Prescriber's Information on Medications for Rheumatic Diseases in Pregnancy

General comments

- All women of childbearing age with rheumatic diseases should receive pre-pregnancy counselling and discussion around contraception.
- Treatment options should be discussed with women considering pregnancy to ensure an informed decision is made.
- The risks to both mother and baby of active inflammatory disease and medication safety need to be considered.
- Women with rheumatic diseases who are planning pregnancy, should have any pregnancy-incompatible medications switched to pregnancy-compatible medications. They should be observed for an adequate period of time to ensure the medication is effective and well tolerated before trying to conceive.
- In general, those patients whose rheumatic disease is optimally controlled on conventional synthetic Disease Modifying Anti Rheumatic Drugs (csDMARDs) with a good safety profile in pregnancy, such as hydroxychloroquine (HCQ), sulfasalazine (SSZ) and azathioprine (AZA), have a better outcome for mother and baby than those maintained on corticosteroids, or those with untreated high disease activity.
- Generally women who have well-controlled rheumatic disease at time of conception and in the preceding 3-6 months on suitable medication for pregnancy, have a low risk of disease flare unless medication is stopped.
- Women who have unplanned pregnancy whilst on a teratogenic medication should be referred to a specialist unit to discuss risks and further investigations required (such as detailed fetal ultrasound, amniocentesis or chorionic villous biopsy).
- Many patients with rheumatic diseases are on multiple medications for other aspects of their disease management. Some of these medications may be compatible with pregnancy (e.g. proton pump inhibitors, calcium channel blockers, aspirin) and some of these may not be compatible with pregnancy (e.g. warfarin, ACE inhibitors, statins). Therefore we encourage all patients contemplating pregnancy to have a full review of their medications with their doctor.

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 in pregnancy 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; 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.

Psoriatic Arthritis (PsA)

- Data about PsA activity is limited to small studies.
- Recent studies report arthritis may improve during pregnancy in nearly 60%.
- Skin psoriasis may improve more than joint disease.

Ankylosing Spondylitis (AS)

- Previous studies found AS disease activity was not altered during pregnancy.
- Recent data suggest these diseases may flare in 25% of patients.
- In patients stopping TNF inhibitors (TNFi) the relative risk of flare was 3.08 (95% CI 1.2–7.9). In spite of initiated TNFi or glucocorticoids (GC) treatment in 62.5% of these patients, disease activity remained elevated throughout pregnancy.
- Patients with AS without TNFi in the preconception period showed persistently high disease activity from pre-pregnancy until the postpartum period.
- While robust, prospective data on disease activity during pregnancies of women with AS are limited, a recent systematic literature review of available data suggests that there may be a small increase in pre-term births but no signal for increased pregnancy loss.
- A recent Swedish registry study assessed 388 deliveries in women with AS and found an increased risk for pre-term birth and caesarean section.

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 conception. 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 4-6 months.
- Baseline antibody status should be established for antiphospholipid antibodies and ENA, particularly for SSA(Ro)/SSB(La).
- Baseline urine including protein:creatinine ratio should be performed.
- In SLE continuation of HCQ is associated with improved disease activity and better 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 pre-eclampsia (PET) in women with SLE, especially if active disease, history of lupus nephritis +/- hypertension or antiphospholipid syndrome.
- End stage renal disease is associated with high maternal and fetal morbidity (e.g. 75% chance PET, >90% Intrauterine Growth Restriction (IUGR, >90% preterm, 50% perinatal mortality). Women with advanced chronic kidney disease who are being considered for renal transplant may have a better chance of a healthy pregnancy post-transplant.

- HCQ should be considered for women with SSA (Ro) or SSB (La) antibodies to reduce the risk of congenital heart block.

