RHEUMATOLOGY

Rheumatology 2015;54:572–587
doi:10.1093/rheumatology/keu394
Advance Access publication 3 December 2014

Review

High-risk pregnancy and the rheumatologist

May Ching Soh[1] and Catherine Nelson-Piercy[1]

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 postpartum woman as part of the multidisciplinary team is discussed.

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

REVIEW

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-eclampsia 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

[1]Division of Women's Health, Women's Health Academic Centre, King's College London, King's Health Partners, London, UK.

Submitted 23 March 2014; revised version accepted 5 August 2014.

Correspondence to: Catherine Nelson-Piercy, Women's Health Academic Centre, King's College London, 10th Floor North Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK.
E-mail: catherine.nelson-piercy@gstt.nhs.uk

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 macrosomic 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 appropriate in rheumatic disease, especially for conditions such as AS that do not respond as 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 malformation [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]. LN—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 1 Drugs commonly used for the treatment of rheumatic diseases and their effect on pregnancy and breastfeeding

Drug	Effects on organogenesis	Effects on fetus/neonate	Breastfeeding	Authors' recommendations on its use in pregnancy
NSAIDs [29, 32–35]	None	Constriction of ductus arteriosus after 27 weeks gestation; oligohydramnios. Transient anuria and renal failure if used before delivery.	✓	Likely a class effect for all NSAIDs. Use if indicated at lowest dose possible until 32 weeks gestation.
COX-2 inhibitors [31, 35–38]	Teratogenic effects in animals, but not in humans	Similar effects to those of NSAIDs on fetal heart and kidneys.	✓	It would be safer to change to an NSAID in pregnancy until more information is available.
Prednisone [20]	None	Rarely has an effect unless used in very large doses—possible cataracts, adrenal insufficiency and infection.	✓	Use lowest dose possible. When commencing steroids in pregnancy, ensure there is a plan to taper the dose. If disease is persistently active, then consider addition of a DMARD/biologic to ensure the woman does not remain on prolonged courses of high-dose steroids.
HCQ [39–41]	None	None	✓	Continue in pregnancy and breastfeeding.
SSZ [42–45]	Likely no effect	None	✓ except in very preterm jaundiced neonates	Commence folic acid supplementation 5 mg/day 3 months prior to pregnancy. In men with fertility problems, it may need to be switched to another agent as it affects spermatogenesis and motility.
MTX [46–53]	Aminopterin syndrome. High rate of pregnancy loss and <15% rate of congenital anomalies if used in pregnancy, but not pre-conception. No effect if paternal MTX use.	If no congenital anomalies, long-term follow-up of children exposed to MTX did not reveal any problems.	×	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.
LEF [54–57]	In animal studies, malformations of the head, rump, vertebral column and limb defects. Increased rate of miscarriage.	If pregnancy continues, no major structural anomalies noted, especially after cholestyramine washout as suggested by the manufacturer.	×	Reliable contraception advised. Washout with cholestyramine 8 g three times per day for 11 days—repeat until drug levels are <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.
AZA [58, 59]	None	Low birthweight and preterm delivery—could be secondary to maternal disease.	✓	Continue in pregnancy and lactation[a].
Ciclosporin [60]	None	Transient immune alterations in the neonate.	✓	Continue in pregnancy; probably safe in breastfeeding, although a wide range of concentrations are excreted in breast milk.
Tacrolimus [61, 62]	None	None	✓	Continue in pregnancy and safe in breastfeeding.

(continued)

Table 1 Continued

Drug	Effects on organogenesis	Effects on fetus/neonate	Breastfeeding	Authors' recommendations on its use in pregnancy
IVIG [63]	None	None	✓	Can be used, but thromboprophylaxis is advised.
CYC [50, 64–68]	CYC embryopathy with high rate of miscarriage.	Transient cytopenia. No long-term effect on the neonate if it survives pregnancy.	×	Use only if there is life-threatening maternal disease after the first trimester. If maternal disease necessitates CYC in the first trimester, discuss termination.
MMF [69–71]	OMENS and congenital cardiac defects.	Most neonates described in the literature had also been exposed in the period of organogenesis. Phenotype is not dose dependent.	×	Discontinue for at least 3 months prior to pregnancy.
Etanercept [72–74]	Animal studies are reassuring. In addition, some centres for assisted reproduction are using it for the treatment of immune-mediated recurrent miscarriages [75].	Active transplacental transfer of these anti-TNF agents with a risk of neonatal immune suppression if drugs are continued throughout pregnancy.	✓	Continue until 32 weeks gestation[b].
Infliximab [76, 77]			✓	Continue until 21 weeks[b].
Adalimumab [78, 79]			✓	Continue until 28 weeks, although evidence is lacking due to difficulty in getting commercially available tests for drug levels[b].
Certolizumab [78, 80]		Passive diffusion of drug means lower levels are achieved in the neonate.	✓	No evidence as yet, but due to very low levels in cord blood, probably safe to continue in pregnancy.
Rituximab [81–83]	None known.	Transient cytopenias and neonatal B cell depression. Did not affect the efficacy of vaccination.	✓	Attempt to discontinue 12 weeks prior to delivery if at all possible to prevent neonatal B cell depression.

