General comments

- All women with rheumatic diseases should receive pre-pregnancy counseling, as well as discussion around contraception.
- Treatment options should be discussed with the mother to ensure an informed decision is made with respect to the balance 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 with DMARDs with a good safety profile in pregnancy such as hydroxychloroquine (HCQ), sulfasalazine (SSZ) and azathioprine (AZA) have a better outcome for mother and infant 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.
- 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.

Spondyloarthropathy (SpA)
• In Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) disease activity does not typically change during pregnancy.

Systemic Lupus Erythematosus (SLE)
• In SLE flares occur in up to two thirds of women during pregnancy. Flares are more likely to occur if disease is active at conception. SLE patients have an increased risk of miscarriage, prematurity, LBW and preeclampsia.
• Risk 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.
• Ideally mothers should embark on pregnancy when SLE disease activity has been stable for at least 6 months.
• In SLE cessation of hydroxychloroquine (HCQ) is associated with increased disease activity (assessed by SLEDAI) 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 pre-eclampsia in women with SLE, especially if active disease, history of lupus nephritis, history of hypertension or antiphospholipid syndrome.

Antiphospholipid Syndrome (APS)
• Low dose aspirin (LDA) should be considered for SLE patients with a history of antiphospholipid antibodies.
• Heparin or low-molecular weight heparin prophylaxis should be considered for women with a history of obstetric antiphospholipid syndrome or history of VTE 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 a low molecular weight heparin 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. If they do fall pregnant, 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 pre-eclampsia.
• Due to the higher risk of developing renal crisis in the early years of diffuses systemic sclerosis, these women might be encouraged to delay pregnancy.
**Thrombosis**

- All women should undergo an assessment of risk of VTE during pregnancy and 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 obstetric/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, these agents might be avoided in preference for agents with lower thrombotic risk.

**Lactation**

- Drug concentrations in breast milk that expose the infant to 0.1% of the maternal dose are generally regarded as safe: those >10% regarded as requiring caution or avoidance. The exception to this is methotrexate (MTX), where despite low levels in breast milk there are concerns about drug accumulation in neonatal tissues.
- Biological DMARDs (bDMARDs) e.g. abatacept, anakinra, belimumab, TNFi, tocilizumab, rituximab, can be present in small amounts in breast milk but unlikely to be absorbed by the neonate due to poor bioavailability.

**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, 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 need to be reviewed 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.

Since 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.

<table>
<thead>
<tr>
<th>Medication</th>
<th>TGA category</th>
<th>Notes for prescribers</th>
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</table>
| Abatacept  | C            | • Due to expected concomitant use of MTX, unplanned pregnancy should be discussed with a specialist in this field  
• > 20 case reports with variable outcomes including some live healthy births. Further database from BMS show 128 maternal exposures with no increase in congenital anomalies and no pattern of congenital anomalies.  
• Recommendations  
  o Pregnancy: there are insufficient data to recommend in pregnancy, but unintentional exposure early in the first trimester is unlikely to be harmful  
  o Lactation: no data upon which to base a recommendation for use in breastfeeding.  
  o Paternal exposure: no data relating to paternal exposure but it is unlikely to be harmful |
| Adalimumab | C            | • See TNF inhibitors |
| Anakinra   | B1           | • Animal studies have not shown evidence of fetal harm  
• No controlled data in human pregnancy  
• Observational data has not shown evidence of harm  
• Recommendations  
  o Pregnancy: use during pregnancy when benefit outweighs risk  
  o Lactation: no data upon which to base a recommendation for use in breastfeeding  
  o Paternal exposure: no data relating to paternal exposure but it is unlikely to be harmful |
| Aspirin    | C            | • 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 antiphospholipid syndrome |
<table>
<thead>
<tr>
<th>Medication</th>
<th>Category</th>
<th>Recommendations</th>
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</table>
| **Azathioprine**    | D        | - Lactation: aspirin is excreted into breast milk at low concentrations. The AMH recommends that ibuprofen is preferred (due to theoretical risk of Reyes syndrome) 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 relating but no theoretical concerns  

| **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       | - 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 hypocalaemic 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 infant. 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 infants the bioavailability is not known. Pamidronate is also highly bound by calcium, further reducing possible absorption from milk.  
- **Recommendations**  
  - 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        | - See TNF inhibitors  

