribed to each patient is important to ensure that all medications prescribed for co-morbidities, particularly those commonly associated with inflammatory rheumatic diseases, are compatible with pregnancy. In the event of pregnancy, patients with pre-existing hypertension should be instructed to switch from angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and chlorothiazide agents associated with congenital anomalies to alternative antihypertensive drugs, such as labetalol nifedipine or methyldopa [113]. In addition, women at moderate or high risk of preeclampsia should avoid excessive dietary salt intake and should take low-dose aspirin [114,115]. Patients receiving an ACE inhibitor to reduce proteinuria before pregnancy might have greater proteinuria as a result of stopping the ACE inhibitor and the increased glomerular filtration rate (of 50–80%) in pregnancy. Even in patients with diabetic nephropathy this change does not signify worsening renal disease and proteinuria often returns to baseline post-partum [116]. Warfarin is contraindicated in pregnancy owing to an increased risk of congenital abnormalities if continued after week 6 of gestation, so patients taking warfarin should switch to LMWH once pregnancy is confirmed [8].

[H1] Management during pregnancy

[H2] General principles

Patients with inflammatory rheumatic diseases who are planning pregnancy or who are pregnant should be managed in a multidisciplinary setting with close obstetric and rheumatological monitoring, involving regular clinical, laboratory and obstetric ultrasound evaluations and the advice of other specialists depending on organ involvement. Risk stratification should be performed according to degree and extent of maternal disease as well as the antibody status of the patient (aPL, anti-SSA/Ro and anti-SSB/La antibodies). The overall goal is to develop an individualised plan

for management to suppress disease activity using a treat-to-target approach during pregnancy to optimise the chance of a successful pregnancy outcome (Figure 3).

[H2] Maintenance and monitoring of disease control

Disease control is maintained by continued prescription of medications that are compatible with pregnancy. For patients with inflammatory arthritis, sulfasalazine and hydroxychloroquine are ideal maintenance therapies [7,9] and with the caveats already discussed biologic DMARDs might be considered. In patients with SLE, hydroxychloroquine is a mainstay of treatment and discontinuation of this drug is associated with an increased risk of flares and APOs in pregnancy [15,16,52]. Other suitable DMARDs include azathioprine, ciclosporin and tacrolimus [7,9].

Glucocorticoids can be used to treat any inflammatory rheumatic disease, particularly to treat disease flares, and should be titrated to the minimum tolerable dose to maintain disease control and limit steroid related side-effects such as hyperglycaemia and bone loss [17,81]. Concomitant use of calcium and vitamin D to the end of lactation is also particularly important for patients treated with glucocorticoids and/or heparin as they are at increased risk of osteoporosis [17,117]. All pregnant patients with SLE at high risk of pre-eclampsia, including those with lupus nephritis or positive for aPL, should be treated with low-dose aspirin (≤150mg daily), which has been shown to reduce the risk of pre-eclampsia in non-SLE high-risk pregnancies [17,118].

When monitoring disease activity in pregnancy, awareness of physiological changes of pregnancy that resemble those of disease flare is important. Examples of such changes include proteinuria (up to 300 mg per day), increased erythrocyte sedimentation rate (up to 70 mm/h), a 2–3-fold rise in serum complement concentrations~~levels~~ or a fall in serum haemoglobin concentrations~~levels~~ **[Au: change to 'serum concentrations' OK?]** (<110g/l) [119]. In addition, increasing degrees of back pain and swelling of the hands, feet and knees are common in late pregnancy and could be mistaken for arthritis flare. Therefore, C-reactive protein is a more accurate indicator of inflammation than erythrocyte sedimentation rate in pregnancy [119] and should be used in this situation for monitoring, except in SLE for which any fall in complement (C3 or C4) of ≥25% is important, even if into the 'normal' range [17] .

