

## REVIEW

# Managing pregnancy in inflammatory rheumatological diseases

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### Abstract

Historically, pregnancy in women with many inflammatory rheumatic diseases was not considered safe and was discouraged. Combined care allows these pregnancies to be managed optimally, with the majority of outcomes being favorable. Disease activity at the time of conception and anti-phospholipid antibodies are responsible for most complications. Disease flares, pre-eclampsia, and thrombosis are the main maternal complications, whereas fetal loss and intrauterine growth restriction are the main fetal complications. Antirheumatic drugs used during pregnancy and lactation to control disease activity are corticosteroids, hydroxychloroquine, sulphasalazine, and azathioprine. Vaginal delivery is possible in most circumstances, with cesarean section being reserved for complications.

### Introduction

Autoimmune rheumatic disease covers a spectrum of conditions, including systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), other inflammatory arthropathies/spondyloarthropathies, systemic sclerosis (SSc), and systemic vasculitides. Historically, pregnancy was not deemed safe in women with multisystem rheumatic diseases, either because of the risk of that their condition would deteriorate or because of their medications. As this review will show, this view has changed and current opinion is that with good disease control, careful planning, and combined management, delivery of healthy babies is often possible. Family size is smaller in women with rheumatic diseases because of a combination of factors, including

disease activity, drug exposure, psychosocial factors, and self-exclusion [1,2].

### Fertility

Inflammatory rheumatological diseases affect women of childbearing age, and fertility is an important consideration. Fertility is not usually affected by the rheumatic diseases; however, factors that impact on female fertility include cytotoxic drugs, amenorrhoea accompanying severe flares, and renal insufficiency [3].

The main cytotoxic drug that poses a threat to fertility is cyclophosphamide. It is known to cause premature ovarian failure, and the risk is dependent on the age at which it is started, the duration of treatment, and the cumulative dose. Boumpas and colleagues [4] showed that none of the women who were under the age of 25 years and who had not more than 7 pulses of intravenous cyclophosphamide developed sustained amenorrhoea. However, all the women who were over 30 years and who received at least 15 intravenous pulses of cyclophosphamide developed sustained amenorrhoea [4]. The risk varies with the regime used, and another study of 84 patients with SLE showed that two thirds of cases had successful pregnancies [5,6].

Elizur and colleagues [7] suggested that fertility preservation should be offered to all women with severe renal/extrarenal manifestations of SLE or other systemic rheumatic diseases requiring cyclophosphamide at doses that might preclude them from having their own biological child. Options available include ovulation induction therapy, oocyte or embryo cryopreservation, or *in vivo* maturation of oocytes. Ovulation induction therapy may promote flares in patients with lupus and precipitate thromboembolism in women with antiphospholipid antibodies [8].

### Effects of the rheumatological disease and pregnancy on the mother

#### Systemic lupus erythematosus

##### 1. Disease activity

There is much debate in the literature as to whether lupus activity increases during pregnancy. Studies have involved varied cohorts of patients and controls, making

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the studies difficult to compare. The hormonal changes that occur in pregnancy seem to be responsible for inducing lupus activity, and it appears that 40% to 50% of patients have a measurable increase in disease activity. The risk of a severe flare is lower and is estimated at 15% to 30%. Flares are typically cutaneous, arthritic, or hematological. The risk of flare is increased if there is evidence of a flare within 6 months prior to conception, active lupus nephritis, very active lupus in the past, and/or discontinuation of medication [9-11]. There is a risk of flares in the postpartum period even if disease has been in remission before and during pregnancy. Diagnosis of lupus flare is important to distinguish from pregnancy-related physiological changes or complications. These features are outlined in Table 1 [12].

## 2. Pregnancy effects

Women with SLE are at an increased risk of developing medical complications during pregnancy, regardless of whether their lupus is active or not [13]. Owing to hormonal changes, the risk of thrombosis is increased two to three times during pregnancy and the first 6 weeks after delivery. There is a 5% to 10% risk that a pregnant woman with SLE will develop a thrombosis during this period, even in the absence of APS [14].

Women with SLE are at higher risk of maternal complications (disease flares, pregnancy-induced hypertension [PIH], pre-eclampsia, eclampsia, diabetes, or thrombosis) and fetal complications (recurrent fetal loss, growth restriction, or fetal distress in labor) [13]. As a result, they tend to have longer hospital stays and a higher rate of cesarean section. Maternal mortality, though rare, is increased approximately 20 times compared with that of women in general in the US [13,15].