| **Colchicine**      | B2       | - 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**
  - Pregnancy: continue during pregnancy if clinically indicated
  - Lactation: considered safe but exposure can be minimised by maximising the time between dose and subsequently feeding.
  - Paternal exposure: no data on which to base recommendation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rating</th>
<th>Summary</th>
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| Corticosteroids | A      | Can be used if DMARDs with a good safety profile in pregnancy (HCQ, SSZ and HCQ) 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, preeclampsia, gestational diabetes (GDM), osteopaenia/porosis and infection. Fetal concerns include prematurity, low birth weight, 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 as increased risk of oral clefts from 1:1000 to 3:1000 with 1st trimester exposure, more recent studies show no link. **Recommendations**
  - Pregnancy: use in pregnancy if other options not suitable
  - Lactation: if prednisolone dose > 20 mg/day aim to breastfeed 4 hours post dose
  - Paternal exposure: compatible with paternal exposure

| Cyclophosphamide | D      | Avoid in pregnancy; can be used in second half of pregnancy if life threatening maternal illness. Lactation: avoid. Paternal exposure: **Recommendations**
  - Pregnancy: use in second half of pregnancy only if no other options not suitable
  - Lactation: avoid
  - Paternal exposure: avoid

| Cyclosporin      | 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**
  - Pregnancy: can be used in pregnancy with careful monitoring
  - Lactation: should not be discouraged
  - Paternal exposure: no data relating but no theoretical concerns

| Etanercept      | D      | See TNF inhibitors
<table>
<thead>
<tr>
<th>Drug</th>
<th>B3</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td></td>
<td>• Avoid in pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No definite evidence of fetal malformations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Common practice is to continue until pregnancy then ceases. Give monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>injections on first day of menses (assuming regular menses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactation: Gold is excreted into breast milk. Caution as possible risk of</td>
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<tr>
<td></td>
<td></td>
<td>long term effects if accumulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy: use in pregnancy if options not suitable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactation: avoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paternal exposure: no data relating but no theoretical concerns</td>
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</tbody>
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<tr>
<th>Drug</th>
<th>C</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golimumab</td>
<td></td>
<td>• See TNF inhibitors</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Drug</th>
<th>D</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td></td>
<td>• Appears safe in pregnancy. Long term follow-up of exposed infants has been</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unremarkable.</td>
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<tr>
<td></td>
<td></td>
<td>• Due to its long half life stopping the drug in pregnancy would not avoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fetal exposure.</td>
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<tr>
<td></td>
<td></td>
<td>• Use in pregnancy women with SLE is associated with improved pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy: can be used in pregnancy; women with SLE should be on HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during pregnancy unless specific contraindication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactation: should not be discouraged. Low levels in breast milk</td>
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<tr>
<td></td>
<td></td>
<td>• Paternal exposure: no data relating but no theoretical concerns</td>
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<tr>
<th>Drug</th>
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<th>Recommendations</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td></td>
<td>• See TNF inhibitors</td>
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<tr>
<th>Drug</th>
<th>X</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Leflunomide</td>
<td></td>
<td>• Contraindicated in pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Usually avoided in young women due to long half life (2 weeks)</td>
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<tr>
<td></td>
<td></td>
<td>• Increased congenital malformations in animals similar doses to humans</td>
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<td></td>
<td></td>
<td>• Prospective human study failed to show increased teratogenic risk, with the</td>
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<tr>
<td></td>
<td></td>
<td>majority having cholestyramine washouts</td>
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<td></td>
<td></td>
<td>• If regularly taken anytime in the 2 years pre desire to conceive, consider</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cholestyramine washout with cholestyramine 8g TDS for 11 days (not necessarily</td>
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<tr>
<td></td>
<td></td>
<td>consecutive)</td>
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<td>• Plasma levels &gt; 0.02mg/L should be verified twice 2 weeks apart. If</td>
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<td>unacceptably high levels persist, additional cholestyramine can be given.</td>
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<tr>
<td></td>
<td></td>
<td>Recommended to wait 3 menstrual cycles post chelation before attempting to</td>
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<tr>
<td></td>
<td></td>
<td>conceive</td>
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<tr>
<td></td>
<td></td>
<td>• For Arava brand-contact Sanofi-Aventis Medical Information Department- 1800</td>
</tr>
<tr>
<td></td>
<td></td>
<td>818 806/option 1, for free plasma testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy: if unplanned pregnancy occurs, stop immediately, commence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cholestyramine washout and see expert opinion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactation: avoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paternal exposure: based on very limited evidence it may be compatible but</td>
</tr>
<tr>
<td></td>
<td></td>
<td>further studies to confirm are warranted</td>
</tr>
</tbody>
</table>
| **Methotrexate** | D | - Known teratogen  
- Contraindicated in pregnancy  
- Current recommendations cease 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 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**  
  o 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  
  o Lactation: avoid  
  o Paternal exposure: based on recent publications low-dose MTX may be compatible with paternal exposure |
| **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**  
  o Pregnancy: cease at least 6 weeks pre-conception  
  o Lactation: avoid  
  o 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 >200,000 pregnant women of > 11 000 pregnant women who received NSAIDs showed no association between nonselective-NSAID exposure and congenital malformations. One study showed increased risk of musculoskeletal malformations subset receiving Cox-2 inhibitors  
- Ibuprofen or diclofenac post 2nd trimester slightly increased risk maternal bleeding, LBW or asthma in infant.  
- 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**  
  o 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. |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>Penicillamine</strong></td>
<td>D</td>
<td></td>
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</tbody>
</table>
|  - 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**  
|  - Pregnancy: avoid in pregnancy  
|  - Lactation: avoid  
|  - Paternal exposure: non-selective NSAIDs are compatible with paternal exposure |
| **Rituximab** | C |  
|  - 200 pregnancies associated with maternal exposure with > 150 know outcomes incl 90 live births  
|  **Recommendations**  
|  - Pregnancy: avoid in pregnancy: BSR recommends delay conception at least 6 months post last dose while ACR recommend a 12 month delay  
|  - Lactation: there are no data upon which to base a recommendation for use in breastfeeding  
|  - Paternal exposure: based on limited evidence is compatible with paternal exposure |
| **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. Additional folic acid supplementation should be discussed prior to pregnancy planning  
|  - Lactation: Moderate transfer to breast milk (40-60% maternal levels). One report of bloody diarrhea in an exposed infant. 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. |
| **TNF inhibitors: Adalimumab Etanercept Certolizumab 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.  
|  - 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 TNFi in 1<sup>st</sup> and 2<sup>nd</sup> trimester when needed as the risk of active disease is greater than potential risk from medication. Suspension in the 3<sup>rd</sup> trimester with resumption post delivery/breast feeding  
|  - In more than 600 pregnancies in patients with rheumatic diseases on TNFi 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 but 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 continue to note on their 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](http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic-Disease/Pregnancy-Rheumatic-Disease))
- 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. Discuss with neonatologist/paediatrician is recommended. Due to lower rates of transfer with etanercept and certolizumab that decision may be revised.
- Avoid BCG vaccination in infant in first 6 months if exposed.

