



Notes on Prescribing Medications for Rheumatic Diseases in Pregnancy

General comments

- All women with rheumatic diseases of childbearing age should receive pre-pregnancy counseling and discussion around contraception.
- Treatment options should be discussed with the mother to ensure an informed decision is made to balance the risk of ceasing/continuing medication and risk of adverse outcomes for mother and baby of poor disease control.
- In general those patients whose rheumatic disease is optimally controlled on conventional synthetic Disease Modifying AntiRheumatic Drugs (csDMARDs) with a good safety profile in pregnancy, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and azathioprine (AZA), have a better outcome for mother and baby than those maintained on corticosteroids.

Rheumatoid Arthritis (RA)

- The level of disease activity in many RA patients will improve during pregnancy. However up to 20% of women suffer increased disease activity compared with control populations.
- Women with RA on average take a longer time to conceive than the general population.
- Initial studies showed no increased rate of spontaneous abortion in women with RA but a more recent registry-based study reported increased rates.
- RA patients have an increased risk of Small for Gestational Age (SGA), premature or low birth weight (LBW) neonates and Caesarean section.
- The data on rates of maternal hypertension and preeclampsia (PET) in RA pregnancies is unclear with some studies reporting increase and others none.

Spondyloarthritis (SpA)

- In Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) disease activity was not considered altered during pregnancy but recent data suggests disease may flare in 25% of patients.

Systemic Lupus Erythematosus (SLE)

- In patients with SLE, flares occur in up to two thirds of women during pregnancy. Flares are more likely to occur if disease is active at conception. Women with SLE have an increased risk of miscarriage, prematurity, LBW and PET.
- Risk of adverse outcomes is higher if the mother has a history of lupus nephritis, especially if the mother has hypertension, proteinuria or elevated serum creatinine at start of pregnancy. Risk in this case also includes the risk of loss of renal function/dialysis.

- Women should embark on pregnancy when SLE disease activity has been stable for at least 6 months.
- In SLE cessation of HCQ is associated with increased disease activity with poor pregnancy outcomes for mother and baby.
- HCQ is considered safe for all SLE patients and should be continued during pregnancy.
- Low dose aspirin (LDA) should be considered for reducing the risk of PET in women with SLE, especially if active disease, history of lupus nephritis, history of hypertension or antiphospholipid syndrome.

Antiphospholipid Syndrome (APS)

- Low dose aspirin should be considered for SLE patients with a history of antiphospholipid antibodies.
- Hydroxychloroquine should be considered for patients with APS.
- Heparin or low-molecular weight heparin (LMWH) prophylaxis should be considered for women with a history of obstetric APS or history of Venous Thromboembolism (VTE) or risk factors for VTE in pregnancy.
- Women treated with warfarin (known teratogen), or another oral anticoagulant, need to be counselled about considering a switch to LMWH during pregnancy. Very rarely there may be exceptional circumstances where the risk of thrombosis is so great that continuation of warfarin for all or part of pregnancy would be considered.

Systemic Sclerosis (SSc)

- Women with SSc have higher risk of IUGR and pre-term deliveries.
- The risk of disease progression in pregnancy is low.
- Assessment for pulmonary hypertension and severe interstitial lung disease prior to pregnancy is extremely important. Women with pulmonary hypertension have high maternal mortality rates in pregnancy and should be discouraged from falling pregnant without specialist obstetric/obstetric medicine pre-pregnancy counselling. If they do conceive, urgent referral should be made to their obstetric/obstetric medicine team for discussion of options.
- Women with renal impairment and hypertension are at increased risk for PET.
- Due to the higher risk of developing renal crisis in the early years of diffuse systemic sclerosis, delaying pregnancy should be discussed.