[a]AZA converts to active metabolite 6-thioguanine nucleotides in 15 min but the half-life of the active metabolite in erythrocytes is weeks to months. [b]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.

Table 2 Presence of anti-TNF agents in cord blood in exposed offspring

Anti-TNF agent	Half-life, days [152]	Percentage in cord blood compared with maternal serum concentration
Infliximab [76–78]	8–10	83–400
Etanercept [72, 73]	4	3.6–7.4
Adalimumab [78]	10–20	98–293
Certolizumab [78]	14	1.5–24.0

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 cytotrophoblast. By week 14, Fc receptors begin to develop on the trophoblasts 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

prior history) and pregnancy outcomes were unknown in 3. Cord drug levels were not documented [154–156].

Certolizumab 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 certolizumab 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 pathognomic 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

Table 3 Circumstances in which women should be advised against pregnancy

Pulmonary hypertension [169]	These women require effective contraception and in the event of an unplanned pregnancy, we advise termination of pregnancy before 12 weeks if possible.
CKD stage 4 or 5	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 >1 g/day fared the worst [102].
Active disease	Severe maternal rheumatic disease in early pregnancy is seldom conducive to the development of a healthy fetus.
Women with APS with recurrent placenta-mediated adverse pregnancy outcomes	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.

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

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.

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).

TABLE 4 Distinguishing a flare of lupus (especially LN) from pre-eclampsia

	Pre-eclampsia	Flare of lupus
Proteinuria	++; >0.3 g/day or protein:creatinine ratio >30	++ in LN
Casts in MSU	Absent	Present if LN
RBCs in MSU	Absent	Present if nephritic
Hypertension	If SBP >20 mmHg or DBP >10 mmHg above baseline BP	May be present
Involvement of skin and joints	No	Malar rash, photosensitive rash or evidence of arthritis
Seizures	Present in eclampsia	Present if there is neurological involvement
Urate	Elevated	Not elevated unless CKD
Albumin	Low	Very low if nephrotic syndrome
LFT	May be affected	Rarely affected in a flare of SLE
C3 and C4	Unchanged from baseline in early pregnancy	Low (or lower from the baseline; complement levels increase in pregnancy)
Anti-dsDNA	Unchanged	Elevated

CKD: chronic kidney disease; DBP: diastolic blood pressure; LFT: liver function test; MSU: midstream urine; RBCs: red blood cells; SBP: systolic blood pressure.

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 4–5 chronic kidney disease and active disease should be advised against pregnancy.

Acknowledgements

M.C.S. is supported by the Rose Hellaby Medical Scholarship from New Zealand, the Asia Pacific League Against Rheumatism Fellowship Grant and the British Maternal and Fetal Medicine Society Bursary for her research into future cardiovascular health in women with SLE who have had previous pregnancy complications.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Ekblom-Kullberg S, Kautiainen H, Alha P *et al*. Reproductive health in women with systemic lupus erythematosus compared to population controls. Scand J Rheumatol 2009;385:375–80.

2 Khamashta MA. Systemic lupus erythematosus and pregnancy. Best Pract Res Clin Rheumatol 2006;20:685–94.

3 Clowse ME, Jamison M, Myers E *et al*. A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol 2008;199:127.e1–6.

4 Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54:899–907.

5 Ambrosio P, Lermann R, Cordeiro A *et al*. Lupus and pregnancy—15 years of experience in a tertiary center. Clin Rev Allergy Immunol 2010;38:77–81.

6 Petri M. The Hopkins Lupus Pregnancy Center: ten key issues in management. Rheum Dis Clin North Am 2007;33:227–35, v.

7 Hanly JG, Gladman DD, Rose TH *et al*. Lupus pregnancy. A prospective study of placental changes. Arthritis Rheum 1988;31:358–66.

8 Magid MS, Kaplan C, Sammaritano LR *et al*. Placental pathology in systemic lupus erythematosus: a prospective study. Am J Obstet Gynecol 1998;179:226–34.

9 Ogishima D, Matsumoto T, Nakamura Y *et al*. Placental pathology in systemic lupus erythematosus

with antiphospholipid antibodies. Pathol Int 2000;50:224–9.

10 Salafia CM, Parke AL. Placental pathology in systemic lupus erythematosus and phospholipid antibody syndrome. Rheum Dis Clin North Am 1997;23:85–97.

11 Ostensen M, Clowse M. Pathogenesis of pregnancy complications in systemic lupus erythematosus. Curr Opin Rheumatol 2013;25:591–6.

12 Clowse ME, Magder LS, Witter F *et al*. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005;52:514–21.

13 Bramham K, Hunt BJ, Bewley S *et al*. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol 2011;38:1906–13.

14 Gladman DD, Tandon A, Ibanez D *et al*. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. J Rheumatol 2010;37:754–8.

15 Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. Lupus 2012;21:1271–83.

16 Skomsvoll JF, Ostensen M, Irgens LM *et al*. Perinatal outcomes in pregnancies of women with connective tissue disease and inflammatory rheumatic disease in Norway. Scand J Rheumatol 1999;28:352–6.

