MANAGING RHEUMATOID ARTHRITIS: INSIGHTS INTO POSTPARTUM ONSET AND HOLISTIC APPROACHES

Abstract

Rheumatoid arthritis (RA) is a common autoimmune condition influenced by a combination of intricate genetic and environmental factors that play a role in its development. Our review examines the multifaceted aspects of RA, focusing on its development following childbirth in women, potential triggers, and strategies for management during breastfeeding and beyond. Diagnosis involves clinical evaluation, serological tests, and imaging studies, emphasizing early and accurate identification for prompt intervention. RA management encompasses disease-modifying drugs, surgery, and physical therapy, while emerging dietary and lifestyle interventions, including fasting, veganism, probiotics, and exercise, hold promise.

Mindfulness, yoga, and exercise training are complementary approaches gaining traction in improving RA symptoms and overall well-being. Balancing symptom control with pregnancy and breastfeeding safety is crucial in managing RA during and after pregnancy. In summary, this review underscores the intricate nature of RA, its potential postpartum occurrence, and a multifaceted management approach, highlighting the need for a holistic strategy tailored to the unique challenges faced by women with RA during this life phase.

Keywords: Rheumatoid arthritis, postpartum onset, diagnosis, management, holistic approaches.

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I. INTRODUCTION

RA stands as the most common type of chronic inflammatory arthritis. and its history dates back thousands of years, with records of using European white willow bark to alleviate pain (1). It is defined as an autoimmune disorder with chronic inflammation affecting the joints, and extra-articular organ such as eyes, lungs, skin, heart, kidney, and peripheral nerves (2). It is primarily characterized by the presence of symmetric polyarthritis and synovitis. If left unaddressed, RA leads to a rapid progression of joint deterioration shortly after its onset, ultimately resulting in permanent physical impairment and deformity in the affected joints (1).

RA impacts roughly 1% of the global population (3) and approximately 1.3 to 1.4 million adults population in the United States is affected by RA (4, 5). RA predominantly affects women, occurring twice as often in females compared to males. A significant number of women with RA are in their reproductive years, making pregnancy management uniquely challenging (6). This condition typically affects women aged 30 to 50, occurring at a rate of 1 in 150 (1). The higher prevalence in females can be linked to estrogen's role in altering the immune response. Nonetheless, the onset of RA is notably shaped by genetic and environmental factors. (7).

Many studies have reported the association of heightened risk of RA onset during period of postpartum. Oka et al reported a postpartum onset rate of 9.7% (8); Felbo et al found a 28.3% postpartum onset rate among female patients (9), and Del Junco et al noted that postpartum onset occurred at a rate five times higher than during other times (10). Silman et al, in their case-control study, identified that within first three months of postpartum risk of RA onset is high (11). The initial exacerbation in the early postpartum period, typically within three months, might be associated with cytotoxic cellular immunity, whereas the emergence of RA symptoms after six months postpartum could be linked to humoral immunity. Iijima et al suggested a cytotoxic cellular reactions being more influential in RA aggravation or induction (12). With the rising occurrence of RA in women following childbirth, it has not merely affected their physical health; it has also exacted a toll on their mental well-being. This is due to the abrupt shift in responsibilities, decreased mobility, diminished quality of life, and increased dependence on others for childcare. In this review, we discussed the factors contributing to the onset of RA following childbirth in women, potential triggers, and approaches to managing the condition during breastfeeding and beyond.

1. **Clinical Features:** RA is marked by morning rigidity and widespread discomfort and inflammation in multiple joints, impacting mobility. These symptoms are commonly observed in joints like the fingers and toes. It also affects knees, feet, hands, elbows, and others joints. Additionally, patients often describe experiencing general symptoms like discomfort, depression, tiredness, and fever. Common symptoms encompass dryness of eyes, xerostomia, forearm rheumatoid nodules, numbness due to neuropathy, and exertional breath shortness or a persistent cough associated with interstitial pneumonia. With advancing joint damage, diverse deformities emerge in fingers like the buttonhole and swan-neck (1).