For most inflammatory rheumatic diseases, the same outcome assessment for non-pregnant patients is used during pregnancy, but the use of modified disease activity scores is recommended in some conditions. For example, a modified 28-joint disease activity score for RA includes a measure of C-reactive protein (DAS28-CRP) and unlike the standard DAS28 lacks the global health score, which can be affected by pregnancy itself [45] . Due to the complexity of SLE assessment in pregnancy, a disease activity index has been developed and validated by modifying the British Isles Lupus Assessment Group (BILAG2004) to create the BILAG2004-Pregnancy index so that physiological changes of pregnancy do not influence the score [120].

[H2] Monitoring for pregnancy complications

Women with inflammatory rheumatic diseases should seek antenatal care early (before 12 weeks of pregnancy) and this care should be managed in a multidisciplinary setting. In addition to routine pregnancy monitoring, clinical assessment of the mother and the baby should include measurement

of blood pressure, urinalysis and blood tests, such as for autoantibody status and disease activity. In addition, obstetric ultrasound scans are required at specified intervals to record fetal anatomy, growth and development as recommended for healthy pregnancy with additional monitoring in the third trimester for SLE and APS pregnancies [17,69].

[H2] Prevention and treatment of pre-eclampsia

There is an increased risk of pre-eclampsia in patients with inflammatory rheumatic diseases, particularly in patients with SLE, previous renal disease or patients treated with concomitant glucocorticoids [14,17,33-36]. Risk factors for pre-eclampsia and APOs in SLE pregnancy include high disease activity at conception and during pregnancy, a history of lupus nephritis, maternal hypertension, presence of aPL, low serum complement concentrations~~levels~~ and thrombocytopenia [121]. All patients with an increased risk of pre-eclampsia should be treated with low-dose aspirin until delivery [17,51]. In addition, they should be monitored for development of pre-eclampsia, which includes measurement of blood pressure and proteinuria~~urine protein —~~ **[Au: change from 'urine protein' to 'proteinuria' OK? Or should it be 'urinalysis'?]** at each visit and fetal ultrasound and uterine artery Doppler ultrasound **[G]** flow studies as ordered by obstetric consultants. Bilateral uterine notching **[Au: do you mean 'The presence of bilateral uterine notching'?]** , indicating abnormal blood flow, between 23 and 25 weeks gestation can be used to predict early-onset preeclampsia and gestational hypertension [122]. In addition, measurement of circulating angiogenic factors (including soluble Fms-like-tyrosine kinase 1, placental growth factor and soluble endoglin), which are dysregulated in preeclampsia in non-autoimmune pregnancies [123], can also be used to predict the risk of various APOs, including preeclampsia in patients with SLE [124].

First-line treatment of hypertension in pregnancy is labetalol, with alternatives being methyldopa and nifedipine; ACE inhibitors, angiotensin II receptor blockers and chlorothiazide diuretics are associated with congenital malformations [125].

Distinguishing between lupus nephritis and preeclampsia is challenging but important, as the management of these conditions is different [126]. Both conditions are characterised by proteinuria, oedema, renal impairment, hypertension and thrombocytopenia. Indicators of lupus nephritis include falling (or failure to rise of) C3 and C4 levels, a rising titre of antibodies specific for double-stranded DNA, active urinary sediment and other clinical indicators of SLE activity, such as skin disease, arthritis and cytopenia [126] . Anti-C1q antibodies are also associated with renal involvement in SLE [127] and might therefore function as a biomarker of active SLE. By contrast, many of these features are lacking in pre-eclampsia and unlike lupus nephritis, in pre-eclampsia C3 and C4 levels often increase [126] . If these tests are indecisive a renal biopsy is required to differentiate between lupus nephritis and pre-eclampsia. Depending on the clinical circumstances and the gestation of the pregnancy, premature delivery of the fetus might be mandated as the only cure for pre-eclampsia is delivery of the baby and potent immunosuppression cannot be given for serious renal lupus flare until after delivery due the increased risk of adverse events that would affect the mother and baby in this situation. Multi-disciplinary care is critical in this situation as inappropriate management could result in the death of the baby and/or mother [118,129].

