REVIEW ARTICLE

Management of Rheumatoid Arthritis in Pregnancy: A Review Article

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory condition, usually affecting females three times more than the males. The peak age of onset is in the childbearing age-group i.e., 19–44 years. Females with RA face difficulties at the time of conception, during pregnancy, and in the lactation period. Certain drugs used for the management of RA have deleterious effects on pregnancy outcomes. Thus, it is increasingly becoming a topic of concern as well as discussion for healthcare providers and medical professionals to guide the affected females in planning for pregnancy, safer pharmacotherapies, and to overcome the phobia related with their disease effects.

Keywords: Chronic inflammatory disease, Pregnancy outcomes, Rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disease of unknown etiology characterized by symmetric polyarthritis. It is the most common form of chronic inflammatory arthritis. It can also cause a variety of extra-articular manifestations, such as vasculitis, nodules, and accelerated atherosclerosis.[1]

RA affects 0.5–1% of the adult population worldwide. Females are more commonly affected than males, which can be attributed to the role of estrogen in enhancing immune response. Genetic and environmental factors play an important role in the pathogenesis of RA.

Genetic predispositions include alleles located within major histocompatibility complex (MHC) and non-MHC genes. Allelic variation in the HLA-DRB1 gene is associated with the production of anti-cyclic citrullinated peptides (CCP) antibodies. Non-MHC genes are namely PTPN22, PAD14, and APOM.[1] Environmental factors include cigarette smoking and Epstein–Barr virus association.[2]

RA affects the synovial tissue and underlying cartilage and bone. It results from a complex mechanism of genetic, environmental, and immunological factors. The hallmark of pathological process in RA is synovial inflammation, a proliferation of various cells, which include T-cells, B-cells, plasma cells, dendritic cells, mast cells, and granulocytes. Rheumatoid synovitis is characterized by focal bone erosion with thinning of reticular cartilage, leading to joint damage and disability. Other systems can also get involved, like lungs and cardiovascular system.[2]

Predominant clinical features include morning stiffness lasting for more than 1 hour, typically in small joints of hands and feet. Joints are usually swollen and tender on presentation. Joints affected are metacarpophalangeal, proximal interphalangeal, and wrists; the distal interphalangeal joint is not involved. Progressive and chronic irreversible deformities, such as swan-neck deformity, boutonniere deformity, and line deformity, result from damage to the tendons, joint capsule, and soft tissues in these small joints. Less common manifestations include acute monoarticular, palindromic rheumatism, and asymmetrical large joint arthritis. Spinal joints are very rarely involved.[2]

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The PARA study, a prospective study was done taking into consideration strict criteria for disease activity found that pregnancy influenced the disease course more with moderate to high disease activity [DAS28- C-reactive protein (CRP) >3.2] and patients with low disease activity (DAS28-CRP <3.2) remained stable throughout the pregnancy.[3] The maternal immune system undergoes a variety of changes in response to the tolerance of antigens of the conceptus, thus these immunomodulatory effects during pregnancy influence autoimmune rheumatic diseases, like RA. Immunomodulation can be attributed to endocrinal changes (increase in progesterone levels, leading to thymic involution and reduced proinflammatory profile[4]; fetal production of human chorionic gonadotropin, leading to recruitment of T regulatory cells)[5,6] and changes in cell-mediated and humoral immunity.[7,8]

Management of RA has revolutionized in recent years. Availability of novel therapies, such as biologic agents, and treatment paradigms, such as "treat to target", have substantially improved treatment outcomes for patients with RA. Unfortunately, data on the safety of many of these medications are limited, and many may be contraindicated during pregnancy and breastfeeding.[9] Careful planning is thus required to stabilize disease activity prior to conception and modify medication regimens. There seems to be a prevalence of fewer children among women with RA than in

the general population. These women also tend to have higher mean age at the first birth.[10] For all women diagnosed with RA, it is important to get a reproductive history. For patients with childbearing potential, the desire to start or extend their family while on treatment should be ascertained. Women who are not currently interested in pursuing pregnancy but desire to conceive in the future should be appropriately counseled about the potential safety, risks, or teratogenicity of medications they are on for RA treatment.[11]

Diagnosis

The clinical diagnosis of RA is largely based on signs and symptoms of chronic inflammatory arthritis. Application of revised European Alliance of Associations for Rheumatology (EULAR) criteria with a score of ≥6 fulfills the requirement of definitive RA (Table 1).

