



REVIEW

Evaluation and management of systemic lupus erythematosus and rheumatoid arthritis during pregnancy

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Abstract Women of childbearing age are at risk for developing systemic rheumatic diseases. Pregnancy can be challenging to manage in patients with rheumatic diseases for a variety of reasons including the impact of physiological and immunological changes of pregnancy on underlying disease activity, the varied presentation of rheumatic disease during pregnancy, and the limited treatment options. Previously, patients with rheumatic disease were often advised against pregnancy due to concerns of increased maternal and fetal morbidity and mortality. However, recent advancements in the understanding of the interaction between pregnancy and rheumatic disease have changed how we counsel patients. Patients with rheumatic disease can have successful pregnancy outcomes, particularly when a collaborative approach between the rheumatologist and obstetrician is applied. This review aims to discuss the effect of pregnancy on patients with the most common rheumatic diseases, the effect of these diseases on the pregnancy itself, and the management of these patients during pregnancy.

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1. Introduction

Healthy pregnancy involves alterations in intravascular volume, thrombotic state, and cell-mediated immunity. These changes can be especially challenging in patients with underlying rheumatic disease because they can both mimic disease activity, making evaluation of disease flares difficult, and they can exacerbate the underlying rheumatic disease.

1.1. Physiologic changes during pregnancy

In general, intravascular volume increases by 30 to 50% in normal pregnancy [1]. This increase in fluid volume can be problematic in rheumatology patients who have cardiac or renal manifestations of their disease. Additionally, pregnancy causes elevated plasma fibrinogen and prothrombin levels and decreased free and total protein S levels, all of which result in a relative thrombophilia. This prothrombotic state, along with increased venous stasis caused by the enlarged uterus, has been shown to significantly increase by five-fold the risk of venous thromboembolism [2]. This is particularly concerning in patients with underlying SLE and/or antiphospholipid antibodies, given their predisposition to thrombosis at baseline.

1.2. Physical changes of pregnancy

Pregnancy can cause fatigue, dyspnea, melasma, increased erythema of the palms and face, headaches, and postpartum hair loss, all of which can be difficult to differentiate from the disease flares of SLE or RA. Increased body weight and hormonally induced pelvic instability contribute to the back pain and joint pain experienced by 50% of women who

are pregnant [3]. Additionally, carpal tunnel syndrome is common during pregnancy particularly during the second and third trimesters [4].

1.3. Laboratory findings

Laboratory findings seen during pregnancy can be hard to distinguish from those found during disease flares. For example, many pregnant women will become modestly anemic during the third trimester due to hemodilution [5]. Thrombocytopenia occurs in approximately 7–10% of normal, uncomplicated pregnancies [6]. Furthermore, elevation of inflammatory markers such as the ESR (up to about 40 mm/h) [7] and the CRP (typically in the range of 2–5 mg/L) is typical [8,9]. This creates a challenge for the clinician given that the tests we use to monitor underlying disease activity may not be reliable during pregnancy. On the other hand, normal pregnancy typically involves increased synthesis of complement components by 10 to 50% [10–12]. Thus, complement levels can still be helpful in monitoring disease activity during pregnancy.

1.4. Pregnancy complications that mimic rheumatic disorders

Pre-eclampsia, eclampsia, and HELLP syndrome can mimic SLE or vasculitis flares. Moreover, pre-eclampsia, can complicate 13 to 35% of SLE pregnancies in SLE compared to 5 to 8% of pregnancies in the general US population [13–15]. In these patients, pre-eclampsia can present early during pregnancy and the differentiation of pre-eclampsia from a severe lupus flare and/or lupus glomerulonephritis can be extremely difficult. Both pre-eclampsia and SLE flares may present with

increasing proteinuria, hypertension, lower extremity edema, thrombocytopenia, and a deterioration in renal function. HELLP syndrome, another complication seen in 0.5% to 0.9% of pregnancies [16], may also present with increased incidence and severity in patients with antiphospholipid syndrome [17]. Thrombotic thrombocytopenic also occurs in SLE patients during pregnancy [18]. Catastrophic antiphospholipid syndrome, a rare thrombotic microangiopathic syndrome affecting at least three organ systems, has likewise been reported [19]. Clinical features that can help to distinguish pre-eclampsia, HELLP syndrome, and eclampsia from SLE and/or lupus nephritis are summarized in Table 1.