[H2] Thromboprophylaxis and anticoagulation

Pregnancy itself is a pro-coagulant state with alterations in both coagulation and fibrinolysis, presumably to reduce blood loss at delivery [119], and this procoagulant risk is increased in various inflammatory rheumatic diseases [130] , particularly APS [61,63,69] . Thromboprophylaxis **[G]** is required with therapeutic anticoagulation in APS and is a consideration with anti-platelet therapy– **[Au: do you mean it should be considered for patients receiving antiplatelet therapy in other conditions?]** in other conditions, principally SLE [17,63,69] . Treatment to prevent recurrent early miscarriage is the only management in obstetric APS supported by clinical trial data [63,69] . Dual treatment with low-dose aspirin and LMWH is the standard-of-care for all patients with APS. Warfarin is contra-indicated in pregnancy due to its teratogenic effects and patients being treated ~~anticoagulated~~ with this anticoagulant drug– **[Au: changed from 'anticoagulated', OK?]** should be switched to a therapeutic dose of LMWH once pregnancy is confirmed [8]. Evidence is lacking regarding the safety of the direct oral anticoagulants apixaban, rivaroxaban, dabigatran and fondaparinux in pregnancy and use of these drugs is therefore not recommended [131].

[H2] Anti-SSA/Ro and anti-SSB/La complications

Using fetal cardiac ultrasound **[G]** , screening for congenital heart block **[G]** in pregnancies of anti-SSA/Ro-positive and/or anti-SSB/La-positive mothers with a previously affected child should begin at 16 weeks of pregnancy [17]. For anti-SSA/Ro-positive and/or anti-SSB/La-positive women with no previous congenital heart block, most fetal cardiologists recommend an initial fetal cardiac ultrasound scan at 16–20 weeks with a repeat at 28 weeks if the initial scan is normal. Once established, complete AVB is irreversible and cardiac pacing **[G]** is almost always required, but specialist management of any associated cardiac disease might improve fetal outcome [132]. Fluorinated glucocorticoids have been used to treat early stages of AVB [133] , but the benefit of this therapy has not been proven. Hydroxychloroquine, however, is associated with a reduction in the rate of recurrent AVB in future pregnancies after an affected pregnancy [134] and a lower rate of AVB in babies born to mothers with anti-SSA/Ro antibodies with or without SLE [135,136]. Non-cardiac neonatal lupus manifestations are transient [137] and specific treatment is not required .

[H2] Management of flares and organ dysfunction

Standard management of inflammatory rheumatic disease flares in pregnancy is to treat with systemic glucocorticoids and add other DMARDs depending upon the disease and type of manifestation (Figure 2). In inflammatory arthritis, addition of sulfasalazine and/or hydroxychloroquine is suitable to maintain disease control [7,9] . For connective tissue disease or vasculitis, azathioprine is preferred [7,9] and in the case of lupus nephritis or cytopenia, tacrolimus can be used alone or in combination with glucocorticoids and/or other DMARDs in pregnancy [138] . In the case of severe maternal inflammatory rheumatic disease, intravenous immunoglobulins and plasma exchange might be therapeutic [139,140] ; premature delivery of the fetus should also be considered, to reduce the adverse consequences of chronic intrauterine asphyxia that can arise from impaired placental function caused by maternal disease [141].

[H1] Post-partum management

[H2] Risk of post-partum flare

Post-partum inflammatory rheumatic disease flares are common but vary considerably in severity and timing, from several days to 3–6 months after delivery [45,46,52,54]. Evidence that increasing the

dose of glucocorticoids will prevent flare does not exist, but it is possible that flares are worsened by patients discontinuing therapy for fear of harming their baby when breastfeeding.

