Chapter 14
The Medical Management of the Rheumatology Patient During Pregnancy

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Risk Assessment of Medications

Congenital anomalies occur in 3 % of normal pregnancies [1]. Therefore, risk assessment of any particular agent during pregnancy needs to take into account this background rate of teratogenicity. For many years, clinicians relied on the FDA risk categories (A, B, C, D, and X) to assess drugs for safety for use in pregnancy. As Briggs, author of the major textbook in this field, points out, these risk assessments are limited because they are "confusing and simplistic" and incorrectly gave the impression that risk increases from category to category [2]. The FDA is currently considering new labeling for pregnancy risk. The approach this chapter will take is to present the available data on medication safety in pregnancy and lactation and to synthesize the information regarding drug safety.

Each pregnant woman has her own view about assuming risk during her pregnancy. For example, some women will avoid any substance that could have potential risk during pregnancy (caffeine, over-the-counter medications, food-additives) while other women will be willing to assume some risk and modify their ingestion of these substances. Similarly, treating physicians have varying tolerance to risk. While one clinician may be willing to prescribe TNF-α blockers during pregnancy, others will be uncomfortable recommending these medications. Therefore, when approaching management decisions of rheumatic diseases during pregnancy, it is helpful for the treating clinician to be aware of both the patient's and their own risk tolerance, in addition to the available medical data. To this end, up-front discussions prior to conception or early in pregnancy regarding what medications may be used safely and comfortably in the case of a disease flare are ideal.

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Table 14.1 Basic principles of disease management during pregnancy

Know the treating clinician and patient's risk tolerance
Discuss potential medications prior to pregnancy
Disease should be in remission prior to conception
Use lowest doses of medications possible
Treat clinical manifestations, not lab test results

The ramifications of treatment choices during pregnancy differ with the various rheumatic diseases. In women with inflammatory arthritis, while disease flares can be painful and decrease functional status they rarely cause permanent joint damage. In contrast, disease exacerbations of systemic rheumatic diseases such as systemic lupus erythematosus or vasculitis can have detrimental effects on a woman's health. For example, a renal flare in an SLE patient during pregnancy not only can compromise the pregnancy but also can impact a woman's long-term renal function. Thus, decisions regarding disease management during pregnancy in these two scenarios may be decidedly different.

Many of these concerns can be avoided by making certain that disease is in remission when a pregnancy is planned, thereby minimizing medication use during pregnancy. This is particularly important in systemic disorders such as systemic lupus erythematosus and vasculitis. It is crucial for those patients with preexisting renal disease to be in remission for 6 months prior to conception to ensure a safe and successful pregnancy [3]. Treating laboratory test results without corresponding clinical manifestations is unnecessary. Likewise, empiric use of glucocorticoids or other medication without evidence of disease activity is unwarranted. Keeping the abovementioned treatment tenets in mind contributes to better pregnancy outcomes (Table 14.1).

Medications

This section will discuss individual medications' safety profiles. For a summary of this information, please refer to Table 14.2.

Aspirin, Nonsteroidal Anti-Inflammatory Drugs, COX-2 Inhibitors

Pain management for rheumatologic disorders includes aspirin, NSAIDs, and COX-2 inhibitors. Animal data on the safety of these medications for use during pregnancy rely on supra-pharmacologic dosing. Therefore, studies that focus on congenital anomalies found in utero exposed rodents may not accurately represent risk of in utero exposure in humans [4].

In humans, a large meta-analysis failed to show increased risk of fetal malformations after aspirin use during pregnancy [5]. Furthermore, aspirin has been used for the management of antiphospholipid syndrome and pre-eclampsia with no untoward effect [6].

