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Research Article

INFLUENCE OF REPRODUCTIVE HEALTH CONCERNS ON TREATMENT DECISIONS FOR WOMEN WITH RHEUMATOID ARTHRITIS: REAL-WORLD DATA INSIGHTS FROM THE KUWAIT RHEUMATOID ARTHRITIS REGISTRY

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Abstract

Background: Rheumatoid arthritis (RA) predominantly affects women, particularly during their reproductive years, necessitating careful consideration of treatment choices. **Objectives:** To assess if the age of female RA patients influences the prescribing patterns of non-pregnancy-compatible versus pregnancy-compatible Disease-Modifying Anti-Rheumatic Drugs (DMARDs) by analyzing treatment trends in a national registry. **Methods:** We conducted a retrospective analysis of prospectively collected data from the Kuwait Registry for Rheumatic Diseases (KRRD) between January 1, 2013, and May 30, 2024. The analysis included 1001 female patients, stratified into two age groups: ≤45 years and >45 years. We examined demographic data, disease activity (DAS28), and initial (at first visit) treatment regimens. Statistical analyses included chi-square tests, t-tests to compare differences between age groups and logistic regression (univariate and multivariate) were performed to determine the association between age, nationality, disease activity, seropositivity, and anti-rheumatic medications, reporting odds ratios (OR) with 95% confidence intervals (CI). Adjustments were made for potential confounders, including baseline DAS28 and rheumatoid factor (RF)/anti-cyclic citrullinated peptide (anti-CCP) status. **Results:** Among the patients, younger women (≤45 years) represented 22.4%, while older patients (>45 years) comprised 77.6%. No difference in the prescription of methotrexate was found between the groups, younger women received leflunomide more often (12.1% vs. 7.6%, p=0.036). Notably, biologics, including TNF inhibitors, were prescribed significantly less to younger women (9.8% vs. 18.4%, p=0.002), possibly reflecting concerns regarding reproductive safety. **Conclusion:** This study reveals that age and reproductive health considerations did not factor into the treatment decision-making process for female RA patients in Kuwait, highlighting a gap between the international treatment guidelines and real-world prescribing patterns. Rheumatologists face challenges in balancing disease control with reproductive safety, emphasizing the need for further research to explore underlying reasons for this approach and develop strategies that optimize treatment while considering reproductive health.

Keywords: Rheumatoid arthritis, females, anti-rheumatic treatment, registry data, real world evidence

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting females, many of which are in their reproductive years [1]. Early use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs), including conventional DMARDs (cDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), is often employed to reach the primary goal of remission or low disease activity (LDA) [2, 3]. Treatment choice is often influenced by various factors such as drug safety and efficacy, cost effectiveness, and more recently, patients' age and comorbidities, such as coronary artery disease and extra-articular manifestations [4, 5]. Therefore, the initial treatment decision plays an important role as it sets the stage for long-term disease control and achievement of the target goal of remission.

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Currently, the European League Against Rheumatism (EULAR) [6] and the American College of Rheumatology (ACR) [7] recommend early and intensive treatment of RA in a treat-to-target (T2T) strategy. According to the EULAR recommendations, the preferred initial treatment is a cDMARD, most commonly methotrexate. The treat-to-target approach mandates an escalation of therapy if the set target point isn't achieved within the specified time frame; this involves dose uptitration of the initial DMARD, switching therapy, or combining biologics or tsDMARDs to the treatment regimen [6, 7]. This approach reflects the dynamic nature of RA management, where the initial treatment choice is the first step in a longer-term strategy to achieve disease control. In this context, treatment decisions can have profound implications, particularly for younger female patients, as reproductive health concerns should be carefully considered to ensure safety during pregnancy while maintaining disease control. EULAR, ACR and the British Society of

Rheumatology (BSR) emphasize that in women of childbearing age, treatment with teratogenic drugs should be avoided in women planning to get pregnant [8-10]. Methotrexate, while highly effective, is contraindicated during pregnancy due to its teratogenic effects and the expectation is that younger women of reproductive age would be treated with safer alternatives as part of their initial therapy. Despite the availability of these treatment options, adherence to this recommendation may vary in real-world practice, as research suggests [11, 12]. This study focuses on whether the prescribing pattern of treatment in female RA patients in Kuwait is in line with international guidelines, particularly regarding pregnancy-compatible choices in women of reproductive age. We hypothesize that younger women (≤45 years) with RA, chosen as an indirect indicator of reproductive health concerns, will be prescribed fewer non-pregnancy-compatible DMARDs, such as methotrexate, compared to older women (>45 years). This study aims to evaluate the initial treatment choices made among female RA patients in these two age groups and to investigate whether patient age, particularly in relation to reproductive health, influences the selection of antirheumatic medications at baseline.