[H2] Drugs and breastfeeding

Drugs that can be used in pregnancy are usually compatible with breastfeeding, but few trials have tested this compatibility (Table 4). Certolizumab pegol is the only TNF inhibitor licensed by the European Medicines Agency and Food and Drug Administration for use during breast-feeding as it has minimal transfer into breast milk [109]. Most inflammatory rheumatic disease flares– **[Au: meaning flares during breastfeeding? Or in general?]** are treated by starting or increasing the dose of existing oral prednisolone or intramuscular methylprednisolone [126] . Hydroxychloroquine is compatible with pregnancy and, although it enters the breast milk [7,9,142] , evidence does not exist that this drug can harm the baby. Similarly, sulphasalazine is commonly used by mothers with various inflammatory conditions. However, 5mg daily folic acid should be taken during pregnancy and breastfeeding to prevent folate deficiency in the baby [7]. Patients treated with LMWH in pregnancy should continue this drug for 6 weeks post-partum [143] and patients previously taking warfarin can re-start this drug during breastfeeding [8, 143] The safety of the direct oral anticoagulants (such as apixaban, rivaroxaban, dabigatran and fondaparinux) during breastfeeding is unknown and these drugs are therefore not recommended during breastfeeding[131].

[H2] Contraception

Contraception should be discussed soon after delivery for women with inflammatory rheumatic diseases and at risk of post-partum flare to ensure that they do not have a further pregnancy that is unplanned [17]. Many women still think that breast-feeding will protect them from further pregnancy . The most appropriate contraception method is probably the method they used before pregnancy. An intrauterine device, such as a hormone-releasing coil, is a viable and safe option for a patient to consider and discuss with their general practitioner. Risk of infection is low in women using intrauterine devices and DMARDs, except in individuals whose behaviour, independent of their disease and its treatment, puts them at increased risk.

[H1] **Conclusions**

Pregnancy in patients with inflammatory rheumatic diseases has the best outcomes if women conceive during disease remission and with appropriate therapy. Persistent disease activity and disease flares in pregnancy are associated with an increased risk of IUGR, having babies that are small for gestational age and premature delivery. During pregnancy, screening and managing active disease and the increased risk of pre-eclampsia are important, particularly in patients with a history of hypertension, RA or SLE (especially lupus nephritis and APS). Women with inflammatory rheumatic diseases require specific advice about drug therapy while trying to conceive, during pregnancy and while breastfeeding and should be aware of the risk of post-partum flares. However, with careful planning, monitoring and treatment, most women with these diseases can have successful pregnancies.

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Author contributions

All authors made substantial contributions to research and discussion of content. IG drafted the article and CSY and CG edited/reviewed the article.

Competing interests

I.G. declares that he has received honoraria and travel grants from UCB and Lupus Academy to speak at educational meetings on topics related to pregnancy in rheumatic disease. C.S.Y. declares that he has consulted for Bristol Myers Squibb, Immupharma and EMD Serono. C.G. declares that she has consulted for and received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, EMD Serono and UCB in relation to lupus clinical trial design and analysis, and has been a member of the speakers' bureau for GlaxoSmithKline and UCB.C.G. also declares that she has participated in clinical trials sponsored by UCB and funded by Arthritis Research UK with drugs supplied by GlaxoSmithKline.

Key points

- Various inflammatory rheumatic diseases carry an increased burden of adverse pregnancy outcomes (APOs).
- Pregnancy can exacerbate some but not all inflammatory rheumatic diseases.
- Pre-pregnancy counselling is required to evaluate and reduce risks of APOs **[Au:OK?]** for each patient.
- Some therapies must be altered before, during and/or after pregnancy.
- Careful monitoring is required throughout pregnancy by a multidisciplinary team.
- Vigilance for disease flare is required post-partum .

Box 1. Prevalence of inflammatory rheumatic diseases in women of child-bearing age (per 100,000)

Rheumatoid arthritis

120 (age 16 to 44) [1]

SLE

80 (age 20 to 49) [3]

Psoriatic arthritis

130 (age 18 to 49) [3]

Axial spondyloarthritis

117 (age 15 to 44) [4]

Sjogren's syndrome

Data unavailable but probably low as it usually occurs after age 40

Systemic sclerosis

7.0* (age 16–39) [5]

Primary systemic vasculitis

Data unavailable but probably low as onset usually occurs after age 40

*Estimated from aggregated male and female prevalence of 8.4, given 83% of patients with SSc are female.

Figure 1: Transplacental transfer of IgG antibodies from maternal blood into the fetal circulation.

