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Pregnancy and autoimmune connective tissue diseases

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Abstract

The autoimmune connective tissue diseases predominantly affect women and often occur during the reproductive years. Thus, specialized issues in pregnancy planning and management are commonly encountered in this patient population. This chapter provides a current overview of pregnancy as a risk factor for onset of autoimmune disease, considerations related to the course of pregnancy in several autoimmune connective tissue diseases, and disease management and medication issues before and during pregnancy and the postpartum period. A major theme that has emerged across these inflammatory diseases is that active maternal disease during pregnancy is associated with adverse pregnancy outcomes, and that maternal and fetal health can be optimized when conception is planned during times of inactive disease and through maintaining treatment regimens compatible with pregnancy.

Keywords

Antiphospholipid antibody syndrome; Autoimmunity; Myositis; Pregnancy; Rheumatoid arthritis; Scleroderma; Sjogren's syndrome; Systemic lupus erythematosus

The autoimmune connective tissue diseases (CTD) are associated with strong female preponderance, and often present before or during the reproductive years [1]. As such, specialized issues in pregnancy planning and management are commonly encountered in this

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patient population, which includes rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), systemic sclerosis (SSc), primary Sjogren's syndrome (PSS) and inflammatory myositis. For decades, women particularly with SLE were advised against pregnancy given high rates of observed poor outcomes, concern for disease flare and lack of evidence for safe treatment options. Indeed, women with SLE/APS especially have higher rates of preeclampsia, intrauterine growth restriction (IUGR), and prematurity [2–4]. However, with advances in disease management, pregnancy outcomes in these populations have improved, and increasingly more women with CTDs are choosing to attempt pregnancies [5]. Furthermore, exciting research in the field is leading to identification of predictors for high risk pregnancies, which will increasingly allow for a personalized approach to pregnancy management. An emphasis on pre-conception counseling and tight disease control in the months leading up to conception are essential components of this new era of pregnancy and CTD. Equally important is the recognition that untreated disease in pregnancy is associated with risks to the mother and child [6], and the preponderance of evidence demonstrates the importance of continuing medications that prevent active disease and that do not harm the baby throughout pregnancy. A thorough understanding of the range of therapeutic options available for treatment during pregnancy is therefore essential, and has expanded over recent years to include monoclonal antibody therapy. In this context, and with increasing accrual of follow-up data for children born to mothers with CTDs, the best practices for management of these pregnancies are evolving rapidly.

PREGNANCY AND SUBSEQUENT RISK OF AUTOIMMUNE CONNECTIVE TISSUE DISEASES

Whether pregnancy is a risk factor for the development of new-onset autoimmune connective tissue disease remains an open question. Among the rheumatic diseases, rheumatoid arthritis has perhaps received the most attention on this topic. As reviewed elsewhere, a significantly decreased risk of RA has been described in several retrospective studies for women who have ever been pregnant compared to nulliparous women [7–10], whereas a number of other studies, including population-based cohort studies, have not detected an association between parity and subsequent risk of RA [11–16]. Conflicting results have been reported in other diseases such as SLE and systemic sclerosis, also reviewed elsewhere [17].

Notably, a large population-based Danish study examining the autoimmune diseases as a group found that risk of development of maternal autoimmune disease significantly increased during the first year postpartum, but subsequently trended in the opposite direction [18]. Onset of RA has particularly been described to occur with increasing frequency during the postpartum period. In fact, a 1953 study concluded that "The onset of rheumatoid arthritis during pregnancy or immediately after it is so common that in certain circumstances pregnancy can be regarded as an aetiological factor" [19]. A 1992 British case-control study found a reduced incidence of RA onset during pregnancy, but a postpartum increase that was of highest magnitude during the first 3 months postpartum (OR 5.6) and remained elevated during the subsequent 9 months [20]. A 1993 case-control study from the Netherlands

reported similar trends [21]. Together these studies underscore the importance of delineating time windows in relation to pregnancy, and suggest that the postpartum period warrants special consideration in terms of risk of autoimmune diseases among women.

PREGNANCY CONSIDERATIONS IN AUTOIMMUNE CONNECTIVE TISSUE DISEASES

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE, or “lupus”), affects females in a 9:1 ratio to males [22,23], with a 2.5 fold increase in prevalence among African Americans [24]. The adverse pregnancy outcomes observed with lupus are well known, and include increased rates of intrauterine growth restriction (IUGR), preterm birth and fetal loss, as well as the syndrome of neonatal lupus (NL), associated with the transplacental passage of autoantibodies, discussed below. A 2006 study using the Nationwide Inpatient Sample in 2002 comparing CTD pregnancies to control pregnancies revealed significantly higher rates of hypertensive disorders (OR 3.3 [95% CI 2.8–4.0]), IUGR (OR 3.5 [95% CI 2.5–4.9]) and Cesarean delivery (OR 1.6 [95% CI 1.4–1.9]) among lupus patients, who had an increased length of hospital stay even after adjustment for Cesarean delivery [25]. A subsequent study focusing on lupus pregnancy within this database for years 2000–2003 revealed that maternal mortality was 20-fold higher among women with SLE, as was preterm labor, preeclampsia, and other comorbidities associated with adverse pregnancy outcomes such as diabetes, hypertension and thrombophilia [3]. Observations that high disease activity at the time of conception, or in the months preceding conception, is an independent predictor for increased risk of adverse pregnancy outcomes including prematurity, IUGR and fetal demise has led to the current recommendations that lupus patients achieve 6 months of disease quiescence prior to attempting conception [26,27]. Furthermore, the benefit of treating lupus to maintain good disease control throughout pregnancy, particularly with hydroxychloroquine (HCQ), has been demonstrated in studies where improved birth outcomes among lupus mothers who continued HCQ were observed when compared to lupus mothers who did not take HCQ in pregnancy [28–30].

In the context of these practice patterns, and with emphasis on a multidisciplinary approach to management from preconception through the postpartum period, improved outcomes have been increasingly observed in lupus pregnancies [5,31]. Furthermore, recent work has focused on identifying predictors of poor pregnancy outcomes in this patient population, which will no doubt continue to improve care, as it may help identify a subset of patients for whom closer follow-up is indicated. Prospective data on predictors of adverse pregnancy outcomes in SLE pregnancies has recently been reported from the PROMISSE study (Predictors of Pregnancy Outcome: Biomarkers In Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus), an ongoing multicenter, prospective observational study of pregnancies in women with antiphospholipid antibodies (aPL), SLE, or both [32]. 385 pregnant women with stable lupus, with and without APS, were enrolled and compared to pregnant control women. In this population, predictors of adverse pregnancy outcomes in lupus pregnancies included African and Hispanic decent, antihypertensive use at baseline, the presence of the lupus anticoagulant (LAC), mild or moderate flare of lupus, moderate

clinical disease activity at baseline and thrombocytopenia. Of note, the lupus patients enrolled in the PROMISSE cohort had very low disease activity: the rate of flare in the second and third trimesters was 2.5% and 3% respectively, which is much lower than flare rates reported in previous pregnancy studies [33]. The enrollment criteria for this study included optimized lupus disease activity (exclusion of patients with urine protein/creatinine ratio of >1000mg/g, creatinine >1.2mg/dL, prednisone use >20mg/d), confirming that effective preconception planning results in favorable outcomes in this population.

Lupus nephritis—In a large meta-analysis of pregnancy outcomes in SLE and lupus nephritis (LN), in which 37 studies with 1842 lupus patients and 2751 pregnancies were included, significant associations were observed between LN and both premature birth and preeclampsia [34]. It can also be difficult to distinguish active LN in pregnancy from preeclampsia. Both are associated with proteinuria and rising creatinine, but examination of urinary sediment will reveal activity in LN as opposed to a bland urinary sediment in preeclampsia. Serum uric acid may be elevated in preeclampsia and could provide another marker to help distinguish between the two processes, but often times the clinical picture is nebulous, highlighting a large knowledge gap that can lead to inappropriate treatment decisions, as gram doses of intravenous (IV) corticosteroid and IV cyclophosphamide would be indicated for severe LN, whereas prompt delivery of the baby would be indicated for preeclampsia.

Antiphospholipid antibody syndrome (APS)

Obstetric antiphospholipid antibody syndrome (OB-APS) was defined according to the updated Sydney classification criteria developed by expert consensus agreement in 2006 [35,36]. aPLs include the lupus anticoagulant, anticardiolipin IgG and IgM and anti-β2-glycoprotein I antibody. In addition to the detection of aPLs on at least two occasions more than 12 weeks apart, OB-APS is defined by any one of the following adverse pregnancy outcomes: 1) otherwise unexplained recurrent pregnancy loss before the 10th week of gestation, 2) otherwise unexplained fetal death ≥10 weeks of gestation, 3) preterm birth before 24 weeks of gestation due to preeclampsia or placental insufficiency [35]. Other OB-APS complications include catastrophic APS, thrombosis, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), IUGR, fetal distress, premature rupture of membranes, and thrombocytopenia [4,37].