### Recommendations
- **Pregnancy:** current evidence supports continuing infliximab until 16 weeks and adalimumab 32 weeks and then cease, while etanercept can be continued until to 32 weeks and throughout pregnancy if indicated. Certolizumab is not actively transported across the placenta due to its lack of an Fc segment, hence there is no rationale to stop it antenatally. 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 recommendation deferring live vaccines
  - **Lactation:** based on limited but reassuring data, women should not be discouraged from breastfeeding while on TNFi
  - **Paternal exposure:** based on limited evidence adalimumab, etanercept and infliximab are compatible with paternal exposure

### Tacrolimus
- **Pregnancy:** 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:** 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 compatible with paternal exposure
| 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 per kg every 2 to 4 weeks.  
• Adequate and well-controlled studies have not been conducted in pregnant women  
• 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**  
  o 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  
  o Lactation: there are no data upon which to base a recommendation for use in breastfeeding  
  o Paternal exposure: there are no data relating to paternal exposure but it is unlikely to be harmful |
| Tofacitinib | D | • Adequate and well-controlled studies have not been conducted in pregnant women  
• 29 pregnancies analyzed, 16 healthy newborns were delivered (57.1%). Of these, 11 of the mothers were receiving tofacitinib monotherapy and five were receiving tofacitinib plus methotrexate. Two of the healthy newborns were of low birth weight.  
• Until better data and follow-up, pregnancy should be avoided  
• **Recommendations**  
  o Pregnancy: Avoid in pregnancy  
  o Lactation: avoid  
  o Paternal exposure: no data on which to base recommendation |
Other useful resources include

- MotherSafe website (http://www.mothersafe.org.au/)
- Mother- ToBaby (www.mothertobaby.org)

Key References

- Current Opinion in Rheumatology: 2014;26:3

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 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.