17 Vinet E, Clarke AE, Gordon C *et al*. Decreased live births in women with systemic lupus erythematosus. Arthritis Care Res 2011;63:1068–72.

18 Vinet E, Labrecque J, Pineau CA *et al*. A population-based assessment of live births in women with systemic lupus erythematosus. Ann Rheum Dis 2012;71:557–9.

19 Nørgaard M, Larsson H, Pedersen L *et al*. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med 2010;268:329–37.

20 Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2011;183:796–804.

21 Fisher JE, Smith RS, Lagrandeur R *et al*. Gestational diabetes mellitus in women receiving beta-adrenergics and corticosteroids for threatened preterm delivery. Obstet Gynecol 1997;90:880–3.

22 Nicklas JM, Zera CA, Seely EW *et al*. Identifying postpartum intervention approaches to prevent type 2 diabetes in women with a history of gestational diabetes. BMC Pregnancy Childbirth 2011;11:23.

23 Lie ML, Hayes L, Lewis-Barned NJ *et al*. Preventing type 2 diabetes after gestational diabetes: women's experiences and implications for diabetes prevention interventions. Diabet Med 2013;30:986–93.

24 Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 2013;12:CD001058.

25 Cowchock FS, Reece EA, Balaban D *et al*. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol 1992;166:1318–23.

26 Østensen M. Glucocorticoids in pregnant patients with rheumatoid arthritis. Z Rheumatol 2000;59(Suppl 2):II/70–4.

27 de Man YA, Hazes JM, van der Heide H *et al*. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. Arthritis Rheum 2009;60:3196–206.

28 van Gelder MM, Roeleveld N, Nordeng H. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and the risk of selected birth defects: a prospective cohort study. PLoS One 2011;6:e22174.

29 Østensen M, Khamashta M, Lockshin M *et al*. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006;8:209.

30 van der Heijden BJ, Carlus C, Narcy F *et al*. Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. Am J Obstet Gynecol 1994;171:617–23.

31 Daniel S, Matok I, Gorodischer R *et al*. Major malformations following exposure to nonsteroidal antiinflammatory drugs during the first trimester of pregnancy. J Rheumatol 2012;39:2163–9.

32 Van den Veyver IB, Moise KJ Jr, Ou CN *et al*. The effect of gestational age and fetal indomethacin levels on the incidence of constriction of the fetal ductus arteriosus. Obstet Gynecol 1993, 82(4 Pt 1):500–3.

33 Alano MA, Ngougmna E, Ostrea EM Jr *et al*. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics 2001;107:519–23.

34 Hickok DE, Hollenbach KA, Reilley SF *et al*. The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor. Am J Obstet Gynecol 1989;160:1525–30; discussion 30–1.

35 Kaplan BS, Restaino I, Raval DS *et al*. Renal failure in the neonate associated with in utero exposure to non-steroidal anti-inflammatory agents. Pediatr Nephrol 1994;8:700–4.

36 Burdan F, Dudka J, Szumilo J *et al*. Prenatal effects of DuP-697—the irreversible, highly selective cyclooxygenase-2 inhibitor. Reprod Toxicol 2003;17:413–9.

37 Cappon GD, Cook JC, Hurtt ME. Relationship between cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure. Birth Defects Res B Dev Reprod Toxicol 2003;68:47–56.

38 Stika CS, Gross GA, Leguizamon G *et al*. A prospective randomized safety trial of celecoxib for treatment of preterm labor. Am J Obstet Gynecol 2002;187:653–60.

39 Sperber K, Hom C, Chao CP *et al*. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatr Rheumatol Online J 2009;7:9.

40 Motta M, Tincani A, Faden D *et al*. Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation. J Perinatol 2005;25:86–9.

41 Klinger G, Morad Y, Westall CA *et al*. Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet 2001;358:813–4.

42 Rahimi R, Nikfar S, Rezaie A *et al*. Pregnancy outcomes in women with inflammatory bowel disease following exposure to 5-amniosalicylic acid drugs: a meta-analysis. Reprod Toxicol 2008;25:271–5.

43 Hernandez-Diaz S, Werler MM, Walker AM *et al*. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608–14.

44 Moody GA, Probert C, Jayanthi V *et al*. The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire. Int J Colorectal Dis 1997;12:220–4.

45 Jarnerot G, Andersen S, Esbjorner E *et al*. Albumin reserve for binding of bilirubin in maternal and cord serum under treatment with sulphasalazine. Scand J Gastroenterol 1981;16:1049–55.

46 Kozlowski RD, Steinbrunner JV, MacKenzie AH *et al*. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med 1990;88:589–92.

47 Lloyd ME, Carr M, McElhatton P *et al*. The effects of methotrexate on pregnancy, fertility and lactation. QJM 1999;92:551–63.

48 Østensen M. Management of early aggressive rheumatoid arthritis during pregnancy and lactation. Expert Opin Pharmacother 2009;10:1469–79.

49 Martínez Lopez JA, Loza E, Carmona L. Systematic review of the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy and breastfeeding). Clin Exp Rheumatol 2009;27:678–84.

50 Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma 2001;2:173–7.

