Rheumatology Medications in Pregnancy

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Conflict of interest

- Outreach Clinics
  - Check up QLD
  - ARA, AbbVie, BMS, Janssen, MSD, Roche, UCB
- National Prescribing Service
- Pharmaceutical companies
  - BMS, UCB
    - conference support
    - advisory board
    - research grant

Rheumatoid Arthritis (RA) and pregnancy

- Women with RA on average take to conceive
  - one-third > 12 months
  - 15% unable to
  - average families smaller
- RA patients have increased risk
  - Small for Gestational Age (SGA)
  - Premature or low birth weight (LBW)
  - Caesarean section

RA activity before and after pregnancy

Before

- Early studies
  - small number, retrospective, “looking back” 75-90%
- 2008
  - seropositive RA better 39%
    - in remission < 25%
- **2017**
  - **worse in pregnancy 29%**
  - same or better 71%

Post

- 1999
  - 80-90% flare by 13 wks
- 2008
  - 39% flare by 26 wks
    - Medication continued
    - Early restart

TGA Classification of Drugs in Pregnancy

A: No increase in malformations or other harmful effects to foetus

B: Limited human data, without increase in malformation or other harmful effects

B1: Studies in animals show no evidence of foetal harm

B2: Studies in animals are inadequate but show no evidence of foetal harm

B3: Studies in animals show increased fetal harm, but significance in humans uncertain

C: Drugs causing or suspected of causing, harmful to foetus excluding malformations

D: Drugs causing or suspected or expected to cause increased foetal malformations or irreversible damage

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

http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm

TGA C

A: No incre

B: Limited l armful effects

B1

B2 e of foetal harm

B3 ficance in hu

C: Drugs ca g malformati

D: Drugs ca malformati

X: Drugs wl to the foetus that possibility of pregnan

tegorisation.htm

Therapeutics Goods Administration (TGA) assigned categories misleading

- Must be reviewed in association with clinical evidence
- Some category D medications are safe in pregnancy
  - Others not
- 06/15 US Food and Drugs Administration (FDA) initiated new system to assist prescription during pregnancy removing letter classification
- Australian TGA has not expressed plans to make any changes

NSAIDs and Cox- 2 inhibitors
Cat C up to week 32, category D after

- Stop when conception planned
- Avoid in first 6-8 weeks if possible
  - older studies ? increase miscarriage
  - newer do not
- Stop 3rd trimester
  - premature closure of ductus arteriosus
- Aspirin 150mg/day throughout pregnancy if clinically indicated

- Breastfeeding
  - ibuprofen & diclofenac preferred
    - shorter t ½
    - inactive metabolites
    - lower breast milk levels

Hydroxychloroquine Cat D

- Can be used
- **Use in pregnancy women with SLE is associated with improved pregnancy outcomes and is recommended unless specific contraindication**
- Can be used whilst breastfeeding
- Paternal exposure: no data relating but likely to be safe

Sulfasalazine Cat A

- Can be used
  - Folic acid supplementation 2-5mg/day commenced at least 1 month prior to pregnancy planning and continued throughout pregnancy
- Can be used whilst breastfeeding
- Associated with reversible azoospermia/oligospermia in men and reduced sperm motility
    - International experts ceasing only after 3 months of unsuccessful conception
      - active RA when medication stopped may affect quality of sperm

Azathioprine Cat D

- Can be used in pregnancy at < 2mg/kg/day
- Can be used when breastfeeding
  - most drug excreted within 4 hours of ingestion.
- Paternal exposure: no data but likely to be safe

Tumour Necrosis Factor inhibitors (TNFi) Cat C/D

- Can be used
  - 2492 pregnancies exposed
    - No increase
      - miscarriages
      - congenital malformations
      - infections in baby
- Stop time depends on
  - specific medication
  - level of disease activity

- Use in 2nd/3rd trimester
  - crosses the placenta
  - avoid live vaccines
- Can be used whilst breastfeeding
- Paternal exposure
  - based on limited evidence is likely to be safe

Corticosteroids Cat A

- Older studies ↑ oral clefts
  - more recent studies no link
- Use if pregnancy safe DMARDs are
  - inadequate
  - contraindicated
  - poorly tolerated
- Use lowest possible dose
  - <20mg/daily
- Can be used whilst breastfeeding
  - If > 20 mg/day breastfeed 4 hours post dose

- Mother risks
  - Delayed conception
  - Weight gain, HT, DM
  - Osteopaenia/porosis
  - Infection
    - dose related
    - more prominent last trimester
- Fetal
  - Premature rupture of membranes
  - Prematurity
  - Low/high birth weight

Methotrexate Cat D

- Pregnancy
  - cease 3 months preconception v stop for ≥1 ovulatory cycle
- Unplanned pregnancy
  - cease immediately
  - institute 5 mg folic acid daily
  - seek expert opinion
- Exposure to low dose MTX (<30mg/week)
  - >40% risk of miscarriage
  - risk of major congenital malformation
- Avoid if breastfeeding
- Paternal exposure
  - > 300 pregnancies after paternal exposure to MTX <30mg/week no increased risk of adverse foetal outcomes compared with non-exposed pregnancies