1.5. Immunological changes during pregnancy

Immune modulation is necessary to maintain pregnancy. Theories for how the fetus, a semi-allogenic transplant, is not rejected by the mother's immune system, include expression of non-classical MHC class I by the trophoblast, and diminished levels of circulating natural killer cells [20]. While this remains an area of active research, what seems likely is that fetal success depends on early immunological modifications of the innate and adaptive immune systems, and changes in the regulatory T cell subset, both of which induce maternal tolerance to the semi-allogenic fetus [21,22]. The most significant immunologic change in normal pregnancy seems to involve a hormone-induced shift towards humoral immunity (causing increased T helper type 2 cytokine production), which in turn inhibits cellular immunity (or Th1 cytokines) [23]. Th-2 anti-inflammatory cytokines (including IL-3, IL-4, IL-5, IL-10, IL-13 and Gm-CSF) have been shown to be involved in humoral-mediated immunity and are likely involved in placental growth and preventing fetal rejection [21–22,24]. Furthermore, there appears to be an interplay between the Th1/Th2 shift and the hormonal changes of pregnancy which correlate with the progressive increase of the

hormones progesterone and estrogen as well as endogenous glucocorticoids [25].

The role of regulatory T cells, a subset of inhibitory CD4+ helper T cells that decrease the immune response to infection, inflammation, and autoimmunity, has also been implicated in the development of maternal–fetal tolerance [26]. A recent murine model of mice lacking the ability to induce regulatory T cells demonstrated increased activated T cell infiltration into the placenta leading to spontaneous abortions [27]. While the mechanisms of immune tolerance during pregnancy need further elucidation, it is clear that these alterations in the immune system can impact the course of underlying rheumatological disorders.

2. Relationship between pregnancy, RA, and SLE

A significant beneficial effect of pregnancy is observed in patients with RA, whereas patients with SLE show either no particular effect or an aggravation of symptoms during pregnancy. The diminished cellular immune response observed in pregnancy may explain the amelioration of disease generally observed in RA patients while the overexpression of Th2 cytokines may trigger an increased autoantibody response and disease activity in women with SLE [28–30]. This section will further explore the relationship between pregnancy, RA and SLE, and will discuss obstetric and fetal outcomes in patients with these diseases.

2.1. Relationship between RA and pregnancy

Older literature [31–33] reported improvement of disease activity in RA patients, suggesting improvement in 54–83% of RA symptoms during pregnancy [34]. More recent prospective studies of larger sample sizes of pregnant women who

Table 1 Differentiation of pre-eclampsia, HELLP syndrome, active lupus nephritis, thrombotic thrombocytopenic purpura, and catastrophic APS.

	Pre-eclampsia	HELLP ^a syndrome	Active lupus nephritis	Thrombotic thrombocytopenic purpura	Catastrophic antiphospholipid syndrome
Timing relative to pregnancy	>20 weeks gestation	>34 weeks, postpartum	Any gestational age	Late second to early third trimester	Second or third trimester, postpartum
Other organ involvement	Absent	Absent	Present	Present	Present
Elevated creatinine (>1.2 mg/dl)	Typically absent	Rare	Common	Variable	Variable
Thrombocytopenia	Absent	Present	Present	Present	Common
Neutropenia	Absent	Absent	Present	Not reported	Not reported
Microangiopathic hemolytic anemia	Absent	Present	Variable	Present	Variable; present if concomitant HELLP or TTP
Complement levels (C3,C4)	Normal	Normal	Typically decreased	Normal	Normal
Elevated liver enzymes	Absent	Present	Absent	Uncommon	Not reported
Active urinary sediment	Absent	Absent	Common	Common	Common
ADAMS-T13 <5%	Absent	Absent	Absent	Common	Not reported
Serum uric acid	Increased	Increased	Normal	Not reported	Not reported

^a HELLP = hemolysis, elevated liver enzymes, and low platelet count.