Thrombosis

- All women should undergo an assessment of risk of VTE during pregnancy. Many women with rheumatic disease may be at increased risk of thrombosis, especially those with SLE, antiphospholipid syndrome or current active inflammation.
- Risk assessment should also take into account other risk factors for VTE (e.g. prior history of VTE, family history of VTE, thrombophilia, obesity, age >35, infections, surgery, smoking, varicose veins, multiple pregnancy).
- Depending on the risks, VTE prophylaxis with LMWH may be considered antenatally or postnatally, in discussion with the obstetrics/obstetrics medicine team involved.

Contraception

- All women with rheumatic disease should be counselled about different options for contraception.
- Women with rheumatic disease should be counselled about the increased thrombotic risk of oestrogen-containing contraceptives. In women with increased risk of thrombosis, such as women with SLE, antiphospholipid syndrome, current active inflammation or other risk factors for VTE, oestrogen-containing contraceptive agents should be avoided in preference for agents with lower thrombotic risk.

Lactation

- Drug concentrations in breast milk that expose the neonate to 0.1% of the maternal dose are generally regarded as safe: those >10% are regarded as requiring caution or avoidance. The exception to this is methotrexate (MTX), which despite low levels in breast milk presents theoretical concerns about drug accumulation in neonatal tissues.
- Biological DMARDs (bDMARDs) e.g. abatacept, anakinra, belimumab, Tumour Necrosis Factor inhibitors (TNFi), tocilizumab, rituximab, can be present in small amounts in breast milk. IgA is the main type of antibody secreted into breastmilk and as large molecules they pass less readily into breast milk through passive transfer. However, the small amounts present in breast milk are unlikely to be absorbed by the neonate due to poor bioavailability.
- Data on targeted synthetic DMARDs (tsDMARDs) such as tofacitinib are limited. However, these medications, unlike the larger sized bDMARDs, are small molecules which might be expected to cross more readily into breastmilk. It is recommended to withhold tsDMARDs until breastfeeding is ceased.

Medication

- Analgesia such as paracetamol and narcotics including tramadol can be used safely where clinically indicated. All narcotics used at high doses near term present a risk of neonatal depression/withdrawal.
- NSAIDs should be ceased when conception is planned and avoided in the first and third trimesters (see table below)

The following table has been designed to offer assistance to those involved in prescribing medications for patients with rheumatic diseases in the pre, peri and post-natal period.

The TGA assigned categories can be misleading and require review in association with clinical evidence. Some category D medications (HCQ, SSZ and AZA) are safe in pregnancy while others e.g. MTX and mycophenolate are not.

In June 2015, the FDA has initiated a new system to assist prescription during pregnancy removing the letter classification. To date the Australian TGA has not expressed a plan to make any changes.

Medication	TGA category	Notes for prescribers
Abatacept	C	<ul style="list-style-type: none"> • Due to expected concomitant use of MTX, unplanned pregnancy should be discussed with a specialist in this field • A significant number of case reports with variable outcomes including some live healthy births have been published. BMS database reports 128 maternal exposures with no increase in congenital anomalies and no pattern of congenital anomalies • EULAR report 152 pregnancies; the noted higher miscarriage and congenital anomalies rate was consistent with the concomitant MTX exposure • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: there are insufficient data to recommend in pregnancy, but unintentional exposure early in the first trimester is unlikely to be harmful ○ Lactation: no data upon which to base a recommendation for use in breastfeeding, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data but likely to be safe
Adalimumab	C	<ul style="list-style-type: none"> • See TNFi
Anakinra	B1	<ul style="list-style-type: none"> • Animal studies have not shown evidence of fetal harm • No controlled data in human pregnancy • Observational data has not shown evidence of harm • EULAR report 40 pregnancies with no increase in miscarriage and congenital anomalies • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: use during pregnancy when benefit outweighs risk ○ Lactation: no data upon which to base a recommendation for use in breastfeeding, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data but likely to be safe
Aspirin	C	<ul style="list-style-type: none"> • Low dose (40-150mg/day) can be continued throughout pregnancy • It may be beneficial in reducing the risk of pre-eclampsia and of miscarriage in women with the obstetric APS • Lactation: aspirin is excreted into breast milk at low concentrations. The Australian Medicine Handbook (AMH) recommends that ibuprofen is preferred (due to theoretical risk of Reyes syndrome in aspirin use) but that single doses can be given. Peak milk levels occur at approx. 3 hours post-dose, with a milk: plasma ratio of 0.03-0.08 • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: continue during pregnancy if clinically indicated ○ Lactation: no data relating to use but no theoretical concerns ○ Paternal exposure: no data but likely to be safe

