Safety of anti-rheumatic drugs for rheumatoid arthritis in pregnancy and lactation

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Abstract

Women with rheumatoid arthritis (RA) are often of childbearing age and therefore questions regarding reproductive health and the use of medications including disease modifying anti-rheumatic drugs (DMARDs) may arise during the clinical consultation. Each patient requires individual assessment in order to effectively manage the disease while minimizing any treatment-associated risks to the fetus. Although good-quality controlled trials are lacking, there is an increasing volume of evidence surrounding the use of immunosuppressive therapies in pregnancy and lactation. This review summarises the currently available information which can be of benefit to clinicians guiding patients and their families through the risks and benefits of continuing RA therapy during pregnancy and lactation. Further studies and ongoing surveillance of drug safety in pregnancy are required to resolve the uncertainties that remain regarding synthetic and biologic DMARDs.

Introduction

Rheumatoid arthritis (RA) has a prevalence of approximately 0.5-1%,, although this varies according to geography, with a female:male ratio of 2:1 to 3:1(1). Pregnancy in the patient with RA is therefore a clinical scenario that is not uncommon, however management is complicated by limited safety data for the commonly used anti-rheumatic drugs. In Australia, the Therapeutic Goods Administration (TGA) pregnancy classification is used to categorise drugs in pregnancy (Table 1). It is important to note that these categories are not hierarchical (ie. assignment of category B does not imply greater safety than category C) and relate to the level of evidence available for a particular drug. Other potential issues with this system are that it does not take into account the route of administration or stage of pregnancy at which a drug is used(2). Furthermore, the clinical context in which a drug is used must be taken into consideration, particularly if cessation of therapy will lead to harm from untreated disease. A similar classification system established by the Food and Drug Authority has been in use in the United States, but is currently being phased out in favour of more detailed descriptions of risk.

Many factors account for the paucity of drug safety data in pregnancy, the most important being the deliberate exclusion of pregnant women from drug trials. Most data are, therefore, derived from case reports, post-marketing surveillance and large registries, all of which provide a considerably weaker level of evidence. Additionally, patients in these studies are often taking multiple medications so it is difficult to attribute observed fetal abnormalities to a particular drug. Safety data are often extrapolated from other conditions, such as inflammatory bowel disease (IBD), however it is unclear how applicable the findings are to RA patients, particularly when dosing regimens differ.

Several new therapies have become available to RA patients over the last decade, in particular the biologic disease modifying anti-rheumatic drugs (bDMARDs). There is little

long-term follow-up data for these drugs at this stage, however increasing numbers of patients are being treated and so ongoing observational data will be forthcoming. Guidelines will need to be updated regularly as more evidence becomes available. Helpful local resources for Australian clinicians include the Australian Rheumatology Association Prescriber's Information on Medications for Rheumatic Diseases in Pregnancy (http://rheumatology.org.au/community/PatientMedicineInformation.asp). Other regularly updated online resources are 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 US National Library of Medicine.

In this review (and Table 2) we summarise the currently available evidence for the safety of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, synthetic disease modifying anti-rheumatic drugs (DMARDs) and bDMARDs in pregnancy and lactation. We reference the TGA categories, as although an imperfect system, they are in common use and remain widely referenced in Australia.

Anti-inflammatory drugs

NSAIDs

Although a general management principle in RA is to discontinue NSAIDs once disease activity is adequately controlled with DMARD therapy, a significant proportion of patients remain on NSAIDs for pain relief. Non-selective NSAIDs are classified as category C drugs in pregnancy. Given that animal and human studies have shown inhibition of ovulation and animal studies inhibition of embryo implantation with NSAID use(3), it is usually

recommended that they are ceased at the beginning of a conception cycle and recommenced once pregnancy is confirmed(4). Several studies have shown an increased risk of spontaneous abortion with NSAIDs(5-7), particularly around the time of conception, however the contribution of the underlying indication for the NSAID is unknown. Although another large study has shown no association with spontaneous abortion(8), it is generally considered prudent to limit NSAID use during the first trimester.

