

Management of rheumatologic diseases in pregnancy

Rheumatic diseases include a variety of chronic multisystem disorders with a high percentage of autoimmune conditions. Many of these diseases affect women of child-bearing age, and so pregnancy poses an important challenge for doctors looking after these women. Knowledge about medication safety, the effect of pregnancy on such diseases, and vice versa, together with preconception counseling and multidisciplinary team care, are basic pillars needed to provide the best obstetric and medical care to these women. In this review, the management of the most common autoimmune rheumatic diseases prior, during and after pregnancy will be discussed, along with the most relevant issues regarding medications.

KEYWORDS: management • medications • pregnancy • pre-pregnancy counseling • rheumatic diseases

Background

The changes in hormonal profiles found in pregnancy induce important immunomodulatory changes with direct consequences on immune-mediated rheumatic diseases. As a result of the shift from Th1 to Th2 lymphocyte dominance, Th1 predominant diseases, such as rheumatoid arthritis (RA), are more likely to remain in remission during pregnancy, whereas autoimmune disorders, such as systemic lupus erythematosus (SLE), characterized by a Th2 response, are more likely to flare.

Not all pregnancies in women with rheumatic diseases should be considered *a priori* high risk. Preconception counseling provides the ideal scenario as the woman's previous obstetric history, organ damage, disease activity, serological profile and additional medical history can be assessed to allow individualized discussion of potential pregnancy complications. In addition, any necessary medication adjustments can be made. Close surveillance throughout pregnancy and the puerperium, and a tailored management approach lead to high rates of successful pregnancies in these women.

Fertility

Fertility in women with rheumatic diseases is generally not affected, although patients with chronic kidney disease (CKD 3–5; eGFR <50 ml/min), amenorrhea due to previous high cumulative dose of cyclophosphamide (CYC) and/or active disease may have reduced fertility [1].

Women with RA, scleroderma and other arthritides have lower birth rates compared with the general population [2], probably

because of diminished sexual relationships as a result of joint pains, reduced joint mobility, fatigue, depression, dyspareunia, reduced libido and altered body image [3]. Concerns about possible deleterious long-term effects of pregnancy on the disease, and teratogenic effects of treatment may also discourage both doctors and patients from the challenge of pregnancy.

Patients who take NSAIDs should be encouraged to stop when trying to conceive because of the risk of luteinized unruptured follicle syndrome [4]. This condition is a well-described anovulatory state characterized by clinical signs of ovulation in the absence of follicular rupture and ovum release due to inhibition of the cyclo-oxygenase-2 needed during follicular development.

Regardless of the cause of infertility, women who are keen to undergo assisted reproductive techniques should be counseled about the increased risk of disease flare (particularly women with SLE) and thromboembolic events [5] (especially in women with ovarian hyperstimulation syndrome, antiphospholipid antibodies (aPL) and/or other prothrombotic risk factors). Identification of high-risk patients, precycle counseling, and adequate thromboprophylaxis and surveillance are mandatory [6]. In patients with SLE and antiphospholipid syndrome [APS], ovarian stimulation with clomiphene, single embryo transfer, avoidance of ovarian hyperstimulation syndrome and use of natural estradiol and/or progestagens through a nonoral route have been suggested as safe approaches [6].

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Connective tissue diseases

■ SLE

Effect of pregnancy on SLE

Pregnancy is considered a high-risk time in lupus patients, as flares during pregnancy have been related to irreversible organ damage [7]. However, whether pregnancy increases the risk of lupus flare is still an unsolved question [8–14]. Some authors have suggested the puerperium as a period of particular high risk for lupus flare [15]. Based on these studies, lupus flare seems unpredictable. However, the risk of flare appears to be dependent on the disease activity 6–12 months prior to conception. Women with quiescent lupus over this period have less risk of flare during pregnancy [12,16], whereas women with active SLE during this time have a high risk of flare [9,17]. Therefore, pregnancy should be planned when the disease has been in remission for at least 6 months.

Active lupus nephritis (LN) at conception confers a higher risk of flare during pregnancy [18], and even those with LN in remission have an increased risk of flare [14]. In women with previous LN, pregnancy does not seem to endanger long-term renal function, although generally the higher the baseline creatinine, the greater the risk of deterioration [14,18,19].

Lupus flares during pregnancy and postpartum are normally nonsevere, characterized by articular, dermatological and mild hematological involvement [9,10,13], and are usually well controlled with short-term introduction or increase of oral steroids. Nonetheless, severe flares with major organ involvement may occur [9].

A recent systematic review established the protective effects of hydroxychloroquine (HCQ) in terms of organ damage, flares, thrombosis, bone mass loss and long-term survival in the general lupus population, as well as the potential to prevent disease activity in pregnant women [20]. Two recent prospective studies corroborated these findings, suggesting that women who had taken HCQ throughout pregnancy presented lower activity scores and had lower prednisone doses at the end of pregnancy [21], whereas those who discontinued HCQ or did not take it at all had higher activity scores, more flares and required higher doses of steroids [22].

Distinguishing pregnancy-related signs and symptoms from certain lupus features may sometimes be difficult. Assessment by experienced physicians is important. Fatigue, arthralgia, hair loss, dyspnea, headaches, malar and palmar erythema, edema, anemia and thrombocytopenia represent some of the most common ambiguous manifestations. In pregnancy, erythrocyte

sedimentation rate is usually raised due to higher fibrinogen production in the liver, hence it is not considered a valid marker of disease activity in pregnancy. Serum C3 and C4 levels also rise in pregnancy due to increased liver production, so even in women with active lupus they may remain within normal range. Relative variation rather than absolute levels of C3 and C4 should be assessed. A drop of 25% or more in serum complement levels in pregnancy may suggest lupus flare [23]. In patients with permanent significant protein loss due to previous LN, proteinuria may increase throughout pregnancy due to increased renal blood flow, without indicating active nephritis [19]. This may be more pronounced in patients who withdraw from angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) shortly before or early in pregnancy. Up to a doubling of proteinuria from the baseline level in early pregnancy is to be expected [19].

Pregnancy may have a detrimental effect on other major organs/systems, such as the heart, CNS, lungs and pulmonary arterial system, with associated high morbidity and mortality [24]. Women with moderate–severe lupus flare or stroke within the previous 6 months, CKD 4–5 ($\text{Cr} > 2.5\text{--}2.8\text{ mg/dl}$, $> 220\text{--}250\text{ }\mu\text{mol/l}$; or $\text{eGFR} < 35\text{ ml/min}$), pulmonary hypertension, moderate–severe cardiomyopathy (ejection fraction $< 30\text{--}40\%$), or severe restrictive lung disease (forced vital capacity $< 50\%$ of predicted) are at highest risk for medical and obstetric complications and should be appropriately counseled, generally against conception or continuation of pregnancy.

