Contraceptive Awareness and Practices in Patients With Rheumatic Diseases Using Disease Modifying Anti-Rheumatic Drugs

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ABSTRACT

Objective: To determine the contraceptive awareness and practices in patients with rheumatic diseases using disease modifying anti-rheumatic drugs.

Study Design: Cross-sectional study.

Place and Duration of Study: Outpatient of Rheumatology, Department at Pakistan Institute of Medical Sciences, Islamabad Pakistan, from Jan to Apr 2021.

Methodology: Patients with any rheumatic disease and taking teratogenic disease modifying anti-rheumatic drugs were included in the study. Patients were asked about if they were counseled regarding the risk of teratogenicity with the anti-rheumatic drugs and when to stop the drug before pregnancy.

Results: Out of total 150 patients, 87 (58.0%) female patients had Rheumatoid arthritis and 26 (17.3%) had Systemic lupus erythematosus. The majority of female patients (104, 69.3%) were using Methotrexate and 21 (14.0%) females were using Leflunomide. Only 53 (35.3%) females were counseled about drug teratogenicity. Most of the female patients (102, 68.0%) were never counseled about the use of contraception while taking anti-rheumatic drugs. The rate of use of contraceptives was even worse and merely 15 (10.0%) females were using contraceptives.

Conclusion: Majority of the patients with rheumatic diseases being treated with teratogenic disease modifying anti-rheumatic drugs, were not using any form of contraception. The rate of contraceptive use and counseling regarding contraceptives was noted to be very low.

Keywords: Anti-rheumatic drugs, Contraceptive use, Rheumatic disease, Teratogenic drugs.

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INTRODUCTION

Autoimmune diseases have complex etiology and are mixture of genetic and environmental factors. Since these diseases are more common in females as compared to males, therefore hormonal and reproductive factors have very limited explanation of this gender difference.[1] Rheumatic diseases usually affect the females in their reproductive age. This may or may not affect their fertility but certainly increases the risk of miscarriages if the disease is not in remission before conception.[2,3]

However, the pregnancy has varying negative effects on the disease activity.[4] The importance of pregnancy timings and method of contraception increases when using specific disease modifying anti-rheumatic drugs (DMARDs). A planned pregnancy with the consultation of physician and obstetrician during the period when disease is well-controlled, significantly enhances the chance of healthy pregnancy and better outcomes for mother and fetus. Various rheumatic diseases have contraindication to some usual methods of contraception, like patients having anti-phospholipid antibody syndrome are at increased risk of thrombosis and miscarriage with estrogen containing oral contraceptives.[5]

These patients in their reproductive age, face several challenges while deciding to conceive because of potential side effects of medication.[6] There are some drugs which are used to control the disease activity but at the same time are contraindicated during pregnancy and lactation. A detailed planning in the supervision of rheumatologist is required to control disease activity before pregnancy.[7] The use of contraceptives may help in prevention of unintended pregnancy as well as delaying pregnancy till disease goes into remission.[8] The risk of poor maternal and fetal outcomes makes many pregnancies as high risk among women with high disease activity. This risk increases significantly when patients are using teratogenic DMARDs at the time of conception.[9]

The objective of the study was to assess the patients' awareness about the drugs teratogenicity and attitude towards contraception. This study highlights

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the importance of planned pregnancies and use of appropriate method of contraception. Furthermore, it draws attention to the role of treating physician and rheumatologist in counseling patients regarding drug teratogenicity and planned pregnancy. As this is an under addressed aspect in the care of rheumatology patients, addressing this issue can help in developing further strategies. Therefore, by avoiding spontaneous conception and preventing unplanned pregnancies in patients with active disease will help improve maternal and fetal outcomes in terms of decrease maternal mortality, intrauterine death, stillbirth and congenital birth defects.

METHODOLOGY

In this cross-sectional study, all the women diagnosed with any of the rheumatic disease and taking teratogenic DMARDs were included. The study was conducted at the OPD of Rheumatology Department, PIMS Hospital, Islamabad, from January to April 2021. All the women in the study were selected by non-probability consecutive sampling. Approval of the study was taken from Hospital Ethical Committee (Approval Letter No: ERB/SZABMU-697), before start of the study. After appropriate counseling, informed written consent was taken from all patients.

The sample size was calculated by using WHO sample size calculator with confidence level of 95%, anticipated population proportion (Rate of contraception use among rheumatic patients) of 55.8%, and Absolute precision of 8%. The Sample size turned out to be 150 patients.

