

Fertility Disorders in Women with Rheumatoid Arthritis: Proportion and Associated Factors

Prévalence et facteurs prédictifs des troubles de la fertilité chez les femmes atteintes de polyarthrite rhumatoïde

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ABSTRACT

Objective: To determine the proportion of fertility disorders in non-menopausal women with rheumatoid arthritis (RA) and to identify associated factors.

Methods: We conducted a cross-sectional observational study including non-menopausal women aged ≥ 18 years diagnosed with RA. Sociodemographic characteristics, disease-related variables, and treatments were collected. Prolonged time to conception was defined as a time to conception exceeding 12 months. Infertility was defined as the absence of pregnancy after 12 months of unprotected and regular intercourse.

Results: Fifty women were included (mean age: 39.1 ± 6.9 years). The mean age at RA diagnosis was 31.1 ± 8.7 years, with a median disease duration of 8.5 years. RA was immunopositive in 27%, and erosive in 80%. Extra-articular manifestations were observed in 34% of patients, predominantly sicca symptoms (28%).

Fertility disorders were identified in 31% of patients: 10% had a prolonged time to conception and 21% had infertility, which was primary in 80% of cases. Pregnancy loss occurred in 48% of women with prior pregnancies.

Receiver operating characteristic (ROC) analysis indicated that RA duration > 6 years was significantly associated with fertility disorders (AUC = 0.692, $p = 0.049$), with a sensitivity of 84.2% and specificity of 55.2%. No significant associations were observed between fertility disorders and disease activity or current treatments.

Conclusion: Fertility disorders are common in women with RA. Disease duration exceeding six years emerged as a significant associated factor. Early disease control and systematic reproductive counseling should be integral components of RA management in women of childbearing age.

Keywords: Rheumatoid arthritis; autoimmune disease; infertility; fertility disorders; women's health

RÉSUMÉ

Objectif: Déterminer la prévalence des troubles de la fertilité chez les femmes non ménopausées atteintes de polyarthrite rhumatoïde (PR) et identifier les facteurs associés.

Méthodes: Nous avons mené une étude transversale incluant des femmes non ménopausées âgées de 18 ans et plus, atteintes de polyarthrite rhumatoïde. Les caractéristiques sociodémographiques, les variables liées à la maladie et les traitements ont été recueillis. La subfertilité a été définie par un délai de conception supérieur à 12 mois ou par la survenue de grossesses non abouties chez les femmes nullipares. L'infertilité a été définie par l'absence de grossesse après 12 mois de rapports sexuels.

Résultats: Cinquante femmes ont été incluses (âge moyen : $39,1 \pm 6,9$ ans). L'âge moyen au diagnostic de polyarthrite rhumatoïde était de $31,1 \pm 8,7$ ans, avec une durée médiane de la maladie de 8,5 ans. La polyarthrite rhumatoïde était séropositive dans 27 % des cas, immunopositive dans 27 % et érosive dans 80 %. Des manifestations extra-articulaires ont été observées chez 34 % des patientes, principalement un syndrome sec (28 %). Des troubles de la fertilité ont été identifiés chez 31 % des patientes : 19 % présentaient une hypofertilité (dont 10 % avec un délai de conception prolongé et 9 % avec des grossesses non abouties), et 12 % une infertilité, primaire dans 80 % des cas. Une fausse couche est survenue chez 48 % des femmes.

L'analyse de la courbe ROC a identifié une durée de polyarthrite rhumatoïde supérieure à 6 ans comme facteur prédictif des troubles de la fertilité (AUC = 0,692, $p = 0,049$), avec une sensibilité de 84,2 % et une spécificité de 55,2 %. Aucune association significative n'a été observée avec l'activité de la maladie ou les traitements.

