Pregnancy and rheumatoid arthritis

It's not all doom and gloom

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Contrary to common belief, some medications to treat rheumatoid arthritis (RA) are safe to use during the preconception period, pregnancy and breastfeeding. As uncontrolled RA is associated with subfertility and poor outcomes for both mother and baby, management should be individualised, balancing risks of active disease against any medication-related risks.

Pregnancy is relatively common in women with rheumatoid arthritis (RA) and poses unique management challenges. The reported prevalence of RA is 1 to 2 per 1000 women, which translates to an estimated 5000 to 10,000 Australian women of childbearing age with RA.[1,2] The average birth rate in Australia of 65 per 1000 women gives an estimate of up to 1300 pregnancies in women with RA per year in Australia.

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Many of these women will have been treated with disease-modifying antirheumatic drugs (DMARDs) to minimise pain and joint damage. Some will have stopped all medications before or shortly after conception, fearful of the adverse effects on the fetus, willing to ignore their pain and suffering for the 'benefit' of their baby. Many will remain anxious about the safety of medications, including DMARDs, for their babies. Almost all will be unaware of the adverse effects of uncontrolled RA on their pregnancy.

This article discusses the management of women with RA before, during and after pregnancy, including choice of appropriate medications to treat this potentially devastating disease.

Relation between RA, fertility and pregnancy

RA and fertility

Women with RA have smaller-sized families on average. The reasons for this may include delay in pursuing pregnancy or an inability to conceive caused by poor disease control, suboptimal medication use, and other patient, physician and psychosocial factors. Nearly one-third of patients with RA required longer than 12 months to conceive, and 15% were unable to conceive.[3] Factors implicated in subfertility in women with RA are shown in Box 1.[3-5] A case that illustrates the potential effects of RA on fertility is described in Box 2.

Impact of pregnancy, birth and breastfeeding on RA

In the past it has been reported that RA improves during pregnancy in all patients. Indeed, early small retrospective studies suggested that it did improve in 75 to 90% of women with RA. However, since substantial advances in the management of patients with RA, population-based studies have shown that only about 25% of women remain in remission throughout pregnancy.[6,7]

Postnatal RA flares are common. A 1999 study showed that 80 to 90% of patients with RA had a flare within three months of

1. FACTORS IMPLICATED IN SUBFERTILITY IN WOMEN WITH RHEUMATOID ARTHRITIS[3-5]

Factors associated with subfertility

- Age over 35 years
- High disease activity
- Depression or anxiety
- Taking NSAIDs
- Taking prednisolone at a dose higher than 7.5 mg/day
- Nulliparity

Factors not associated with subfertility

- Prior therapy with methotrexate
- Smoking
- Time since diagnosis of rheumatoid arthritis
- Taking sulfasalazine
- Rheumatoid factor or autoantibodies to cyclic citrullinated peptide

2. CASE: A 35-YEAR-OLD WOMAN WITH RHEUMATOID ARTHRITIS AND DIFFICULTY CONCEIVING

Ms AB, aged 35 years, has a 10-year history of seropositive erosive rheumatoid arthritis (RA) maintained on low-dose once-weekly methotrexate plus sulfasalazine and hydroxychloroquine. She has a 13-year-old son from a previous relationship and is keen to conceive with her new partner. Her RA is well controlled and, in view of the planned pregnancy, she has ceased methotrexate.

Six months later, her disease activity is formally assessed as highly active using the Disease Activity Score (DAS28 – a composite tool that includes the number of swollen tender joints, inflammatory markers and a global score of patient health). Ms AB is not pregnant and is self-medicating with prednisolone to manage her RA symptoms.

After failing to conceive for 12 months, Ms AB begins discussions about IVF. Her RA treatment is optimised with hydroxychloroquine, sulfasalazine and a tumour necrosis factor (TNF) inhibitor. Within three months, her RA is assessed as 'low activity'. Six months later she conceives naturally and gives birth at term to a healthy daughter.

giving birth.[6] However, a study a decade later reported that only 39% had a flare by 26 weeks after the birth. The difference in postpartum flare rates may be explained by continued or early recommencement of DMARDs in the later cohort.[7]

As postnatal flares are common, it is difficult to know whether breastfeeding further increases the risk. There are numerous benefits of breastfeeding for both women and their babies. Women with RA who want to breastfeed should be encouraged to do so but supported if they choose not to.