Despite several case-control studies suggesting an association between NSAID use in early pregnancy and gastroschisis and cardiac malformations(9), large population-based studies have found no conclusive evidence that non-selective NSAIDs are teratogenic in humans(4). Renal failure and coagulopathy have been reported with proglonged, high-dose NSAID use later in pregnancy(10). Data regarding the safety of cyclooxygenase (COX)-2 inhibitors are limited, although one study of 114 women exposed to COX-2 inhibitors in pregnancy showed an increase in musculoskeletal malformations compared with controls(11). Given the lack of data in this area, COX-2 inhibitors should continue to be avoided in pregnancy.

Because COX-1 and COX-2 are expressed in the endothelium and smooth muscle of the ductus arteriosus, all NSAIDs can lead to premature closure of the ductus arteriosus in the third trimester(9) and should be ceased prior to 30 weeks' gestation.

Corticosteroids

Like NSAIDs, corticosteroids are best considered an adjunct for temporary disease control but in clinical practice these drugs are still used by a substantial number of RA patients. The non-fluorinated corticosteroids prednisolone and prednisone, both classified as category A drugs, are 90% metabolised by the enzyme placental dehydrogenase, leaving 10% of drug to

reach the fetus(3). The fluorinated corticosteroids betamethasone and dexamethasone are not metabolised by placental dehydrogenase, however, and are the drugs of choice when the fetus rather than the mother is the target of therapy. Animal studies have shown an association between glucocorticoids and cleft palate, cataracts, fetal loss and fetal growth restriction(12, 13). Despite disparate results from several human studies(3), a meta-analysis of case-control studies examining exposure to corticosteroids in the first trimester suggested an odds ratio (OR) of 3.35 for oral clefts, indicating a three-fold increase in risk(14). A 2014 population-based study, however, found no association between corticosteroid use and oral clefts(15). There is no evidence of any other congenital abnormalities with corticosteroid exposure in humans. Given the potential risk of oral clefts, it is preferable to minimise glucocorticoid dose in the first trimester of pregnancy.

Corticosteroid use later in pregnancy is associated with gestational diabetes mellitus, pregnancy-induced hypertension, premature rupture of membranes and intrauterine growth restriction, so doses are best minimised during the third trimester(4). If intra-articular injections are required, the non-fluorinated methylprednisolone is the preferred agent as lower concentrations are likely to reach the fetus, although systemic absorption is likely to be minimal.

Synthetic DMARDs

Sulfasalazine

Sulfasalazine (SSZ) is used alone or as part of combination therapy in RA, but is also prescribed extensively in IBD, and much of its pregnancy safety data come from this setting. As no fetal harm has been demonstrated with SSZ in animal studies and it is generally

considered safe in pregnancy, it is classified as a category A drug. Although there are case reports of congenital malformations with SSZ exposure(9), these were not confirmed in larger population-based studies(16) or a 2008 meta-analysis(17). There is a case report of reversible congenital neutropenia following maternal SSZ at a dose of 3 g daily(18), so it is recommended that doses should not exceed 2 g daily. As SSZ is a folate antagonist, folate supplementation should be taken pre-conception and throughout pregnancy.

In males, the sulfapyridine component of SSZ is well-recognised to impede spermatogenesis and reduce sperm motility and quality(19). These changes are reversible so it is recommended that SSZ is discontinued by males with RA three months prior to attempting conception.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an anti-malarial with immunomodulatory activity used as monotherapy or in combination therapy for RA. Despite theoretical concerns of retinal toxicity and ototoxicity extrapolated from the use of chloroquine in pregnancy, multiple human studies in patients with connective tissue diseases (including two large controlled studies(20, 21)) have shown no increased risk of congenital abnormalities with HCQ exposure. There are few studies addressing the safety of HCQ in RA. In clinical practice HCQ is therefore considered safe in pregnancy in the patient with RA, but because of the lack of data it is classified as a category D drug.

