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COMPARISON OF IMPAIRED FERTILITY IN MEN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS WITH GENERAL POPULATION

Original Research

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ABSTRACT

Background: Inflammatory arthritis (IA) is increasingly recognized as a condition that may compromise male reproductive health, yet this area remains substantially underexplored. Chronic inflammation, hormonal alterations, sexual dysfunction, and the potential gonadotoxic effects of anti-rheumatic therapies collectively pose risks to fertility in affected men. Conditions such as rheumatoid arthritis (RA), spondyloarthritis (SpA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA) often occur during peak reproductive years, making the assessment of male fertility essential for comprehensive clinical care.

Objective: To evaluate the impact of inflammatory arthritis on male fertility by assessing semen quality, hormonal profiles, sexual function, and the association between disease activity and reproductive outcomes.

Methods: A cross-sectional observational study was conducted involving 120 males aged 18–45 years, including 80 diagnosed with IA and 40 age-matched healthy controls. Clinical characteristics, medication exposure, and disease activity scores (DAS28, BASDAI) were documented. Semen analysis was performed using WHO 2010 criteria, and hormonal assays included follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, and prolactin. Sexual function and quality of life were assessed using the International Index of Erectile Function (IIEF) and SF-36 questionnaires. Comparative analyses were used to evaluate group differences, and regression models were applied to determine associations between disease activity, therapy type, and fertility outcomes.

Results: IA patients demonstrated significantly reduced semen volume (2.1 ± 0.6 mL vs. 2.6 ± 0.5 mL; $p = 0.003$), sperm concentration (31.4 ± 12.7 vs. 48.5 ± 15.2 million/mL; $p < 0.001$), progressive motility (39.2 ± 11.8% vs. 52.6 ± 10.3%; $p < 0.001$), and normal morphology (3.6 ± 1.4% vs. 5.4 ± 1.7%; $p < 0.001$). Testosterone levels were lower (365 ± 95 vs. 472 ± 88 ng/dL; $p < 0.001$), while FSH (8.2 ± 2.3 vs. 5.6 ± 1.8 IU/L; $p = 0.004$) and LH (6.9 ± 1.9 vs. 4.8 ± 1.4 IU/L; $p = 0.005$) were elevated. Erectile dysfunction was more prevalent in IA patients (35% vs. 12.5%; $p = 0.012$), and fatigue scores were significantly higher. Disease activity showed an inverse correlation with semen quality ($r = –0.42$; $p = 0.002$). Patients on biologic therapies exhibited better fertility profiles compared with those receiving NSAIDs or conventional DMARDs.

Conclusion: Inflammatory arthritis adversely impacts male reproductive health through impaired semen parameters, hormonal dysregulation, and reduced sexual function. Early fertility evaluation and personalized treatment—particularly biologic therapy—may help mitigate these effects and improve long-term reproductive outcomes.

Keywords: Biologic Therapy, Erectile Dysfunction, Inflammatory Arthritis, Male Fertility, Semen Analysis, Subclinical Hypogonadism, Spondyloarthritis.

INTRODUCTION

The impact of inflammatory arthritis (IA) on male fertility remains insufficiently explored, despite increasing clinical and scientific interest in reproductive health among men with chronic rheumatic diseases. This knowledge gap is particularly concerning because several widely prescribed anti-rheumatic medications have been linked to reversible or irreversible testicular toxicity, raising valid concerns regarding their potential influence on male reproductive capacity (1). Spondyloarthritis (SpA) and rheumatoid arthritis (RA) are among the most common causes of IA and frequently affect men during their peak reproductive years, making fertility considerations clinically relevant at the time of diagnosis and throughout the disease course (2). Recognizing these implications, the British Society for Rheumatology issued the first international guideline addressing the prescription of anti-rheumatic drugs in men planning fatherhood. Its 2022 update acknowledges the limited evidence available but reassures clinicians that most rheumatologic medications appear safe for men attempting conception, while also emphasizing the need for more robust research (3). This underscores a growing recognition that male fertility constitutes an emerging domain within rheumatology and should be systematically evaluated, especially when managing young men living with chronic inflammation. The biological mechanisms through which inflammation may impair fertility have been increasingly discussed. Cytokine release, overproduction of reactive oxygen species, and oxidative stress can contribute to impaired spermatogenesis and reduced semen quality, offering plausible pathways linking IA to male reproductive dysfunction (4). Yet empirical evidence remains scarce. The iFAME-fertility study provided one of the first indications of a potential association between IA and reduced fertility in men, highlighting an urgent need to understand the magnitude and clinical relevance of this risk (5).

