Review

High-risk pregnancy and the rheumatologist

May Ching Soh1 and Catherine Nelson-Piercy1

Abstract

Rheumatologists are increasingly involved in the care of young women who, in the age of biologic therapy, are now gaining control of their rheumatic diseases and attempting pregnancy. With careful planning, most women with rheumatic diseases have successful pregnancies. This article focuses specifically on the highest-risk pregnancies and controversial areas. We discuss the women at risk of complications, the types of maternal and fetal complications, the treatments that can be used in pregnancy (and breastfeeding) and longer-term outcomes that could affect the mother. SLE, RA, ANCA-associated vasculitides, large vessel vasculitis (e.g. Takayasu’s) and other CTDs (e.g. scleroderma) are among the conditions covered. The evidence and controversies regarding the recommendations for the use of biologics in pregnancy are discussed. The role of the rheumatologist in pregnancy planning and caring for the pregnant and post-partum woman as part of the multidisciplinary team is discussed.

Key words: pregnancy complications, biologics, anti-phospholipid antibodies, vasculitis, connective tissue diseases.

What is a high-risk pregnancy?

A pregnancy is deemed to be high risk when either the mother or the developing fetus, or both, are at increased risk of complications during the pregnancy, delivery or post-partum. The risks for the fetus include preterm delivery (<37 weeks gestation), multiple gestations, congenital anomalies and poor fetal growth, placental abruption and stillbirth. Mothers may suffer from pregnancy-induced hypertension (elevated blood pressure after 20 weeks’ gestation), pre-eclampsia (pregnancy-induced hypertension with proteinuria >0.3 g/24 h), eclampsia (pre-eclam- sia with seizures), gestational diabetes mellitus (GDM), sepsis, a flare or worsening of their underlying disease and thrombotic events.

Challenges for the rheumatologist

Many rheumatic diseases affect women of childbearing age. Their fertility is usually unaffected (unless there has been prior CYC use causing premature ovarian failure) [1]. However, these women, especially those with SLE, are at increased risk of adverse pregnancy outcomes that include pre-eclampsia (14–23%), eclampsia, preterm delivery (20–31%) [2–4] and fetal growth restriction (5–23%) [4, 5]. These complications are often collectively known as maternal–placental syndrome (MPS) as they are a result of poor placentation [6–11]. Flares of SLE are associated with worse obstetric outcomes [12]. Women with LN have a particularly high risk of pre-eclampsia and preterm deliveries, especially if their disease is active within 6 months of conception [13–15]. For the fetus/neonate there is an increased risk of miscarriage, preterm birth, low birth weight, admission to neonatal special care units and neonatal death [16–19].

In addition, women with rheumatic diseases are often older, have underlying co-morbidities (i.e. hypertension, concurrent renal disease, steroid-induced diabetes, obesity, pulmonary hypertension) and take multiple medications that are sometimes not compatible with pregnancy.

Most drugs are not licensed for use in pregnancy, as most drug trials exclude pregnant women. Therefore much information on drug safety in pregnancy comes from either animal studies or extrapolation from non-pregnant subjects. For some older drugs, information on safety in pregnancy has accumulated over a prolonged period of time. Decisions about medication use in pregnancy involve a delicate balance between the theoretical potential harm of the drug to the developing fetus and the risk of flare or uncontrolled underlying disease that could harm both the mother and fetus. Considering the dramatic

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therapeutic advances achieved for most rheumatic conditions over the last decade, it is not surprising that knowledge about the safety of these newer agents is lagging behind and women are often advised to discontinue them prior to pregnancy. Reproductive potential should always be part of any discussion regarding a young woman’s illness and any potential therapies.

How to manage disease flares

Presentations of a flare are not usually altered by pregnancy, although some symptoms overlap with normal physiological changes in pregnancy. The frequency and severity of flares can be affected by pregnancy and delivery. A general overview of the management of flares of common rheumatic diseases in pregnancy follows.