Antiphospholipid Syndrome (APS)

- Low dose aspirin (LDA) should be considered for SLE patients with a history of antiphospholipid antibodies for PET prophylaxis.
- Hydroxychloroquine should be considered for patients with APS.
- Prophylactic dose heparin (usually low-molecular weight heparin) during pregnancy and for 6 weeks postpartum, should be considered for women with a history of obstetric APS or risk factors for VTE in pregnancy.
- Pregnant women with thrombotic APS require therapeutic anticoagulation throughout pregnancy, usually therapeutic dose low-molecular weight heparin, as well as LDA.
- Women treated with warfarin (known teratogen), or another oral anticoagulant, need to be counselled about switching to LMWH during pregnancy. 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 intrauterine growth restriction (IUGR) and pre-term deliveries.
- The risk of disease progression in pregnancy is low.
- Assessment for pulmonary arterial hypertension (PAH) and severe interstitial lung disease prior to pregnancy is extremely important. Women with PAH have high maternal mortality rates in pregnancy (approximately 25%) and should be discouraged from pregnancy without specialist obstetric/obstetric medicine pre-pregnancy counselling. It is worth noting that some pulmonary vasodilator medications (e.g. bosentan) reduce the efficacy of hormonal contraceptives. If they do conceive, urgent referral should be made to their obstetric/obstetric medicine team for discussion of options including pulmonary vasodilator drugs.
- Women with renal impairment and hypertension are at increased risk for PET, IUFR, preterm delivery and perinatal mortality.
- Due to the higher risk of developing renal crisis in the early years of diffuse SSc, delaying pregnancy should be discussed.
- Scleroderma renal crisis is uncommon (2% of SSc pregnancies). However, in this situation, use of ACE inhibitors or angiotensin receptor blockers is recommended, as the risk of maternal or fetal death with untreated disease outweighs the risk of these medications.

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, APS or current active inflammation.
- Risk assessment should also take into account other risk factors for VTE e.g. prior history and/or 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.
- The most effective contraceptives are long-acting reversible contraceptives (e.g. intrauterine devices (IUD) or subdermal progestin implants) and these medications are suitable for use in women with rheumatic disease.
- 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 or APS, current active inflammation or other risk factors for VTE, oestrogen-containing contraceptive agents should be avoided in preference for agents with lower thrombotic risk such as progestin-only or IUD contraceptives.

Lactation

- Drug concentrations in breast milk that expose the neonate to <10% of the maternal dose are generally regarded as safe: those >10% are regarded as requiring caution or avoidance. Exceptions to this include methotrexate (MTX), which despite low levels in breast milk presents theoretical concerns about drug accumulation in neonatal tissues. Conversely, sulfasalazine and cyclosporine have levels in breast milk >10% but are considered compatible with breastfeeding in healthy term infants.
- Biological DMARDs (bDMARDs) e.g. abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, TNFi, tocilizumab, ustekinumab, can be present in small amounts in breast milk. IgA is the main type of antibody secreted into breastmilk. bDMARDs are large molecules so they pass less readily into breast milk through passive transfer. 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 baricitinib, tofacitinib and upadacitinib are limited. However, these medications, unlike 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 opioids including tramadol can be used safely where clinically indicated. All opioidsused at high doses near term present a risk of neonatal depression/withdrawal.
- NSAIDs should avoided in the third trimester (see table below).

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

The Therapeutics Goods Administration (TGA) assigned categories can be misleading. They must be reviewed in association with clinical evidence. Some category D medications (e.g. HCQ and AZA) are safe in pregnancy while others (e.g. MTX and mycophenolate) are not.

In June 2015, the US Food and Drugs Administration (FDA) 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	• 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 >120 maternal exposures with no increase in congenital anomalies and no pattern of congenital anomalies.
		• EULAR reported >150 pregnancies; the higher miscarriage and congenital anomalies rate was consistent with the concomitant MTX exposure.
		• **Recommendations**
		  ○ **Pregnancy: there is 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. However, 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	• See TNFi