Methotrexate

Methotrexate (MTX), the methyl derivative of amniopterin, is a folate antagonist that inhibits dihydrofolate reductase and has long formed the backbone of therapy in most patients with

moderate to severe RA. MTX is embryotoxic and teratogenic in both animals and humans and high-dose use in pregnancy is associated with the amniopterin/MTX syndrome, features of which include cranial-facial abnormalities, limb foreshortening, growth deficiency and developmental delay/mental retardation(22). MTX is therefore classified as a category D drug and its use in pregnancy is contra-indicated.

Much of the literature regarding the teratogenicity of MTX stems from its high-dose use as a chemotherapy agent in malignancy. The prevalence of congenital abnormalities with low dose weekly MTX exposure (5 to 25 mg/week) in RA is less clear(3). A 2014 prospective multi-centre cohort study of 188 pregnancies exposed to low-dose weekly MTX found an increased risk of spontaneous abortion (adjusted OR 2.2, 95% CI 1.3-3.2) and major birth defects (adjusted OR 3.1, 95% CI 1.0-9.5) compared to women without autoimmune disease(23). None of the abnormalities seen, however, were definite examples of MTX embryopathy. A 2009 review of low-dose weekly MTX in 101 RA patients found that spontaneous abortion occurred in 19 (18%) pregnancies, and congenital malformations in 5 (9%) of 55 live births(24). The risk of congenital abnormalities is thought to be highest with MTX exposure at six to eight weeks gestation at doses of 10 mg weekly or higher, although this is based on limited data(25).

Given that MTX accumulates in cells and can leach out of tissues for several weeks, it is recommended that this drug be ceased at least three months prior to conception. Folic acid supplementation should be continued throughout the pre-conception period and first trimester of pregnancy. Although there are no reports of teratogenicity in the offspring of males on MTX(26), it is commonly advised that men cease MTX one to three months prior to conception.

Leflunomide

Leflunomide (LEF) is a pyrimidine antagonist with antiproliferative activity used in moderate to severe RA. Despite limited experience in human pregnancies, LEF is classified as a category X drug given theoretical risks extrapolated from its mechanism of action and animal studies that have shown it to be both embryotoxic and teratogenic. Abnormalities observed in animals include growth retardation and cranial, ophthalmic, skeletal and cardiac abnormalities(27, 28).

As the active metabolite of LEF is detectable in plasma for up to two years following drug cessation, women planning to conceive should undergo a cholestyramine washout using cholestyramine 8g three times daily for 11 days. Plasma LEF concentration should then be measured and must be <0.02mg/L on two occasions at least 14 days apart. The manufacturer recommends this procedure also be followed in men, although there is no evidence of abnormalities in the offspring of men taking LEF.

There is one case report of right eye blindness and cerebral palsy in an infant born prematurely after LEF exposure during the first 21 weeks of gestation prior to cholestyramine washout, although causality could not be determined(29). A prospective cohort study of 64 women with RA who received LEF during the first trimester and underwent cholestyramine washout revealed no difference in major structural defects, compared with 108 controls with RA who were not treated with LEF and 78 healthy controls(30). An extension of this study reported outcomes in an additional 45 women exposed to LEF during or in the two years prior to pregnancy(31). There were two (12.5%) major structural defects in the 16 women who had first trimester LEF exposure but none in the 29 who were exposed prior to

conception. The authors concluded that there is too little evidence to draw firm conclusions, however, the 12.5% rate of abnormalities is four times the background rate of 3% in the general population.

If an unplanned pregnancy does occur in the setting of exposure to MTX or LEF, they should be ceased immediately and the patient referred to a genetics counsellor and maternal-fetal medicine specialist for discussion of risk and further management. Additionally, patients on LEF should undergo a cholestyramine washout.

Biologic DMARDs

Biological DMARDS are parenterally administered antibodies which are, in Australia, reserved for the treatment of patients with severe RA that is refractory to standard DMARD therapy. As these drugs are relatively new, studies of analogous monoclonal antibodies in animals are limited, as are human safety data. Most of the human data come from large drug registries (including those maintained by manufacturers) and the IBD literature, where tumour-necrosis-factor (TNF)-inhibitor use in pregnancy is more prevalent given the clear association of increased IBD activity with poor pregnancy outcomes(32). Because there is active transport of IgG maternal antibodies across the placenta during the second and third trimesters, biologics possessing the Fc portion of the immunoglobulin molecule will be transported into the fetal circulation from the second trimester onwards, with levels increasing throughout pregnancy and even exceeding maternal concentrations if continued until birth(33). Currently all biologics are classified as category C in pregnancy except for etanercept which is classified as category B2.