Pre-eclampsia is defined as PIH in association with proteinuria (greater than 0.3 g in 24 hours) and edema, but virtually any organ may be affected. This is a common pregnancy-related complication in SLE. About 25% of women with SLE develop pre-eclampsia, and the risk is higher for women with pre-existing hypertension, a history of lupus nephritis, or anti-phospholipid antibodies [13,15]. Differentiating between active lupus nephritis and pre-eclampsia is crucial, and it is important to note that the two can coexist. The presence of hypertension with recent-onset proteinuria makes pre-eclampsia more likely than lupus nephritis, as hypertension is very rarely an early sign of active renal disease. Red or white cells in the urine in the presence of proteinuria are more likely to be due to lupus nephritis (after excluding infection, bleeding, or calculi). Urinary casts are the best marker for active renal lupus. Blood tests that help to distinguish active renal disease from pre-eclampsia include an increase in anti-double-stranded DNA (anti-dsDNA) titres or a 25% decrease in

**Table 1. Features that help to distinguish systemic lupus erythematosus disease activity from pregnancy-induced changes**

Unreliable features	Reliable features
Facial/palmar erythema	Palpable lupus rash
Arthralgia	Synovitis
Anemia	Alopecia (localized)
Low platelets	Leucopenia (new, not drug-related)
Hypertension	Red cells or casts (or both) in urine
Proteinuria	Rising anti-dsDNA (anti-double-stranded DNA) antibodies
Low C4 with normal C3	25% decrease in C3 and C4 (may be in normal range)
Classical pathway activation	Alternative pathway activation

complement levels (C3 and C4) (even within the normal range) or both [12].

## Antiphospholipid syndrome

### 1. Disease activity

APS is characterized by the presence of anti-phospholipid antibodies and either vascular thrombosis or pregnancy morbidity [16]. Primary APS occurs in isolation in 50% of patients, whereas secondary APS can be associated with any other autoimmune disease, most commonly SLE. The increased risk of thrombosis during all pregnancies is increased further in patients with APS and most often presents as deep vein thrombosis, pulmonary emboli, stroke, hepatic infarction, recurrent miscarriages, and premature delivery for fetal distress or pre-eclampsia. Anti-phospholipid antibodies may also initiate an inflammatory process involving the activation of complement that affects placental function and results in poor pregnancy outcomes [17]. Patients with lupus anticoagulant and/or previous pulmonary emboli are at risk of pulmonary hypertension that may deteriorate in pregnancy which is associated with a 50% risk of maternal mortality [18,19].

### 2. Pregnancy effects

The presence of anti-phospholipid antibodies predisposes the patient to PIH, pre-eclampsia, and eclampsia, the last of which usually presents as one or more convulsions superimposed on pre-eclampsia. Pre-eclampsia may occur in patients with APS pregnancy earlier than in healthy women, from 22 weeks [20]. HELLP syndrome is a thrombotic microangiopathic disorder consisting of hemolysis, elevated liver enzymes, and low platelets. It presents typically in the third trimester but in patients with APS may present with pre-eclampsia earlier than in healthy women, even as early at 15 weeks of gestation [21-24].

## **Rheumatoid arthritis and other inflammatory arthropathies/spondyloarthropathies**

### **1. Disease activity**

In RA, provided that disease activity is stable at the time of conception, approximately 75% of patients notice an improvement in their condition within the first trimester and approximately a quarter go into remission [25]. The risk of flares is increased in the postpartum period, and the majority of women have flares within the first 3 months after delivery but only about 40% are of moderate severity [25,26]. The immunological basis for these changes remains uncertain but is thought to involve changes in regulatory T cells, monocytes, and galactosylation levels of immunoglobulin G [27-31].

Pregnancy generally improves physical functioning in patients with RA but not in those with ankylosing spondylitis. Emotional and mental health during pregnancy are unaffected in both conditions [32]. Women with spondyloarthropathy generally notice an improvement in their peripheral arthritis and uveitis during pregnancy [33]; however, spinal disease tends to remain unchanged or worsen. Postpartum flares are common in the first 3 months following delivery and are unrelated to disease activity during pregnancy, duration of lactation, or time of return of menses [14].

### **2. Pregnancy effects**

Pregnancy outcomes for women with RA and spondyloarthropathies tend to be favorable; however, these women have increased lengths of hospital stay, increased rate of premature rupture of membranes, and higher cesarean section delivery rates in comparison with healthy women [15]. There is no increased risk of pre-eclampsia in RA [34].

## **Systemic sclerosis**

### **1. Disease effects**

Scleroderma, the skin changes of SSc, tends not to change in pregnancy. Raynaud phenomenon usually improves because of the physiological increase in cardiac output. Gastroesophageal reflux disease is seen to worsen but is a common presentation in all pregnant women. Recurrent vomiting can cause Mallory-Weiss tears in the esophagus already thinned by disease-related fibrosis; therefore, prompt management is of importance in the prevention of life-threatening bleeding [35]. One of the most serious complications that occurs in pregnant women with SSc is renal crisis due to acute-onset severe hypertension. A daily increase in serum creatinine and lack of proteinuria in the early stages support a diagnosis of renal crisis due to SSc. Renal crisis is most common in patients with early diffuse SSc (within 5 years of symptom onset), anti-tropoisomerase and anti-RNA polymerase III antibodies, and exposure to high-dose corticosteroids

[35]. Pulmonary hypertension is another serious complication and is associated with 50% maternal mortality, and most vigilance is required 48 to 72 hours after delivery. Screening should be done before pregnancy, and termination should be offered if the complication is diagnosed in pregnancy [36].