Steroids are almost invariably used to treat flares of rheumatic diseases in pregnancy. In the past there was significant concern about the link between corticosteroid use and fetal malformations, particularly orofacial clefts. Recently a Danish population-based study covering a 12-year period has provided reassuring evidence against a link between orofacial clefts and steroid use [20]. The risk of steroids comes from their immunosuppressive effects and increasing insulin resistance. Pregnancy is an insulin-resistant state and exogenous steroids increase the risk of GDM [21]. GDM further increases a woman’s risk of adverse outcomes, including macromomotic fetus, iatrogenic preterm delivery and a longer-term risk of developing type 2 diabetes [22, 23]. In addition, steroid use is associated with increased risk of infection and high doses are associated with preterm delivery from premature rupture of membranes [24, 25]. The fetus receives <10% of the maternal dose of prednisolone because of placental metabolism [26]. Association between steroid use and poor pregnancy outcome is probably a result of disease activity, for which steroid use is a surrogate marker [27].

NSAIDs are not teratogenic, but should be avoided after 32 weeks gestation because of the risk of premature closure of the ductus arteriosus and subsequent development of pulmonary hypertension in the neonate [28, 29]. There is a dose-dependent but reversible effect of NSAIDs on fetal renal function (urine output), although rare cases of fetal anuria and end-stage renal failure have been reported [30]. Use before 32 weeks gestation is often inappropriate in rheumatic disease, especially for conditions such as AS that do not respond well to steroid therapy.

Data on the safety of cyclooxygenase 2 (COX-2) inhibitors in pregnancy are emerging, with a single population-based study demonstrating no increased risk of fetal malformations [31].

HCQ may be added in as therapy for flares, though the onset of action is slow. AZA should also be continued in pregnancy. It may be added as a steroid-sparing agent. Commonly used DMARDs to treat flares of rheumatic diseases and their impact on pregnancy and breastfeeding are discussed in Table 1. The role of cytotoxic agents and biologic agents is discussed below.

Management of active disease may occasionally require cytotoxic immunosuppressants. CYC, MTX and MMF are teratogenic and have the potential to cause fetal malformation [46, 64–66, 69–71]. LEF blocks de novo pyrimidine synthesis. Neonates of women exposed to LEF in early pregnancy do not have an increased rate of major malformations or a specific pattern of malformations, although most women did undergo washout with cholestyramine in early pregnancy [54, 90].

MMF use in the first trimester is associated with a typical constellation of fetal abnormalities, but there is no relationship between the dose ingested and the severity of the phenotype. Minimal exposure to MMF in early pregnancy has resulted in malformations [69–71].

CYC is teratogenic when given in the first trimester, but long-term studies have not demonstrated any difference in growth and development of the children (age range 3–19 years) exposed to CYC chemotherapy later in pregnancy [91, 92]. With immune suppression, sepsis was the most common complication in pregnancy [3]. Clinicians should be vigilant for the risk of sepsis in immunosuppressed pregnant patients; a low threshold for giving antibiotics is appropriate.

Pregnancy is a naturally prothrombotic state. The Royal College of Obstetricians and Gynaecologists Green-top Guideline No. 37a highlights active inflammatory disease as a risk factor for venous thromboembolism (VTE). Active inflammatory disease is difficult to define in pregnancy; advice should be sought from a trust-nominated thrombosis expert as to whether and for how long thromboprophylaxis with low molecular weight heparin (LMWH) is recommended [93]. In practice this decision is individualized and takes account of the underlying disease, the presence of other risk factors for VTE (BMI >30, immobility), whether the patient is admitted to hospital and the severity of the flare.

SLE

Despite extensive study, unanswered questions remain.

Flares and the risk of adverse pregnancy outcome in women with SLE

Flares occur in up to 60% of pregnancies and are often difficult to quantify and predict [94]. Most flares are mild and are more common in those with active disease at conception. Risk factors for poor obstetric outcome include pulmonary hypertension, past adverse obstetric history, chronic kidney disease, active (especially renal) disease and recent stroke (<6 months) [95].

