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Original Article

Is rheumatoid arthritis an innocent bystander in female reproductive problems? A comparative study of fertility in Nigerian women with and without rheumatoid arthritis

Richard Oluyinka Akintayo[1], Olufemi Opeyemi Aworinde[2], Osaze Ojo[3], Foluke Comfort Akintayo[4], Olawale Matthias Akinlade[5], Rasheed Olaide Awodun[6], Sakiru Oyetunji Isa[6]

Abstract

Objective: Contrary to the old belief that rheumatoid arthritis (RA) is rare in sub-Saharan Africa, recent reports have increasingly recognized that the burden of the disease has probably been long under-appreciated in West Africa. Thus, fertility and other attributes of the reproductive lives among women with RA have not received research attention in Africa. We aimed to compare the fertility between married Nigerian women with and without RA.

Methods: A comparative study of 50 women with RA and 50 women without RA was conducted via the specialist rheumatology clinics at two teaching hospitals in Nigeria. The participants were aged 18 years or older. Patients with RA were recruited on the basis of the fulfillment of the 1987 American College of Rheumatology classification criteria for RA, whereas the control participants were age-matched to the patients. Using an interviewer-administered questionnaire, demographic and clinical information was collected from each participant. Clinical details at the time of diagnosis of RA were extracted from the hospital records of the patients. The patients were tested for rheumatoid factor and anti-cyclic citrullinated peptide antibody, and the disease activity was assessed using the Clinical Disease Activity Index. The functional status was determined using the Steinbrocker functional classification. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp.; Armonk, NY, USA). The proportions of individuals with history of infertility, irregular menstruation, and menopausal states were compared between the two groups using χ^2 and Fisher's exact tests, whereas the durations of infertility and parities were compared using Mann-Whitney U and independent t-tests, respectively.

Results: A positive history of infertility was found in 22 (44%) patients and 14 (28%) controls (p=0.096), while 17 (34%) patients and 23 (46%) controls were found to be postmenopausal (p=0.221). History of irregular menstruation was present in 15 (30%) patients and 4 (8%) controls (p=0.005). The median duration of infertility was 60 (range: 16-132) months among the patients and 36 (range: 12-72) months among the controls (p=0.036), while the mean parity was 2.85±1.8 among the patients and 3.77±2.2 among the controls (p=0.027). A significant association was found between infertility and functional class as well as methotrexate treatment.

Conclusion: Infertility is not uncommon among patients with RA, and like many aspects of rheumatic diseases, it may have been under-recognized in the Nigerian patients.

Keywords: Fertility, connective tissue disease, rheumatoid arthritis, autoimmunity, Africa

ORCID IDs of the authors:
R.O.A. 0000-0002-4177-8981;
O.O.A. 0000-0001-5484-8312;
O.O. 0000-0002-8624-4334;
F.C.A. 0000-0001-5271-9189;
O.M.A. 0000-0002-5395-4479;
R.O.A. 0000-0001-5663-9485;
S.O.I. 0000-0002-4957-0106.

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[1] Department of Rheumatology, Lagos State University Teaching Hospital, Ikeja, Nigeria
[2] Department of Obstetrics and Gynaecology, Bowen University, Iwo, Osun State, Nigeria
[3] Department of Rheumatology, Kubwa General Hospital, Abuja, Nigeria
[4] Department of Family Medicine, Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Nigeria
[5] Department of Medicine, Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Nigeria
[6] Department of Medicine, University of Ilorin Teaching Hospital, Nigeria

Address for Correspondence: Foluke Comfort Akintayo, Department of Family Medicine, Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Nigeria

E-mail: akintayofoluke@gmail.com

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune rheumatic disease affecting mostly the joints, as well as several other organs. There is a reported worldwide prevalence of 0.5%-1%, with the female preponderance being up to five times the male cases for individuals younger than 50 years and double the male cases for individuals older than 60 years (1, 2). Prevalence may considerably vary across countries, races, age groups, and gender, and recent reports have suggested that RA may be far more common in sub-Saharan Africa than previously reported (3, 4). The manifestations of RA are protean and may be classified as articular and extra-articular features.

Infertility is a disease of the reproductive system defined by the failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (5). Rheumatic diseases may impair fertility (actual

production of children) and fecundity (time to achieve pregnancy) in addition to the fact that a high disease activity has a negative effect on sexual function (6). In addition to being of clinical concern, infertility is a public health problem carrying several stigmata and is an important cause of marital disharmony (7).

