Management of rheumatologic disorders during pregnancy

Rheumatologic disorders disproportionally affect women during their childbearing years. In addition, rheumatologic disorders behave differently and unpredictably during pregnancy. This article will discuss the management of the more common rheumatologic diseases during pregnancy. An approach to the pregnant patient with an underlying rheumatic disorder will be discussed as well as a review of medications and their safety for use during pregnancy and lactation.

KEYWORDS: immunosuppressive agents ▪ medications ▪ pregnancy ▪ rheumatoid arthritis ▪ rheumatologic disorders ▪ systemic lupus erythematosus

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe principles of management of rheumatologic disorders during pregnancy
- Describe general strategies for management of rheumatologic disorders during pregnancy
- Describe principles of medication use during pregnancy and lactation

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Most rheumatologic disorders disproportionally affect women during their reproductive years. Thus, issues regarding childbearing and the management of rheumatic disorders during pregnancy are commonly encountered by clinical rheumatologists. Not only do clinicians make treatment decisions with the knowledge that the mother and the fetus may have competing needs, but also rheumatologic disorders behave differently and unpredictably during pregnancy. This article will discuss the management of the more common rheumatologic diseases during pregnancy. Differences in disease activity, approaches used in pregnant rheumatologic patients and medication use during pregnancy and lactation will be covered.

Pregnancy is a time of immunologic and physiologic change. The fetus is a hemiallograft and adjustments to the maternal immune system occur in order to maintain pregnancy. Explanations for why the fetus survives maternal immune surveillance vary. One thought is that since the trophoblast does not express MHC Ia antigens, the HLA antigens present in the fetus do not stimulate the maternal immune system. Another explanation is that successful pregnancy is accompanied by a suppression of cell-mediated immunity and T helper type-I cytokines such as IFN-γ and TNF-α. Additionally, lower levels of circulating natural killer cells are found during pregnancy. It is hypothesized that these mechanisms plus others help ensure fetal survival [1]. Nonetheless, these alterations in the immune system can impact the disease course of underlying rheumatologic disorders.

Physiologic changes that happen with pregnancy can cause signs and symptoms difficult to differentiate from rheumatologic disease flares. Increased blood volume with a resultant physiologic anemia occurs [2]; thrombophilia and increased co-aguability likewise happen [3]. Musculoskeletal pain can be difficult to interpret as pregnancy itself leads to joint and skeletal complaints [4]. Furthermore, laboratory testing typically used to evaluate rheumatologic disease activity may be challenging to interpret during pregnancy. For example, in healthy pregnancies the erythrocyte sedimentation rate and the synthesis of complement components both increase and therefore these tests may not be good markers for disease activity [5].

Rheumatologic disorders themselves behave differently during pregnancy. Rheumatoid arthritis tends to improve or remit in 42–70% of patients during pregnancy [6]. Other inflammatory arthritic conditions such as psoriatic arthritis also improve. On the other hand, the clinical course of ankylosing spondylitis seems to be immune from pregnancy-induced changes [7]. Collagen vascular diseases likewise behave differently during pregnancy. While there is controversy in the literature, the consensus is that moderate-to-severe systemic lupus erythematosus (SLE) tends to worsen during pregnancy while milder disease appears to have a flare rate comparable to the nonpregnant state [8,9]. In other diseases, such as progressive systemic sclerosis and dermatomyositis/polymyositis, we have limited information as these diseases tend to affect women at the tail end of childbearing years. Similarly, we have limited information regarding the course of vasculitidies during pregnancy. Finally, it is often difficult to predict how an individual patient will fare during pregnancy. What is clear though is that women whose systemic rheumatologic disease either begins during pregnancy or flares early on tend to have complicated clinical courses. This is particularly true for systemic diseases in which multiple organ systems are involved.

