Irish Journal of Medical Science (1971 -) (2019) 188:169–172
https://doi.org/10.1007/s11845-018-1829-7

REVIEW ARTICLE

Updated pharmacological management of rheumatoid arthritis for women before, during, and after pregnancy, reflecting recent guidelines

Kieran E. Murray[1,2] · Louise Moore[1] · Celine O'Brien[3] · Anne Clohessy[3] · Caroline Brophy[3] · Patricia Minnock[1] · Oliver FitzGerald[1,2] · Eamonn S. Molloy[1,2] · Anne-Barbara Mongey[1,2] · Shane Higgins[3] · Mary F. Higgins[3] · Fionnuala M. Mc Auliffe[3] · Douglas J. Veale[1,2]

Received: 22 January 2018 / Accepted: 25 April 2018 / Published online: 10 May 2018

Abstract

Background Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease which can cause significant disability, morbidity, mortality, and impaired fertility. It commonly affects women of childbearing age. Managing rheumatoid arthritis (RA) in the perinatal period poses challenges. There is concern about the teratogenic effects of many traditional disease-modifying anti-rheumatic drugs (DMARDs) and an ever-growing list of new therapeutic options with limited data in pregnancy and breastfeeding.

Aims We aimed to create a standardized approach to pharmacological management of RA patients seen in our newly established Rheumatology and Reproductive Health Service.

Methods We reviewed relevant publications on the use of anti-rheumatic drugs in pregnancy. These include recent guidelines from The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) and the European League Against Rheumatism (EULAR).

Results After considering relevant publications, we developed a Saint Vincent's University Hospital/National Maternity Hospital consensus protocol for evidence-based medication in pregnancy in RA.

Conclusions RA tends to improve during pregnancy and flare postpartum. Several anti-rheumatic medication options during pregnancy and breastfeeding are now available including anti-tumor necrosis factor (anti-TNF) agents. Good disease control at all stages of reproduction is important to ensure best outcome for both mother and baby.

Keywords Arthritis · Peripartum · Pregnancy · Rheumatoid arthritis · Teratogen

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease which can cause significant disability, morbidity, and mortality. RA affects women three times more often than men, commonly in their childbearing years [1]. There are concerns about the teratogenic effects of many traditional disease-modifying anti-rheumatic drugs (DMARDs) and an ever-growing list of new therapeutic options with limited data in pregnancy and breastfeeding.

Active RA in pregnancy is associated with a number of negative outcomes for both mother and baby. These include increased incidence of low birth weight, pre-term delivery, cesarean section, and pre-eclampsia [2, 3]. But, thankfully, outcomes for women with well-controlled RA are comparable to the general population [4].

Kieran E. Murray and Louise Moore are joint first authors

✉ Kieran E. Murray
kemurray@hotmail.com

[1] Rheumatic Musculoskeletal Disease Unit, Our Lady's Hospice an Dublin d Care Services, Harold's Cross, Ireland

[2] Rheumatology Department, University College Dublin and St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland

[3] UCD Perinatal Research Centre, Obstetrics and Gynaecology, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland

Before pregnancy, a key aim is to establish the RA patient in remission on medications that are relatively safe in pregnancy; this is usually achieved by the judicious use of synthetic and biological DMARDs. A specific withdrawal period is required for teratogenic medications such as methotrexate and leflunomide. Clinicians should be encouraged to enquire about family planning at the first consultation and each review thereafter, to allow all patients opportunity to discuss any concerns they may have.

Pre-conceptual risk assessment and counseling should be ideally performed in every woman with systemic autoimmune diseases before attempting pregnancy [5]. This is an opportune time to alter medication management if required and to refer for a pre-conceptual review with maternal medicine if available. This facilitates access to numerous specialities. Complex patients may benefit from a multidisciplinary approach from obstetrics, hematology, rheumatology, and respiratory or other specialties. This may be possible in a combined clinic.