METHODS

Study design

This is a retrospective analysis of the prospectively collected data from the Kuwait Registry for Rheumatic Diseases (KRRD), an ongoing database that captures information on RA patients in Kuwait starting at the time of diagnosis and quarterly follow up thereafter. The KRRD enrolls individuals aged 18 years and older who meet the ACR and EULAR criteria for RA [13], gathered from government hospitals throughout Kuwait. The registry collects detailed patient information, including demographics, baseline disease activity as measured by the Disease Activity Score in 28 joints (DAS28) and the antirheumatic treatments provided. The baseline data corresponds to the information collected at the time of enrollment. Antirheumatic medications were categorised into two groups: pregnancy compatible, including (hydroxychloroquine, sulfasalazine, certolizumab) and pregnancy incompatible (methotrexate, leflunomide). The initial treatment was defined as medication given at the first encounter after diagnosis of RA was established. Our study focused exclusively on female RA patients enrolled in the cohort between January 1, 2013, and May 30, 2024, totalling 1001 participants. Patients were stratified by age into two groups: ≤45 years and >45 years. The age cutoff was selected as an indicator of reproductive health and pregnancy-related concerns. Baseline data on disease activity, including DAS28 score, seropositivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), and treatment regimens initiated at the first visit were analyzed.

Ethical Approval

This study was conducted in compliance with the ethical guidelines and principles outlined by relevant institutional review boards. Ethical approval was issued by the Joint Committee for the Protection of Human Subjects in the research of the Health Sciences and the Kuwait Institute for Medical Specialization (2012/VDR/JC/882). KRRD provided anonymized patient data, ensuring no personally identifiable information was used during the analysis. All procedures involving human data were carried out in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients whose data were included in the registry, and their participation was voluntary.

Statistical Analysis

All statistical analyses were conducted using JAMOVI (version 2.5.7.0). Descriptive statistics were used to summarize baseline demographic and clinical characteristics, with means and standard deviations (SD) reported for continuous variables and frequencies for categorical variables. Differences between age groups (≤45 years and >45 years) were assessed using independent t-tests for continuous variables and chi-square tests for categorical variables. A significance level of $p < 0.05$ was considered statistically significant. Logistic regression analyses (both univariate and multivariate) were performed to determine the association between age, nationality, disease activity, seropositivity, and the prescription patterns of anti-rheumatic medications with odds ratios (OR) and 95% confidence intervals (CI) reported. Adjustments were made for potential confounders, including baseline Disease Activity Score in 28 joints (DAS28) and RF/anti-CCP status.

Outcomes

Primary Outcome: The primary outcome was assessing the proportion of female RA patients in each age group initially prescribed pregnancy-incompatible versus pregnancy-compatible DMARDs.

Secondary Outcomes: Assessing the use of combination therapy versus monotherapy as an initial treatment strategy.

RESULTS

Patient Demographics, Baseline Disease Activity and Serology Status

The study included 1001 female RA patients, stratified into two age groups: 22.4% were ≤ 45 years (n=224) and 77.6% were > 45 years (n=777). Patient characteristics are shown in Table 1. The mean baseline DAS28 score was similar between the two groups (3.1 vs. 3.0, p=0.3901); Seropositivity for either RF and/or Anti-CCP was observed in 84.8% of the cohort, with a higher proportion in younger patients (89.3%) compared to older patients (83.6%). On the other hand, seronegativity was more frequent in older patients (16.4% vs. 10.7%)

Initial Therapeutic Agent Choice and Treatment Strategy:

Table 2 demonstrates the medication prescribed during the initial visit and the initial treatment strategy between the groups.