Effect of SLE on pregnancy

SLE patients are at risk of multiple medical and obstetric complications during pregnancy. A recent study from the USA showed that lupus patients have a 20-fold increased risk of maternal mortality and a higher rate of hypertension, pregestational diabetes, renal impairment, pulmonary hypertension, major infections, thrombotic events and other hematologic complications, compared with the general population [25]. Furthermore, the risk of preeclampsia, cesarean section, preterm labor and intrauterine growth restriction (IUGR) was two- to four-fold higher in women with SLE, particularly in patients with chronic hypertension, renal impairment and women on high-dose oral steroids [25]. Conversely, those with SLE in remission without major organ involvement are likely to have a normal pregnancy outcome.

Approximately 25% of all lupus pregnancies end in preterm (<37 weeks) delivery [26]. Disease activity [17], hypertension [27] and hypothyroidism [28] have been identified as risk factors for preterm delivery. Fetal growth restriction secondary to placental insufficiency is frequent in lupus pregnancies [29], even in those with mild disease [30], with an incidence of 6–35% of small for gestational age babies [31].

Pregnancy loss occurs in up to one in five pregnancies of lupus patients (compared with ~one in ten in controls), with a high percentage of stillbirths (up to four- to six-fold seen in controls) [26]. Hypertension, proteinuria >500 mg/day, thrombocytopenia and secondary APS have been recognized as risk factors for pregnancy loss [31].

Patients with nonreversible organ damage are more prone to developing complications and further damage both during and after gestation [7], this is especially true in women with CKD, which has been related to higher rates of fetal loss [17]. Women with active SLE during the 6 months prior to conception or high clinical activity in pregnancy, often associated with corticosteroid use, have worse pregnancy outcomes compared with those with low or no activity [17,32,33]. Likewise, patients with hypocomplementemia or positive anti-dsDNA antibodies have been shown to have the highest risk of pregnancy loss and preterm birth [27]. Patients with active LN are at particularly high risk for poorer pregnancy outcome [34], therefore they should be advised to postpone pregnancy until at least 6 months (ideally 12–18 months) after the last LN flare. There is no evidence to suggest that different subclasses of LN affect this risk [34]. Women with creatinine >2.5–2.8 mg/dl (>220–250 μ mol/l; eGFR<35 ml/min), on dialysis or with renal transplant present the highest complication rates [19]. A history of LN, as with any cause of CKD, is associated with an increased risk of hypertensive disorders in pregnancy [34].

Overall, women with SLE have a three- to four-fold increased chance of developing preeclampsia [33,35], compared with the general population [36]. Risk factors for developing preeclampsia in the general population have been extensively described elsewhere [19,20]. Differentiating preeclampsia from LN may not be straight forward, as both may involve hypertension, worsening proteinuria, edema, renal impairment and thrombocytopenia, and sometimes both may overlap. Findings indicative of preeclampsia are severe headache, visual problems (including flashing lights), epigastric

or right upper quadrant tenderness, nausea or vomiting, clonus (>2 beats), deranged liver function tests, rising uric acid level and signs of hemolysis [201]. Features indicative of LN are onset before 20 weeks of gestation, active urinary sediment, low or falling complement levels, high or increasing anti-dsDNA, and evidence of lupus flare involving other organs. If renal biopsy is indicated (because the result would inform management by confirming or refuting a diagnosis of LN and the class), special care should be taken owing to the higher bleeding risk after biopsy in pregnancy [37]. New biomarkers of preeclampsia and further studies regarding their behavior in SLE populations may be of value in the future.

■ Scleroderma/systemic sclerosis

As the average age of onset of scleroderma is the early 40s, until the end of last century, most women would have completed their pregnancies before the onset of the disease. At present, that is changing as women frequently delay pregnancy.

Pregnancy does not seem to affect disease activity in the majority (63–72%) of women with scleroderma/systemic sclerosis (SSc). A third will either improve or worsen in pregnancy [38,39]. Importantly, SSc may be associated with an increased risk of developing hypertensive disorders in pregnancy, including preeclampsia, possibly related to associated hypertension. Women should be closely monitored for signs of renal crisis and preeclampsia throughout pregnancy [40].

Clinically, Raynaud's phenomenon generally improves, whereas gastro-esophageal reflux disease worsens, which may be complicated by Mallory–Weiss tears and severe bleeding. Skin involvement usually remains stable or improves, but may worsen postpartum. Other features such as edema, shortness of breath and arthralgias may be difficult to differentiate from pregnancy itself and must be carefully assessed.

Importantly, recent onset of scleroderma symptoms (<4 years), diffuse cutaneous involvement or anti-Scl-70 (anti-topoisomerase-I) or anti-RNA-polymerase-III antibodies are associated with increased risk of suffering more active and aggressive disease than longstanding SSc and the presence of anticentromere antibodies [41]. Patients with marked malabsorption, CKD (Cr>2.5–2.8 mg/dl, >220–250 μ mol/l; or eGFR<35 ml/min), pulmonary hypertension, moderate–severe cardiomyopathy (ejection fraction <30–40%) or severe restrictive lung disease (forced vital capacity <50% of predicted) are at highest risk for medical and obstetric

complications and should be appropriately counseled, generally against conception or continuation of pregnancy [42]. Thorough assessment of scleroderma organ involvement and full autoantibody screen are important prior to conception in order to allow accurate counseling.

Renal crisis does not occur more frequently in pregnancy. However, if it does happen, management must be with ACEI despite the risks to the baby, as it is lifesaving for the mother [43]. Preeclampsia can present with similar features as renal crisis, and ACEI should be considered if there is doubt about the diagnosis. SSc renal crisis, however, does not derange liver function tests, is often characterized by rapidly rising serum creatinine and rarely presents major proteinuria or pathologic urinary sediment.

A previous renal crisis does not contraindicate future pregnancies, but women are generally persuaded to delay pregnancy for several years until their disease stabilizes. The best treatment approach for hypertension control in pregnancy after a previous renal crisis remains unknown. A trial without ACEI before attempting conception may be of help to assess blood pressure (BP) control with other medications, as well as renal function and proteinuria response [42]. If, after having withdrawn ACEI, BP is not well controlled on other drugs, an ACEI should be restarted owing to the severe deleterious effects of uncontrolled BP on the mother's renal function and the baby. A compromise may be to keep a low dose of ACEI plus other hypertensives, after proper counseling.