Principles for management

There are several principles that are useful to adhere to when treating patients with rheumatic diseases during pregnancy (Box 1). First, ideally pregnancies should be planned. This allows for adjustments in medication to occur prepregnancy. Second, disease should be in remission for 6 months prior to pregnancy. This is particularly important in individuals who have prior renal disease, SLE, mixed connective tissue disease, polymyositis/dermatomyositis or vasculitides. Disease that is active at the time of conception tends to worsen during pregnancy. Individuals who have SLE with active renal disease at the time of conception are particularly vulnerable to high pregnancy morbidity and even mortality. Ideally, patients should have a good working relationship with their rheumatologist and obstetrician and hopefully all the involved providers can work closely together. In patients with a history of moderate or severe rheumatologic disorder, a consultation with a high-risk obstetrician affiliated with a tertiary care facility is advisable. Both the patient and the clinician should discuss medication use that is acceptable to the patient during pregnancy. Patient preference and risk tolerance for medication use during pregnancy is highly individualized and impacts and limits medication use.

Box 1. Pregnancy planning.

- Disease should be in remission or under good control at the time of conception.
- Individuals with renal disease or severe vasculitis should have their disease in remission for 6 months prior to conception.
- Establish a good working relationship between the rheumatologist and the person providing obstetrical care.
- Discontinue as many medications as clinically appropriate prior to conception.

General approach to management

Since many women with rheumatoid arthritis and other forms of inflammatory arthritis will go into remission during pregnancy, in most situations one can plan to discontinue medications prior to pregnancy or at the time of conception (specifics are discussed later). Most arthritis flares can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs), beginning after implantation and up until the third trimester, and low-dose glucocorticoids. Occasionally, an individual patient's disease pattern or prior pregnancy history warrants a different approach. For example, women who have fared poorly in a previous pregnancy or who are unable to be weaned off their medications without severe disease flares may require a different approach. In these circumstances, one may elect to keep patients on their medications throughout a pregnancy with the understanding that there may be some risks associated with some of the medications that are being used. Certain medications are absolutely contraindicated (leflunomide and methotrexate) and must be discontinued.

Systemic lupus erythematosus and other collagen vascular diseases are more challenging to manage during pregnancy. Ample evidence suggests that individuals with SLE should remain on their antimalarial medications during pregnancy as these drugs may circumvent disease flares [10]. For many patients, NSAIDs until the third trimester and low-dose glucocorticoids can be used to manage disease manifestations such as mild skin rashes, joint pain and serositis. However, some patients may have severe flares that impact other organ systems. In particular, renal flares or new onset renal disease can be particularly challenging to manage. In a patient who has not had previously diagnosed renal disease who presents with manifestations of renal disease (hypertension, proteinuria or active sediment), a kidney biopsy can be done [11]. In those patients with established renal disease, differentiating renal flare from pre-eclampsia can be extremely difficult [12]. The differentiation, however, can have clinical implications because the treatment for pre-eclampsia is immediate delivery while in the case of lupus flare, one may elect to try to treat the flare with medications. In general, elevation of anti-dsDNA antibodies, low white blood cell count, low complements and active urinary sediment suggest a lupus flare while normal or elevated white blood cell counts, normal or elevated complement levels and an elevated uric acid level suggest pre-eclampsia. In both clinical situations high blood pressure and low platelets can be seen so they are not particularly useful in differentiating from these disorders. High-dose glucocorticoids, azathioprine and cyclosporine may be used to treat renal disease and severe flares. Cyclophosphomide should be avoided in all but life-threatening circumstances. Current evidence suggests that mycophenolate mofetil should also be avoided.

Medication use during pregnancy & lactation

One of the most challenging aspects of treating patients with medications during pregnancy is that there are oftentimes competing needs of the fetus and the patients. Some of the medications that we traditionally use to treat rheumatologic conditions (e.g., methotrexate and cyclophosphamide) are contraindicated during pregnancy. For other medications, such as steroids and some immunosuppressive agents (e.g., cyclosporine and azathioprine), data on their safety during pregnancy are conflicting. Furthermore, we often base our recommendations on US FDA safety in pregnancy ratings that may be based on incomplete data or animal studies (Table 1). The American College of Rheumatology published their own guidelines in 1996 but since that time many new medications have come into use [13]. Thus, the clinician is often left making treatment decisions without clear guidelines. The following section discusses the safety of the antirheumatic therapies aspirin, NSAIDs, and cyclooxygenase (COX)-2 inhibitors, antimalarials, glucocorticoids and other immunosuppressive agents, antimetabolites, cytotoxic agents, intravenous immune globulin and biologics during pregnancy (Table 2). Treatment recommendations and approaches to patients will be made wherever possible.

