Disease Modifying Anti-Rheumatic Drugs: Review on Pregnancy and Lactation

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ABSTRACT

Rheumatic diseases occur commonly in patients of childbearing age. The compatibility of different Disease Modifying Anti-Rheumatic Drugs (DMARDs) during pregnancy and lactation can affect the management decision when treating these patients. With the development of promising biologics DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) in various rheumatic diseases, their safety in pregnancy and lactation is an issue for both patients and clinicians. Recently, three different guidelines on the compatibility of DMARDs during pregnancy and lactation has been published by ACR, EULAR and BSR respectively. This article summarizes their recommendations on the management of patients on DMARDs during pregnancy and lactation.

Keywords: Pregnancy; Lactation; csDMARDs; bDMARDs; tsDMARDs; Rheumatic Disease.

INTRODUCTION

Disease modifying anti-rheumatic drugs (DMARDs) are a group of medications which can modify the disease progression of the rheumatic diseases, which commonly occur in patients of childbearing age. It is important to clarify the compatibility of DMARDs in pregnancy, paternal exposure and lactation as this can affect the choice of drugs. Besides conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), there are various biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) available. However, data regarding their safety in pregnancy and lactation is limited. In recent years, the American College of Rheumatology (ACR), European League against Rheumatism (EULAR) and the British Society for Rheumatology (BSR) have published their own guidelines on this aspect [1-4]. BSR has also made its recommendation on paternal compatibility on various DMARDs, which has far limited evidence available [3,4].

In a general population, it is estimated that 15 to 20% of pregnancies ended up in miscarriage and the background rate of congenital anomalies ranges between 1–5% [5-7].

Since June 30, 2015, the US food and drug administration (FDA) has adopted a new system called the Pregnancy and Lactation Labelling Rule (PLLR) to replace the previous FDA letter category which has been used since 1979 [8]. There are several reasons why the old category has been replaced. In the FDA letter category, each drug is categorized into A, B, C, D, X groups mainly based on the type of data available and the level of uncertainty, rather than the reproductive risk. However, the alphabetical order A, B, C, D, X misleadingly implies increasing risk and this has led to unnecessary switching or discontinuation of the drugs in women contemplating pregnancy or pregnant women, or even unnecessary termination of pregnancy [1,9]. The new PLLR has eliminated the letter categories and the information is expressed in

narrative descriptions with a summary statement up front, followed by a clinical considerations section and supporting data. The hope is that this can provide more comprehensive information aiding physicians in assisting patients of childbearing age with family planning [8].

MATERNAL COMPATIBILITY

The recommendations from ACR, EULAR and BSR are summarized in Table 1.

All three parties agree that hydroxychloroquine, sulfasalazine, azathioprine, cyclosporin A, tacrolimus and TNF alpha inhibitor (TNFi) are compatible or relatively low risk during pregnancy [1-3]. High-risk medications which include methotrexate, mycophenolate mofetil, leflunomide or cyclophosphamide should be avoided during pregnancy and they should be stopped before conception with various durations of time [1-3]. Medications with insufficient evidence include rituximab, belimumab, tocilizumab, abatacept, anakinra,

Table 1. Comparison between ACR, EULAR and BSR suggestions about maternal compatibility.

	ACR [1]	EULAR [2]	BSR [3, 4]
Hydroxychloroquine	Compatible	Compatible	Compatible
Sulfasalazine	Compatible	Compatible	Compatible with 5 mg folic acid/day
Methotrexate	Not compatible	Not compatible	Not compatible, stop at least 3 mths before conception
Leflunomide	Not compatible	Insufficient data	Not compatible
Azathioprine	Relatively low risk	Compatible	Compatible if < 2 mg/kg
Cyclosporin A	Relatively low risk	Compatible	Compatible
Tacrolimus	Relatively low risk	Compatible	Compatible
Mycophenolate mofetil	Not compatible	Not compatible	Not compatible, stop at least 6 wks before conception
Cyclophosphamide	Not compatible	No. Or for severe, refractory maternal disease in 2 nd , 3 rd trimester if indicated.	Not compatible
Intravenous immunoglobulin	Not mentioned	Compatible	Compatible
TNF alpha inhibitor	Comment as a group, compatible, stop at 30–32 wks		
Infliximab		Compatible up to 20 wks	Compatible but stop at 16 wks
Etanercept		Continued up to 30–32 wks, if indicated, can continue throughout pregnancy	Compatible but stop at 3 rd trimester
Adalimumab		Compatible up to 20 wks	Compatible but stop at 3 rd trimester
Certolizumab		Compatible throughout pregnancy	Compatible
Golimumab		Limited data, alternative should be considered	No data
Rituximab	Insufficient data	Stop unless no other alternatives	No, stop at least 6 mths before conception
Belimumab	Insufficient data	Stop unless no other alternatives	No
Tocilizumab	Insufficient data	Stop unless no other alternatives	No, stop at least 3 mths before conception
Abatacept	Insufficient data	Stop unless no other alternatives	No
Anakinra	Insufficient data	Stop unless no other alternatives	No
Ustekinumab	Insufficient data	Stop unless no other alternatives	Not mentioned
Tofacitinib	Insufficient data	Insufficient data, stop 2 mths before conception	Not mentioned