Poor pregnancy outcomes, including second trimester pregnancy loss, fetal growth restriction and preeclampsia have been observed in association with APS for years [33,38–43], but only recently has it been recognized that the lupus anticoagulant (LAC), among the three aPLs, is the primary predictor of poor pregnancy outcomes in women both with or without SLE, and with or without other aPLs [44]. Of the 144 women enrolled in the PROMISSE study between 2003 and 2011, 28 had adverse pregnancy outcomes defined as otherwise unexplained fetal demise after 12 weeks gestation, neonatal death prior to discharge associated with complications of prematurity, preterm delivery prior to 34 weeks because of gestational hypertension, preeclampsia or placental insufficiency, or small for gestational age (birth weight <5th percentile). 39% of women with LAC had adverse pregnancy outcomes compared to 3% of those without LAC ($p<0.0001$). Of the remaining

aPLs, only IgG aCL at ≥40 units/ml appeared to also be associated with adverse pregnancy outcomes (8% vs 43% who were also positive for LAC; p= 0.002). In multivariate analysis, the other contributors to obstetric risk included SLE (RR= 2.16; 95% CI 1.27–3.68; p=0.005), a history of thrombosis (RR = 1.90; 95% CI 1.14–3.17; 0=0.01), age (RR= 1.56 for every 5 years decrease in age; 95% CI: 1.18–2.08;p=0.002), and race (RR= 3.24 for white vs non-white; 95% CI: 1.16–9.07; p=0.03).

Regarding treatment of patients with anticoagulation in the PROMISSE study, the patients' physicians made all treatment decisions. Upon study entry, of 75 women who were treated with heparin, 56 were receiving low molecular weight heparin (LMWH) and 19 were receiving unfractionated heparin (36 at therapeutic doses and 39 at prophylactic doses). Of 97 women who regularly took aspirin, all but one took 81 mg per day, the other took 325 mg a day. No benefit of heparin was found, and a protective effect of aspirin was not significant after adjustment for the predictors mentioned above. However, the study was not designed or powered as a treatment trial.

Low dose aspirin to mitigate the risk of fetal loss in women with APS has been used for years [45]. More recent systematic reviews and meta-analyses comparing the use of low dose aspirin versus low dose aspirin and heparin in pregnant women with aPLs and recurrent miscarriage has shown that combination treatment with aspirin and heparin is superior to aspirin alone in conferring a significant benefit in live births [46,47]. LMWH has been accepted as the standard of care when treating pregnant women with APS [48]. Heparin does not cross the placenta and is considered safe for the embryo-fetus. LMWH may offer some advantages over unfractionated heparin. The most notable is that LMWH is less likely to cause heparin-induced thrombocytopenia, osteoporosis and is more bioavailable than unfractionated heparin.

Despite this treatment, and even with comprehensive medical and obstetric management, around 30% of APS pregnancies will still result in pregnancy loss [43]. Other proposed therapies to prevent adverse pregnancy outcomes in OB-APS are being investigated, including the use of HCQ, for which prospective trials data are lacking, but for which encouraging results from *in vitro* and animal models exist [49]. Mechanistically, the anti-inflammatory, anti-thrombotic and pro-endothelial effects of HCQ, in addition to its safety profile in pregnancy, suggest a potential protective effect in OB-APS [50]. Lacking substantial clinical data on the ability of HCQ to affect adverse pregnancy outcomes in OB-APS, an expert panel was recently convened to formulate an opinion about its use for prevention of OB-APS based on available literature and expert judgment of clinical OB-APS scenarios [49]. They concluded that adding HCQ could be considered in selected cases or after standard treatment failure with aspirin and a heparin agent. Specific scenarios where the majority opinion was to add HCQ included women with previous thrombosis or previous ischemic placenta-mediated complications.

Rheumatoid arthritis (RA)

A widely held perception based on retrospective data is that the majority of RA patients experience spontaneous remission during pregnancy, and a tendency toward postpartum flare within 3–4 months. Newer prospective data from RA patients followed during and after

pregnancy, and with objective assessments of disease activity, have provided a more complete picture related to disease activity during and after pregnancy. Of importance, because physiologic changes of pregnancy influence standard disease assessment parameters, such as the Global Health scale of the Disease Activity Score (DAS) and erythrocyte sedimentation rate (ESR) levels, modified assessment tools for use in studies of RA pregnancies have been suggested [51]. The DAS28-CRP without the Global Health scale (and excluding ESR as an inflammatory marker) has been shown to perform well in pregnancy [51]. A major study of 84 RA patients in the Netherlands recruited between 2002–2006 indeed found that mean disease activity scores (by modified DAS28-CRP) declined during pregnancy despite reduced rates of medication use compared to before conception [52]. Approximately 25% of women experienced RA remission during the 3rd trimester, a substantial yet smaller proportion than previously expected. Based on EULAR response criteria among the 52 women with moderate baseline disease activity in the first trimester (DAS28 >3.2), 30.8% had a “moderate” response and 17.3% had a “good” response between the first and third trimesters. In the postpartum period, disease activity increased, with greater than one third of the women having a moderate or severe flare (defined by revised EULAR response criteria), even in the context of increased medication use after delivery.

In terms of pregnancy outcomes, a national study in the US of approximately 1400 RA pregnancies in 2002 documented IUGR in 6.4% and premature rupture of membranes in 3.9% -- rates that were 1.5–2 times higher than in the general obstetric population even when controlling for factors such as maternal age [25]. Significant progress has also been made in recent prospective studies with respect to understanding the contribution of disease severity to pregnancy outcomes in RA. Data now indicate that for women with well-controlled RA, pregnancy outcomes are comparable to the general obstetric population [53], whereas higher levels of RA disease activity are associated with increased risk of less favorable pregnancy outcomes [53,54]. de Man et al found that among 152 Dutch RA patients with singleton pregnancies, higher levels of disease activity in the third trimester were independently associated with lower birth weight, controlling for several covariates including smoking, maternal age, and prednisone use [53]. Further, prednisone use during pregnancy was linked to lower gestational age at birth (no effect of prednisone dose observed), with deliveries on average 1 week earlier and more often occurring at <37 weeks compared to RA patients not taking prednisone during pregnancy [53]. The earlier gestational age underlies an association between prednisone use and lower birth weight. In a North American study, which enrolled 440 pregnant women with RA between 2005–2015, Bharti et al found that RA disease severity, measured in early pregnancy, was predictive of preterm delivery and small for gestational age [54]. Consistent with the Dutch study, prednisone use (=10 mg) during pregnancy was also associated with preterm birth, and not thought to simply serve as a marker of disease severity, as the relationship between disease severity and preterm delivery also held up.

Systemic sclerosis (SSc, or scleroderma)

As with SLE, pregnancy in women with systemic sclerosis (SSc) was previously considered fraught and discouraged due to concern for poor outcomes [55]. Newer research has revealed

a more favorable picture of SSc pregnancies; however, certain patterns of increased risk do exist. In a US study based on the 2002–2004 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, SSc was associated with increased risk of hypertensive disease of pregnancy, including preeclampsia, IUGR and increased length of hospital stay [56]. Retrospective data on 214 women with SSc, 167 women with RA, and 2015 healthy controls in the US have also identified an increase in premature births and low birth weight for babies born to SSc mothers [57]. These finding were later confirmed in a study of pregnancy outcomes in an Italian multicenter study of 109 pregnancies among 99 women with SSc from 2000 to 2010, in which data was obtained prospectively starting a year before conception [58]. The mean age at conception was 31.9 years in this population; 54 had limited cutaneous SSc, 48 diffuse cutaneous SSc, 6 fulfilled Leroy and Medsger criteria for early SSc, and 1 scleroderma sine sclerosis [59,60]. When compared to a control population, preterm deliveries were found to be significantly increased among women with SSc (25% vs 12%), including severe preterm deliveries defined as <34 weeks gestation (10% vs 5%). IUGR and low birth weight were also increased, and in multivariate analysis, the use of corticosteroids was associated with preterm deliveries (OR 3.63, [95% CI 1.12–11/78). No significant differences in pregnancy outcomes were found in diffuse vs limited cutaneous subsets. While no woman in the study had pulmonary hypertension or severe cardiac or renal disease at baseline, 2 women had severe GI disease associated with intestinal malabsorption, one with IUGR and one delivering preterm, and 3 women had severe lung fibrosis associated with forced vital capacity <50%, none with obstetrical complications. The use of folic acid and the presence of anti-topoisomerase were protective, and in general Raynaud's phenomenon and digital ulcers improved temporarily starting in the second trimester; however, the effect did not persist after pregnancy. In general, disease stayed stable during pregnancies. These authors concluded that women with SSc can have successful pregnancies, but are at higher risk than the general population for preterm deliveries, low birth weight babies and IUGR, and should be cautioned against pregnancy if severe target organ damage is present.

