Rheumatoid arthritis and pregnancy

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Many medications for rheumatoid arthritis are not safe in pregnancy, so careful management is required for women of child-bearing age. Dr Andrea Bendrups presents a brief review.

Several important issues need to be addressed when treating women of child-bearing age who have rheumatoid arthritis. If the patient does not wish to become pregnant and is taking medications that are not safe in pregnancy, reliable contraception must be ensured. On the other hand, if the patient wishes to become pregnant, the choice of medications leading up to and during pregnancy should be considered carefully.

The case below highlights some of the factors clinicians should address in this patient group.

Case scenario

Carol, a 30-year-old woman with seropositive rheumatoid arthritis (RA), is attending your practice for the first time. She has just moved interstate to join her partner and to start a new job and, as she works locally, states her intention to become a regular patient of the practice. She takes methotrexate (20 mg, weekly), folic acid (10 mg, weekly), hydroxychloroquine (200 mg, daily), naproxen (1000 mg, daily, as needed) and a progestogen mini-pill for contraception.

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Fertility issues

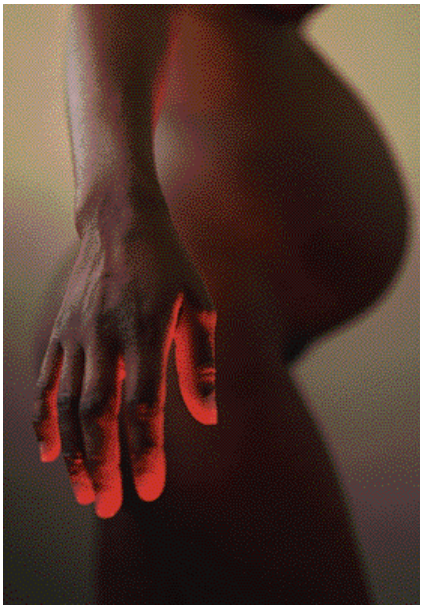
Adequacy of contraception

The absolute requirement for reliable contraception for women taking methotrexate needs to be stressed with Carol, even at this first consultation. The mini-pill does not prevent ovulation and has significant requirements to ensure its efficacy (e.g. regularity of dose and time of dosing, normal gastrointestinal absorption) that make it an inappropriate contraceptive for women taking a teratogen such as methotrexate. More reliable contraceptive methods need to be discussed with her.

Effect of RA on fertility and pregnancy

RA does not significantly reduce fertility, except when the severity of systemic inflammation is sufficient to suppress ovulation.

Many women with RA enjoy either partial or complete remission from their symptoms during pregnancy, allowing them to reduce or cease their medications. However, the disease usually reactivates postpartum, so regular supervision by the GP is advisable.



PHOTOLIBRARY

Figure. For women with rheumatoid arthritis who wish to become pregnant, the choice of medications leading up to and during pregnancy should be considered carefully.

Specific joint problems in women with RA may affect pregnancy outcomes. For example, patients with RA-affected hip joints need an alternative to the traditional lithotomy position (e.g. lateral or 'all fours' positions) for vaginal delivery, or they may require Caesarean section. For some patients cervical spine instability may complicate intubation. Adverse effects of medication can also affect pregnancy outcomes.

RA drugs

Disease modifying antirheumatic drugs (DMARDs) are the mainstays of RA therapy and are usually started when RA is diagnosed. DMARDs include methotrexate (Methoblastin), sulfasalazine (Pyralin EN, Salazopyrin), leflunomide (Arabloc, Arava) and hydroxychloroquine (Plaquenil). Corticosteroids are now used only in very specific situations, such as intra-articular injections for inflamed joints.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used only when there is active inflammation in RA. However, they are one of the most common classes

Rheumatoid arthritis medications in pregnancy

NSAIDs

NSAIDs should be stopped if possible in women planning to become pregnant. NSAIDs can be continued until the second trimester if the woman becomes pregnant while taking them, but should be ceased before the third trimester.