were monitored closely from before pregnancy until 6 months after delivery showed improvement in 62% of women with decreased arthralgias, joint swelling, and morning stiffness [35,36]. These studies also demonstrated that complete remission of RA occurred mainly in the third trimester; nonetheless, 57–80% of patients experienced initial arthritis relief in the first trimester [34]. These studies also noted that once improvement occurs it usually persists and often becomes more complete as gestation progresses. These improvements were not associated with changes in levels of anti-citrullinated protein antibodies or rheumatoid factor. Furthermore, a recent Dutch study showed that women with RA who were negative for both rheumatoid factor and anti-citrullinated protein antibodies were more likely to have improvement in RA symptoms during pregnancy compared to women who are antibody positive (75% versus 39%) [37]. Postpartum, however, there is a transient increased risk of developing RA or exacerbating already established RA, particularly in the initial 3 to 12 months postpartum [34,38]. Other studies have demonstrated that the risk of developing RA is modestly reduced after the first postpartum year although this finding remains controversial [39–41].

Three potential etiologies of the increased risk of disease development in the first postpartum year include: 1) the concept of microchimerism, which describes the role of fetal cells persisting in the maternal circulation and leading to the development of RA, 2) the effect of parity, and 3) the role of lactation.

2.1.1. Concept of microchimerism in the development of RA
RA is associated with various HLA allelic variants that encode a so-called 'shared epitope' [42]. Given that a proportion of RA patients do not possess the shared epitope, the development of RA in these patients could be due to the migration of shared epitope containing fetal cells to the mother during pregnancy—the concept of fetal microchimerism [43,44]. However, the results are conflicting and fetal microchimerism has also been suggested to confer a protective role against developing RA. One recent study suggested that fetal cells in the mother may confer a vaccine-like protection on both RA development not only during pregnancy but also for 1 to 5 years following the last pregnancy [45]. Thus, the role of fetal microchimerism in the development of RA during and after pregnancy is unclear.

2.1.2. Role of parity

The effect of parity on the development of RA has also been studied but has yielded disparate results. Some studies have found that nulliparity is protective against developing RA [46,47], while others suggest that it is a risk factor for the development of RA [48,49], and still others demonstrate no significant relationship between parity and RA risk [50,51]. One recent prospective case–control study of women with newly diagnosed RA showed a significantly decreased risk of RA in parous women compared to nulliparous women [45]. The risk reduction for RA in parous women correlated with maternal age, and was shown to be significant for women younger than 45 years of age. This study also showed that shorter time interval from last childbirth strongly and significantly correlated with reduced RA risk. In another recent prospective study of women with recent onset inflammatory polyarthritis, women with at least one or more births prior to

symptom onset were shown to have less functional disability over time and milder disease activity than nulliparous women [52]. This suggests that being parous may not only reduce RA risk but also improves functional status.

2.1.3. Role of lactation

The increased risk of RA disease onset after delivery could be related to lactation. One study found that breastfeeding increases the risk for the development of RA within the first year after a first pregnancy, possibly due to the pro-inflammatory role of elevated prolactin levels [53]. In contrast, data from the Nurses' Health Study demonstrated that breastfeeding for at least 12 months was inversely related to the development of RA, with an effect that appeared to be related to the duration of nursing [54]. These conflicting results underscore the complexity of trying to understand the role of lactation in the risk of development of RA.

2.1.4. Pregnancy outcome in RA patients

While the traditional teaching is that there is no risk to pregnancy outcome in women with RA, a recent study challenges this belief. In a series of 128 first births and 151 subsequent births of Norwegian women with chronic inflammatory arthritides, a higher frequency of premature rupture of the membranes, premature births, lower birth weight, higher perinatal mortality, and cesarean section rate was reported when compared to 335,249 first births and 464,751 subsequent births in reference subjects. However, only the lower mean birth weight and elective cesarean section rate were statistically significant [55]. These findings must be interpreted with caution as there was no data on medication use during pregnancy that could potentially influence birth weight and no data on patient and physician preference in regard to elective cesarean section rate. Another study did demonstrate that lower birth weights were independently associated with disease activity [56].

2.2. Relationship between SLE and pregnancy

Women with SLE typically have normal fertility [57] but may have complicated pregnancies. Unlike in RA, some studies report increased SLE disease activity during pregnancy. Furthermore, there are more pregnancy complications seen in SLE as upwards of one third of pregnancies in SLE patients will result in preterm birth, one third will result in cesarean section, and one fifth or more will be complicated by pre-eclampsia [58].