Obstetric outcomes can be improved through careful planning, including quiescent disease for at least 6 months prior to conception [12, 96], continued use of HCQ in pregnancy [97–99], prompt treatment of disease flares and careful monitoring of women with Ro and La antibodies for congenital heart block [100, 101]. LNi—past or present—is a risk factor for adverse obstetric outcome with an ~30% risk of preterm delivery, small for gestational age (SGA) neonates and pre-eclampsia [102, 103]. It is reassuring that renal function is preserved in women.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effects on organogenesis</th>
<th>Effects on fetus/neonate</th>
<th>Breastfeeding</th>
<th>Authors’ recommendations on its use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs [29, 32–35]</td>
<td>None</td>
<td>Constriction of ductus arteriosus after 27 weeks gestation; oligohydramnios. Transient anuria and renal failure if used before delivery.</td>
<td>✓</td>
<td>Likely a class effect for all NSAIDs. Use if indicated at lowest dose possible until 32 weeks gestation.</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>Teratogenic effects in animals, but not in humans</td>
<td>Similar effects to those of NSAIDs on fetal heart and kidneys.</td>
<td>✓</td>
<td>It would be safer to change to an NSAID in pregnancy until more information is available. Use lowest dose possible.</td>
</tr>
<tr>
<td>Prednisone [20]</td>
<td>None</td>
<td>Rarely has an effect unless used in very large doses—possible cataracts, adrenal insufficiency and infection.</td>
<td>✓</td>
<td>Continue in pregnancy and breastfeeding. Comment on folic acid supplementation.</td>
</tr>
<tr>
<td>HCQ [39–41]</td>
<td>None</td>
<td>None</td>
<td>✓</td>
<td>Continue in pregnancy and breastfeeding. Comment on folic acid supplementation.</td>
</tr>
<tr>
<td>SSZ [42–45]</td>
<td>Likely no effect</td>
<td>None</td>
<td>✓</td>
<td>Continue in pregnancy and breastfeeding. Comment on folic acid supplementation.</td>
</tr>
<tr>
<td>MTX [46–53]</td>
<td>Aminopterin syndrome, High rate of pregnancy loss and &lt;15% rate of congenital anomalies if used in pregnancy, but not pre-conception. No effect if paternal MTX use.</td>
<td>If no congenital anomalies, long-term follow-up of children exposed to MTX did not reveal any problems.</td>
<td>X</td>
<td>Reliable contraception advised. Discontinue at least 3 months prior to pregnancy with daily high-dose folic acid supplementation. exposed fetuses should be scanned as early as possible (at 16 weeks gestation) to determine whether there are any congenital anomalies to facilitate elective termination if the mother wishes.</td>
</tr>
<tr>
<td>LEF [54–57]</td>
<td>In animal studies, malformations of the head, rump, vertebral column and limb defects. Increased rate of miscarriage.</td>
<td>If pregnancy continues, no major structural anomalies noted, especially after cholestyramine washout as suggested by the manufacturer.</td>
<td>X</td>
<td>Reliable contraception advised. Washout with cholestyramine 8g three times per day for 11 days—repeat until drug levels are &lt;0.03 μg/ml taken 2 weeks apart. If exposed in early pregnancy, offer washout and reassure the woman that birth outcomes of exposed women are no different from disease-matched controls.</td>
</tr>
<tr>
<td>AZA [58, 59]</td>
<td>None</td>
<td>Low birthweight and preterm delivery—could be secondary to maternal disease.</td>
<td>✓</td>
<td>Continue in pregnancy and lactation.</td>
</tr>
<tr>
<td>Ciclosporin [60]</td>
<td>None</td>
<td>Transient immune alterations in the neonate.</td>
<td>✓</td>
<td>Continue in pregnancy; probably safe in breastfeeding, although a wide range of concentrations are excreted in breast milk.</td>
</tr>
<tr>
<td>Tacrolimus [61, 62]</td>
<td>None</td>
<td>None</td>
<td>✓</td>
<td>Continue in pregnancy and safe in breastfeeding.</td>
</tr>
<tr>
<td>Drug</td>
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<tr>
<td>IVIG [63]</td>
<td>None</td>
<td>None</td>
<td>✓</td>
<td>Can be used, but thromboprophylaxis is advised.</td>
</tr>
<tr>
<td>CYC [50, 64-68]</td>
<td>CYC embryopathy with high rate of miscarriage.</td>
<td>Transient cytopenia. No long-term effect on the neonate if it survives pregnancy.</td>
<td>×</td>
<td>Use only if there is life-threatening maternal disease after the first trimester. If maternal disease necessitates CYC in the first trimester, discuss termination.</td>
</tr>
<tr>
<td>MMF [69-71]</td>
<td>OMENS and congenital cardiac defects.</td>
<td>Most neonates described in the literature had also been exposed in the period of organogenesis. Phenotype is not dose dependent.</td>
<td>×</td>
<td>Discontinue for at least 3 months prior to pregnancy.</td>
</tr>
<tr>
<td>Etanercept [72-74]</td>
<td>Animal studies are reassuring. In addition, some centres for assisted reproduction are using it for the treatment of immune-mediated recurrent miscarriages [75].</td>
<td>Active transplacental transfer of these anti-TNF agents with a risk of neonatal immune suppression if drugs are continued throughout pregnancy.</td>
<td>✓</td>
<td>Continue until 32 weeks gestation⁵.</td>
</tr>
<tr>
<td>Infliximab [76, 77]</td>
<td></td>
<td></td>
<td></td>
<td>Continue until 21 weeks⁵.</td>
</tr>
<tr>
<td>Adalimumab [78, 79]</td>
<td></td>
<td></td>
<td></td>
<td>Continue until 28 weeks, although evidence is lacking due to difficulty in getting commercially available tests for drug levels⁶.</td>
</tr>
<tr>
<td>Certolizumab [78, 80]</td>
<td>Passive diffusion of drug means lower levels are achieved in the neonate.</td>
<td>Transient cytopenias and neonatal B cell depression. Did not affect the efficacy of vaccination.</td>
<td>✓</td>
<td>No evidence as yet, but due to very low levels in cord blood, probably safe to continue in pregnancy.</td>
</tr>
<tr>
<td>Rituximab [81-83]</td>
<td>None known.</td>
<td></td>
<td>✓</td>
<td>Attempt to discontinue 12 weeks prior to delivery if at all possible to prevent neonatal B cell depression.</td>
</tr>
</tbody>
</table>