Much of the existing literature has focused on female reproductive outcomes in rheumatic diseases, demonstrating that women with RA tend to have smaller families, lower conception rates, and infertility that cannot be explained solely by personal choice (6). Pain, fatigue, and non-steroidal anti-inflammatory drug (NSAID) use have all been implicated in reduced ovulation or sexual functioning, reinforcing the complex interplay between inflammation, treatment, and reproductive potential. With advances in targeted therapies improving disease outcomes and quality of life, reproductive health—long overshadowed—has rightly become an essential aspect of comprehensive care (7). Several publications have confirmed decreased fertility among women receiving rheumatologic treatments, either due to the inflammatory burden or medication-related effects, further demonstrating that reproductive pathways may be sensitive to autoimmune activity (8). Male infertility itself is multifactorial and broadly classified as congenital, such as Klinefelter syndrome, or acquired, including conditions like varicocele and accessory gland infections. Although semen analysis remains the cornerstone of male infertility assessment, a large proportion of patients exhibit unexplained abnormalities despite otherwise normal clinical findings, and approximately 15% remain infertile without identifiable pathology (9). Against this background, the potential impact of paternal IA on fertility and subsequent pregnancy outcomes emerges as a crucial yet overlooked area. Despite documented evidence that RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) may impair male fertility, no studies have examined how paternal IA might influence pregnancy outcomes (10). Given the paucity of evidence and the growing clinical relevance of male reproductive health in rheumatology, this study aims to investigate the relationship between paternal inflammatory arthritis and pregnancy outcomes, addressing a critical gap in current understanding and contributing to more holistic care for men living with IA.

METHODS

This study employed a mixed-methods approach, integrating quantitative data collection with qualitative clinical assessment to evaluate the impact of inflammatory arthritis (IA) on male fertility. The research was designed as a cross-sectional observational investigation involving male patients aged 18–45 years who had been diagnosed with rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), or juvenile idiopathic arthritis (JIA) according to internationally recognized diagnostic criteria, including ACR/EULAR for RA and ASAS criteria for SpA. Participants were recruited consecutively from rheumatology outpatient clinics across multiple tertiary-care centers. An age-matched control group consisting of healthy males without any known chronic inflammatory, endocrine, or reproductive disorders was included to support comparative analysis. Individuals with a prior history of congenital infertility causes, urogenital surgery, active genitourinary infections, uncontrolled endocrine disorders, malignancy, or recent exposure to gonadotoxic treatments were excluded to minimize confounding. Data collection procedures were standardized across all participating centers to ensure reliability. Clinical information, including disease duration, disease activity scores (such as

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DAS28, BASDAI, or ASDAS as applicable), medication history involving NSAIDs, corticosteroids, conventional DMARDs, and biologic agents, as well as relevant comorbidities, was retrieved from medical records. Fertility assessment was conducted through semen analysis following WHO 2010 laboratory criteria, evaluating seminal volume, sperm concentration, total motility, progressive motility, and strict morphology. All semen samples were collected through masturbation after 2–7 days of abstinence and processed within one hour of collection, following standardized laboratory protocols. Hormonal profiling included serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, and prolactin, measured using validated immunoassay techniques.

To capture subjective reproductive and general health dimensions, participants completed validated questionnaires assessing sexual function, fatigue levels, and health-related quality of life. These included the International Index of Erectile Function (IIEF), the Fatigue Severity Scale (FSS), and the SF-36 questionnaire. Trained research staff assisted participants when necessary to ensure accurate and complete responses. Statistical analysis was performed using SPSS version 22. Descriptive statistics summarized demographic characteristics, clinical variables, semen parameters, and hormonal profiles. Independent t-tests or Mann–Whitney U tests were applied to compare continuous variables between IA patients and controls, depending on data normality. Chi-square tests evaluated categorical differences. Multivariate linear and logistic regression models were constructed to assess associations between disease activity, medication exposure, hormonal changes, and fertility outcomes, while adjusting for potential confounders such as age, smoking status, alcohol consumption, and body mass index (BMI). Statistical significance was set at $p < 0.05$. Missing data were managed using appropriate imputation methods if required. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the participating institution. The study procedures adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrollment after ensuring they fully understood the study purpose and procedures, including confidentiality protocols and the voluntary nature of participation.