Women with scleroderma have higher rates of adverse pregnancy outcome in most case-control studies [44,45]. However, these risks should not discourage women from pregnancy provided they receive appropriate antenatal care. SSc is associated with increased risk of preterm delivery (14–29%), IUGR, longer hospitalization and, in women with longstanding diffuse scleroderma, miscarriage [38–40]. Women with limited scleroderma generally have better pregnancy outcomes than those with diffuse disease. In many cases, the unfavorable pregnancy outcomes may precede the diagnosis of the disease, but there is a trend towards worse outcomes after diagnosis of the disease. In cases of likely preterm delivery, corticosteroids for fetal lung maturation should not be given as they may precipitate a renal crisis. Epidural anesthesia and venous access are recommended during labor. Episiotomy or cesarean section may be performed with caution, as wound healing is not usually impaired and there is no contraindication for such procedures [42].

■ Undifferentiated connective tissue disease

Three prospective studies identified more than 125 pregnancies in women with undifferentiated connective tissue disease (UCTD). Flare of symptoms occurred in approximately a third [46–48], and there was a small tendency for UCTD to evolve into well-defined disease. Women with UCTD suffered worse pregnancy outcomes, with more frequent preeclampsia, IUGR and preterm deliveries compared with background.

■ Sjögren's syndrome

Although Sjögren's syndrome (SS) is generally diagnosed beyond the age of 40 years, there are considerable numbers of women who plan pregnancy after diagnosis. Despite the lack of published data regarding pregnancy in SS patients, we would recommend planning pregnancy when the disease is inactive and well controlled with safe medications (see below). There are no data concerning the use of drugs such as pilocarpine (US FDA class C) and cevimeline (FDA class C) in pregnancy. Most patients with SS are anti-Ro positive and women require appropriate pre-pregnancy counseling (see below).

■ Polymyositis/dermatomyositis

Polymyositis and dermatomyositis in women are usually diagnosed after the child-bearing age. Two small series suggest that approximately half will flare during pregnancy, while disease activity seems to be the main predictor of obstetric complications [49,50]. Women with quiescent disease are more likely to have uncomplicated pregnancies, whereas those with active polymyositis/dermatomyositis have higher risk of preterm delivery and pregnancy loss.

■ Mixed connective tissue disease

The available evidence for mixed connective tissue disease comes from a few small retrospective studies and case reports. Overall, flare rates and pregnancy outcomes in these women seem to resemble those seen in SLE rather than those in RA or in SSc, thus their pregnancy counseling and management should probably be similar to that described in SLE [51].

RA & other chronic inflammatory arthritides

RA is less common in women of child-bearing age than in older women (0.1–0.2% vs 2–5%), but its incidence in pregnancy is increasing as women delay child-bearing [52].

Contrary to previous research [53], recent prospective studies show that only 48–66% of women with RA experience improvement in pregnancy, with only approximately 20% becoming quiescent by the third trimester [54,55]. This change may be due to new treatment regimes, as women receive more aggressive treatments and enter pregnancy with more stable disease so they have less margin to improve [54,55]. A recent prospective study that included 118 pregnant women with RA showed that those with positive rheumatoid factor and anti-cyclic citrullinated antibody (anti-CCP) were less likely to improve during pregnancy. However, all women had the same chance of flare postpartum regardless of their serological profile, and antibody levels had no relationship with activity either pre- or post-natally [56].

Most women with psoriatic arthritis (PsA) generally improve or even remit in pregnancy, whereas the majority with ankylosing spondylitis (AS) stay unaltered or worsen during pregnancy [57,58]. The minority of AS patients who markedly improve while pregnant usually have AS with accompanying diseases, such as psoriasis, ulcerative colitis or small joint arthritis. In cases of juvenile RA, quiescent disease is not generally reactivated by pregnancy, and active disease at conception ameliorates in approximately 60% [57,58]. Postpartum flares occur within the first 4 months in most patients with chronic inflammatory arthritides [55,59]. Furthermore, new-onset of RA is three- to five-fold more likely during this postpartum period [54,60]. A prospective study including 112 women showed that pregnancy and oral contraceptive use do not significantly influence long-term joint damage or disability in RA. Interestingly, patients with multiple pregnancies and long-term oral contraception had less radiographic joint damage and better functional levels [61].

The few available studies on pregnancies in women with RA suggest that outcomes are worse than in the general population [62,63], and some have found that hypertensive disorders, including preeclampsia, are more frequent [62–65] and often related to preterm deliveries, although this may be confounded by corticosteroid use or underlying disease severity.

Children born to women with inflammatory arthritides, including RA, are more likely to be small for gestational age, to be born preterm (<37 weeks) and to have lower birth weight [63–66], which seems to be particularly associated with disease activity and corticosteroid treatment [62,67]. Women with RA may have higher

risk for fetal deaths [66]. Cesarean section is more common in RA, and probably related to the high rates of induction of labor and elective sections chosen by obstetricians [62,63,65,66].

Vasculitis

Systemic vasculitides are rare and therefore data on pregnancy outcome are limited to a few case series and case reports. Overall, it seems that if women embark on pregnancy with vasculitis in remission their risk of complications is low, and therefore, pregnancy should ideally be planned after prolonged quiescent disease. Disease flares can occur at any stage of pregnancy and postpartum.

Erythrocyte sedimentation rate is not a reliable marker for disease activity monitoring during pregnancy, but C-reactive protein levels remain reliable [68]. Clinically, infections and vasculitis can mimic each other, and excluding infection is important for correct management, especially in patients on immunosuppressive drugs [69]. Vasculitis flare may also be difficult to distinguish from preeclampsia. An active urinary sediment and other systemic clinical manifestations usually point towards the former, whereas isolated proteinuria and the presence of characteristic clinical manifestations of preeclampsia (hypertension, headache, epigastric pain, edema and small baby) may indicate the latter.

Low-dose steroids (prednisone <7.5–10 mg) and azathioprine are the cornerstones of maintenance treatment during pregnancy. However, in severe flares or life-threatening situations, CYC should be considered as the drug of choice. As the latter is contraindicated during the first and early second trimesters, intravenous immunoglobulins (IVIG) may be a useful option to control the disease until CYC can be used [69].