A detailed history of the problem, its onset, progression with time, relieving and aggravating factors, pattern of joint involvement and joint stiffness associated with inactivity, and improvement with activity points toward inflammatory joint disorder, such as RA, is assessed. The objective of clinical assessment is to identify signs of inflammatory arthritis, such as swelling, tenderness, and restriction of joint movements. Extra-articular manifestations include rheumatoid nodules, anemia, thrombocytosis, pleural effusion, pericarditis, and entrapment neuropathies.[3] Nonspecific inflammatory markers, such as CRP and erythrocyte sedimentation rate (ESR), are elevated.

Serological tests should be performed to detect RA factor and anti-CCP antibodies. RA factor is less specific than anti-CCP antibodies as RA factor can be raised in various other diseases (like Diabetes, Bacterial Endocarditis, Cancer, Chronic infections).[1,12]

Synovial fluid aspiration and analysis may reveal raised white blood cell (WBC) count (5,000–50,000 WBC/μL) with neutrophilic predominance.

Joint imaging includes X-ray and magnetic resonance imaging (MRI), MRI being better in detecting joint effusion and early bone changes.[13]

History of comorbidities, obstetric history, and family history of autoimmune diseases should also be elicited.

Management

Management protocol in a case scenario of a female with RA who wishes to conceive, is pregnant, or is in the lactational phase needs comprehensive approach (Flowchart 1).

Rheumatologists and obstetricians must work in integration to educate the patients about the potential fertility issues; pregnancy outcomes in RA; disease activity during pregnancy and in the postpartum period; and medication use in the preconception period, during pregnancy, and lactation.

GOAL: Balance between good disease control and the risk of medications used.

Frequent queries of females attempting for pregnancy:

- Does RA affect the chances of getting pregnant?
  Ans: RA may be associated with impaired fertility due to many reasons but adequate preconception counseling and understanding the disease course result in successful outcomes.
- Does RA affect the pregnancy outcome?
  Ans: RA disease activity improves during pregnancy and with rationale use of anti-rheumatoid drugs, and weighing their safety against side effects is equivalent to healthy female pregnancy outcomes.[14]
- Does RA affect the offspring?
  Ans: Safer pharmacotherapies (with lesser side effects and low placental transfer levels) result in viable and healthy offspring.
- Desirable RA status and condition of the patient?
  Ans: Pain and disability associated with RA may limit the patient to attempt or carry out the pregnancy and have a negative effect on sexual function. However, with effective treatment, better disease control can be helpful in achieving the pregnancy.

Females with RA who are planning for pregnancy must be counseled thoroughly before conception due to the following reasons:

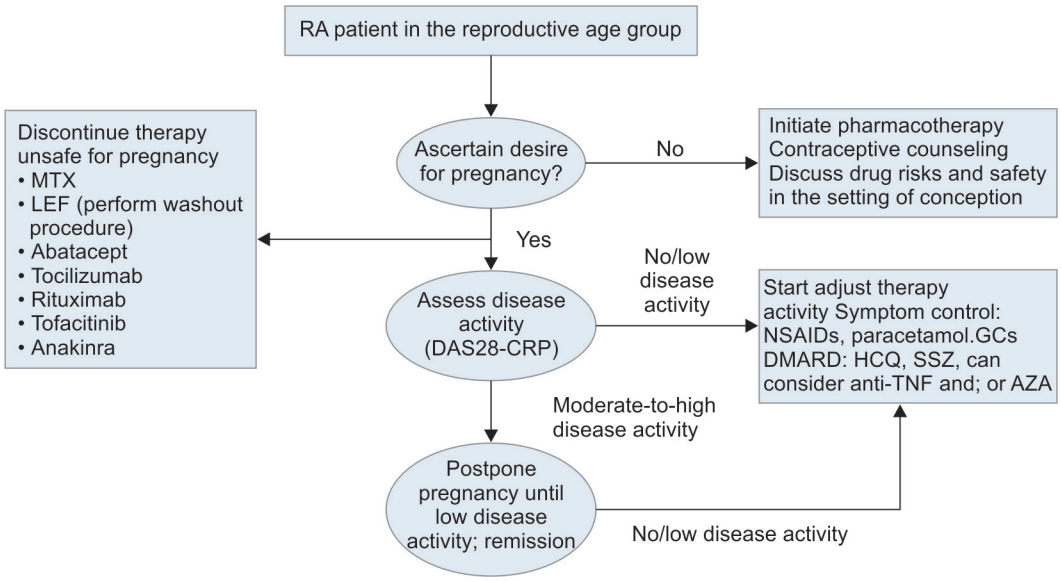
- RA may impair fertility and prolong the time to achieve pregnancy as is seen in high disease activity cases. Several studies have shown that women with RA have fewer children than healthy women.[15]
- Fertility impairment can be attributed partly due to disease severity and treatment with teratogenic disease-modifying antirheumatic drugs (DMARDs), which require postponement of pregnancy. Thus, infertility is related to age and problems arise more frequently in women who have postponed their first pregnancy to the fourth decade of life.[16]
- Late maternal age of conception, nulliparity, daily dose of prednisone higher than 7.5 mg, and previous use of nonsteroidal