ustekinumab and tofacitinib. They should be avoided during pregnancy if possible [1-3].

Methotrexate (MTX) is contraindicated in pregnancy due to high risk of miscarriage (25%) and congenital malformation (9–17%), which includes cleft palate, hydrocephalus, anencephaly, meningoencephalocele, congenital stenosis of tubular long bones and abnormal facial features (low-set ears, micrognathia) etc. [10,11]. It is recommended to be stopped for 3 months before conception [3]. For women who have received low-dose MTX within 3 months prior to conception, folic acid 5 mg per day should be prescribed prior to and throughout pregnancy. MTX is a folic acid antagonist and may theoretically induce maternal folic acid deficiency which may be harmful to the fetus [3,12]. For those with accidental pregnancy, MTX should be stopped immediately and folic acid 5 mg per day should be prescribed [3]. Obstetrician should be informed to evaluate the fetal risk.

Leflunomide (LEF) is a high-risk medication according to ACR while both EULAR and BSR do not recommend leflunomide in pregnant women due to insufficient evidence. It has demonstrated embryotoxicity and marked teratogenicity, including neural tube defects, cleft palate and limb malformations in animal studies [10]. For women wishing to get pregnant, they should undergo either washout with cholestyramine (8 g TDS for 11 days) or drug discontinuation for 2 years prior to conception and a drug level check before pregnancy [1]. For those women taking leflunomide with accidental conception, leflunomide should be stopped immediately and cholestyramine washout should be administered until undetectable plasma levels are achieved [3]. According to leflunomide registry, women exposed to leflunomide in early pregnancy who undergone cholestyramine washout show no increase in adverse pregnancy outcomes [13].

Mycophenolate mofetil (MMF) is associated with miscarriage and congenital malformation including cleft lip and palate, anomalies of the distal limbs, heart, esophagus and kidneys [2,14]. A possible characteristic phenotype including cleft lip and palate, microtia, and external auditory canals has been reported in six cases [15]. It is contraindicated during pregnancy and should be withdrawn at least 6 weeks before pregnancy [2,3,16]. MMF has been demonstrated to have drug-drug interaction with combined oral contraceptives

and significantly lower the level of the levonorgestrel level by 15% [16]. It is important to inform women on MMF that the drug may decrease the effectiveness of oral contraceptives and they should seek alternative contraception [16].

Cyclophosphamide can cause congenital malformations with a specific pattern termed “cyclophosphamide embryopathy”, which includes growth restriction, ear and facial abnormalities, absence of digits and hypoplastic limbs [17]. According to the drug information, female should avoid pregnancy for up to 1 year [18]. The risk of teratogenicity is highest during the 1st trimester. Its use in the 2nd and 3rd trimesters may be associated with low birth weight and neonatal pancytopenia. Its use might be justified in life-threatening conditions after the 1st trimester [2,19,20]. Because cyclophosphamide can induce infertility, it is necessary to inform patients and discuss the various methods to preserve fertility. For females, feasible methods include cryopreservation of embryos or mature oocytes. Gonadotropin-releasing hormone (GnRH) agonists theoretically suppress ovarian function and may protect the ovary from toxic insult. However, the ovarian follicles remain exposed to the DNA damaging effect and its benefit is unproven. It should be used 10 to 14 days prior to initiation of cyclophosphamide [21].

Sulfasalazine has not been shown to have any increase risk for miscarriage or congenital malformation. Although neural tube defects have been reported, the causal relationship has not been established. Sulfasalazine inhibits absorption and metabolism of folic acid and periconceptional folic acid supplementation can decrease the risk of neural tube defects. It is recommended that folate supplement 5 mg per day should be prescribed with sulfasalazine throughout the pregnancy [2,3].