Pregnancy itself may reduce the activity of RA [6]. In 1938, Hench suggested that remission rates during pregnancy were greater than 70% [7]. Later studies suggest that this rate is lower, with a recent prospective study giving a remission rate of 48% [3]. The exact mechanism of this improved disease control is unclear; one theory is downregulation of the maternal immune system with the presence of the fetus. It can be tempting to withdraw anti-rheumatic medications and treat symptomatically with steroids during pregnancy. Recent data would suggest that this may not be the best approach [8].

The postpartum period can be a difficult for the patient, the baby, and the treating healthcare providers. It is important to explain this to patients, their partners, and/or family. There is an increased rate of disease flare. A 2008 study showed a deterioration in RA control in 39% of patients postpartum [3]. One should also consider the additional strain of caring for an infant.

It may be difficult to differentiate what is normal postpartum from a disease flare, particularly for first time mothers. Breastfeeding and medication safety is another consideration. Postpartum complications such as wound infection may delay re-institution of RA medications.

Methods

Upon commencement of a multidisciplinary Rheumatology and Reproductive Health Service, a systematic approach to prescribing anti-rheumatic drugs in women of childbearing age was required. Thus, the published data and guidelines were reviewed to develop a unified approach.

Methotrexate and leflunomide are completely contraindicated at conception and in pregnancy. They require specific washout periods of 3 months recommended for methotrexate and 2 years for leflunomide [9, 10]. An elimination protocol using cholestyramine or activated charcoal may also be used when circumstances warrant more rapid drug elimination of leflunomide such as with pregnancy [10]. Thus, we carefully consider whether to use these agents in women of childbearing age and always stress to women on these medications the importance of adequate contraception during any period of use and the withdrawal period.

Steroids are considered generally safe if required in pregnancy. Fetal risks with steroids include a slight increase risk of pre-term delivery and a small risk of oral cleft with first trimester use. There is also of course the well-known side effect profile to the mother (including increased risk of infection). Thus, we aim to use the lowest effective dose for the shortest time possible in active disease. Non-fluorinated steroids, such as prednisolone or hydrocortisone, are generally preferred as they are metabolized by the placenta and have less fetal effects.

NSAIDs can contribute to the infertility and subfertility seen in RA due to anovulation [11]. Their use in early pregnancy can be associated with increased risk of miscarriage. In the third trimester, they may cause premature closure of ductus arteriosus.

Tumor necrosis factor (TNF) inhibitors may be safer than previously believed although we should not underestimate the risks. In 2010, a 4-month-old baby died from disseminated BCG [12]. His 28-year-old mother was treated with infliximab [TNF alpha inhibitor] throughout pregnancy for inflammatory bowel disease. The previously healthy infant received his BCG at 3 months of age.

Yet, there is now extensive experience and guidelines to support the use of biologics around and during pregnancy. Many rheumatologists would continue their use for at least the initial stages of pregnancy.

The updated BSR guidelines advise on timing of discontinuation of TNF inhibitors in pregnancy and breastfeeding. It is important to notice the differing timelines for the different biologic agents in these guidelines. Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors. Infliximab may be continued until 16 weeks. Etanercept and adalimumab may be continued until the end of the second trimester. Golimumab is unlikely to be harmful in the first trimester. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age [9].

There is little data available for the use of non-TNFi biologics in pregnancy or breastfeeding. BSR guidelines suggest stopping rituximab 6 months and tocilizumab 3 months prior to conception. Unintentional exposure to anakinra or abatacept in the first trimester is unlikely to be harmful. There are no data on the use of any of these agents in breastfeeding. EULAR guidelines suggest discontinuing tofacitinib 2 months prior to conception and to avoid breastfeeding while on the medication.

Lactation

Guidelines consider numerous anti-rheumatic drugs compatible with breastfeeding. Our approach is summarized in the chart below.