Corticosteroids

Maternal doses of prednisolone up to 40mg have not been associated with teratogenicity but are associated with obstetric complications such as gestational diabetes mellitus and pre-eclampsia. Intra-articular nonfluorinated corticosteroids (e.g. methylprednisolone acetate [Depo-Medrol, Depo-Nisolone]) can be used safely.

Fish oils

Fish oils containing omega-3 fatty acids can be used safely in pregnancy.

DMARDs

Sulfasalazine (Pyralin EN, Salazopyrin) has been shown to be safe in pregnancy in many studies. Hydroxychloroquine (Plaquenil) can be continued safely during pregnancy if required. Methotrexate (Methoblastin) should not be used in pregnancy. Patients taking methotrexate should use reliable contraception, and women planning to become pregnant should cease methotrexate three months before stopping contraception.

Leflunomide (Arabloc, Arava) should not be used in pregnancy. Women planning to become pregnant should undergo an elimination program with cholestyramine (Questran Lite) and then wait three months before stopping contraception.

bDMARDs

bDMARDs (e.g. etanercept [Enbrel], infliximab [Remicade], adalimumab [Humira], anakinra [Kineret]) should be avoided in pregnancy.

of drugs used in the pregnancy-prone population, particularly the over-the-counter preparations (e.g. aspirin, ibuprofen). Another option for patients with RA are fish oils containing omega-3 fatty acids, as some patients benefit from their mild anti-inflammatory effect.

Antibodies directed against the cytokines tumour necrosis factor (TNF) and interleukin-1 are examples of the growing class of biological disease modifying antirheumatic drugs (bDMARDs). This class includes etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira) and anakinra (Kineret). These drugs are currently indicated for severe and treatment-resistant RA only.

Cyclosporin A (Cicloral, Cysporin, Neoral, Sandimmun) is occasionally used for the treatment of RA that is unresponsive to other medication.

RA medications and pregnancy

Women beginning treatment for RA need to consider the implications of their drug choice with respect to future pregnancy. The Australian Drug Evaluation Committee's publication '*Prescribing Medicines in Pregnancy*' (http://www.tga.gov.au/docs/html/medpreg.htm) attempts to give advice on all drugs, often on the basis of incomplete and limited species data, in order to give clinicians a working idea of the risks associated with their use during pregnancy. Some published guidelines categorise the risk according to trimester, which does assist prepregnancy counselling and management.[1]

There are very few prospective placebo-controlled trials of drug safety in pregnancy. However, data do accumulate because, depending on the age group surveyed, between 30 and 50% of all pregnancies are unplanned and many women taking medication choose to take a risk rather than terminate a pregnancy.

A summary of advice regarding RA medications in pregnancy is shown in the box on this page.

NSAIDs

NSAIDs are classified as category C on the basis of their metabolic and placental blood flow effects in the third trimester. Category C drugs are those which have caused, or may be suspected of causing, harmful effects on the fetus without causing anatomical malformations.

Recent data have suggested a five- to seven-fold increased risk of miscarriage in women taking NSAIDs around the time of conception.[2] However, this and other studies have shown no increase in malformations or any other obstetric complication in the women who had an ongoing pregnancy.[3] These data suggest NSAIDs should be stopped if possible if a woman expresses an intention to become pregnant. However, if pregnancy occurs despite their use, they can be continued into the second trimester. NSAIDs should be ceased before the third trimester because of the possibility of early closure of the fetal ductus arteriosus or of oligohydramnios via an effect on fetal renal function.

There are insufficient data to comment on the use of COX-2 selective NSAIDs in early pregnancy, so it is prudent to switch from a COX-2 to either a nonselective NSAID or a simple analgesic if a pregnancy occurs or is planned.

Corticosteroids

If anti-inflammatory medications are required after the second trimester, changing from NSAIDs to prednisolone

is recommended. There are important differences between types of corticosteroids that determine their safety in pregnancy. Hydrocortisone and prednisolone are largely metabolised (90%) by placental dehydrogenase, but fluorinated cortico-steroids (e.g. betamethasone and dexamethasone) are not, making the latter the drugs of choice when treating the fetus (e.g. to induce lung maturation prior to premature deliveries). Intra-articular nonfluorinated corticosteroids (e.g. methylprednisolone acetate [Depo-Medrol, Depo-Nisolone]) can be used to treat isolated troublesome joints and may avoid the need for systemic corticosteroid treatment.