### **2. Pregnancy effects**

Women with SSc have a higher rate of hypertensive disease, including pre-eclampsia, and have an increased length of hospital stay compared with normal women [15]. Elevated liver function tests and proteinuria with edema are more common in pre-eclampsia and HELLP syndrome than in SSc renal crisis. Hypertension or renal dysfunction due to pre-eclampsia, but not due to active SSc, will be resolved by delivery [12].

## **Vasculitides**

### **1. Disease effects**

There are very few prospective studies of vasculitides in pregnancy. Vasculitides can occur at any age but are generally more frequent in men and in women beyond their reproductive period [37]. Planning conception at a time of disease inactivity usually allows women with Wegener granulomatosis (WG), polyarteritis nodosa (PAN), or Churg-Strauss syndrome to remain well during pregnancy. They are at risk of deterioration during pregnancy and the first 6 weeks after delivery should conception occur when the disease is inadequately treated or newly active [38,39].

Only 38 cases of WG have been reported in the literature: 21 were in remission at conception, 13 were diagnosed during pregnancy, and 4 had active disease at the time of conception. Flares have a bimodal distribution, most commonly occurring either in the first or second trimester or in the month after delivery. Maternal death has been reported twice, once following therapeutic abortion and once 1 month after delivery [38,40,41].

There are eight reports of pregnancy and PAN [12,39,42]. Conceiving at a time when PAN is active puts the mother at higher risk of death; hence, therapeutic abortion is recommended in the early phase of pregnancy, or high-dose corticosteroids with cyclophosphamide are recommended in the late stages [39].

In Churg-Strauss syndrome, respiratory and cardiac systems are most commonly affected during relapse. Asthma is more common but cardiac involvement can lead to irreversible myocardial damage requiring heart transplantation, so careful pre-pregnancy screening and management of pregnancy are critical [39,43].

In Takayasu arteritis (TA), severe aortic valvular disease and aortic aneurysm are risk factors for maternal morbidity and fatality; therefore, pregnancy is discouraged in these patients [39]. Less frequently, heart

failure, renal insufficiency, and cerebral hemorrhage have been reported. Despite these complications, the outcome of pregnancy is generally favorable provided that there is little delay in seeking medical advice [44].

Behçet disease (BD) improves during pregnancy in most patients; however, exacerbations occurred in about a sixth of patients in a case control study [45]. BD is associated with an increased risk of thrombosis and vascular involvement, including central venous thrombosis [46].

## 2. Pregnancy effects

Hypertensive disease is more common in women with WG and renal involvement than in normal pregnant women. It is the presenting feature in TA and pregnancy, and pre-eclampsia complicated 62% of cases in a recent single-center Indian study [47]. Pregnancy complications and cesarean section were significantly higher in BD patients than in controls [45], as with most other vasculitides, particularly TA and WG. Like lupus nephritis, renal vasculitis needs to be distinguished from pre-eclampsia; however, blood tests (c-ANCA [anti-neutrophil cytoplasmic antibody and classical cytoplasmic staining complete heart block] and anti-PR3 [anti-proteinase-3]) are helpful only in diagnosing renal vasculitis due to WG.

## Effects of the autoimmune disease on the fetus

### Fetal loss

'Fetal loss' incorporates spontaneous abortion from less than 10 weeks, miscarriages from 10 to 19 weeks, and stillbirths from 20 weeks of gestation. The most important factors in predicting fetal loss in SLE, APS, SSc, and vasculitis are previous fetal loss, disease activity at conception (especially renal), maternal hypertension, and the presence of anti-phospholipid antibodies [12,48]. Fetal loss is not increased in those with inflammatory arthropathies or spondyloarthropathies in the absence of maternal complications.

### Intrauterine growth restriction

The risk of intrauterine growth restriction (IUGR) in SLE and APS pregnancies is about three times that in controls [15]. The risk of IUGR is increased in those with active disease at conception and in those with anti-phospholipid antibodies [9,11,16]. IUGR increases the risk of premature delivery and is thought to occur due to uteroplacental dysfunction secondary to thrombosis and complement activation; however, the exact mechanisms are unknown [17].

### Premature delivery

Premature delivery, which is defined as occurring before 38 weeks of gestation, is common in lupus, APS, SSc, and

the vasculitides [12,13,35,44,49]. Pre-term delivery is not associated with RA [34]. The most important complication of premature delivery is respiratory distress syndrome. In this condition, the newborn can suffer from respiratory distress due to insufficient surfactant. If premature delivery is imminent, the mother should be given a course of corticosteroids to promote fetal lung development at least 24 hours before birth. The current UK guidelines recommend two doses of betamethasone 12 mg intramuscularly (12 hours apart) or four doses of dexamethasone 6 mg (12 hours apart) [50].