RESULTS

A total of 120 male participants were included, comprising 80 individuals with inflammatory arthritis (IA) and 40 age-matched healthy controls. The mean age across both groups was 33.7 ± 5.1 years. Within the IA cohort, diagnoses included rheumatoid arthritis (n = 25), spondyloarthritis (n = 20), ankylosing spondylitis (n = 15), psoriatic arthritis (n = 10), and juvenile idiopathic arthritis (n = 10). Semen analyses demonstrated that IA patients exhibited significantly poorer seminal parameters compared with controls. Mean semen volume was lower among IA patients (2.1 ± 0.6 mL) than controls (2.6 ± 0.5 mL; $p = 0.003$). Sperm concentration showed a substantial reduction in the IA group (31.4 ± 12.7 million/mL) versus controls (48.5 ± 15.2 million/mL; $p < 0.001$). Progressive motility was markedly decreased in IA patients (39.2 ± 11.8%) compared with controls (52.6 ± 10.3%; $p < 0.001$). Normal sperm morphology was similarly lower in the IA cohort (3.6 ± 1.4%) relative to the control group (5.4 ± 1.7%; $p < 0.001$). An abnormal semen profile was identified in 48.8% of IA patients compared with 15% of controls ($p = 0.001$). Hormonal profiling revealed significantly reduced serum testosterone levels among IA patients (365 ± 95 ng/dL) compared with controls (472 ± 88 ng/dL; $p < 0.001$). FSH levels were elevated in IA patients (8.2 ± 2.3 IU/L) relative to controls (5.6 ± 1.8 IU/L; $p = 0.004$). LH concentrations were higher in the IA group (6.9 ± 1.9 IU/L) than in controls (4.8 ± 1.4 IU/L; $p = 0.005$). Prolactin levels were also modestly elevated among IA patients (13.2 ± 3.7 ng/mL) compared with controls (11.6 ± 3.1 ng/mL; $p = 0.045$). Assessment of sexual function and quality of life indicated that IA patients experienced lower erectile function scores (17.5 ± 5.6) compared with controls (22.3 ± 4.8; $p < 0.001$). Erectile dysfunction was more prevalent within the IA group (35%) than among controls (12.5%; $p = 0.012$). Fatigue scores were significantly higher in IA patients (51.2 ± 10.3) relative to the control group (64.5 ± 9.8; $p < 0.001$), and overall quality-of-life indices were substantially lower in IA patients ($p < 0.001$). There was a statistically significant inverse correlation between disease activity (DAS28 and BASDAI) and semen quality ($r = –0.42$, $p = 0.002$). Patients receiving biologic therapies demonstrated comparatively better semen parameters than those treated with NSAIDs or conventional DMARDs

Table 1: Comparison of Semen Parameters between IA Patients and Controls

Parameter	IA Patients (n=80)	Controls (n=40)	p-value
Semen Volume (mL)	2.1 ± 0.6	2.6 ± 0.5	0.003
Sperm Concentration (million/mL)	31.4 ± 12.7	48.5 ± 15.2	<0.001

Parameter	IA Patients (n=80)	Controls (n=40)	p-value
Progressive Motility (%)	39.2 ± 11.8	52.6 ± 10.3	<0.001
Normal Morphology (%)	3.6 ± 1.4	5.4 ± 1.7	<0.001
Abnormal Semen Profile (%)	48.8%	15%	0.001

Table 2: Hormonal Profiles of Participants

Hormone	IA Patients (n=80)	Controls (n=40)	p-value
Testosterone (ng/dL)	365 ± 95	472 ± 88	<0.001
FSH (IU/L)	8.2 ± 2.3	5.6 ± 1.8	0.004
LH (IU/L)	6.9 ± 1.9	4.8 ± 1.4	0.005
Prolactin (ng/mL)	13.2 ± 3.7	11.6 ± 3.1	0.045