2. **Pathology:** Comprehensive genomic investigations among RA patients have underscored the human leukocyte antigen D-related B1 gene (HLA-DRB1) as the predominant gene associated with disease susceptibility. Furthermore, various other genes have also been recognized. Disease-specific anti-cyclic citrullinated peptide (Anti-CCP) antibodies are highly linked to the progressive damage of bone or cartilage (1).

   Within RA, a combination of genetics, environmental factors, and citrullination triggers autoimmune responses, resulting in self-reactive T and B cells accumulating in synovial tissues. This disrupts self-tolerance, leading to autoantibody production, immune complex deposition, and histological damage (resembling a type III allergic reaction). RA synovitis involves angiogenesis, synoviocyte proliferation, lymphocyte infiltration, and pro-inflammatory cytokine release. Furthermore, synoviocytes stimulated by cytokines generate matrix metalloproteinases (MMPs) responsible for cartilage degradation. Both synoviocytes and lymphocytes express receptor activator of nuclear factor kappa B ligand (RANKL), which triggers osteoclast activation and, consequently, leads to joint erosion.

   Within RA, a combination of genetic and environmental factors, along with the citrullination of molecules, initiates epigenetic modifications that stimulate autoimmunity (13-16).

II. CAUSES/REASONS

The emergence of post-partum RA arises from a multifaceted interplay of genetic, environmental, and immunological factors.

1. **Genetic Factors:** Numerous compelling factors strongly support the significant role of genetics in the advancement of RA. These aspects encompass the higher occurrence of RA within families, with estimates indicating that familial risk contributes to approximately 40-50% of individuals with the condition , with the most pronounced risks observed in first-degree relatives (FDRs) (17). Moreover, the influence of genetic factors on RA is highlighted by the higher prevalence of the disease within specific racial groups, such as North American Natives, where RA rates range from 5% to 7% (18-20). Genetic predispositions involve specific alleles found within both major histocompatibility complex (MHC) and non-MHC genes. Notably, allelic variations in the gene HLA-DRB1 are linked to the production of anti-cyclic citrullinated peptides (CCP) antibodies production. Non-MHC genes, including PAD14, PTPN22, and APOM, also play a role in genetic susceptibility to RA (21).

2. **Environmental Factors:** While some associations between environmental, dietary, and lifestyle factors and rheumatoid arthritis (RA) may vary across individual studies or show inconsistent results, there are several environmental factors that consistently exhibit strong connections with RA. The most robust of these associations is with tobacco exposure. Several studies have documented odds ratios indicating a significant link between smoking and RA, with some estimates suggesting that smoking contributes to roughly 20-30% of the environmental risk associated with RA (22). Smoking is believed to contribute to increased citrullination and when combined with a susceptible genetic background, this citrullination process can result in the presentation of citrullinated proteins and the production of anti-cyclic citrullinated peptide antibodies (ACPA). It's

worth noting that smoking's effects on immunity extend beyond this mechanism and can have various local and systemic impacts on the immune system (23-25).

3. **Immunological Factors:** The maternal immune system experiences several alterations in response to tolerating the antigens of the conceptus (the developing embryo/fetus). These immunomodulatory effects during pregnancy and after pregnancy have an impact on autoimmune rheumatic diseases, such as RA. These immune system modifications can be attributed to various factors:

- **Endocrinal Changes:** There is an elevation in progesterone levels during pregnancy, which leads to thymic involution (a reduction in thymus size and activity) and a decreased proinflammatory immune profile. This hormonal shift contributes to immune system regulation. The primary factor often responsible is hormonal fluctuations post-childbirth. These hormonal changes can result in joint and ligament laxity, increasing joint stress and the potential for inflammation. Additional factors contributing to this condition encompass weight gain, alterations in physical activity, and joint injuries.