## Neonatal lupus

Neonatal lupus is a model of passive autoimmunity in mothers who carry anti-Ro (SSA) or anti-La (SSB) antibodies or both. Antibodies cross the placenta from about week 16 and are associated with (a) irreversible congenital complete heart block (CHB) in the fetus or (b) transient photosensitive rash on the face or scalp or various liver and hematological abnormalities or neurological manifestations in the newborn or (c) both. CHB is defined as atrioventricular block diagnosed *in utero*, at birth, or within the neonatal period (0 to 27 days after birth) and is present in approximately 1% to 2% of women with anti-Ro/La antibodies [51-53]. CHB is permanent, and although most children do well with pacemakers, the cumulative probability of survival at 3 years of age was only 80% in one report [52]. Neonatal lupus rash is present in 10% to 20%, and laboratory abnormalities (anemia, thrombocytopenia, neutropenia, and abnormal liver function tests) were detected in up to 27% of babies in a prospective study [51]. The risk of recurrence of CHB is about 20% in a subsequent pregnancy after an affected child [53].

Women who are at risk of having a baby with CHB are recommended to have regular monitoring [54], but guidelines vary among countries and among units. In the UK, the midwife should listen to fetal heart rate on a weekly basis to identify bradycardia from week 16 onwards and the baby should have heart rate confirmed while being scanned monthly. Formal fetal echocardiography occurs at the 20-week anomaly scan, and further echocardiograms are done if an abnormality is suspected. Partial heart block can be identified on fetal electrocardiogram [54]. Intravenous immunoglobulin (IVIG) has been reported to successfully treat severe thrombocytopenia associated with neonatal lupus [55], but IVIG does not prevent recurrence of CHB [56]. All babies born to mothers with anti-Ro/La should have an electrocardiogram after birth to look for first- and second-degree heart block as they may progress to third-degree later.

## Neonatal autoimmune thrombocytopenia

Transmission of anti-platelet antibodies across the placenta in women with APS is recognized to cause

thrombocytopenia in infants. Occasionally, this presents as intracranial hemorrhage [57]. Thrombocytopenia usually resolves within 6 months as the mother's antibodies are cleared from the circulation. IVIG may be used as treatment for severe thrombocytopenia [58].

### Pre-pregnancy considerations

To avoid or reduce the complications discussed above, pre-pregnancy planning and screening must be carefully undertaken. Combined care involving rheumatologists, nephrologists, hematologists, or other relevant physicians, obstetricians, and anesthesiologists is preferred for all but simple inflammatory arthropathies. Management of the pregnant patient with inflammatory rheumatological disease should be tailored to the individual's disease activity and history. Pregnancy during disease remission provides the best results as described above, and patients should be advised not to get pregnant until the disease has been well controlled for 6 months on non-teratogenic drugs that can be continued in pregnancy to reduce the risk of flares. A review of all medication that might affect pregnancy should be undertaken.

Side effects of teratogenic medication, such as methotrexate, cyclophosphamide, mycophenolate mofetil, or leflunomide, must be discussed prior to commencing treatment, and information on contraceptive methods should be offered with advice on when the drugs and contraception should be stopped prior to pregnancy (Table 2). Most contraceptive choices, including emergency contraceptive choices, can be offered to patients with rheumatological diseases, but there is a potential risk of thrombosis in APS if the patient is not fully anticoagulated. Estrogen-containing contraceptives can be used with care in patients with mild non-active lupus but, owing to the increased risk of thrombosis, should be avoided in women with anti-phospholipid antibodies or APS [59-61].

Disease activity should be assessed by standard criteria for each disease and potential risk factors for pregnancy complications – including anti-Ro/-La and anti-phospholipid antibodies (including IgG and IgM anti-cardiolipin and  $\beta$ 2 glycoprotein-I antibodies and lupus anticoagulant), hypertension, and diabetes and raised serum creatinine, 24-hour proteinuria, or protein/creatinine ratio – should be identified [12,48]. Echocardiography and lung function tests should be done if there have been cardiac, lung, or thrombotic complications, particularly if there is a risk of pulmonary hypertension [18,19,36].

As with other women planning pregnancy, a healthy diet and appropriate exercise are recommended and smoking, using illicit drugs, or drinking alcohol are discouraged. Folic acid (0.4 mg) should be started 3 months prior to pregnancy and continued until

12 weeks of gestation to prevent neural tube defects [62]. Women taking folate antagonists such as sulphasalazine are usually advised to take 5 mg daily throughout pregnancy and lactation.

### Management of pregnancy

#### Drugs

A summary of drugs available for use in patients with inflammatory rheumatological conditions in pregnancy is provided in Table 2. Specific attention should be given to the most commonly used drugs: analgesia, corticosteroids, sulphasalazine, azathioprine, hydroxychloroquine, aspirin, and heparin and those that are contraindicated [49,63-66].

Paracetamol is the first-line analgesic. Mild opioids such as codeine or pethidine are preferred if needed, as they can be easily reversed. The concerns are that the newborn may present with respiratory depression or opioid dependency or both [67]. Tramadol has embryotoxic effects in animals and should be avoided.