Table 1: Classification criteria for rheumatoid arthritis (*Source:* Aletaha D, et al. Arthritis Rheum 2010;62:2569)

Joint involvement	• 1 large joint (shoulder, elbow, hip, knee, ankle)	0
	• 2–10 large joints	1
	• 1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	• 4–10 small joints	3
	• >10 joints (at least 1 small joint)	5
Serology	• Negative RF and negative ACPA	0
	• Low-positive RF or low-positive anti-CCP antibodies (≤3 times ULN)	2
	• High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute phase reactants	• Normal CRP and normal ESR	0
	• Abnormal CRP or abnormal ESR	1
Duration of symptoms	• <6 weeks	0
	• ≥6 weeks	1

Note: These criteria are aimed at the classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of ≥6 fulfills requirements for definite RA.[1]
ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joints; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal

Flowchart 1: Algorithm in the management of RA in pregnant patients [*Source:* Management of rheumatoid arthritis during pregnancy: challenges and solutions (Krause and Makol)[9]]



anti-inflammatory drugs (NSAIDs), but not of methotrexate, were variables associated with increased time to achieve pregnancy. By preventing the rupture of the luteinized follicle, NSAIDs can impair ovulation and lengthen the time of pregnancy.[17]

- Anti-Mullerian hormone , an indicator for ovarian reserve, was found to be equivalent in women with RA and healthy non-age-matched controls.[18]
- Remission of disease activity during pregnancy is more likely in women who are rheumatoid factor (RF) negative.[19] Individuals who responded during pregnancy, as defined by EULAR response criteria, were more likely to be both CCP and RF negative. Antibody status was not associated with flares postpartum.[20,21]

Medical Management

Before Pregnancy

- Folic acid supplementation prior to conception. It is specifically recommended for patients on methotrexate within 3 months prior to conception and has to be continued throughout the pregnancy.
- NSAIDs are considered safe in pregnancy with an occasional risk of miscarriages.
- Glucocorticoids are relatively safe to use during pregnancy in low to moderate doses.[22] Women are counseled about the risk of congenital anomalies (cleft lip/palate) with first-trimester use. Other adverse effects are prematurity and low birth weight.
- DMARDs
  - Methotrexate (MTX): MTX should be stopped at least 1 to 3 months prior to conception in women because of its teratogenic risk and should be avoided throughout pregnancy. It causes spontaneous abortion and embryopathy. If a woman is found to be using MTX during pregnancy, she can be advised elective termination pregnancy.[23]
  - Hydroxychloroquine (HCQ): HCQ can be safely continued during pregnancy, and is the preferred DMARD of choice.[24]
  - Leflunomide (LEF): Pregnancy should be avoided in patients on LEF until undetectable serum concentrations (< 0.02 mg/L) are verified because of reports of teratogenicity. It is discontinued at least two years prior to conception or by the use of an enhanced drug elimination procedure using cholestyramine. Defects associated with LEF exposure are occult spinal dysraphism, unilateral ureteropelvic junction obstruction, and microcephaly.[25]
  - Sulfasalazine (SSZ) and azathioprine (AZA): They can be continued during pregnancy. There is no risk of congenital abnormalities, abortions, and prematurity associated with these drugs.[26]
- BIOLOGICALS
  - Tumor necrosis factor (TNF)-alpha inhibitors (infliximab, etanercept, adalimumab)—these agents are linked with VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb abnormalities).