The mechanisms underlying the interaction of pregnancy and SLE are complex. SLE is characterized by a predominant humoral response characterized by Th2 cytokine-driven disease [29], which is similar to the immunologic state of pregnancy. In particular, overexpression of Th2-type cytokines, including IL-10, seems to play a central role in the pathogenesis of SLE as well as in inducing disease flares [59]. IL-6, another Th2 cytokine, has been shown to be a potent contributor to the differentiation of Th0 into Th2 cells and increased levels of this cytokine have been measured in SLE patients with active disease [60].

The potential worsening of lupus during pregnancy may also be due to increased sex hormone levels [61]. During pregnancy, estrogen levels progressively increase, and in animal models,

there has been suggestion that elevated estrogen levels are associated with increased lupus activity [62].

2.2.1. SLE disease flares during pregnancy

Clinically, there are contradictory findings in the literature regarding whether lupus flares are more common in pregnancy compared to the non-pregnant state. This controversy may be partially explained by differences in the definition of a lupus flare, assessment of disease activity, and the challenge of differentiating normal pregnancy related complications from increased lupus activity. To address these challenges in assessing flare rate, there have been numerous efforts to create a pregnancy-related version of SLE disease activity indexes such as the ECLAM, SLEDAI, SLAM and LAI, to make studies more comparable. Despite these efforts, results from recent observational and prospective studies demonstrate unclear results, with some studies suggesting that there is an increase in flare rate of SLE during pregnancy whereas others report an unchanged SLE flare rate during pregnancy [63–70]. Nonetheless, the pendulum seems to have swung to the side of those who hold that overall, lupus does flare during pregnancy [63]. Measurable SLE disease activity is thought to be present in 40%–50% of pregnancies, with the most common manifestations being lupus nephritis, cutaneous disease, arthritis, and hematologic disease, namely thrombocytopenia [71]. Up to 75% of SLE patients who flare during pregnancy will have lupus nephritis [71]. There is further disagreement regarding the timing of flares. Some have suggested that lupus flares are thought to occur at any time during pregnancy, whereas others suggest there may be an increased risk during the third trimester as well as in the first few months postpartum [66,72,73].

A point on which there seems to be general agreement is that the risk of flare during pregnancy is increased in SLE patients who have had active disease within six months prior to conception [63,74], in those who discontinue disease modifying medications such as hydroxychloroquine [74] or in those with active glomerulonephritis at the time of conception [75]. Patients who start a pregnancy during a period of stable remission and who continue their SLE medications experience few flares that are mostly mild and readily controlled with a small increase in prednisone dose [74]. This highlights the importance of preconception counseling of all patients with SLE, careful evaluation of the mother's condition before pregnancy, and monitoring throughout the entire duration of the pregnancy.

The other major risk factor for flare during pregnancy is a history of active renal disease in the six months prior to conception. Patients with active lupus nephritis not only have an increased risk of disease flare but also are more likely to progress to ESRD. This progression is more likely in those with more severe underlying disease and those patients with baseline creatinine values greater than 1.4 mg/dl [76]. Patients with preexisting hypertension, proteinuria, and azotemia are also at increased risk for renal exacerbations [77]. Thus, pregnancies in women with lupus nephritis should be planned, preferably after six months of quiescent disease.

2.2.2. Pregnancy outcomes in women with SLE

Women with SLE have been shown to have a 2 to 4-fold higher rate of pregnancy complications than the non-SLE population [78]. For example, pre-eclampsia occurs in upward of 23% of

women with SLE (in particular to those with co-existing antiphospholipid syndrome) versus 7% of control populations. Additional risks to the mother include gestational diabetes, hypertension, pre-term labor, and higher cesarean section rates [78]. These data are somewhat difficult to interpret as they do not account for medication use of patient and physician preference in terms of timing and type of delivery. While several studies have suggested a fetal sex ratio disparity in patients with SLE, proposing that fewer males are born to women with SLE, a recent study did not confirm this finding [79].