Monotherapy vs. Combination Treatment Strategy

Mono-DMARD therapy (single cDMARD use) was the initial strategy used in 58% of the cohort shown in Figure 1(A). In Table 2, mono-DMARD was more frequently prescribed in the younger group (61.6%) compared to the older group (57.3%), although this difference was not statistically significant (p=0.2461).

Table 1. Baseline Characteristics

	≤ 45 Years (N=224)	> 45 Years (N=777)	Total (N=1001)	p value
DAS28				0.390[1]
Mean (SD)	3.0 (1.4)	3.1 (1.3)	3.1 (1.3)	
BMI				0.696[1]
Mean (SD)	28.5 (4.6)	28.4 (4.7)	28.4 (4.7)	
RF/CCP Status				0.085[2]
N-Miss	75	211	286	
Seropositive [3]	133 (89.3%)	473 (83.6%)	606 (84.8%)	
Seronegative [4]	16 (10.7%)	93 (16.4%)	109 (15.2%)	
Deformities				0.224[2]
N-Miss	22	89	111	
No	191 (94.6%)	633 (92.0%)	824 (92.6%)	
Yes	11 (5.4%)	55 (8.0%)	66 (7.4%)	
Nationality				< 0.001[2]
Kuwait	108 (48.2%)	473 (60.9%)	581 (58.0%)	
Other Nationality	116 (51.8%)	304 (39.1%)	420 (42.0%)	

Linear Model ANOVA, 2. Pearson's Chi-squared test. DAS28 = Disease Activity Score in 28 joints; BMI = Body mass index; RF = Rheumatoid Factor; anti-CCP = anti-cyclic citrullinated peptide antibodies. Seropositive = either positive RF or anti-CCP positive or both. Seronegative = both RF and anti-CCP are negative

Table 2. Initial therapeutic Agents' choice and Treatment Strategy

	≤ 45 Years (N=224)	> 45 Years (N=777)	Total (N=1001)	p value
Methotrexate	133 (59.4%)	504 (64.9%)	637 (63.6%)	0.132
Sulfasalazine	28 (12.5%)	90 (11.6%)	118 (11.8%)	0.708
Leflunomide	27 (12.1%)	59 (7.6%)	86 (8.6%)	0.036*
Hydroxychloroquine	71 (31.7%)	238 (30.6%)	309 (30.9%)	0.761
TNF inhibitor (TNFi)[(1)]	22 (9.8%)	143 (18.4%)	165 (16.5%)	0.002*
Non-TFNi[(2)]	56 (25.0%)	179 (23.0%)	235 (23.5%)	0.541
Combination (cDMARDs + Biologics)	41 (18.3%)	182 (23.4%)	223 (22.3%)	0.105
Mono Biologics	45 (20.1%)	150 (19.3%)	195 (19.5%)	0.794
Mono cDMARDs	138 (61.6%)	445 (57.3%)	583 (58.2%)	0.246

TNFi: Infliximab, Adalimumab, Golimumab, Etanercept, Certolizumab pegol. 2-Non-TNFi: Rituximab, Tocilizumab, Abatacept. cDMARDs = Conventional Disease-Modifying Antirheumatic Drugs, bDMARDs= Biological Disease-Modifying Antirheumatic Drugs.

There was no significant difference in the use of monobiologic therapy, with 20.1% of younger patients and 19.3% of older patients receiving biologics as monotherapy (p=0.7941). Combination therapy (cDMARDs with biologics) was used slightly more in older patients (23.4% vs. 18.3%, p=0.105), though the difference was not statistically significant. The overall frequency of therapeutic medications used in the cohort is demonstrated in Figure 1(B).

