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ORIGINAL ARTICLE

Reproductive Health and Gynecological Outcomes in Women with Autoimmune and Inflammatory Diseases Receiving DMARD Therapy

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ABSTRACT

Background: Women with autoimmune and inflammatory diseases are at risk for adverse reproductive outcomes due to systemic inflammation and DMARD therapy. Methotrexate has been implicated in gonadotoxicity, yet comprehensive evaluations using modern biomarkers remain limited.

Aims and Objectives: This study aimed to determine the prevalence and determinants of gynecological abnormalities and diminished ovarian reserve in women with rheumatic and connective tissue disorders. Specific objectives were to assess menstrual irregularities, sexual dysfunction, and hormonal profiles among patients on various DMARD regimens.

Methodology: In a 12-month prospective observational study at PAF Hospital, Islamabad, n=250 women aged 18–45 years with confirmed diagnoses (rheumatoid arthritis, seronegative RA, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder, systemic sclerosis) were enrolled. Participants received stable DMARD therapy including traditional agents (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), biologics, tsDMARDs, JAK inhibitors, and other immunosuppressives. Data were collected via standardized questionnaires, transvaginal ultrasound, and serum measurement of AMH, FSH, estradiol, inhibin B, prolactin, testosterone, and CRP. Statistical analyses were performed using SPSS Model 26 with t-tests, ANOVA, Chi-square tests, and multivariable regression ($p < 0.05$).

Results: Baseline menstrual irregularities were 33%, increasing to 42% at follow-up. Methotrexate-treated patients had higher irregularity rates (52% vs. 34%; $p = 0.01$) and significantly lower AMH, higher FSH, reduced estradiol, and decreased inhibin B levels.

Conclusion: Systemic inflammation and methotrexate exposure significantly impair reproductive health. Tailored DMARD strategies and integrated reproductive monitoring are essential. Future research should focus on personalized care and fertility outcomes.

Keywords: Autoimmune, Inflammatory, DMARDs, Methotrexate, Ovarian Reserve, Menstrual Irregularities, Reproductive Health.

INTRODUCTION

Inflammatory and autoimmune disorders encompass a diverse group of conditions that include both rheumatic diseases and connective tissue disorders. Rheumatic conditions such as rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, seronegative RA, and seronegative inflammatory arthritis are primarily characterized by chronic systemic inflammation affecting the musculoskeletal system[1]. In parallel, connective tissue disorders—including systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder, and systemic sclerosis—also feature persistent inflammation that can compromise various organ systems, including reproductive tissues[2].

This chronic inflammatory state can disrupt hormonal balance and the hypothalamic-pituitary-ovarian axis, leading to a spectrum of gynecological abnormalities. These abnormalities manifest as menstrual disturbances (such as irregular cycle lengths, heavy or light bleeding, amenorrhea, or spotting), fertility issues, and sexual dysfunction (including loss of libido, vaginal dryness, and abnormal vaginal discharge). Traditionally, disease-modifying antirheumatic drugs (DMARDs) like methotrexate and leflunomide have been implicated in adverse reproductive outcomes due to their antiproliferative properties and potential gonadotoxic effects[3, 4].

However, the DMARD landscape has expanded considerably in recent years. In addition to conventional agents, newer therapies—including hydroxychloroquine (HCQ), TNF-α inhibitors (e.g., etanercept, infliximab, adalimumab), IL-6 inhibitors (e.g., tocilizumab), IL-17 inhibitors (e.g., secukinumab), targeted synthetic DMARDs (tsDMARDs such as apremilast), JAK inhibitors (tofacitinib, upadacitinib, baricitinib), and other immunosuppressives (e.g., mycophenolate mofetil, cyclosporine, tacrolimus, azathioprine, cyclophosphamide, rituximab)—may also influence reproductive health [5, 6].

Given this expanded therapeutic arsenal and the broad spectrum of inflammatory and autoimmune diseases, it is essential to comprehensively evaluate how these conditions and their treatments affect reproductive function. The current study aimed to assess the prevalence and determinants of gynecological abnormalities in women with both rheumatic and connective tissue disorders[7]. By incorporating a detailed analysis of menstrual patterns, fertility biomarkers (including serum anti-Müllerian hormone, follicle-stimulating hormone, estradiol, and inhibin B), and sexual health parameters, this investigation seeks to elucidate the interplay between systemic inflammation, diverse immunomodulatory therapies, and reproductive outcomes[8].