⁵AZA converts to active metabolite 6-thioguanine nucleotides in 15 min but the half-life of the active metabolite in erythrocytes is weeks to months. If given beyond the recommended gestation, the neonate should not receive any live vaccines for the first 6 months of life. The two live vaccines commonly given in the neonatal period are BCG and the rotavirus vaccine. Adapted from [84]. ✓: safe for breastfeeding; ×: unsafe or not recommended for breastfeeding; COX-2: cyclooxygenase 2.
who have had previous nephritis despite a higher risk of pre-eclampsia [13–15].

Significance of Ro and La antibodies

Even in the absence of clinical symptoms in the mother, Ro and La antibodies can cross the placenta to cause congenital heart block and neonatal lupus syndromes. The risk of congenital heart block is low, at 2%, but 15–20% with a previously affected child [101]. Most fetal cardiologists recommend a fetal cardiac scan at 16–20 weeks gestation, with repeat at 28 weeks if the initial 20-week scan was normal. Fetal cardiac auscultation with each clinic visit is advised. If there is evidence of progressive heart block (picked up on auscultation or scans) and cardiac failure (evidence of hydrops) in the fetus, then a decision needs to be taken for optimal timing for a planned delivery (or termination of the pregnancy). No interventions have been shown to reverse established heart block [104]. Randomized controlled studies are not possible due to the rarity of the condition.

Prophylactic treatment with IVIG in women with a previously affected fetus have been tried with little success [105, 106]. HCQ is associated with a significant reduction in recurrent congenital heart block in the offspring of women who are anti-Ro and anti-La positive [odds ratio (OR) 0.23 (95% CI 0.06, 0.92), \(P=0.037\)] [100].

Neonatal cutaneous lupus is a florid, photosensitive erythematous rash that usually fades after 6 months. It is more common than heart block. Its true prevalence is difficult to determine due to a high rate of unreported cases and ethnic variations, but it has been linked to future autoimmune disease in neonates [107–109].

Safety of B cell depletion therapies in women planning pregnancy

B cell depletion therapy (BCDT) for severe refractory disease is an attractive option, especially for young women, as it does not seem to affect fertility, in contrast to, for example, CYC [110–112]. These immunoglobulins (Igs) cross the placenta via active transport from the second trimester [113, 114]. Neonatal drug concentrations can be higher than maternal serum concentrations, and the drug persists for up to 6 months after delivery [81–83, 113]. However, neonatal response to vaccination appears unimpaired [81–84, 115].

Rituximab’s global drug safety database contains data on 153 pregnancy outcomes. There were 59% live births, 21% first-trimester miscarriages, one fetal loss at 20 weeks from an umbilical cord knot and 18% elective terminations. Most (76%) were term deliveries. These are surprisingly good outcomes considering the indications for which rituximab was used (predominantly for haematological malignancies and often combined with other chemotherapeutic agents). There were three cases of transient neonatal cytopenia and B cell suppression that resolved and four neonatal infections that were deemed unrelated to rituximab use [83].