Antibodies such as anti-SSA/Ro and anti-SSB/La cross the placental barrier by active transplacental transfer via Fc receptor expressed on neonatal syncytiotrophoblast cells. Antibody transfer can have

implications for the fetus and baby, including neonatal lupus syndrome. Maternal antibodies are cleared from the baby's circulation within the first 6–9 months of life.

Figure 2. Treat-to-target strategy for management of inflammatory rheumatic diseases in pregnancy.

Treatment during pregnancy aims to maintain disease control and reduce the risk of adverse pregnancy outcomes. Medications that are compatible with pregnancy should be continued and intensified appropriately during pregnancy in case of disease flare. Appropriate treatment depends on the disease and type of manifestation.

APS, antiphospholipid syndrome; IVIG, intravenous immunoglobulins; LMWH, low-molecular-weight heparin; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Figure 3. Optimisation of management of inflammatory rheumatic diseases in pregnancy.

For patients with inflammatory rheumatic diseases, the chance of a successful pregnancy outcome is optimised by the development of an individualised plan to suppress disease activity using a treat-to-target approach. Patients who are planning pregnancy or who are pregnant should be managed in a multidisciplinary setting with close obstetric and rheumatological monitoring, with risk stratification according to the degree and extent of maternal disease as well as the antibody status of the patient.
APS, antiphospholipid syndrome; AVB, atrioventricular block.

Table 1. Considerations for rheumatic diseases in pregnancy

Disease	Disease activity during and after pregnancy	Adverse pregnancy outcomes	Risk factors for adverse pregnancy outcomes
Rheumatoid arthritis	~48–60% reduction during pregnancy ~39–50% flare rate post-partum [45,46]	Pregnancy-induced hypertension, IUGR, pre-term birth, small for gestational age, low birthweight [26-31]	Active disease at conception and during pregnancy
Psoriatic arthritis	~40-50% reduction during pregnancy Variable flare rate post-partum [40,41,55]	No increased risk [40,41]	N/A
Axial spondyloarthritis	~80% active~~/~~ and stable [Au:OK?] during pregnancy and post-partum, with exacerbation most likely in the second and third trimesters [53,54]	Pre-term birth, small for gestational age, emergency or elective caesarean section [31]	Active disease at conception and during pregnancy
SLE	~25% flare rate in pregnancy [51]	Pregnancy loss, pregnancy-induced hypertension, IUGR, pre-term birth, small for gestational age, low birthweight, caesarean section, congenital heart block, neonatal lupus [14,33-37]	Active disease at conception and during pregnancy, hypertension, lupus nephritis, APS, anti-SSA/Ro antibodies, anti-SSB/La antibodies
APS	~2–10-fold increased risk of thrombosis in pregnancy and post-partum [66]	Pregnancy loss, pregnancy-induced hypertension, IUGR, pre-term birth, caesarean section	Antiphospholipid antibodies (particularly triple positivity for aCL, anti-β2GP1 and lupus anticoagulant)
Sjögren syndrome	N/A	Congenital heart block, neonatal lupus, pregnancy loss, pre-term birth, caesarean section [42]	Anti-SSA/Ro antibodies, anti-SSB/La antibodies
Systemic sclerosis	N/A	Pre-term birth, small for gestational age [43]	Rapidly progressive diffuse disease

APS, antiphospholipid syndrome; aCL, anticardiolipin antibodies; anti-β2GP1, anti-β2 glycoprotein-1 antibodies; IUGR, intrauterine growth restriction; SLE systemic lupus erythematosus.

Table 2. Anti-rheumatic drugs recommended by BSR and EULAR for use at conception and during pregnancy [7-9]

Drug class	Compatible with pregnancy	Some evidence of lack of harm	Contraindicated
Analgesic	Conventional NSAIDs (up to 32 weeks of pregnancy), amitriptyline, opiates	N/A	COX2 inhibitors, gabapentin, pregabalin
Anti-thrombotic	Low-dose aspirin, heparin	N/A	Warfarin, apixaban, rivaroxaban, dabigatran, fondaparinux
Glucocorticoids	Glucocorticoids	N/A	N/A
Conventional DMARDs	Hydroxychloroquine, sulfasalazine, azathioprine, tacrolimus, ciclosporin	Leflunomide	Methotrexate, cyclophosphamide, mycophenolate mofetil
Biologic DMARDs	Certolizumab pegol, infliximab, adalimumab, etanercept, golimumab	Anakinra, canakinumab, tocilizumab, abatacept	Rituximab, belimumab, ustekinumab, rilonacept
Targeted synthetic DMARDs	N/A	N/A	Apremilast, tofacitinib, baricitinib

BSR, British Society for Rheumatology; COX2, cyclooxygenase 2.