Aspirin, NSAIDs & COX-2 inhibitors

Aspirin, NSAIDs and COX-2 inhibitors are used liberally for pain management and control of inflammation. While these medications are teratogenic when used in high doses in animals, in humans, large case series have failed to show any increased rate of teratogenicity for aspirin and NSAIDs [14]. In fact, low-dose aspirin is part of the treatment regimen used for antiphospholipid antibody syndrome and its obstetrical complications. In humans, nonsteroidals do not cause fetal malformations but can cause premature closure of the ductus arteriosus when used during the third trimester [15] so these medications should be discontinued early in the third trimester. There are limited data on the use of COX-2 inhibitors during pregnancy. While there are no reports of teratogenicity in offspring exposed to these medications during pregnancy, these medications ought to be avoided as there is not adequate information to clearly conclude their safety. The COX-2 activity that is blocked by both traditional NSAIDs and selective COX-2 inhibitors may be necessary for implantation, thus I recommend that patients discontinue these medications during a menstrual cycle that they are trying to conceive and resume either at the time of a confirmed pregnancy test or at the start of menses [16]. The American Academy of Pediatrics considers aspirin and most nonsteroidals to be compatible with breast-feeding [17].

Antimalarials

The antimalarial agents hydroxychlorquine and chloroquine are used for the treatment of several rheumatologic conditions. Eye toxicity has been found in animals exposed to these medications *in utero* [18]. The FDA considers these medications to be a category C for use during pregnancy – a rating based upon a single case report in which congenital defects, such as retinal pigment deposition and mental retardation, and a still birth occurred in four separate pregnancies in the same woman who took 250 mg of chloroquine phosphate twice daily throught the pregnancies [19]. These medications have been used for years during pregnancy at lower doses for malarial prophylaxis with no untoward effect [20]. Several case series have shown that these medications may be used at rheumatologic doses with no increased rate of fetal malformations [21]. Clearly, practitioners believe that these medications are safe during pregnancy as a survey of North American rheumatologists revealed that 69% maintained patients on this medication during pregnancy [22]. Moreover, SLE patients who are maintained on their antimalarials during pregnancy may fare better [10]. Current evidence and practice suggests that antimalarials are compatible with pregnancy. In persons whose disease is well controlled with these medications it makes sense to continue the medications during pregnancy.

Whether one can breast-feed while on this medication is somewhat controversial as the American College of Rheumatology feels that this medication is incompatible with breast-feeding in spite of the American Academy of Pediatrics opposing view that this medication can be used in nursing mothers [1,17]. However, the consensus opinion of expert rheumatologists suggests that antimalarials are compatible with nursing [23].

Gold

Use of gold salts for the treatment of inflammatory arthritic conditions has decreased due to the widespread use of other disease-modifying antirheumatic drugs and biologics. In animals, the gold salts can cause congenital abnormalities such as hydrocephaly and hydronephrosis [24]. In humans there are limited data on pregnancies in which gold therapy was continued, thus it seems reasonable to discontinue gold

Table 1. US FDA use-in-pregnancy ratings.

Rating	Description
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus
B	No evidence of risk in humans. Either animal findings show risk but human findings do not or, if no adequate human studies have been performed, animal findings are negative
C	Risk cannot be ruled out. Human studies are lacking and results of animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk
D	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk
X	Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient

Table 2. Summary of toxicities of antirheumatic therapies in humans.