Studies have shown that women with RA have fewer children than those without RA. In a study including 578 women with RA, 21% reported that they had fewer children than they wanted (8). A prolonged time to achieve pregnancy was observed in a Dutch study of 245 women with RA, wherein 42% of the patients had a delay of more than 12 months to conception (9). Maternal age, nulliparity, disease activity, daily dose of prednisolone higher than 7.5 mg, and previous use of non-steroidal anti-inflammatory drugs (NSAIDs) (but not of methotrexate) were the variables associated with increased time to achieve pregnancy. By preventing the rupture of the luteinized follicle, NSAIDs can impair ovulation and lengthen the time to pregnancy (10). Other factors that could contribute to the subfertility in patients with RA include use of potentially teratogenic disease-modifying antirheumatic drugs (DMARDs) which in turn necessitates the postponement of pregnancy; voluntary limitation of family size due to problems encountered because of the disease or concerns regarding prognosis; and reduced levels of anti-Mullerian hormone, which is an indicator for ovarian reserve in women and, hence, their fertility (6, 11, 12). Furthermore, time to pregnancy has been shown to be longer in patients with a higher disease activity (13). There is no known reported study of the relationship between RA and fertility in West Africa. The aim of this study was to determine the relationship between RA and fertility (if any) among a population of Nigerian women with RA.

Table 1. Characteristics of the patients

	Frequency	Percentage
Functional class		
I	19	38.0
II	19	38.0
III	8	16.0
IV	4	8.0
RF		
Positive	40	80.0
Negative	10	20.0
Anti-CCP		
Positive	33	66.0
Negative	17	34.0
Presence of ExRA	27	54.0
MTX use	42	84.0
HCQ use	27	54.0
SSZ use	18	36.0
Biologic use	2	4.0
Herbal medication use	24	48.0
Prednisolone use	45	90.0
CDAI at diagnosis		
Remission	0	0.0
Low	5	10.0
Moderate	9	18.0
High	36	72.0
CDAI at present		
Remission	7	14.0
Low	23	46.0
Moderate	9	18.0
High	11	22.0

RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide antibody; ExRA: extra-articular manifestation of rheumatoid arthritis; MTX: methotreaxate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; CDAI: Clinical Disease Activity Index

Methods

Fifty married women who met the definition of RA according to the 1987 American College of Rheumatology classification criteria were recruited (14), and 50 apparently healthy age-matched married women were recruited as controls The eligible participants were aged 18 years or older. The patients were enlisted via the rheumatology clinics of two teaching hospitals in Nigeria while the control participants were drawn from the relatives of the patients attending the two clinics. The first hospital has one of the two public specialist rheumatology clinics in mainland Lagos located in the south-western Nigeria and the second has one of the two public specialist rheumatology clinics in the north-central geopolitical zone of Nigeria. RA is reported to be the most frequently encountered systemic autoimmune condition in the first hospital while it is observed to be second only to systemic lupus erythematosus in the second hospital.

The first hospital has patients visiting from Lagos state and from the entire south-west Nigeria. Lagos being the commercial capital of the country, the residents here essentially belong to every state and tribe of Nigeria. Therefore, the most diverse Nigerian ethnicity is seen in the typical public hospital in Lagos. The second hospital is a referral center that receives predominantly Yoruba patients from the north-central and south-western Nigeria. Other tribes that commonly visit the second hospital are the Nupes, Fulanis, Hausas, and Igbos.

Demographic and clinical information was collected from each participant using an interviewer-administered questionnaire. Data obtained included age, occupation, socio-economic status, level of education, town of residence, menopausal status, age at menarche, menstrual regularity, age at menopause, parity, history of infertility, duration of illness, and age at diagnosis. Each patient was examined by a rheumatologist.

Rheumatoid factor (RF) was measured using nephelometry method, whereas anti-cyclic citrullinated peptide antibody was analyzed using enzyme-linked immunosorbent assay. Disease activity was assessed using the Clinical Disease Activity Index (CDAI), under which remission was defined as CDAI less than 2.8, low disease activity as CDAI score between.8 and 10, moderate disease activity as CDAI score between and 22, and high disease activity as CDAI score greater than 22. Functional status was determined according to the Steinbrocker functional classification. Class I represents a complete ability to perform all the usual duties without handicaps; class II, adequate for normal activities despite a handicap of discomfort or limited motion of one of the joints; class III, limited to little or none of the duties of usual occupation or self-care; class IV, incapacitated, largely or wholly bed-ridden, or confined to wheel chair with little or no self-care. Ethical approval was obtained from the research and ethics committee of both hospitals.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version (20 IBM Corp.; Armonk, NY, USA). χ^2 and Fisher's exact tests were used, as appropriate, to test the differences between proportions, whereas independent t-test and Mann-Whitney U test were used to test the differences between the means and medians, respectively, of continuous variables.