Inclusion Criteria: All the married female patients aged 18-44 years and diagnosed with rheumatic diseases like rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, polymyositis, any type of vasculitis, mixed connective tissue disease, Overlap syndrome and Ankylosing spondylitis and using any teratogenic DMARDs (methotrexate, leflunomide, mycophenolate mofetil or cyclophosphamide) were included in the study.

Exclusion Criteria: Unmarried females and patients not using any teratogenic DMARD were excluded from the study.

Data regarding baseline demographic details including age, duration of disease, disease diagnosis were recorded along with details of DMARDs intake. Patients were asked about if they were counseled regarding the risk of teratogenicity with these anti rheumatic drugs and when to stop the drug before pregnancy. Simultaneously patients were also inquired about any prior counseling regarding use of contraception, duration of contraception usage and appropriate mode of contraception. Moreover, they were asked about the use of emergency contraceptive pill (ECP), number of children they already have, any child born with an anomaly and history of miscarriages while taking anti rheumatic drugs. All this information was recorded by the principal investigator in the structured proforma.

All the collected data was entered and analyzed by using Statistical Package for the Social Sciences (SPSS) version 25. Mean and standard deviation were calculated for age, and duration of disease. Frequency and percentages were calculated for qualitative variables like if they were counseled about the contraception, appropriate method of contraception, their knowledge and practice about contraception, duration and type of contraceptive method used. Results were presented in the form of tables.

RESULTS

In this study, 150 female patients having any rheumatologic disease were included. Most of the patients 76 (50.7%) belonged to the age group between 30-40 years followed by 52 (34.7%) patients, who belonged to age group between 18-34 years. Majority of the females 87 (58%) had Rheumatoid Arthritis (RA) followed by 26 (17.3%) and 18 (12%) who had Systemic lupus erythematosus (SLE) and Scleroderma (SSc) respectively. All the women in the study were using teratogenic DMARDs and the most of female patients 104 (69.3%) were using Methotrexate (MTX), followed by 21 (14%) females who were using Leflunomide (LFU). Infertility was very common among these patients having rheumatologic disease, with very few (less than 5), who had a successful pregnancy. The parity distribution after the diagnosis of rheumatic disease showed that 104 (69.3%) patients had zero fertility followed by 29 (19.3%) patients who had parity of one after diagnosis of the disease. Most of the patients (51, 34%) had duration of disease less than 5 years and 50 (33.3%) patients had 5-8 years. Almost 40 (26.7%) patients had disease duration between 8-12 years as elaborated in Table-I.

Most of the females 97 (64.7%) were never counseled about the teratogenicity of the drug. Only 53 (35.3%) female patients had been counseled about drug teratogenicity. In the entire study population, only 10 (6.7%) female patients had the knowledge of drug teratogenicity. Out of 140 (93.3%) female patients in the study were unaware of the teratogenicity of the drugs they were using. There was significant lack of

knowledge about the time to stop the teratogenic drug before conception in all the women using DMARDs. Only 3 (1.3%) females were mindful of the exact time to stop the teratogenic drug prior to the conception. The counseling rate regarding the use of contraception was also very limited and only 48 (32%) females gave positive response about counseling regarding contraceptive usage. Whereas most of the patients 102 (68%) were never counseled about the use of contraception while taking anti-rheumatic drugs as elaborated in Table-II.

Table-I: Demographic distribution of the study population (n=150).

Demographic Characteristics	n (%)
Age of the Patient (Years)	
18-30 years	52 (34.7%)
30-40 years	76 (50.7%)
>40 years	22 (14.7%)
Disease Diagnosed	
Rheumatoid arthritis	87 (58%)
Systemic lupus erythrematosus	26 (17.3%)
Scleroderma	18 (12%)
Polymyositis/dermatomyositis	5 (3.3%)
Mixed connective tissue disease/overlap syndrome	9 (6%)
Vasculitis	5 (3.3%)
Anti-Rheumatic Drugs in Use	
Methotrexate	104 (69.3%)
Leflunomide	21 (14%)
Mycophenolate mofetil	5 (3.3%)
Cyclophosphamide	8 (5.3%)
Methotrexate + lefluonamide combination	3 (2%)
Other	9 (6%)
Parity (After Diagnosis of Disease)	
0	104 (69.3%)
1	29 (19.3%)
2	15 (10%)
3	2 (1.3%)
Duration of Disease (Years)	
<5	51 (34%)
5-8	50 (33.3%)
8-12	40 (26.7%)
>12	9 (6.0%)

Table-II: Distribution of Knowledge about teratogenicity in the study population (n=150).