Conclusion: les troubles de la fertilité sont fréquents chez les femmes atteintes de polyarthrite rhumatoïde. Une durée de la maladie supérieure à six ans s'est révélée être un facteur prédictif significatif. La prise en charge précoce de la maladie et un accompagnement systématique en matière de fertilité devraient faire partie intégrante du traitement de la polyarthrite rhumatoïde chez les femmes en âge de procréer.

Mots clés: Polyarthrite rhumatoïde ; maladie auto-immune ; infertilité ; troubles de la fertilité ; santé des femmes

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INTRODUCTION

Infertility is defined as the failure to achieve conception after 12 months of regular unprotected sexual intercourse (1). Its prevalence in the general population is estimated to range between 16.5% and 17.8% (2), infertility appears to be more frequent among women with autoimmune diseases, including systemic lupus erythematosus and primary Sjögren's syndrome, and particularly in RA, where a prolonged time to conception has consistently been reported (3,4).

Rheumatoid arthritis is a chronic autoimmune inflammatory disease primarily affecting the joints, with a global prevalence ranging from 0.46% to 1% (5,6). It predominantly affects women of reproductive age, with a female-to-male ratio of approximately 3:1 to 4:1 (7,8). These epidemiological features raise concerns regarding the gynecological and reproductive consequences of RA, particularly impaired fertility.

Despite growing interest in this issue, data on fertility disorders in women with RA remain limited and heterogeneous. The underlying mechanisms are likely multifactorial, involving chronic inflammation, disease duration and activity, treatment exposure, and sociodemographic factors.

The objective of this study was to determine the proportion of fertility disorders in non-menopausal women with RA and to identify clinical, epidemiological, and disease-related factors associated with these disorders.

METHODS

Study design and population

We conducted a descriptive, observational, cross-sectional study including non-menopausal women aged ≥ 18 years diagnosed with RA according to the 1987 American College of Rheumatology (ACR) criteria and/or the 2010 ACR/EULAR classification criteria.

Non inclusion criteria included the presence of another chronic inflammatory rheumatic disease or autoimmune disorder including primary or secondary Sjögren's syndrome, psychiatric, cognitive, or sensory impairments that could affect data reliability, a history of gynecological surgery (hysterectomy or oophorectomy), known endocrinopathies affecting reproductive function, and refusal to participate.

Participants were recruited consecutively over a 12-month period, from March 2024 to February 2025.

Data collection

Data were collected using a standardized anonymous questionnaire administered by a single trained examiner after obtaining informed consent.

Collected variables included sociodemographic and anthropometric data (age, marital status, education level, employment status, socioeconomic level, smoking status, and body mass index).

RA-related variables included age at diagnosis, disease duration, disease activity indices (patient global assessment, pain visual analog scale, CDAI, SDAI, and DAS28-CRP), functional disability assessed using the Health Assessment Questionnaire (HAQ) (9), extra-articular manifestations, comorbidities, immunological status, and radiographic erosions. Current treatments, including symptomatic therapies and disease-modifying antirheumatic drugs (csDMARDs, tsDMARDs, bDMARDs), were recorded. Previous treatment exposures were not systematically collected due to incomplete availability of historical data, particularly for patients previously followed in other centers. Therefore, only current treatments at the time of inclusion were analyzed.

The reproductive profile included gravidity, parity, age at first conception, and obstetric history (spontaneous abortions, pregnancy loss, intrauterine fetal death, voluntary or therapeutic termination of pregnancy, and ectopic pregnancy), as well as the presence of a prolonged time to conception or infertility.

Prolonged time to conception was defined as a time to conception exceeding 12 months of regular unprotected intercourse (3,10).

Infertility was defined according to the World Health Organization as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse and was classified as primary or secondary (2,5,11).

Statistical analysis

Statistical analyses were performed using SPSS software (version 25). Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages. Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Associations were assessed using Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant.