Myositis

Data on inflammatory myositis and pregnancy are sparse, reflecting the rarity of disease and onset that typically occurs after the reproductive years. A 2014 review of 36 publications comprised only 78 pregnancies from 59 women [61]. Approximately 60% of the pregnancies occurred among women with preexisting myositis, and an overall trend was that disease activity, especially during early pregnancy, appeared to be associated with adverse pregnancy outcomes, whereas treatment of disease during pregnancy (with corticosteroids or IVIG) appeared to be beneficial [61]. Based on the available data, neonatal outcome was described as generally good, with preterm delivery and small for gestational age reported as the main complications [61]. The most extensive individual study, also published in 2014 and thus not included in the above review, included a total of 102 pregnancies from a retrospective Spanish cohort of 51 women with idiopathic inflammatory myopathies diagnosed between 1983–2013 [62]; 80% of women were classified as dermatomyositis, and 20% as polymyositis according to Bohan and Peter criteria for definite or probable myositis [63,64]. The authors concluded that pregnancy did not appear to be associated with adverse maternal or fetal outcomes, and that clinical improvement tended to occur during pregnancy,

while postpartum relapse was common [62]. They also found no evidence for pregnancy as a trigger of myositis [62].

Sjogren's Syndrome

Incidence of primary Sjogren's syndrome (PSS) is highest during postmenopausal years. However, it can occur at any age, and indeed, a pregnancy resulting in neonatal lupus (NL, discussed below) may be the earliest indication of PSS associated with anti-Ro/La antibodies [65]. Pregnancy outcomes beyond cardiac NL have not been studied as extensively as in SLE or APS, but from small case control studies, it appears that PSS may be associated with lower mean birthweights in offspring, older maternal age, and more common delivery by Cesarean section or vacuum extraction than in the background population [66]. A study of over 100 pregnancies from women with primary and secondary SS revealed that only the presence of concomitant SLE and likely aPL were associated with higher rates of spontaneous abortion and premature deliveries when compared to controls [67]. As discussed below, however, appropriate screening for the presence of NL is essential in the management of pregnancy in patients with primary or secondary SS and anti-Ro/La antibodies.

Neonatal lupus syndrome

Neonatal lupus (NL) syndrome represents passively acquired autoimmunity resulting from transplacental transfer of maternal anti-Ro/SSA (52 or 60 kD) or La/SSB (48 kD) antibodies. While transient features of the syndrome (characteristic rash of NL, hepatic and hematologic abnormalities) may be observed, the major morbidity and mortality associated with NL involve the developing fetal cardiac tissue, leading to autoimmune congenital heart block (ACHB) due to inflammatory and fibrotic changes of the AV node, in addition to more severe complications including endocardial fibroelastosis (EFE) and dilated cardiomyopathy that may develop even in the absence of conduction abnormalities [68,69].

While the overwhelming majority of ACHB cases involve anti-Ro positive mothers, isolated anti-La associated cases have also been reported, representing less than 1% of total cases [70–72]. Therefore recommendations for screening and therapy apply to mothers positive for either autoantibody. Among mothers positive for anti-Ro/SSA, an incidence of ACHB of 2% is widely accepted, and comes from a large prospective study of pregnancy outcomes in 100 anti-Ro positive women [73]. The estimated recurrence of heart block in subsequent pregnancies for a mother with a previous child born with ACHB is around 18% [74]. Among children born with ACHB, a 20% overall mortality rate, with 79% 3-year survival, has been observed, with pacemaker requirement in 64% [72].

Recommendations for early, non-invasive diagnosis of ACHB involve fetal echocardiography with Doppler mechanical PR interval measurement beginning between weeks 16–18 and continuing weekly through week 26 [75]. While there is support for the use of fluorinated steroids (FS) aimed at reversing incomplete heart block presumably due to ongoing inflammation, treatment recommendations have been less clear for advanced heart block until recent evidence against their use was published [76–78]. A 2015 retrospective study from the Research Registry for Neonatal Lupus (RRNL) of babies from anti-Ro+

pregnancies born with isolated advanced ACHB revealed similar outcomes for those who received FS (n=71) within one week of detection compared to those who received no treatment (n=85) [79]. The risk of development of extranodal disease in this study was similar, revealing that 14 (19.7%) of 71 fetuses exposed to FS developed extranodal disease compared to 17 (20%) of 85 unexposed fetuses, with an unadjusted hazard ratio of 1.02 (95% CI 0.51–2.06; p=0.96). FS furthermore failed to improve survival, with deaths in 7/71 (9.9%) of FS-exposed compared with 7/80 (8.8%) of untreated [HR=1.19 (95% CI 0.42–3.40; p=0.74)]. Likewise, FS treatment did not prevent future pacemaker implantation, with 42/64 (66%) of FS-exposed live births paced compared to 60/78 (75%) of untreated [HR=0.94 (95% CI 0.64 to 1.40; p=0.77)]. These data therefore do not support the use of FS for fetuses with isolated advanced heart block, which, in addition to extranodal cardiac disease, remains a marker of poor outcome [77,78].

Support for the use of hydroxychloroquine (HCQ) for prevention of cardiac NL comes from an analysis of 257 anti-SSA/Ro positive SLE pregnancies at high risk for cardiac NL in the RRNL database [80]. The authors compared outcomes of 40 mothers who had taken HCQ throughout their pregnancies, having started within 10 weeks of gestation, to 217 mothers unexposed to HCQ, subsequent to the birth of a child with cardiac-NL. The recurrence rate of cardiac-NL in HCQ exposed fetuses was 7.5% (3 of 40) compared with 21.2% (46 of 217) in the unexposed group (P=0.05), a significant association that persisted after multivariable analysis adjusting for maternal race/ethnicity, anti-SSB/La status, and confounding by indication. The authors therefore concluded that HCQ therapy may be protective in subsequent pregnancies among mothers with a history of having a child with cardiac NL. An open label prospective trial, the Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH) study (NCT01379573) is currently recruiting, which will assess the effect of HCQ in preventing recurrence of cardiac NL in high-risk women with a previously affected child.

There is no convincing evidence in support of β-agonists, IVIG therapy or plasmapheresis for prevention of cardiac-NL lupus, and no agreement on appropriate dose or schedule [81–83].

Contraindications to pregnancy

Contraindications to pregnancy for women with lupus in particular, and rheumatic connective tissue diseases in general, include pulmonary hypertension defined by a mean pulmonary artery pressure of ≥25 mm Hg at rest, measured during right heart catheterization [84,85], advanced heart failure, severe restrictive lung disease (FVC <1L), chronic renal failure (Cr > 2.8 mg/dL), previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin, stroke or severe lupus flare within the previous 6 months [86].

PRECONCEPTION MANAGEMENT ISSUES

Opportunities for pregnancy optimization begin in advance of conception, and fall into two broad categories – ovarian protection and orchestration of pregnancy timing and relevant medication adjustments.

Ovarian protection in the context of gonadotoxic therapy

For the subset of premenopausal CTD patients facing treatment regimens with gonadotoxic agents, such as cyclophosphamide (CYC), ovarian protection options and co-management with reproductive endocrinology specialists warrant consideration. As cumulative exposure to CYC is associated with increased risk of diminished ovarian reserve and premature ovarian insufficiency (POI) [87], minimizing overall CYC exposure is a treatment goal. In general, daily oral CYC regimens are associated with higher cumulative exposure compared to IV. The “Euro-lupus” regimen, a low-dose IV CYC regimen consisting of six 500mg CYC pulses every 2 weeks, followed by maintenance therapy with azathioprine (AZA), results in 3 grams of total CYC exposure, which is substantially lower than cumulative doses resulting from standard 6 month courses [88]. Induction with mycophenolate mofetil (MMF) is another alternative for induction therapy for mild lupus nephritis [89,90]. However, standard CYC induction is indicated for patients with severe lupus nephritis with renal insufficiency, or those who have not responded to MMF.

Studies in both rheumatic and non-rheumatic disease populations suggest that adjunctive GnRH-a treatment during CYC therapy has ovarian protective effects [91,92]. The regimen used at our institution utilizes depot-leuprolide acetate 3.75 mg/month (and more recently a 11.25 mg 3 month preparation); the first injection should be timed 10 days before the next CYC pulse in order to avoid CYC administration while ovaries are hyperstimulated due to a transient GnRH-a induced estrogen surge. When IV CYC is required urgently, GnRH-a administration is delayed until 10–21 days before the subsequent (second) IV CYC treatment. An estradiol patch of 0.05 or 0.1 mg (to be worn continuously and begun after onset of withdrawal symptoms) may be used to avoid estrogen withdrawal symptoms and reduce the risk of osteoporosis; this is contraindicated for APS or other patients with hypercoagulability. Depot medroxyprogesterone acetate (DPMA) 150 mg every 3 months or IUD for contraception are concurrently used unless otherwise contraindicated. This regimen is continued during bolus CYC administration.