Knowledge	n (%)
Counseled About Drug-Teratogenicity	
Yes	53 (35.3%)
No	97 (64.7%)
Knowledge About Teratogenic Drug	
Yes	10 (6.7%)
No	140 (93.3%)
Knowledge About the Exact Time to Stop Teratogenic Drug Before Conception	
Yes	2 (1.3%)
No	148 (98.7%)
Counseled Regarding Contraception Usage	
Yes	48 (32%)
No	102 (68%)

In our study, only few females 15 (10%) were using contraception while taking DMARDs while the rest were not practicing any contraceptive method. Among the patients who were using contraceptives; 8 (5.3%) were using barrier methods followed by 6 (4.0%) patients, who were using the natural methods. The most common reason of not using contraceptives was poor counseling in 92 (61.3%) female patients, followed by 27 (18.0%) females who wanted to conceive and 10 (6.7%) who felt burden of medication and fear of side effects. A minor number 6 (4.0%) of females had religious concerns for not using contraceptives. No one in the study population was using appropriate mode of contraceptive method based on the diagnosis and type of DMARDs as per guidelines. Only 6 (4%) females were counseled about the emergency contraceptive pills but none of them used it after unprotected sex to avoid pregnancy as shown in Table-III.

Table-III: Distribution of contraceptive use in the study population (n=150).

Contraception Types	n (%)
Using contraception	
Yes	15 (10%)
No	135 (90%)
Mode of Contraception Being Used	
Barrier methods	8 (5.3%)
Natural methods	6 (4%)
Other methods	1 (0.7%)
Not using Contraceptive	135 (90%)
Possible Reasons for not Using Contraception	
Never counseled	92 (61.3%)
Wants to conceive	27 (18.0%)
Medication burden/ Afraid of side effects	10 (6.7%)
Religious concerns	6 (4.0%)
Using Contraceptives	15 (10.0%)
Use of Appropriate Contraception Method	
No	150 (100%)
Counseling regarding use of Emergency Contraceptive Pill	
Yes	6 (4.0%)
No	144 (96.0%)
Use of Emergency Contraceptive Pill	
No	150 (100%)

Majority of the females 137 (91.3%) never conceived while using DMARDs. Only 13 (8.7%) females got pregnant while using DMARDs. From the total study population, 5 (3.3%) pregnant females ended up with spontaneous abortion, 3 (2) ended up with premature birth and only 5 (3.3%) gave alive birth. Among these pregnant females 5 (3.3%) gave birth with normal vaginal delivery, 3 (2%) with c-section (Table-IV).

DISCUSSION

In this cross sectional study, we enrolled 150 married females of the reproductive age group between 18-

Table-IV: Distribution of Conception and delivery in the study population (n=150).

Conception	n (%)
Conception While Using Dmards?	
Yes	13 (8.7%)
No	137 (91.3%)
Outcome of Pregnancy?	
Spontaneous abortion	5 (3.3%)
Premature birth	3 (2%)
Alive birth	5 (3.3%)
Not Conceived	137 (91.3%)
Mode of Delivery?	
Normal Vaginal Delivery	5 (3.3%)
C-Section	3 (2.0%)
Abortion	5 (3.3%)
Not Conceived	137 (91.3%)

44 years. Majority (58% and 17%) of them were suffering from RA and SLE respectively, followed by other rheumatic disorders in different proportion. This stusy demonstrated a huge gap in adequate patient-clinician communication and discussions about teratogenic DMARDs, family planning and pregnancy. As shown by the results of our study, less than half of the patient population (35%) were counseled about drug teratogenicity. Almost 68% of the young females were at risk of unintended pregnancies because they were never counseled about contraception and its importance. Most of them put themselves and the life of upcoming baby at stake from unplanned pregnancy and feto-toxic effects of the drug they were taking. Poorly controlled disease at the time of conception significantly increases the risk of poor pregnancy outcomes like IUGR, preeclampsia, fetal loss, preterm birth and cesarean section.[10]

All the patients included in our study population were using either alone or combination of highly teratogenic drugs (Category X) i.e., Methotrexate, Leflunomide, Mycophenolate Mofetil or Cyclophosphamide, that need to be stopped almost 3-6 months (varied for different drugs) before conception.[11,12] Our study revealed that a very low proportion of patient who knew exact time to stop the drug before conception i.e., merely 3% which was lower than the results shown by a local study done by Mustaq *et al*.[13]