Anakinra	B1	• Animal studies have not shown evidence of fetal harm.
		• No controlled data in human pregnancy, however, observational data has not shown evidence of harm.
		• EULAR report 40 pregnancies with no increase in miscarriage or congenital anomalies.
		• Has not been found to cross full term human placenta.
		• Unintentional exposure in first trimester unlikely to be harmful.
		• **Recommendations**
		  ○ **Pregnancy: use during pregnancy when benefit outweighs risk.**
		  ○ **Lactation: no data upon which to base a recommendation for use in breastfeeding. However, 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	• Low dose (40-150mg/day) can be continued throughout pregnancy. • It may be beneficial in reducing the risk of pre-eclampsia and 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** ○ **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	• Can use in pregnancy at a dose ≤2mg/kg/day, 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 of >1300 pregnancies showed 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 in infection rates in babies exposed in breast milk (n=16, case control). • **Recommendations** ○ **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.**
Baricitinib	D	• Adequate and well-controlled studies have not been conducted in pregnant women. Therefore until better data and follow-up, pregnancy should be avoided. • The product information sheet recommends women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment and for at least 1 week after the final treatment. • **Recommendations** • **Pregnancy: avoid in pregnancy.** • **Lactation: avoid as no data.** • **Paternal exposure: no data on which to base recommendation.**
Belimumab	C	• > 150 pregnancies reported with higher miscarriage and congenital anomalies; concomitant medication possible confounder with no studies with disease-matched controls. • Unintentional exposure in first trimester unlikely to be harmful. • **Recommendations** ○ **Pregnancy: avoid in pregnancy unless clinical situation indicates.** ○ **Lactation: there are no data upon which to base a recommendation for use in breastfeeding. However, 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	• 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	• Animal studies with rats found bisphosphonates crossed the placenta and accumulated in fetal bones. • There are no adequate well-controlled studies in pregnant women to fully assess on fetal risk in humans. • The small amount of human data that has been published has not found a significant risk. • There are few RCTs of bisphosphonates being used in premenopausal women; long-term efficacy and safety data are limited in this group. • Given their biological half-life in bone of up to 10 years prescription to premenopausal women should be carefully considered. • 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** o **Pregnancy: due to their long half life in bone, the use of bisphosphonates in women of reproductive age should be limited to special circumstances. In cases where they have been used, cease 3 months pre conception although no data of harm.** o **Lactation: no data relating to use but no theoretical concern.** o **Paternal exposure: no data on which to base recommendation.**
Certolizumab	C	• See TNFi
Ciclosporin	C	• 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** o **Pregnancy: can be used in pregnancy with careful monitoring.** o **Lactation: breastmilk levels >10% but considered safe. Can be used whilst breastfeeding.** o **Paternal exposure: no data relating but likely to be safe.**
Colchicine	B2	• Based on studies of low doses 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** o **Pregnancy: continue during pregnancy if clinically indicated.** o **Lactation: considered safe but exposure can be minimised by maximising the time between dose and subsequent feeding.** o **Paternal exposure: no data on which to base recommendation.**

Corticosteroids	A	• Can be used if csDMARDs or bDMARDs with acceptable safety profile in pregnancy (HCQ, SSZ, AZA, TNFi) are inadequate, contraindicated, or poorly tolerated. • Use lowest possible dose (pref. <20mg/daily) to control activity. • Maternal complications include delayed conception in RA, PET, gestational diabetes (GDM), osteopaenia/porosis (especially with heparin), 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 11 beta-hydroxysteroid dehydrogenase 2 inactivates most steroids, except betamethasone and dexamethasone, which decreases fetal exposure; <10% of active 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** ○ **Pregnancy: can use during conception and pregnancy if clinically indicated and other options not suitable.** ○ **Lactation: if prednisolone dose > 20 mg/day aim to breastfeed 4 hours post dose.** ○ **Paternal exposure: compatible.**
Cyclophosphamide	D	• Teratogenic and gonadotoxic. • Cease 6 weeks prior to conception. • Avoid in pregnancy; can be used in second half of pregnancy if life-threatening maternal illness. • **Recommendations** ○ **Pregnancy: use in second half of pregnancy only if other options not suitable.** ○ **Lactation: avoid.** ○ **Paternal exposure: avoid due to risk of teratogenicity.**
Etanercept	D	• See TNFi
Golimumab	C	• See TNFi
Hydroxychloroquine	D	• 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 pregnant women with SLE is associated with improved pregnancy outcomes and thus recommended. • **Recommendations** ○ **Pregnancy: can use during conception and in pregnancy; women with SLE should be on HCQ during pregnancy unless specific contraindication due to improved pregnancy outcomes.** ○ **Lactation: compatible.** ○ **Paternal exposure: limited data but likely to be safe.**
Infliximab	C	• See TNFi
Ixekizumab	C	• IgG4 monoclonal antibody that binds to IL-17A with no adequate/well controlled studies in humans. • In studies in monkeys, no effects on reproductive organs, menstrual cycles or sperm; no embryotoxicity or teratogenicity; and no effect on baby's immune system from 0-6mths of age. Does cross placenta and