Azathioprine	D	<ul style="list-style-type: none"> • At a dose not exceeding 2mg/kg/day used in pregnancy as fetal liver lacks enzyme to convert to active metabolites • Meta-analysis in IBD patients showed no association with LBW or congenital abnormalities; association with preterm birth • EULAR report > 1300 pregnancies with no increase in miscarriage and congenital anomalies in disease matched controls • Lactation: if used breastfeed 4 hours post dose as most drug excreted within 4 hours of ingestion. No change infection rates in babies exposed in breast milk (n=16, case control) • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: continue during pregnancy if clinically indicated ○ Lactation: no data relating to use but no theoretical concerns ○ Paternal exposure: no data but likely to be safe
Belimumab		<ul style="list-style-type: none"> • > 150 pregnancies reported with higher miscarriage and congenital anomalies; concomitant medication possible confounder with no studies with disease-matched controls • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: avoid in pregnancy unless clinical situation indicates ○ Lactation: there are no data upon which to base a recommendation for use in breastfeeding, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data but likely to be safe
Biological DMARDs	See individual product	<ul style="list-style-type: none"> • Monoclonal antibodies are transported across the placenta via active Fc receptor transport from week 16 and increases as pregnancy progresses, in proportion to maternal dose
Bisphosphonates	B3	<ul style="list-style-type: none"> • There are no adequate and well-controlled studies in pregnant women to fully assess on fetal risk in humans. Human data limited to 8 cases. Of the two cases where pamidronate was given in the 2nd trimester one newborn was hypocalcaemic but not the other • There are insufficient data upon which to recommend bisphosphonates in pregnancy or to advise a specific time for them to be stopped pre-conception. Given their biological half-life in bone of up to 10 years and no evidence of harm from limited reports of their use in pregnancy, a pragmatic recommendation is that they should be stopped 3 months in advance of pregnancy • Lactation: From case study data, breastfeeding during pamidronate treatment does not appear to harm the neonate. Pamidronate has low lipid solubility and in case studies the drug was not detectable in the breast milk. Oral bioavailability in adults is very low, but in neonates the bioavailability is not known. Pamidronate is also highly bound by calcium, further reducing possible absorption from milk • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: cease 3 months pre conception although no data of harm ○ Lactation: no data relating to use but no theoretical concern ○ Paternal exposure: no data on which to base recommendation
Certolizumab	C	<ul style="list-style-type: none"> • See TNFi