51 Dalrymple JM, Stamp LK, O'Donnell JL *et al*. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2008;58:3299–308.

52 Weber-Schoendorfer C, Chambers C, Wacker E *et al*. Pregnancy outcome after rheumatologic methotrexate (MTX) treatment prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumatol 2014;66:1101–1.

53 Weber-Schoendorfer C, Hoeltzenbein M, Wacker E *et al*. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. Rheumatology 2014;53:757–63.

54 Cassina M, Johnson DL, Robinson LK *et al*. Pregnancy outcome in women exposed to leflunomide before or during pregnancy. Arthritis Rheum 2012;64:2085–94.

55 Fukushima R, Kanamori S, Hirashiba M *et al*. Teratogenicity study of the dihydroorotate-dehydrogenase inhibitor and protein tyrosine kinase inhibitor leflunomide in mice. Reprod Toxicol 2007;24:310–6.

56 Brent RL. Teratogen update: reproductive risks of leflunomide (Arava); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. Teratology 2001;63:106–12.

57 Chambers CD, Johnson DL, Robinson LK *et al*. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 2010;62:1494–503.

58 Cleary BJ, Kallen B. Early pregnancy azathioprine use and pregnancy outcomes. Birth Defects Res A Clin Mol Teratol 2009;85:647–54.

59 Sau A, Clarke S, Bass J *et al*. Azathioprine and breastfeeding: is it safe? BJOG 2007;114:498–501.

60 Bar Oz B, Hackman R, Einarson T *et al*. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation 2001;71:1051–5.

61 Kainz A, Harabacz I, Cowlrick IS *et al*. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. Transplantation 2000;70:1718–21.

62 Bramham K, Chusney G, Lee J *et al*. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. Clin J Am Soc Nephrol 2013;8:563–7.

63 Branch DW, Porter TF, Paidas MJ *et al*. Obstetric uses of intravenous immunoglobulin: successes, failures, and promises. J Allergy Clin Immunol 2001;108:S133–8.

64 Enns GM, Roeder E, Chan RT *et al*. Apparent cyclophosphamide (Cytoxan) embryopathy: a distinct phenotype? Am J Med Genet 1999;86:237–41.

65 Vaux KK, Kahole NC, Jones KL. Cyclophosphamide, methotrexate, and cytarabine embryopathy: is apoptosis the common pathway? Birth Defects Res Part A Clin Mol Teratol 2003;67:403–8.

66 Zemlickis D, Lishner M, Erlich R *et al*. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide. Teratog Carcinog Mutagen 1993;13:139–43.

67 Soh MC, Hart HH, Bass E *et al*. Pregnancy complicating Wegener's granulomatosis. Obstet Med 2009;2:77–80.

68 Clowse ME, Magder L, Petri M. Cyclophosphamide for lupus during pregnancy. Lupus 2005;14:593–7.

69 Ang GS, Simpson SA, Reddy AR. Mycophenolate mofetil embryopathy may be dose and timing dependent. Am J Med Genet A 2008;146A:1963–6.

70 Anderka MT, Lin AE, Abuelo DN *et al*. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. Am J Med Genet A 2009;149A:1241–8.

71 Lin AE, Singh KE, Strauss A *et al*. An additional patient with mycophenolate mofetil embryopathy: cardiac and facial analyses. Am J Med Genet A 2011;155A:748–56.

72 Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT *et al*. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. Rheumatology 2010;49:2225–7.

73 Murashima A, Watanabe N, Ozawa N *et al*. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. Ann Rheum Dis 2008;68:1793–94.

74 Ostensen M, Eigenmann GO. Etanercept in breast milk. J Rheumatol 2004;31:1017–8.

75 Clark DA. Anti-TNFalpha therapy in immune-mediated subfertility: state of the art. J Reprod Immunol 2010;85: 15–24.

76 Mahadevan U, Terdiman JP, Church J. Infliximab levels in infants born to women with inflammatory bowel disease. Gastroenterology 2007;132(Suppl 1):A144.

77 Zelinkova Z, de Haar C, de Ridder L *et al*. High intrauterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther 2011;33:1053–8.

78 Mahadevan U, Wolf DC, Dubinsky M *et al*. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:286–92; quiz e24.

79 Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol 2013;108:1426–38.

80 Wolf D, Mahadevan U. Certolizumab pegol use in pregnancy: low levels detected in cord blood. Arthritis Rheum 2010;62(Suppl 10):718.

81 Friedrichs B, Tiemann M, Salwender H *et al*. The effects of rituximab treatment during pregnancy on a neonate. Haematologica 2006;91:1426–7.

82 Klink DT, van Elburg RM, Schreurs MW *et al*. Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. Clin Dev Immunol 2008; 2008:271363.

83 Chakravarty EF, Murray ER, Kelman A *et al*. Pregnancy outcomes after maternal exposure to rituximab. Blood 2011;117:1499–506.

84 Soh MC, Nelson Piercy C. Update of the management of rheumatoid arthritis in pregnancy. Expert Rev Obstet Gynecol 2012;7:77–96.

85 Kimby E, Sverrisdottir A, Elinder G. Safety of rituximab therapy during the first trimester of pregnancy: a case history. Eur J Haematol 2004;72:292–5.