Corticosteroids can be divided into non-fluorinated steroids (prednisolone and methylprednisolone) and fluorinated steroids (betamethasone and dexamethasone) [64]. Approximately 90% of prednisolone is metabolized by the enzyme 11- $\beta$ -hydroxysteroid dehydrogenase in the placenta; as a result, about 10% reaches the fetus. It is widely used, therefore, to treat maternal disease or flares (or both) in pregnancy. Fluorinated steroids are not metabolized by the placenta and reach the fetus in their active form. These steroids are used to treat or prevent fetal complications, but reversal of CHB has not been achieved [54,64,68]. All steroids increase the maternal risk of hypertension, pre-eclampsia, premature rupture of membranes, infection, and diabetes, so the lowest effective dose must be used (ideally not more than 15 mg/day).

Sulphasalazine has been used for many years for arthropathies and inflammatory bowel disease in pregnancy. Hydroxychloroquine is an anti-malarial used mainly in the treatment of SLE and reduces the risk of maternal disease flare and possibly thrombosis and does not cause fetal damage. Women are recommended to continue with hydroxychloroquine throughout pregnancy and lactation [14,69]. Azathioprine is a cytotoxic immunosuppressant used mainly in SLE and vasculitis. The fetus lacks the enzyme inosinotriphosphorylase, which is required to convert azathioprine to its active metabolite 6-mercaptopurine, and therefore azathioprine is safe to use in pregnancy. Azathioprine can be used to control severe maternal disease, and doses of not more than 2 mg/kg per day are associated with few side effects [64].

#### Treatment and prevention of flares

Provided that conception occurs during remission, the risk of flares is low. The patient's condition should be kept

**Table 2. Commonly used drugs in inflammatory rheumatological diseases, their fetal effects, and recommendations during pregnancy**

Class	Drug	Fetal effects	Recommendation
Analgesic	Paracetamol	Not known to be harmful	Can be used during pregnancy
Analgesic (high dose) and antiplatelet agent (low dose)	Aspirin	Low dose (antithrombotic dose) 75 mg daily is safe and lowers risk of premature delivery and pre-eclampsia. At higher doses (analgesic doses), there is potential risk of impaired renal function, pulmonary hypertension, or clotting ability in newborn.	Can be continued throughout pregnancy
Anti-inflammatory (analgesic) drugs	NSAIDs	If given within 14 days of delivery, premature closure of ductus arteriosus, which can lead to pulmonary hypertension. Possible risk of cardiac septal defects and gastroschisis	Discontinue at 32 weeks of gestation, earlier if premature delivery suspected. Need 2-week gap between stopping NSAIDs and delivery. If needs to be used, ibuprofen preferred to diclofenac as shorter half-life.
Analgesic	Codeine	Respiratory depression and withdrawal symptoms in neonate if opioid used during delivery	Use at lowest effective dose, but avoid during labor.
Analgesic	Pethidine	Respiratory depression and withdrawal symptoms in neonate if opioid used during delivery	Can be used during pregnancy
Analgesic	Tramadol	Embryotoxicity in animals	Avoid during pregnancy
Analgesic	Morphine	Respiratory depression and withdrawal symptoms in neonate if opioid used during delivery	Avoid during pregnancy
Anti-inflammatory (analgesic) agent	Cyclo-oxygenase inhibitors (COX inhibitors)	Impaired renal function, decreased fetal urine output, development of oligohydramnios. Teratogenic in animal studies.	Should be avoided
Immunosuppressive agents	Corticosteroids	Prolonged treatment >15 mg/day increases risk of premature rupture of membranes and preterm labor. Increased risk of oral cleft and palate at high doses.	Can be continued in pregnancy but should be lowest effective dose. (See 'Drugs' subsection of 'Management of pregnancy' section.)
Disease-modifying agent	Hydroxychloroquine	No associated congenital abnormalities or malformations	Can be continued throughout pregnancy
Disease-modifying agent	Sulphasalazine	Folic acid antagonist. Associated with two- to threefold increased risk of oral clefts and cardiovascular anomalies. Risk diminished by concomitant use of folic acid throughout pregnancy.	Can be continued in pregnancy but requires folic acid supplementation throughout pregnancy
Disease-modifying agent	Azathioprine	Small risk of depressed hematopoiesis in infant in doses of >2 mg/kg per day	Can be continued in pregnancy, not more than 2 mg/kg per day
Disease-modifying agent	Ciclosporin	No increase in rate of birth defects but risk of maternal hypertension and intrauterine growth restriction	Can be continued in pregnancy up to dose of 2.5 mg/kg per day
Disease-modifying agent	Cyclophosphamide	Embryopathy with growth defects, developmental delay, craniofacial defects, or distal limb defects	Discontinue at least 3 months prior to conception. Effective contraception vital during this time.
Disease-modifying agent	Methotrexate	Increased risk of congenital abnormalities in central nervous system, cranial ossification, limbs, palate, and growth retardation.	Discontinue 3 months prior to conception. Wait at least one menstrual cycle after stopping drug before trying to conceive.
Disease-modifying agent	Leflunomide	Inhibits <i>de novo</i> synthesis of pyrimidine in activated lymphocytes, leads to increased risk of embryotoxicity and teratogenicity in animals.	Stop 2 years before conception or use washout procedure with cholestyramine.
Disease-modifying agent	Mycophenolate mofetil	Recently identified phenotype of craniofacial malformations affecting oral cavity and ears as well as ocular anomalies. Less frequently, limb abnormalities, with congenital cardiovascular, renal, or central nervous system malformations.	Discontinue and switch to azathioprine at least 3 months prior to conception.
Disease-modifying agent	Gold salts	Cross placenta, found in fetal liver and kidneys, no evidence of increase in neonatal malformations in small number of reports available	May be continued
Biological agent	Tumor necrosis factor-alpha inhibitors (for example, infliximab, etanercept, adalimumab)	No toxic effects in animals, sporadic adverse events in humans but insufficient to determine toxicity or safety	Discontinue at missed period or positive pregnancy test.