TNF inhibitors

TNF-inhibitors are the best studied of the biologics. Infliximab is a chimeric monoclonal antibody, etanercept is a soluble receptor inhibitor and adalimumab, golimumab and certolizumab are humanised antibodies to TNF. Because etanercept is a fusion protein, there is less transplacental passage than of complete antibodies(34). Certolizumab lacks an Fc component and thus cannot be actively transported across the placenta(35). There was initial concern stemming from a 2009 uncontrolled study of voluntarily reported events that infliximab and etanercept were associated with the VACTERL spectrum of anomalies (vertebral abnormalities, anal atresia, cardiac defects, tracheo-oesophageal, renal and limb abnormalities)(36). Multiple subsequent studies have not confirmed this association, nor any increased risk of congenital anomalies(37-40). Other concerns about TNF inhibitors and other biologics relate to the potential immunosuppressive effect on the infant after birth. There is a single case report of death from disseminated BCG following BCG vaccination of a three-month-old infant who was exposed to infliximab throughout his mother's pregnancy(41). It is therefore recommended that administration of live vaccines (BCG, rotavirus, varicella and measles, mumps, rubella) is postponed until the infant is six months of age if there has been TNF-inhibitor exposure during pregnancy. Because very little TNF-inhibitor passes into the fetal circulation during the first trimester, it is currently considered low risk to continue therapy throughout the peri-conception period and at least until pregnancy is confirmed. In individual cases of severe maternal disease, TNF-inhibitors have been continued until the start of the third trimester, although studies of long-term outcome in children following exposure during pregnancy are lacking. Given that smaller amounts of certolizumab pass into the fetal circulation, it may have a theoretical safety advantage over other TNF-inhibitors(35).

Rituximab

Rituximab is a monoclonal antibody directed against CD20 on B cells. The largest report of rituximab in pregnancy identified 231 patients, with RA the indication for therapy in 41 patients(42). There was concomitant exposure to teratogenic medications in over 50% of patients, most commonly MTX but also combination chemotherapy. Of the 153 pregnancies with known outcome there were 90 live births, 22 of which were premature, and one neonatal death at six weeks. Haematologic abnormalities were present in 11 neonates and infection in four, none of whom had haematologic abnormalities. Two congenital malformations were reported. Although no worrying signals were identified in this study, given the lack of population-based, prospective data and the long half-life of rituximab, women are recommended to avoid pregnancy for 12 months following rituximab infusion.

Abatacept

Abatacept is a cytotoxic T-lymphocyte antigen (CTLA)-4 immunoglobulin fusion protein that blocks co-stimulation of T-cells by antigen presenting cells. There is a single case report of a healthy baby born at term to a mother with RA who was administered abatacept at 2.5 weeks gestation and also continued MTX until the pregnancy was confirmed(43). Eight other pregnancies have been reported in RA patients after abatacept exposure, seven of whom were on concomitant MTX and one on LEF(44). Spontaneous abortion occurred in three patients, two of whom had a past history of spontaneous abortion, and two had elective terminations. Given the lack of information, abatacept is not recommended in pregnant patients and it is recommended to wait 14 weeks after the last infusion before attempting conception(44).

Tocilizumab

Tocilizumab is a humanised interleukin (IL)-6 receptor antibody. In the largest report of tocilizumab exposure in pregnancy(45), 33 pregnancies were reported in 32 patients from eight tocilizumab trials. Twenty-six patients were on concomitant MTX. Thirteen pregnancies were electively terminated and there were seven spontaneous abortions. Of the 11 deliveries, 10 were healthy and one infant died of acute respiratory distress syndrome three days after emergency caesarean section for intrapartum fetomaternal haemorrhage. A further six pregnancies were reported from a Japanese biologics registry(46). There was one spontaneous abortion and five healthy births at full term with no congenital anomalies. Given the paucity of data, pregnancy is not recommended for patients on tocilizumab and a period of three months after the last infusion is generally recommended before attempting conception.