RESULTS

Population characteristics (Table 1)

A total of 50 women were included, with a mean age of 39.1 ± 6.9 years. Thirty-seven women (74%) were married, eight (16%) were single, four (8%) were divorced, and one (2%) was widowed. Most participants had primary or secondary education (70%), were unemployed (62%), and belonged to a middle socioeconomic group (66%). The mean body mass index was 26.8 ± 5.6 kg/m² (range: 15.4–39.2).

Active smoking was reported by 4% of patients, with a mean exposure of 8.5 pack-years; half had quit smoking at the time of the study.

Table 1. Baseline characteristics of the study population (N = 50)

Variable	Value
Sociodemographic and anthropometric characteristics	
Age, years	39.1 ± 6.9
Marital status,	
Married	37 (74)
Single	8 (16)
Divorced	4 (8)
Widowed	1 (2)
Primary or secondary education, n (%)	35 (70)
Unemployed, n (%)	31 (62)
Middle socioeconomic level, n (%)	33 (66)
Body mass index, kg/m ²	26.8 ± 5.6
Overweight or obese, n (%)	30 (60)
Active smoking, n (%)	2 (4)
Smoking exposure, pack-years	8.5*
Rheumatoid arthritis characteristics	
Age at RA diagnosis, years	31.1 ± 8.7
Disease duration, years	8.5 [1–27]
Disease activity	
DAS28-CRP	4.0 ± 1.3
CDAI	19.4 ± 12.7
SDAI	22.9 [14–39.7]
HAQ score	0.7 [0.4–1.4]
Extra-articular manifestations	
Sicca symptoms, n (%)	17 (34)
Rheumatoid nodules, n (%)	14 (28)
Comorbidities	
Hypertension, n (%)	3 (6)
Diabetes, n (%)	2 (4)
Osteoporosis, n (%)†	1 (2)
Osteopenia, n (%)†	4 (11)
Seropositive RA, n (%)	9 (26)
Radiographic erosions, n (%)	13 (27)
Current treatments at study inclusion	
Corticosteroid use, n (%)	40 (80)
Corticosteroid dose, mg/day	
csDMARD use, n (%)	7.5 [5–10]
Methotrexate use, n (%)	45 (90)
Methotrexate dose, mg/week	35 (70)
bDMARD monotherapy, n (%)	17.5 [15–20]
bDMARD combination therapy, n (%)	5 (11)
tsDMARD use, n (%)	6 (13)
tsDMARD use, n (%)	1 (2)

Rheumatoid arthritis characteristics

The mean age at RA diagnosis was 31.1 ± 8.7 years, with a median disease duration of 8.5 years (range: 1–27). Overall disease activity was moderate (mean DAS28-CRP: 4 ± 1.3; mean CDAI: 19.4 ± 12.7; median SDAI: 22.9 [14–39.7]).

Functional disability was mild to moderate in most patients, with a median HAQ score of 0.7 [0.4–1.4]; severe disability was observed in 10%.

Extra-articular manifestations were present in 34% of patients, mainly sicca symptoms (28%) and rheumatoid nodules (6%). Among patients who underwent bone densitometry (70%), osteoporosis and osteopenia were identified in 11% and 26%, respectively. Hypertension and diabetes were reported in 4% and 2%, respectively. Sixty percent of patients were overweight or obese. No

malignancy or depressive disorder was reported.

RA was immunopositive in 27% of patients, and radiographic erosions were present in 80%.

At study inclusion, 72% of patients were receiving corticosteroids (median dose: 7.5 mg/day [5–10]). csDMARDs were prescribed in 90%, predominantly methotrexate (70%) at a median dose of 17.5 mg/week [15–20]. bDMARD therapy was used as monotherapy in 11%, in combination therapy in 13%, and tsDMARD in 2%.

Fertility-related data

Gynecological history

After excluding the eight single women, the median parity was 2.5 [0.8–4] (range: 0–7). Eight patients (19%) were nulliparous. The median number of live-born children was 2 [0–3].