Colchicine	B2	<ul style="list-style-type: none"> Based on studies of low doses as used in Familial Mediterranean Fever (FMF), it is considered safe in pregnancy May aid fertility in female FMF patients Arrests cell division in animals and plants and has adversely affected spermatogenesis in humans and in some animal species under certain conditions Recommendations <ul style="list-style-type: none"> Pregnancy: continue during pregnancy if clinically indicated Lactation: considered safe but exposure can be minimised by maximising the time between dose and subsequent feeding. Paternal exposure: no data on which to base recommendation
Corticosteroids	A	<ul style="list-style-type: none"> Can be used if cs +/- DMARDs with acceptable safety profile in pregnancy (HCQ, SSZ, HCQ, TNFi) are inadequate, contraindicated, or poorly tolerated Use lowest possible dose (pref. <20mg/daily) to control activity Main risks are maternal including delayed conception in RA, PET, gestational diabetes (GDM), osteopaenia/porosis and infection; the latter is dose related and more prominent in the last trimester Fetal concerns include prematurity, LBW, chorioamnionitis, premature rupture of membranes, and adrenal suppression Placental 11beta hydroxysteroid dehydrogenase 2 inactivates most steroids, except betamethasone and dexamethasone, which decreases fetal exposure; 10% of prednisolone dose reaches fetus While older studies reported possible increased risk of oral clefts from 1:1000 to 3:1000 with 1st trimester exposure, more recent studies show no link Recommendations <ul style="list-style-type: none"> Pregnancy: use in pregnancy only if other options not suitable Lactation: if prednisolone dose > 20 mg/day aim to breastfeed 4 hours post dose Paternal exposure: compatible
Cyclophosphamide	D	<ul style="list-style-type: none"> Avoid in pregnancy; can be used in second half of pregnancy if life threatening maternal illness Recommendations <ul style="list-style-type: none"> Pregnancy: use in second half of pregnancy only if no other options not suitable Lactation: avoid Paternal exposure: avoid
Cyclosporin	C	<ul style="list-style-type: none"> Can be used in pregnancy at lowest effective dose; suggested not to exceed 10mg/kg/day Monitoring of maternal blood pressure, renal function, blood glucose and drug levels is required May have higher risk of prematurity and IUGR Recommendations <ul style="list-style-type: none"> Pregnancy: can be used in pregnancy with careful monitoring Lactation: should not be discouraged Paternal exposure: no data relating but likely to be safe
Etanercept	D	<ul style="list-style-type: none"> See TNFi

Gold	B3	<ul style="list-style-type: none"> • Avoid in pregnancy • No definite evidence of fetal malformations • Common practice is to continue until pregnancy then cease. Give monthly injections on first day of menses (assuming regular menses) • Lactation: Gold is excreted into breast milk. Caution as possible risk of long term effects if accumulation • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: use in pregnancy if other options not suitable ○ Lactation: avoid ○ Paternal exposure: no data relating but likely to be safe
Golimumab	C	<ul style="list-style-type: none"> • See TNFi
Hydroxychloroquine	D	<ul style="list-style-type: none"> • Appears safe in pregnancy. Long term follow-up of exposed neonates has been unremarkable • Due to its long half life stopping in pregnancy would not avoid fetal exposure • Use in pregnancy women with SLE is associated with improved pregnancy outcomes and is recommended • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: can be used in pregnancy; women with SLE should be on HCQ during pregnancy unless specific contraindication ○ Lactation: should not be discouraged. Low levels in breast milk ○ Paternal exposure: no data relating but likely to be safe
Infliximab	C	<ul style="list-style-type: none"> • See TNFi
Leflunomide	X	<ul style="list-style-type: none"> • Contraindicated in pregnancy • Usually avoided in young women due to long half-life (2 weeks) • Increased congenital malformations in animals similar doses to humans • Prospective human study of > 100 pregnancies failed to show increased teratogenic risk, with the majority having cholestyramine washouts • If regularly taken anytime in the 2 years pre-desire to conceive, consider washout with cholestyramine 8g TDS for 11 days (not necessarily consecutive) • Plasma levels > 0.02mg/L should be verified twice 2 weeks apart. If unacceptably high levels persist, additional cholestyramine or charcoal washout can be given. Recommended to wait 3 menstrual cycles post chelation before attempting to conceive • For Arava brand-contact Sanofi-Aventis Medical Information Department- 1800 818 806/option 1, for free plasma testing • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: if unplanned pregnancy occurs, stop immediately, commence cholestyramine washout and seek expert opinion ○ Lactation: avoid ○ Paternal exposure: based on very limited evidence it may be compatible but further studies to confirm are warranted