86 Krahenmann F, Østensen M, Stallmach T *et al*. In utero first trimester exposure to low-dose methotrexate with increased fetal nuchal translucency and associated malformations. Prenat Diagn 2002;22:489–90.

87 Lewden B, Vial T, Elefant E *et al*. Low dose methotrexate in the first trimester of pregnancy: results of a French collaborative study. J Rheumatol 2004;31:2360–65.

88 Østensen M, Hartmann H, Salvesen K. Low dose weekly methotrexate in early pregnancy. A case series and review of the literature. J Rheumatol 2000;27:1872–5.

89 Perez-Aytes A, Ledo A, Boso V *et al*. In utero exposure to mycophenolate mofetil: a characteristic phenotype? Am J Med Genet A 2008;146A:1–7.

90 Chambers CD, Johnson DL, Robinson LK *et al*. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 2010;62:1494–503.

91 Aviles A, Diaz-Maqueo JC, Talavera A *et al*. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. Am J Hematol 1991;36:243–8.

92 Aviles A, Niz J. Long-term follow-up of children born to mothers with acute leukemia during pregnancy. Med Pediatr Oncol 1988;16:3–6.

93 Royal College of Obstetricians and Gynaecologists. Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk: (Green-top 37a). http://www.rcog.org.uk/womens-health/clinical-guidance/reducing-risk-of-thrombosis-greentop37a (9 September 2014, date last accessed).

94 Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. Arthritis Rheum 1991;34:1538–45.

95 Ruiz-Irastorza G, Khamashta MA. Lupus and pregnancy: ten questions and some answers. Lupus 2008;17: 416–20.

96 Clowse ME. Lupus activity in pregnancy. Rheum Dis Clin North Am 2007;332:237–52.

97 Parke A, West B. Hydroxychloroquine in pregnant patients with systemic lupus erythematosus. J Rheumatol 1996;23:1715–8.

98 Levy RA, Vilela VS, Cataldo MJ *et al*. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001;10: 401–4.

99 Clowse ME, Magder L, Witter F *et al*. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54:3640–7.

100 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN *et al*. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76–82.

101 Izmirly PM, Llanos C, Lee LA *et al*. Cutaneous manifestations of neonatal lupus and risk of subsequent congenital heart block. Arthritis Rheum 2010;62:1153–7.

102 Imbasciati E, Gregorini G, Cabiddu G *et al*. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. Am J Kidney Dis 2007;49:753–62.

103 Smyth A, Oliveira GH, Lahr BD *et al*. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol 2010;5:2060–8.

104 Eliasson H, Sonesson SE, Sharland G *et al*. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation 2011;124:1919–26.

105 Friedman DM, Llanos C, Izmirly PM *et al*. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: results of a multicenter, prospective, open-label clinical trial. Arthritis Rheum 2010;62:1138–46.

106 Pisoni CN, Brucato A, Ruffatti A *et al*. Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. Arthritis Rheum 2010;62:1147–52.

107 Neiman AR, Lee LA, Weston WL *et al*. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. J Pediatr 2000;137:674–80.

108 Moretti D, Cimaz R, Vannucci G *et al*. Cutaneous neonatal lupus: a case report and review of the literature. Int J Dermatol 2013 Jul 24. doi: 10.1111/j.1365-4632.2012.05809.x. [Epub ahead of print].

109 Chang C. The pathogenesis of neonatal autoimmune and autoinflammatory diseases: a comprehensive review. J Autoimmun 2013;41:100–10.

110 Furtado J, Isenberg DA. B cell elimination in systemic lupus erythematosus. Clin Immunol 2013;146:90–103.

111 Braun-Moscovici Y, Butbul-Aviel Y, Guralnik L *et al*. Rituximab: rescue therapy in life-threatening complications or refractory autoimmune diseases: a single center experience. Rheumatol Int 2012.

112 Harward LE, Mitchell K, Pieper C *et al*. The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease. Lupus 2013;22: 81–6.

113 Simister NE. Placental transport of immunoglobulin G. Vaccine 2003;21:3365–9.

114 Saji F, Samejima Y, Kamiura S *et al*. Dynamics of immunoglobulins at the feto-maternal interface. Rev Reprod 1999;4:81–9.

115 Decker M, Rothermundt C, Hollander G *et al*. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. Lancet Oncol 2006;7:693–4.

116 Østensen M, Förger F. Treatment with biologics of pregnant patients with rheumatic diseases. Curr Opin Rheumatol 2011;23:293–98.

117 Merrill JT, Neuwelt CM, Wallace DJ *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222–33.

118 Navarra SV, Guzman RM, Gallacher AE *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.

119 Manzi S, Sanchez-Guerrero J, Merrill JT *et al*. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis 2012;71: 1833–8.

120 Auyeung-Kim DJ, Devalaraja MN, Migone TS *et al*. Developmental and peri-postnatal study in cynomolgus monkeys with belimumab, a monoclonal antibody directed against B-lymphocyte stimulator. Reprod Toxicol 2009;28:443–55.

121 Vaidyanathan A, McKeever K, Anand B *et al*. Developmental immunotoxicology assessment of rituximab in cynomolgus monkeys. Toxicol Sci 2011;119: 116–25.

