Rheumatoid Arthritis and Pregnancy

Safety Considerations in Pharmacological Management
Introduction

Pregnancy can pose a challenge to the physician caring for women with rheumatoid arthritis (RA). While many women with RA experience a spontaneous improvement in joint pain and inflammation during pregnancy, in others it remains active and they continue to need ongoing therapy. It is important to tailor the treatment regimen so that the disease is stabilized prior to conception and to use medications that are safe throughout pregnancy and lactation.

The safety profile of relevant drugs used for RA, particularly the new biologicals, pre-conception, during pregnancy and with breastfeeding have been summarized.

Recommendations for relatively safe drug options for RA management in pregnant women and, where available, preconception recommendations for men using RA medications are also discussed.
RECOMMENDATIONS

**NSAIDs**

- **US FDA pregnancy category**
  - Category B (refer table 1 for definitions of FDA pregnancy categories).

- **Potential Fetal Toxicity**
  - Premature closure of ductus arteriosus and impaired renal function with third trimester exposure

- **Recommendations**
  - Chronic use of NSAIDs should be avoided in pregnancy, especially in the third trimester.
  - The use of NSAIDs should be considered with caution before the 24th week, with intermittent use of low-dose NSAIDs with a short half-life being preferred.
  - A few NSAIDs are considered safe for use during lactation. The American Academy of Pediatrics (AAP) considers diclofenac, flufenamic acid, ibuprofen, indomethacin, mefenamic acid, naproxen, piroxicam and tolmetin to be compatible with breastfeeding.
  - Breastfeeding immediately before a dose may help to minimize infant exposure to the medication.

**Corticosteroids**

- **US FDA pregnancy category**
  - Category B (refer table 1 for definitions of FDA pregnancy categories).

- **Potential Fetal Toxicity**
  - Possible risk for oral clefts with first trimester exposure
Recommendations
- Corticosteroids may be used for RA during pregnancy at the lowest effective dose.
- Mothers should be counseled regarding the low risk of oral clefts with first-trimester exposure.
- Breastfeeding while on corticosteroids carries minimal risk of exposure to the infant, which may be further decreased by nursing immediately before or more than 4 hours after the dose.

DMARDs Considered Safe during Pregnancy and Lactation

Chloroquine and Hydroxychloroquine

- **US FDA pregnancy category**
  - Category C (refer table 1 for definitions of FDA pregnancy categories).

- **Potential Fetal Toxicity**
  - No increased risk reported at doses commonly used in RA

- **Recommendations**
  - Antimalarials are considered safe for use during pregnancy and lactation.
  - Hydroxychloroquine may be preferred over chloroquine because of its better-studied safety profile.

Sulfasalazine

- **US FDA pregnancy category**
  - Category B (refer table 1 for definitions of FDA pregnancy categories).
Potential Fetal Toxicity
- No increased risk reported at doses commonly used in RA

Recommendations
- Antimalarials Sulfasalazine may be safely continued during pregnancy. Folic acid supplementation remains important.
- Male infertility from sulfasalazine is reversible; men should discontinue sulfasalazine 3 months prior to attempting conception.
- The AAP considers sulfasalazine compatible with breastfeeding when used with caution, but avoid breastfeeding if infant premature, hyperbilirubinaemic or deficient in glucose-6-phosphate dehydrogenase

Azathioprine

US FDA pregnancy category
- Category D (refer table 1 for definitions of FDA pregnancy categories).

Potential Fetal Toxicity
- Sporadic congenital anomalies
- Transient immune alterations

Recommendations
- Azathioprine is classified as an FDA Category D drug. However, given the current evidence on favourable human safety in pregnancy and lactation, azathioprine may be used during pregnancy and while breastfeeding.

DMARDs Contraindicated during Pregnancy and Lactation

Methotrexate

US FDA pregnancy category
- Category X (refer table 1 for definitions of FDA pregnancy categories).
Potential Fetal Toxicity
- Sporadic congenital anomalies
- Transient immune alterations

Recommendations
- Methotrexate is contraindicated in pregnancy and lactation.
- It is recommended that conception be postponed until 3 months after cessation of therapy for both women and men.
- Adequate folate supplementation is advised pre-conception and throughout pregnancy.
- The AAP does not recommend use of methotrexate while breastfeeding.

Leflunomide

US FDA pregnancy category
- Category X (refer table 1 for definitions of FDA pregnancy categories)

Potential Fetal Toxicity
- Embryotoxicity in animals

Recommendations
- Leflunomide is contraindicated in pregnancy and lactation.
- Discontinue 2 years prior to conception or initiate washout with cholestyramine.
- Drug washout is recommended in women and men taking leflunomide before planning a family, with a goal of plasma levels of the active metabolite of <0.02 mg/mL as there has been no demonstrable risk in animals below this level.
- This can be achieved with an 11-day washout with cholestyramine at 8 g three times daily. This reduces the active metabolite half-life to 1 day, compared with 96 days if cholestyramine were not used.
Biological Response Modifiers

Tumour Necrosis Factor Inhibitors

➢ US FDA pregnancy category
  • Category B (refer table 1 for definitions of FDA pregnancy categories).

➢ Potential Fetal Toxicity
  • Case reports of VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal, Renal and Limb anomalies)

➢ Recommendations
  • Given limited human safety data during pregnancy and breastfeeding, the current recommendation is that these medications are discontinued at the first missed period and are avoided during lactation.
  • Based on limited human data, men may not need to discontinue use when planning a family.

Anakinra

➢ US FDA pregnancy category
  • Category B (refer table 1 for definitions of FDA pregnancy categories).