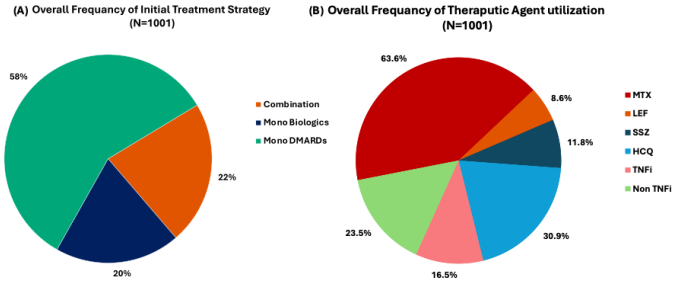

Figure 1. (A) Frequency treatment strategy utilized in the overall female cohort. combination = cDMARD+Biologic, Mono Biologic = Biologic agent monotherapy, Mono DMARDs = cDMARDs monotherapy, (B) The frequency of therapeutic agents used in the overal female cohort. MTX = Methotrexate, LEF = leflunomide, SSZ = sulfasalazine, HCQ = Hydroxychloroquine, TNFi = TNFinhibitors, None TNFi = None TNF inhibitor biologics

Conventional DMARDs (cDMARDs) Therapy:

Methotrexate (MTX) was prescribed to 59.4% of younger and 64.9% of older patients, this difference was not statistically significant (p=0.1321). Leflunomide (LEF) was prescribed more frequently in the younger group (12.1%) compared to the older group (7.6%), with a statistically significant difference (p=0.036). As shown in Table 3, there was a trend to prescribe leflunomide to younger patients compared to older patients OR (univariate) 1.69 (95% CI: 0.94–2.95, p = 0.070) and 1.58 (95% CI: 0.87–2.78, p = 0.118) (multivariate). However, these associations were not statistically significant. Non-Kuwaiti patients were significantly more likely to be prescribed LEF than Kuwaitis, OR (univariate) 1.84 (95% CI: 1.10–3.12, p = 0.022) and 1.77 (multivariate) (95% CI: 1.05–3.01, p = 0.034), while disease activity at baseline (DAS-28) and seropositivity for RF and/or anti-CCP didn't show a significant association with the prescription of LEF. The use of Hydroxychloroquine (HCQ) and Sulfasalazine (SSZ) did not differ significantly between the age groups (p=0.7611 for HCQ and p=0.7081 for SSZ).

Biologic DMARDs (bDMARDs) Therapy

A higher proportion of older patients were treated with Tumor Necrosis Factor inhibitors (TNFi) compared to younger patients (18.4% vs. 9.8%, p=0.0021). Patients aged > 45 years were more likely to receive TNFi therapy than those ≤ 45years, with an OR of 2.09 (95% CI: 1.20–3.93, p = 0.014) in univariate analysis and OR of 1.94 (1.09-3.69, p=0.032) in multivariate analysis, demonstrated in table 3. Non-Kuwaiti patients had higher odds of not receiving TNFi therapy compared to Kuwaiti patients, OR (univariate) 3.18, 95% CI: 2.02–5.15, p < 0.001), OR (multivariate) 3.00, 95% CI: 1.90–4.89, p < 0.001). Etanercept (ETN) was used more in the older group (5.0% vs. 1.3%, p=0.0161). Adalimumab (ADA) was more frequently used in older patients (8.4% vs. 4.9% p=0.0851). Rituximab was also prescribed, though the differences between the age groups were not statistically significant (97(12.5%) vs. 30(13.4%), P=0.7191).

Targeted Synthetic DMARDs (tsDMARDs) Therapy

A total of 15 patients only were receiving JAK inhibitors, with a higher proportion of use in the younger group (3.1% vs. 1.0%, p=0.0231.

Table 3. Logistic regression analysis (univariable and multivariable) of Leflunomide and anti-TNF prescribing pattern