2.2.3. Fetal outcomes in patients with SLE

Pregnancy loss, which remains one of the most concerning complications of pregnancy, can be seen with increased frequency in patients with SLE. Notably, this frequency has dropped significantly over the past few decades from levels as high as 43% in the 1960s to 17% in the early 2000s [80]. In SLE patients, approximately 20% of pregnancies will result in miscarriage (a pregnancy loss before 20 weeks gestation) or stillbirth (a pregnancy loss after 20 weeks gestation) [81]. Compared to the general population, the risk of miscarriage is not significantly elevated, however the risk of stillbirth is still significantly higher. The elevated risk of stillbirth is thought to be due to two major risk factors; increased lupus activity and the presence of antiphospholipid antibodies [82,83]. The most common fetal morbidity in lupus pregnancy is prematurity or intrauterine growth restriction [84]. Fetal growth and development is most often threatened by disease activity, impaired maternal renal function, or presence of aPL [85].

Patients with a combination of either high clinical activity of SLE and low complement or positive anti-dsDNA have the highest rate of pregnancy loss and preterm birth [86,87]. Active underlying renal disease in the six months prior to conception or during pregnancy can also lead to increased risk for fetal complications, including spontaneous abortion, premature delivery, intrauterine growth retardation, and pre-eclampsia [88]. Placental pathology such as decidual thrombi, infarction, and vasculopathy can cause poor outcomes in lupus pregnancies, irrespective of the presence of antiphospholipid antibodies. The placental injury may stem from hypercoagulability, hypertension, or immune-mediated vessel damage [89,90]. In addition to underlying disease, medications such as glucocorticoids and other immunosuppressive agents can contribute to an increased risk of prematurity, small-for-gestational age infants, and increased cesarean section rate.

Fetuses of mothers who are shown to have positive anti-Ro and/or anti-La antibodies have a 2% risk for photosensitive rash, thrombocytopenia, liver function test abnormalities, and congenital heart block [91]. With the exception of congenital heart block, the other clinical manifestations are thought to resolve by 4 to 6 months. In those women who have had a previous child with one of these complications, the risk of reoccurrence in a subsequent pregnancy is 17% [92]. While we advocate monitoring anti-Ro and anti-La antibody exposed fetuses from 18 to 26 weeks of gestation for the development of congenital complete heart block, to date there is no proven therapy to prevent this disorder [93]. Nonetheless, recent data suggest that women with anti-Ro and anti-La antibodies who were taking hydroxychloroquine

during pregnancy may have a reduced incidence of congenital complete heart block [94].

3. Management of rheumatic disease in pregnancy

There are several principles that are important in managing women with rheumatic diseases during pregnancy. First, a team approach involving the patient, the obstetric care provider, and the rheumatologist should be employed. Close follow-up with good communication is essential for a good pregnancy outcome for both the mother and the fetus. Whether a patient needs to be followed by an obstetrician who specialized in maternal–fetal medicine is dependent on the patient's diagnosis, disease severity, and prior pregnancy history. Second, it is important to understand both the patient's and provider's tolerance for risk when it comes to management decisions. No treatment or medication is risk-free and patients and prescribing providers need to understand their own sentiments regarding the use of specific medications during pregnancy. Third, if possible, pregnancies should be planned. This helps insure that patients are under good disease control with medications that can be adjusted or used during pregnancy prior to conception. Increased disease activity at the time of conception portends poor outcomes no matter what the underlying rheumatologic disorder. Finally, the provider and the patients should discuss a management plan that will be comfortable to all for use in the case of a flare during pregnancy. Postpartum monitoring in these patients is also essential, as disease flares and thromboembolic complications can occur within six months following delivery [70].

Deciding on an appropriate medication use during pregnancy is a challenge as there is a paucity of data regarding the safety of medications during pregnancy. This lack of data is primarily due to the ethical and logistical constraints of evaluating the safety of drugs during pregnancy. The drug safety information currently available is largely based on classification systems (such as the Food and Drug Administration categories), voluntary reports, or uncontrolled retrospective observational studies. This information, in turn, is often based upon animal studies in which supra-pharmacological dosing of drugs was used. Alternatively, case reports or series may inaccurately represent true risk. Not surprisingly, given the confusing nature of the risk categories, the FDA is considering new labeling for pregnancy. Attributing risk to any particular medication is tricky and the clinician is left making treatment decisions with limited data on the true risk of a particular medication. Below, we will try to synthesize information regarding drug safety with the understanding that recommendations may be in conflict with the existing FDA risk assessments. In all cases, the potential risks and benefits of each medication should be carefully discussed with patients so that they can make an informed decision.