Results

The mean ages of the patients and controls were 48.5 (SD=12.9) years and 48.0 (SD=12.8) years, respectively. The median duration since onset of RA in the patients was 60 (range, 2-360) months. The mean age of onset of the disease was 42.4 (SD=14.0) years, whereas the mean age at diagnosis was 42.9 (SD=14.1) years. As shown in Table 1, 45 (90%) patients were under steroid treatment with prednisolone at a mean dose of 11.1 mg daily. The median duration of treatment with prednisolone was 12 (range,

Table 2. Fertility and menstrual characteristics of patients and controls

	Patient (n=50)	Control (n=50)	χ^2	p
Fertility				
Positive hx of infertility (%)	22 (44)	14 (28)	-----	0.096
Negative hx of infertility (%)	28 (56)	36 (72)		
Menopausal state				
Pre-menopausal (%)	33 (66)	27 (54)	-----	0.221
Postmenopausal (%)	17 (34)	23 (46)		
Menstrual regularity				
Regular (%)	35 (70)	46 (92)	7.862	0.005

p: p value; χ^2: chi-square value; %: percentage

Table 3. Comparison of the characteristics of the patients and controls

	Patient mean, SD	Control mean, SD	p
Height (m)	1.64, 0.1	1.63, 0.1	0.418
Weight (kg)	75.12, 16.7	69.91, 16.0	0.118
Age at menarche (years)	14.90, 1.8	14.60, 2.2	0.459
Age at at menopause (years)	52.07, 4.2	49.79, 3.8	0.107
Parity (n)	2.85, 1.8	3.77, 2.2	0.027
Length of infertility in months [median (range)]	60.00 (16-132)	36.00 (12-72)	0.036

SD: standard deviation; p: p value

Table 4. Comparison of characteristics of patients with and without a history of infertility

	Positive Hx of Infertility n=22 (%)	Negative Hx of Infertility n=28 (%)	χ^2	p
Menstrual regularity				
Regular	13 (59.1)	22 (78.6)	-----	0.136
Irregular	9 (40.9)	6 (21.4)		
Functional class				
I	9 (40.9)	11 (39.3)	16.337	0.001
II	8 (36.4)	10 (35.7)		
III	0 (0.0)	7 (25.0)		
IV	5 (22.7)	0 (0.0)		
Rheumatoid factor				
Positive	18 (81.8)	22 (78.6)	-----	1.000
Negative	4 (18.2)	6 (21.4)		
Anti-CCP				
Positive	16 (72.7)	17 (60.7)	-----	0.373
Negative	6 (27.3)	11 (39.3)		
MTX treatment	14 (63.6)	28 (100.0)	-----	0.001
HCQ treatment	12 (63.2)	14 (53.8)	-----	0.532
SSZ treatment	9 (47.4)	9 (33.3)	-----	0.337
Herbal medications	14 (70.0)	10 (50.0)	-----	0.197
Prednisolone current use	20 (90.9)	26 (92.9)	-----	1.000
Presence of ExRA	8 (36.4)	14 (50.0)	-----	0.335

Hx: history; p: p value; χ2: chi-square value; %: percentage

1-216) months. Forty (80%) and 33 (66%) patients exhibited positive results for the presence of RF and anti-CCP antibody, respectively. A total of 30 (60%) patients were in remission or exhibited a low disease activity. Methotrexate was the most widely used DMARD, with 42 (84%) patients being administered this.

Fertility

As shown in Table 2, history of infertility was documented in 44% of the patients and 28% of the controls, but the difference did not reach statistical significance. Of these, primary infertility was seen in 5 (10%) patients and 3 (6%) controls, whereas secondary infertility was seen in 17 (34%) patients and 11 (22%) controls. The patients were significantly more likely to have irregular menstruation (p=0.005).

Table 3 shows a comparison of the characteristics between the patients and the controls. A significant difference was found between the mean parities of the patients and the controls as the women without RA were likely to have more children (p<0.05). Similarly, the length of infertility was significantly higher in the patients (p<0.05). Conversely, there were no significant differences in the ages at menarche and menopause between the two groups.

Factors Associated with History of Infertility

Table 4 shows the results of a subgroup analysis of the patients while comparing the characteristics of those with and without a history of infertility. All patients belonging to class IV functional status had a history of infertility, whereas there was no significant difference in the proportions of women with a history of irregular menstruation between those with and without the history of infertility. Furthermore, there was a significant association between the use of methotrexate and absence of history of infertility (p=0.0.5), whereas a duration of illness longer than 2 years was significantly associated with a history of infertility (p=0.0.5). The serologic status was not associated with history of infertility.