Drug safety in lactation

The benefits of breastfeeding to both mother and infant are well documented. The National Health and Medical Research Council recommend that infants are exclusively breastfed to around six months of age, with continuation to 12 months and beyond for as long as mother and child desire. Postpartum flare as well as existing joint damage may complicate breastfeeding in women with RA. Whilst some drugs are safe in lactation, others are not and if instituted require cessation of breastfeeding. Many women find this a difficult decision to make and may need to be reassured by their educated health practitioners that control of their RA is important to limit further joint damage. Ultimately this is a decision to be made on a case-by-case basis by the patient and their clinician with full discussion of risks and benefits to mother and infant.

Drugs diffuse into breastmilk in differing amounts depending on their physical properties and pharmacokinetics(47). Recommendations regarding drug safety are made based on theoretical concerns, measured drug levels in breastmilk and infant serum, and case reports (47). Short-term administration of NSAIDs is generally considered low risk(48), with short-acting NSAIDs such as ibuprofen preferred(49). Given their anti-platelet effect they should be avoided if there is thrombocytopenia in the infant. Doses should be administered just after breastfeeding in order to minimise infant exposure at the next feed. Prednisolone is also considered safe in breastfeeding, with several reports suggesting no adverse effects in children breastfed during long-term use(49). Delaying feeding for four hours after a dose is recommended to minimise infant exposure(49).

In terms of synthetic DMARDs, HCQ and SSZ are considered safe in breastfeeding whilst MTX and LEF are not. Exposure to HCQ through breastmilk has not been demonstrated to have any long-term effect on visual function or neurodevelopmental outcomes(50). There is a single case report of bloody diarrhoea in a two-month-old infant exposed to SSZ through breastfeeding, with resolution upon cessation of the mother's dose of 3g/day(51). SSZ exposure should be avoided in infants who are premature, have hyperbilirubinaemia or glucose-6-phosphate dehydrogenase deficiency given that its metabolites can displace bilirubin and cause neonatal jaundice(52). Therefore, SSZ is considered safe in full-term infants provided they are monitored closely for adverse events.

Neither MTX nor LEF are compatible with breastfeeding. As MTX is excreted into breastmilk in very low concentrations(53) it is unknown whether the once-weekly doses used in RA pose any risk to infant safety. Given theoretical concerns about accumulation in infant tissues, immunosuppression and adverse effects on growth, however, it is not recommended.

Likewise there are no published data regarding safety of LEF in lactation but given theoretical risks to the infant and its long half-life, its use is not recommended.

Although there are limited data regarding the safety of TNF-inhibitors in lactation, the theoretical risk of harm to the infant is low given the poor diffusion of high molecular weight proteins into breastmilk and anticipated minimal absorption by the infant due to destruction of the drug in the gastrointestinal tract. Infliximab, adalimumab and etanercept have all been demonstrated to be excreted into breastmilk in small amounts(47). Certolizumab was undetectable in breastmilk in a single case report of its use in breastfeeding(33) and there are no data on golimumab. If a decision is made to use TNF-inhibitors during breastfeeding, informed patient consent is required and the infant should be monitored for possible side effects. There is still no information regarding rituximab, abatacept or tocilizumab in breastfeeding so they are best avoided.

Conclusion

Preconception counseling including review of medications is crucial in young women with RA. Maintaining low disease activity prior to conception and throughout pregnancy and breastfeeding will result in better outcomes for mother and baby. Although good-quality controlled trials are lacking, the currently available data presented in this review is of benefit when guiding patients and their families through the risks and benefits of continuing RA therapy. Further studies and ongoing surveillance of drug safety in pregnancy are required to resolve the uncertainties that remain regarding synthetic and biologic DMARDs.

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