*Continued overleaf*

**Table 2. Continued**

Class	Drug	Fetal effects	Recommendation
Biological agent	Abatacept	Crosses placenta in animals, no data in human pregnancies	Discontinue at least 10 weeks prior to conception.
Biological agent	Anakinra	No evidence with human pregnancy	Discontinue use prior to conception.
Biological agent	Rituximab	Actively transported across placenta, with neonatal levels being higher than maternal levels. Can lead to transient B-cell depletion in neonate, no infections reported.	Discontinue 1 year prior to conception.
Prevention or treatment of osteoporosis	Bisphosphonates	Cross placenta and accumulate in fetal bone, causing bone abnormalities in animals.	Discontinue 2 years before planned pregnancy as retained in human skeleton and released in circulation for at least 2 years after stopping drug.
Prevention or treatment of osteomalacia and osteoporosis	Calcium and vitamin D supplements	Therapeutic doses unlikely to be harmful	Can be continued in pregnancy
H2 blocker to reduce gastric acid production	Ranitidine	Not known to be harmful	Can be continued in pregnancy (extensive experience)
Proton pump inhibitors	Omeprazole (lansoprazole)	Not known to be harmful	May be continued (less experience)
Anti-hypertensive agent	Angiotensin-converting enzyme inhibitors	Adversely affect fetal and neonatal blood pressure control and renal function. Skull defects and oligohydramnios have been reported.	Discontinue 3 months prior to conception. Contraindicated in pregnancy except possibly in scleroderma renal crisis.
Anti-hypertensive agent and vasodilator	Calcium channel blockers	No significant abnormalities	Can be continued in pregnancy (more experience with nifedipine than amlodipine or others)
Anticoagulant	Heparin	Does not cross placenta and is not associated with congenital defects.	Can be continued in pregnancy, but owing to heparin-induced osteopenia, calcium and vitamin D supplements are needed
Anticoagulant	Warfarin	Risk of fetal warfarin syndrome	Contraindicated in first and third trimesters of pregnancy but can be used in postpartum period

NSAID, non-steroidal anti-inflammatory drug.

stable on medication that can be continued throughout pregnancy, such as prednisolone, hydroxychloroquine, sulphasalazine, and azathioprine. If these drugs are stopped, there is an increased risk of flare [14,69,70].

Mild flares of lupus, vasculitis, or arthritis are usually treated with low-dose prednisolone (less than 15 mg per day). Higher doses or intravenous pulse methylprednisolone is used for severe flares. Non-teratogenic medication such as azathioprine, ciclosporin, or tacrolimus may be used. Cyclophosphamide and mycophenolate mofetil are occasionally used when all other options have been exhausted in the third trimester [11,38,39].

#### Management of recurrent pregnancy losses

Managing recurrent fetal losses depends on understanding the mechanism(s) underlying fetal loss. Three specific causes have been identified: disease activity (which is controlled as discussed above), maternal complications such as pre-eclampsia, or thrombosis. Thrombosis is most commonly associated with anti-phospholipid

antibodies, and treatment occurs in one of two ways. The first is the use of antiplatelet/anticoagulant therapy, mainly aspirin and heparin. In the literature, there is much debate about the correct regime, and optimal doses have not been agreed upon. The current recommended guideline for women who have recurrent miscarriages is combination therapy of low-dose aspirin with low-molecular-weight heparin [64,71,72]. A randomized, controlled trial found no difference between giving aspirin only versus giving aspirin and heparin [73]. However, in that trial (as in a number of studies), not all patients had confirmed APS according to the Sydney criteria, making results difficult to interpret [16].