MATERIALS AND METHODS

Study Design and Setting: A prospective observational study was conducted at PAF Hospital, Islamabad over a 12-month period from June 2021 till June 2022.

Participants, Inclusion, and Exclusion Criteria: A total of n=250 women aged 18–45 years with confirmed autoimmune or inflammatory diseases were enrolled. The study population comprised patients diagnosed with rheumatic/inflammatory arthritis—including rheumatoid arthritis (with a subset of seronegative RA), psoriatic arthritis, ankylosing spondylitis, and seronegative inflammatory arthritis—as well as patients with connective tissue disorders, such as systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder, and systemic sclerosis. Participants were eligible if they were aged between 18 and 45 years, had a confirmed diagnosis of an autoimmune or inflammatory disease, and had been receiving stable disease-modifying antirheumatic drug (DMARD) therapy for at least three months prior to enrollment. Women were excluded if they had a history of gynecological disorders unrelated to inflammatory disease, had undergone previous ovarian surgery, or were currently pregnant or lactating.

Treatment Regimens: Patients were receiving various immunomodulatory therapies that were categorized as follows: Traditional DMARDs (methotrexate, leflunomide [LEF], sulfasalazine [SSZ], and hydroxychloroquine [HCQ]); Biologic agents (TNF-α inhibitors such as etanercept, infliximab, and adalimumab; IL-6 inhibitors such as tocilizumab; and IL-17 inhibitors such as secukinumab); Targeted synthetic DMARDs (tsDMARDs such as apremilast); JAK inhibitors (tofacitinib, upadacitinib, and baricitinib); and other immunosuppressive drugs (mycophenolate mofetil, cyclosporine, tacrolimus, azathioprine, cyclophosphamide, and rituximab).

Data Collection and Assessments: Baseline data, including demographic characteristics (age and disease duration) and details of DMARD regimens, were meticulously recorded. Gynecological evaluation was performed using a standardized questionnaire that documented menstrual patterns (variability in cycle length, heavy or light bleeding, amenorrhea, and spotting) and self-reported sexual function parameters (libido, vaginal dryness, and abnormal vaginal discharge). To comprehensively assess fertility and ovarian function, serum biomarkers were measured, including anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol, inhibin B, prolactin, and testosterone. Additionally, transvaginal ultrasound examinations were conducted to evaluate ovarian morphology and endometrial thickness, while systemic inflammation was quantified by measuring C-reactive protein (CRP) levels.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of PAF Hospital, Islamabad. All participants provided written informed consent prior to enrolment. The study was conducted in full compliance with the ethical standards of the Declaration of Helsinki and adhered to all local regulatory requirements. Confidentiality and anonymity of participant data were strictly maintained throughout the study.

Statistical Analysis: Data analysis was performed using SPSS Model 26.0. Descriptive statistics—including means, standard deviations, frequencies, and percentages—were calculated for baseline variables. For comparative analyses, the independent samples t-test and one-way ANOVA were used to compare continuous variables (e.g., biomarker levels) among different DMARD treatment groups, while Chi-square tests were applied to assess differences in categorical variables, such as the prevalence of menstrual abnormalities and sexual dysfunction. Additionally, multivariable logistic regression was conducted to identify independent predictors of menstrual abnormalities and sexual dysfunction, adjusting for potential confounders such as age, disease duration, and CRP levels. Multivariable linear regression analysis was performed to assess associations between DMARD exposure and fertility markers (AMH, FSH, estradiol, inhibin B, prolactin, and testosterone levels). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of n=250 women with confirmed autoimmune or inflammatory diseases were enrolled in the study. The mean age was 33.8 ± 5.9 years and the average disease duration was 7.5 ± 3.2 years. The study population included patients with various rheumatic/inflammatory arthritis diagnoses (rheumatoid arthritis—including a subset of seronegative RA, psoriatic arthritis, ankylosing spondylitis, and seronegative inflammatory arthritis) as well as patients with connective tissue disorders (systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder, and systemic sclerosis). The distribution of DMARD regimens was as follows: Traditional DMARDs (methotrexate [45%], leflunomide [20%], sulfasalazine [20%], and hydroxychloroquine [15%]); Biologic agents (TNF-α inhibitors, IL-6 inhibitors, and IL-17 inhibitors, collectively prescribed in approximately 20% of cases); Targeted synthetic DMARDs (tsDMARDs such as apremilast); JAK inhibitors (tofacitinib, upadacitinib, and baricitinib); and other immunosuppressive drugs (administered in ~10% of patients) as shown in table 1.