Table 14.2 Potential side effects and toxicities of rheumatic disease medications during pregnancy and lactation

Drug	Maternal	Fetal	Breastfeeding
Minimal risk			
Hydroxychloroquine	None	None	Compatible
Sulfasalazine	None	None	Compatible
IVIG	Risk of hepatitis C	Risk of hepatitis C, SGA, autoantibodies	No data probably compatible
Heparin	Bleeding	None	Compatible
LMW Heparin	Bleeding	None	Compatible
Some risk			
Aspirin and NSAIDs	Reduced fertility	Possible increase in miscarriage Premature closure of the ductus arteriosus after 28 weeks	Compatible
Glucocorticoids	PROM, glucose intolerance, hypertension osteoporosis	SGA, adrenal hypoplasia, 3.4-fold risk of cleft palate Flourinated glucocorticoids promote lung maturity	Compatible-doses > 20 mg/day discard breast milk for first 4 h following dose
Azathioprine	None	SGA, prematurity, IUGR	Contraindicated
6-Mercaptopurine	None	SGA, prematurity, IUGR	Contraindicated
Cyclosporine A	Renal insufficiency	SGA, prematurity, IUGR	Contraindicated
Tacrolimus	None	SGA, prematurity, IUGR, transient hyperkalemia in neonates	Little transmitted in breast milk
Etanercept	None	VACTERL syndrome reported but unproven	Currently contraindicated but little absorbed by infants GI tract
Adalimumab	None		
Infliximab	None		
Certalizimab	None	Minimal placental transfer	
Colchicine	None	Limited studies without issues	
High risk			
Methotrexate		Embryotoxic skeletal and facial malformations	Contraindicated
Leflunomide		Multiple congenital anomalies	Contraindicated
Mycophenolate mofetil		Shortened digits and hypoplastic nails, auditory canal atresia, cleft lip and palate	Contraindicated
Cyclophosphamide		Micrognathia, hypertelorism ocular coloboma, SGA, limb abnormalities, coronary artery agenesis, tumors in offspring	Contraindicated
Warfarin		Embryopathy, eye defects, deafness, congenital heart disease, hypoplasia of extremities, developmental retardation	Compatible
Unknown risk			
Rituximab			Contraindicated
Abatacept			Contraindicated
Anakinra			Contraindicated
Tocilizumab			Contraindicated
Belimumab			Contraindicated

SGA small for gestational age, *PROM* premature rupture of the membranes, *IUGR* intrauterine growth restriction

NSAIDs may be used during the first two trimesters with no increased risk of fetal malformations [7]. After the 30th week of gestation, NSAIDs can contribute to the premature closure of the ductus arteriosus and increase the risk of pulmonary hypertension [8]; therefore, NSAIDs need to be discontinued prior to the 30th week of gestation to circumvent these issues.

Recently, there has been concern that use of NSAIDs early in pregnancy can increase the risk of spontaneous abortions prior to 20 weeks of gestation. One nested case–control study of 4,705 spontaneous miscarriages demonstrated an odds ratio of 2.43 for spontaneous miscarriages in those exposed to NSAIDs versus those who were not exposed [9]. In contrast, in another study of 2,780 pregnancies there was no increased NSAID exposure in the 367 women who experienced a spontaneous miscarriage [10]. Given the conflicting data, NSAIDs ought to be used judiciously during the first trimester of pregnancy and discontinued by week 28.

There is limited information on the safety of COX-2 inhibitors during pregnancy. Accordingly, use of these medications during pregnancy should be limited or avoided. In animal studies, COX-2 inhibitors can impede both ovulation and implantation [11, 12]. Thus, both NSAIDs (because of their COX-2 inhibitory effect) and COX-2 inhibitors ought to be discontinued during a conception cycle in order to circumvent ovulation and implantation issues.

The American Academy of Pediatrics considers aspirin and most NSAIDs compatible with nursing [13].