Leflunomide		No	Yes	OR (univariable)	OR (multivariable)
Age years	> 45	521 (92%)	45 (8%)	-	-
	≤ 45	130 (87.2%)	19 (12.8%)	1.69 (0.94-2.95, p=0.070)	1.58 (0.87-2.78, p=0.118)
Nationality	Kuwait	373 (93.2%)	27 (6.8%)	-	-
	Non-Kuwaiti	278 (88.3%)	37 (11.7%)	1.84 (1.10-3.12, p=0.022)	1.77 (1.05-3.01, p=0.034)
DAS28	Mean (SD)	3.2 (1.4%)	3.2 (1.3%)	1.01 (0.83-1.21, p=0.948)	1.00 (0.83-1.20, p=0.996)
RF/CCP	Seropositive	551 (90.9%)	55 (9.1%)	-	-
	Seronegative	100 (91.7%)	9 (8.3%)	0.90 (0.41-1.80, p=0.783)	0.99 (0.44-1.99, p=0.976)
ANTI TNF		No	Yes	OR (univariable)	OR (multivariable)
Age years	> 45	465 (82.2)	101 (17.8)	-	-
	≤ 45	135 (90.6)	14 (9.4)	2.09 (1.20-3.93, p=0.014)	1.94 (1.09-3.69, p=0.032)
Nationality	Kuwait	311 (77.8)	89 (22.2)	-	-
	Non-Kuwaiti	289 (91.7)	26 (8.3)	3.18 (2.02-5.15, p<0.001)	3.00 (1.90-4.89, p<0.001)
DAS28	Mean (SD)	3.2 (1.4)	2.9 (1.1)	1.19 (1.02-1.39, p=0.025)	1.19 (1.02-1.40, p=0.033)
RF/CCP	Seropositive	517 (85.3)	89 (14.7)	-	-
	Seronegative	83 (76.1)	26 (23.9)	0.55 (0.34-0.91, p=0.018)	0.63 (0.38-1.07, p=0.077)

OR = Odds Ratio; DAS28 = Disease Activity Score in 28 joints; RF/CCP = Rheumatoid Factor or anti-Cyclic Citrullinated Peptide antibody positivity; Seropositive = either positive RF or anti-CCP positive or both; Seronegative = both RF and anti-CCP are negative.; TNFi =Tumor Necrosis Factor Inhibitors

DISCUSSION

RA is a chronic systemic autoimmune disease that predominantly affects women, often during their childbearing years [1]. As a result, treatment decisions in female patients require looking at optimal disease control while considering reproductive health and pregnancy safety. EULAR, BSR and ACR guidelines highlight the importance of avoiding teratogenic drugs such as MTX and LEF in women of reproductive potential, especially when pregnancy is planned or possible in the near future [8-10].

Initial therapeutic agent choice and treatment strategy

In this cohort of 1001 female RA patients from KRRD, treatment decisions at baseline appeared to be influenced more by general RA management principles than by reproductive considerations. MTX was the most frequently prescribed initial DMARD across both age groups. The overall treatment strategy is toward csDMARDs prescription, while biologics and tsDMARDs were used more selectively.

Conventional DMARDs (cDMARDs) Therapy

Among cDMARDs, MTX remained the main treatment for both age groups, prescribed in 59.4% of patients aged ≤45 years and 64.9% of those >45 years. Although this difference was not statistically significant (p=0.132), it raises concerns given MTX's well-known teratogenicity [8-10]. Even more unexpected was the significantly higher prescription of LEF in the younger group (12.1% vs. 7.6%, p=0.036).LEF, similar to MTX, has teratogenic risk and requires an extended elimination process using cholestyramine during pre-conception, given its long half-life [8-10].This practice may suggest that reproductive safety may not be consistently considered when initiating cDMARDs in women of childbearing age. On the other side, the use of HCQ and SSZ, both considered safe in pregnancy, did not significantly differ between age groups. HCQ was prescribed to 31.7% of younger and 30.6% of older patients (p=0.761), while SSZ use was 12.5% and 11.6%, respectively (p=0.708). The lack of an increased preference for these pregnancy compatible options in the younger group highlights a potential missed opportunity to be consistent with guideline recommendations for women of reproductive age[8-10].

In addition, multivariable analysis revealed that non-Kuwaiti patients were significantly more likely to receive leflunomide (OR 1.77, p=0.034), suggesting that systemic or socioeconomic factors may influence cDMARD selection within the Kuwaiti healthcare context. Indeed, the healthcare system in Kuwait, although a universal care system, limits access to biologics and tsDMARDs for non-Kuwaiti patients, which certainly can affect the decision-making process.