#### Treatment and prevention of hypertension

Non-teratogenic anti-hypertensives should be taken before and during pregnancy. Labetalol, nifedipine, methyldopa, and hydralazine are used to control hypertension. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated because

**Table 3. Disease-specific complications that may affect use of analgesia and anesthesia**

Disease	Complications that may affect use of analgesia and anesthesia
Systemic lupus erythematosus	Pericarditis or valvular abnormalities Pulmonary hypertension, pleural effusions, or lupus pneumonitis Peripheral neuropathies, central nervous system dysfunction (seizures), or psychological problems Hematological abnormalities (anemia, thrombocytopenia, or coagulopathy) Lupus nephritis
Antiphospholipid syndrome	Coexisting autoimmune disease, secondary organ involvement, and thrombotic phenomena, including pulmonary hypertension Anticoagulation
Rheumatoid arthritis	Cervical spine involvement (exclude atlantoaxial anterior subluxation and avoid excessive manipulation of neck during general anesthesia) Hip disease that might prevent vaginal delivery Pleural/pericardial effusions and pulmonary parenchymal involvement
Ankylosing spondylitis	Assess presence of extra-articular (cardiopulmonary) features and use of opiate analgesics Temporo-mandibular joint dysfunction, cervical and lumbar spine (for general, epidural, or spinal anesthesia), and hip involvement (for vaginal delivery)
Systemic sclerosis	Renal disease, systemic hypertension, pulmonary hypertension, or cardiac dysfunction Assess peripheral pulses, peripheral venous access, extent of Raynaud phenomenon, and skin involvement
Vasculitis	Organ ischemia (cardiac, renal, cerebral, and limb) and intravascular volume Monitor hypertension and end organ complications or thrombosis

of teratogenicity. They are the mainstay of treatment in renal crisis of SSc and may be used after appropriate discussion with the mother if hypertension is life-threatening [36]. Aspirin may reduce pre-eclampsia and prematurity. Many centers use it in high-risk pregnancies, including lupus and other systemic autoimmune diseases, to reduce the risk of pre-eclampsia and thrombosis [74,75]. If pre-eclampsia is severe or progresses to eclampsia, delivery is the definitive treatment.

**Treatment of esophageal reflux and dyspepsia**

Dyspepsia is a common symptom in pregnant women and can be worsened by aspirin, non-steroidal anti-inflammatory drugs, and corticosteroids. Antacids such as gaviscon are rarely sufficient. Ranitidine, a histamine-2-antagonist, is used at doses of between 150 and 600 mg daily, especially in patients with SSc [76,77]. There is less experience with proton pump inhibitors such as omeprazole, but they are probably safe in pregnancy [76,78].

**Delivery**

Women with chronic disease generally want to have a ‘natural’ delivery like healthy women. With effective pre-pregnancy planning and joint care, vaginal delivery should be possible; cesarean delivery is reserved for obstetric emergencies, those with a history of cesarean section who do not want a trial of vaginal delivery, and women with severe hip disease. However, to reduce the risk of stillbirth in patients with APS or active disease, induction may be advisable at 38 to 39 weeks. Detailed plans for delivery should be made by a multi-disciplinary team that includes the obstetrician, anesthetist, and relevant physicians at 36 weeks of gestation or earlier in

**Table 4. Benefits of breastfeeding**

Reduced risk in child	Reduced risk in mother
Infections	Type 2 diabetes
Atopic dermatitis	Breast cancer
Asthma (young children)	Ovarian cancer
Obesity	Postpartum depression (if not stopped early)
Type 1 and 2 diabetes	
Childhood leukemia	
Sudden infant death syndrome	
Necrotising enterocolitis	

patients with complications. Owing to the risk of placental insufficiency in SLE, APS, SSc, and vasculitis, babies need to be monitored by growth scans every 4 weeks throughout pregnancy and closely monitored during delivery for any signs of fetal distress. Disease-specific considerations for anesthesia are listed in Table 3.

Epidural can be offered for routine vaginal deliveries. For cesarean section, neuroaxial anesthetic can be performed; general anesthetic is reserved for obstetric emergencies (for example, placental abruption, uterine rupture, prolapsed umbilical cord, or fetal distress). The last dose of heparin should be given 12 hours before the epidural will be administered, and the first dose after delivery should be 12 hours later. Aspirin may be given up until the time of delivery and is compatible with spinal and epidural anesthesia, although practice still varies among centers [79].

**Breastfeeding**

Breastfeeding has multiple health benefits for both the mother and child (Table 4) [80]. Table 5 summarizes