Drug	Maternal/paternal effects	Effects on fetus	Breastfeeding
Aspirin, NSAIDs	None	Premature closure of the ductus arteriosus – discontinue third trimester	Compatible
COX-2 inhibitors	None	Unknown	
Gold	None	†	Compatible
Antimalarials	May improve pregnancy outcome in SLE patients	Case reports of pigment deposition in the retina, cochleovestibular and mental retardation. Current evidence suggest that this medication is safe during pregnancy	Conflicting data but most would consider compatible
Sulfasalazine	None	Cleft palate, VSD, coarctation of the aorta reported but generally considered safe during pregnancy Oligospermia	One case report of infant with bloody stool but considered compatible with nursing
Glucocorticoids	PROM Hypertension Glucose intolerance Osteoporosis Osteonecrosis	SGA Adrenal hypoplasia Promotes lung maturity Cleft palate§ Still birth§	Crosses into breast milk at low concentration, well tolerated
Azathioprine	PROM	SGA Rated class D but used in transplant patients	Limited data‡
6-mercaptopurine		SGA Prematurity Intrauterine growth retardation Cleft palate IBD literature suggests that it may be safe	†
Cyclosporine A	Renal insufficiency	SGA Used in transplant patients during pregnancy	Limited data
Mycophenolate mofetil	†	Case report showed shortened fifth digit and other anomalies – contraindicated during pregnancy	†
Methotrexate	†	Embryotoxic Skeletal abnormalities Facial abnormalities	Contraindicated based on current literature
Leflunomide	†	Embryotoxic	Contraindicated
Cyclophosphamide	Decreased fertility in men and women	Teratogenic – contraindicated	Contraindicated
Chlorambucil	†	Teratogenic – contraindicated	Contraindicated
IVIG	†	SGA Autoantibodies but generally considered compatible with pregnancy	†
TNF-α blockers	†	VACTERL anomalies? Conflicting information recommend discontinuing	Contraindicated based on current literature‡
Rituximab	†	†	†
Abatacept	†	†	†

†No information available; ‡Conflicting information; §Theoretical risk – or case reports only.
COX: Cyclooxygenase; IBD: Inflammatory bowel disease; IVIG: Intravenous immune globulin; NSAID: Nonsteroidal anti-inflammatory drug; PROM: Premature rupture of the membranes; SGA: Small for gestational age offspring; SLE: Systemic lupus erythematosus; VSD: Ventricular septal defect.

therapy during pregnancy with the knowledge that this medication's long half-life means that significant stores of gold salts are probably still present [25]. This medication may be given to lactating mothers.

Sulfasalazine

Sulfasalazine, which was traditionally used for the treatment of inflammatory bowel disease, has been used to treat rheumatologic disorders since the 1990s. Sulfasalazine's metabolite sulfapyridine crosses the placenta and can displace bilirubin from albumin, although this may have limited clinical impact [26]. Large case series have failed to show an increased risk of teratogenicity in infants exposed to this medication *in utero* [27,28]. Some clinicians recommend additional folic acid in pregnant women on this medication as sulfasalasine can inhibit the absorption of this supplement. This medication may be used during pregnancy and is a good option for women who have active inflammatory arthritis.

Sulfasalazine interferes with both spermatogenesis and sperm motility. Therefore, we recommend discontinuing this medication for 3 months before attempting conception [29]. The American Academy of Pediatrics warns against using this medication in nursing mothers as there was one case report of bloody diarrhea in a breast-fed infant whose mother was taking sulfasalazine [30]. Nonetheless, the consensus opinion of a panel of experts is that this case report aside, this medication is compatible with nursing, although caution should be used in babies who have hyperbilirubinemia [23].

Immunosuppressive agents

Immunosuppressive agents are used in the treatment of rheumatic diseases, transplant recipients and other disorders. Owing to the number of transplant registries worldwide, we now have information on the outcomes of a significant number of pregnancies in which the mother ingested immunosuppressive agents. Glucocorticoids, azathioprine, 6-mercaptopurine, cyclosporine and mycophenolate mofetil are the major immunosuppressive agents used in the treatment of rheumatic diseases.