On balance, rituximab appears safe in pregnancy, though the manufacturers still recommend avoiding pregnancy for at least 12 months. If clinically indicated for severe maternal disease in which other options are not available, then ideally the last dose should be given 6 months before birth and the neonate should have prompt treatment of any infections [84, 116]. Flares of SLE can occur in the third trimester, particularly as the effects of BCDT—stopped at the start of pregnancy—wane. Starting treatment with AZA when disease is quiescent just before the next dose of BCDT is due could prevent flares.

Use of belimumab in pregnancy

Belimumab is the first targeted biologic agent developed specifically for SLE [117–119]. Animal studies have shown a reduction in the density of lymphoid tissue B lymphocytes on immunohistochemistry, similar to the effects of rituximab [120, 121]. At 12 months the exposed offspring’s growth and neurodevelopment were all within normal limits [120]. A pregnancy registry has been set up by the manufacturer [122].

APS and aPL

APS is associated with poor pregnancy outcomes, including recurrent early miscarriage and features of placental insufficiency such as pre-eclampsia, intra-uterine growth restriction and SGA neonates [123]. Women who have had thrombotic complications have poorer outcomes than those with only obstetric complications [124, 125]. Low-dose aspirin (75–100 mg/day) is often prescribed to reduce the risk of miscarriage and pre-eclampsia.

Controversies of LMWH use: who should be offered treatment?

Women with previous thrombosis require LMWH prophylaxis in pregnancy. LMWH has also been shown to improve outcomes in those with previous placenta-mediated adverse outcomes such as severe early-onset pre-eclampsia with growth restriction [126, 127]. However, the use of LMWH to prevent recurrent early pregnancy loss is controversial, with large randomized trials in the general population not demonstrating improved outcome [128–131]. Even in women with specific thrombophilias, a systematic review of 43 studies failed to show improved obstetric outcomes with the use of LMWH [132].

Do women with persistent aPL have the same obstetric risks as those with APS?

aCLs were found in 10% and lupus anticoagulant in 8% of healthy blood donors [133, 134]. Most studies of women with aPL are muddied by the inclusion of women with SLE or a single titre measurement of aPL in pregnancy. A cross-sectional study comparing obstetric outcomes in women (without SLE) with persistently positive aPL and those with obstetric APS and also with the normal population showed that those with persistently positive aPL (without a clinical history of APS) on aspirin had similar obstetric outcomes compared with the normal population [135].
A review on recurrent pregnancy loss concluded that aCL is less likely to play a major role [136]. In SLE, however, lupus anticoagulant was the strongest predictor of adverse pregnancy outcome [137].

RA and JIA

The adage that RA improves in pregnancy no longer holds true. Population-based studies show that less than a quarter of women will remain in remission throughout pregnancy [138, 139]. Women without anti-CCP antibodies and RF were more likely to improve in pregnancy, but post-partum flares were similar in those with and without these antibodies [140]. The Norfolk Register shows that women who have been pregnant have better functional outcomes than nulliparous women [141, 142]. This may reflect a beneficial effect of pregnancy on disease outcome or that predominantly women with milder disease become pregnant. Women who have more than one pregnancy have fewer erosions and better functional outcomes [143].

Approximately 30% of women with JIA will continue to have symptoms in adulthood. Some may have had joint destruction severe enough to require a prosthesis (especially hip prostheses) [144]. Hip replacements are not an indication for elective caesarean section.

Prevalence of adverse pregnancy outcomes in women with RA

Obstetric outcomes in women with RA are similar to the general population. The prevalence of pre-eclampsia is 3–11% (OR 0.6–2.22) [4, 145–148], low birthweight neonates 10% [144, 148, 149], SGA 6–16% [16, 19, 145–149] and preterm delivery 10–15% (OR 1.15–1.91) [146, 149]. Those with active RA had much lighter neonates compared with those with quiescent RA [150]. Those with severe RA were at greater risk of preterm delivery [adjusted OR 2.27 (90% CI 1.35, 3.81)] and SGA neonates [adjusted OR 3.68 (95% CI 2.27, 5.98)] [19]. Rates of stillbirth are twice as high compared with the normal population [19] and in primiparous women, the risk of perinatal mortality was three times higher [145].

Controversies regarding the use of anti-TNF and other biologics in pregnancy

Increasing evidence supports the safety of biologics in pregnancy. Etanercept, infliximab, adalimumab, golimumab and certolizumab all have different molecular structures, transplacental transport and half-lives (Table 2).