TABLE 1. RELATIVE RISK OF ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH RHEUMATOID ARTHRITIS

Adverse outcome	Increased risk in RA
Hypertension/pre-eclampsia	Uncertain
Pregnancy loss	No
Pre-term delivery, including premature rupture of membranes	Yes
Caesarean delivery	Yes
Low birth weight/small for gestational age	Yes

Abbreviation: RA = rheumatoid arthritis.

RA and pregnancy outcome

The relative risk of adverse pregnancy outcomes in women with RA is shown in Table 1. To date, published data are unclear as to whether patients with RA who are pregnant have higher rates of maternal hypertension and pre-eclampsia.[8,9] Pregnancy loss does not seem to be increased among patients with RA. Preterm birth, Caesarean delivery and low-birth-weight and small-for-gestational-age infants are more common among women with RA.[9] Preterm birth is most common among patients with moderate-to-severe disease activity.[10]

As the long-term adverse outcomes of small-for-gestational-age infants include an increased risk of cardiovascular mortality, hypertension and diabetes in adulthood, the potential impact of uncontrolled RA activity on both maternal and fetal outcomes should be taken into account.[11]

RA medication and pregnancy

In assessing the overall impact of RA medication on the fetus, the following should be taken into account:

- the specific medication
- gestational age
- the risk to the mother and fetus if RA is untreated.

No studies have adequately tested the effects of DMARDs on human outcomes, and so we have so far relied on observational data from incidental exposures. Until 1993, women of childbearing potential were excluded from randomised controlled trials. Although they are now eligible for inclusion in pharmaceutical trials, pregnancy is prohibited, noted as an 'adverse effect'.

Shepard's principles of teratology state that the agent must be present during crucial periods of development and that experimental models must corroborate findings (i.e. there must be biological plausibility, with the medication acting directly on embryo, fetus or placenta). In Australia, medications are classified according to the TGA categorisation of risk of drug use in pregnancy (Box 3). Unfortunately, the letters in this system are often misinterpreted as gradings. Patients, their families, allied health professionals and many doctors fail to grasp the relevant issues, and patients cease medications for unwarranted reasons.

To avoid such problems in the USA, a pregnancy and lactation-labelling rule was implemented in 2015. This rule mandates removing all pregnancy letter categories from prescription medications in the next three to five years and replacing them with an integrated risk summary for use during pregnancy and lactation and for women and men with reproductive potential. To date, the TGA has no plans to modify the Australian procedure.

Optimising RA treatment in pregnancy

There is increasing evidence that some medications used to treat RA are compatible with pregnancy, whereas others are not. In light of the evidence that RA does not improve during pregnancy for all women and that active RA has potentially adverse outcomes for both the mother and baby, patients should be counselled about the use of medications during the preconception period, pregnancy and the postnatal period. Women of childbearing age with RA need a plan for possible pregnancy. It is also helpful to discuss management options with those who are not actively contemplating pregnancy, so that they are aware of them.

Recommendations on medication use in pregnancy are summarised in Box 4.[12-15] Cases that illustrate the safe use of DMARDs throughout pregnancy and the consequences of inadequately controlled disease are described in Boxes 5 and 6, respectively.

More details of medication TGA categories and recommendations for pregnancy, breastfeeding and paternal exposure are shown in Table 2.[12-15]

3. TGA CATEGORIES FOR RISK OF DRUG USE DURING PREGNANCY

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

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

- **B1:** Studies in animals show no evidence of fetal harm
- **B2:** Studies in animals are inadequate but show no evidence of fetal harm
- **B3:** Studies in animals show increased fetal harm, but significance in humans is uncertain

C: Drugs causing or suspected of causing harm to fetus excluding malformations

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

X: Drugs that 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

4. RECOMMENDATIONS ON USE OF MEDICATIONS FOR MANAGING RHEUMATOID ARTHRITIS IN PREGNANCY[12-15]

Commonly used medications

Compatible with pregnancy

- Hydroxychloroquine
- Sulfasalazine (with folate 5 mg daily)
- Biological disease-modifying antirheumatic drugs (bDMARDs)*
- NSAIDs*
- Glucocorticoids

Cessation recommended before conception

- Methotrexate
- Leflunomide

Uncommonly used medications

Compatible with pregnancy

- Azathioprine
- Cyclosporin
- Tacrolimus

Teratogenic or unknown

- Mycophenolate
- Tofacitinib

* Advice varies between medications and stages of pregnancy.

5. CASE: A 34-YEAR OLD WOMAN WHO TOOK DMARDS THROUGHOUT PREGNANCY

Ms CD is 34 years old and was diagnosed with rheumatoid arthritis (RA) with positive rheumatoid factor/cyclic citrullinated peptide antibodies six months before her wedding eight years ago. She was treated initially with hydroxychloroquine and once-weekly low-dose methotrexate.