Discussion

This study evaluated 50 married Nigerian women with RA, alongside 50 apparently healthy age-matched married women who served as controls. The mean age of patients is in keeping with previous national and international studies (4, 15). The median duration since onset of RA of 60 months in our patients is longer than that reported by Sorensen and Hetland (16) and Chan et al. (17) in developed countries, but similar to that reported by Adelowo et al. (4) and Mody and Cardiel (18) who posited that early diagnosis remains a great

challenge for the management of RA in developing countries. This might be due to the fact that low-income countries face several competing economic and health-related issues, leading to chronic diseases not being viewed as priorities in the presence of scarce financial resources as well as the dearth of rheumatologists in sub-Saharan Africa.

Rheumatoid factor positivity observed in our study (80%) is significantly higher than that reported by a previous Nigerian study (38.5%) (4). This may be attributable to the methods of performing the investigation, latex agglutination in the previous study and nephelometry in the index study. Moreover, the previous study is retrospective, whereas the current study is prospective. The ACPA positivity (66%) value observed in our study is similar to values reported from other parts of the world (44%-74%) (19).

We found that the history of infertility was more common in patients with RA (44%) than in controls (28%), but the difference did not reach significance. This trend is similar to the findings of previous studies reporting that 42% of patients with RA had infertility (9, 11). However, the small sample size in our study limited the power of detecting a narrow significance. Following a review of recent findings, Provost et al. (20) concluded that infertility in patients with RA is a common, albeit under-recognized, finding. The high prevalence of infertility in patients with RA is attributable to many reasons. There is ample evidence that autoimmune disorders influence the reproductive life of patients for various reasons (21). One of the factors identified in this study was the disparity in the prevalence of menstrual irregularity between the two groups, which was found to be significant. Anovulation manifesting as oligo/amenorrhea is known to be an important etiology of infertility (22). The menstrual irregularity could be due to the autoimmune disease affecting the ovarian function or the use of prednisolone (6, 12). The mean dose of daily prednisolone used by the patients with RA was 11.1 mg and 90% of these patients were on this medication. Daily doses of prednisolone higher than 7.5 mg have been associated with an increased time to achieve pregnancy (6).

It is possible that high disease activity may contribute to a smaller family size and a higher incidence of infertility in patients with RA. If that holds, high disease activity in a high proportion of patients at presentation in this study may have an important contribution to the infertility. Severe illness has been found to reduce sexual function due to pain and immobility. Abdel-Nasser and Ali (23) studied 52 female patients with RA and found that 32 patients had difficulties in sexual performance including 9 who were totally unable to engage in a sexual intercourse because of arthritis. More than 60% of female patients with RA experienced variable degrees of sexual disability and diminished sexual desire and satisfaction. Difficulties in sexual performance were related more to disability and hip involvement, whereas diminished desire and satisfaction were influenced more by perceived pain, age, and depression. Similarly, the use of DMARDs has been associated with infertility in patients with RA and has been reported in association with methotrexate. Methotrexate has been linked with premature ovarian failure and amenorrhea, both of which may account for infertility in patients with RA (24, 25). Conversely, methotrexate use was found to be associated with a lower rate of infertility in this study. This finding probably reflects a possible link between receiving specialist rheumatology care and lower rates of infertility as methotrexate is the most commonly prescribed DMARD for RA by rheumatologists in Nigeria.

Other possible causes of infertility in patients with RA include sexual disorders, age at onset of disease, parity at onset of disease, and use of NSAIDs (6, 9, 23). The parity of the controls was found to be higher than that of patients with RA. This is supported by the finding of a longitudinal study conducted by Clowse et al. (11) in a cohort of women with RA, which found that 55% of the participants had a family size smaller than they had earlier planned. This was attributed to the choice of the patient partly influenced by the life-altering impact of RA as well as infertility.

Infertility is not uncommon among patients with RA. It is, however, largely overlooked and under-reported. West African patients with RA are among the least studied for the impact and course of the disease. The reproductive health of these individuals is one of the many aspects of the challenges faced by them that scarcely receive any attention. The use of various DMARDs reduces the disease activity, but the reproductive health of women, who are the ones predominantly affected by RA, should also be taken into consideration when formulating a treatment plan.

Ethics Committee Approval: Ethics committee approval was received for this study from the research and ethics committees of both hospitals.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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