Among all forms of primary systemic vasculitis, Takayasu's arteritis deserves special attention as it is a disease characteristically diagnosed in women of child-bearing age. Eight case series published in the literature identified more than 145 women, with Japanese and Indian predominance, showing variable maternal and fetal outcomes [70–77]. Overall, Takayasu's arteritis does not seem to worsen during pregnancy, and the most important factor for poor outcomes seems to be the development of hypertension and related disorders, including preeclampsia. Peripheral BP monitoring may be challenging in these women, and BP checking in different extremities or invasive monitoring may be necessary. Patients with stenosis of the aorta and/or its

principal branches should receive comprehensive cardiovascular assessment together with antenatal review by an obstetric anesthetist in order to plan the best mode of delivery and anesthesia [69].

The impact of antineutrophil cytoplasmic antibody (ANCA)-related vasculitis on pregnancy outcomes will depend on the activity and long-term organ damage, with preeclampsia and prematurity being the most common complications [69].

Behçet's syndrome can present with a broad range of clinical features, varying from mild mucocutaneous lesions to severe CNS involvement or thrombosis in both venous and arterial systems. This heterogeneity impacts on outcome data in and out of pregnancy [78]. At present, it is still unclear whether pregnancy influences the activity of Behçet's, although it seems that remissions are achieved in a large proportion, regardless of HLA-B51 serology profile [79]. However, flare rates between 25 and 65% were described in two case series, where the main manifestations were arthritis and mucocutaneous ulcerations [80,81]. With regard to pregnancy outcomes, the rate of miscarriage seems to be higher in these women, whereas the risk for other obstetric complications seems not to be increased [79]. The etiology and pathogenesis of thromboembolic events in patients with Behçet's is unclear. Pregnant women are theoretically at higher risk of these thromboembolic events. Close medical and obstetric monitoring are hence recommended throughout pregnancy and postpartum.

aPL & APS

aPL are found more frequently in patients with SLE (30–40%) than in any other autoimmune rheumatic disease or in the general population (1–5%) [82], and represent one of the major risk factors for poor obstetric outcome. Several studies have identified aPL-positive women at increased risk of developing preeclampsia, IUGR, prematurity and fetal loss [83–86]. Positivity for both anticardiolipin antibodies and lupus anticoagulant; triple aPL positivity (anticardiolipin antibodies, lupus anticoagulant and anti- β 2-glycoprotein-I); high titres of anticardiolipin antibodies; or history of thrombotic APS multiply such risk [84,87]. Moreover, women with thrombotic APS have worse obstetric outcomes than those with obstetric APS or aPL carriers [87,88]. As the existence of aPL also raises the risk for maternal thrombosis, rechecking aPL shortly prior to pregnancy in patients with a previous diagnosis of SLE or other rheumatic disease is advisable.

Treatment of women with obstetric APS is still controversial and should be individualized, as most of the evidence is based on observational studies [89]. A detailed discussion of APS in pregnancy is out with the remit of this review and readers are directed to a recent review on this topic [90]. Current recommendations include low-dose aspirin (LDA) alone or with additional prophylactic low-molecular-weight heparin (LMWH), as soon as pregnancy is confirmed, for women with recurrent early miscarriages (<10 weeks of gestation), and LDA plus prophylactic LMWH for women with previous fetal death (>10 weeks of gestation) and/or preterm delivery (<34 weeks of gestation due to uteroplacental problems) [89,91].

Neonatal lupus syndromes

Anti-Ro and/or anti-La antibodies may be found in patients with SLE, SS, RA, UCTD and healthy asymptomatic carriers [92]. The prevalence of these antibodies in the general population may be up to 1–3% [93]. These antibodies cross the placenta by active transport between the 16th and 30th weeks of gestation, and may cause several clinical syndromes in the fetus and neonate known as neonatal lupus syndrome (NNLS), involving skin, heart, liver and/or cytopenias [94,95]. Although no specific antibody profile for NNLS has so far been detected, high levels of anti-Ro/La have been described as a risk factor for NNLS [96].

Cutaneous neonatal lupus is the most common manifestation, and the risk of an affected child amongst anti-Ro/La-positive mothers is approximately 5% [94]. It generally presents within the first 2 weeks of life as erythematous geographical lesions in light-exposed areas (generally face and scalp) that resemble those seen in subacute cutaneous lupus. The rash may worsen with ultraviolet light exposure and usually disappears within 3–6 months without residual scarring, when maternal antibodies are cleared from the baby's circulation [94].

Congenital heart block (CHB) is the most severe form of NNLS and affects approximately 2% of babies born to anti-Ro/La-positive mothers [97]. This risk increases six- to ten-fold to 18% if the mother has already had a child affected by CHB, and up to 50% if she has had two affected children [94,97]. Interestingly, in the majority of children with CHB the mother will have anti-Ro and/or anti-La antibodies [94]. CHB normally develops during 16 and 24 weeks of gestation and presents with a fetal bradycardia (<60 beats per minute) [94]. The risk of perinatal death

amongst affected children is approximately one in five, and most surviving children need a permanent pacemaker [94]. Incomplete forms such as first- or second-degree heart block may be present, which can progress to complete forms during childhood [94]. Regardless of the underlying disease, there is no correlation between the severity of the mother's illness and the risk or degree of NNLS in the offspring.

Other less frequent cardiac manifestations have also been described as part of NNLS, such as cardiomyopathy [98] and endocardial fibroelastosis [99]. Early diagnosis is crucial in CHB, and fetal cardiac ultrasound is the accepted technique [100]. Current recommendations include serial weekly fetal echocardiograms between 16 and 26 weeks of gestation, and fortnightly between 26 and 32 weeks to pregnant women with anti-Ro and/or anti-La antibodies, although some centers may prefer to offer to listen to fetal heart rate at each visit and perform a fetal cardiology scan at 20 and 28 weeks [94,100].

Different treatment regimens for CHB have been attempted. Fluorinated steroids (betamethasone and dexamethasone), because they are less extensively metabolized by the placenta, are generally reserved for cases with myocarditis, hydrops or incomplete heart block, as a chance for reversibility has been described [94,101]. The use of steroids should be reserved for incomplete heart block to prevent progression and not used as prophylactic treatment, as the high doses that are usually administered (dexamethasone 4–8 mg/day until the end of the pregnancy) have important side effects for both the mother (i.e., diabetes, hypertension, osteoporosis and infections) and the fetus (i.e., oligohydramnios, IUGR and adrenal suppression) [94].

IVIG treatment has been shown to inhibit placental transfer of anti-Ro/La antibodies and consequent fetal heart damage in a murine model [102]. Nevertheless, two multicenter prospective studies failed to demonstrate a reduced risk of CHB in women with previous affected children treated with IVIG during pregnancy [103,104]. In a different study, plasmapheresis also failed to prevent CHB [105].

Two recent case–control studies suggest that, in mothers with SLE with anti-Ro/La, exposure to HCQ during pregnancy may decrease the risk of fetal CHB [106,107].