Compatible with breastfeeding	Inadequate data about lactation	Contraindicated while breastfeeding
Corticosteroids	TNF inhibitors	Methotrexate
NSAIDs	Abatacept	Leflunomide
Hydroxychloroquine	Anakinra	
Sulfasalazine[a]	Rituximab	
Azathioprine	Tocilizumab	
	Tofacitinib	

[a] Concerns with prematurity, glucose-6-phosphate deficiency, and hyperbilirubinemia

Results

From reviewing previous studies and guidelines, we have created a joint Saint Vincent's University Hospital/National Maternity Hospital approach to medications for RA in women of childbearing age. The table summarizes our approach to managing RA in and around pregnancy:

	DMARDs	Biologics	Steroids	Analgesics
Before pregnancy	Stop MTX 3 months prior to conception	Continue TNF inhibitors	None/as low as possible	Stop NSAIDs if difficulties in conceiving
	Wash out leflunomide (two years)	Stop other biologics before conception		Use paracetamol
	Consider HCQ/SSZ			
During pregnancy	Continue HCQ/SSZ, may taper	Often stopped during trimester 2	None/as low as possible	Avoid NSAIDs
		Consider certolizumab throughout pregnancy		Use paracetamol
After pregnancy	Continue HCQ/SSZ Avoid leflunomide, MTX if breastfeeding	Aim to restart biologics within 2 weeks (consider wound healing, infection, and breastfeeding)	None/as low as possible	Consider restarting NSAIDs, ideally ibuprofen if breastfeeding Use paracetamol

DMARDs disease-modifying anti-rheumatic drugs, *MTX* methotrexate, with 5 mg folic acid weekly, *HCQ* hydroxychloroquine, *SSZ* sulfasalazine (with 5 mg folic acid daily), *TNF* tumor necrosis factor, *NSAIDs* non-steroidal anti-inflammatory drugs

Conclusions

Women with active RA might have increased subfertility and infertility. Patients should be encouraged to discuss their pregnancy plans with their healthcare providers at every consultation. Good disease control at all stages of reproduction ensures best outcomes for mother and baby. RA tends to improve during pregnancy and flare postpartum. Consideration should be given to the treatment of disease flares during pregnancy. There are now numerous anti-rheumatic drug options during pregnancy and breastfeeding with more widespread use of anti TNF agents in this group.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not required as this study was a review of the relevant literature and guidelines on the topic.

References

1. Wallenius M, Salvesen KA, Daltveit AK, Skomsvoll JF (2014) Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta Obstet Gynecol Scand 93(3):302–307
2. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KÅ, Nordvåg BY, Koldingsnes W, Mikkelsen K, Kaufmann C, Kvien TK (2011 Jun) Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum 63(6):1534–1542
3. de Man YA, Dolhain RJ, van de Geijn FE et al (2008) Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum 59(9):1241–1248
4. de Man YA, Hazes JM, van der Heide H et al (2009 Nov) Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. Arthritis Rheum 60(11):3196–3206
5. Østensen M, Andreoli L, Brucato A, Cetin I, Chambers C, Clowse MEB, Costedoat-Chalumeau N, Cutolo M, Dolhain R, Fenstad MH, Förger F, Wahren-Herlenius M, Ruiz-Irastorza G, Koksvik H, Nelson-Piercy C, Shoenfeld Y, Tincani A, Villiger PM, Wallenius M, von Wolff M (2015) State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev 14(5): 376–386
6. Østensen M, von Esebeck M, Villiger PM et al Therapy with immunosuppressive drugs and biological agents and use of contraception in patients with rheumatic disease. J Rheumatol 34:1266–1269
7. Hench PS (1938) The ameliorating effect of pregnancy on chronic atropic infections rheumatoid arthritis, fibrosititis and intermittent hydrarthrosis. InProc Staff Meet Mayo Clin 13:161–175
8. Krause ML, Amin S, Makol A (2014 Oct) Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskelet Dis 6(5):169–184
9. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, Arthanari S, Cunningham J, Flanders L, Moore L, Crossley A, Purushotham N, Desai A, Piper M, Nisar M, Khamashta M, Williams D, Gordon C, Giles I, on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group (2016 Sep) BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 55(9):1693–1697
10. European Medicines Agency, Leflunomide (Arava) 10mg tablets, European Product Assessment Report updated June 2016
11. Brouwer J, Hazes J, Dolhain R et al (2015) Fertility of women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 74:1836–1841
12. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J (2010) Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. Crohns Colitis 4(5): 603–605