Inadequate disease control led to an application for a tumour necrosis factor (TNF) inhibitor. When she wished to conceive, methotrexate was withdrawn and she continued on etanercept.

Since then, she has had three pregnancies and given birth to four healthy babies while taking hydroxychloroquine plus a TNF inhibitor (etanercept during the first pregnancy, adalimumab during the second and certolizumab during the third). Her children are aged 4 and 2 years and twins aged 9 months.

6. CASE: A 32-YEAR-OLD WOMAN WITH THE CONSEQUENCES OF INADEQUATELY CONTROLLED RHEUMATOID ARTHRITIS

Ms EF, aged 32 years, lives in a regional area and presents at a rheumatology outreach clinic. She was diagnosed at the age of 28 years with rheumatoid arthritis (RA) with positive rheumatoid factor/cyclic citrullinated peptide antibodies. She was treated with methotrexate and achieved good RA control. After a year's therapy, she wanted to conceive. She recalls being told she 'had to stop all medications' and 'there were no other options'. During the following nine months preconception, she reports she 'felt awful'.

During her first pregnancy she reports feeling 'well', but the history strongly suggests she tolerated active RA. Four weeks after the birth, her RA flared. She had difficulty holding her baby and breastfeeding. Believing the only treatment she could have was prednisolone, she self-medicated with 25 to 50 mg prednisolone per day and struggled with depression.

Despite active RA she conceived again, this time with twins, who she carried to 37 weeks of pregnancy, again feeling 'well'. She did not consult a rheumatologist because of the challenge of travelling 1000 km to the specialist she had consulted initially and her recollection of being told 'nothing can be done'.

On review at the outreach clinic four weeks after the birth of the twins, assessment confirms a high swollen tender joint count, Cushingoid appearance, irreversible erosive joint disease and significant functional impairments, some of which may have been preventable with optimal care.

She is treated with sulfasalazine and hydroxychloroquine. Nine months later, her RA is moderately well controlled, but the plan is to recommence methotrexate when she finishes breastfeeding.

TABLE 2. TGA PREGNANCY CATEGORY AND RECOMMENDATIONS FOR MEDICATIONS USED TO TREAT RHEUMATOID ARTHRITIS[12-15]

Medication	TGA category	Recommendation for		
		Pregnancy	Breastfeeding	Paternal exposure
Nonselective NSAIDs	C up to gestational week 32, D thereafter	Use with caution in first trimester Withdraw at gestational week 32 to avoid premature closure of ductus arteriosus	Excreted into breast milk No published evidence of harm	Compatible
Low-dose aspirin	C	Continue if clinically indicated	No data No theoretical concerns	No data No theoretical concerns
Glucocorticoids	A	Compatible	Compatible	Compatible
Disease-modifying antirheumatic drugs (DMARDs)				
Anakinra	B1	Limited evidence Unintentional exposure unlikely to be harmful	No data No theoretical concerns	No data No theoretical concerns
Azathioprine	D	Compatible at dose up to 2 mg/kg/day	Compatible	Compatible
Cyclosporin	C	Compatible	Compatible	Compatible
Hydroxychloroquine	D	Compatible	Compatible	Not to be discouraged
Leflunomide	X	Contraindicated Cease 2 years preconception or use cholestyramine washouts and check serum levels If unplanned pregnancy then cease immediately, initiate washout, carefully evaluate fetal risk with local experts No human evidence of increased congenital abnormalities if washout given	Not recommended – no data	Based on very limited evidence, may be compatible
Methotrexate	D	Contraindicated Cease 3 months preconception If unplanned pregnancy then cease immediately, start folate 5 mg/day and continue until fetal risk has been carefully evaluated with local experts	Not recommended – insufficient data	Based on limited evidence, may be compatible
Mycophenolate	D	Contraindicated Cease more than 6 weeks preconception	Not recommended – no data	Based on limited evidence, may be compatible
Sulfasalazine	A	Compatible when coprescribed with folate 5 mg/day	Compatible in healthy, full-term infants	Conception may possibly be enhanced by ceasing 3 months before planned conception
Tacrolimus	C	Compatible	Compatible	Compatible

NSAIDs

Cessation of NSAIDs should be considered when conception is planned. Past reports on NSAIDs in the general population suggested the possibility of a low risk of miscarriage, but more recent studies do not support this finding. However, because of a possible adverse effect of NSAIDs on ovulation, a trial period off NSAIDs could be considered in women with a delayed time to pregnancy.