Medications during pregnancy & breastfeeding

Most data regarding medication safety in pregnancy and lactation come from retrospective

case series and isolated case reports. The pregnancy categories of the US FDA are of little help for the clinician dealing with women with chronic diseases during pregnancy and lactation. However, a recent expert consensus has described the safety in pregnancy and lactation of many of the drugs used in autoimmune and rheumatic diseases [108]. A summary of safety of these drugs is shown in TABLE 1.

■ Frequently used medications

NSAIDs are generally safe drugs in pregnancy if they are used in short limited courses, but may be associated with renal and cardiac failure, hypertension and fluid overload in the mother, and oligohydramnios and renal impairment in the fetus if used for long periods. Their use should be withheld towards the end of pregnancy (>30–32 weeks) owing to increased risk of early closure of the baby's ductus arteriosus [108]. At present there are no reliable data on selective COX-2 inhibitors and they should therefore be avoided.

Treatment with LDA (75–100 mg/day) or dipyridamole is safe, whereas clopidogrel or ticlopidine are not recommended [108]. If indicated, aspirin should be continued throughout pregnancy. There is no evidence to suggest that aspirin needs to be discontinued before labor or due to planned epidural anesthesia in order to decrease hemorrhagic complications.

Antimalarials are one of the fundamental treatments in SLE because of their protective properties on activity, damage, long-term survival and thrombosis [20], and are also used in other disorders such as RA or UCTD. HCQ is the preferred drug due to its low rate of side effects. Its safety profile for both the mother and the baby has been widely researched, with no reported fetal neurosensory toxicity or malformations [109]. By contrast, chloroquine has been associated with increased risk of retinopathy in the mother and fetal ototoxicity [20]. HCQ should be continued throughout and after pregnancy in lupus patients, and probably in patients with RA. Mepacrine, by contrast, should be avoided because of the lack of safety data.

Nonfluorinated corticosteroids (prednisone, methylprednisolone and hydrocortisone) are largely metabolized by placental 11 β -hydroxysteroid dehydrogenase, and thus minimal amounts reach the fetal circulation (<10% of total dose) [108]. Even so, the use of these drugs is related to several undesirable complications in the mother such as hypertension, preeclampsia, diabetes, infections and premature rupture of

Table 1. Safety of drugs in rheumatic diseases in pregnancy and breastfeeding.

Drug	US FDA class	Safety	
		Pregnancy	Breastfeeding
NSAIDs	B (but D if >30 weeks of gestation)	Safe (if <30 weeks and intermittent use)	Safe
COX-II inhibitors	C (but D if >30 weeks of gestation)	Unknown	Unknown
Aspirin/dipyridamole	B	Safe	Safe
Clopidogrel/ticlopidine	B	Safe (but stop prior to delivery)	Probably
Hydroxychloroquine	C	Safe	Safe
Prednisolone/methylprednisolone	C	Safe	Safe
Azathioprine	D	Safe	Safe
Sulfasalazine	B	Safe (folate 5 mg once daily supplementation preconception and throughout pregnancy)	Safe
Ciclosporin	C	Safe	Probably
Tacrolimus	C	Safe	Probably
Mycophenolate	D	Avoid (consider in second–third trimester if severe disease)	Avoid
Methotrexate	X	Avoid	Avoid
Leflunomide	X	Avoid	Avoid
Cyclophosphamide	D	Avoid (consider in second–third trimester if severe disease)	Avoid
Anti-TNF agents	B	Safe (first and second trimesters)	Safe (not excreted in breast milk and probably broken down by the baby's GI tract)
Certolizumab	B	Probably	Probably
Anakinra	B	Probably	Probably
Rituximab	C	Avoid (consider in severe disease)	Unknown (probably)
Abatacept	C	Unknown	Unknown (probably)
Tocilizumab	C	Unknown	Unknown (probably)
Belimumab	C	Unknown	Unknown (probably)
Intravenous immunoglobulins	C	Safe	Safe
Endothelin receptor antagonists	X	Avoid	Avoid
Phosphodiesterase 5-inhibitors	B	Safe	Safe
Prostaglandin derivatives	B	Safe	Safe
Labetalol	C	Safe	Safe
Methyldopa	B	Safe	Safe
Nifedipine/amlodipine	C	Safe	Safe
Hydralazine	C	Safe	Safe
Doxazosin	C	Safe	Avoid if possible
Angiotensin converting enzyme inhibitors	C (first trimester)/D (second–third trimesters)	Avoid	Safe
Angiotensin receptor blockers	C (first trimester)/D (second–third trimesters)	Avoid	Probably

GI: Gastrointestinal; iv.: Intravenous.

Table 1. Safety of drugs in rheumatic diseases in pregnancy and breastfeeding (cont.).

Drug	FDA class	Safety	
		Pregnancy	Breastfeeding
Warfarin	X	Avoid	Safe
Bisphosphonates (oral/iv.)	C/D	Avoid	Avoid
Statins	X	Avoid	Avoid

GI: Gastrointestinal; iv.: Intravenous.

membranes [33], hence minimum maintenance doses (prednisone <7.5 mg/day), combined with steroid sparing agents are recommended, rather than higher (prednisone >7.5 mg/day) sustained doses. Stress doses of hydrocortisone at delivery are recommended in patients on long-term therapy. Nonfluorinated corticosteroids are minimally excreted into breast milk (5–25%) and, therefore, compatible with breastfeeding. At high doses (>prednisone 40 mg/day) consider timing breastfeeding to 4 h after the dose [108].

The majority of the immunosuppressive drugs are contraindicated during pregnancy and breastfeeding, with the exception of azathioprine, sulfasalazine, ciclosporin and tacrolimus [108]. With regards to the latter drugs, their use should be justified and the aim should be to keep them at the lowest effective dose. In women of child-bearing age taking pregnancy-contraindicated immunosuppressants such as mycophenolate mofetil, methotrexate, leflunomide or CYC, safe and effective contraception is necessary. If pregnancy is considered, these drugs should be switched to safer alternatives (e.g., azathioprine, sulfasalazine and tacrolimus) and conception should be delayed for at least 3 months, in order to monitor new flares or side effects from the change in drug regime [108].

A recent meta-analysis showed that sulfasalazine is not related to teratogenic effects [110]. However, women should be advised to take high-dose folic acid (5 mg/day) from 3 months prior to conception until at least the end of the first trimester, in order to prevent neural tube defects. The same folic acid regime is recommended in women who were taking methotrexate. Because of the long half-life of the active metabolite of leflunomide, it may be detectable in plasma up to 2 years after withdrawal of the drug. The manufacturer recommends cholestyramine 8 mg tds to enhance elimination for 10–14 days or until plasma levels of leflunomide are undetectable [108].