The mean age at first conception was 26.2 ± 4.9 years (range: 17–35). No cases of ectopic pregnancy or therapeutic termination were reported. Among interrupted pregnancies, spontaneous abortion or missed miscarriage was the most common, accounting for 20 cases (48%). Intrauterine fetal death was reported in 2 cases (5%), while voluntary termination of pregnancy accounted for 8 cases (19%).

Fertility disorders

Fertility disorders (prolonged time to conception or infertility) were identified in 13 of 42 women (31%).

Four patients experienced a time to conception exceeding 12 months (10%) and infertility affected nine patients (21%), including four cases of primary infertility (80%) and five cases of secondary infertility (20%).

Analytical study

Comparative analysis based on sociodemographic characteristics showed significant differences in marital and employment status according to the presence of fertility disorders. Women with fertility disorders were more frequently divorced and professionally active (Table 2).

Table 2. Comparison between Group A and Group B according to epidemiological parameters

Parameters		Group A (N=13)	Group B (N=29)	P
		n (%)	n (%)	
Age (mean ± SD)		41 ± 7	39 ± 5	0.214
Marital status	Mariée	8 (62)	29 (100)	0.000
	Divorcée	4 (31)	0	
	Veuve	1 (8)	0	
Occupational status	Active	8 (62)	10 (34)	0.019
	Non active	5 (38)	19 (66)	
Educational level	Analphabète	0	2 (7)	0.767
	Primaire	6 (46)	9 (31)	
	Secondaire	3 (23)	12 (41)	
	Universitaire	4 (31)	6 (21)	
BMI (mean ± SD)		26.2 ± 6.2	27.8 ± 5.7	0.424
Smoking		1 (8)	1 (3)	0.562

BMI: Body Mass Index in kg/m², SD: Standard Deviation, N: number, p < 0.05

Regarding RA-related variables, disease duration was significantly longer in women with fertility disorders (Table 3), whereas no significant differences were observed for other disease parameters.

Table 3. Comparison of Groups A and B according to rheumatoid arthritis-related data

		Group A (N=13)	Group B (N=29)	P
		n (%)	n (%)	
Diagnostic age (mean ± SD)		30±9	33±8	0.425
Disease duration (median)		11[8,19]	5[4,13]	0.040
Immunological profile	Immunopositive	6/11 (55)	2/21 (10)	0.299
	Erosive	11 (85)	22 (76)	0.098
Presence of EAM	Ocular	5 (38)	7 (24)	0.354
	Cutaneous	1 (8)	2 (7)	0.771
Presence of de Comorbidities	HTA	0	1 (3)	0.510
	Diabetes	0	1 (3)	0.510
	BMI>25	6 (46)	20 (69)	0.198
	Osteopenia or Osteoporosis	2/10 (20)	9/19 (47)	0.514
Coxitis		3 (23)	4 (14)	0.455

EAM: Extra-articular manifestations, **HTA:** hypertension, **BMI:** body mass index, **n:** number, **p<0.05**

ROC curve analysis demonstrated that disease duration had a significant ability to discriminate fertility disorders (AUC = 0.692, $p = 0.049$: je garde une décimale ou pas ?). The optimal cutoff was >6 years, with a sensitivity of 84.2% and specificity of 55.2%. The positive and negative predictive values were 45.8% and 88.9%, respectively.

No significant associations were found between fertility disorders and disease activity, functional impairment, or treatments received at the time of the study (Tables 4 and 5).

Table 4. Comparison of Groups A and B according to rheumatoid arthritis activity parameters and functional impact

