Awareness Regarding Drug Teratogenicity, Contraception and Mode of Contraception Used by Patients with Rheumatologic Diseases

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Abstract. Objective of the current study is to find the awareness regarding drug teratogenicity, contraception and mode of contraception in rheumatology patients. A cross sectional descriptive study has been done at Fauji Foundation Hospital, Rawalpindi, Pakistan. Patients in rheumatology outdoor with rheumatoid arthritis (RA), systemic lupus erythromatosis (SLE), Scleroderma (SSc) or polymyositis were included in the study and asked questions about demographic details, duration of disease, medications taken by the patient. After that specific questions regarding counseling on medications, teratogenic potential of the drugs and any prior counseling regarding contraception and mode of contraception used by the patients were asked. 52 patients all females were enrolled. Mean age ±SD (in years) is 39.25±5.43; disease duration ±SD (in years) is 5.69±4.67. 22(42.3%) patients were on methotrexate, 11(21.2%) on leflunomide, 7(13.5%) on Mycophenolate mofetil, 1(1.9%) on cyclophosphamide, 11 (21.2%) were taking methotrexate and leflunomide combination. Only 27(51.9%) patients were counseled regarding teratogenicity of drugs and 21(40.4%) patients knew correctly, the possible teratogenic drug they are taking. Only 12(23.1%) patients knew the correct time to stop the drug before conception. 18(34.6%) patients were counseled regarding using contraception with these drugs. 29(55.8%) patients were using contraception and amongst these 18(34.6%) were using barrier methods, 4(7.7%) employed coitus interuptus, 3(5.8%) used oral contraceptive pills, 3(5.8%) had placed intrauterine device, 4(7.7%) had undergone tubal ligation and 1(1.9%) had hysterectomy. 4 (7.7%) patients used emergency contraceptive pill (ECP) once in their lifetime while taking medicines. It has become to make a conclusion about disease awareness, drug teratogenicity and contraception is under addressed aspect of the management in rheumatologic diseases.

Key words: drug teratogenicity, contraception methods, rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, rheumatology drugs.

Introduction

Rheumatic diseases like rheumatoid arthritis (RA), systemic lupus erythromatosis (SLE), and scleroderma (SSc) are mainly diseases of the females. They mainly start during the fertile years of the women especially SLE and RA. Most of the patients are married at this point of life and they have desires to have a family and kids as this is the basic human requirement. But due to their diseases there are certain limitations. Firstly, there is difficulty for them to conceive and they are more childless than the general

population (Wallenius et al., 2012: 202-207). Along with difficulty conceiving there is increased risk of miscarriages and early fetal losses mainly if the disease is active during or before pregnancy (Makol and Krause, 2016: 23-36).

Secondly the medicines which are used for the treatment of these rheumatic diseases like methotrexate (MTX), leflunomide (Lef), mycophenolate mofetil (MMF), cyclophosphamide (CYC) and biologic DMARDs are highly teratogenic and they cause miscarriages, fetal losses, fetal malformations and have serious effects on fetal growth and development if they are taken during the period of organogenesis or before that (Flint et al., 2016: 1693). MMF and cyclophosphamide are the most teratogenic of all the drugs. So these medicines are contraindicated in pregnancy and most of them in lactation as well. Non-steroidal anti-inflammatory drugs are also not safe during pregnancy and should be avoided (Makol et al., 2011: 1973; Bazzani et al., 2015).

There is British society of rheumatology and British health professionals in rheumatology guidelines that defines the exact period to stop a teratogenic drug before conception. Like for methotrexate it is 3 months, for leflunomide its 1 year, for cyclophophamide it is 3 months and for mycophenoalte mofetil it is 6 weeks, for tociluzimab it is 3 months, rituximab it is 6 months (Makol and Krause, 2016: 23-36). Certolizumab is a TNF inhibitor that can be used in all trimesters of pregnancy. If patient accidently get pregnant on this medication, there is risk of fetal malformation and an increased risk of miscarriages. According to a study, among 101 MTX exposed pregnancies, 19 had miscarriages (23% of pregnancies); 55 had live births (66% of pregnancies); and 5 of them had minor neonatal malformations (5% of pregnancies). The rate of induced abortions was 18% (Martínez Lopez et al., 2009: 678). Similar was observed with cyclophosphamide. The chance of miscarriage with mycophenolate use during pregnancy might be close to 50% (1 in every 2 pregnancies) (Coscia et al., 2015: 42-55). There are various startegies to counter such cases as for example leflunomide wash out with chlostyrmaine and giving folic acid daily with methotrexate (Flint et al., 2016: 1693). There is a lot of safety data on the safety of lefulonaide in pregnancy but still in guidelines it should be stopped before pregnancy (Chambers et al., 2010: 1494). If pregnancy is inevitable and/or patient's choice, then it should be fully planned and disease should be in remission before conception. In all rheumatic diseases like RA, SLE there are more chances of a successful pregnancy if disease is controlled (Cortes-Hernandez et al., 2002: 643).

To avoid pregnancy and unplanned pregnancies every patient should be counseled regarding the risk of teratogenicity with the drugs if they are teratogenic and about the importance of planned pregnancies with rheumatic diseases. Time interval to stop the teratogenic drug before conception and shifting the patient's treatment to safer medicines before conception should be shared with each patient in detail. Various guidelines endorse safe pregnancy planning if patient is on immunosuppressive medication (Singh et al., 2012: 625-639). Compatibility with pregnancy and lactation was found for antimalarials, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, intravenous immunoglobulin and glucocorticoids. Patient should be shifted to safer immunosuppressive options if patient has any chronic rheumatic diseases (Flint et al., 2016: 1693).