		theoretical risk that use during pregnancy may affect neonatal immunity. • Unknown whether excreted in human breastmilk or absorbed systemically after ingestion; excreted at low levels in monkeys. Absorption by the infant unlikely after the first few weeks post-partum and likely destroyed in infant's gastrointestinal tract as ixekizumab is a large protein molecule. • **Recommendations** ○ **Pregnancy: washout period is 65 days so recommended to stop 10 weeks before conception and avoid during pregnancy as there is no data in humans.** ○ **Timing with caesarean delivery: stop at least one dosing cycle before; restart once there is good wound healing (usually 14 days post-op), all sutures/staples have been removed, and there is no evidence of infection.** ○ **Lactation: no data in humans on which to base recommendation but likely safe.** ○ **Paternal exposure: no data in humans, as a precaution stop 10 weeks before conception (risk is likely low).**
Leflunomide	X	• Contraindicated in pregnancy. • Usually avoided in young women due to long half-life (2 weeks). • Increased congenital malformations in animals exposed to similar doses to humans. • Teratogenic potential in humans is still under debate, however available evidence has not found it to be a major human teratogen. Prospective human study of > 100 pregnancies failed to show increased teratogenic risk. • If regularly taken any time in the 2 years prior to conception, 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 on 1800 818 806/option 1, for free plasma testing. • In case of unplanned pregnancy cease leflunomide immediately, cholestyramine washout should be started; contact a specialist in the field to discuss management and monitoring of pregnancy. • **Recommendations** ○ **Pregnancy: cease 2 years preconception. If unplanned pregnancy, cease immediately, commence cholestyramine washout and seek expert opinion.** ○ **Lactation: avoid.** ○ **Paternal exposure: based on very limited evidence it may be compatible but further studies are needed.**

Methotrexate	D	• Known teratogen; contraindicated in pregnancy.
		• Current recommendations cease 1-3 months preconception.
		• In case of unplanned pregnancy, cease MTX immediately and institute 5mg folic acid daily; contact specialist in the field to discuss management and monitoring of pregnancy.
		• Exposure to low dose MTX (<30mg/week) may be associated with >40% risk of miscarriage but risk of major congenital malformation if continue to term only 6.6% (OR 1.8 compared to disease matched controls).
		• Prospective observational data assessing almost 300 pregnancies after paternal exposure to MTX <30mg/week showed no increased risk of adverse fetal outcomes compared with non-exposed pregnancies.
		• **Recommendations**
		  ○ **Pregnancy: British Society of Rheumatology (BSR) recommend ceasing 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 seek expert opinion.**
		  ○ **Lactation: avoid.**
		  ○ **Paternal exposure: based on recent publications low-dose MTX may be compatible.**

Mycophenolate	D	• 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**
		  ○ **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	• 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. • Fetal renal dysfunction due to NSAIDs can lead to oligohydramnios which can cause further complications. • **Recommendations** o **Pregnancy: NSAIDs should be stopped when conception planned. Avoid nonselective NSAIDs in the first 6-8 weeks if possible: older studies suggest increase in miscarriage. Cease by 3rd trimester (especially from week 30) due to premature closure of ductus arteriosus. If using for periods of >48hrs between 20-30 weeks consider ultrasound monitoring of amniotic fluid to screen for oligohydramnios. Avoid COX-2 inhibitors at time of conception and during pregnancy as more clearly associated with impaired fertilisation/implantation and malformations.** ○ **Lactation: ibuprofen and diclofenac preferred (shorter t½, inactive metabolites, lower breast milk levels); sulindac and indomethacin (enteropathic circulators) not recommended. Data on celecoxib indicates low levels in breast milk and considered safe.** ○ **Paternal exposure: non-selective NSAIDs are compatible.**
Penicillamine	D	• 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** ○ **Pregnancy: avoid.** ○ **Lactation: avoid.** ○ **Paternal exposure: no data on which to base recommendation.**