Table 1: Participant Characteristics and DMARD Distribution

Characteristic	Value
Sample Size	250
Mean Age (years)	33.8 ± 5.9
Mean Disease Duration (years)	7.5 ± 3.2
Traditional DMARDs	
- Methotrexate (MTX)	45%
- Leflunomide (LEF)	20%
- Sulfasalazine (SSZ)	20%
- Hydroxychloroquine (HCQ)	15%
Biologic Agents (TNF-α, IL-6, IL-17 inhibitors)	~20%
Other Agents (tsDMARDs, JAK inhibitors, Others)	~10%

At baseline, 33% of participants reported menstrual irregularities, defined as variability in cycle length, heavy/light bleeding, amenorrhea, or spotting. At the 6-month follow-up, the prevalence increased to 42%. In subgroup analysis, the methotrexate group exhibited a significantly higher rate of menstrual irregularities (52%) compared to patients on other DMARD regimens (34%; p = 0.01, Chi-square test). In addition, self-reported sexual dysfunction—manifested as loss of libido, vaginal dryness, and abnormal vaginal discharge—was more common in patients with elevated C-reactive protein (CRP) levels, indicating a role of systemic inflammation as shown in table 2.

Ovarian reserve and function were assessed by measuring several serum biomarkers. The methotrexate group demonstrated significantly lower anti-Müllerian hormone (AMH) levels (1.5 ± 0.3 ng/mL) compared to the non-methotrexate group (2.6 ± 0.5 ng/mL; p = 0.002, independent samples t-test). In parallel, follicle-stimulating hormone (FSH) levels were higher in the methotrexate group (8.2 ± 2.1 IU/L versus 6.5 ± 1.8 IU/L; p = 0.01). Estradiol levels were slightly reduced in the methotrexate group (78 ± 15 pg/mL vs. 85 ± 18 pg/mL; p = 0.04), and inhibin B levels were also lower (45 ± 10 pg/mL vs. 60 ± 12 pg/mL; p = 0.003). Although prolactin values showed a modest elevation in patients with high CRP levels, and testosterone levels were measured as supplementary markers, the differences in these parameters were not statistically significant (p > 0.05) as shown in table 2.

Table 2: Gynecological Outcomes and Fertility Biomarkers

Parameter	Methotrexate Group (Mean ± SD)	Non-Methotrexate Group (Mean ± SD)	Statistical Test & p-value
*Menstrual Irregularities (%)	52%	34%	χ^2, p = 0.01
AMH (ng/mL)	1.5 ± 0.3	2.6 ± 0.5	t-test, p = 0.002
FSH (IU/L)	8.2 ± 2.1	6.5 ± 1.8	t-test, p = 0.01
Estradiol (pg/mL)	78 ± 15	85 ± 18	t-test, p = 0.04
Inhibin B (pg/mL)	45 ± 10	60 ± 12	t-test, p = 0.003
Prolactin (ng/mL)	18 ± 4	16 ± 3	t-test, p = 0.08 (NS)
Testosterone (ng/dL)	35 ± 8	33 ± 7	t-test, p > 0.05 (NS)

*Menstrual irregularities include variations in cycle length, heavy/light bleeding, amenorrhea, and spotting.

To further elucidate the relationship between DMARD exposure, systemic inflammation, and reproductive outcomes, multivariable regression analyses were conducted using SPSS Model 26.0. In the multivariable logistic regression model—adjusting for age, disease duration, and CRP levels—methotrexate exposure was found to be an independent predictor of menstrual irregularities (odds ratio ^{2} = 1.75; 95% confidence interval [CI]: 1.12–2.74; p = 0.015). Multivariable linear regression analysis demonstrated that methotrexate use was significantly associated with lower AMH levels (β = -0.85; 95% CI: -1.30 to -0.40; p =

0.001) and higher FSH levels. In addition, increasing age and elevated CRP levels were independently associated with decreased AMH levels (β = -0.03 per year, p = 0.01; β = -0.20 per unit increase, p = 0.01, respectively), and similar trends were observed for estradiol and inhibin B as shown in table 3.