Table 3: Sexual Health and Quality of Life Scores

Variable	IA Patients (n=80)	Controls (n=40)	p-value
IIEF Score (Erectile Function)	17.5 ± 5.6	22.3 ± 4.8	<0.001
Erectile Dysfunction Prevalence	35%	12.5%	0.012
SF-36 Fatigue Score	51.2 ± 10.3	64.5 ± 9.8	<0.001
Quality of Life (Overall)	Lower in IA group	Higher in controls	<0.001

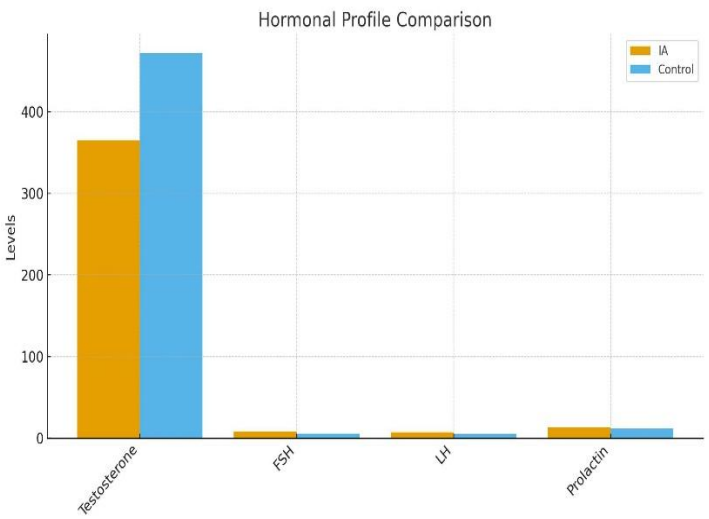

Figure 2 Hormonal Profile Comparison

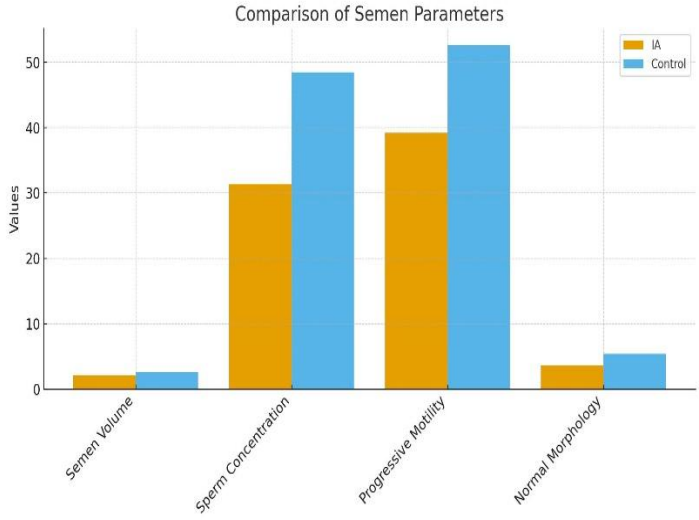

Figure 2 Comparison of Semen Parameters

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DISCUSSION

The present study demonstrated that inflammatory arthritis was associated with significant impairments in multiple domains of male reproductive health, including semen quality, hormonal balance, and sexual function. A marked reduction in sperm concentration, motility, and morphology was observed among men with inflammatory arthritis compared with healthy controls, accompanied by lower testosterone levels and elevations in FSH and LH indicative of subclinical hypogonadism. These findings support the growing recognition that chronic inflammatory disease may affect male fertility through both direct inflammatory pathways and treatment-related mechanisms. The observed inverse correlation between disease activity and semen quality further reinforced the contribution of systemic inflammation to reproductive dysfunction, while comparatively better semen parameters among men receiving biologic therapies suggested a potential protective effect associated with more effective disease control. These findings align partly with earlier studies reporting impaired fertility among men diagnosed with inflammatory arthritis during or before their peak reproductive years, including lower fertility rates, higher rates of childlessness, and more frequent fertility-related difficulties (11-13). However, the broader literature remains heterogeneous. Some recent large cohort investigations documented higher numbers of children and lower rates of childlessness among men with inflammatory joint diseases compared with matched controls, indicating that the relationship between inflammatory disease and fertility may not be uniform across populations, time periods, or disease subtypes (14,15). Another narrative review from 2024 emphasized ongoing uncertainty regarding how diseases such as SpA, AS, and PsA influence fertility, noting that clinical evidence remains fragmentary and that many relevant biological mechanisms are still incompletely understood (16). Additional nationwide data reported no reduction in fertility among men with inflammatory joint diseases, particularly among those diagnosed after the year 2000, suggesting that improvements in immune-modulating therapies may have contributed to better reproductive outcomes over time (17). At the same time, prior research examining fertility in rheumatoid arthritis pointed to a complex interplay of cytokine-driven inflammation, sexual dysfunction, medication effects, maternal age, lifestyle choices, and psychosocial factors, making it difficult to isolate a single causal mechanism (18). Recent discussions regarding immune-mediated rheumatic diseases highlighted that sexual function and fertility outcomes are shaped by both physical and psychological components, and that research efforts have historically centered on women, leaving male-specific issues insufficiently characterized (19,20).