Biologic DMARDs (bDMARDs) Therapy

With regards to TNFi, they were significantly more likely to be prescribed for women >45 years (18.4% vs. 9.8%, p=0.002). This finding is important because almost all TNFi agentsare now considered safe during conception and pregnancy [9]. Despite this, their underuse in the younger group may reflect either a conservative approach to biologic use in early treatment or prescriber uncertainty about safety in the context of reproductive health. Etanercept was used more in the older group (5.0% vs. 1.3%, p=0.016), and adalimumab use showed a non-significant trend toward higher use in older patients (8.4% vs. 4.9%, p=0.085). Multivariable analysis supported these findings, with patients aged ≤45 significantly less likely to receive TNFi therapy (OR 1.94, p=0.032). Notably, non-Kuwaiti patients were three times less likely to receive TNFi (OR 3.00, p<0.001), suggesting systemic healthcare disparities related to nationality, or access to biologics. This can be particularly important since Kuwait provides universal health care and open access to nationals with restrictions on biologics to non-Kuwaiti residents. These findings underscore the need to examine real-world equity in biological prescribing in addition to clinical appropriateness.

Targeted Synthetic DMARDs (tsDMARDs) Therapy

Only 15 patients in the entire cohort were prescribed JAKis, with greater use among younger women (3.1% vs. 1.0%, p=0.023). Although the absolute numbers are small, this result is unexpected given the limited safety data for JAKis in pregnancy [8-10]. Given the limited pregnancy safety data for tsDMARDs, it is reassuring that their use was minimal in this cohort. However, the higher proportion among younger women may suggest either a gap in awareness of reproductive safety data or challenges in aligning real-world treatment with theoretical best practices in this subgroup.

Monotherapy vs. Combination Treatment Strategy

The overall treatment strategy showed a slightly higher proportion of younger women being treated with monotherapy (61.6%) compared to older women (57.3%), though the difference was not statistically significant (p=0.246). While not statistically significant, this may reflect a more conservative therapeutic approach in women of reproductive age. Alternatively, it could suggest under-treatment, which has been a concern in the past when physicians, due to concern for pregnancy safety, would go for less aggressive regimens in women planning pregnancy [14]. However, it has been documented that untreated or poorly controlled RA during pregnancy is associated with adverse maternal and fetal outcomes, emphasizing the need for effective disease suppression with pregnancy compatible therapies [15]. Combination therapy involving either csDMARDs with bDMARDs or tsDMARDs was more frequent among older women (23.4% vs. 18.3%, p=0.105), possibly indicating a more aggressive strategy in older patients or less concern about pregnancy-related complications. The similar rates of monobiologic use between the two age groups (20.1% vs. 19.3%) reinforce the fact that patient age was not a major determinant of treatment intensity at baseline. Our findings are also consistent with the broader literature, suggesting that female sex and younger age are associated with differences in RA treatment response and disease phenotype. Women are likely to report higher disease activity scores and worse functional outcomes, even when inflammatory markers are similar to those in men [16, 17]. This discrepancy underscores the importance of optimizing treatment in women early in the disease course to prevent long-term disability and poor quality of life. Finally, it is important to acknowledge that while international guidelines emphasize shared decision-making and individualized treatment planning, real-world implementation can be variable. Our findings suggest that while the treat-to-target principle is generally followed, there may be room for improvement in considering reproductive planning in the intensity and type of RA treatment, particularly in younger female patients. Limited access to specialized reproductive counseling, cultural factors, and differences in physician training or comfort with discussing reproductive issues may all contribute to suboptimal consideration of reproductive health in RA management. Addressing these barriers through physician education, standardized reproductive health assessments and multidisciplinary collaboration with obstetrics and maternal-fetal medicine may help bridge the gap between guideline recommendations and clinical practice.

Limitations

This study has several limitations, including the discrepancy in the number of patients assessed in each group, which may affect data analysis. Additionally, addressing prescribing patterns, such as rheumatologists' preferences, patients' preferences, and considerations of accessibility and affordability, particularly for expatriate patients, still needs to be elaborated in future research could lead to a more comprehensive understanding of treatment decisions in this patient population.

Conclusion

The study reveals that age and reproductive health concerns are not completely integrated into anti-rheumatic treatment decision-making for women with RA in Kuwait, contrary to international guidelines. Rheumatologists often face the challenge of balancing tight disease control and reproductive safety, which is evident from the results of our cohort. This issue necessitates further research to explore potential reasons for this approach and develop strategies for optimizing RA disease activity management in women while also considering their reproductive health.

Disclosure: This is an investigator study from the KRRD registry.

Conflict of Interest: The authors declare no conflict of interest.

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