For biologics, which are either monoclonal antibodies or fusion proteins, the placental transfer to the fetus is related to the Fc portion. Neonatal Fc receptors (FcRn) bind the Fc portion of IgG and transport the antibodies across the placenta. The FcRn is not expressed by the placenta in the 1st trimester but its expression increases with gestational age and IgG is efficiently transferred across placenta during the 3rd trimester, hence causing elevated maternal IgG levels in the newborn [22,23]. This affects the compatibility of biologics during pregnancy.

For TNFi, they do not associate with miscarriage and major birth defects [2,3]. However, the extensive placental transfer to fetus during the 3rd trimester might cause immunosuppression of the newborn and increase the risk of postnatal infection [1,2]. It has been reported that a newborn exposed to infliximab throughout the pregnancy died of disseminated *Bacillus Calmette-Guerin* following BCG vaccination at 3 months old [24]. In order to minimize in utero exposure, different guidelines have different suggestions at the time to stop the biologics (Table 1). Infliximab has prolonged bioavailability and high rate of placental transfer and hence it should be stopped from 16 weeks of gestation for it to be undetectable in cord blood at delivery [3]. It is recommended to postpone the administration of live vaccines (e.g. BCG, rotavirus) in infants who have been exposed to TNFi in utero throughout the pregnancy till 6 months after birth [1-3] as TNFi (infliximab, adalimumab) can be detected in newborn blood up to 6 months after delivery [25].

Certolizumab is a synthesized pegylated Fab fragment without Fc portion so it would not be actively transferred across the placenta [1,10]. It is compatible with all three trimesters of pregnancy [2]. However, there is still a low placental transfer of the drugs via passive diffusion across the placenta and the safety of administering live vaccine in exposed infants is unknown [1,26]. According to latest version of drug labeling, it is recommended to wait a minimum of 5 months following the mother's last dose during pregnancy before administration of live vaccine.

For etanercept, its Fc portion is modified and its binding to cytotrophoblasts is not effective. Transplacental passage of etanercept to the neonate is less efficient and the cord etanercept levels is only 3.6–7.4% of maternal drug levels [27,28]. EULAR suggests that it can be continued up to 30 to 32 weeks of gestation and if indicated, it may be considered for use throughout pregnancy due to low rate of transplacental passage [2].

For golimumab, there are no adequate and well-controlled studies in pregnant women and hence data to support its use during pregnancy are lacking and alternatives should be used [2]. It should be used during pregnancy only if clearly needed.

For rituximab, belimumab, tocilizumab, abatacept, ustekinumab and anakinra, while unintentional exposure early in the 1st trimester is unlikely to be

harmful, there was insufficient data to recommend these medications during pregnancy [1-3]. Rituximab, belimumab, tocilizumab, abatacept and ustekinumab should be stopped at least 6 months, 4 months (after last dose), 3 months, 14 weeks (after last dose) and 15 weeks (after last dose) before conception respectively [3,29-31]. There is no published information to suggest how long anakinra should be stopped before conception.

For tofacitinib, animal studies show fetocidal and teratogenic effect at exposures higher than the maximum recommended human dose (MRHD). There are also reductions in live litter size, postnatal survival, and pup body weights at exposures higher than the MRHD [32]. EULAR has reviewed one case series (abstract) which includes 27 pregnancies. There is a higher miscarriage rate but there is concomitant MTX exposure. There is no increased rate of congenital malformation. Because of insufficient data, it should be stopped 2 months before conception [2].

PATERNAL COMPATIBILITY

For paternal compatibility, only BSR has made its suggestion and it is summarized in Table 2. However, it should be emphasized that most of the suggestions are based on limited evidence and the information should be interpreted with caution.

BSR concludes that hydroxychloroquine, sulfasalazine, azathioprine, cyclosporin A, tacrolimus, methotrexate, leflunomide, mycophenolate mofetil, intravenous immunoglobulin, infliximab, etanercept, adalimumab and rituximab are compatible with paternal exposure [3]. Cyclophosphamide is regarded as high-risk medication and it should be avoided [3]. Medications with insufficient evidence include certolizumab, golimumab, belimumab, tocilizumab, abatacept, anakinra, ustekinumab and tofacitinib. They should be avoided if possible [3].