It was observed in this study that, though one third of the patient population was counseled about drug teratogenicity but almost 93% of the sample population failed to recall the culprit drug during the questionnaire session. This showed that a significant proportion of patient had not benefited from the counseling session, which highlighted the need for repeated counseling regarding drug teratogenicity. Similarly only half of those counseled for contraception actually practiced it. The exact reason for not using contraception in those who have been counseled are unclear.[10,13] It is therefore, imperative to consider the basic education level and socioeconomic status of the patient which may impact the interpretation of information provided by physician, important demographic feature though not considered in our study but was included in a study done by Singla *et al*, in India.[14]

Almost two third of patient population in our study had a disease duration ranging from 5-12 years, having a long duration of illness which signifies multiple outpatient visits, hardly 10% of patients were using some form of contraception. Barrier methods was the most common mode of contraception practiced by population (5.3%) followed by natural methods (4%). Not a single patient in the study appeared to be using appropriate method of contraception as per guidelines.[12] A recent study conducted by Birru Talabi *et al*, showed that 32% patients used the prescribed contraceptive which is significantly higher when compared to our study. The same study also pointed that the patients' compliance to contraception was better when such patients were under treatment of gynecologist.[15] Another study on young females with SLE reported that 59% had not received any contraceptive advice in the prior year, 12% never used contraception, and 10% used contraception inconsistently. Yazdany *et al,* in the same study pointed out that women using potentially teratogenic medications were not likely to received contraceptive counseling or use contraception than women using non-teratogenic medications.[16] San Francisco-Lupus-Outcomes study conducted at University of California, enrolled 68 female patients with SLE, almost one third of them did not receive any contraception counseling when starting with new drugs. Old age, white race, and higher SLE disease activity were independently associated with not receiving contraception counseling.[17] Regardless of whatever the underlying reasons, results of our study were no different from the studies done abroad, even with different cultural, socioeconomic and educational differences.

A small study conducted locally at Fauji foundation hospital Rawalpindi, by Mustaq *et al*, analyzed 52 female patients. Results of this study were slightly different in one aspect, showing higher rate of drug teratogenicity counseling i.e., 51% (vs. 35% in our study).[12] Although, there was no significant difference in contraceptive counseling between the two studies, the former

revealed higher percentage of patients using some form of contraception.

Our study presented some important aspects that has not been sophisticated by study done at FFH, Rawalpindi. Lack of counseling (61%) followed by the desire to have children (18%) was the most common reason among those not using contraception when inquired during the study. Out of 150 patients included in the study,[13] patients conceived while using DMARDs, 5 out of 13 underwent spontaneous abortions, 3 of them have a premature delivery while 5 have uneventful pregnancy. Outcome of these unplanned pregnancies was another differentiating point, which was addressed in our study. A systemic review (1961 to 2007) done by Lopez *et al*, revealed that 101 patients were exposed to MTX from conception till first trimester, out of them 23% had miscarriages, 66% were successful to deliver a healthy baby and 5% had minor congenital malformations. The rate of induced abortions was 18%. [18] Data retrieved from literature is inconsistent with the results shown by our study.

Contraceptive advice is an integral part of rheumatology clinics because most of the affected patients are young females who are living in fertile years of their life. Significant portions of these patients do not practice contraception at all or at least the recommended method of contraception as shown in this study. Awareness regarding drug teratogenicity, contraception and mode of contraception is an under-addressed part in rheumatology consultations. Hospitals providing rheumatology services should consider an organized contraception clinic in the locality where contraception receipt and advice must be provided in handouts to all the young females using teratogenic DMARDs. A proper liaison between gynecologist and rheumatologists about an individual patient regarding planned pregnancy must be done as it improves patients care and increase the chances of a healthy baby.

LIMITATIONS OF STUDY

This study is second of its type conducted locally in a tertiary care hospital, it has certain limitations. It was single center study having a relatively small sample size compared to studies done internationally. It failed to address the reasons of patient-physician communication gap that lead to poor outcome of contraceptive use. Whether the rheumatologists working in outpatients were over occupied because of increase work burden and patient overload or it was simply a poor recall on part of patients considering their educational status. Considering our cultural and religious norms, most of the female patients were reluctant to discuss the pregnancy and contraception issues with a male doctor, which our study missed. Moreover, the study had not included any patients taking biologic DMARDs which are also teratogenic. The study could have been expanded to include male patient and their attitude towards contraception while taking DMARDs.

CONCLUSION

Majority of the patients with rheumatic diseases being treated with teratogenic disease modifying anti-rheumatic drugs, were not using any form of contraception. The rate of contraceptive use and counseling regarding contraceptives was noted to be very low.

Conflict of Interest: None.

Authors' Contribution

SG: Conception, design of study write up of the manuscript, MMK: Design of study and interpretation of data, UR: Supervisor of the study, ST: Data collection and analysis, SZ: Data collection and analysis.

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