Rituximab	C	• >250 pregnancies associated with maternal exposure with >150 known outcomes including 90 live births; increased miscarriage confounded by disease indication. • Not teratogenic and only 2nd/3rd trimester associated with neonatal B cell depletion. • **Recommendations** ○ **Pregnancy: avoid in pregnancy. BSR recommends delay conception at least 6 months post last dose while ACR recommend a 12-month delay.** ○ **Timing with caesarean delivery: treatment should be stopped 3-6 months prior to elective surgery: restart once there is good wound healing (usually 14 days post-op), all sutures/staples have been removed, and there is no evidence of infection.** ○ **Lactation: there is limited data upon which to base a recommendation for use in breastfeeding. However, 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	• Development toxicity studies showed no harm to fetuses of pregnant monkeys exposed during organogenesis. • Half-life is 27 days, hence, washout would need to be 19 weeks preconception. • **Recommendations** ○ **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.** ○ **Timing with caesarean delivery: stop at least one dosing cycle before; restart once there is good wound healing (usually 14 days post-op), all sutures/staples have been removed, and there is no evidence of infection.** ○ **Lactation: there are no data upon which to base a recommendation. However, 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	• Appears safe in pregnancy. • Due to inhibition of folic acid absorption/metabolism it may cause folic acid deficiency. • **Recommendations** ○ **Pregnancy: can be used in pregnancy. Folic acid supplementation of 2-5mg a day should be commenced at least 1 month prior to pregnancy planning and continued throughout pregnancy.** ○ **Lactation: moderate transfer to breast milk (40-60% maternal levels). One report of bloody diarrhoea in an exposed neonate. Can be used whilst breastfeeding.** ○ **Paternal exposure: associated with reversible azoospermia/oligospermia in men and reduced sperm motility. International experts have recommended ceasing only after 3 months of unsuccessful conception because active RA, which may occur when the medication is stopped, may also affect the quality of sperm.**

TNF inhibitors: (TNFi)
Adalimumab
Certolizumab
Etanercept
Golimumab
Infliximab
	See individual product for category	• 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.
		• In more than 2400 pregnancies in patients with rheumatic diseases on TNFi, the live birth, miscarriage and congenital abnormality rate is comparable with the general population.
		• 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.
		• Multiple publications from pregnancy registries including Organisation of Teratology and Information Specialist (OTIS) had not raised concerns regarding adverse outcomes.
		• Recent publications reported women who discontinued their TNFi during pregnancy had a higher risk of peri- or postpartum flare, compared to those who continued their TNFi throughout pregnancy.
		• ACR confirm in patient resources (link) that TNFi are acceptable during pregnancy and lactation.
		• EULAR and BSR state continuation of TNFi during the first part of pregnancy should be considered.
		• Due to active placental transfer of the Fc-dependent monoclonal antibodies during the 3rd trimester, TNFi treatment is usually suspended.
		• Etanercept may be considered for use throughout pregnancy due to low rate of transplacental passage.
		• Data concerning certolizumab, which has no Fc component and minimal transplacental transfer, found undetectable or minimal infant levels in mothers continuing treatment during the third trimester.
		• If a TNFi is continued later in pregnancy, live vaccines should be avoided in the first 6 months. Rotavirus is the only current live vaccine in the first 6 months of Australian immunisation schedule. 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 to tuberculosis.
		• **Recommendations**
		  ○ **Pregnancy**
		  • **Current evidence supports continuing infliximab until 16 weeks and adalimumab until 32 weeks and then cease.**
		  • **Etanercept can be continued until 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 confirms no clinically significant cord or neonatal levels of certolizumab.**
		  • **Insufficient data for golimumab but it is unlikely to be harmful in the first trimester (? stop by 24-32 wks).**
		  • **If clinically indicated to continue later in gestation than the above, deferring live vaccines until after 6 months is recommended.**
		  • **Timing with caesarean delivery: where possible stop at least one dosing cycle before major surgery and restart once there is good wound healing (usually 14 days post-op), all sutures/staples have been removed, and there is no evidence of infection.**

