CLINICAL DISPARITY IN RHEUMATOID ARTHRITIS PATIENTS WITH HISTORY OF SPONTANEOUS ABORTION: POTENTIAL LINK TO METABOLIC SYNDROME AND UNDER TREATMENT

Suzan S. El-Adle[1], Eman F. Mohamed[2], Nermeen Samy[3], Hanan Taha[4], Rasha Fawzy[5], Faten Ismail[6], Samar Tharwat[7], Maha Nassr[8], Soha Senara[8], Hanan El-Saadany[9], Hanan M. Fathi[8], Doaa Mosad[10], Safaa Sayed[1], Marwa A Amer[11], Saad El-Zokm[12], Abdelazeim Elhefny[3], Khaled El Hadidi[1], Tahsin S. El Hadidi[13], Tamer A. Gheita[1], Shereen Elwan[9]
on behalf of the Egyptian College of Rheumatology RA Study Group

[1]Rheumatology Department, Faculty of Medicine, Cairo University – Cairo, Egypt
[2]Internal Medicine Department, Rheumatology Unit, Faculty of Medicine (Girls), Al-Azhar University – Cairo, Egypt
[3]Internal Medicine Department, Rheumatology Unit, Faculty of Medicine, Ain-Shams University – Cairo, Egypt
[4]Internal Medicine Department, Rheumatology Unit, Faculty of Medicine, Beni-Suef University – Beni-Suef, Egypt
[5]Rheumatology Department, Faculty of Medicine, Benha University – Kalyoubia, Egypt
[6]Rheumatology Department, Faculty of Medicine, Minia University – Minia, Egypt
[7]Internal Medicine Department, Rheumatology Unit, Faculty of Medicine, Mansoura University – Dakahlia, Egypt
[8]Rheumatology Department, Faculty of Medicine, Fayoum University – Fayoum, Egypt
[9]Rheumatology Department, Faculty of Medicine, Tanta University – Gharbia, Egypt
[10]Rheumatology Department, Faculty of Medicine, Mansoura University – Dakahlia, Egypt
[11]Rheumatology Department, Faculty of Medicine, Alexandria University – Alexandria, Egypt
[12]Rheumatology Department, Faculty of Medicine, Al-Azhar University – Damiette, Egypt
[13]Agouza Rheumatology Centre – Egypt

Abstract. Objective: *The aim of the work was to describe the characteristics of married rheumatoid arthritis (RA) female patients with history of spontaneous abortion and compare them to those without.* ***Patients and methods:*** *Three hundred and four female RA with history of abortion compared with another 304 RA married patients of matched age without history of abortion. Patients were subjected to full history taking and clinical examination. The routine laboratory investigations were done in addition to rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibody. Also, plain x-ray hands were performed to detect erosions. Disease activity score (DAS28) and health assessment questionnaire (HAQ) were assessed.* ***Results:*** *In this study 3.5 % of patients with history of abortion out of a large RA cohort (n = 8750), had a mean age of 42.8 ± 11.4 years and disease duration of 6.2 ± 5.4 years. 14 (4.6 %) were smokers. There was a significant increase in the frequency of metabolic syndrome in those with abortion (17.4%) than in those without (10.9%) (p = 0.008). Methotrexate (MTX) and hydroxychloroquine (HCQ) were less frequently used among patients with a history of spontaneous abortion (67.8% and 68.8%) compared to those without (82.6% and 78%) (p = 0.005 and p = 0.037 respectively). Disease activity and the functional status were comparable between those with and without abortion.* ***Conclusion:*** *Spontaneous abortion in RA females was higher in those with metabolic syndrome. Reluctance and/or incompliance in using the basic DMARD treatment with MTX or HCQ in controlling the disease may add to the possibility of abortion.*

Key words: *rheumatoid arthritis; abortion; metabolic syndrome; methotrexate; hydroxychloroquine*

Introduction

Production of cytokines and distribution of immune cells during pregnancy may provide key information for predicting pregnancy outcome, full term, or loss [1]. Rheumatoid arthritis (RA) is an autoimmune disease, commonly seen in females with a 4-5 times higher incidence below the age of fifty years [2]. Hormonal influences play a role in the female preponderance as estrogens have a proinflammatory activity and are capable of activating B cells [3]. RA may be seen in female reproductive age [4] with a special concern during pregnancy, regarding the medications given [5], and fetal outcomes [6]. In a previous study on a large cohort of Egyptian RA patients, more than 90% of females were married [7].