Table 3: Multivariable Regression Analysis

Predictor Variable	Outcome	Coefficient/OR (95% CI)	p-value
Methotrexate (Yes vs. No)	Menstrual Irregularities	OR = 1.75 (1.12 – 2.74)	0.015
Methotrexate (Yes vs. No)	AMH Levels	β = -0.85 (-1.30 to -0.40)	0.001
Age (per year increase)	AMH Levels	β = -0.03 (-0.05 to -0.01)	0.01
CRP (per unit increase)	AMH Levels	β = -0.20 (-0.35 to -0.05)	0.01

*A negative β coefficient for AMH indicates that as methotrexate exposure, age, or CRP increases, ovarian reserve—as measured by AMH—decreases.

Overall, the analyses revealed that among the 250 women studied, systemic inflammation and methotrexate exposure were significantly associated with adverse gynecological outcomes. Patients on methotrexate had higher rates of menstrual irregularities and exhibited a diminished ovarian reserve, as evidenced by lower AMH, higher FSH, and altered estradiol and inhibin B levels. Although prolactin levels showed a modest, non-significant elevation with high CRP, and testosterone levels remained within normal limits, the data support the conclusion that both inflammatory activity and specific DMARD therapies—especially methotrexate—adversely impact reproductive health. All statistical analyses were performed using SPSS Model 26 with a significance threshold of $p < 0.05$.

DISCUSSION

This study investigated the impact of systemic inflammation and various DMARD regimens on reproductive health in 250 women with autoimmune and inflammatory diseases. Our findings reveal that methotrexate exposure is significantly associated with adverse gynecological outcomes, including increased menstrual irregularities and a diminished ovarian reserve [9]. Specifically, patients on methotrexate demonstrated lower anti-Müllerian hormone (AMH) levels, higher follicle-stimulating hormone (FSH) levels, reduced estradiol, and decreased inhibin B compared to those on alternative DMARDs. These hormonal alterations suggest that methotrexate may impair ovarian function, corroborating previous reports of its gonadotoxic effects[10].

Moreover, the study confirmed that elevated systemic inflammation—as reflected by higher C-reactive protein (CRP) levels—is linked to both menstrual irregularities and reduced ovarian reserve[11]. This relationship supports the notion that chronic inflammation can disrupt the hypothalamic-pituitary-ovarian axis, thereby contributing to reproductive dysfunction. Our multivariable regression analyses further established methotrexate use, advanced age, and increased CRP as independent predictors of reduced ovarian reserve[6].

The comprehensive evaluation of reproductive biomarkers, including AMH, FSH, estradiol, inhibin B, prolactin, and testosterone, provided a nuanced understanding of the reproductive disturbances in this patient population. While prolactin showed a modest, non-significant elevation and testosterone levels remained stable, the significant differences observed in AMH, FSH, estradiol, and inhibin B emphasize the need for vigilant reproductive monitoring in women undergoing methotrexate therapy[12, 13].

In addition to the clear associations with methotrexate, our study highlights the importance of individualized treatment strategies for women of reproductive age with autoimmune conditions. Given that DMARDs such as leflunomide, sulfasalazine, and hydroxychloroquine—and newer agents like biologics, tsDMARDs, and JAK inhibitors—were also part of the treatment landscape, future studies should explore the comparative long-term effects of these therapies on reproductive outcomes [14, 15].

Limitations of our study include its observational design and a relatively short follow-up period of six months, which may not fully capture the long-term reproductive implications of chronic DMARD exposure[16]. Additionally, while the study assessed several key biomarkers, reproductive health is multifactorial, and factors such as endometrial receptivity and ovulatory function were not comprehensively evaluated. Future research should incorporate a longer follow-up period and a broader spectrum of reproductive assessments to better elucidate these complex relationships[17, 18].

CONCLUSION

The study demonstrates that systemic inflammation and methotrexate exposure are significantly associated with adverse reproductive outcomes in women with autoimmune and inflammatory diseases. Specifically, methotrexate use was linked to increased menstrual irregularities and a diminished ovarian reserve, as evidenced by lower AMH, higher FSH, reduced estradiol, and decreased inhibin B levels. These findings underscore the importance of integrating reproductive health monitoring into the management of women on DMARD therapy, particularly those on methotrexate. Tailoring treatment regimens based on individual reproductive risk profiles may help preserve fertility and improve overall quality of life. Further long-term studies are warranted to explore the effects of other DMARDs and biologic agents on reproductive outcomes, ensuring a balanced approach between disease control and reproductive health.

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