Glucocorticoids

Glucocorticoids are frequently used to control the symptoms of many rheumatologic disorders. The non-flourinated preparations, prednisone and methylprednisolone, that are generally used in rheumatology are not metabolized well by the placenta and therefore reach the fetus in low concentrations [14]. In contrast, the flourinated forms such as betamethasone and dexamethasone reach the fetus at higher concentrations and are thus used later in pregnancy to hasten fetal lung maturity when an early delivery is anticipated [15]. Animal studies of in utero exposure to glucocorticoids during pregnancy have demonstrated increased aggressive behavior in offspring [16]. There are also reports of congenital anomalies, in particular, cleft palate formation [17]. The data in humans are more equivocal. One large case series of over 800 asthmatic patients who were maintained on prednisone (average dose 8 mg) during pregnancy showed no increased rate of congenital anomalies [18]. In contrast, a meta-analysis of studies of prednisone exposure (of any dosage) during pregnancy demonstrated a 3.4 fold increased rate of cleft palate formation in offspring exposed to prednisone in utero [19]. In a more recent review of 1,449 pregnancies in which mothers used either inhaled or oral corticosteroids 1 month prior to conception through the first trimester, only one cleft palate occurred, a rate lower than the control group [20]. Based on the available data, one can conclude that there may be a small increased risk of cleft palate formation in fetuses exposed to glucocorticoid therapy during the first trimester. After 12–14 weeks of gestation,

the palate has formed and this risk ends. Glucocorticoid use during the second and third trimesters brings risks to the mother as well, such as increased incidence of pregnancy-induced hypertension, gestational diabetes, osteoporosis, and adrenal suppression. Despite these issues, glucocorticoids offer a viable option for disease management during pregnancy. For those patients who have been on steroids throughout pregnancy, stress dose steroids are indicated for labor and delivery or cesarean section.

Very little prednisone is transferred to breast milk. For those women taking under the equivalent of 20 mg of prednisone daily nursing can proceed as usual. In those women taking greater than 20 mg of prednisone, women should wait 4 h after their dose of prednisone to nurse [21].

Antimalarials

Antimalarials are used in the management of systemic lupus erythematosus and mild inflammatory arthritis. In the USA, hydroxychloroquine is the preferred form. Animal studies have demonstrated retinal toxicity in rodents exposed to antimalarials in utero [22]. Initially, hydroxychloroquine and chloroquine were considered contraindicated during pregnancy based on one case series published in 1964 detailing multiple pregnancies in the same woman who took hydroxychloroquine during pregnancy [23]. All of the offspring exposed to hydroxychloroquine developed ocular or hearing issues. However, larger case series of offspring exposed to hydroxychloroquine during pregnancy have failed to demonstrate a higher than background rate of congenital anomalies [24]. Most recently, a comprehensive review evaluated the exposure of 588 offspring born to mothers treated with either chloroquine or hydroxychloroquine. There were no cases of fetal ocular toxicity in any of these offspring [25]. This suggests that the risk of in utero exposure to antimalarials is negligible. Furthermore, a survey of North American rheumatologists revealed that most rheumatologists will maintain their patients on antimalarials throughout pregnancy [26]. Importantly, there is strong evidence that maintaining women with SLE on their antimalarials during pregnancy improves both patient and pregnancy outcomes [27]. Furthermore, recent evidence suggests that this medication may have a role in secondary prevention of congenital complete heart block (CCHB) in anti-Ro, anti-La positive women who have previously given birth to a child with CCHB [28]. Hydroxychloroquine may be continued during breastfeeding.

Sulfasalazine

Sulfasalazine is used for the management of inflammatory arthritis and inflammatory bowel disease. Sulfasalazine and its metabolite sulfapyridine do cross the placenta [29]. While birth defects have been reported in case reports of offspring whose

mothers took sulfasalazine during pregnancy [30], large studies have failed to confirm this finding. Importantly, since sulfasalazine can impede the absorption of folic acid in the gastrointestinal tract, pregnant women should take additional folic acid while on this medication [31]. Sulfasalazine is permitted in women who are breastfeeding although rarely infants may develop diarrhea.

Immunosuppressive Agents

Immunosuppressive agents are often critical in the management of SLE, vasculitis, and in some cases inflammatory arthritis. In rheumatology, azathioprine and 6-mercaptopurine, mycophenolate mofetil, cyclosporine, and tacrolimus are the most commonly used medications in this class. Most of the information on the safety of these medications during pregnancy can be gleaned from the organ transplant literature. International registries have data on thousands of offspring born to mothers with organ transplants who are usually maintained on immunosuppressive medications for the duration of pregnancy.