Maternal doses of prednisolone up to 40 mg have not been associated with teratogenicity but are associated with obstetric complications such as gestational diabetes mellitus and pre-eclampsia.[4]

Fish oils

Fish oils containing omega-3 fatty acids can be used in pregnancy, and their mild anti-inflammatory activity may make it possible for patients who wish to become pregnant to cease NSAIDs.

DMARDs

Hydroxychloroquine

Human studies of hydroxychloroquine have failed to confirm the teratogenic effects (ototoxicity) observed with high dose chloroquine in rats,[5] so it has become standard practice to continue it through pregnancy if required. The tissue half-life of hydroxychloroquine is long (one to two months) so patients need to take this into account if they wish to eliminate the drug before they become pregnant.

Sulfasalazine

There is a large literature on the safety of sulfasalazine in women during pregnancy.[6] It is used predominantly by women with inflammatory bowel disease, but can be continued in women with RA when necessary.

Methotrexate

Methotrexate interferes with the biosynthesis of purines via the enzyme dihydrofolate reductase. A somatic teratogenic syndrome (the aminopterin syndrome) has been described in pregnant women being treated for malignancies with high dose methotrexate. Although the estimated half-life of methotrexate is five to eight hours, the elimination half-life is variable (up to 50 hours). Detectable levels can leach out of tissues for up to several weeks after cessation.

Recent small studies of accidental pregnancy exposure suggest no increased risk of fetal abnormality provided methotrexate is ceased before the critical gestation (8 to 10 weeks after the first day of the last menstrual period).[7] Termination of pregnancy therefore may be avoided when methotrexate is ceased early after pregnancy is detected, when gestational dates are confirmed with ultrasound and if mothers have used folic acid supplements regularly (as all patients taking methotrexate should). However, avoiding exposure by using contraception and ceasing methotrexate three months prior to conception is recommended.[8]

Leflunamide

Leflunamide is a pyrimidine synthesis inhibitor and animal studies have associated it with fetal death and teratogenicity. Its very long half-life makes just ceasing it insufficient to ensure elimination from plasma, so an elimination program with cholestyramine (Questran Lite, 8 mg, three times a day for 11 days) is recommended. Delaying pregnancy for three months following the washout treatment is also recommended.

Cyclosporin A

Cyclosporin A is occasionally used for the treatment of RA or systemic lupus erythematosus (SLE) that is unresponsive to other medication, and it was used extensively in renal transplant recipients in the past. There is an extensive literature on its use in transplant patients in pregnancy showing it is not associated with increased risk of teratogenicity, but the babies born to these mothers have a greater incidence of intrauterine growth restriction. Also the mothers have a greater than normal risk of hypertension and pre-eclampsia. Determining whether these complications are due to cyclosporin A rather than to maternal comorbidities is difficult, however.

bDMARDs

Human TNF inhibitors do not cross-react with TNF of other species so they have not been used to generate safety data in animal models. However, analogous mouse studies with murine anti-TNF have not shown embryo toxicity or teratogenic effects.

Early reports of TNF inhibitor use in Crohn's disease and RA with accidental fetal exposure have shown no significant difference in the rate of fetal malformations compared with conventional therapy or controls.[9] However, as data are limited, use of bDMARDs such as the TNF antagonists etanercept, infliximab and adalimumab and the interleukin-1 antagonist anakinra should be avoided in pregnancy.

Use of RA drugs in potential fathers

Apart from the reversible effect of sulfasalazine on sperm motility and therefore fertility,[10] little has been published concerning the impact of paternal use of RA medications on fertility or pregnancy outcomes. Because of damaging effects on dividing cells, men are usually counselled to cease methotrexate or leflunamide at least three months prior to planning a pregnancy. A review of the clinical experience of methotrexate in men is available at www.motherisk.org.[11] MT

A list of references is available on request to the editorial office.

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