Table 3. TNF inhibitors used during pregnancy

TNF inhibitor	Half-life	Recommended discontinuation time during pregnancy [7,9]
Infliximab	8–9.5 days	16–20 weeks
Etanercept	70 hours	24–32 weeks
Adalimumab	14 days	20–24 weeks
Certolizumab	14 days	Safe throughout pregnancy
Golimumab	12 days	Limited data available; possibly safe in first trimester

Table 4. Anti-rheumatic drugs recommended by BSR and EULAR for use during breastfeeding [7-9]			
Drug class	**Compatible with breastfeeding**	**Consider if benefits outweigh potential risks**	**Contraindicated**
Analgesic	Conventional NSAIDs, Amitriptyline	Opiates	N/A
Anti-thrombotic	Low dose aspirin, heparin, warfarin	N/A	Apixaban, rivaroxaban, dabigatran, fondaparinux
Glucocorticoids	Glucocrticoids	N/A	N/A
Conventional DMARDs	Hydroxychloroquine, sulfasalazine, azathioprine, tacrolimus, ciclosporin	N/A	Methotrexate, cyclophosphamide, mycophenolate mofetil
Biologic DMARDs	Certolizumab pegol, infliximab , adalimumab, etanercept, golimumab	Anakinra, canakinumab, abatacept, tocilizumab, rituximab, belimumab, ustekinumab	N/A
Targeted synthetic DMARDs	N/A	N/A	Apremilast, tofacitinib, baricitinib

Glossary Terms

Cyclophosphamide-induced gonadal toxicity – Gonadal damage induced by cyclophosphamide, leading to reduced ovarian function.

Gestational hypertension – New-onset hypertension presenting after 20 weeks gestation without significant proteinuria.

Preeclampsia - New-onset hypertension presenting after 20 weeks gestation with significant proteinuria. Indicative of maternoplacental dysfunction.

Intrauterine growth restriction – Reduced fetal growth resulting in an estimated weight below the 10th percentile for gestational age.

Small for gestational age - Term used to describe a baby who is smaller than usual for the number of weeks of pregnancy. These babies usually have birthweights below the 10th percentile for gestational age.

Endocardial fibroelastosis - A rare heart disorder of infants and children that is characterised by a thickening within the muscular lining of the heart chambers due to an increase in the amount of supporting connective tissue (inelastic collagen) and elastic fibres.

Placental insufficiency - Failure of the placenta to deliver sufficient nutrients and oxygen to the fetus during pregnancy.

Minimum tolerable dose of corticosteroid – The minimum dose required to maintain disease control and reduce complications such as steroid-induced diabetes mellitus, hypertension and infections in the mother.

Rescue therapy – Treatment given after a patient has failed to respond to standard therapy.

Ductus arteriosus - A blood vessel in the fetus connecting the main pulmonary artery to the proximal descending aorta, allowing most blood from the right ventricle to bypass the lungs. Premature closure of this blood vessel leads to progressive right heart dysfunction, congestive heart failure and intrauterine death.

Uterine artery Doppler ultrasound – A technique used to measure uterine artery blood flow between mother and baby.

Thromboprophylaxis – In this context, the prevention of thromboembolic disease by pharmacologic means.

Fetal cardiac ultrasound – Technique used to evaluate the structure of the fetal heart.

Screening for congenital heart block – The use of fetal cardiac ultrasound at 16–18 weeks of pregnancy in anti-Ro/SSA-positive mothers.

Cardiac pacing –Technique used to regulate heart rate involving the fitting of a pacemaker.