		Group A (N=13)	Group B (N=29)	P
		n (%)	n (%)	
NA		2 (15)	11 (38)	0.291
MS (mean ± SD)		28.5±39	34.8±45	0.661
VAS pain (mean ± SD)		5.7±2	5.1±2	0.475
PGA (median)		6±2	6±3	0.570
CRP (median)		4.5[2,10.1]	8.3[3.9,3]	0.213
DAS28 CRP (mean ± SD)		4±1.2	4.1±1.2	0.830
Activity_DAS	Inactive or low	3 (23)	8 (28)	0.759
	Moderate or high	10 (77)	21 (72)	
CDAI (mean ± SD)		23.6±	17.6±	0.146
Activity_CDAI	Inactive or low	2 (15)	9 (31)	0.286
	Moderate or high	11 (85)	20 (69)	
SDAI (median)		22.9[16,39]	23.1[15,41]	0.630
Activity_SDAI	Inactive or low	1 (8)	5 (17)	0.414
	Moderate or high	12 (92)	24 (83)	
HAQ (median)		1.1[0.5,1.75]	0.8[0.4,1.25]	0.247

VAS: Visual Analog Scale, **GPA:** Patient Global Assessment, **MS:** Morning stiffness in minutes, **NA:** Nocturnal awakenings, **CRP:** C Reactive Protein, **DAS28 CRP:** Disease Activity Score 28 CRP, **CDAI:** Clinical Disease Activity Index, **SDAI:** Simplified Disease Activity Index, **HAQ:** Health Assessment Questionnaire, **N:** number, **p<0.05**

Table 5. Comparison of Groups A and B according to rheumatoid arthritis treatment received at the time of the study

		Group A (N=13)	Group B (N=29)	P
		n (%)	n (%)	
Treatment	Corticosteroid use	10 (77)	20 (69)	0.608
	Corticosteroid posology (median)	7.5[5,10]	7.5[5,10]	0.837
CsDMARDs		9 (69)	26 (90)	0.195
bDMARDs		5 (38)	4 (14)	0.072
tsDMARDs		0	1 (3)	0.559

CsDMARDs: Conventional synthetic Disease-Modifying Anti-rheumatic Drugs, **bDMARDs:** biologic Disease-Modifying Anti-rheumatic Drugs, **tsDMARDs:** targeted synthetic Disease-Modifying Anti-rheumatic Drugs, **N:** number, **p<0.05**

DISCUSSION

Data regarding fertility in women with RA remain scarce and inconsistent. Our findings contribute additional evidence by highlighting a high proportion of fertility disorders and identifying disease duration as a significant associated factor. Regarding reproductive outcomes, several studies have reported a reduced family size among women with RA compared with the general population (3,4,12–15), and this trend seems to be present even before the diagnosis of RA (3). The idea of an early alteration in fertility among women with RA has been supported since 1958 (13). However, other studies found no significant differences (16,17).

Pregnancy loss has also been variably reported. While some studies observed rates comparable to the general population (17–19), others suggested higher frequencies, particularly in the context of unplanned pregnancies and methotrexate exposure (20). In our study, the median number of live-born children was two, comparable to the global fertility rate reported by the ONU (2.2 children per woman) (21). However, nearly half of previously pregnant women reported at least one pregnancy loss, exceeding rates reported in the general population (15–30%), according to WHO estimates (22).

Fertility disorders in RA are generally explored through two dimensions: subfertility and infertility.

A prolonged time to conception, has been widely reported in women with RA, with prevalences ranging from 25% to 42%, significantly higher than in the general population (3,4,23). A recent study reported a median conception delay of 19.1 months in 78 women with RA (23). In the general population, the prevalence of women with a conception delay of more than 12 months is estimated at 9%, ranging from extremes of 3.5% to 24.2% depending on the geographical area (10). In our study, the overall rate of prolonged time to conception was 10% which is closer to that reported in the general population. This discrepancy may be explained by differences in study design, population characteristics, and definitions used.

Several factors have been proposed to explain delayed conception in RA. Advanced maternal age at conception is a well-established factor (23); however, in our cohort, the mean age at first conception was 26.15 ± 4.9 years, which remains within the reproductive norm (24).