Glucocorticoids

Glucocorticoids are a mainstay of therapy in many rheumatologic disorders. The preparations most commonly used to treat rheumatologic disorders, prednisone and prednisolone, are not readily metabolized by the placenta and reach the fetus at very low concentration. By contrast, betamethasone and dexamethasone reach the fetus at higher concentrations and are used to hasten lung maturity in cases where premature delivery is anticipated [31]. In animals, glucocorticoids increase the incidence of cleft palate formation in offspring [32]. In humans, while there have been case reports of cleft palate occurring in infants exposed to glucocorticoids *in utero*, larger case series (mean dose 8 mg/day) have failed to substantiate this finding [33,34]. On the other hand, a meta-analysis of exposure to glucocorticoid during pregnancy calculated a 3.4-fold increased risk of cleft palate formation [35]. In addition to the potential for cleft palate development, glucocorticoids contribute to premature rupture of the membranes and small for gestational age babies, in addition to increasing maternal risk of gestational diabetes, hypertension and osteoporosis.

While the increased risk of cleft palate is a calculated risk of exposure to glucocorticoids *in utero* prior to the 14th week of gestation, the risk of teratogenicity decreases in the second trimester. Clinicians should try to use the minimal dose possible that will relieve symptoms and, for patients who have required prolonged glucocorticoid therapy, stress dose steroids should be given during labor or when a cesarean section is performed. Glucocorticoids are compatible with breast-feeding. At doses greater than 20 mg a day, breast milk produced within 4 h of the steroid dose should be pumped and discarded [36].

Azathioprine & 6-mercaptopurine

The purine analog azathioprine and its major metabolite 6-mercaptopurine are used for immunosuppression in a variety of disorders. Trophoblastic damage occurs when rats are injected with high doses of this medication [37]. In humans, azathioprine is metabolized *in vivo* to 6-mercaptopurine. However, the placenta does not metabolize azathioprine effectively and minimal amounts of the active ingredient reach the fetus [38].

While case reports of craniofacial malformations and chromosomal abnormalities have been reported in offspring exposed to azathioprine *in utero* [39], larger case series have failed to substantiate this increased risk of congenital anomalies. In 142 transplant recipients who were given azathioprine during pregnancy, there were some anomalies seen, but this was not thought to be above the background rate of congenital anomalies [40].

While small for gestational age infants and premature rupture of the membranes were reported in some of these pregnancies there has been no reports of increased number of congenital anomalies above the background rate. Although the FDA considers this medication to be class D the transplant literature suggests that azathioprine may be used in pregnant patients who require immunosuppression. 6-mercaptopurine is teratogenic in animals causing cleft palate formation, microcephaly and dilatation of the cerebral ventricles [41].

In humans, there are few case series available for review. One case series of 155 women with inflammatory bowel disease who had conceived at least one pregnancy showed that there was no difference in the number of congenital anomalies in those taking 6-mercaptopurine and those who had not [42]. Given that there are many alternatives to this medication, I would recommend discontinuing this medication during pregnancy. Men should stop this medication 3 months prior to trying to conceive [43].

Both azathioprine and 6-mercaptopurine hypothetically can cause immunosuppression in newborns and the American Academy of Pediatrics warns against using these medications in nursing mothers [17]. Nonetheless, a recent review of this topic suggests that minimal amounts of these medications reach the newborn in an active form and, therefore, the actual risk of prescribing these drugs to nursing mothers may be over stated [44].

Cyclosporine

In rodents, cyclosporine crosses the placenta in very low concentrations [45]. Pregnant rodents administered high doses (25 mg/kg/day) of cyclosporine have increased fetal mortality and renal abnormalities. In humans, there are differing opinions on whether or not cyclosporine A crosses the placenta in significant concentrations [46,47]. Regardless, there seems to be no increased risk of teratogenicity over background rates. In one study of 154 pregnancies in renal transplant patients in which the mothers were taking cyclosporine A, there was no higher rate of complications or congenital anomalies in babies exposed to cyclosporine A *in utero*. Other transplant series and registries have confirmed these findings [48]. In a report of 500 pregnancies in which mothers were taking cyclosporine there was no increased risk of congenital anomalies. Live birth rates were lower but this might reflect the sicker patient population being maintained on cyclosporine A [49]. Finally, a meta-analysis concluded that cyclosporine does not appear to be a major teratogen, although it may be associated with increased rates of prematurity [50]. The literature suggests that cyclosporine may be used for immunosuppression during pregnancy. Like azathioprine, the American Academy of Pediatrics considers cyclosporine A to be incompatible with nursing because of the risk of immunosuppression in the offspring, however, a review of the literature suggests that minimal amounts of this drug get secreted into breast milk and that it may be compatible with nursing [17,44].