122 GlaxoSmithKline. Belimumab (Benlysta^{TM}) Pregnancy Registry. http://pregnancyregistry.gsk.com/belimumab.html (9 September 2014, date last accessed).

123 Soh MC, Nelson-Piercy C. Antiphospholipid syndrome in pregnancy. Exp Rev Obstet Gynaecol 2010;5:741–61.

124 Bramham K, Hunt BJ, Germain S *et al*. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus 2010;19:58–64.

125 Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. Obstet Gynecol 2003;101:1333–44.

126 Rey E, Garneau P, David M *et al*. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. J Thromb Haemost 2009;7:58–64.

127 Gris JC, Chauleur C, Faillie JL *et al*. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. Thromb Haemost 2010;104:771–9.

128 Laskin CA, Spitzer KA, Clark CA *et al*. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. J Rheumatol 2009;36:279–87.

129 Rodger MA. An update on thrombophilia and placenta mediated pregnancy complications: what should we tell our patients? Thromb Res 2013;131(Suppl 1):S25–7.

130 Clark P, Walker ID, Langhorne P *et al*. SPIN (Scottish Pregnancy Intervention) Study: a multicentre randomised controlled trial of low molecular weight heparin and low dose aspirin in women with recurrent miscarriage. Blood 2010;115:4162–7.

131 Kaandorp SP, Goddijn M, van der Post JA *et al*. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010;362:1586–96.

132 Tan WK, Lim SK, Tan LK *et al*. Does low-molecular-weight heparin improve live birth rates in pregnant women with thrombophilic disorders? A systematic review. Singapore Med J 2012;53:659–63.

133 Vila P, Hernandez MC, Lopez-Fernandez MF *et al*. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost 1994;72:209–13.

134 Shi W, Krilis SA, Chong BH *et al*. Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. Aust N Z J Med 1990;20:231–6.

135 Soh MC, Pasupathy D, Gray G *et al*. Persistent antiphospholipid antibodies do not contribute to adverse pregnancy outcomes. Rheumatology 2013;52:1642–7.

136 Clark CA, Laskin CA, Spitzer KA. Anticardiolipin antibodies and recurrent early pregnancy loss: a century of equivocal evidence. Hum Reprod Update 2012;18: 474–84.

137 Lockshin MD, Kim M, Laskin CA *et al*. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum 2012;64:2311–8.

138 Barrett JH, Brennan P, Fiddler M *et al*. Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study in the United Kingdom performed prospectively from late pregnancy. Arthritis Rheum 1999;42:1219–27.

139 de Man YA, Dolhain RJ, van de Geijn FE *et al*. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum 2008;59:1241–8.

140 de Man YA, Bakker-Jonges LE, Goorbergh CM *et al*. Women with rheumatoid arthritis negative for anti-cyclic citrullinated peptide and rheumatoid factor are more

likely to improve during pregnancy, whereas in autoantibody-positive women autoantibody levels are not influenced by pregnancy. Ann Rheum Dis 2010;69:420–3.

141 Camacho EM, Lunt M, Farragher TM *et al*. Reproductive history and functional outcome in women with recent-onset inflammatory polyarthritis [abstract]. Arthritis Rheum 2010;62(Suppl 10):779.

142 Camacho EM, Farragher TM, Lunt M *et al*. The relationship between post-onset pregnancy and functional outcome in women with recent onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 2010;69:1834–7.

143 Drossaers-Bakker KW, Zwinderman AH, Vliet Vlieland TP *et al*. Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup. Arthritis Rheum 2002;47:383–90.

144 Ostensen M. Pregnancy in patients with a history of juvenile rheumatoid arthritis. Arthritis Rheum 1991;34:881–7.

145 Wallenius M, Skomsvoll JF, Irgens LM *et al*. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum 2011;63:1534–42.

146 Skomsvoll JF, Ostensen M, Irgens LM *et al*. Pregnancy complications and delivery practice in women with connective tissue diseases and inflammatory rheumatic disease in Norway. Acta Obstet Gynecol Scand 2000;79:490–5.

147 Wolfberg AJ, Lee-Parritz A, Peller AJ *et al*. Association of rheumatologic disease with preeclampsia. Obstet Gynecol 2004;103:1190–3.

148 Lin HC, Chen SF, Chen YH. Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. Ann Rheum Dis 2010;69:715–7.

149 Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. Matern Child Health J 2006;10:361–6.

150 Bowden AP, Barrett JH, Fallow W *et al*. Women with inflammatory polyarthritis have babies of lower birth weight. J Rheumatol 2001;28:355–9.

151 Mahadevan U, Cucchiara S, Hyams JS *et al*. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol 2011;106:214–23; quiz 24.

152 Tracey D, Klareskog L, Sasso EH *et al*. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 2008;117:244–79.

153 Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. Rheumatology 2014;53:1377–85.

154 Pham T, Bachelez H, Berthelot J-M *et al*. Abatacept therapy and safety management. Joint Bone Spine 2012;79:3–84.

155 European Medicines Agency. Scientific Discussion for Orencia (abatacept). London: European Medicines Agency, 2010.

156 Ojeda-Uribe M, Afif N, Dahan E *et al*. Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. Clin Rheumatol 2013;32:695–700.