The use of immunosuppressive drugs during pregnancy does not generally hamper the correct development of the newborn's immune system or its response to scheduled vaccinations [111].

Anti-TNF therapy is frequently used in RA, AS and other chronic arthritides. All women should have tuberculosis screening before starting these medications, and should undergo appropriate treatment if previous latent infection is detected. Likewise, live vaccinations are not recommended in patients receiving anti-TNF therapy.

Despite a dubious association between anti-TNF drugs and congenital malformations described by some authors [112], several groups have demonstrated no increased risk of malformations in fetuses exposed to these drugs [113,114], based on different registries and databases. Anti-TNF drugs are monoclonal IgG antibodies and, therefore, behave similarly to maternal IgG antibodies both in terms of active transplacental transfer and their persistence in neonatal circulation up to 6 months postpartum. As the transplacental transfer does not notably start until the end of the second trimester, the fetus is not exposed during the first trimester, and hence the risk for teratogenicity is very low. The current available data on infliximab-exposed pregnancies show that in women who remain on this treatment during the third trimester, cord blood levels are two- to three-fold higher than in the mother's circulation [115]. However, it seems that these children have no problems in developing appropriate immunologic responses to regular vaccinations [116], although there are no specific data regarding live vaccinations. Anti-TNF agents are poorly excreted in breast milk, and hence breastfeeding is considered to be safe [117–119].

Despite the few cases available in the literature, certolizumab (a pegylated anti-TNF), which does not cross the placenta is considered to be safe due to the low levels detected in both cord blood and breast milk. Wider experience is needed in order to corroborate these data [120].

Rituximab is a chimeric anti-CD-20 monoclonal antibody used in several severe conditions such as SLE, RA or vasculitis. Two recent retrospective series identified 240 exposed pregnancies in women with different autoimmune and hematological diseases, including data from clinical trials and isolated reports of

maternal exposure. Pregnancy outcomes were available for 162 exposures. Over 61% (n = 99) resulted in live births of which 26% delivered preterm, while the first trimester miscarriage rate was 20%. Eleven neonates had hematological abnormalities, but none presented infectious complications. Two cases of congenital malformations were described (clubfoot in a twin and cardiac malformations in a singleton). Given the maternal indications for its use and the heterogeneity of the reports, until more robust data are available women should be counseled against pregnancy for 6–12 months after rituximab exposure due to the risk of neonatal B-cell depletion [114,121]. Neonates who were exposed to this biologic during the second or third trimester should receive close white blood cell and infection surveillance.

Anakinra, a recombinant IL-1 receptor antagonist, is thought to be safe in pregnancy and breastfeeding (US FDA category B), although experience in human pregnancies is still scarce and it is unknown whether it is excreted in human breast milk [122,123].

Current recommendations are to withhold abatacept (a selective costimulation modulator that inhibits T-cell activation) and tocilizumab (an IL-6 receptor inhibitor), because of the lack of data regarding their use in pregnancy and breastfeeding.

Belimumab is a human monoclonal antibody that inhibits B-cell activating factor, and the first biologic drug licensed for the treatment of SLE. Experience in pregnancy is scarce, hence the current recommendation is to withdraw it at least 4 months prior to conception [124].

IVIg can be safely used in pregnancy and lactation, and is useful when there is a desire to withhold strong immunosuppressants especially in situations where infection and flare cannot be easily differentiated [108].

Summary of drug treatment of connective tissue disease in pregnancy

Mild flares during pregnancy can be treated with NSAIDs, HCQ and low-dose oral steroids. For moderate or severe disease, the use of methylprednisolone pulses or high-dose oral steroids followed by rapid reduction of oral steroids to low maintenance doses, combined with safe immunosuppressants, biologic agents and/or IVIg may be necessary. More severe cases may require a risk/benefit assessment and prioritization of the mother's welfare over fetal concerns, and therefore the use of stronger agents such as mycophenolate mofetil or CYC.

■ Drugs to treat pulmonary hypertension

Endothelin receptor antagonists such as bosentan, sitaxsentan and ambrisentan are considered to be category X by the FDA. Their effect in human pregnancies is still unknown, but they are teratogenic in rodents and conception should be delayed for at least 3 months after stopping these agents.

Phosphodiesterase-5 inhibitors such as sildenafil and tadalafil are considered category B by the FDA. Their use in human pregnancy has not resulted in fetal side effects [125].

Prostaglandin derivatives such as prostacyclin (epoprostenol) and iloprost are considered to be category B by the FDA and have been safely used in pregnancy and breastfeeding [126].

■ Antihypertensive therapy

The drugs of choice for managing hypertension in pregnancy are labetalol, methyldopa and nifedipine, and, less frequently, hydralazine, amlodipine and doxazosin [201]. ACEI and ARB may cause fetal renal impairment and oligohydramnios, and they are associated with an increased risk of miscarriage [127] and malformations [128]. Therefore, these drugs are generally contraindicated during pregnancy. More recent data suggest that exposure to ACEI and ARB in the first trimester may not relate to an increased risk of malformations in the fetus [127,129]. Postnatally, methyldopa should be avoided because of higher risk of depression, and ARBs avoided because of lack of data [201].

■ Anticoagulants

Heparins (both unfractionated and LMWH) do not cross the placenta and are safe during pregnancy and breastfeeding. By contrast, warfarin and coumadin are teratogenic during organogenesis (6–10 weeks of gestation) and they should be avoided during this period. Their use is related to an increased risk of miscarriage, still birth and fetal bleeding [108]. Current recommendations include switching to LMWH as soon as pregnancy is confirmed [202]. This regime is generally continued throughout pregnancy, although switching back to warfarin during the second and third trimesters with close international normalized ratio monitoring is another option for special situations such as previous thromboembolic events on therapeutic dose of LMWH, some women with mechanical heart valves or in countries/settings where both the health system and the women cannot afford the expense of LMWH. Vitamin K antagonists are safe in lactation [108].

Fondaparinux crosses the placenta (fetal levels ~10% of maternal ones) suggesting that, although less innocuous than heparin, it could be safely used with caution [108].

Currently, little is known about the safety of the new anticoagulants (e.g., rivaroxaban and dabigatran) during pregnancy and lactation, and, therefore, their use is not recommended [108].