- **Fetal Contributions:** The fetus itself plays a role in immunomodulation. The production of human chorionic gonadotropin (hCG) by the developing fetus can lead to the recruitment of T regulatory cells (Tregs), which are essential for immune tolerance and regulation.

- **Alterations in Immune Responses:** Pregnancy also induces changes in cell-mediated and humoral immunity. These changes help create an environment that promotes immune tolerance to the developing fetus, preventing the maternal immune system from attacking it as a foreign entity.

These immunomodulatory effects during pregnancy are crucial for the successful progression of pregnancy and the protection of the developing fetus. However, they can also influence the course of autoimmune diseases such as RA in pregnant individuals, potentially leading to improvements in disease symptoms during pregnancy and postpartum periods due to the shift towards a more immune-tolerant state.

The postpartum period presents a heightened vulnerability for women when it comes to RA flares and the potential development of RA. The incidence of RA is notably increased following the first pregnancy, especially during the initial 9 months after childbirth. Postpartum flares can impact up to 90% of RA patients, with a higher likelihood within the first 3 months, and this risk is particularly pronounced after the first pregnancy (26, 27).

III. DIAGNOSIS

The diagnosis of RA primarily relies on clinical judgment. However, due to the diverse ways RA can present and strong evidence indicating that the best long-term outcomes result from early intervention, updated classification criteria were introduced in 2010 by the

American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). These criteria aim to promote the timely initiation of therapy (28).

These criteria allocate weighted scores to four domains: serology, joint distribution, serology, the indication of an acute phase response, and duration of symptom. A classification of 'definite' RA is established if a patient scores 6 or more out of a possible maximum of 10 according to these criteria. This approach helps healthcare professionals identify and classify RA cases more accurately, facilitating early intervention and improved patient outcomes (28).

Thus, to arrive at a clinical diagnosis, a comprehensive assessment is conducted, including:

1. **Patient History:** A detailed history of the condition, including its onset, progression over time, factors that worsen or alleviate symptoms, the pattern of joint involvement pattern, and stiffness of joints related to inactivity, as well as improvements with activity. These factors help identify the presence of an inflammatory joint disorder like RA.

2. **Physical Examination:** Assessment of clinical symptoms aiming the identification of objective signs of inflammatory arthritis, which may include joint swelling, tenderness, and limitations in joint mobility.

3. **Extra-Articular Manifestations:** RA can affect other parts of the body, leading to manifestations such as rheumatoid nodules, thrombocytosis, anemia, pleural effusion, pericarditis, and entrapment neuropathies. Identifying these extra-articular symptoms is crucial for a comprehensive diagnosis(29).

4. **Laboratory Markers:** Individuals with RA often exhibit elevated levels of nonspecific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These markers can provide additional supportive evidence for the diagnosis.

5. **Serological Tests:** This test is conducted to detect two specific markers: anti-cyclic citrullinated peptide (anti-CCP) antibodies RA factor. However, it's important to note that these markers have different levels of specificity.

6. **RA Factor:** RA factor is less specific because it can also be elevated in various other conditions such as diabetes, bacterial endocarditis, cancer, and chronic infections. Therefore, while a positive RA factor test can be suggestive of RA, it is not conclusive on its own and needs to be considered alongside other clinical and laboratory findings (21, 30).

7. **Anti-CCP Antibodies:** Anti-CCP antibodies are more specific to RA. Their presence is strongly associated with the disease and is less likely to be elevated in other conditions. A positive anti-CCP antibody test can provide stronger evidence of RA (31).

Additionally, for a more comprehensive evaluation, synovial fluid aspiration and analysis can be performed. In RA, synovial fluid analysis often reveals an increased white

blood cell (WBC) count, typically ranging from 5,000 to 50,000 WBC/µL, with a predominance of neutrophils.