3.1. General tenets of management of RA during pregnancy (with discussion of particular medications in Section 3.3)

Given that RA disease activity is likely to improve during pregnancy in the majority of patients, the most critical

period regarding management of the disease is in the pre-conception stage. Since several RA medications are contraindicated during pregnancy and breastfeeding, the counseling of RA patients on drug safety during pregnancy should be part of routine care of women with RA who may become pregnant. In the preconception period, the clinician should aim to discontinue also any medications with teratogenic properties, substituting safer medications to achieve low disease activity or remission.

3.2. General tenets of management of SLE during pregnancy

Diseases such as SLE and vasculitis should be in clinical remission on medications that are compatible with pregnancy for 6 months prior to conception. Baseline testing such as blood counts, antibody titers, antiphospholipid antibody status, urinalysis, renal and liver function tests, and complement levels, are helpful to attain pre-conception or very early during pregnancy so that they can be used for comparison later in pregnancy. Frequency of follow-up visits during pregnancy depends upon the underlying diagnosis and disease severity. In most circumstances involvement of a maternal–fetal medicine specialist is advisable.

Management of lupus flares in pregnancy must be individualized and take into account the severity and type of organ involvement. In general, immunosuppression with non-fluorinated glucocorticoids, azathioprine, or cyclosporine is allowable. All patients with SLE should be maintained on hydroxychloroquine during pregnancy because not only is it safe but it also reduces the risk of disease flares and potentially prevents the development of complete congenital heart block.

3.3. Specific medications for the management of rheumatologic disorders during pregnancy (summarized in Table 2)

3.3.1. Aspirin and NSAIDs and COX-2 inhibitors

Aspirin has been used for the management of pre-eclampsia and antiphospholipid syndrome. This medication is not teratogenic. NSAIDs may be used throughout the first two trimesters. After 30 weeks of gestation, there is a risk of premature closure of the ductus arteriosus and increased risk of neonatal bleeding [95]. There is insufficient data to conclude whether Cox-2 inhibitors are safe for use during pregnancy [96]. Both NSAIDs and COX-2 inhibitors should be avoided during a conception cycle as they can potentially interfere with ovulation and implantation [97].

3.3.2. Glucocorticoids

The non-fluorinated glucocorticoids, prednisone and prednisolone are frequently used for disease management in rheumatology. While these medications can increase the risk of cleft palate formation 3.4 fold if used during the first trimester, after this time the risk is of maternal gestational hypertension and diabetes as well as small for gestational age infants and premature rupture of the membranes [98]. Often, glucocorticoids are the only option and if need be can be used throughout pregnancy as long as the mother is aware of the

Table 2 Safety of drugs used to treat rheumatic diseases.

Pregnancy risk category	Drug	FDA classification for use in pregnancy	Comments
Minimal risk	Aspirin, NSAIDs	C (first two trimesters) D (third trimester)	Avoid in third trimester. Increased risk of premature closure of the ductus arteriosus and increased risk of neonatal bleeding after 30 weeks.
	Prednisone	B	Non-fluorinated corticosteroids associated with small risk of cleft palate; can be used to treat severe flares
	Hydroxychloroquine	C	Considered safe and recommended to prevent lupus flares in pregnancy.
	Sulfasalazine	B	Potential risk of fetal kernicterus or agranulocytosis following maternal use.
	Cyclosporine A	C	Monitor renal function; no known increased risk of congenital anomalies and may be used for treatment of lupus.
	Azathioprine	D	Has been safely used in transplant patients during pregnancy.
	IVIG	C	May be used for certain lupus manifestations; no known increased fetal risk.
Contraindicated	Methotrexate	X	Discontinue at least 3 menstrual cycles prior to conception.
	Leflunomide	X	Elevated fetal risk in animal studies.
	Cyclophosphamide	X	Associated with significant fetal risk. Reserved for life-threatening disease in mother.
Insufficient data	Rituximab	C	Discontinue rituximab one year prior to conception. Given paucity of safety data for biologics, recommend avoidance during pregnancy.
	Abatacept	C	
	Tocilizumab	C	
	Belimumab	C	
	Anakinra	B	
	Tumor necrosis factor-alpha blockers	B	Recommend discontinuation during pregnancy but may be used on case-by-case basis.

increased risk of cleft palate formation during the first trimester.