Spontaneous abortion (SA) is a common disorder of pregnancy affecting about 12% of first-trimester pregnancies. Early miscarriage before the 12th week of gestation is frequently not identified or described, however late miscarriage complicates < 1% of pregnancies [8]. Women with RA who are plan-

ning a pregnancy usually inquire if they have a higher risk of SA, and the response is not clear-cut [9]. Only a few reports on miscarriage in RA have been published since 2000 [9-11] while stillbirth has been sparsely examined in women diagnosed with RA [9]. A call for studies on the risks of SA and stillbirth are essential in RA as new treatment opportunities such as biologics and the treat-to-target principle have altered the RA population [12].

In patients with immunologically mediated abortion (IMA), the immune tolerance mechanism is impaired. It is cell-mediated for early abortion or later by both cell-mediated and humoral mechanisms with the production of autoantibodies. Diagnostic workup adopted to select IMA patients is crucial and involves immune profile including the rheumatoid factor (RF) [13]. SA is more common than fetal stillbirth during the course of RA disease [14]. Interestingly, among women aged < 35 years, the risk of SA was higher in women with RA compared to those without [15]. Moreover, in the rare instance that pregnancies put the mother or fetus (or both) at serious risk, rheumatologists must discuss the option of elective pregnancy termination [16]. Abortion may raise an issue about the disease activity and serological findings related to RA [17] and may cast shadows on the disease risk and burden in these patients [18].

The aim of the present study was to describe the characteristics of married RA patients with history of spontaneous abortion and compare them to those without.

Patients and methods

The study included 304 adult RA patients fulfilling the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria [19] with a history of abortion that were recruited from multiple university teaching hospitals and a rheumatology practice centre out of a large cohort of RA patients. Another 304 RA married female patients of matched age and disease duration with no history of abortion were included as a control group. The patients' provided informed consents to participate and the study was in accordance to the 1964 Helsinki declaration.

Patients were subjected to full history taking and clinical examination. The presence of co-morbidities and medications received were recorded. The laboratory investigations performed included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and kidney function tests, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and antinuclear antibody (ANA). Disease activity score (DAS28) [20] and health assessment questionnaire (HAQ) [21] were assessed. Metabolic syndrome (MetS) was diagnosed according to the Adult Treatment Panel (ATP III) criteria [22].

Statistical analysis: Data were collected on a standardized data sheet and stored in an electronic database. The missing data from the various areas were considered. Statistical Package for Social Sciences (SPSS) version 25 was used. Variables were presented as frequencies and percentages or mean and standard deviation. A comparison was done using Chi-square test or Mann Whitney U tests. P value < 0.05 was considered significant.

Results

The study included 304 RA patients with history of abortion out of a large cohort of 8750 female RA patients (3.5%). Characteristics of the patients with and without abortion are presented in table 1 and 2. Lupus anticoagulant (LAC) and anti-cardiolipin (ACL) antibodies were assessed in only 9 patients (3 had both measured) and anti-β2 glycoprotein in one and all were negative.

Table 1. Demographic features, co-morbidities, clinical manifestations, disease activity and functional status of the rheumatoid arthritis patients with and without history of abortion