Azathioprine and its metabolite 6-mercaptopurine are used to manage inflammatory bowel disease and transplant rejection. In rheumatology, azathioprine is preferentially used and is administered to those with lupus nephritis, skin disorders, and vasculitis. Animal studies have demonstrated teratogenicity with azathioprine [32]. However, the human placenta lacks the enzyme that metabolizes azathioprine to its active metabolite 6-mercaptopurine; therefore, very little of the active form of this medication enters fetal circulation [33]. The gastroenterology and transplant literature provides reassuring data that in utero exposure to azathioprine does not increase the risk of congenital anomalies [34, 35]. The data on the safety of 6-mercaptopurine stems from the gastroenterology literature and while less robust than the data on azathioprine, this literature likewise suggests low risk to fetuses exposed in utero [36]. Although the food and drug administration categorizes these as category D for safety in use during pregnancy, the existing evidence suggests that these medications, in particular azathioprine, may be used when immunosuppression is required during pregnancy such as a flare or new onset lupus nephritis. This viewpoint is endorsed by the American Gastroenterological Association Institute [37]. Breastfeeding is not generally recommended for those women taking these medications, although in some circumstances, the benefit of continuing these medications during lactation may outweigh the potential risks. Cyclosporine A has been used for management of some of the renal manifestations of systemic lupus erythematosus and less frequently in inflammatory arthritis. While animal studies demonstrate suggest that this agent is teratogenic, studies in humans are more encouraging [38, 39]. As with azathioprine, very little cyclosporine A is transported across the placenta [40]. Data gleaned from transplantation registries have not shown an increased risk of congenital anomalies in cyclosporine exposed offspring [41]. However, maternal increases in creatinine in pregnant women taking cyclosporine and fetal growth restriction have been reported [41]. While not completely benign, cyclosporine can be used during pregnancy when immunosuppression is required.

The American Academy of Pediatrics does not consider cyclosporine compatible with nursing [13]. Nonetheless, other studies suggest that very little cyclosporine is detected in the blood of nursing infants whose mothers are taking cyclosporine [42].

Mycophenolate mofetil has revolutionized the way we treat lupus nephritis. While formerly, therapy was limited to high dose steroids and cyclophosphamide, studies in the past decade have proven the efficacy of this medication in both the induction and maintenance phases of lupus nephritis therapy [43]. Initially, limited data suggested that these medications could potentially be used during pregnancy; however, recent case series have suggested a fairly high rate of congenital anomalies [44]. What is particularly concerning is that a particular pattern of malformations including cleft lip and palate, micrognathia, microtia, and external auditory canals were observed [45]. The FDA now considers this medication as category D for safety in pregnancy and has mandated a patient educational program for women of child-bearing age who begin this drug. Mycophenolate mofetil is contraindicated in women who are breastfeeding.

Tacrolimus is an immunosuppressive agent that has predominately been used to prevent solid organ transplant rejection. More recently, however, this medication has been used for the therapy of lupus nephritis [46]. Several transplant series have suggested that tacrolimus is tolerated during pregnancy with few side effects and no increased rate of congenital anomalies [47, 48]. Thus, like other agents also used for the immunosuppression of organ transplant recipients, tacrolimus appears to be compatible with pregnancy. Little of this agent gets transferred to breast milk suggesting that it may be compatible with nursing [49].

Methotrexate

Since the early 1980s when methotrexate was shown to be effective in the treatment of rheumatoid arthritis, this medication has become the mainstay of therapy for rheumatoid arthritis and other inflammatory arthritides [50]. It can be used in other rheumatologic disorders as well. Methotrexate is profoundly abortogenic and teratogenic, and because of these effects methotrexate is now standard therapy for the medical termination of ectopic pregnancies [51]. In pregnant rodents, this agent causes skeletal abnormalities in the offspring and increased fetal resorption rate [52, 53]. In humans, severe cranial-facial anomalies, absent limbs, and mental retardation have been reported [54]. The peak risk period for exposure is between 6 and 8 weeks of gestation at doses of methotrexate greater than 10 mg a week [55]. Lloyd and colleagues suggest that there is no safe window, with a 10/42 chance of abnormality in a fetus exposed to methotrexate during the first trimester: they suggest discontinuing the medication for 6 months prior to conception [56]. Donnenfeld and associates suggest that the medication should be discontinued 12 weeks before conception because of the high spontaneous abortion rate [57]. Given that it may not be feasible to discontinue this medication far in advance of pregnancy, current recommendations are to discontinue methotrexate in men 3 months prior to conception