Mycophenolate mofetil

Mycophenolate mofetil (Cellcept®) is a purine synthesis inhibitor that has been used to prevent organ rejection. More recently, it has been used in the treatment of lupus nephritis [51]. In animals, this agent may cause problems with meiosis [52]. In humans, there have been several case reports of congenital anomalies in offspring exposed to mycophenolate mofetil during pregnancies [23]. This medication is considered to be a category C by the FDA. Given the existing information, this medication should be discontinued during pregnancy. There are limited data on the safety of mycophenolate mofetil during lactation, therefore current recommendations are to avoid this medication in nursing mothers.

Methotrexate

Methotrexate is a folate antagonist that is the cornerstone of therapy for the treatment of rheumatoid arthritis and other inflammatory arthritidies [53]. In both rodent models and in humans, this medication is both profoundly teratogenic and abortogenic. It is now used as a nonsurgical treatment of ectopic pregnancy [54]. In both animal models and humans, severe craniofacial anomalies can occur after exposure to this medication *in utero* [55,56]. Most of the toxicity appears to occur during the sixth to eighth week of gestation and at doses greater than 10 mg a week [57,58]. The FDA considers this medication to be category X. Patients who are on this medication should use a reliable form of birth control. Men should discontinue this medication 3 months prior to attempting conception. Women should wait at least one ovulatory cycle after stopping methotrexate before trying to get pregnant. While in actuality very little of this medication gets secreted into breast milk, the current recommendations are to avoid this medication in lactating women [17].

Cyclophosphamide

Cyclophosphamide is a cytotoxic agent that is used to treat SLE renal disease and vasculitic conditions [59]. In murine models, cyclophosphomide causes chromosomal damage in embryos [60]. In humans, cyclophosphamide exposure during early pregnancy can cause congenital anomalies such as limb and digit malformation and coronary artery abnormalities [61]. There have been case reports of pregnant women being treated for Wegener's granulomatosis and Hodgkin's lymphoma with cyclophosphomide after the 17th week of gestation with no untoward affects on the fetus [62,63]. Nonetheless, cyclophosphamide should be avoided during pregnancy except in life-threatening situations. Cyclophosphamide is transferred to breast milk and should not be used in nursing mothers [17].

Cyclophosphomide can cause premature ovarian failure with resultant infertility in women. In particular, treatment of women over the age of 30 years with cumulative doses of over 10 g and greater than 15 pulses of therapy increase

the risk for infertility. This risk can be mitigated somewhat by concomitant use of lupron or oral contraceptives may offset this effect [64].

Chlorambucil

Chlorambucil is an alkylating agent that is occasionally used in the treatment of rheumatic disorders. In both rats and in humans, skeletal and renal malformations have occurred [65,66]. Given the myriad of alternative therapies this medication should be avoided during pregnancy and lactation.

Intravenous immune globulin

Intravenous immune globulin is rarely used for the treatment of rheumatic conditions, however, there are conditions such as dermatomyositis and refractory antiphospholipid syndrome in which it may be utilize. Data on its use during pregnancy are limited. Case reports suggest that it is safe and it has been used for the management of antiphospholipid syndrome and in some cases of congenital complete heart block with no adverse effects on the offspring [67,68]. There are limited data on the safety of this medication in nursing mothers.