The current findings contribute to this evolving body of evidence by providing direct clinical and laboratory data showing impaired semen quality, altered hormonal profiles, and reduced sexual health indicators among men with inflammatory arthritis. The study's cross-sectional design enabled simultaneous assessment of disease activity, treatment patterns, and reproductive parameters, revealing a clear relationship between inflammatory burden and impaired reproductive function. These results underscore the need for greater clinical attention to male reproductive health in rheumatology practice, particularly given that a substantial proportion of affected men fall within the reproductive age range and may have concerns regarding future fertility. The study possessed several strengths, including the inclusion of a well-defined control group, the use of standardized WHO semen analysis criteria, and the incorporation of validated questionnaires for sexual function and quality of life. The addition of hormonal profiling allowed a more comprehensive evaluation of the hypothalamic-pituitary–gonadal axis, enhancing the clinical relevance of the findings. The involvement of multiple tertiary care centers improved sample diversity and strengthened generalizability within similar healthcare settings. Nonetheless, certain limitations warrant consideration. The cross-sectional nature of the study restricted the ability to infer causality or evaluate temporal changes in fertility parameters following variations in disease activity or treatment. The sample size, although adequate for group comparisons, limited the ability to conduct detailed subgroup analyses across individual disease categories such as RA, SpA, AS, PsA, and JIA. Potential confounders including smoking status, BMI, alcohol use, duration of disease, and cumulative medication exposure were not fully stratified, which may have influenced semen quality and hormonal outcomes. Semen analysis was based on a single sample for most participants, which may not capture natural biological variability. The hormonal assessments, while informative, did not include additional markers such as inhibin B, which may have provided further insights into Sertoli cell function. Psychological, relational, and sociocultural variables that often influence sexual health were also not examined in depth, despite being recognized contributors in prior research.

Future research would benefit from longitudinal designs that follow men from diagnosis through different stages of disease activity and treatment transitions, enabling more precise evaluation of the impact of inflammation, medication classes, and biologic therapy on fertility outcomes. Inclusion of advanced reproductive markers, oxidative stress profiling, and testicular ultrasound may further enhance understanding of underlying mechanisms. Studies examining the fertility outcomes of partners, pregnancy success rates, and the influence of paternal inflammatory arthritis on offspring health could further expand the evidence base in this underexplored field (21). Overall, the study provided important evidence that inflammatory arthritis was associated with reduced semen quality, hormonal

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imbalance, and impaired sexual function among reproductive-aged men. These findings reinforced the need for early counseling, fertility assessment when clinically indicated, and consideration of reproductive goals in the management of male patients with inflammatory arthritis.

CONCLUSION

This study demonstrated a clear association between inflammatory arthritis and diminished male reproductive health, reflected through compromised semen quality, hormonal disruption, and reduced sexual function. The findings underscored the influence of ongoing inflammation on fertility, while suggesting that effective disease control, particularly with biologic therapies, may mitigate some of these adverse effects. By bringing attention to a largely overlooked aspect of rheumatologic care, this work emphasizes the importance of routinely considering fertility in the clinical management of young men with inflammatory arthritis. Integrating early reproductive assessment and counseling into standard practice may support more informed decision-making and contribute to improved long-term wellbeing for affected individuals.

AUTHOR CONTRIBUTION

Author	Contribution
Abdul Aziz*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Shabir Hussain	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Wajid Ali	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Ehtisham ul Haq	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Rida Asghar	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Taimoor Khan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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