Timing of pregnancy and contraception

It is increasingly recognized that the risks of pregnancy associated with connective tissue diseases can be minimized if conception is planned and undertaken during a period of minimally active disease. Pre-pregnancy planning further allows for appropriate medication adjustments to be made when relevant. With an estimated 45% of pregnancies in the US each year unintended [93], early discussion of future pregnancies, even if not currently contemplated, should be a priority in women with autoimmune CTDs. In terms of time windows, women with active disease, such as lupus nephritis, are generally advised that 6 months or more of inactive disease is desirable before conception and is associated with more favorable maternal and fetal outcomes [94].

Contraception—Pregnancy timing clearly relies on reliable and safe contraception options. Due to thrombotic risks associated with many forms of hormonal contraception, special considerations pertain to their use in rheumatic disease patients given their underlying risk for thrombosis even in the absence of aPLs [95,96]. For aPL negative patients, combined and progestin-only contraceptives are acceptable. Long-acting reversible

contraception (LARC) methods, which include the intrauterine device (IUD) and birth control implant, offer highly effective contraception and are an attractive option for many women with rheumatic diseases. DMPA by intramuscular injection is another highly effective option that lasts 3 months, though long-term use is associated with osteoporosis, which is a particular concern for patients with significant cumulative corticosteroid exposure.

It should be noted that data providing support for use of oral contraceptives in the SLE population, such as from the SELENA-OC randomized controlled trial [97], were based on formulations with 2nd generation progestins. Newer 3rd generation pill, patch and vaginal rings carry a higher risk of venous thrombosis in the general population and may be prudent to avoid in rheumatic disease patients. The birth control implant also contains a 3rd generation progestin for which it is unclear whether there is an increased risk of venous thrombosis.

For aPL positive patients, combined pills, patch and ring methods are contraindicated and classified by CDC “Medical Eligibility Criteria for Contraceptive Use” as Category 4: “unacceptable health risk (method not to be used)” [98]. Progestin only options (including progestin only pills, injections, implants and IUD) are classified as Category 3: “theoretical or proven risks usually outweigh the advantages.” The copper-IUD, which lasts 10 years and contains no hormones, is categorized by CDC as having no restriction for use in SLE patients with positive (or unknown) aPL status [98]. However, due to increased menstrual bleeding it is not recommended for patients with severe thrombocytopenia [98]. Levonorgestrel (LNg)-IUDs containing a 2nd generation progestin and lasting 3–5 years after placement, are classified by the CDC for aPL positive patients as Category 3. However, decreased menstrual bleeding after the first 3 months may be a benefit for patients on warfarin; in patients for whom pregnancy may be riskier than contraception, this may be a viable option to consider with caution.

Medication adjustments prior to pregnancy—Medications for which a washout period is indicated prior to pregnancy include methotrexate, mycophenolate mofetil (MMF), and leflunomide. While medications are considered in more depth below, a general guide is that a 1–3 month period prior to conception is sufficient for washout of most medications used for rheumatic diseases (see also section on “Medications contraindicated in pregnancy”). If medication adjustments are needed in advance of pregnancy, a 6-month period is ideally advisable in order to establish whether disease stability can be maintained in the context of new treatment regimens.

MEDICATIONS DURING AUTOIMMUNE CTD PREGNANCIES

It is of paramount importance that multidisciplinary management involving the patient and care team address decisions about drug therapy prior to and during pregnancy. As stated throughout, untreated, active disease during pregnancy increases risk of adverse pregnancy outcomes. Here we review safety data and recommendations pertaining to some of the most frequently used medications in rheumatic disease pregnancies and highlight key issues. It is not an exhaustive list, and we refer the reader to guidance put forth by expert bodies related

to anti-rheumatic drugs and their uses before and during pregnancy, and in lactation. Both a European League Against Rheumatism (EULAR) task force [99] and the British Society for Rheumatology/British Health Professionals in Rheumatology [100,101] recently published recommendations, which provide timely and expertly adjudicated information that will serve the rheumatology community well.

Medications compatible with pregnancy

Non-steroidal anti-inflammatory drugs (NSAIDs)—There is no evidence of increase in congenital malformations associated with non-selective COX inhibitors, and they can be continued safely during the first and second trimesters. However, there is insufficient data to make recommendations about selective COX II inhibitors, and they should therefore be avoided in pregnancy. With the exception of low dose aspirin, NSAIDs should be discontinued in the third trimester due to risk of prolongation of labor and premature closure of ductus arteriosus [102,103].

Glucocorticoids—Oral glucocorticoids are widely used as treatment for connective tissue diseases as they are both rapidly acting and efficacious. When glucocorticoids are needed in pregnancy, it has been generally recommended to use the lowest effective dose for the shortest duration of time. Whereas fluorinated glucocorticoids (*e.g.*, dexamethasone, betamethasone) cross the placenta, and may be indicated for treatment of fetal conditions including lung development in prematurity, non-fluorinated glucocorticoids (*e.g.*, prednisone, prednisolone) cross the placenta at a much lower rate. At doses of ≤20 mg, approximately 10% of non-fluorinated glucocorticoids cross into the fetal circulation [104,105]. Thus, prednisone and prednisolone at these doses are considered safe for treating mild manifestations of maternal rheumatic diseases throughout pregnancy.

In addition to the known risks associated with glucocorticoids, in particular hypertension and diabetes, their use during the first trimester also increases the risk of cleft palate formation by 2–3 fold, although the absolute risk is still considered low, with baseline risk of approximately 1/1000 live births [106,107]. A meta-analysis of 10 studies observed over a 30+ year time period revealed a non-significant increase in risk of major malformations associated with *in utero* exposure [107]. Use of glucocorticoids later in pregnancy increases the risk of premature rupture of membranes and small for gestational age births, and high or prolonged doses puts the newborn at risk for adrenal insufficiency [102]. However, use of high dose intravenous glucocorticoids may be necessary for treatment of severe disease manifestations during pregnancy and should not be withheld if indicated.

Antimalarial therapy (hydroxychloroquine and chloroquine)—Antimalarials, such as chloroquine and hydroxychloroquine (HCQ), are used as monotherapy or in combination with other immunosuppressives to treat many CTDs, most commonly SLE. An increase in the rate of disease flare has been observed in SLE patients with quiescent disease who discontinued HCQ [108]. Given its known safety profile in pregnancy [80,109], and the acknowledged risk to both mother and fetus associated with heightened lupus disease activity in pregnancy, discontinuing HCQ during pregnancy is not advised. Indeed, several studies have suggested that HCQ therapy in SLE improves birth outcomes: in a study of 118

lupus pregnancies in which 41 women were treated with HCQ and compared to 77 SLE women who were not taking HCQ, significantly lower rates of preterm delivery (15.8% vs 44.2%; p= 0.006) and IUGR (10.5% vs 28.6%; p=0.03) were observed in the group taking HCQ [29]. In another retrospective study of outcomes of lupus pregnancies, 56 women who took HCQ through their pregnancies were compared with 163 who took no HCQ, and 38 who stopped HCQ either three months prior to conception or during their first trimesters out of concern for medication exposure to the baby [30]. While pregnancy outcomes were not different between the three groups, lupus disease activity was significantly higher in the women who had stopped HCQ therapy, necessitating increase in background steroid therapy. The safety data for HCQ is also reassuring: while HCQ has been demonstrated in cord blood and breast milk, although at lower concentrations than found concomitantly in maternal blood, no increased risk of congenital defects, spontaneous abortions, retinal or otoxoticy in offspring of CTD mothers exposed to *in utero* HCQ has been observed [110–112]. The recommendation that HCQ be continued during pregnancy as a DMARD, steroid sparing agent was strongly confirmed by the EULAR task force recently, along with a consensus that HCQ is compatible with breastfeeding [99,110,113]. While less is known about the effect of chloroquine, there is no evidence that it is unsafe to use in pregnancy and breastfeeding.

Steroid sparing immunosuppressive medications—In addition to antimalarials, azathioprine (AZA), sulfasalazine, tacrolimus and cyclosporine are considered to be safe for use throughout pregnancy [102].

Sulfasalazine—Sulfasalazine is a disease modifying anti-rheumatic medication used for mild RA symptoms primarily, and is considered safe for use in pregnancy [53,99,100]. Large administrative database linkage studies as well as meta-analyses have revealed no increase in miscarriage or congenital malformations associated with its use in pregnancy for treatment of inflammatory bowel or rheumatic diseases [114,115]. Sulfasalazine inhibits absorption and metabolism of folic acid; folic acid antagonists as a group, when taken during the first two months since the last menstrual period, have been associated with a greater than doubling of risk for neural tube defects [116]. While causality in relation to sulfasalazine specifically has not been confirmed, some guidelines specify that folic acid supplementation of 5 mg/day be taken in conjunction with sulfasalazine during pregnancy [100]. Recommendations for breastfeeding are complicated by the potential effects of mesalamine (5-aminosalicylic acid) and sulfapyridine, the active components of sulfasalazine, in a G6PD deficient or premature infant and the risk of hyperbilirubinemia [99]. Therefore, some recommend that breastfeeding while taking sulfasalazine be restricted to full term, healthy infants [100].

