Management of pregnancy in women with rheumatoid arthritis

"For unplanned pregnancies, cease teratogenic medications immediately and refer to a genetics counsellor and maternal–fetal medicine specialist"

Summary

- Rheumatoid arthritis (RA) disease activity may improve during pregnancy but postpartum flares are common.
- Patients taking disease-modifying antirheumatic drugs should be counselled about effective contraception.
- Knowledge about drug safety in pregnancy is limited but the Therapeutic Goods Administration categories and online resources are a guide to the data currently available.
- Begin prepregnancy counselling as early as possible to allow for cessation of teratogenic medications and optimisation of RA disease control.
- For unplanned pregnancies, cease teratogenic medications immediately and refer to a genetic counsellor and maternal–fetal medicine specialist for risk assessment and advice.

Rheumatoid arthritis (RA) is a common condition which occurs more frequently in women than men.[1] Its prevalence is about 2% in Australia, and this is predicted to increase to 3% by 2032.[2] Therefore, the need to manage pregnancy in a woman with RA is not an uncommon clinical scenario. Clinicians must be aware of the teratogenicity of certain disease-modifying antirheumatic drugs (DMARDs) used to treat RA, and must ensure that women taking these drugs are using reliable contraception. Clinicians also have an important role to play in prepregnancy counselling to facilitate informed decision making. We,[3] and others,[4] have identified unmet information needs among women with RA, including needs relating to contraception, pregnancy planning, pregnancy and early parenting. The aim of our review is to highlight pertinent issues in managing pregnancy in women with RA.

Effect of RA on fertility and pregnancy

Despite having normal ovarian reserves,[5] women with RA have fewer children than women in a control group,[6] and take longer to conceive.[7] The reasons for smaller family size have not been fully elucidated but may include personal choice, uncontrolled inflammatory disease, sexual dysfunction secondary to RA and the effects of non-steroidal anti-inflammatory drugs on ovulation and implantation.[8] Clinicians should be aware of the possibility of subfertility, discuss this issue with prospective parents, and refer to reproductive specialists, when appropriate.

A recent registry-based study reported increased rates of spontaneous abortion in women with RA, although previous studies suggested no increased risk.[9] Increased rates of prematurity, pre-eclampsia, caesarean delivery and infants with a low birth weight have been reported in women with RA.[10-13] A Dutch study found that women taking prednisolone had higher rates of preterm delivery, and those with high disease activity were more likely to have caesarean delivery and infants with a low birth weight, but patients with well controlled RA had pregnancy outcomes comparable with those of the general population.[14]

Effect of pregnancy and lactation on RA

It was reported as early as 1938 that RA disease activity improved in 90% of women during pregnancy,[15] and numerous subsequent studies have reported similar observations. A more recent prospective study of pregnant women with RA supports this finding, but suggests that rates of remission are more modest than traditionally thought, and that complete remission is uncommon.[16] In this study, 39% of patients had flared by 26 weeks postpartum, confirming another long-held observation that women with RA are at increased risk of flare in the postpartum period. Women should be educated about the likelihood of postpartum flares and safe strategies to manage these events.

Because prolactin, a pituitary hormone integral to breastfeeding, is proinflammatory in animal models,[17] the effect of breastfeeding on postpartum RA activity has been investigated. Despite two small studies suggesting that breastfeeding was associated with postpartum flares of RA,[18,19] subsequent larger studies have not confirmed this association.[20,21]

Prepregnancy counselling

Given the teratogenicity of several DMARDs, treating practitioners have an obligation to ensure that patients with RA are counselled regularly about the importance of reliable contraception while taking these agents.[22] One study found that 28% of women taking methotrexate (MTX) or leflunomide (LEF) used ineffective contraception.[23] Another reported that despite 84% of women receiving correct contraceptive advice, one-third of women taking MTX or LEF were not using any contraception.[24]

It is estimated that up to 49% of pregnancies in the general population are unintended.[25] If an unplanned pregnancy occurs in the setting of exposure to teratogenic drugs, the medications should be ceased immediately and the patient referred to a genetic counsellor and maternal–fetal medicine specialist for discussion of risk and further management.

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doi: 10.5694/mja15.00365

Women with RA may question their practitioner about the possibility of RA inheritance. Controlled cohort studies have shown a relative risk of RA of 1.5–4.5 in first-degree relatives.[26] Despite this modest increase in relative risk, patients can be reassured that the absolute risk of RA in their offspring remains small.

Good disease control before conception results in the best chance of low disease activity during pregnancy and a reduced risk of postpartum flare.[16] Teratogenic medications need to be ceased and the several months it may take to ensure stability on a new drug regimen should be taken into account when planning pregnancy. Recommendations about cessation of medications before conception also extend to men on MTX and LEF (although there are no reports of teratogenicity in the children of men on either drug),[27,28] and sulfasalazine (SSZ), which is known to reversibly impede spermatogenesis and reduce sperm motility and quality.[29] A preconception referral to a maternal–fetal medicine specialist or obstetrician with an interest in high-risk pregnancy should also be considered.

Safety of drug therapy in pregnancy

Because of ethical concerns, pregnant and lactating women are specifically excluded from premarketing drug trials. Most pregnancy drug safety data are, therefore, derived from animal studies or postmarketing surveillance, case reports and large registries. In Australia, the Therapeutic Goods Administration pregnancy classification is used to categorise the safety of drugs in pregnancy (https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy). It is not a hierarchical system, ie, it is not implied that a category B drug is safer than a category C drug. Although the pregnancy classification is widely used, in certain situations it is of limited use to clinicians in determining suitability of therapy. For example, while hydroxychloroquine (HCQ) and MTX are both category D drugs, only HCQ is considered safe in pregnancy, according to Australian practice guidelines.[30]

Of the DMARDs in current use, MTX and LEF are contraindicated in pregnancy and breastfeeding, and HCQ and SSZ are compatible with pregnancy.[31] Of the biological agents, tumour necrosis factor (TNF) inhibitors may be continued until pregnancy is confirmed, with use in later gestation determined on a case-by-case basis,[32] but all other biological agents should be avoided. If TNF inhibitors are used during pregnancy, live vaccinations should be avoided in the infant until 6 months of age, because of the risk of immunosuppression.[33]

Given the evolving nature of drug safety data, online resources are particularly helpful for clinicians. MotherToBaby (www.mothertobaby.org), a service of the Organization of Teratology Information Specialists, and LactMed (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm), run by the United States National Library of Medicine, are two useful and regularly updated websites.

Competing interests: This was an investigator-initiated review, but we received research grants from UCB and AbbVie. Neither company had any input into the design or execution of our review.

Provenance: Not commissioned; externally peer reviewed. ■

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