Disease duration has shown inconsistent associations in the

literature. Some studies suggest no relationship, whereas others report a cumulative negative effect over the number of years of the disease (23), where each additional year of RA increases the risk of delayed conception by 6%; these results were statistically significant (HR per year = 1.06; 95% CI [1.02–1.15]; $p = 0.03$). Our findings support the latter hypothesis, as a disease duration greater than six years was significantly associated with fertility disorders.

Disease activity has also been implicated, with some studies demonstrating an association between higher disease activity and delayed conception. Indeed, Brouwer et al (4) demonstrated that a higher DAS28 before conception was associated with a significant delay in reproduction, with a reduction in the conception rate of 19% per unit of DAS28 (CI= 0.71–0.93, $p=0.02$). In our study, no such relationship was observed. This discrepancy may be explained by the cross-sectional design, which does not allow assessment of disease activity at the time of conception.

Treatment-related factors have also been suggested. Nonsteroidal anti-inflammatory drugs and higher doses of corticosteroids (>7.5 mg/day) may impair ovulation and implantation (25) and prolong the time to conception(4,12,17,26–28). While bDMARD therapies could potentially improve fertility by better controlling inflammation. A retrospective study suggests a shortening of the conception time for women with RA treated with bDMARDs and wishing to conceive (29).

In our study, no association was found between fertility disorders and ongoing treatments. This may again be explained by the study design, which does not allow for temporal or causal interpretations.

The proportions of infertility varies according to studies. Some authors report a higher prevalence of infertility in women with RA who are of childbearing age. Indeed, it was observed in 25% of RA women in a study with a statistically significant difference compared to control women from the general population ($p = 0.04$) (15), whereas about 10% of the general population faced this problem during the same period. Furthermore, one study suggested the existence of a link between infertility and the subsequent development of RA (14).

Conversely, the study by Del Junco et al found no significant difference between women with RA and the general population(23).

In our study, infertility affected 12% of the participants, with 10% being primary infertility, which is a rate similar to that of the general population (between 16.5% and 17.8%) (2).

The underlying mechanisms remain poorly understood and are likely multifactorial.

Methotrexate has been suspected to affect ovarian reserve (30,31), although available data are conflicting. Furthermore, in women with RA who had never received Methotrexate, a reduced AMH level was observed (32).

Obesity, which is a risk factor for RA (33), could also promote female infertility, particularly by increasing the risk of dysovulation related to excess weight (34–36).

However, neither body mass index nor treatment exposure was associated with fertility disorders in our study. It should be noted that ovarian reserve markers, such as anti-Müllerian hormone (AMH), were not assessed.

Overall, our findings highlight the complexity of fertility

impairment in RA, likely resulting from an interplay between disease-related, treatment-related, and individual factors.

While these findings provide further insight into reproductive outcomes in women with RA, they should be interpreted in light of several methodological limitations. This study has several limitations that should be acknowledged. First, the relatively small sample size and the single-center recruitment may have limited the statistical power to detect weaker associations and may reduce the generalizability of our findings. Second, the cross-sectional design precludes establishing temporal or causal relationships between RA-related factors and fertility disorders. In particular, information regarding whether pregnancies occurred before or after the diagnosis of RA was not collected, preventing an accurate assessment of the direct impact of RA on reproductive outcomes. Third, reproductive data were partly based on patient self-report, which may have introduced recall bias, particularly for events occurring many years before inclusion. Fourth, the absence of a control group limits direct comparisons with women from the general population. In addition, ovarian reserve was not assessed using biomarkers such as anti-Müllerian hormone (AMH), and male partner fertility was not evaluated, although both may substantially influence fertility outcomes. Finally, because of the limited sample size, multivariable analyses were not performed, and residual confounding cannot be excluded.

CONCLUSION

Fertility disorders affect nearly one-third of women with RA, with disease duration exceeding six years emerging as a significant associated factor. These findings support the need for early and optimal disease control, along with systematic and personalized reproductive counseling in women of childbearing age. Further prospective multicenter studies are required to better elucidate the underlying mechanisms and to develop targeted strategies for fertility preservation in this population.

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