Selective cyclo-oxygenase (COX)-2 inhibitors should be avoided during pregnancy, as safety data are limited. If a nonselective NSAID other than low-dose aspirin is taken during pregnancy then it should be ceased at gestational week 32 to avoid premature closure of the ductus

TABLE 2. TGA PREGNANCY CATEGORY AND RECOMMENDATIONS FOR MEDICATIONS USED TO TREAT RHEUMATOID ARTHRITIS[12-15] *continued*

Medication	TGA category	Recommendation for		
		Pregnancy	Breastfeeding	Paternal exposure
Biological disease-modifying antirheumatic drugs (bDMARDs)				
Abatacept	C	Limited evidence Unintentional exposure unlikely to be harmful	No data No theoretical concerns	No data No theoretical concerns
Adalimumab	C	Continue until gestational week 20 then cease unless continuation is clinically indicated	Based on limited but reassuring data, breastfeeding should not be discouraged	Based on limited evidence, compatible
Certolizumab	C	Continue if clinically indicated	Based on limited but reassuring data, breastfeeding should not be discouraged	No data No theoretical concerns
Etanercept	D	Continue if clinically indicated	Based on limited but reassuring data, breastfeeding should not be discouraged	Based on limited evidence, compatible
Golimumab	C	Limited evidence Unintentional exposure unlikely to be harmful	Based on limited but reassuring data, breastfeeding should not be discouraged	No data No theoretical concerns
Infliximab	C	Continue until gestational week 20, then cease unless continuation is clinically indicated	Based on limited but reassuring data, breastfeeding should not be discouraged	Based on limited evidence, compatible
Rituximab	C	Limited evidence Cease 6 months before conception Unintentional exposure unlikely to be harmful	No data No theoretical concerns	Based on limited evidence, compatible
Tocilizumab	C	Limited evidence Cease at least 3 months preconception Unintentional exposure unlikely to be harmful	No data No theoretical concerns	No data No theoretical concerns
Tofacitinib	D	Avoid	Avoid	No data

arteriosus. Low-dose aspirin may be continued throughout the pregnancy.

Glucocorticoids

Initial human studies on glucocorticoids in pregnancy reported an increased incidence of cleft palate in newborns, and this statement persists in the literature despite more recent findings that do not support the association.[16] Prednisolone use by pregnant women with RA is associated with a higher risk of small-for-gestational-age infants. At doses higher than 7.5 mg per day, prednisolone is also associated with subfertility.[3] In addition, the general adverse effects of corticosteroids (increased infection, weight gain, hypertension, diabetes and osteoporosis) are more common in pregnancy. Hence, use of prednisolone during pregnancy should be carefully considered and minimised when possible to reduce the risks to the mother and baby.

DMARDs

A full description of all DMARDs and their role in pregnant women with RA is beyond the scope of this article. Key points are highlighted below. More details are available in *Prescriber's Information on Medications for Rheumatic Diseases in Pregnancy* from the Australian Rheumatology Association (http://www.rheumatology.org.au/gps/clinicalguidelines.asp).[15]

TABLE 3. MODE OF ACTION OF BIOLOGICAL DMARDS CURRENTLY SUBSIDISED BY THE PBS FOR SEVERE ACTIVE RHEUMATOID ARTHRITIS

Mode of action	Drug
Tumour necrosis factor (TNF) inhibition	Adalimumab
	Certolizumab
	Etanercept
	Golimumab
	Infliximab
CD20 inhibition	Rituximab
Interleukin 6 inhibition	Tocilizumab
T-cell costimulation inhibition	Abatacept
Janus kinase inhibition	Tofacitinib

Hydroxychloroquine

Hydroxychloroquine is recommended for use during pregnancy because of strong evidence for its favourable risk–benefit profile.[12] Nevertheless, its TGA pregnancy category is D, which can make patients and others needlessly anxious.

Sulfasalazine

Sulfasalazine (TGA category A) coprescribed with folate 5 mg daily (as sulfasalazine inhibits folate absorption) is recommended to treat women with RA before and during pregnancy.[12]

Methotrexate

Methotrexate is the first DMARD recommended in all international RA treatment guidelines because its benefits outweigh its risks. Methotrexate is not recommended in pregnancy but because of its frequency of use, exposure to low-dose methotrexate before or early in pregnancy has been reported. A study compared 324 women exposed to methotrexate around the time of conception (136 before and 188 after conception) with 459 disease-matched control subjects and 1107 control subjects without autoimmune disease. The incidence of major birth defects was not significantly different in the preconception exposure group (3.5%), disease-matched group (3.6%) and nonautoimmune disease group (2.9%), but was higher in the post-conception exposure group (6.6%).[17] No malformations consistent with methotrexate embryopathy were detected.