Sulfasalazine is compatible with paternal exposure based on low quality studies. However, it is associated with oligospermia, reduced sperm mobility and increase proportion of abnormal sperm. The effect is reversible and sperm quality improves if the drug is stopped for more than 12 months [3].

For IVIG, there is no study to assess the paternal exposure. However, based on maternal compatibility, BSR comments that it is unlikely to be harmful and compatible with paternal exposure [3].

Table 2. BSR suggestion of paternal compatibility.

	BSR suggestion [3]	Studies	No. of subjects
Hydroxychloroquine	Yes, limited data	1 cohort, 1 case series	13
Sulfasalazine	Yes	3 cohort, 1 case control	237
Methotrexate	Yes	4 cohorts, 3 case series, 1 case report	263
Leflunomide	Yes, limited data	1 cohort, 1 case report	2
Azathioprine	Yes	6 cohort, 1 case control, 2 case series	602
Cyclosporin A	Yes, limited data	2 cohort, 2 case series	254
Tacrolimus	Yes, limited data	3 cohort	120
Mycophenolate mofetil	Yes, limited data	3 cohort	72
Cyclophosphamide	No	No study identified	
IVIG	Yes	No study identified	
Infliximab, Etanercept, Adalimumab	Yes, limited data	5 cohort, 2 case series, 1 case-control study	131
Certolizumab	No data		
Golimumab	No data		
Rituximab	Yes, limited data	1 cohort	11
Belimumab	No data, unlikely to be harmful		
Tocilizumab	No data, unlikely to be harmful		
Abatacept	No data, unlikely to be harmful		
Anakinra	No data, unlikely to be harmful		

For the risk of paternal exposure with methotrexate, drug labeling from FDA suggests men should wait at least 3 months before conception [34]. BSR has reviewed 4 cohorts, 3 case series and 1 case report including 263 pregnancies; it has concluded that low-dose MTX may be compatible with paternal exposure [3].

For leflunomide, although BSR comments that it may be compatible with paternal exposure, the suggestion is based on 1 cohort and 1 case report which only included 2 pregnancies with paternal exposure to leflunomide within 3 months of conception and subsequent paternal exposure in at least 1 case with no reported washout. There is no adverse fetal outcome identified [3]. As the drug is detected in human semen and animal studies have not been conducted, drug labeling of teriflunomide (active metabolite of leflunomide) suggests that men wishing to father a child should undergo washout or wait until verification that the plasma drug metabolite concentration is less than 0.02 mg/L [33].

For cyclophosphamide, there is no established human data. However, study of male rats shows that there are higher rates of fetal loss and malformations. According to drug labeling from FDA, male patients should avoid conception for up to 4 months [35]. It can also decrease fertility in men. Cryopreservation of semen can be considered to preserve male fertility. Testosterone 100 mg IM every 15 days may be useful as shown in a small study [36].

It should be noted that tofacitinib and ustekinumab are not reviewed by BSR. There is a cohort study of prenatal (maternal/paternal) exposure to tofacitinib in patients with ulcerative colitis. It identifies 14 cases with paternal exposure and no congenital malformation is found [37]. There is no study for ustekinumab on paternal exposure.

BREASTFEEDING

The compatibility of DMARDs with breastfeeding is summarized in Table 3.

Table 3. Summary of ACR, EULAR, BSR compatibility of DMARDs with breastfeeding.

	ACR [1]	EULAR [2]	BSR [3]
Hydroxychloroquine	Compatible	Compatible	Compatible
Sulfasalazine	Compatible	Compatible	Compatible
Methotrexate	Incompatible	Avoid, limited data	Incompatible
Leflunomide	Incompatible	Avoid, no data	No data
Azathioprine	Insufficient data	Compatible	Compatible
Cyclosporin A	Insufficient data	Compatible	Compatible, limited data
Tacrolimus	Insufficient data	Compatible	Compatible, limited data
Mycophenolate mofetil	Incompatible	Avoid, no data	Incompatible
Cyclophosphamide	Incompatible	Avoid, limited data	Incompatible
IVIG	Compatible	Compatible	Compatible
TNFi	Not mentioned	Compatible	Compatible except golimumab
Rituximab	Insufficient data	Avoid, no data	No data
Belimumab	Insufficient data	Avoid, no data	No data
Tocilizumab	Insufficient data	Avoid, no data	No data
Abatacept	Insufficient data	Avoid, no data	No data
Ustekinumab	Not mentioned	Avoid, no data	Not mentioned
Anakinra	Not mentioned	Avoid no data	No data
Tofacitinib	Insufficient data	Avoid, no data	Not mentioned