Parameter n (%) or mean ± SD	Abortion in rheumatoid arthritis patients			p
	all (n = 608)	with (n = 304)	without (n = 304)	
Age (years)	42.1 ± 11.3	42.8 ± 11.4	42.3 ± 11.1	0.09
Disease duration (years)	5.8 ± 5.2	6.2 ± 5.4	5.4 ± 4.97	0.06
Age at onset (years)	36.2 ± 10.8	36.5 ± 11.2	35.8 ± 10.3	0.4
Body mass index (BMI)	29.2 ± 5	30.1 ± 4.9	28.1 ± 5.04	**< 0.0001**
Smoking	26 (4.3)	14 (4.6)	12 (3.9)	0.68
Co-morbidities				
Diabetes mellitus	72 (11.8)	37 (12.2)	35 (11.5)	0.8
Hypertension	151 (24.8)	88 (28.9)	63 (20.7)	0.02
Metabolic syndrome	86 (14.1)	53 (17.4)	33 (10.9)	0.008
Osteoporosis	9 (1.5)	4 (1.3)	5 (1.6)	0.74

Continuation of Table 1

Asthma	13 (2.1)	8 (2.6)	5 (1.6)	0.4
Thyroid dysfunction	12 (2)	9 (3)	3 (1)	0.08
Manifestations				
Rheumatoid nodules	133 (21.9)	70 (23)	63 (20.7)	0.78
Sjögrens syndrome	79 (13)	42 (13.8)	37 (12.2)	0.68
Neurological	51 (8.3)	32 (10.5)	19 (6.3)	0.09
Vasculitis	33 (5.4)	18 (5.9)	15 (4.9)	0.99
Gastrointestinal	102 (16.8)	53 (17.4)	49 (16.1)	0.83
Cardiovascular	65 (10.7)	35 (11.5)	30 (9.9)	0.82
Chest	76 (12.5)	30 (9.9)	46 (15.1)	0.02
Fibromyalgia syndrome	123 (20.2)	58 (19.1)	65 (21.4)	0.29
Renal	17 (2.8)	8 (2.6)	9 (3)	0.61
DAS28	4.4 ± 1.3	4.4 ± 1.42	4.4 ± 1.2	0.81
HAQ	0.92 ± 0.63	0.97 ± 0.69	0.88 ± 0.58	0.29

DAS28: disease activity score, HAQ: health assessment questionnaire. Bold values are significant at $p < 0.05$

Table 2. Laboratory investigations and medications received by rheumatoid arthritis patients with and without history of abortion

Parameter	**Abortion in rheumatoid arthritis patients**			**p**
n (%) or mean ± SD	**all (n = 608)**	**with (n = 304)**	**without (n = 304)**	
Laboratory investigations				
Hemoglobin (g/dl)	11.1 ± 1.4	11.1 ± 1.39	11.2 ± 1.4	0.45
TLC ($x10^3/mm^3$)	7.1 ± 2.6	6.9 ± 2.56	7.3 ± 2.63	0.09
Platelets ($x10^3/mm^3$)	270 ± 93.3	274.2 ± 92.1	265.5 ± 94.6	0.29
ESR (mm/1sthr)	43.8 ± 25	43.6 ± 27.5	44 ± 22.5	0.85
CRP (mg/dl)	17.7 ± 19.7	17.2 ± 21.9	18.3 ± 17.5	0.004
AST (IU/l)	24.9 ± 9.6	24.7 ± 9.4	25.1 ± 9.8	0.66
Creatinine (mg/dl)	0.81 ± 0.5	0.81 ± 0.47	0.8 ± 0.52	0.74
Cholesterol (mg/dl)	213 ± 66	205.3 ± 67.9	221.5 ± 63.02	0.051
Triglycerides (mg/dl)	128.3 ± 52.4	138.2 ± 59.3	117.1 ± 40.8	0.003
HDL (mg/dl)	76.1 ± 37.6	70.2 ± 41.9	82.8 ± 30.8	0.015
LDL (mg/dl)	105.2 ± 39.8	107.7 ± 42.4	102.3 ± 36.6	0.33
SUA (mg/dl)	5.1 ± 1.5	5.08 ± 1.4	5.1 ± 1.5	0.88
RF	419 (68.9)	215 (70.7)	204 (67.1)	0.19
Anti-CCP	312 (51.3)	158 (52)	154 (50.7)	0.69
Double seropositivity	240 (39.5)	130 (42.8)	110 (36.2)	0.1
ANA	101 (16.6)	51 (16.8)	50 (16.4)	0.82
Medications				
Steroids	443 (72.9)	213 (70.1)	230 (75.7)	0.18
Hydroxychloroquine	446 (73.4)	209 (68.8)	237 (78)	0.037
Azathioprine	10 (1.6)	4 (1.3)	6 (2)	0.46
Low dose aspirin	11 (1.8)	5 (1.6)	6 (2)	0.66
Methotrexate	397 (65.3)	206 (67.8)	251 (82.6)	0.005
Leflunomide	243 (40)	114 (37.5)	129 (42.4)	0.68
Biologics	55 (9)	31 (10.2)	24 (7.9)	0.26