Methotrexate	D	<ul style="list-style-type: none"> • Known teratogen; contraindicated in pregnancy • Current recommendations cease 1-3 months preconception • In case of unplanned pregnancy cease MTX immediately and institute 5 mg folic acid daily; contact specialist in the field to discuss management and monitoring of pregnancy • There are > 200 cases of healthy pregnancies exposed to low dose MTX (<30mg/week) recorded in the literature with 1 case of MTX embryopathy • 113 pregnancies after paternal exposure showed no increased risk of adverse foetal outcomes compared with 412 non-exposed pregnancies • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: British Society Rheumatology (BSR) recommend cease 3 months preconception: Up to Date recommends stopping for ≥1 ovulatory cycle. In unplanned pregnancy cease MTX immediately, institute 5 mg folic acid daily and contact specialist in the field to discuss management and monitoring of pregnancy ○ Lactation: avoid ○ Paternal exposure: based on recent publications low-dose MTX may be compatible
Mycophenolate	D	<ul style="list-style-type: none"> • Avoid in pregnancy as proven human teratogen; use in pregnancy is associated with miscarriage and major birth defects (facial, ear, cleft lip, NTD, cardiac, limbs, heart, oesophagus) • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: cease at least 6 weeks pre-conception ○ Lactation: avoid ○ Paternal exposure: based on very limited evidence it may be compatible but further studies to confirm are warranted
NSAIDs and Cox-2 inhibitors	C up to week 32 category D after	<ul style="list-style-type: none"> • Animal models suggest NSAIDs incl. COX-2 inhibitors may theoretically inhibit fetal implantation and/or decrease fertility • 2 large studies of pregnant women showed no association between nonselective-NSAID exposure and congenital malformations; 1 study showed increased risk of musculoskeletal malformations in subset receiving Cox-2 inhibitors • Ibuprofen or diclofenac post 2nd trimester slightly increased risk maternal bleeding, LBW or asthma in neonate • Dose dependent but reversible effect of NSAIDs on fetal renal function and rare cases of fetal anuria and end stage renal failure have been reported • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: NSAIDs should be stopped when conception planned. Avoid in the first 6-8 weeks if possible: older studies suggest increase in miscarriage. Cease by 3rd trimester due to premature closure of ductus arteriosus ○ Lactation: ibuprofen and diclofenac preferred (shorter t 1/2, inactive metabolites, lower breast milk levels); sulindac and indomethacin (enteropathic circulators) and COX 2 (insufficient data) not recommended ○ Paternal exposure: non-selective NSAIDs are compatible

Penicillamine	D	<ul style="list-style-type: none"> • Is teratogenic in animal studies • Serious connective tissue abnormalities have been reported in babies exposed in utero • Case study data suggests daily dose at ≤ 500 mg may reduce the incidence of penicillamine-induced toxicity in the newborn • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: avoid in pregnancy ○ Lactation: avoid ○ Paternal exposure: no data on which to base recommendation
Rituximab	C	<ul style="list-style-type: none"> • >250 pregnancies associated with maternal exposure with > 150 known outcomes incl 90 live births; increased miscarriage confounded by disease indication • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: avoid in pregnancy: BSR recommends delay conception at least 6 months post last dose while ACR recommend a 12-month delay ○ Lactation: there is limited data upon which to base a recommendation for use in breastfeeding, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: based on limited evidence is likely to be safe
Secukinumab	C	<ul style="list-style-type: none"> • Is a human IgG1 monoclonal antibody that binds IL-17A • Development toxicity studies showed no harm to foetuses of pregnant monkeys exposed during organogenesis • $t_{1/2}$ is 27 days hence washout would need to be 19 weeks preconception • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: in the absence of any human data avoid in pregnancy; in unplanned pregnancy contact specialist in the field to discuss management and monitoring of pregnancy ○ Lactation: there are no data upon which to base a recommendation, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data on which to base recommendation
Sulfasalazine	A	<ul style="list-style-type: none"> • Appears safe in pregnancy • Due to inhibition of folic acid absorption/metabolism it may cause folic acid deficiency • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: can be used in pregnancy. Folic acid supplementation of 5mg a day should be commenced prior to pregnancy planning and continued throughout pregnancy ○ Lactation: moderate transfer to breast milk (40-60% maternal levels). One report of bloody diarrhea in an exposed neonate. Can be used with caution ○ Paternal exposure: associated with reversible azoospermia/oligospermia in men and reduced sperm motility. Consider stopping 3 months before attempting conception