TNF-α blockade & inhibitors

Biologics that block TNF-α have revolutionized the treatment of rheumatoid arthritis and inflammatory joint disease. While these medications are rated category B for use during pregnancy there have been two cases reported to the FDA of possible anomalies consistent with VACTERL syndrome [69]. The significance of this finding is unclear as the actual number of exposed pregnancies is unknown [70]. Nonetheless, I recommend that patients with well-controlled disease discontinue these medications during pregnancy (at least at the time of a confirmed pregnancy test) until further information is available. For patients in whom discontinuation of TNF-α blockers will precipitate a severe disease flare, I discuss the potential risks associated with continuing these medications during pregnancy with the patients and make a joint decision on management. Whether the newer PEGylated forms of these medications can even cross the placenta is unclear. Manufacturing information suggests that little if any of these preparations reach the fetus. This may imply that the PEGylated formularies will be compatible with pregnancy.

While data are limited regarding the safety of these medications in nursing mothers, current recommendations are to avoid these medications during lactaion.

Leflunomide

Leflunomide is used to treat a variety of inflammatory disorders. This extremely teratogenic (risk category is X) medication is absolutely contraindicated in pregnancy. Owing to its extremely long half-life, drug elimination with cholestyramine (8 g three-times a day given for 11 days) or waiting 2 years is currently recommended for both women and men who are on this medication and would like to become pregnant. This medication should be avoided in lactating women.

Rituximab & other experimental therapy

Current recommendations would be to avoid these medications during pregnancy as there are limited data on the safety of these medications during pregnancy. Prolonged B-cell depletion in offspring exposed to this medication during pregnancy can occur [71]. How long before conception these medications can be safely given is unclear. There are insufficient data to conclude anything regarding the safety of other newer biologics such as abatacept and tocilizimab. Given this paucity of information, these medications should be discontinued during pregnancy and lactation.

Conclusion

Developing a reasonable treatment strategy for rheumatologic patients who desire pregnancy can be difficult. Disease control, open communication between the rheumatologist, the obstetrician and the patient, and counseling prior to pregnancy are the best steps to ensuring a good pregnancy outcome. Often, disease

Table 3. Treatment recommendations.†

Symptoms/conditions	Treatment options
Mild symptoms: arthralgias, mild joint inflammation, skin rashes, mild serositis, maintenance therapy (SLE)	NSAIDs (first two trimesters only, not during ovulation if conception is being attempted) Antimalarials Low-dose glucocorticoids (<5–10 mg/day prednisone equivalent)
Moderate disease	Glucocorticoids (higher doses), sulfasalazine for inflammatory arthritis, azathioprine, cyclosporine
Severe disease	Pulse steroids, IVIG, azathioprine, cyclosporine
Life threatening	Cyclophosphamide – only in life-threatening circumstances

†Methotrexate, 6-mercaptopurine, leflunomide and chlorambucil should be avoided.
IVIG: Intravenous immune globulin; NSAID: Nonsteroidal anti-inflammatory drug; SLE: Systemic lupus erythematosus.

control in the mother must be weighed against the potential for teratogenicity of medications in the fetus. Table 3 represents one approach to the management of rheumatic diseases during pregnancy. Mild symptoms can be treated with nonsteroidals and COX-2 inhibitors up until the third trimester, or low doses of glucocorticoids. If glucocorticoids are used in the first trimester, patients ought to be counseled regarding the increased risk of cleft palate formation. Pregnant women should be educated that the use of glucocorticoids later in pregnancy can predispose the mother to gestational diabetes or pregnancy-induced hypertension. Patients who are on a stable dose of antimalarials should stay on these medications. For more active disease, higher doses of glucorticoids, azathioprine and cyclosporine may be used, although patients should be aware of the conflicting recommendations from the FDA. For severe diseases, pulse steroid therapy and intravenous immune globulin can be added. In all but life-threatening situations, cytotoxic agents should be avoided. At this point, the limited data on the biologics during pregnancy suggest that these medications ought to be discontinued during pregnancy for most patients. Most importantly, careful conversations between the patient and their treating physician(s) should occur so that potential hazards to the fetus and the mother are fully disclosed prior to the initiation of any medicinal therapy during pregnancy.