Imaging studies, such as magnetic resonance imaging (MRI) and X-rays are valuable for assessing joint damage and inflammation. Ultrasound is highly sensitive for early detection of joint erosions, soft tissue evaluation, and subclinical synovitis in rheumatology. It's particularly useful for assessing tenosynovitis and can aid in predicting disease persistence. Patients readily accept ultrasound, and it enhances shared decision-making by showing inflammation visually (32). MRI is particularly useful for detecting joint effusion (accumulation of fluid in the joint space) and early bone changes associated with RA (33).

As part of the diagnostic process, it's essential to gather a complete medical history, including information about comorbidities, obstetric history (as some medications used to treat RA may have implications for pregnancy), and a family history of autoimmune diseases. This comprehensive assessment helps in the accurate diagnosis and management of RA by considering both the patient's clinical presentation and potential risk factors.

Patients who display a combination of atypical and typical features suggestive of RA should undergo a comprehensive evaluation to explore various rheumatologic diseases. This step is essential to ensure an accurate diagnosis and the initiation of appropriate treatment.

IV. POSTPARTUM RA MANAGEMENT

RA treatment is an ongoing process with the primary objective of alleviating pain, reducing inflammation, preventing joint deformities, and restoring normal joint function. This approach seeks to maintain physical, social, and mental well-being, as well as the ability to work effectively. Treatment strategies encompass rest, pharmacotherapy, intra-articular hydrocortisone injections, physiotherapy, occupational therapy, and, when necessary, surgical interventions (34).

Most RA patients receive disease-modifying antirheumatic drugs (DMARDs) such as chloroquine, methotrexate, cyclosporine, minocycline, sulfasalazine, and leflunomide to impede disease progression and joint damage. Methotrexate remains the most widely used DMARD for RA. Hydroxychloroquine, sulfasalazine, and minocycline are commonly given to mild and moderate cases, while cyclophosphamide is reserved for severe ones. Tumor necrosis factor (TNF) inhibitors, such as entanercept and infliximab, show promise, though long-term results are pending (34).

Surgical interventions may be considered to relieve pain and improve joint function. Surgery temporarily slows joint destruction by removing invasive tissue, clearing debris from the articular capsule, smoothing rough cartilage, correcting joint angles, and stabilizing painful joints. Physiotherapy and occupational therapy are vital for managing RA, enhancing muscle strength, and preserving joint mobility (34).

In postpartum RA management, women with symptom-free periods can continue their pregnancy medication regimen. Those experiencing postpartum flares or at risk of flaring can resume pre-pregnancy treatments with adjustments, particularly for breastfeeding mothers. Non-breastfeeding patients can resume pre-pregnancy medications based on their symptoms (35).

Regarding medication use during breastfeeding, non-steroidal anti-inflammatory drugs (NSAIDs) are permissible, while aspirin should be avoided. Low-dose glucocorticoids are generally safe, with a recommendation of gap of four hours before nursing. Some DMARDs like hydroxychloroquine, sulfasalazine, and azathioprine are compatible with breastfeeding, except sulfasalazine in premature infants or those with specific conditions. It is possible to either continue or begin TNF inhibitors during lactation. Conversely, methotrexate, leflunomide, and certain targeted synthetic DMARDs are not advisable during breastfeeding due to potential transfer into breast milk (35).

When achieving remission, drug withdrawal should follow a specific sequence: glucocorticoids, anti-inflammatory drugs, biological DMARDs, and synthetic DMARDs. Criteria include meeting remission standards, maintaining it for six months with consistent dosages and no Glucocorticoids (1). The likelihood of achieving post-DMARD withdrawal remission is higher when anti-CCP antibodies are absent (36), deep remission is achieved, and there is no ultrasound-detected synovitis (37, 38).