Azathioprine—Azathioprine (AZA) is a thiopurine inhibitor, inhibiting synthesis of DNA and RNA precursors adenine and guanine. AZA has been used for over 50 years in organ transplantation, and in SLE is used as a steroid sparing agent and for maintenance therapy following CYC induction [117]. Of available drug options for SLE during pregnancy, AZA is considered to have the best benefit to risk ratio for active disease for which CYC or MMF would otherwise be indicated. As administered, AZA is inactive,

requiring nonenzymatic and enzymatic intracellular metabolism to its active metabolites, not all of which have been detected in the fetal circulation, indicating that the placenta may form a “relative barrier” to AZA and its metabolites. As thiopurine metabolism is altered during pregnancy, monitoring of 6-thioguanine nucleotide and 6-methylmercaptopurine levels during pregnancy could be considered; these assays are available through some commercial laboratories [118,119]. Potential rare side effects in the newborn may include transient hypogammaglobulinemia and pancytopenias, which tend to normalize within 10 weeks of birth [120–124]; a complete blood count in newborns and vigilance for neonatal infection after *in utero* AZA exposure has been recommended by some [116,117]. Recent data also suggest a potential association with developmental delays in offspring [125], which warrants vigilance in the pediatric setting given the clear benefit of early interventions. It should be emphasized that given strong evidence that active maternal disease is associated with adverse maternal and fetal outcomes, the benefits of AZA treatment outweigh potential risks, and this medication should not be withheld during pregnancy.

Tacrolimus—Tacrolimus is a calcineurin inhibitor that has been used successfully in both the maintenance of stable disease and treatment of lupus nephritis flare in pregnancy in several case series, in which no adverse outcomes were observed [126,127]. It is considered safe for use in pregnancy [128,129]; the lowest effective dose should be used and levels must be followed to avoid toxicity.

Cyclosporin—Much of what is known about cyclosporin in pregnancy comes from the transplant literature, in which it does not appear to increase the risk of fetal malformations or adverse pregnancy outcomes. It can be continued during pregnancy at the lowest effective dose [99].

Cyclophosphamide (CYC)—Women of child bearing age who are started on CYC for severe manifestations of rheumatic diseases must have highly effective birth control due to its known teratogenic and abortifacient properties [117]. The use of CYC in pregnancy is contraindicated in the first trimester of pregnancy, but long term follow-up studies have not demonstrated any developmental abnormalities in children exposed to CYC in later pregnancy [130,131]. The use of CYC during later stages of pregnancy must be carefully considered, and used if no other safer option is available for treating disease flare.

Biologics

TNF inhibitors: Tumor necrosis factor inhibitors are prescribed regularly for use in moderate to severe RA and psoriatic arthritis and appear to be safe in pregnancy. In a large, multi-center observational prospective study looking at women with inflammatory arthritis taking biological drugs immediately before or during gestation, the rate of fetal malformation was found to be similar to that expected in the general population, without any increase in neonatal adverse events; it was noted that 95% of the population was taking TNF inhibitors, with a mean exposure time prior to discontinuation of the drug being 41 days after last menstrual period [132]. Studies comparing TNF-inhibitor levels in maternal blood to fetal cord blood at time of delivery have shown variability across different anti-TNF agents [133]. Concentrations of the anti-TNF IgG1 monoclonal antibodies infliximab and

adalimumab were higher in infants and their cord blood at birth than in their mothers; furthermore, infliximab and adalimumab were detected in infant blood for up to 6 months [133]. This is in contrast to certolizumab, a PEGylated anti-TNF monoclonal antibody, which is present in much lower levels in cord blood at time of delivery. Etanercept, the fusion protein of TNF receptor to the constant region of IgG1 antibody, is also found in lower concentrations in newborn cord blood compared to concentrations in maternal blood, supporting its lower rate of cross-placental transport [134,135]. Early concern for association of *in utero* exposure to etanercept and infliximab with VACTERL (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limp abnormalities) has since been challenged, in part due to the possibility of confounding by exposure to concomitant teratogenic medications [136,137], and because subsequent studies and systematic reviews across all anti-TNF agents have revealed no congenital anomalies or serious complications within this medication class [134,138,139].

Given the persistence of therapeutic levels of these anti-TNF agents in exposed infants, a concern for infant infection and response to vaccination has been raised. This is illustrated by a case report from 2010 of an infant exposed to infliximab *in utero* who received the Bacillus Calmette-Guerin vaccine (BCG) at 3 months and subsequently died of disseminated BCG infection at 4.5 months [140]. This case has raised the issue of withholding live vaccines (*e.g.*, varicella, rotavirus, measles, mumps, rubella, intranasal influenza, BCG) in infants exposed to anti-TNF agents *in utero* until at least 6 months of age, a recommendation which has been adopted by several groups of gastroenterologists [119]. The British guidelines suggest that live vaccines in the infant be avoided until 7 months of age when these drugs are used later in pregnancy (after 16 weeks for infliximab, and after 2nd trimester for etanercept and adalimumab) [100].

Other biologic agents: Little data exists regarding the safety of pregnancy and breastfeeding during therapy with rituximab, anakinra, ustekinumab, tocilizimab, abatacept, and belimumab. Therefore, it is recommended that alternative medications be considered during pregnancy and breastfeeding [99].

Breastfeeding—Medications considered safe in breastfeeding include NSAIDs, glucocorticoids, cyclosporin, and HCQ due to minimal to low exposure in the breast milk and a long history of safe use [112]. Caution regarding breastfeeding during therapy with AZA is recommended in thiopurine methyltransferase deficient mothers and children [99], and with sulfasalazine in premature babies as discussed above [100]. Biologic agents such as anti-TNF inhibitors are considered safe as their size reduces the likelihood of bioavailability due to poor gut absorption [99]. A general recommendation to reduce risk of exposure while nursing is to recommend that mothers avoid feeding at the time of peak levels in the breast milk, which usually occurs several hours after they take their medications.

Medications contraindicated in pregnancy

Methotrexate, leflunomide, and mycophenolate mofetil are contraindicated in pregnancy and lactation. It is recommended that therapy with any of these medications be discontinued prior to conception, anywhere from 6 weeks in the case of mycophenolate mofetil to at least

3 months in the case of methotrexate, and patients be transitioned to a medication that is safe for use in pregnancy, such as AZA [99,100,141]. For leflunomide, due to the long half-life of its active metabolite and individual variation in drug clearance, it may take up to two years after cessation of treatment for metabolite levels to become non-detectable [142]. Documentation of metabolite blood levels of <0.02 μg/ml is recommended prior to conception for women who have taken leflunomide within the preceding two years [142,143]. A cholestyramine drug elimination procedure is recommended for women with detectable metabolite levels planning conception and those who inadvertently become pregnant while on leflunomide, with subsequent documentation of maternal blood levels maintained at <0.02 μg/ml for 14 days [142,143]. Reassuringly, the Organization of Teratology Information Specialists (OTIS) Collaborative Research Group reported on 64 women with RA who were treated with leflunomide during pregnancy (95.3% of whom received cholestyramine), among whom no substantial increased risk of adverse pregnancy outcomes was observed when compared to RA patients not treated with leflunomide and normal pregnant controls [143].

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References

1. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009; 33:197–207. DOI: 10.1016/j.jaut.2009.09.008 [PubMed: 19819109]
2. Clowse MEB, Magder LS, Witter F, et al. Early risk factors for pregnancy loss in lupus. Obstet Gynecol. 2006; 107:293–9. DOI: 10.1097/01.AOG.0000194205.95870.86 [PubMed: 16449114]
3. Clowse MEB, Jamison M, Myers E, et al. A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol. 2008; 199:1–12. DOI: 10.1016/j.ajog.2008.03.012 [PubMed: 18585519]
4. Nodler J, Moolamalla SR, Ledger EM, et al. Elevated antiphospholipid antibody titers and adverse pregnancy outcomes: analysis of a population-based hospital dataset. BMC Pregnancy Childbirth. 2009; 9:11.doi: 10.1186/1471-2393-9-11 [PubMed: 19291321]
5. Clark, Ca; Spitzer, Ka; Laskin, Ca. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. J Rheumatol. 2005; 32:1709–12. [PubMed: 16142865]
6. Clowse MEB, Magder LS, Witter F, et al. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum. 2005; 52:514–21. DOI: 10.1002/art.20864 [PubMed: 15692988]
7. Del Junco DJ, Annegers JF, Coulam CB, et al. The relationship between rheumatoid arthritis and reproductive function. Br J Rheumatol. 1989; 28(Suppl 1):33. discussion 42–5. [PubMed: 2819346]
8. Hazes JM, Dijkmans Ba, Vandenbroucke JP, et al. Pregnancy and the risk of developing rheumatoid arthritis. Arthritis Rheum. 1990; 33:1770–5. [PubMed: 2260999]
9. Spector TD, Roman E, Silman aJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum. 1990; 33:782–9. [PubMed: 2363734]
10. Guthrie KA, Dugowson CE, Voigt LF, et al. Does pregnancy provide vaccine-like protection against rheumatoid arthritis? Arthritis Rheum. 2010; 62:1842–8. DOI: 10.1002/art.27459 [PubMed: 20309863]
11. Jørgensen KT, Pedersen BV, Jacobsen S, et al. National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and pre-eclampsia? Ann Rheum Dis. 2010; 69:358–63. DOI: 10.1136/ard.2008.099945 [PubMed: 19289384]