In the case of unplanned conception, the woman should cease taking methotrexate immediately while either continuing folate (5 mg daily) or using folinic acid (15 mg six-hourly for one day then eight-hourly for two days). Expert advice should be sought from a rheumatologist or obstetric medicine physician.

Limited evidence suggests that unplanned conception when the father is taking methotrexate is safe. In 113 pregnancies with paternal methotrexate exposure there was no increase in risk of adverse fetal outcomes compared with pregnancies in which fathers were not exposed.[18]

Leflunomide

A study of leflunomide in pregnancy showed no increase in adverse pregnancy outcomes among pregnant women who stopped taking leflunomide in the first trimester and followed the cholestyramine washout protocol (8 g three times daily for 11 days).[19] In the case of unplanned conception, leflunomide should be stopped immediately and cholestyramine washout given until leflunomide plasma levels are undetectable. Expert advice should be sought.

7. PRACTICE POINTS ON RHEUMATOID ARTHRITIS AND PREGNANCY

- Individualised management plans for women with rheumatoid arthritis (RA) contemplating pregnancy should balance current knowledge about medication-related risks against the risks of active disease.
- Active RA is associated with subfertility and poor outcomes for both mother and baby.
- RA does not always go into remission during pregnancy.
- Several medications can be used safely to treat RA during the preconception period, pregnancy and breastfeeding.
- Rheumatologists and GPs need to work together to advise patients on the optimal management of RA, including the safest medications to use before, during and after pregnancy for mothers as well as their babies.

Biological DMARDs

All patients with RA receiving biologic therapy and considering pregnancy (or found to be pregnant) should discuss their individualised management plan with their treating rheumatologist. Modes of action of biological DMARDs currently subsidised by the PBS for patients with severe active RA are listed in Table 3. With the exception of certolizumab, they are all large molecules with an IgG-like structure and, like other maternal immunoglobulins, are actively transported across the placenta from gestational week 16, with the transport rate increasing later in pregnancy up until birth. The exception, certolizumab, is a pegylated antibody molecule with a much lower transport rate across the placenta.

Measurement of drug levels in cord blood of babies born of mothers taking tumour necrosis factor (TNF) inhibitors has shown high levels of adalimumab and infliximab but lower levels of etanercept and certolizumab.[20] Analyses of large databases have shown no adverse pregnancy outcomes in pregnant women with RA or inflammatory bowel disease who were exposed to TNF inhibitors compared with the general population.[21] However, a small

prospective trial showed that cessation of TNF inhibitors in pregnancy was associated with an increased rate of flares.[22] This finding was supported by a systematic review of data from more than 2000 pregnancies.[23]

Consequently, it is currently recommended to continue TNF inhibitor therapy during pregnancy when indicated. Paternal exposure to TNF inhibitors is also considered low risk.[24] To limit exposure of the fetus, it is generally recommended that infliximab and adalimumab are withheld from gestational week 20 and restarted after the birth,[25] with the decision reviewed in light of the clinical indications. Etanercept and certolizumab can be continued throughout pregnancy if clinically indicated.

Biological DMARDs with other modes of action cannot currently be recommended in pregnancy until further information is gathered. If exposures have occurred inadvertently then the pregnancy can continue, but expert opinion from both the rheumatologist and an obstetric medicine physician should be sought.

Breastfeeding is considered safe for women receiving biological DMARDs as these medications are unlikely to be absorbed by the baby, owing to digestion in the stomach. Avoidance of live vaccines for the first six months is recommended in neonates who have been exposed to biological DMARDs during the third trimester, other than certolizumab and etanercept, based on the death of an infant due to disseminated BCG infection after vaccination when infliximab had been continued throughout the pregnancy. Live vaccines recommended for infants aged under 6 months in Australia include rotavirus vaccine and (for specific indications) BCG.

Conclusion

It is important to maintain optimal disease control in patients with RA who are planning pregnancy, are pregnant or have recently given birth, for the health of both the mother and the baby. Some practice points on RA and pregnancy are summarised in Box 7. A number of prescribed DMARDs are safe to continue during these times. Preconception discussion of management options should be part of routine clinical practice for all women of childbearing age with RA. This will help ensure successful outcomes for mother and baby. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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