Leflunomide Cat X

- Pregnancy
  - Cease 2 years preconception
  - Unplanned pregnancy
    - cease immediately
    - commence cholestyramine washout
    - seek expert opinion
- Avoid if breastfeeding
- Paternal exposure
  - based on very limited evidence it may be compatible but further studies to confirm are warranted

DMARDs and pregnancy/breastfeeding/paternal compatibility

DMARD	TGA category	pregnancy compatibility	breastfeeding compatibility	Paternal compatibility
Hydroxychloroquine (HCQ)	D	YES	YES	YES
Sulfasalazine (SSZ)	A	YES	YES	YES
Azathioprine (AZA)	D	YES	YES	YES
Tumour Necrosis Factor Inhibitors (TNFi)	C/D	YES	YES	YES
Methotrexate	D	NO	NO	YES
Leflunomide	X	NO	NO	PROBABLY

Australian Rheumatology Association

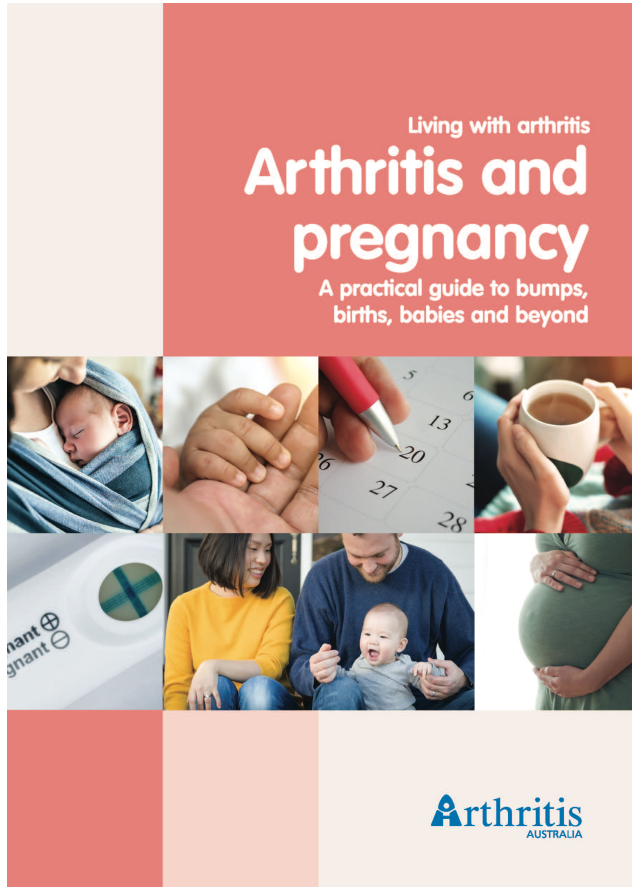
Guidance on Prescribing Medications for Rheumatic Diseases inPregnancy

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 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.
- 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, 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.

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.

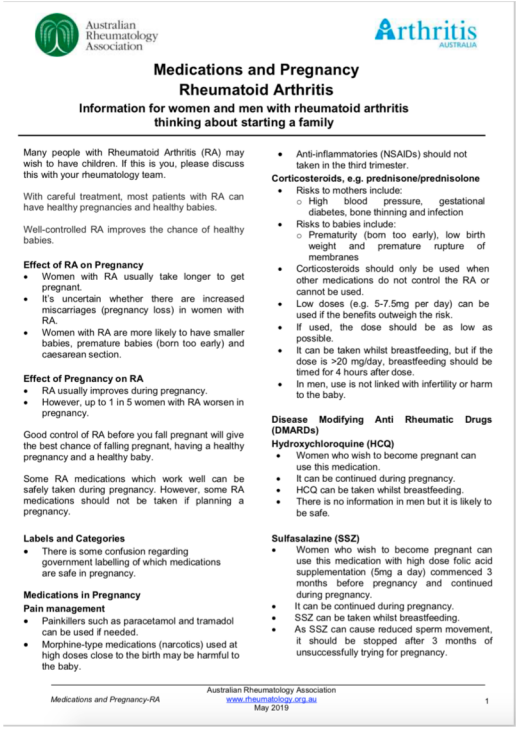


- https://rheumatology.org.au/gps/documents/ARAPregnancyPrescribingGuidanceupdateApr19.pdf

Pregnancy-compatible DMARDs

- Better outcome for mother and baby when RA optimally controlled on “safe” DMARDs
  - Hydroxychloroquine
  - Sulfasalazine
  - Azathioprine
  - TNF inhibitors

than maintained on corticosteroid
untreated high disease activity



Australian Rheumatology Association

Arthritis AUSTRALIA

Medications and Pregnancy
Rheumatoid Arthritis
Information for women and men with rheumatoid arthritis thinking about starting a family

Many people with Rheumatoid Arthritis (RA) may wish to have children. If this is you, please discuss this with your rheumatology team.

With careful treatment, most patients with RA can have healthy pregnancies and healthy babies.

Well-controlled RA improves the chance of healthy babies.