12. Hernández Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology. 1990; 1:285–91. [PubMed: 2083305]
13. Karlson EW, Mandl La, Hankinson SE, et al. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. Arthritis Rheum. 2004; 50:3458–67. DOI: 10.1002/art.20621 [PubMed: 15529351]
14. Heliövaara M, Aho K, Reunanen A, et al. Parity and risk of rheumatoid arthritis in Finnish women. Br J Rheumatol. 1995; 34:625–8. [PubMed: 7670780]
15. Brun JG, Nilssen S, Kvåle G. Breast feeding, other reproductive factors and rheumatoid arthritis. A prospective study. Br J Rheumatol. 1995; 34:542–6. [PubMed: 7633797]
16. Merlino, La; Cerhan, JR.; Criswell, La, et al. Estrogen and other female reproductive risk factors are not strongly associated with the development of rheumatoid arthritis in elderly women. Semin Arthritis Rheum. 2003; 33:72–82. DOI: 10.1016/S0049-0172(03)00084-2 [PubMed: 14625816]
17. Marder W, Somers EC. Is pregnancy a risk factor for rheumatic autoimmune diseases? Curr Opin Rheumatol. 2014; 26:321–8. DOI: 10.1097/BOR.0000000000000047 [PubMed: 24646947]
18. Khashan AS, Kenny LC, Laursen TM, et al. Pregnancy and the risk of autoimmune disease. PLoS One. 2011; 6:e19658.doi: 10.1371/journal.pone.0019658 [PubMed: 21611120]
19. Oka M. Effect of pregnancy on the onset and course of rheumatoid arthritis. Ann Rheum Dis. 1953; 12:227–9. [PubMed: 13105216]
20. Silman A, Kay A, Brennan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum. 1992; 35:152–5. [PubMed: 1734904]
21. Lansink M, de Boer A, Dijkmans BA, et al. The onset of rheumatoid arthritis in relation to pregnancy and childbirth. Clin Exp Rheumatol. 1993; 11:171–4. [PubMed: 8508559]
22. Cooper GS, Gilbert KM, Greidinger EL, et al. Recent advances and opportunities in research on lupus: environmental influences and mechanisms of disease. Environ Health Perspect. 2008; 116:695–702. DOI: 10.1289/ehp.11092 [PubMed: 18560522]
23. Somers EC, Thomas SL, Smeeth L, et al. Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. Arthritis Rheum. 2007; 57:612–8. DOI: 10.1002/art.22683 [PubMed: 17471530]
24. Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol (Hoboken, NJ). 2014; 66:369–78. DOI: 10.1002/art.38238
25. 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. DOI: 10.1002/art.21663 [PubMed: 16508972]
26. Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990–2010. Scand J Rheumatol. 2015; 44:377–84. DOI: 10.3109/03009742.2015.1013982 [PubMed: 26087812]
27. Buchanan NM, Khamashta M, Kerslake S, et al. Practical management of pregnancy in systemic lupus erythematosus. Fetal Matern Med Rev. 1993; 5:223.doi: 10.1017/S0965539500000917
28. Levy R, Vilela V, Cataldo M, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus. 2001; 10:401–4. DOI: 10.1191/096120301678646137 [PubMed: 11434574]
29. Leroux M, Desveaux C, Parcevaux M, et al. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Lupus. 2015; :1384–91. DOI: 10.1177/0961203315591027 [PubMed: 26082465]
30. Clowse MEB, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum. 2006; 54:3640–7. DOI: 10.1002/art.22159 [PubMed: 17075810]
31. Derksen RH, Bruinse HW, de Groot PG, et al. Pregnancy in systemic lupus erythematosus: a prospective study. Lupus. 1994; 3:149–55. [PubMed: 7951299]
32. Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: A cohort study. Ann Intern Med. 2015; 163:153–63. DOI: 10.7326/M14-2235 [PubMed: 26098843]

33. Schreiber K. Pregnancies in women with systemic lupus erythematosus and antiphospholipid antibodies. Lupus. 2016; :1–3. DOI: 10.1177/0961203315627201
34. Smyth A, Oliveira GHM, 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. DOI: 10.2215/CJN.00240110 [PubMed: 20688887]
35. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006; 4:295–306. DOI: 10.1111/j.1538-7836.2006.01753.x [PubMed: 16420554]
36. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999; 42:1309–11. DOI: 10.1002/1529-0131(199907)42:7<1309::AID-ANR1>3.0.CO;2-F [PubMed: 10403256]
37. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet (London, England). 1993; 342:341–4.
38. Tincani A, Bazzani C, Zingarelli S, et al. Lupus and the antiphospholipid syndrome in pregnancy and obstetrics: clinical characteristics, diagnosis, pathogenesis, and treatment. Semin Thromb Hemost. 2008; 34:267–73. DOI: 10.1055/s-0028-1082270 [PubMed: 18720306]
39. Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. Rheumatology (Oxford). 2011; 50:1684–9. DOI: 10.1093/rheumatology/ker139 [PubMed: 21652586]
40. Ruffatti, a; Calligaro, a; Hoxha, a, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis Care Res (Hoboken). 2010; 62:302–7. DOI: 10.1002/acr.20098 [PubMed: 20391475]
41. Derksen RHWM, de Groot PG. The obstetric antiphospholipid syndrome. J Reprod Immunol. 2008; 77:41–50. DOI: 10.1016/j.jri.2006.12.003 [PubMed: 17239960]
42. Branch DW. Antiphospholipid antibodies and fetal compromise. In. Thrombosis Research. 2004; : 415–8. DOI: 10.1016/j.thromres.2004.08.005 [PubMed: 15507272]
43. Bramham K, Hunt BJ, Germain S, et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus. 2010; 19:58–64. DOI: 10.1177/0961203309347794 [PubMed: 19897518]
44. 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. DOI: 10.1002/art.34402 [PubMed: 22275304]
45. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: A randomized, controlled trial of treatment. Obstet Gynecol. 2002; 100:408–13. DOI: 10.1016/S0029-7844(02)02165-8 [PubMed: 12220757]
46. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obs Gynecol. 2010; 115:1256–62. \r00006250-201006000-00023 [pii]. DOI: 10.1097/AOG.0b013e3181deba40
47. Mak A, Cheung MW-L, Cheak AA, et al. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology (Oxford). 2010; 49:281–8. DOI: 10.1093/rheumatology/kep373 [PubMed: 19965971]
48. Davis SM, Branch DW. Thromboprophylaxis in pregnancy: Who and how? Obstet Gynecol Clin North Am. 2010; 37:333–43. DOI: 10.1016/j.ogc.2010.02.004 [PubMed: 20685557]
49. Sciascia S, Branch DW, Levy Ra, et al. The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies. Evidence and clinical judgment. Thromb Haemost. 2015; 115:285–90. DOI: 10.1160/TH15-06-0491 [PubMed: 26421409]
50. Rainsford KD, Parke AL, Clifford-Rashotte M, et al. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology. 2015; 23:231–69. DOI: 10.1007/s10787-015-0239-y [PubMed: 26246395]