157 Berger CT, Recher M, Steiner U *et al*. A patient's wish: anakinra in pregnancy. Ann Rheum Dis 2009;68:1794–95.

158 Fischer-Betz R, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). Clin Exp Rheumatol 2011;29:1021–3.

159 Rubbert-Roth A, Goupille P, Moosavi Sea. First experiences with pregnancies in RA patients receiving tocilizumab therapy [abstract]. Arthritis Rheum 2010;62(Suppl 10):384.

160 Cheent K, Nolan J, Shariq S *et al*. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis 2010;4:603–5.

161 Kane S, Ford J, Cohen R *et al*. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol 2009;43:613–6.

162 Ben-Horin S, Yavzori M, Katz L *et al*. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol 2010;8:475–6.

163 Stengel JZ, Arnold HL. Is infliximab safe to use while breastfeeding? World J Gastroenterol 2008;14:3085–7.

164 Chung L, Flyckt RL, Colon I *et al*. Outcome of pregnancies complicated by systemic sclerosis and mixed connective tissue disease. Lupus 2006;15:595–99.

165 Taraborelli M, Ramoni V, Brucato A *et al*. Brief report: successful pregnancies but a higher risk of preterm births in patients with systemic sclerosis: an Italian multicenter study. Arthritis Rheum 2012;64:1970–7.

166 Mukerjee D, St George D, Coleiro B *et al*. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–93.

167 Lidar M, Langevitz P. Pregnancy issues in scleroderma. Autoimmun Rev 2012;11:A515–9.

168 Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256–65.

169 Kiely DG, Condliffe R, Wilson VJ *et al*. Pregnancy and pulmonary hypertension: a practical approach to management. Obstet Med 2013;6:144–54.

170 Madden BP. Pulmonary hypertension and pregnancy. Int J Obstet Anesth 2009;18:156–64.

171 Steen VD, Conte C, Day N *et al*. Pregnancy in women with systemic sclerosis. Arthritis Rheum 1989;32:151–7.

172 Baethge BA, Wolf RE. Successful pregnancy with scleroderma renal disease and pulmonary hypertension in a patient using angiotensin converting enzyme inhibitors. Ann Rheum Dis 1989;48:776–8.

173 Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998;41:1613–9.

174 Montanelli G, Beretta L, Santaniello A *et al*. Effect of dihydropyridine calcium channel blockers and glucocorticoids on the prevention and development of scleroderma renal crisis in an Italian case series. Clin Exp Rheumatol 2013;31(Suppl 76):135–9.

175 Steen VD. Pregnancy in women with systemic sclerosis. Obstet Gynecol 1999;94:15–20.

176 Steen VD. Pregnancy in scleroderma. Rheum Dis Clin North Am 2007;33:345–58, vii.

177 Bussone G, Berezne A, Pestre V, Guillevin L, Mouthon L. The scleroderma kidney: progress in risk factors, therapy, and prevention. Curr Rheumatol Rep 2011;13:37–43.

178 Hidaka N, Yamanaka Y, Fujita Y *et al*. Clinical manifestations of pregnancy in patients with Takayasu arteritis: experience from a single tertiary center. Arch Gynecol Obstet 2012;285:377–85.

179 Suri V, Aggarwal N, Keepanasseril A *et al*. Pregnancy and Takayasu arteritis: a single centre experience from North India. J Obstet Gynaecol Res 2010;36:519–24.

180 Matsumura A, Moriwaki R, Numano F. Pregnancy in Takayasu arteritis from the view of internal medicine. Heart Vessels 1992;7(Suppl):120–4.

181 de Jesus GR, d'Oliveira IC, dos Santos FC *et al*. Pregnancy may aggravate arterial hypertension in women with Takayasu arteritis. Isr Med Assoc J 2012;14:724–8.

182 Ishikawa K, Matsuura S. Occlusive thromboaortopathy (Takayasu's disease) and pregnancy. Clinical course and management of 33 pregnancies and deliveries. Am J Cardiol 1982;50:1293–300.

183 Mandal D, Mandal S, Dattaray C *et al*. Takayasu arteritis in pregnancy: an analysis from eastern India. Arch Gynecol Obstet 2012;285:567–71.

184 Lakhi NA, Jones J. Takayasu's arteritis in pregnancy complicated by peripartum aortic dissection. Arch Gynecol Obstet 2010;282:103–6.

185 Pagnoux C, Le Guern V, Goffinet F *et al*. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology 2011;50:953–61.

186 Koukoura O, Mantas N, Linardakis H *et al*. Successful term pregnancy in a patient with Wegener's granulomatosis: case report and literature review. Fertil Steril 2008;89:457.e1–5.

187 Sahni V, Agarwal SK, Singh NP *et al*. Successful pregnancy in untreated limited Wegener's granulomatosis. Med J Malaysia 2005;60:492–4.

188 Bessias N, Moulakakis KG, Lioupis C *et al*. Wegener's granulomatosis presenting during pregnancy with acute limb ischemia. J Vasc Surg 2005;42:800–4.