Effect of RA on Pregnancy
- Women with RA usually take longer to get pregnant.
- It's uncertain whether there are increased miscarriages (pregnancy loss) in women with RA.
- Women with RA are more likely to have smaller babies, premature babies (born too early) and caesarean section.

Effect of Pregnancy on RA
- RA usually improves during pregnancy.
- However, up to 1 in 5 women with RA worsen in pregnancy.

Good control of RA before you fall pregnant will give the best chance of falling pregnant, having a healthy pregnancy and a healthy baby.

Some RA medications which work well can be safely taken during pregnancy. However, some RA medications should not be taken if planning a pregnancy.

Labels and Categories
- There is some confusion regarding government labelling of which medications are safe in pregnancy.

Medications in Pregnancy
Pain management
- Painkillers such as paracetamol and tramadol can be used if needed.
- Morphine-type medications (narcotics) used at high doses close to the birth may be harmful to the baby.
- Anti-inflammatories (NSAIDs) should not taken in the third trimester.

Corticosteroids, e.g. prednisone/prednisolone
- Risks to mothers include:
  - High blood pressure, gestational diabetes, bone thinning and infection
- Risks to babies include:
  - Prematurity (born too early), low birth weight and premature rupture of membranes
- Corticosteroids should only be used when other medications do not control the RA or cannot be used.
- Low doses (e.g. 5-7.5mg per day) can be used if the benefits outweigh the risk.
- If used, the dose should be as low as possible.
- It can be taken whilst breastfeeding, but if the dose is >20 mg/day, breastfeeding should be timed for 4 hours after dose.
- In men, use is not linked with infertility or harm to the baby.

Disease Modifying Anti Rheumatic Drugs (DMARDs)
Hydroxychloroquine (HCQ)
- Women who wish to become pregnant can use this medication.
- It can be continued during pregnancy.
- HCQ can be taken whilst breastfeeding.
- There is no information in men but it is likely to be safe.

Sulfasalazine (SSZ)
- Women who wish to become pregnant can use this medication with high dose folic acid supplementation (5mg a day) commenced 3 months before pregnancy and continued during pregnancy.
- It can be continued during pregnancy.
- SSZ can be taken whilst breastfeeding.
- As SSZ can cause reduced sperm movement, it should be stopped after 3 months of unsuccessfully trying for pregnancy.

Medications and Pregnancy-RA Australian Rheumatology Association www.rheumatology.org.au May 2019 1

Tumour Necrosis Factor Inhibitors (TNFi)
- Women who wish to become pregnant can use these medications.
- Check with your rheumatologist for the latest recommendations
- If continuing a TNFi in the third trimester is needed, it is wise to avoid live vaccines in your baby - please discuss with your rheumatologist and/or obstetric physician, and paediatrician.
- TNFi can be taken whilst breastfeeding.
- Use in men is probably safe but there's limited information.

Non-TNFi biological DMARDs including abatacept, rituximab, tocilizumab
- Due to limited information, it is currently recommended to avoid these medications during pregnancy.
- If an unplanned pregnancy occurs, you should see a specialist in the field to discuss the pregnancy.
- Breastfeeding information is limited, but the amount in milk is likely to be very low, and it is probably destroyed in the baby's gut.
- There is no information on which to base recommendation for fathering but they are likely to be safe.

Tofacitinib and baricitinib
- Due to limited information it is currently recommended to avoid this medication in pregnancy.
- If an unplanned pregnancy occurs the medication should be stopped and you should see a specialist in the field to discuss the pregnancy.
- Breastfeeding is not recommended.
- There is no information on which to base recommendation for fathering but they are likely to be safe.

DMARDs that should be AVOIDED during pregnancy

Methotrexate (MTX)
- This medication can harm the baby
- It should be stopped 3 months before trying to become pregnant
- If unplanned pregnancy occurs, MTX should be stopped immediately, 5 mg folic acid daily started and a specialist in the field should be seen to discuss the pregnancy.
- Breastfeeding should be avoided.
- Based on recent information, low-dose MTX appears safe with fathering.

Leflunomide (LEF)
- LEF is not recommended for use in pregnancy.
- It should be stopped 2 years before trying to fall pregnant or a cholestyramine washout is recommended.
- If unplanned pregnancy occurs, LEF should be stopped immediately, cholestyramine washout should be started and a specialist in the field should be seen to discuss the pregnancy.
- Avoid breastfeeding.
- Based on limited information LEF may be compatible with fathering but further studies to confirm are needed.

Remember with careful medical and obstetric management, most patients with RA can have successful pregnancies. If you have any questions please ask your rheumatologist.

More detailed information can be found at:
Arthritis Australia (https://arthritisaustralia.com.au/wordpress/wp-content/uploads/2018/06/ArthAus_ArthPregnancy_180529_final_low-res.pdf)
American College of Rheumatology Website. (https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic-Disease/Pregnancy-Rheumatic-Disease)

Your GP or other members of your care team may find the **Australian Rheumatology Association (ARA) Guidance on Prescribing Medications for Rheumatic Diseases in Pregnancy** helpful. https://rheumatology.org.au/gps/documents/ARAPregnancyPrescribingGuidanceupdateApr19.pdf