51. de Man, Ya; Hazes, JMW.; van de Geijn, FE., et al. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. Arthritis Rheum. 2007; 57:716–22. DOI: 10.1002/art.22773 [PubMed: 17530669]
52. de Man YA, Dolhain RJEM, 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. DOI: 10.1002/art.24003 [PubMed: 18759316]
53. De Man YA, Hazes JMW, 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. DOI: 10.1002/art.24914 [PubMed: 19877045]
54. Bharti B, Lee SJ, Lindsay SP, et al. Disease severity and pregnancy outcomes in women with rheumatoid arthritis: Results from the organization of teratology information specialists autoimmune diseases in pregnancy project. J Rheumatol. 2015; 42:1376–82. DOI: 10.3899/jrheum.140583 [PubMed: 25877497]
55. Cook WA. Letter: Raynaud Phenomenon in pregnancy. JAMA. 1976; 235:145–6. [PubMed: 946017]
56. Chakravarty EF, Khanna D, Chung L. Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol. 2008; 111:927–34. DOI: 10.1097/01.AOG.0000308710.86880.a6 [PubMed: 18378753]
57. Steen VD, Medsger Ta. Fertility and pregnancy outcome in women with systemic sclerosis. Arthritis Rheum. 1999; 42:763–8. DOI: 10.1002/1529-0131(199904)42:4<763::AID-ANR21>3.0.CO;2-V [PubMed: 10211892]
58. 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. DOI: 10.1002/art.34350 [PubMed: 22213060]
59. ARA Subcommittee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980; 23:581–90. [PubMed: 7378088]
60. LeRoy EC, Medsger J. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001; 28:1573–6. [PubMed: 11469464]
61. Di Martino, SJ. Myositis and Pregnancy. In: Bermas, BL.; Sammaritano, LR., editors. Contraception and Pregnancy in Patients with Rheumatic Disease. New York, NY: Springer; 2014. p. 185-97.
62. Pinal-Fernandez I, Selva-O'Callaghan A, Fernandez-Codina A, et al. 'Pregnancy in adult-onset idiopathic inflammatory myopathy': report from a cohort of myositis patients from a single center. Semin Arthritis Rheum. 2014; 44:234–40. DOI: 10.1016/j.semarthrit.2014.05.004 [PubMed: 24906908]
63. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975; 292:344–7. DOI: 10.1056/NEJM197502132920706 [PubMed: 1090839]
64. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975; 292:403–7. DOI: 10.1056/NEJM197502202920807 [PubMed: 1089199]
65. Shahane A, Patel R. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014; 247doi: 10.2147/CLEP.S47399
66. Hussein SZ, Jacobsson LTH, Lindquist PG, et al. Pregnancy and fetal outcome in women with primary Sjogren's syndrome compared with women in the general population: a nested case-control study. Rheumatology. 2011; 50:1612–7. DOI: 10.1093/rheumatology/ker077 [PubMed: 21531959]
67. Takaya M, Ichikawa Y, Shimizu H, et al. Sjögren's syndrome and pregnancy. Tokai J Exp Clin Med. 1991; 16:83–8. [PubMed: 1780917]
68. Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: Development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001; 37:238–42. DOI: 10.1016/S0735-1097(00)01048-2 [PubMed: 11153745]
69. Nield LE, Silverman ED, Taylor GP, et al. Maternal anti-Ro and anti-La antibody - Associated endocardial fibroelastosis. Circulation. 2002; 105:843–8. DOI: 10.1161/hc0702.104182 [PubMed: 11854125]

70. Buyon JP, Winchester RJ, Slade SG, et al. Identification of mothers at risk for congenital heart block and other neonatal lupus syndromes in their children: Comparison of enzyme-linked immunosorbent assay and immunoblot for measurement of anti-SS-A/Ro and anti-SS-B/La antibodies. Arthritis Rheum. 1993; 36:1263–73. DOI: 10.1002/art.1780360911 [PubMed: 8216420]
71. Jaeggi ET, Hamilton RM, Silverman ED, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: A single institution's experience of 30 years. J Am Coll Cardiol. 2002; 39:130–7. DOI: 10.1016/S0735-1097(01)01697-7 [PubMed: 11755298]
72. Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. Autoimmune congenital heart block: complex and unusual situations. Lupus. 2016; 25:116–28. DOI: 10.1177/0961203315624024 [PubMed: 26762645]
73. Brucato, a; Doria, A.; Frassi, M., et al. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. Lupus. 2002; 11:716–21. DOI: 10.1191/0961203302lu252oa [PubMed: 12475001]
74. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol. 1998; 31:1658–66. DOI: 10.1016/S0735-1097(98)00161-2 [PubMed: 9626848]
75. Friedman D, Duncanson L, Glickstein J, et al. A review of congenital heart block. Images Paediatr Cardiol. 2003; 5:36–48. [PubMed: 22368629]
76. Friedman DM, Kim MY, Copel JA, et al. Prospective Evaluation of Fetuses With Autoimmune-Associated Congenital Heart Block Followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study. Am J Cardiol. 2009; 103:1102–6. DOI: 10.1016/j.amjcard.2008.12.027 [PubMed: 19361597]
77. Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011; 124:1927–35. DOI: 10.1161/CIRCULATIONAHA.111.033894 [PubMed: 21969015]
78. 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. DOI: 10.1161/CIRCULATIONAHA.111.041970 [PubMed: 21986286]
79. Izmirly PM, Saxena A, Sahl SK, et al. Assessment of fluorinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fetal conduction system. Ann Rheum Dis. 2015; annrheumdis – 2015–208311. doi: 10.1136/annrheumdis-2015-208311
80. 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. DOI: 10.1161/CIRCULATIONAHA.111.089268 [PubMed: 22626746]
81. Saxena A, Izmirly PM, Mendez B, et al. Prevention and Treatment In Utero of Autoimmune-Associated Congenital Heart Block. Cardiol Rev. 2014; 22:263–7. DOI: 10.1097/CRD.0000000000000026 [PubMed: 25050975]
82. Trucco SM, Jaeggi E, Cuneo B, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. J Am Coll Cardiol. 2011; 57:715–23. DOI: 10.1016/j.jacc.2010.09.044 [PubMed: 21292131]
83. ØStensen M. Intravenous immunoglobulin does not prevent recurrence of congenital heart block in children of SSA/Ro-positive mothers. Arthritis Rheum. 2010; 62:911–4. DOI: 10.1002/art.27317 [PubMed: 20131249]
84. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013; 62:D42–50. DOI: 10.1016/j.jacc.2013.10.032 [PubMed: 24355641]
85. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J. 2011; 32:3147–97. DOI: 10.1093/eurheartj/ehr218 [PubMed: 21873418]

86. de Jesus GR, Mendoza-Pinto C, de Jesus NR, et al. Understanding and Managing Pregnancy in Patients with Lupus. Autoimmune Dis. 2015; 2015:943490.doi: 10.1155/2015/943490 [PubMed: 26246905]
87. Mok CC, Lau CS, Wong RW. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. Arthritis Rheum. 1998; 41:831–7. DOI: 10.1002/1529-0131(199805)41:5<831::AID-ART9>3.0.CO;2-1 [PubMed: 9588734]
88. Houssiau, Fa; Vasconcelos, C.; D'Cruz, D., et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002; 46:2121–31. DOI: 10.1002/art.10461 [PubMed: 12209517]
89. Riskalla MM, Somers EC, Fatica RA, et al. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. J Rheumatol. 2003; 30:1508–12. [PubMed: 12858449]
90. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005; 353:2219–28. DOI: 10.1056/NEJMoa043731 [PubMed: 16306519]
91. Marder W, McCune WJ, Wang L, et al. Adjunctive GnRH-a treatment attenuates depletion of ovarian reserve associated with cyclophosphamide therapy in premenopausal SLE patients. Gynecol Endocrinol. 2012
92. Somers EC, Marder W, Christman GM, et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum. 2005; 52:2761–7. DOI: 10.1002/art.21263 [PubMed: 16142702]
93. Finer LB, Zolna MR. Declines in Unintended Pregnancy in the United States, 2008-2011. N Engl J Med. 2016; 374:843–52. DOI: 10.1056/NEJMsa1506575 [PubMed: 26962904]
94. Hayslett JP. Maternal and fetal complications in pregnant women with systemic lupus erythematosus. Am J Kidney Dis. 1991; 17:123–6. [PubMed: 1992652]
95. Sammaritano LR. Therapy insight: guidelines for selection of contraception in women with rheumatic diseases. Nat Clin Pract Rheumatol. 2007; 3:273–81. quiz 305–6. DOI: 10.1038/ncprheum0484 [PubMed: 17471246]
96. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis. 2009; 68:238–41. DOI: 10.1136/ard.2008.093013 [PubMed: 18782792]
97. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005; 353:2550–8. DOI: 10.1056/NEJMoa051135 [PubMed: 16354891]
98. CDC. US Medical Eligibility Criteria for Contraceptive Use, 2010: Adapted from the World Health Organization Medical Eligibility Criteria for Contraceptive Use (4). 2010; 59(RR04):1–6. [accessed 1 Apr2016] http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm.
99. Skorpen CG, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. 2016; :1–16. DOI: 10.1136/annrheumdis-2015-208840
100. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016; :kev404.doi: 10.1093/rheumatology/kev404 [PubMed: 26750124]
101. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice: Table 1. Rheumatology. 2016; :kev405.doi: 10.1093/rheumatology/kev405 [PubMed: 26750125]
102. Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006; 8:209.doi: 10.1186/ar1957 [PubMed: 16712713]
103. Clowse, MEB. Chapter 36 – Pregnancy in Women with SLE. 8. Elsevier Inc; 2013.
104. Benediktsson R, Calder AA, Edwards CR, et al. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol (Oxf). 1997; 46:161–6. [PubMed: 9135697]