Future perspective

Many rheumatologic disorders impact women during their childbearing years. Currently, we are limited in our inability to predict which patients will go into remission during pregnancy and which patients will flare. Furthermore, data on medication safety are often limited or incomplete. As we better understand the immune mechanisms that underlie these diseases, we will hopefully have a deeper awareness of the way in which pregnancy modulates disease activity. Furthermore, drug development may lead to newer therapies that present limited risk to the fetus and newborn and therefore may be used with impunity during pregnancy and lactation.

Executive summary

Background

- Rheumatologic disorders impact women during their childbearing years.
- Rheumatologic disorders behave unpredictably and differently during pregnancy.
- Immunologic and physiologic changes that occur during pregnancy can impact rheumatologic disorders.
- Decisions regarding treatment must weigh up the risks and benefits to the mother and the developing fetus.

Principles for management

- Ideally pregnancies should be planned.
- Renal disease and systemic vasculitis should be in remission for 6 months prior to conception.
- The rheumatologist and the obstetrician should work together to manage the patient during a pregnancy.

General approach to management

- For inflammatory arthritis one can consider discontinuing medications either prior to conception or at the beginning of pregnancy as many patients will go into remission during pregnancy.
- For systemic lupus erythematosus patients, antimalarials should be continued during pregnancy. Disease should be stable or in remission for 6 months prior to conception. Close monitoring for disease activity should be performed throughout pregnancy.
- Lupus flares can be difficult to differentiate from pre-eclampsia.
- For vasculitides, disease should be in remission for 6 months prior to conception.

Medication use during pregnancy & lactation

- The competing needs of the fetus and the patient should be considered.
- Incomplete information regarding many medications makes prescribing decisions challenging.
- Nonsteroidal anti-inflammatory drugs can be used from implantation up until the third trimester.
- Glucocorticoids can be used with the caveat that there is a threefold increase risk of cleft palate formation if these medications are used in the first trimester. In the second and third trimester use of these medications are associated with increased risk of gestational diabetes and pregnancy-induced hypertension.
- Hydroxychloroquine may be used during pregnancy.
- Azathioprine and cyclosporine may be used during pregnancy.
- Methotrexate, leflunomide, penicillamine, gold, mycophenolate mofetil and cyclophosphamide should be avoided during pregnancy.

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- ▪ of interest
- ▪▪ of considerable interest

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MedscapeCME Management of rheumatologic disorders during pregnancy

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1 Your patient is a 32-year-old nulliparous white woman with systemic lupus erythematosus (SLE) who wishes to conceive. On the basis of the above review by Dr. Bermas, which of the following principles regarding rheumatologic disorders during pregnancy is most likely to apply to her disease course and management?

- ☐ **A** The course of her SLE during pregnancy is likely to be similar to her previous course
- ☐ **B** Renal disease and systemic vasculitis should be in remission for 2 months prior to conception
- ☐ **C** Once she conceives, the obstetrician alone should manage her care
- ☐ **D** Decisions regarding treatment must consider and balance the risks and benefits to the mother and to the developing fetus

2 The patient in question 1 has stable disease for 6 months on antimalarials and becomes pregnant. According to the above review, which of the following strategies is most likely to apply to management of her SLE during pregnancy?

- ☐ **A** Antimalarials should be discontinued
- ☐ **B** Lupus flares during pregnancy are easily distinguished from pre-eclampsia
- ☐ **C** She should be closely monitored for disease activity throughout pregnancy
- ☐ **D** Patients with inflammatory arthritis either remain stable or have exacerbations during pregnancy

3 On the basis of the above review, which of the following statements about medication use for rheumatologic disorders during pregnancy is most likely correct?

- ☐ **A** Glucocorticoids used in the first trimester are associated with a 3-fold increased risk for cleft palate
- ☐ **B** Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in the second trimester
- ☐ **C** Glucocorticoids used in the first trimester are associated with increased risk for gestational diabetes and pregnancy-induced hypertension
- ☐ **D** Azathioprine and cyclosporine are contraindicated during pregnancy