TLC: total leucocytic count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, HDL: high density lipoprotein, LDL: low density lipoprotein, SUA: serum uric acid, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, ANA: antinuclear antibody. Bold values are significant at $p < 0.05$

Discussion

Pregnancy is a risky time for various patients with rheumatic diseases, particularly affecting women of childbearing age and the risk – to both the mother and foetus – is high [16]. The frequency of pregnancy loss is increased in patients with different autoimmune diseases than in the general population [23]. It has been proposed that natu-

ral-killer cell expressed immunoglobulin-like receptors are related to both RA and recurrent SA [24]. The causes of recurrent SA are unknown; however, the presence of antinuclear antibodies (ANA) and other antibodies in some women suggests the possibility of underlying autoimmune disease [23]. The use of highly effective contraception was at the fore front of the 2020 ACR guideline for the management of reproduction health in patients with rheumatic diseases [16]. Associations of particular HLA antigens with several rheumatic diseases are well established, though the precise nature of this relation remains unclear. The association between DR antigens and a wide variety of connective tissue disorders is well known and RA is strongly linked to HLA-DR4 [25]. HLA-DR5 was over represented in women with recurrent SA and was related to the presence of ANA suggesting the likelihood of an underlying autoimmune disease [23].The low prevalence of HLA-DR5 and DR7 antigens in RA patients from the Middle East indicates a protective role for these antigens against the disease susceptibility [25]. A complex interaction exists between RA disease and fertility-related issues. Despite a high rate of infertility in RA, the mechanisms involved are still obscure and plausible causes involve the overproduction of inflammatory cytokines, suppressed sexual activity and medications used [26].

In this study, associated abortion was reported in 304 (3.5%) patients out of a large cohort (n = 8750) of female RA cases. Such a low frequency points to the rarity of such condition for this special group. In accordance, in Southern Brazil, he results suggest that mannose-binding lectin (MBL) deficiency and gene polymorphisms were risk factors for the occurrence of miscarriage in 4.5% of RA patients [27]. In a work from Norway on 1578 women with RA, early SA was reported in 26.2%, late in 4.5% and still birth in 1.3% whereas the relative risks of early and late miscarriage were 1.2 and 1.4, respectively [9]. On the contrary, in another Brazilian study on the gynecological and obstetrics background in RA females, none had a history of abortion [3]. RA declines a couple's potential to succeed in childbearing [26]. The increased risks for cesarean delivery, prematurity, and longer hospitalization at birth among infants born to women with RA may be due to the pathophysiologic changes associated with RA or medications used to treat the disease [10].

In this work, the age at disease onset was similar yet tended to be higher in those with a history of abortion. It has been reported that the duration of reproductive years and the number of pregnancies were linked to the disease onset as RA patients had more pregnancies than in the normal population [3].

Currently there was an association between the presence of MetS and the history of having abortion. Until recently, a study focusing on the association between history of abortion and metabolic diseases were limited. It was found that women with a history of abortion remained at 1.25 times more likely to have MetS [28].

It was found that patients with neurological manifestations had a higher frequency of abortion history. Neuralgia of the cranial and spinal nerves is very often associated with abortion and perhaps even more common in patients with rheumatic diseases [29].