➢ Potential Fetal Toxicity
  • No increased risk reported

➢ Recommendations
  • Given limited human safety data during pregnancy and breastfeeding, the current recommendation is that anakinra be discontinued at the first missed period and are avoided during lactation.

Abatacept

➢ US FDA pregnancy category
  • Category C (refer table 1 for definitions of FDA pregnancy categories).
Potential Fetal Toxicity
- Inadequate human safety data

Recommendations
- Abatacept is not recommended in pregnancy or lactation.
- Women of childbearing potential and men are advised to use effective contraception during treatment and for at least 10 weeks, ideally 18 weeks, following the last infusion, before planning a pregnancy.

Rituximab

- US FDA pregnancy category
  - Category C (refer table 1 for definitions of FDA pregnancy categories).

- Potential Fetal Toxicity
  - Case reports of transient lymphopenia

Recommendations
- Rituximab is not recommended in pregnancy or lactation.
- Women of childbearing potential and men are advised to use effective contraception during treatment and for at least 1 year after the last dose before attempting to conceive.

Tocilizumab

- US FDA pregnancy category
  - Category C (refer table 1 for definitions of FDA pregnancy categories).

- Potential Fetal Toxicity
  - Inadequate human safety data

Recommendations
- Tocilizumab is not recommended in pregnancy or lactation.
- Women of childbearing potential and men are advised to use effective contraception during treatment and to discontinue tocilizumab at least 3–6 months prior to conception.
Table 1: FDA definitions of pregnancy category

<table>
<thead>
<tr>
<th>FDA pregnancy category</th>
<th>Risk summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks</td>
</tr>
<tr>
<td>FDA pregnancy category</td>
<td>Risk summary</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits</td>
</tr>
</tbody>
</table>
Conclusion

- Particularly for women with RA in their reproductive years, the short- or long-term desirability of pregnancy needs to be considered when choosing immunomodulating therapy.

- Educating both women and men about appropriate contraception is key to avoiding unplanned pregnancies while on RA drugs that may be teratogenic or that have unknown safety profiles.

- A strategy for RA management during pregnancy is necessary for the health of the mother and to limit potential toxicity to the fetus.

- A successful pregnancy with disease stability is best achieved by ensuring disease quiescence pre-conception, the use of safe medications during pregnancy and close rheumatological follow-up during pregnancy and post-partum.

- Disease flares can be managed acutely with intraarticular or oral corticosteroids.

- Choice of medications post-partum will depend on whether breastfeeding is anticipated.
Drugs used in the management of rheumatoid arthritis and their safety profiles for conception, pregnancy and lactation in women of childbearing potential

<table>
<thead>
<tr>
<th>Drug</th>
<th>US FDA pregnancy category</th>
<th>Potential fetal toxicity</th>
<th>Recommendations</th>
</tr>
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</table>
| NSAIDs        | B                         | Premature closure of ductus arteriosus and impaired renal function with third trimester exposure | • Avoid use in third trimester  
• Use with caution before the 24th week; if used, consider NSAIDs with short half-life, at low dose and intermittently  
• Breastfeed immediately prior to NSAID dose |
| Corticosteroids| B                         | Possible risk for oral clefts with first trimester exposure                               | • Use lowest effective dose during pregnancy  
• Breastfeed immediately prior to or from 4 hours after dose |
| DMARDs        |                           |                                                                                          |                                                                                                       |
| Chloroquine, Hydroxychloroquine | C              | No increased risk reported at doses commonly used in RA    | • Safe to continue during pregnancy and lactation |
| Sulfasalazine | B                         | No increased risk reported at doses commonly used in RA    | • Use folic acid supplementation pre-conception and during pregnancy  
• Safe to continue during pregnancy  
• Safe to continue during lactation, but avoid breastfeeding if infant premature, hyperbilirubinaemic or G6PD deficient |
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<th>US FDA pregnancy category</th>
<th>Potential fetal toxicity</th>
<th>Recommendations</th>
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<tr>
<td>Azathioprine</td>
<td>D</td>
<td>Sporadic congenital anomalies and Transient immune alterations</td>
<td>• Safe to continue during pregnancy and lactation, if necessary, based on available human safety data</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>CNS, skeletal and cardiac abnormalities ('aminopterin syndrome')</td>
<td>• Contraindicated in pregnancy and lactation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Discontinue use 3 months prior to conception</td>
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<td></td>
<td>• Continue folic acid use pre-conception and during pregnancy</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>X</td>
<td>Embryotoxicity in animals</td>
<td>• Contraindicated in pregnancy and lactation</td>
</tr>
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<td>• Discontinue 2 years prior to conception or initiate washout with cholesteryramine 8 g tid for 11 days with plasma levels &lt;0.02mg/L on two separate tests 2 weeks apart</td>
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<tr>
<td>Biologicals</td>
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<tr>
<td>TNF inhibitors a</td>
<td>B</td>
<td>Case reports of VACTERL</td>
<td>• Inadequate human safety data available to support use in pregnancy or lactation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Discontinue with first missed period</td>
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<td>Abatacept</td>
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<td>Rituximab</td>
<td>C</td>
<td>Case reports of transient lymphopenia</td>
<td>• Inadequate human safety data available to support use in pregnancy or lactation • Use adequate contraception during treatment and for 12 months after last dose before attempting to conceive</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>C</td>
<td>Inadequate human safety data</td>
<td>• Inadequate human safety data available to support use in pregnancy or lactation • Use adequate contraception during treatment and for up to 6 months after last dose before attempting to conceive</td>
</tr>
</tbody>
</table>

a- Etanercept, infliximab, adalimumab, golimumab, certolizumab.

VACTERL- Vertebral anomalies, Anal atresia, Cardiac defects, TracheoEsophageal, Renal and Limb abnormalities.