Recommendations regarding their use should be individualized. Older advice to stop biologics when planning pregnancy in women with rheumatic diseases is no longer appropriate given that the time to pregnancy can be very long in some women. When deciding whether to continue, restart or stop biologic therapy in pregnant women with rheumatic diseases, it is important to consider the likely disease course in pregnancy and what other therapies may be available to women and are likely to control the disease and symptoms. Thus, for example, in women with severe AS established on biologic therapy in whom steroids may not offer an effective alternative, continuation or reintroduction of biologics in pregnancy may be justified.

Infliximab, adalimumab and golimumab are IgG1 monoclonal antibodies—the Ig subclass with the most active transport across the placenta. In early pregnancy, transfer is limited by a cytrophoblast. By week 14, Fc receptors begin to develop on the trophectoderm and active transport is increasingly efficient as pregnancy progresses, thus at the time of delivery infliximab and adalimumab levels in the neonate (as measured in umbilical cord blood) often exceed maternal levels [76, 78] (Table 2). While there are recommendations that these drugs should be discontinued at 28–30 weeks gestation, the evidence to support this is lacking. In a study where infliximab infusions were given to pregnant women with IBD, infliximab was detected in cord blood at two to three times maternal therapeutic levels, even when infliximab was discontinued at 26 weeks gestation. The only woman (and neonate) that had undetectable drug levels had discontinued infliximab at 21 weeks gestation [77]. Adalimumab has a shorter half-life and excellent transplacental transfer, so when used in late pregnancy, levels in the neonate exceed maternal levels [78]. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD in Pregnancy suggests that it could be discontinued 6–8 weeks before delivery, while other authors have suggested the second trimester if IBD is quiescent [79, 151].

Etanercept has a much shorter half-life and may not bind quite as effectively to the placental Fc receptors; etanercept levels have been demonstrated to be much lower, at 3.6–7.4% (1:30 to 1:14 in neonates compared with maternal levels) [72, 73, 152]. Some experts recommend that etanercept can be continued until 30–32 weeks gestation if needed [153].

Abatacept also has a modified Fc portion human IgG1. In animal studies, fetal drug levels were 1.2–2.4 times lower than in the mother. In phase I/II studies, 10 women became pregnant; 3 had elective terminations, 3 had early first trimester miscarriage (of which 2 had a

<p>| Table 2 Presence of anti-TNF agents in cord blood in exposed offspring |
|----------------------|------------------|---------------------|</p>
<table>
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<th>Percentage in cord blood compared with maternal serum concentration</th>
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<tr>
<td>Infliximab [76–78]</td>
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prior history) and pregnancy outcomes were unknown in 3. Cord drug levels were not documented [154–156].

Cetoriluzumab has a monovalent Fab fragment and is reliant on slow diffusion to move across the placenta. Cord blood levels are low [78, 80]. Among gastroenterologists, there are now calls for cetoriluzumab to be a first-line anti-TNF agent in women of childbearing age [79].

There is currently insufficient evidence on anakinra [157, 158], golimumab and tocilizumab [159] to inform clear recommendations about their use in pregnancy.

The reason for the extreme caution in the use of anti-TNF in late pregnancy was precipitated by the death of a 4.5-month-old infant from disseminated tuberculosis following routine BCG vaccination at 3 months of age. The mother’s IBD was treated with infliximab and her last infusion was 2 weeks prior to delivery [160]. We would recommend that any neonate who has had exposure to anti-TNF agents in utero should not receive any live vaccines for the first 6 months of life. All other routine vaccinations can be undertaken. There are no reported defects in the immune responses of neonates [77].

It is predominantly maternal IgA antibodies that are excreted into breast milk. Despite small amounts of IgG1 drug molecules excreted in breast milk, studies have shown that the neonate’s drug levels continue to fall even while breastfeeding [72, 73, 161–163]. It is unlikely that these large proteinaceous molecules in breast milk survive passage through the neonate’s alimentary tract to allow adequate absorption, so drug levels in neonates are unlikely to reach therapeutic significance.

We have summarized the use of other DMARDs in pregnancy in Table 1.

Scleroderma

Scleroderma is rare in childbearing years, but for some women with scleroderma, pregnancy is associated with a markedly increased risk of adverse obstetric and maternal outcome [164, 165]. The different rates of complications reported probably relate to the heterogeneity of underlying disease severity, and it is important to stratify women with scleroderma into those at high risk of complications and those in whom pregnancy may not be so risky.