		○ **Lactation: based on limited but reassuring data, women should be supported if they wish to breastfeed while on TNFi. Data confirms no clinically significant levels of certolizumab in breast milk.** ○ **Paternal exposure: based on limited evidence is likely to be safe.**
Tacrolimus	C	• 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** ○ **Pregnancy: compatible throughout pregnancy at the lowest effective dose with suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels.** ○ **Lactation: can be used whilst breastfeeding.** ○ **Paternal exposure: based on limited evidence is likely to be safe.**
Tocilizumab	C	• 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/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. • Concentrations in breastmilk have been measured at 1/500 – 1/1000 in 2 patients on IV tocilizumab peaking at D3 post infusion with no adverse events in the child. • **Recommendations** ○ **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.** ○ **Timing with caesarean delivery: cease IV tocilizumab at least 4 weeks before surgery, and cease subcutaneous tocilizumab at least 2 weeks before surgery. Like other biologics, it may be restarted once there is good wound healing (usually 14 days post-op), all sutures/staples have been removed, and there is no evidence of infection.** ○ **Lactation: based on limited data breastfeeding is likely to be safe as per other large molecule drugs.** ○ **Paternal exposure: no data relating but no theoretical concerns.**

Tofacitinib	D	• 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. • Precise timing of ceasing tofacitinib is unknown, but due to its short half-life, the discontinuation at least 1 month before conception should be adequate. • **Recommendations** ○ **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: avoid.** ○ **Paternal exposure: no data on which to base recommendation.**
Upadacitinib	D	○ Newer JAK inhibitor with limited data in humans. ○ Animal studies (rats, rabbits) during organogenesis showed increase in fetal malformations including skeletal and cardiac malformations, and spontaneous abortions. ○ Until better data and follow-up contraception should be used during treatment and for 4 weeks after the final dose. ○ Unknown whether excreted in human milk, however animal studies show excretion in milk (up to 30 fold higher exposure in milk compared to maternal plasma). ○ **Recommendations** ○ **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: lack of data and avoid as potential risk to newborn/infant.** ○ **Paternal exposure: no data on which to base recommendation.**
Ustekinumab	B1	• Development toxicity studies showed no harm to fetuses of pregnant monkeys exposed during organogenesis. • $t_{1/2}$ is 21 days hence washout would need to be 15 weeks preconception. • **Recommendations** ○ **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 for prescribers

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

And for patients

- Arthritis Australia (https://arthritisaustralia.com.au/managing-arthritis/living-with-arthritis/pregnancy/)
- American College Rheumatology (http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic- Disease/Pregnancy-Rheumatic-Disease)

Key References

- 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.
- BSR biologic DMARD safety guidelines in inflammatory arthritis. Holroyd CR et al. Rheumatology 2019;58:e3-e42. doi:10.1093/rheumatology/key208.
- 2020 ACR guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Sammaritano LR et al. Arthritis & Rheumatology 2020;72(4):529-556. doi:10.1002/art.41191.
- 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.
- Management of pregnancy in women with rheumatoid arthritis. Ngian G-S et al, Med J Aust 2016; 204 (2): 62-63.
- 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.
- Maternal and Fetal Outcomes in a Cohort of Patients Exposed to Tumour Necrosis Factor Inhibitors throughout Pregnancy. Genest, G et al. J Rheumatol First Release July 1 2018; doi:10.3899/jrheum.171152
- Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. van den Brandt et al. Arthritis Research & Therapy (2017) 19:64
- Pregnancy outcomes and disease activity in women with axial spondyloarthritis: a systematic literature review. A. Moltó 10.1136/annrheumdis-2018-eular.3056
- Paternal exposure to antirheumatic drugs—What physicians should know: Review of the literature. Micu MC et al https://doi.org/10.1016/j.semarthrit.2018.01.006

Further references available on request.

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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 fetus 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 fetus 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 fetus 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 fetus 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 fetus 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 fetus 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