**Table 5. Commonly used anti-rheumatic drugs and their use during breastfeeding**

Drug	Crosses into breast milk	Compatible with lactation
Paracetamol	Amount too small to be harmful	Can be continued during breastfeeding
Aspirin	Possible risk of Reye syndrome In large doses, could impair platelet function	Low doses (antithrombotic dose of 75 mg/day) acceptable, but avoid in large doses
NSAIDs	Very small quantities in human breast milk Potential risk of jaundice and kernicterus	Approved for use (use short-acting NSAIDs such as ibuprofen)
Codeine	Amount usually too small to be harmful; however, mothers vary in capacity to catabolize codeine and infant at risk of morphine overdose	Use lowest effective dose if needed, but try to avoid
Pethidine	Present in breast milk but not known to be harmful	Can be used
Tramadol	Amount probably too small to be harmful	Should be avoided
Morphine	Therapeutic doses unlikely to affect infant Withdrawal symptoms in infants of dependent mothers	Therapeutic doses may be used if needed, but try to avoid
Corticosteroids	Trace amounts of hydrocortisone and up to 25% of maternal levels of prednisolone detectable in breast milk	Breastfeed 4 hours after last dose to minimize exposure if prednisolone of greater than 20 mg
COX-2 (cyclo-oxygenase-2) inhibitors	Insufficient data in humans	Avoid due to theoretical risk
Hydroxychloroquine	Found in breast milk but no abnormalities reported	Can be continued during breastfeeding
Methotrexate	Excreted in low concentrations into breast milk	Contraindicated
Leflunomide	No published data available	Contraindicated due to theoretical risk
Sulfasalazine	Negligible amounts secreted in breast milk	To be used with folic acid supplements
Gold salts	Excreted in breast milk and absorbed by infant Can lead to rash, nephritis, hepatitis, and hematological problems	Should be avoided
Azathioprine	Azathioprine and its metabolites detected in breast milk in low amounts, but abnormalities rare	May be used at not more than 2 mg/kg per day after discussion with mother weighing up risk-benefit
Cyclosporin	Wide variability in drug disposition	May be used after discussion with mother weighing up risk-benefit, preferably at doses lower than 2.5 mg/kg per day
Cyclophosphamide	Excreted in breast milk	Contraindicated
Mycophenolate mofetil	No human studies	Contraindicated due to theoretical risk
Tumor necrosis factor-alpha antagonists (for example, infliximab, etanercept, and adalimumab)	Etanercept excreted in breast milk Infliximab undetectable No studies with adalimumab	Not enough data, therefore should be avoided
Anakinra	Unknown whether excreted in breast milk	Not enough data, therefore should be avoided
Abatacept	Not known whether excreted in breast milk or whether absorbed systematically after ingestion	Contraindicated due to theoretical risk
Rituximab	Unknown whether excreted in breast milk	Not enough data, therefore should be avoided
Intravenous immunoglobulin	No published data	May be used during breastfeeding after discussion
weighing up risk-benefit		
Heparin and low-molecular-weight heparin	Not excreted in breast milk	Can be continued during breastfeeding
Warfarin	Minimal excretion in breast milk	Can be used while breastfeeding

NSAID, non-steroidal anti-inflammatory drug.

recommendations for treatment during lactation [49,63-66]. It is widely agreed that prednisolone, sulphasalazine, and hydroxychloroquine are acceptable [64,69, 81]. Azathioprine use during lactation remains more controversial [64,81] but has been used by us and others without obvious harm to the infant, as levels of the active metabolites are rare in breast milk and undetectable in the baby [64,82,83].

## Conclusions

With careful planning, most women with inflammatory rheumatological diseases can have successful pregnancies (Table 6). It is important that conception occur when the disease has been inactive for at least 6 months and while the mother is taking non-teratogenic drugs. The mother and fetus require regular monitoring throughout pregnancy so that any complications can be detected

### Table 6. Key points in the management of patients with rheumatological diseases in pregnancy

With thorough pre-pregnancy planning, most pregnancies in women with inflammatory rheumatic diseases are low-risk and have a favorable outcome.

Fertility is generally not affected by autoimmune rheumatic disease.

Systemic lupus erythematosus is the most widely studied rheumatic disease in pregnancy, and it is important to differentiate active lupus disease from pathophysiological changes of pregnancy.

Antiphospholipid syndrome is secondary to another autoimmune disease in 50% of cases. Anti-phospholipid antibodies are associated with an increased risk of thrombosis, fetal loss, pre-eclampsia, intrauterine growth restriction, and premature labor.

Rheumatoid arthritis and Behçet disease usually improve during pregnancy but are still associated with a risk of flare in the postpartum period.

Disease at the time of conception is the most important factor in determining maternal and fetal outcome.

HELLP (hemolysis, elevated liver enzymes, and low platelets) and pre-eclampsia occur in women with autoimmune rheumatic disease (especially, antiphospholipid syndrome) earlier than in healthy women and must be distinguished from disease activity and treated appropriately.

Neonatal lupus is specific to mother with anti-Ro/La antibodies and can lead to irreversible congenital complete heart block, requiring a permanent pacemaker in affected children.

Drug therapy must be reviewed prior to conception and during pregnancy and breastfeeding in order to rule out any potential harmful side effects to the fetus/child.

Vaginal delivery is generally deemed safe. Cesarean sections are reserved for patients with obstetric complications.

early and managed appropriately. Combined care involving obstetricians, rheumatologists, other relevant physicians, and anesthesiologists will promote the best outcomes for mother and baby.

#### Abbreviations

APS, antiphospholipid syndrome; BD, Behçet disease; CHB, complete heart block; HELLP, hemolysis, elevated liver enzymes, and low platelets; IUGR, intrauterine growth restriction; IVIG, intravenous immunoglobulin; PAN, polyarteritis nodosa; PIH, pregnancy-induced hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TA, Takayasu arteritis; WG, Wegener granulomatosis.

#### Competing interests

The authors declare that they have no competing interests.

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