Complications of scleroderma in pregnancy

Pulmonary hypertension occurs in 8–12% of patients with scleroderma and is now the most frequent cause of death [166]. In pregnancy, maternal mortality from pulmonary hypertension ranges between 17% and 33%. Women with transthoracic echocardiography (estimated pulmonary pressure >30 mmHg at rest) or cardiac catheter evidence of pulmonary hypertension should be strongly advised against pregnancy [166].

Sildenafil and epoprostenol have been used in pregnancy [167, 168]. LMWH reduces the thromboembolic risk. Planned caesarean section with regional anaesthesia and careful avoidance of major haemodynamic shifts is usually recommended [168, 169].

Scleroderma renal crises are rare but may complicate the third trimester when rising blood pressure and proteinuria are often mistaken for pre-eclampsia [170]. Renal biopsy histology reveals pathognomonic features of onion skin renal arterioles. Women with recent-onset and rapidly progressive skin disease are at particular risk [170]. In these exceptional circumstances, a trial of an angiotensin-converting enzyme (ACE) inhibitor (usually contraindicated in pregnancy) is indicated [166, 171]. The authors recommend continuing ACE inhibitors in pregnancy in women with known renal scleroderma.

Antenatal steroid use for fetal lung maturity and precipitation of a scleroderma renal crisis

In the event of likely preterm delivery, two doses of 12 mg of betamethasone or dexamethasone given to the mother 24 h apart are used to accelerate fetal lung maturity. Such large doses of steroids could potentially precipitate a scleroderma renal crisis, although none of the cases of renal crisis reported in the literature appear to have been precipitated by this [170, 172–175]. If renal crisis occurs in pregnancy, ACE inhibitors must be started [176]. The decision to use high dose antenatal steroids will need to be carefully weighed up and individualized to each woman’s risk of a renal crisis [177].

Vasculitides: large vessel and small vessel

Takayasu’s arteritis

Takayasu’s arteritis affects mainly women, with 80% diagnosed during childbearing age, many during pregnancy [178, 179]. Pregnancy appears to be beneficial to Takayasu’s. Follow-up CRP and digital plethysmography during pregnancy have shown an improvement that persists for a year post-partum [180].

Hypertension is often worsened by pregnancy [180]. Pre-eclampsia affects up to 75% of pregnant women, although more recent studies show lower rates likely due to better pre-pregnancy blood pressure control and the use of aspirin to prevent pre-eclampsia [181]. Fetal growth restriction (11–52%) is likely related to a combination of hypertension and suboptimal placental perfusion from vascular narrowing of the abdominal aorta and its branches [178, 179]. There is a correlation between disease severity—two or more vessels affected and Ishikawa class IIb or greater—and poor obstetric outcomes [182]. Aortic dissections may occur post-partum if blood pressure is poorly controlled when maternal peripheral vascular resistance increases [184].

Systemic necrotizing vasculitides

The literature on systemic necrotizing vasculitides in pregnancy is limited, as the age of onset is usually >40 years [185]. Maternal deaths related to severe flares of granulomatosis with polyangiitis in pregnancy or post-partum are reported [67, 185–195], although a recent case series showed that women who conceive in remission had good outcomes, regardless of ANCA titres. This cohort
was young with limited disease and treatment-related damage [196]. Pregnancy-safe immunosuppressants should be continued in pregnancy as the catastrophic effects of a severe flare outweigh any risks from the drugs.

CYC has been used in life-threatening maternal disease with good outcomes [67, 185]. There have been maternal (and fetal) deaths from severe flares when AZA was used as monotherapy (plus steroids) for a flare in pregnancy [191, 192, 197, 198]. In the future, rituximab may become the preferred option for flares [199–201].

What are the other risks to women with rheumatic disease?

Pregnancy is an immune-tolerant state, but with parturition, immune reconstitution occurs and post-partum flares or even de novo diagnoses of autoimmune diseases are not uncommon [202, 203]. Other longer-term effects could relate to the vascular changes that occur in pregnancy.