and three menstrual cycles in women. Given the extreme teratogenicity of this medication, women taking methotrexate need to be counseled about reliable contraceptive methods. Methotrexate is not compatible with nursing.

Leflunomide

Leflunomide is used to manage inflammatory arthritis and skin manifestations of SLE. Like methotrexate, this medication is profoundly teratogenic in animals [58]. There are few case reports of congenital anomalies of infants exposed to this medication in utero [59]. Recently there was a report on 45 pregnancies in which inadvertent exposure to leflunomide occurred either just prior to conception or during gestation [60]. The authors reported 2 of 16 offspring exposed to leflunomide in utero had major malformations and three more had minor anomalies. While the authors conclude that leflunomide is not a major teratogen, the numbers presented in the study suggest a higher than background rate of congenital anomaly. Thus, patients who are taking leflunomide should be carefully counseled regarding appropriate contraception. While this medication has a half-life of 15 days, its major metabolite, teriflunomide, stays in the circulation for up to 2 years. Thus, leflunomide needs to either be discontinued 2 years prior to conception, or cholestyramine washout (8 g three times a day for 11 days) must be completed. Leflunomide is not considered compatible with nursing.

Cyclophosphamide

Cyclophosphamide is generally reserved for use for SLE nephritis and vasculitic disorders. This medication is profoundly teratogenic in both animals and humans [61, 62]. In general, this medication should be avoided during pregnancy. There have been case reports of cyclophosphamide being used in the third trimester of pregnancy with no untoward effects; thus in life-threatening circumstances later in pregnancy, this medication can be considered [63, 64]. There is a significant risk of premature ovarian failure when this medication is used in premenopausal women. Age greater than 30, cumulative dose of greater than 10 g and duration of therapy are all risk factors [65]. This medication is not compatible with nursing.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) has been used for refractory thrombocytopenia and dermatomyositis. While data on the use of this medication during pregnancy are limited, there have been several case reports suggesting safety of IVIG during

pregnancy [66]. Moreover, this medication has also been used to manage refractory obstetric complications of the antiphospholipid antibody syndrome without inducing congenital malformations [67]. There is a small risk of hepatitis C exposure with IVIG use. This medication may be used during lactation.

Biologics

In the past two decades, biologics have changed the management and outcomes of rheumatic disorders. In particular, the TNF-α antagonists have revolutionized the treatment of inflammatory arthritis. The FDA has rated these medications as category B for safety in use during pregnancy. Nonetheless, in 2008, there were two potential cases of VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, and Limb dysplasia) syndrome reported [68]. Given that the true denominator of actual exposures was unknown and likely underestimated, subsequent editorials and opinion articles concluded that the risk of congenital anomalies was negligible [69]. A later analysis from the European Surveillance of Congenital Anomalies did not reveal an increased risk of congenital anomaly after in utero TNF-α exposure [70]. Preliminary data suggests that the PEGylated form of these agents may not cross the placenta in significant concentration and does not lead to an increased incidence of anomalies [71]. There are no data on safety of these agents during breastfeeding; some physicians permit use while nursing.

Rituximab

Current package insert information on rituximab is that this medication should be discontinued 1 year prior to conception. Nonetheless, several case reports have shown that this medication may be used closer to pregnancy with relative impunity [72, 73]. Given that IgG antibodies do not cross the placenta until the 12th week of pregnancy [74], little if any of this medication should reach the fetus prior to the second trimester of pregnancy. Later in pregnancy, this medication could impact the fetus's immune system as there are reports of the B-cell depletion lasting well until the first year of neonatal life [75]. There are no data on safety of breastfeeding while receiving rituximab.