Recent studies on RA management have highlighted the role of $CD4^+$ T cell activation and differentiation in RA progression (39). The findings from these studies indicate that fasting for duration of 7 to 10 days, while consuming a restricted diet consisting of items such as broth made of vegetables, herbal teas, and juices, may be effective (40), can temporarily suppress T-cell activation, potentially providing relief from RA symptoms. Additionally, a vegan diet, combined with fasting and followed by a year of veganism, has demonstrated significant reductions in joints that are both swollen and tender, there is pain, along with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (41, 42). The influence of dietary fiber and whole grains on RA management remains inconclusive, but within recommended limits, they may offer certain health benefits. Furthermore, phytochemicals found in fruits and vegetables, such as anthocyanins, resveratrol, and kaempferol, exhibit anti-inflammatory properties and hold the potential to slow down RA progression (7).

Probiotics, particularly Lactobacillus casei, show promise in reducing pro-inflammatory cytokines and alleviating RA symptoms (7). Moreover, vitamin D supplementation in RA patients has led to reduced disease flares, pain levels, and Disease Activity, although statistical significance was not consistently achieved (43). Elimination diets, which exclude food allergens, have demonstrated effectiveness in alleviating RA symptoms by reducing the activation of macrophages and other immune cells involved in inflammation (7). Adopting healthy dietary habits, particularly following a Mediterranean diet, along with regular physical activity, could potentially reduce the risk of RA, associated comorbidities, and the advancement of the disease. This includes consuming fatty fish, olive oil, whole grains, legumes, fruits, and vegetables while limiting or avoiding sugar-sweetened drinks, excessive salt, alcohol, and coffee to maintain overall health and well-being(44) (7).

In recent years, managing RA has expanded beyond medication alone, with alternative approaches like meditation, yoga, and mindfulness gaining attention for improving patients' quality of life. Mindfulness reduces stress, positively impacting well-being, depression, and anxiety. It's particularly beneficial for RA patients with recurrent depression. Mindfulness-based interventions helping RA individuals by improving symptoms (45). On the other hand, yoga seems to deliver more favorable results concerning RA disease activity indicators, while mindfulness helps with pain perception and joint tenderness but has limited impact on objective RA disease activity parameters (45). Exercise is essential for treating RA, improving function without harming disease activity. All RA patients should incorporate aerobic and resistance training. More research is needed to determine optimal exercise types and doses for different stages of RA (46). Managing RA during pregnancy and postpartum requires a tailored approach, considering both maternal and infant health. Treatment choices should be made carefully, balancing the need for symptom control with pregnancy and breastfeeding safety.

V. CONCLUSION

To sum up, rheumatoid arthritis (RA) is a persistent autoimmune inflammatory condition that has a profound effect on the quality of life for those who have it. It is estimated to affect roughly 1% of the worldwide population, with a greater occurrence among women, particularly those in their reproductive years. The onset of RA postpartum is a well-documented phenomenon, with a heightened risk in the first months after childbirth.

RA diagnosis relies on a comprehensive assessment, combining patient’s medical history, physical examination, assessment of laboratory markers, and imaging studies. The 2010 classification criteria by the American College of Rheumatology and European League Against Rheumatism have greatly improved the accuracy of diagnosis and timely intervention. Management of this condition encompasses a wide treatment range, including DMARDs, physiotherapy, occupational therapy, as well as, in some cases, surgical interventions. During pregnancy, treatment plans may need to be adjusted to ensure both maternal symptom control and infant safety. Medication choices during breastfeeding should consider the potential impact on the infant.

Recent studies have explored dietary interventions, including fasting and veganism, as well as the role of dietary components like dietary fibers, phytochemicals, probiotics, and vitamin D in RA management. While promising, further research is needed to establish their efficacy definitively.

Mindfulness, yoga, and exercise training have gained attention as complementary approaches to managing RA, offering improvements in well-being, stress reduction, and physical function. These therapies should be considered as part of a comprehensive treatment plan.

In summary, managing RA during and after pregnancy requires a multidisciplinary approach, taking into account the unique challenges faced by women in the postpartum period. It is essential to tailor treatment plans to individual needs, balancing symptom control, and safety for both the mother and her child. Advances in research continue to provide

insights into new strategies for effectively managing RA and improving the quality of life for those affected by this condition.

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