■ Others

Although they are considered as class C by the FDA, the safety of bisphosphonates (BPs) in human pregnancies is unknown. A recent review of the literature [130] identified 78 cases of mothers exposed to bisphosphonates before conception or during pregnancy. In total, 69 resulted in live births (88.5%) and none of the infants had serious adverse events secondary to bisphosphonates. Due to insufficient robust data, pregnancy should be postponed for at least 6 months after withdrawal of bisphosphonates [108].

The available data regarding the teratogenic risk of statins are contradictory, thus they are considered contraindicated in pregnancy. Their pleiotropic effects of vascular protection have been suggested to be of potential benefit in the management of preeclampsia. Statins have shown positive effects on serum markers involved in preeclampsia in murine models [131]. The ongoing StAmp trial in the UK will hopefully provide some insight into the role of statins during pregnancy and the possible effect on pregnancy outcomes.

Pregnancy management plan

Pre-pregnancy counseling, risk assessment and stratification, multidisciplinary approach, tailored antenatal and postnatal management plan, an experienced high level neonatal unit and early recognition of flares and complications (either medical and/or obstetric), are essential cornerstones to optimize the chance of both maternal and fetal successful outcomes.

The preconception visit should include a detailed summary of previous obstetric history and chronic organ damage, and recent serological profile (RF, anti-CCP, aPL, anti-Ro/La, anti-dsDNA and complement). It is important to ascertain current disease activity and last flare date, additional medical history and risk factors of interest (e.g., diabetes, hypertension, cardiac and cardiovascular problems, nephropathy, smoking and alcohol history, and their complications), and baseline BP, urine analysis and renal function. Harmful or unsafe medications should be stopped or changed to safer ones prior to

pregnancy, and discussion of planned scans and visits undertaken. All women should ideally take folic acid (0.4 mg/day) 12 weeks before and after conception in order to reduce the risk of fetal neural tube defects, and should be encouraged to stop smoking and to reduce/cease their alcohol intake. Concomitant prophylactic calcium and vitamin D supplements should be prescribed to women on corticosteroids, heparin and/or at high risk for osteoporosis or vitamin D deficiency. Hemoglobinopathy profile assessment may be indicated in certain circumstances and immunity to rubella should be confirmed [132].

Presence of aPL/APS and/or anti-Ro/La, poor previous obstetric history, independent risk factors for preeclampsia, severe irreversible organ damage, other medical comorbidities and active disease are associated with obstetric and medical complications. Accordingly, the main risks for the mother and the baby should be discussed. Women with active disease should postpone conception until stable disease remission is achieved, particularly those with internal organ involvement and damage. Pregnancy should be discouraged in patients with severe flare or stroke over the last 6 months, pulmonary hypertension, moderate–severe heart failure, severe restrictive lung disease (FVC<1L), CKD stage 4–5 (eGFR<30 ml/min), uncontrolled hypertension and previous severe early onset (<28 weeks) preeclampsia despite therapy with aspirin plus heparin.

Women considered at high risk should be managed in a multidisciplinary medical/rheumatological/obstetric clinic throughout pregnancy, continuing with adequate joint postpartum care. Women with mild disease and/or considered to be at low risk of complications could be managed by their obstetricians and midwives with medical visits as needed.

The frequency of antenatal visits will depend on the past history and the progress of the current pregnancy. As a guide, from 16 weeks to 28 weeks of gestation women should be reviewed every 4 weeks, fortnightly from 28 to 34 weeks of gestation, and weekly from 34 weeks onwards. Every visit should include urine analysis and maternal assessment, with special attention to hypertension and other features of preeclampsia. Women with previous renal and/or hypertensive diseases should have more frequent BP checks, and those on steroids should be screened for gestational diabetes. Confirmation and quantification of proteinuria by protein-creatinine ratio is mandatory if urine dipstick is positive for protein. Regular blood tests including full blood count, liver function tests, renal profile

and activity markers such as C-reactive protein, anti-dsDNA and complement every 4–8 weeks are recommended in those with severe or active disease.

Anomaly scan and uterine artery Doppler is recommended at approximately 20 weeks of gestation, and the latter should be repeated at approximately the 24th week if abnormal. Abnormal waveforms predict preeclampsia/IUGR, and the negative predictive value of normal results for good obstetric outcomes is high [133].

Ultrasound scans (including biophysical profile, amniotic fluid volume assessment and umbilical artery Doppler) are recommended in patients with active inflammatory disease or may be indicated depending on previous obstetric history and the progress of current pregnancy. In women with anti-Ro/La, regular fetal echocardiography between 18–28 weeks of gestation is offered to identify CHB [94].

In patients with spinal involvement, scleroderma and reduced respiratory function, and in those receiving therapeutic LMWH, anesthetic review should be arranged. Elective cesarean section is usually only required for obstetric indications.

As discussed above, patients with SLE, RA, UCTD and/or aPL have a higher risk of developing preeclampsia compared with the general population. LDA started early in pregnancy significantly reduces the risk of preeclampsia and its complications in women at higher risk [134]. Dipyridamole probably has similar effects [201]. In addition, all women with aPL should take LDA to decrease their risk of miscarriage [91].

A recent meta-analysis of 13 randomized trials comparing the intake of at least 1 g of calcium daily versus placebo during pregnancy showed a >50% reduction in the risk of preeclampsia and a 25% reduction in the risk of preterm delivery [135]. Calcium supplementation is therefore appropriate in some of these patients.

All women should be carefully assessed regarding risk factors for venous thromboembolism prior to conception and periodically throughout pregnancy, and should receive appropriate thromboprophylaxis if indicated [202].

Women receiving high-prophylactic or therapeutic doses of LMWH should discontinue it or swap to prophylactic doses (enoxaparin 0.6 mg/kg once daily; e.g., 40 mg if weight 50–90 kg) 24 h prior to the planned delivery. Those on prophylactic doses of LMWH should discontinue LMWH once labor is established. Re-establishment of LMWH should be postponed until the placenta is delivered. Epidural

anesthesia can be safely used 12 or 24 h after the last dose of LMWH on prophylactic or high-prophylactic/therapeutic doses, respectively. LMWH can be restarted 2 h after the epidural catheter has been removed [136].

Postpartum

Because of a high risk of disease flare and thrombosis, close surveillance for 2–3 months after delivery is important. A medical visit should be arranged in the first 4–6 weeks postpartum, which should consist of thorough history review, physical examination, urine analysis, BP check and blood tests including full blood count, liver function tests, renal profile and activity markers such as erythrocyte sedimentation rate, C-reactive protein, anti-dsDNA and complement.