    In patients with active disease who are on TNF-alpha inhibitors, these medications can be continued but should be discontinued around 32 weeks of gestation.[27]
  - Abatacept—pregnancy should be attempted after 14 weeks of last exposure to abatacept. It is linked with congenital abnormalities, such as cleft lip/palate, congenital aortic anomaly, skull malformations, pyloric stenosis, ventricular septal defect, and congenital arterial malformation.
  - Rituximab—it is advisable to wait for 12 months prior to conception if the patient is taking rituximab.[28]
  - Anakinra, tocilizumab, and tofacitinib—there are insufficient data to support the use of these drugs during pregnancy.

During Pregnancy

- Although pregnancy has a beneficial effect on RA disease activity, it is necessary to keep the patient in the lowest disease activity state or remission throughout the pregnancy and the postpartum period, in order to have favorable

outcomes.[29] Remission criteria are defined by ≤1 swollen or tender joint. It is more likely seen in RF- and anti-CCP-negative patients.

- Patients with pregnancy complications, such as gestational diabetes, pregnancy-induced hypertension, and preeclampsia, should be followed accordingly based upon usual obstetric practice.
- Usual management is performed for patients who require a cesarean delivery, other than particular attention to the risks of cervical spine disease in patients who require intubation.
- Recommendations for exercise and physical activity do not differ for most patients with RA from other pregnant women, except when modifications may be required because of limitations due to active arthritis or prior joint injury or deformity.

Medical Management during Pregnancy (Table 2)

- NSAIDs—they can be safely given during the pregnancy but should be avoided in the third trimester as there is an increased risk of premature closure of the ductus arteriosus. In case of new-onset flare or deterioration during pregnancy, NSAIDs are the preferred choice of treatment.[30]
- Glucocorticoids—prednisone is a commonly used drug.
  In patients in whom NSAIDs are inadvisable, we use the lowest dose of prednisone necessary for disease control. Prednisone dosing should not be more than 10 mg/day. Nonfluorinated glucocorticoids, including prednisone, prednisolone, and methylprednisolone, cross the placenta at very low concentrations and are metabolized to inactive metabolites in the placenta before reaching the fetus; thus, they are relatively safe to use during pregnancy in low to moderate doses.[30]
- DMARDS—(HCQ, SSZ, and AZA) can be continued and used in patients with an inadequate response to NSAIDs or prednisone. For moderately active disease, patients can be maintained on HCQ and/or SSZ.[24]
  Neither MTX nor LEF should be used during pregnancy.
- BIOLOGICALS—TNF inhibitors may be continued during pregnancy.[28] However, the duration of use depends upon the specific agent and the balance of individual risks and benefits.

  Although 2016 professional society guidelines advised that infliximab be discontinued at week 16 of gestation and that etanercept and adalimumab be discontinued at the start of the third trimester, the use of these drugs can be extended, if necessary, to a later gestational age if benefits of disease control outweigh potential risks for an individual patient. The major concern has been that continuing TNF-alpha blockade may increase the risk of neonatal infection or that there may be complications from live vaccines.

  Golimumab, like the other TNF inhibitors, can also be continued until the start of the third trimester; however, less information is available regarding golimumab.[30]
  Certolizumab may be continued throughout pregnancy. It crosses the placenta in low to undetectable amounts.
  There are insufficient data to conclude pregnancy safety for the small molecule targeted synthetic DMARDs (tsDMARDs), such as the Janus kinase (JAK) inhibitors.
- Resistant or flaring disease activity
  Glucocorticoids (oral or intraarticular) can be used to manage disease flares or persistent moderately to highly active disease that is not adequately controlled with other medications.[31]
  Glucocorticoid therapy during pregnancy may increase the risk of premature rupture of the membranes and intrauterine growth restriction and, in the mother, may increase the risk of pregnancy-induced hypertension, gestational diabetes, osteoporosis, and infection. The lowest effective dose of glucocorticoids should be used.
  In patients with disease refractory to routine management or with continued flares during pregnancy, despite the use of glucocorticoids, if not already taking these medications, TNF inhibitors can be used.