Other Biologics

The safety during pregnancy and lactation of the other commonly used biologics in rheumatology including anakinra, abatacept, tocilizumab, and belimumab is unknown. Therefore, we recommend avoiding these medications during pregnancy and discontinuing these medications for at least several months prior to conception.

Anti-coagulants

In women with the antiphospholipid syndrome and other clotting disorders, anti-coagulation during pregnancy may be necessary. Warfarin, a potent anti-coagulant, is extremely teratogenic. First trimester exposure, in particular during the 6–9th weeks of gestation can lead to a pattern of anomalies including nasal hypoplasia, eye defects, hypoplasia of the extremities, deafness, and congenital heart disease [76]. While some clinicians may allow patients to stay on this medication until a positive pregnancy test, others will advocate transitioning patients to either unfractionated or fractionated heparin once conception is attempted. These latter two classes of medication are compatible with pregnancy and nursing [77, 78]. Adjustments to delivery timing and type may need to be adjusted in women taking these medications during pregnancy.

Colchicine

Colchicine is used in the management of gout and pseudogout and for familial Mediterranean fever (FMF). While crystal-induced arthropathies are rare in reproductive age women, FMF can and does occur in women of child-bearing age. One case series of 238 colchicine-exposed pregnancies did not show an increased rate of major congenital anomalies when compared with controls [79]. In another study of 179 pregnancies in which women with FMF were taking colchicine, not only was there no congenital malformation but also there was a trend towards better outcome for those women who were treated with colchicine [80]. Thus, in women who need to be on colchicine for disease management of FMF, one can consider maintaining patients on this medication during pregnancy. Data on breastfeeding while taking colchicine are limited.

Inadvertent Drug Exposure During Pregnancy

Inadvertent exposure to potentially teratogenic medications during pregnancy poses a difficult clinical challenge to the practicing rheumatologist. Patients and clinicians views on family planning are firmly grounded in religious, ethical, and cultural beliefs. Ethics literature suggests that the clinician's role is to be non-directive, providing information and support but not decisions [81]. If a drug exposure to a known teratogen occurs early in pregnancy, the clinician's role is to provide pregnant women with available information regarding other cases of exposure and potential risk. Referral to a geneticist with expertise in this area may be helpful. Later in pregnancy, a high sensitivity ultrasound to screen for potential anomalies can augment this information so that patients can make an informed decision about how they would like to proceed with the pregnancy.

Conclusion

Treating the pregnant rheumatology patient can be challenging but extremely rewarding. While not all medications can be used safely during pregnancy, most disease flares can be adequately managed during pregnancy. If possible, pregnancies should be planned so that the underlying rheumatologic disease is under good control and medications can be appropriately adjusted for safety. Ideally, pre-pregnancy evaluation with both the rheumatologist and in cases of complicated disease, a maternal–fetal obstetrical specialist, should be done. This pre-conception counseling is an ideal time to discuss and formulate a plan in case of flares.

In general, NSAIDs can be used judiciously from after implantation (first missed menstrual cycle) up until the third trimester. Glucocorticoids may be used throughout pregnancy with the caveat that patients ought to be counseled about the small increased risk of cleft palate formation in fetuses exposed during the first trimester. Hydroxychloroquine ought to be continued throughout pregnancy. The immunosuppressive medications azathioprine, cyclosporine, and tacrolimus can be used for more severe disease, while mycophenolate mofetil cannot. Methotrexate, leflunomide, and cyclophosphamide are contraindicated for use during pregnancy. Intravenous immunoglobulin can be used throughout pregnancy. Many rheumatologists will discontinue TNF-α blockers either prior to pregnancy or at the time of the first missed menstrual cycle. Based on existing literature, those patients with severe inflammatory arthritis can probably be continued on TNF-α blockers during pregnancy. The other biologics should be discontinued for several months prior to conception (Table 14.2).

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