105. Bramham K, Thomas M, Nelson-Piercy C, et al. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. Blood. 2011; 117:6948–51. DOI: 10.1182/blood-2011-02-339234 [PubMed: 21527518]
106. Bermas BL. Non-steroidal anti inflammatory drugs, glucocorticoids and disease modifying anti-rheumatic drugs for the management of rheumatoid arthritis before and during pregnancy. Curr Opin Rheumatol. 2014; 26:334–40. DOI: 10.1097/BOR.0000000000000054 [PubMed: 24663106]
107. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000; 62:385–92. DOI: 10.1002/1096-9926(200012)62:6<385::AID-TERA5>3.0.CO;2-Z [PubMed: 11091360]
108. Bykerk V, Sampalis J, Esdaile JM, et al. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. N Engl J Med. 1991; 324:150–4. DOI: 10.1056/NEJM199101173240303 [PubMed: 1984192]
109. Diav-Citrin O, Blyakhman S, Shechtman S, et al. Pregnancy outcome following in utero exposure to hydroxychloroquine: A prospective comparative observational study. Reprod Toxicol. 2013; 39:58–62. DOI: 10.1016/j.reprotox.2013.04.005 [PubMed: 23602891]
110. Costedoat-Chalumeau N, Amoura Z, Aymard G, et al. Evidence of transplacental passage of hydroxychloroquine in humans. Arthritis Rheum. 2002; 46:1123–4. DOI: 10.1002/art.10150 [PubMed: 11953993]
111. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum. 2003; 48:3207–11. DOI: 10.1002/art.11304 [PubMed: 14613284]
112. Noviani M, Wasserman S, Clowse MEB. Breastfeeding in mothers with systemic lupus erythematosus. 2016; :1–7. DOI: 10.1177/0961203316629555
113. 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.doi: 10.1186/1546-0096-7-9 [PubMed: 19439078]
114. Viktil K, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150 000 pregnant women and expectant fathers. Scand J Rheumatol. 2012; 41:196–201. DOI: 10.3109/03009742.2011.626442 [PubMed: 22401133]
115. Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: A meta-analysis. Reprod Toxicol. 2008; 25:271–5. DOI: 10.1016/j.reprotox.2007.11.010 [PubMed: 18242053]
116. Hernández-Díaz S, Werler MM, Walker AM, et al. Neural tube defects in relation to use of folic acid antagonists during pregnancy. Am J Epidemiol. 2001; 153:961–8. DOI: 10.1093/aje/153.10.961 [PubMed: 11384952]
117. Marder W, McCune WJ. Advances in immunosuppressive therapy. Semin Respir Crit Care Med. 2007; 28:398–417. DOI: 10.1055/s-2007-985612 [PubMed: 17764058]
118. Jharap B, de Boer NKH, Stokkers P, et al. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut. 2014; 63:451–7. DOI: 10.1136/gutjnl-2012-303615 [PubMed: 23424097]
119. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the Management of IBD in Pregnancy. Gastroenterology. Published Online First: 2015.
120. DeWitte DB, Buick MK, Cyran SE, et al. Neonatal pancytopenia and severe combined immunodeficiency associated with antenatal administration of azathioprine and prednisone. J Pediatr. 1984; 105:625–8. [PubMed: 6481541]
121. Coté CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. J Pediatr. 1974; 85:324–8. [PubMed: 4372551]
122. Nørgård B, Pedersen L, Christensen LA, et al. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. Am J Gastroenterol. 2007; 102:1406–13. DOI: 10.1111/j.1572-0241.2007.01216.x [PubMed: 17437503]

123. Matalon ST, Ornoy A, Lishner M. Review of the potential effects of three commonly used antineoplastic and immunosuppressive drugs (cyclophosphamide, azathioprine, doxorubicin on the embryo and placenta). Reprod Toxicol. 18:219–30. DOI: 10.1016/j.reprotox.2003.10.014 [PubMed: 15019720]

124. Goldstein LH, Dolinsky G, Greenberg R, et al. Pregnancy outcome of women exposed to azathioprine during pregnancy. Birth Defects Res A Clin Mol Teratol. 2007; 79:696–701. DOI: 10.1002/bdra.20399 [PubMed: 17847119]

125. Marder W, Ganser MA, Romero V, et al. In utero azathioprine exposure and increased utilization of special educational services in children born to mothers with systemic lupus erythematosus. Arthritis Care Res (Hoboken). Published Online First: November 2012.

126. Webster P, Wardle a, Bramham K, et al. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus. 2014; 23:1192–6. DOI: 10.1177/0961203314540353 [PubMed: 24928830]

127. Alsuwaida A. Successful management of systemic lupus erythematosus nephritis flare-up during pregnancy with tacrolimus. Mod Rheumatol. 2011; 21:73–5. DOI: 10.1007/s10165-010-0340-4 [PubMed: 20680376]

128. 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. DOI: 10.2215/CJN.06400612 [PubMed: 23349333]

129. Armenti VT, Constantinescu S, Moritz MJ, et al. Pregnancy after transplantation. Transplant Rev. 2008; 22:223–40. DOI: 10.1016/j.trre.2008.05.001

130. Avilés A, Niz J. Long-term follow-up of children born to mothers with acute leukemia during pregnancy. Med Pediatr Oncol. 1988; 16:3–6. [PubMed: 3340063]

131. Avilés A, Díaz-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. [PubMed: 1707227]

132. Bazzani C, Scrivo R, Andreoli L, et al. Prospectively-followed pregnancies in patients with inflammatory arthritis taking bimological drugs: an Italian multicentre study. Clin Exp Rheumatol. 2015; 33:688–93. [PubMed: 26311348]

133. 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. DOI: 10.1016/j.cgh.2012.11.011 [PubMed: 23200982]

134. Hoffman MB, Farhangian M, Feldman SR. Psoriasis during pregnancy: characteristics and important management recommendations. Expert Rev Clin Immunol. 2015; 11:709–20. DOI: 10.1586/1744666X.2015.1037742 [PubMed: 25873365]

135. Berthelsen BG, Fjeldsøe-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. DOI: 10.1093/rheumatology/keq185 [PubMed: 20581374]

136. JDC, AL, LRR, et al. A safety assessment of tumor necrosis factor antagonists during pregnancy: A review of the food and drug administration database. J Rheumatol. 2009; 36:635–41. DOI: 10.3899/jrheum.080545 [PubMed: 19132789]

137. Winger EE, Reed JL. Was risk properly assessed in Carter, et al's safety assessment of tumor necrosis factor antagonists during pregnancy? J Rheumatol. 2009; 36:2122.doi: 10.3899/jrheum.090141 [PubMed: 19738224]

138. Marchioni RM, Lichtenstein GR. Tumor necrosis factor-α inhibitor therapy and fetal risk: a systematic literature review. World J Gastroenterol. 2013; 19:2591–602. DOI: 10.3748/wjg.v19.i17.2591 [PubMed: 23674866]

139. Nielsen OH, Loftus EV, Jess T. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. BMC Med. 2013; 11:174.doi: 10.1186/1741-7015-11-174 [PubMed: 23902720]

140. 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. DOI: 10.1016/j.crohns.2010.05.001 [PubMed: 21122568]

141. Ramsey-Goldman R, Schilling E. Immunosuppressive drug use during pregnancy. Rheum Dis Clin North Am. 1997; 23:149–67. DOI: 10.1016/S0889-857X(05)70320-3 [PubMed: 9031380]

142. Sanofi. [accessed 1 Apr 2016] Arava & Pregnancy: Counseling guidelines for women of childbearing potential. http://www.arava.com/hcp/about/pregnancy.aspx

143. Chambers CD, Johnson DL, Robinson LK, et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum. 2010; 62:1494–503. DOI: 10.1002/art.27358 [PubMed: 20131283]

PRACTICE POINTS

- Pre-conception counseling should be conducted routinely for reproductive age females with autoimmune connective tissue diseases, with the goal of planning for pregnancies during periods of disease quiescence in order to optimize maternal and fetal outcomes
- During pregnancy and the postpartum period, frequent monitoring by a multidisciplinary team is imperative
- Active disease may be more detrimental to the fetus than potential side effects of medications, thus medications necessary for disease control and that are deemed compatible with pregnancy should not be withheld

RESEARCH POINTS

- Longitudinal cohort studies including reproductive endpoints and postmarketing surveillance of drugs used during pregnancy and breastfeeding are imperative and should include assessment of long term outcomes of children of these pregnancies
- Differentiation between lupus nephritis and preeclampsia remains a great clinical challenge; there is an urgent need to identify biomarkers or clinical tools that will aid in this setting
- There is a critical need to develop and evaluate strategies for the prevention and progression of cardiac neonatal lupus

SUMMARY

Increasingly more women with connective tissue diseases are attempting pregnancy, with improved outcomes as multidisciplinary disease management becomes more widespread. Effective preconception counseling should be part of routine clinical care of these women, with emphasis on safe and effective contraception, pregnancy planning that allows time for anticipatory medication adjustments, and continuation of treatment to maintain remission throughout pregnancy with medications that will not harm the baby. Recent identification of risk factors that predict adverse pregnancy outcomes in women with SLE, including the presence of the lupus anticoagulant, will allow for closer follow-up of these higher risk patients, and hopefully improve outcomes for mothers and their children. Accumulating data on the safety of biologic therapy in pregnancy is also evolving thanks to the OTIS Collective Research Group and long term surveillance data, adding to the options for safe and effective treatment of rheumatic diseases in pregnancy.