Postpartum Management

Pregnancy outcome in patients with low disease activity and limited drug therapy is almost similar to healthy women. For patients who remain clinically quiescent in the postpartum period, the pregnancy medication regimen can be continued. For women who flare postpartum or who have a high likelihood of flaring, their prepregnancy regimen can be resumed with adjustment to medications for women who are breastfeeding. The demands of caring for a newborn can be particularly challenging in women with RA who are flaring in the postpartum period or who have restricted joint mobility. Patients with RA may need additional support or help during this time.

- Medication use during breastfeeding:
  - NSAIDs can be used, but aspirin should be avoided.
  - Glucocorticoids can be taken in low doses. In patients taking 20 mg/day or greater, waiting at least four hours after the dose prior to nursing is sufficient to substantially reduce exposure to the nursing child.
  - DMARDs (HCQ, SSZ, and AZA) are generally compatible with breastfeeding in healthy, full-term infants. However, women taking SSZ should avoid breastfeeding premature infants or those with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.[32]
  - TNF inhibitors can be continued or initiated during lactation.

Table 2: Different categories of drugs according to safety[9]

Preferred medications (if required)	*Medications relatively safe to use (require individualized approach)*	*Contraindicated medications*	*Inadequate data to support safety*
Glucocorticoids[a]	TNF-alpha inhibitors	Methotrexate	Anakinra
NSAIDS[b]	Azathioprine	Leflunomide	Abatacept
Hydroxychloroquine			Tocilizumab
Sulfasalazine			Tofacitinib
			Rituximab[c]

[a]Counseling advised regarding possible cleft lip/palate abnormalities; [b]Avoid in the third trimester due to the risk of premature closure of ductus arteriosus; [c]Recommendation is to avoid in pregnancy due to hematologic abnormalities and infection risk

- MTX and LEF should be avoided in breastfeeding women.[32]
- The JAK inhibitors and other tsDMARDs should be avoided in lactating women as these agents get transferred into breast milk.

- In patients who flare during the postpartum period, medications compatible with nursing should be used (glucocorticoids or NSAIDs).
- In those patients who choose not to breastfeed, their prepregnancy medications can be resumed according to symptoms.

Fetal Outcome

Perinatal mortality is rarely seen. The most common outcome is preterm (<37 weeks) delivery with increased risk seen in patients with high disease activity at conception or during pregnancy.[33,34] The use of high-dose prednisone (>10 mg/day) is also associated with preterm delivery. Thus, prednisone should be either taken in a low dose or discontinued after the third trimester. Infants exposed to TNF-alpha inhibitors in utero should not receive live vaccines for the first six months of life (rotavirus and bacillus Calmette–Guérin to be avoided).[35]

Paternal Medication Use

There are two main issues regarding paternal exposure to medications. The first is the use of medication in men planning to conceive, and the second is the use of medication after conception has occurred. The latter concern is insignificant as there is minimal risk of placental transfer of medication via semen.

SSZ may cause abnormalities in sperm count and function; therefore, semen analysis is recommended in patients who have a delay in conception.[36] However, it is not associated with teratogenicity.

Other medications, like TNF inhibitors, immunosuppressive agents, and AZA, can be safely used.

Paternal use of methotrexate is not associated with teratogenicity, thus it need not to be discontinued.[37] There are insufficient data on the safety of abatacept, tofacitinib, or tocilizumab.[38]

Conclusion

The best condition for a successful outcome is planned pregnancy with low disease activity, and preferably in the remission period. However, modification of treatment to minimize fetal toxicity while maintaining adequate disease control can be difficult in patients whose RA flares or remains active during pregnancy. Therefore, disease activity should be monitored throughout the pregnancy for timely interventions as and when required.

Thus, an integrated approach is needed to address the difficulties being faced by the females in the course of pregnancy outcomes right from the preconception period to the lactation phase. This includes detailed patient counseling prior to therapy initiation and planning of pregnancy, adjusting therapy, and regular monitoring during pregnancy.

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