Hydroxychloroquine and sulfasalazine are compatible with breastfeeding. However, for sulfasalazine, its active metabolite can displace bilirubin and it should be avoided in premature infants, infants with hyperbilirubinemia or infants deficient in G6PD [46]. For azathioprine, cyclosporin A and tacrolimus, ACR suggests that further research is necessary and breastfeeding should be avoided [1]. However, EULAR and BSR suggest that women on these medications can continue breastfeeding based on limited evidence [2,3]. These 3 medications can be secreted at very low levels in breast milk [38-41]. However, based on small studies, there is no adverse effects on infants observed when their nursing mothers used these three drugs [40,42]. It is recommended to avoid breastfeeding for 4 hours after a dose of azathioprine and this can markedly decrease the dose received by the infant through breastfeeding [43]. For cyclosporin A and tacrolimus, it is recommended that the breastfed infants should be monitored, possibly including measurement of serum levels to rule out toxicity if there is concern [44,45].

For methotrexate, leflunomide, mycophenolate mofetil and cyclophosphamide, all three parties agree that these medications should be avoided because of theoretical risk and insufficient data to support their use [1-3].

For TNFi, the level of drug at breast milk is low and hence most of them are compatible with breastfeeding. For golimumab, although there is no clinical data to support its use during lactation, EULAR comments that it is compatible with breastfeeding as it is a large protein molecule and absorption is unlikely due to low bioavailability [2,3].

Rituximab, belimumab, tocilizumab, abatacept, ustekinumab, anakinra and tofacitinib have no data on compatibility with breastfeeding and they should be avoided during lactation.

CONCLUSION

Current suggestions from ACR, EULAR, BSR and drug labels are summarized in Table 4. These guidelines offer guidance for managing patients with rheumatic diseases in pregnancy. Patients planning to start a family should

Table 4. Summary of the DMARDS in pregnancy, paternal exposure and lactation.

Drug	Maternal	Paternal	Lactation
Hydroxychloroquine	Compatible	Compatible	Compatible
Sulfasalazine	Compatible Folic acid 5 mg/day	Compatible	Compatible Avoid if premature infants, infants with hyperbilirubinemia, or G6PD deficiency
Methotrexate	Contraindicated Stop 3 mths folic acid 5 mg/day	May be compatible Drug label: Stop 3 mths before conception	Avoid
Leflunomide	Contraindicated Stop 2 yrs/washout	May be compatible Drug label: Stop/washout	Avoid
Azathioprine	2 mg/kg/day	Compatible	EULAR/BSR: Compatible ACR: Insufficient LactMed: withhold breastfeeding for 4 hrs since last dose
Cyclosporin A	Compatible	Compatible	EULAR/BSR: Compatible ACR: Insufficient LactMed: check infant serum drug level
Tacrolimus	Compatible	Compatible	EULAR/BSR: Compatible ACR: Insufficient LactMed: check infant serum drug level
Mycophenolate mofetil	Contraindicated Stop 6 wks before conception	May be compatible	Avoid
Cyclophosphamide	Contraindicated Stop 1 yr before conception	Stop 4 mths	Avoid
IVIG	Compatible	Compatible	Compatible
Infliximab	Compatible/ Stop after 16 wks	Compatible	Compatible
Etanercept	Compatible/ Stop after 30 wks	Compatible	Compatible
Adalimumab	Compatible/ Stop after 20 wks	Compatible	Compatible
Certolizumab	Compatible	Insufficient data	Compatible
Golimumab	Compatible No data when to stop	Insufficient data	No data
Rituximab	Stop 6 mths before	Compatible	No data
Belimumab	Stop 4 mths before	No data	No data
Tocilizumab	Stop 3 mths before	No data	No data
Abatacept	Stop 14 wks before	No data	No data
Anakinra	No data	No data	No data
Ustekinumab	Stop 15 wks before	No data	No data
Tofacitinib	Stop 2 mths before	No data	Insufficient

be well informed on the safety of different DMARDS in pregnancy, possible need for drug switching or discontinuation, duration of discontinuation before conception, effect on pregnancy and fetal outcome. A

management plan should be made, taking into account disease control and safety of drug usage before conception, throughout pregnancy and/or breastfeeding. Hopefully in the near future, there would be more supportive data

on the safety of these medications, especially new agents in pregnancy and/or lactation.

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