<p>TNF inhibitors: Adalimumab Etanercept Certolizumab Golimumab Infliximab</p>	<p>See individual product for category</p>	<ul style="list-style-type: none"> • Based on several observational studies of pregnancy 12-20% of RA patients will receive TNFi therapy partly or throughout pregnancy • Etanercept has been used to improve outcomes in a study of 30 patients with recurrent fetal loss • 1533 IBD pts exposed to TNFi no increased risk of adverse pregnancy outcome nor congenital anomalies; no higher risk of neonatal infections nor growth at 12 months even if breastfeeding • European Crohn's and Colitis Organisation (ECCO) endorses use in 1st and 2nd trimester when needed as the risk of active disease is greater than potential risk from medication. Suspension in the 3rd trimester with resumption post delivery/breast feeding is endorsed • In more than 2400 pregnancies in patients with rheumatic diseases on TNFi the live birth rate, miscarriage and congenital abnormality comparable with general population • Multiple publications from pregnancy registries including Organisation of Teratology and Information Specialist (OTIS) had not raised concerns regarding adverse outcomes. A 2015 abstract reported an odds ratio of 2.77 (1.04-7.35) of major birth defects for etanercept. No specific pattern has been reported and the biological plausibility of drug related effect is not supported • The ACR confirm in patient resources that TNFi are acceptable during pregnancy and lactation (http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic-Disease/Pregnancy-Rheumatic-Disease) • EULAR and BSR state continuation of TNFi during the first part of pregnancy should be considered. • Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage. • Due to active placental transfer of the Fc-dependent monoclonal antibodies during the 3rd trimester, TNFi treatment is usually suspended. If a TNFi is continued later in pregnancy live vaccines should be avoided in the first 6 months. Current Australian immunization schedule includes rotavirus in first 6 months as live vaccine. Discussion with neonatologist /paediatrician is recommended. Due to lower rates of transfer with etanercept and certolizumab that decision may be revised • Avoid BCG vaccination in infants in first 6 months if exposed • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: current evidence supports continuing infliximab until 16 weeks and adalimumab 32 weeks and then cease; etanercept can be continued until to 32 weeks and throughout pregnancy if indicated. Certolizumab is not actively transported across the placenta hence there is no rationale to stop it antenatally. Data confirm no clinically significant cord or neonatal levels of certolizumab. Insufficient data for golimumab but it is unlikely to be harmful in the first trimester. If clinically indicated to continue later in gestation than the above, deferring live vaccines is recommended ○ Lactation: based on limited but reassuring data, women should not be discouraged from breastfeeding while on TNFi. Data confirm no clinically significant levels of certolizumab in breast milk ○ Paternal exposure: based on limited evidence is likely to be safe
--	--	---