In the current study, RF, anti-CCP and double seropositivity tended to be higher in RA patients with history of abortion. In a study on women with recurrent SA, and not known to have RA, it was found that the frequency of RF was higher than in a matched group of women who got pregnant but did not have any previous abortion [1]. An increase in RF has been reported in the serum of women with a history of recurrent SA [*30]*. Auto-antibodies such as RF and anti-CCP link the innate and acquired immune response [*31*]. As the roles of some infectious agents in recurrent abortions are well known, there might be a relation between microbial abortion and the production of these auto-antibodies [1].

In this work there was a similar disease activity in those with and without a history of abortion. The RA patients must balance the risk of uncontrolled disease activity (itself a pregnancy risk) and use of medications such as methotrexate (MTX) which are known teratogens. These risks are enhanced when pregnancies are accidental [16].

Anti-phospholipid (APL) antibodies were measured in only 10 patients with a history of abortion and all were negative. However, persistent APL antibodies are associated with dysregulated B-cell subsets and has been reported in RA patients with recurrent pregnancy loss [32].

In this study, MTX and hydroxychloroquine (HCQ) were less frequently used among patients with a history of SA. Other DMARDs, biologic therapy and steroids received by the patients were similar. Rheumatologists have voiced concerns about potential restrictions on the cornerstone drug MTX, because of its abortion-inducing effects at extremely high doses [16]. Such concerns are of limited importance in Egypt due to different cultural and/ or religious beliefs and socioeconomic status [33]. If planned pregnancy is discussed with the physician, the RA patient is shifted to be given HCQ and SSZ

instead of MTX 3-6 months before pregnancy, a low dose suitable corticosteroid, patient's education, and a baseline evaluation of disease activity [34]. HCQ is a molecule with extensive safety data during pregnancy with potential actions: antithrombotic, vascular protective, immunomodulatory, improved glucose tolerance, lipid lowering and anti-infectious that could be effective against unexplained recurrent miscarriage besides its relatively low cost [35]. In this work there was a tendency to higher frequency of receiving biologic therapy by patients with a history of abortion. However, many biologic drugs are currently available as potentially effective during pregnancy and breastfeeding [36]. In fact, anti-TNF biologics are promising for maintaining remission in RA and may be prescribed in the first half of pregnancy at least [37].

A careful follow up of the RA patient, the way and time for the proper planning to get pregnant and an eye of the pediatrician on her future fetal outcome, is recommended. It is compulsory to advance the patient's education and to take into consideration the underlying factors involved in infertility and pregnancy loss [26]. The adherence to an ultimate clinical pathway of pregnancy management in women with RA may restore the risk of unfavorable pregnancy outcome to that anticipated for the general population [38].

Although early miscarriage, fetal loss and stillbirth in RA women are not typically reported, information on the prevalence and risk is still inadequate. It has been reported that there was no significantly increased miscarriage or SA rate in women with RA [39, 40]. However, a tendency to a rise in the still birth rate in RA women has been expressed [40]. The chance of a live birth was extraordinarily lower in RA women receiving assisted reproductive technology treatment in comparison to those without RA due to an impaired chance of embryo implantation [41]. There is still limited research with respect to pregnancy loss in RA women however; it should be taken critically [26].

The lack of detailed information about primary infertility, follow-up, immunological profile or autoantobodies related to abortion and fetal outcome are considered limitations to this work. Moreover, the frequency of abortion in relation to that in the general population should have been considered.

In conclusion, the rate of spontaneous abortion in RA is low yet it may be speculated to be higher in those with metabolic syndrome or alterations of its components. Reluctance and/or incompliance in using the basic DMARD treatment with MTX or HCQ in controlling the disease may add to the possibility of abortion.