Pre-eclampsia is a disease of the maternal endothelium that manifests clinically as placental insufficiency or MPS [204]. In unselected populations, women with pre-eclampsia are four times more likely to develop hypertension and twice as likely to develop heart disease and stroke in the future [205]. There could be shared pathophysiological pathways between pre-eclampsia and future cardiovascular disease (CVD) brought on by the stress of pregnancy or pre-existing maternal cardiovascular risk factors that are present in these women who then develop placental insufficiency in pregnancy [205, 206]. The risk of subsequent CVD increases with the severity of the pregnancy complications that reflect MPS [adjusted hazard ratio for CVD 3.1 (95% CI 2.2, 4.5)]. The highest risk for CVD was associated with intrauterine death in the index pregnancy [adjusted hazard ratio 4.4 (95% CI 2.4, 7.9)] [207]. Hence a woman’s future cardiovascular risk can be predicted in part by her obstetric outcomes—a risk factor now acknowledged by the American Heart Association [208, 209]. A summary of women who should be advised against pregnancy is given in Table 3.

### TABLE 3 Circumstances in which women should be advised against pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension [169]</td>
<td>These women require effective contraception and in the event of an unplanned pregnancy, we advise termination of pregnancy before 12 weeks if possible.</td>
</tr>
<tr>
<td>CKD stage 4 or 5</td>
<td>Prospective studies involving women with CKD have demonstrated increased risk of pre-eclampsia (36–40%) and preterm delivery (54–80%) [210]; small for gestational age infants and perinatal mortality rates 3-fold higher and 5-fold higher, respectively [102, 210–212]. Women with CKD 4/5 prior to pregnancy are at greater risk of an accelerated decline in renal function with the risk of reaching end stage and needing renal replacement therapy either in pregnancy or shortly after [213]. Women with CKD and proteinuria &gt;1 g/day fared the worst [102].</td>
</tr>
<tr>
<td>Active disease</td>
<td>Severe maternal rheumatic disease in early pregnancy is seldom conducive to the development of a healthy fetus.</td>
</tr>
<tr>
<td>Women with APS with recurrent placenta-mediated adverse pregnancy outcomes</td>
<td>Women with recurrent intrauterine death, early-onset severe pre-eclampsia, HELLP syndrome and severe intrauterine growth restriction with poor neonatal survival despite treatment with aspirin and LMWH may wish to continue attempting pregnancy though their chances of successful outcome are low.</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; LMWH: low molecular weight heparin; HELLP: haemolysis, elevated liver enzymes, low platelets syndrome.

What can the rheumatologist offer?

Planned pregnancies are key to optimal maternal and fetal outcomes [214, 215]. Concurrent prescription of contraceptives is advised, particularly with teratogenic medication. The rheumatologist should advise women to seek antenatal care early—before 12 weeks—and communicate with obstetric services to ensure that reliable information about baseline function, medications and laboratory tests is transmitted.

Poorly controlled disease leading to MPS is likely to be more deleterious to the developing fetus than the medications used to treat it [4, 144, 215, 216]. Flares of SLE should be promptly treated with steroids. Differentiating a flare from pre-eclampsia can be challenging (Table 4).

Most medications are safe beyond organogenesis. In life-threatening maternal disease, maternal well-being takes precedence over that of her neonate. The decision to continue or restart anti-TNF/biologic therapy in pregnancy and when to discontinue it should be individualized to the underlying disease, maternal disease activity in pregnancy, the degree of transplacental transfer in later gestation, the ability of other therapies to control symptoms and the woman’s wishes. Delivery may be planned if close to term or if there are specific fetal concerns. However, delivery alone rarely improves active maternal disease without concomitant use of immunosuppressant therapy. Preterm and surgical deliveries are more common in women with rheumatic diseases, but could relate to provider-initiated preterm delivery [109, 217–219]. The need for optimal maternal health and ongoing medication adherence in pregnancy cannot be overemphasized [99].

While early post-partum follow-up with a rheumatologist is ideal, a documented pre-emptive management plan (or rescue plan) in the event of a flare is useful, particularly given that attending appointments may be problematic for women caring for a newborn [201]. Most medications are safe when breastfeeding (Table 1).
In the longer term, women with rheumatic disease are also at greater risk of developing CVD. Rheumatologists should be alerted by the history of an adverse pregnancy outcome as a risk factor and may therefore consider lowering their threshold for primary prevention [220–221].

**Rheumatology key messages**

- Pregnancy planning is key for optimal maternal and fetal outcomes in women with rheumatic diseases.
- Biologics are safe, but if possible should be discontinued before the third trimester because of transplacental transfer.
- Women with pulmonary hypertension, stage 4 chronic kidney disease and active disease should be advised against pregnancy.

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