Tacrolimus	C	<ul style="list-style-type: none"> • There are no controlled data in human pregnancy but the risk of congenital malformations appears low • Use in human pregnancy has been associated with premature delivery risk, neonatal hyperkalemia, and renal dysfunction • Should be used during pregnancy only if there is no safer alternative and the benefit outweighs the risk to the fetus • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: is compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels ○ Lactation: breastfeeding should not be discouraged ○ Paternal exposure: based on limited evidence is likely to be safe
Tocilizumab	C	<ul style="list-style-type: none"> • In animal reproduction studies, administration of tocilizumab to cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at dose exposures 1.25 times the human dose exposure of 8 mg per kg every 2 to 4 weeks • Adequate and well-controlled studies have not been conducted in pregnant women • Outcomes of > 200 pregnancies have been reported with increased miscarriage confounded by MTX co-prescription; no increase in congenital anomalies has been reported • Outcomes of all pregnancies with exposure in pivotal RA trials and long-term extension reported 33 pregnancies, 26 had concomitant MTX; 11 normal deliveries, 7 spontaneous abortions, 13 therapeutic abortions • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: in the absence of data it should be stopped at least 3 months pre-conception, but unintentional exposure early in the first trimester is unlikely to be harmful. Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus ○ Lactation: there are no data upon which to base a recommendation for use in breastfeeding, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data relating but no theoretical concerns
Tofacitinib	D	<ul style="list-style-type: none"> • Adequate and well-controlled studies have not been conducted in pregnant women • 29 pregnancies analyzed, 16 healthy newborns were delivered (57.1%). Eleven of the mothers were receiving tofacitinib monotherapy and five were receiving tofacitinib plus MTX. Two of the healthy newborns were of low birth weight • Until better data and follow-up, pregnancy should be avoided • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: avoid in pregnancy ○ Lactation: avoid ○ Paternal exposure: no data on which to base recommendation

Ustekinumab	B1	<ul style="list-style-type: none"> • Is a human IgG1 monoclonal antibody that binds the p40 subunit of IL-12 and IL-23 • Development toxicity studies showed no harm to foetuses of pregnant monkeys exposed during organogenesis • $t_{1/2}$ is 21 days hence washout would need to be 15 weeks preconception • Recommendations <ul style="list-style-type: none"> ○ Pregnancy: in the absence of any human data avoid in pregnancy; in unplanned pregnancy contact specialist in the field to discuss management and monitoring of pregnancy ○ Lactation: there are no data upon which to base a recommendation, but as it is a high molecular weight protein the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the neonatal gastrointestinal tract ○ Paternal exposure: no data on which to base recommendation
-------------	----	--

Other useful resources include

- MotherSafe website (www.mothersafe.org.au)
- MotherToBaby (www.mothersafe.org.au)
- LactMed (<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>)

Key References

- Psoriasis in those planning a family, pregnant or breastfeeding. The Australasian Psoriasis Collaboration. Rademaker M et al. Australasian Journal of Dermatology 2017 doi: 10.1111/ajd.12641.
- BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I and II: Flint J et al. Rheumatology (Oxford) 2016; 55 (9): 1693-1702.
- The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation.
- Götestam Skorpen C, et al. Ann Rheum Dis 2016; 75:795–810 Current Opinion in Rheumatology: 2014; 26:3.
- Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk: Gerald Briggs, Roger K. Freeman (2014): Lippincott Williams and Wilkins: Philadelphia, United States.
- Wallenius M, Salvesen K, Daltveit A, et al. Miscarriage and stillbirth in women with rheumatoid arthritis. J Rheumatol 2015; 42: 1570-1572.
- Management of pregnancy in women with rheumatoid arthritis: Ngian G-S et al, Med J Aust 2016; 204 (2): 62-63.
- <http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic-Disease/Pregnancy-Rheumatic-Disease>

Further references available on request.

Drs Claire Barrett, Kate Poulsen, Laurel Young for the Therapeutics Committee
Australian Rheumatology Association
 145 Macquarie Street, SYDNEY NSW 2000
 Tel: 02 9252 2356 Fax: 02 9252 2328 Email: admin@racp.edu.au

Appendix 1

Australian categorisation of drugs in pregnancy; these are **different** to the FDA Categories. This categorisation applies only to recommended therapeutic doses in women in the reproductive age group.

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X: Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category. Drugs in category D are NOT absolutely contraindicated in pregnancy. Moreover, in some cases the D category has been assigned on the basis of suspicion.
www.tga.gov.au/docs/html/medpreg.htm