Conflict of interest: *The authors declare no conflict of interest*

Funding: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

Acknowledgment: *Collaborators and members of the Egyptian College of Rheumatology: Nevin Hammam (Assuit), Hala A Raafat (Cairo), Samah A El-Bakry (Ain Shams), Iman I El-Gazzar (Cairo), Samar M Fawzy (Cairo), Nahla N Eesa (Cairo), Nora Y El-Said (Cairo), Rawhya El Shereef (Minia), Mervat I Abd Elazeem (Beni-Suef), Amany El-Bahnasawy (Mansoura), Maha Nassr (Fayoum), Abdel Hafeez Moshrif (AlAzhar), Mohamed N Salem (Beni-Suef), Rasha M Fawzy (Benha), Asmaa Khalifa (Sohag), Nouran M Abaza (Ain Shams), Ahmed M Abdalla (Aswan), Amany R El-Najjar (Zagazig), Noha A Azab (Cairo), Soha Senara (Fayoum), Safaa Sayed (Cairo), Emad El-Shebini (Menoufiya), Dina H El-Hammady (Helwan), Ahmed Y Ismail (Beni-Suef), Wael Abdel Mohsen (South-Valley), Othman Hammam (Assuit).*

References

1. Hadinedoushan H, Aflatounian A, Anvari M. The Role of IL-2 and rheumatoid factor in recurrent spontaneous abortion. Biochemia Medica.2008;18(2):201-5
2. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann NY Acad Sci 2006;1069: 212-22.
3. Cavalcante AFDS, Martin P, Skare TL. Gynecological/ obstetric background and rheumatoid arthritis: A cross-sectional study in Brazilian patients. Rev Bras Ginecol Obstet. 2021;43(5):357-61.
4. Chakravarty EF. Rheumatoid arthritis and pregnancy: beyond smaller and preterm babies. Arthritis Rheum. 2011;63: 1469-71.
5. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis. 2014;74(10):1836-41.
6. Nørgaard M, Larsson H, Pedersen L, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med. 2010; 268: 329-37.
7. Gheita TA, Raafat HA, El-Bakry SA, Elsaman A, El-Saadany HM, Egyptian College of Rheumatology (ECR) Rheumatoid Arthritis Study Group. Rheumatoid arthritis study of the Egyptian College of Rheumatology (ECR): Nationwide presentation and worldwide stance. Rheumatol Int. 2022; epub ahead of print.
8. Delabaere A, Huchon C, Deffieux X, Beucher G, Gallot V, Nedellec S, et al. Epidemiology of loss pregnancy. J Gynecol Obstet Biol Reprod 2014;43:764-75.
9. Wallenius M, Salvesen KÅ, Daltveit AK, Skomsvoll JF. Miscarriage and Stillbirth in Women with Rheumatoid Arthritis. J Rheumatol. 2015;42(9):1570-2.
10. Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. Matern Child Health J 2006;10:361-6.
11. Clowse ME, Chakravarty E, Costenbader KH et al. Effects of infertility, pregnancy loss, and patient concerns on family