All women with aPL should receive prophylactic LMWH for at least 7 days after delivery [91,202]. Some experts recommend extending this treatment for 4–8 weeks postpartum [90]. Those who received prophylactic doses of LMWH during pregnancy or those with high venous thromboembolic risk should continue this treatment for 6 weeks postpartum [202]. Women with previous thrombosis often require long-term anticoagulation. In that case, LMWH should be switched to warfarin or coumadin when the risk of hemorrhage is reduced (usually 5–7 days postpartum) [202]. After delivery, therapeutic LMWH can be safely used as a single dose daily (e.g., enoxaparin 1.5 mg/kg once daily).

Counseling on contraception is of great importance in rheumatologic diseases as planned pregnancy is associated with less complications and higher pregnancy success rates.

Barrier methods, including condom and diaphragm, represent an effective form of contraception (83–97% success) and the only protective method against sexually transmitted infections [137].

Hormonal methods include oral contraceptives (OC; combined or progesterone-only) and subcutaneous devices (i.e., implants, injectables, skin patches and vaginal rings). Despite the classic advice against the use of estrogen-containing OC in women with lupus, current evidence supports the safety of combined OC in well-defined SLE patients with stable and/or low-active disease [138]. However, because of the increased risk of thrombosis, combined OC are contraindicated in patients with aPL and/or other risk factors such as moderate–severe active disease, and a history of thrombosis, hypertension, smoking or obesity [203]. Progesterone-only

preparations are safe and do not affect disease activity or thrombosis risk [139], but may reduce bone density when used for >2 years [140]. The latter effect seems to be reversible after

discontinuation. Interactions between hormonal contraceptives and other medications the patient may be taking may provoke contraceptive failure and/or alterations in metabolism of such drugs.

Executive summary

- Fertility in women with rheumatic diseases is generally not affected, although chronic kidney disease, amenorrhea due to cyclophosphamide, active disease and NSAIDs may reduce fertility.

Systemic lupus erythematosus

- Pregnancy should be planned when the disease has been in remission for at least 6 months.
- Unless there are contraindications, all systemic lupus erythematosus patients should remain on hydroxychloroquine throughout and after pregnancy.
- Systemic lupus erythematosus patients are at risk of multiple medical and obstetric complications during pregnancy, especially those with active disease and/or nonreversible organ damage.

Rheumatoid arthritis & other arthritides

- Approximately 50–66% of women with rheumatoid arthritis, and the majority of women with psoriatic arthritis and junior rheumatoid arthritis improve in pregnancy. By contrast, most women with ankylosing spondylitis stay unaltered or worsen.
- Postpartum flares occur within the first 4 months in most patients with chronic inflammatory arthritides.
- Women with chronic inflammatory arthritides, especially those with active disease, have higher risk of preterm delivery and small for gestational age babies. Patients with rheumatoid arthritis have a higher risk of hypertensive disorders in pregnancy.

Scleroderma/systemic sclerosis

- Pregnancy does not seem to affect disease activity in the majority of women with systemic sclerosis.
- Systemic sclerosis is associated with increased risk of developing hypertensive disorders in pregnancy and higher rates of adverse pregnancy outcome.
- A previous renal crisis does not contraindicate further pregnancies, but pregnancy should be delayed for several years until the disease stabilizes.
- Corticosteroids for fetal lung maturation should not be given as they may precipitate a renal crisis.

Vasculitis

- Overall, if the disease is in remission pre-pregnancy a low rate of complications and good pregnancy outcomes are reported.
- Hypertensive disorders, including preeclampsia, are associated with poorer outcomes.

Antiphospholipid antibodies & antiphospholipid syndrome

- Antiphospholipid antibodies represent one of the major risk factors for poor obstetric outcome.
- Women with double or triple positivity, and/or those with thrombotic antiphospholipid syndrome have the worst obstetric outcomes.

Undifferentiated connective tissue disease, polymyositis/dermatomyositis & mixed connective tissue disease

- Outcomes of patients with undifferentiated connective tissue disease and mixed connective tissue disease resemble those seen in systemic lupus erythematosus.
- Active polymyositis/dermatomyositis is related to preterm delivery and pregnancy loss.

Neonatal lupus syndromes

- In patients with anti-Ro and/or anti-La, cutaneous neonatal lupus is seen in approximately 5% of their offspring, whereas congenital heart block is seen in approximately 2%.
- Repeated fetal echocardiograms from the 18th week of gestation are recommended in women with these antibodies.

Medications

- Azathioprine, sulfasalazine, ciclosporin and tacrolimus are safe in pregnancy and lactation.
- Steroids are safe but related to side effects and complications if used for long periods and at doses of prednisolone >7.5 mg/day. Limited boluses of methylprednisolone are safe.
- Among biologics, anti-TNF agents seem to be safe in the first and second trimesters and lactation.

Pregnancy management plan

- Pre-pregnancy assessment is vital, with emphasis on previous obstetric and medical history, serology profile, disease activity and the extent of any organ damage.
- An individual antenatal and postnatal plan and multidisciplinary team input are essential to achieve good maternal and fetal outcomes.

Postpartum

- Close surveillance for 2–3 months after delivery is important owing to the high risk of disease flare and thrombosis.
- Counseling on contraception should be incorporated as routine care at this stage.

Intrauterine device (either nonhormonal devices – e.g., copper coil – or progesterone intrauterine system [IUS] – e.g., Mirena® hormonal devices) are also safe. IUSs are extremely effective (98% success) and reduce menstrual bleeding, which is useful in women on warfarin. Intrauterine devices have a 5% chance of expulsion and confer a higher pelvic infection risk (1%), and are thus generally preferred in patients with a single sexual partner [141].

Future perspective

Results of ongoing studies looking for biomarkers of disease activity of different rheumatic diseases may be helpful in order to predict flares, tailor the treatment and management to each patient's profile, and to differentiate disease activity from preeclampsia in ambiguous cases. Early serological, urinary and ultrasound markers of preeclampsia and other poor obstetric outcomes are a promising and developing field of research, which may allow a better tailoring of treatment and surveillance during pregnancy.

Well-designed prospective studies based on international consensus are needed in order to confirm the findings from observational studies, to clarify contradictory results between old and new

studies, and to incorporate new risk factors not previously described. With regards to less common disorders, publication of larger series may lead to a better understanding of their behavior in pregnancy and the best management approach.

As randomized trials of medications in pregnancy are not generally conducted, greater experience with drugs such as biologics, pulmonary hypertension medications, new anticoagulants and other new treatments may help to inform counseling and decide on the best treatment options. Results of ongoing randomized trials investigating the value of statins for preeclampsia and the role of HCQ for the prevention of CHB may bring interesting new insights into the approach of these disorders.

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