189 Bellisai F, Morozzi G, Marcolongo R *et al*. Pregnancy in Wegener's granulomatosis: successful treatment with intravenous immunoglobulin. Clin Rheumatol 2004;23:533–5.

190 Palit J, Clague RB. Wegener's granulomatosis presenting during first trimester of pregnancy. Br J Rheumatol 1990;29:389–90.

191 M'Rad S, Moalla M, Ben Miled K *et al*. Wegener's granulomatosis and pregnancy. A case. Rev Med Interne 1989;10:69–72.

192 Milford CA, Bellini M. Wegener's granulomatosis arising in pregnancy. J Laryngol Otol 1986;100:475–6.

193 Talbot SF, Main DM, Levinson AI. Wegener's granulomatosis: first report of a case with onset during pregnancy. Arthritis Rheum 1984;27:109–12.

194 Mackworth-Young CG, Morgan SH, Hughes GR. Wegener's granulomatosis: onset during puerperium. Arthritis Rheum 1984;27:1314–5.

195 Cooper K, Stafford J, Turner-Warwick M. Wegener's granuloma complicating pregnancy. BJOG 1970;77:1028–30.

196 Tuin J, Sanders JS, de Joode AA *et al*. Pregnancy in women diagnosed with antineutrophil cytoplasmic antibody-associated vasculitis: outcome for the mother and the child. Arthritis Care Res 2012;64:539–45.

197 Harber MA, Tso A, Taheri S *et al*. Wegener's granulomatosis in pregnancy—the therapeutic dilemma. Nephrol Dial Transplant 1999;14:1789–91.

198 Pauzner R, Mayan H, Hershko E *et al*. Exacerbation of Wegener's granulomatosis during pregnancy: report of a case with tracheal stenosis and literature review. J Rheumatol 1994;21:1153–6.

199 Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

200 Jones RB, Tervaert JW, Hauser T *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.

201 Jayne D. Rituximab treatment for vasculitis. Clin J Am Soc Nephrol 2010;5:1359–62.

202 Ruiz-Irastorza G, Lima F, Alves J *et al*. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Br J Rheumatol 1996;35:133–8.

203 Wallenius M, Skomsvoll JF, Irgens LM *et al*. Postpartum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry. Ann Rheum Dis 2010;69:332–6.

204 Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation 2011;123:2856–69.

205 Bellamy L, Casas JP, Hingorani AD *et al*. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.

206 Magnussen EB, Vatten LJ, Lund-Nilsen TI *et al*. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007;335:978.

207 Ray JG, Vermeulen MJ, Schull MJ *et al*. Cardiovascular health after maternal placental

syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005;366:1797–803.

208 Mosca L, Benjamin EJ, Berra K *et al*. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011;57:1404–23.

209 Fraser A, Nelson SM, Macdonald-Wallis C *et al*. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation 2012;125:1367–80.

210 Bramham K, Briley AL, Seed PT *et al*. Pregnancy outcome in women with chronic kidney disease: a prospective cohort study. Reprod Sci 2011;18:623–30.

211 Piccoli GB, Attini R, Vasario E *et al*. Pregnancy and chronic kidney disease: a challenge in all CKD stages. Clin J Am Soc Nephrol 2010;5:844–55.

212 Nevis IF, Reitsma A, Dominic A *et al*. Pregnancy outcomes in women with chronic kidney disease: a systematic review. Clin J Am Soc Nephrol 2011;6:2587–98.

213 Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. N Engl J Med 1996;335:226–32.

214 Andreoli L, Bazzani C, Taraborelli M *et al*. Pregnancy in autoimmune rheumatic diseases: the importance of counselling for old and new challenges. Autoimmun Rev 2010;10:51–4.

215 Chakravarty E, Clowse ME, Pushparajah DS *et al*. Family planning and pregnancy issues for women with systemic inflammatory diseases: patient and physician perspectives. BMJ Open 2014;4:e004081.

216 Liu J, Zhao Y, Song Y *et al*. Pregnancy in women with systemic lupus erythematosus: a retrospective study of 111 pregnancies in Chinese women. J Matern Fetal Neonatal Med 2012;25:261–6.

217 Chakravarty EF, Colon I, Langen ES *et al*. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. Am J Obstet Gynecol 2005;192:1897–904.

218 Clowse ME, Wallace DJ, Weisman M *et al*. Predictors of preterm birth in patients with mild systemic lupus erythematosus. Ann Rheum Dis 2013;72:1536–9.

219 Barnabe C, Faris PD, Quan H. Canadian pregnancy outcomes in rheumatoid arthritis and systemic lupus erythematosus. Int J Rheumatol 2011;2011:345727.

220 Soh MC, Nelson Piercy C, Dib F *et al*. Association between cardiovascular disease and main cause of death from cardiovascular causes with maternal-placental syndrome in Swedish women with systemic lupus erythematosus—a population-based retrospective study. Ann Rheum Dis 2014;73(Suppl 2):137.

221 Soh MC, Nelson-Piercy C, Dib F *et al*. 10.2 Association of the history of maternal-placental syndrome and cardiovascular disease in women with systemic lupus erythematosus. Arch Dis Child Fetal Neonatal Ed 2014;99(Suppl 1):A15.