size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res 2012;64:668-74.
12. Smolen JS. Treat-to-target: rationale and strategies. Clin Exp Rheumatol 2012;30 Suppl 73:S2–6.
13. Giacomucci E, Bulletti C, Polli Vet al. Immunologically mediated abortion (IMA). J Steroid Biochem Mol Biol. 1994;49(2-3):107-21
14. Wallenius M, Salvesen KA, Daltveit AK, Skomsvoll JF. Increased rates of spontaneous abortions, but not stillbirths in rheumatoid arthritis. Ann Rheum Dis 2013;72 Suppl 3:A761–2.
15. Nathan NO, Mørch LS, Wu CS et al. Rheumatoid arthritis and risk of spontaneous abortion: a Danish nationwide cohort study. Rheumatology (Oxford). 2020;59(8):1984-91.
16. The Lancet Rheumatology. Editorial: The demise of Roe v Wade: ramifications for rheumatology. The Lancet Rheumatology. 2022;4(8):e525.
17. Al Rayes H, Sultana A, Alotaibi AM et al. Adverse Impact of Rheumatoid Arthritis on Pregnancy Outcomes: A Saudi Arabia Prospective Multicenter Study. Research and Reviews 2021(13):167-75.
18. Chang MK, Lee CH, Park JS et al. Incidence and prevalence of seropositive rheumatoid arthritis among Korean women of childbearing age:a nationwide population-based study. KJIM 2022; epub ahead of print
19. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569-81.
20. Prevoo ML, Van't Hof MA, Kuper HH et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8.
21. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45
22. National cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults; Third report of the national cholesterol education program expert panel (NCEP) on detection, evaluation and treatment of high blood choleaterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
23. Smith JB, Cowchock FS, Hankinson B, Iftekhar A. Association of HLA-DR5 with recurrent spontaneous abortion in women treated with paternal leukocytes. Possible subclinical autoimmune disease. Arthritis Rheum. 1989;32(12):1572-6.
24. Kuśnierczyk P. Killer cell immunoglobulin-like receptor gene associations with autoimmune and allergic diseases, recurrent spontaneous abortion, and neoplasms. Front Immunol. 2013;4:8.
25. Sattar MA, al-Saffar M, Guindi RT et al. Association between HLA-DR antigens and rheumatoid arthritis in Arabs. Ann Rheum Dis. 1990;49(3):147-9.
26. Fattah A, Asadi A, Shayesteh MRH et al. Fertility and infertility implications in rheumatoid arthritis; state of the art. Inflamm Res. 2020;69(8):721-9.
27. Cieslinski JZ, Goeldner I, Skare TL et al. Mannose-binding lectin deficiency and miscarriages in rheumatoid arthritis. Autoimmunity. 2017;50(7):409-413
28. Xu B, Zhang J, Xu Y et al. Association between history of abortion and metabolic syndrome in middle-aged and elderly Chinese women. Front Med. 2013;7(1):132-7.
29. Napier ADL. The Relationship between Neuralgia and Abortion: A Clinico-Speculative Note. Trans EdinbObstet Soc. 1889; 14:37-44.
30. Iijima T, Tada H, Hidaka Y et al. Effects of autoantibodies on the course of pregnancy and fetal growth. Obstet-Gynecol 1997;90(3):364-9.
31. Chaiamnuay S, Bridges SL Jr. The role of B cells and autoantibodies in rheumatoid arthritis: Pathophysiology 2005;12(3):203-16.
32. Ota K, Dambaeva S, Lee J et al. Persistent high levels of IgM antiphospholipid antibodies in a patient with recurrent pregnancy losses and rheumatoid arthritis. Am J Reprod Immunol. 2014;71(3):286-92
33. Gheita TA, Eesa NN. Rheumatology in Egypt: back to the future. Rheumatol Int. 2019;39(1):1-12
34. ACR subcommittee on RA guidelines. Guidelines for the management of rheumatoid arthritis 2002 updates. Arthr Rheum 2002;46(2): 328-46.
35. Pasquier E, De Saint-Martin L, Marhic G et al. Hydroxychloroquine for prevention of recurrent miscarriage: study protocol for a multicentre randomised placebo-controlled trial BBQ study. BMJ Open 2019;9:e025649
36. Murray KE, Moore L, O'Brien C et al. Updated pharmacological management of rheumatoid arthritis for women before, during, and after pregnancy, reflecting recent guidelines. Ir J Med Sci. 2019;188:169-72.
37. Østensen M, Andreoli L, Brucato A et al. State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev. 2015;14:376-86.
38. Bortoluzzi A, Andreoli L, Carrara G et al. Improved Pregnancy Outcome in Patients With Rheumatoid Arthritis Who Followed an Ideal Clinical Pathway. Arthritis Care Res (Hoboken). 2021;73(2):166-72.
39. Silman A, Roman E, Beral V, Brown A. Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis. Ann Rheum Dis. 1988;47:979.
40. Spector TD, Silman A. Is poor pregnancy outcome a risk factor in rheumatoid arthritis? Ann Rheum Dis. 1990;49:12.
41. Nørgård BM, Larsen MD, Friedman S et al. Decreased chance of a live born child in women with rheumatoid arthritis after assisted reproduction treatment: a nationwide cohort study. Ann Rheum Dis. 2019;78:32834.

Submitted: 02.09.2023

✉ *Correspondence address:*
Tamer A Gheita, MD
Professor of Rheumatology,
Faculty of Medicine, Cairo University, Egypt
e-mail: gheitamer@cu.edu.eg; gheitamer@hotmail.com
Phone: +201004567975
ORCiD: 0000-0002-1155-9729