3.3.3. Hydroxychloroquine

Hydroxychloroquine is considered safe for use during pregnancy [99,100]. Patients with SLE in particular those with antiphospholipid antibodies and anti-Ro and anti-La antibodies should be maintained on these medications during pregnancy [101].

3.3.4. Azathioprine, mycophenolate mofetil and cyclophosphamide

The immunosuppressive agents, azathioprine and 6-mercaptopurine are currently rated category D for safety in use during pregnancy. Nonetheless, thousands of transplant patients have been maintained on these medications during pregnancy with no increase rate of congenital anomalies in offspring [102–105]. The existing evidence suggests that these medications may be used when immunosuppression during pregnancy is necessary. Similarly, cyclosporine does not lead to an increased risk of congenital anomaly and also can be used although renal function needs to be carefully monitored when this medication is used. [106]. Tacrolimus also may be used during pregnancy [107].

In contrast, mycophenolate mofetil, also considered a category D for use during pregnancy, has been linked with reports of congenital anomalies suggesting that this agent is truly teratogenic [108]. We recommend avoiding this medication during pregnancy. Cyclophosphamide should be reserved for treatment of life-threatening manifestations of lupus and

carries significant risk to the fetus especially if used during the first two trimesters of pregnancy and patients should be counseled accordingly [109].

3.3.5. Methotrexate and leflunomide

Methotrexate and leflunomide are profoundly teratogenic and should be avoided during pregnancy [110–112]. Patients on these medications should be on reliable forms of birth control. While a recent report suggested that leflunomide did not have as severely a negative impact on pregnancy, these data should be interpreted with caution as there were still a significant percentage of birth defects reported in those fetuses exposed to these medications during pregnancy [113].

3.3.6. Intravenous immunoglobulin

Intravenous immunoglobulin is indicated in the treatment of thrombocytopenia during pregnancy. While rarely used for the treatment of rheumatic conditions, no fetal adverse effects of intravenous immunoglobulin have been reported [114].

3.3.7. Tumor necrosis factor-alpha (TNF-α) blockers

The data on the safety of the TNF-α blockers during pregnancy illustrate the complexity of evaluating the safety of medications for use during pregnancy [115]. While a concerning report of two possible VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, and Limb dysplasia) syndromes occurring in fetuses exposed to TNF-α blockers was reported, subsequent analysis questioned the significance

of this report [116]. TNF- α blockers are currently considered a category B for safety in use during pregnancy. In general, we recommend the discontinuation of these medications during pregnancy given that many patients with inflammatory arthritis will get better during pregnancy. In patients who have severe inflammatory arthritis consideration can be given to maintaining them on their tumor necrosis factor- α (TNF- α) blockers during pregnancy.

3.3.8. Biologics

There are limited data on the safety of the other biologics during pregnancy [117]. Given the paucity of information on rituximab, belimumab, abatacept, tocilizumab and actemera, it is best to avoid these medications during pregnancy. In general, these medications should be discontinued up to one year (rituximab) prior to conception.

4. Conclusion

Pregnancy in a woman with rheumatic disease can have an increased risk of adverse maternal and fetal outcomes. In the past, concern for maternal and fetal health prompted physicians to advise patients with rheumatic disease to avoid childbirth and in some cases to terminate pregnancies when they occurred. More recently, both maternal and fetal outcomes have improved making pregnancy a viable option for most women with rheumatic disorders. Some diseases, such as RA and inflammatory arthritides seem to be mitigated by pregnancy while others, such as SLE, may worsen. General tenets for the management of rheumatological disorders during pregnancy include ensuring that the patient's disease is under good control or ideally in remission prior to conception. This is particularly important in patients with underlying renal disease. Understanding of what medication options are acceptable for the patient to take during pregnancy is crucial for developing a treatment plan for disease flares. In the future, newer drugs with forms that do not cross the human placenta may give us more choices for treating our rheumatology patients during pregnancy.

Appropriate counseling on treatment regimens both prior to conception and during disease is essential. One of the most important factors in ensuring a successful pregnancy in these patients is close collaboration between the maternal-fetal medicine specialist and the rheumatologist throughout the entire duration of the pregnancy. With close collaboration between specialists, pregnancy in women with SLE and RA can usually be managed successfully.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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