Apart from counseling of teratogenic medications, patients should also be counseled regarding the use of contraception and the mode of contraception that is safer for them. Counseling regarding the use of Emergency contraceptive pills (ECPs) should be done in case of not using contraception to avoid unplanned pregnancy. Rheumatic patients especially who are on some teratogenic drug must be counseled about taking

emergency contraceptive pill or plan B within 72 hour of unprotected sex to avoid pregnancy (Committee On Adolescence, 2012: 1174-1182; American College of Obstetricians and Gynecologists, 2010: 1100-1109). In developing countries like Pakistan mother and child health care programs still need appropriate administration in all the regions of the country. Along with it, strict adherence to false religious beliefs about contraception quadruples the risk of poor fetal outcomes with the use immuno-suppressive medicines.

The objective of the study is to assess the patient's awareness about the drugs teratogenicity and contraception. As this is an under addressed aspect in the care of rheumatology patients. Most rheumatologists and medical specialists dealing with rheumatic diseases think that this is the responsibility of the gynecologist to counsel the patients regarding contraception and pregnancy (Ostensen, 2011 315-316). On the other hand, gynecologists have a fear about the rheumatic diseases and they don't counsel the patient properly, may be because of lack of knowledge about the management in rheumatic diseases. It's the prime responsibility of the treating rheumatologist to counsel, treat and manage all aspects of patient's diseases about drug teratogenicity, pregnancy and contraception counseling along with general management of the disease (Briggs et al., 2016).

Material and Methods

Study was started after taking consent from the ethical committee of the hospital. It is a cross sectional descriptive study including 52 patients, all females of ages between 20 to 44 years, married, having any of the rheumatic disease like rheumatoid arthritis, systemic lupus erythromatosis, scleroderma and polymyositis, taking either methotrexate, leflunomide, MMF, or CYC were recruited in the study. The duration of the study was 3 months from 01st September 2018 to 31st December 2018. Baseline demographic details were noted along with disease they have, duration of the disease and medicines they were taking. Patients were asked about if they were counseled regarding the risk of teratogenicity with these drugs; which drug is teratogenic and when to stop the teratogenic drug before pregnancy. Simultaneously patients were also inquired about any prior counselling regarding use of contraception, duration of contraception usage and mode of contraception. Moreover, they were also asked about the use of ECP, number of children they have, any child born with an anomaly and history of miscarriages while they took anti rheumatic drugs.

Data was analyzed using SPSS version 23.0. Mean and Standard deviation (SD) were calculated for numeric variables like age and duration of the disease. Percentages were calculated for diseases, patients counseled about teratogenicity and contraception.

Results

A total of 52 patients were analyzed with mean Age(years)±SD of 39.25±5.43.the mean duration of disease(years) mean±SD was 5.69±4.67. The rest of results are shown in the Table 1.

Table 1. Data as received after analysis of questionnaire

Disease	Rheumatoid arthritis 38(73.1 %) Systemic lupus erythromatoses 6 (11.5%) Scleroderma 4(7.7%) Polymyositis 4(7.7%)
Medications taking	Methotrexate 22(42.3%)

	Leflunomide 11(21.2%) Mycophenolate mofetil 7(13.5%) Cyclophophamide 1(1.9%) Methotrexate+Lefluonamide combination 11(21.2%)
Counseled about drug teratogenicity	Yes 27(51.9%) No 25(48.1%)
Knowing about teratogenic drug	Yes 21(40.4%) No 31(59.6%)
Knowing the exact time to stop teratogenic drug before pregnancy	Yes 12(23.1%) No 40(76.9%)
Counseled regarding contraception usage	Yes 18(34.6%) No 34(65.4%)
Using contraception	Yes 29(55.8%) No 23(44.2%)
Mode of contraception used	Barrier methods 18(34.6%) Natural methods 4(7.7%) OCP 3(5.8%) IUD 3(5.8%) Tubal ligation 4(7.7%) Hysterectomy 1(1.9%) Husbands vasectomy 0(0%)
Used ECP	Yes 4(7.7%) No 48(92.3%)
Any children anomaly while taking drugs	Yes 0(0%) No 52(100%)
No of patients having miscarriages while on anti-rheumatic drugs	Yes 8(15.38%) No 44 (84.62%)

Discussion

As seen from the results of this study drug teratogenicity counseling is not done by most of the treating rheumatologists. Only half of the patients were counseled that the medicines they are taking may be injurious to the fetus if they conceive a pregnancy while being on these medications. This is a dilemma that physicians are prescribing these teratogenic medications and not explaining the adverse effects of these drugs to mother or the fetus. Only 35% patients knew about the teratogenic potential of medicine they took medications like hydroxychloroquine, sulphasalazine, prednisolone, non-steroidal anti-inflammatory drugs (NSAIDS), proton pump inhibitors in addition to MTX, LEF etc. Out of these 35%, only 20 % know the correct time to stop the teratogenic medication before pregnancy. Only one third patients were counselled regarding use of contraception so that they don't get pregnant. Serious responsibility lies on the shoulders of the treating physicians as the risks to mother and fetus cannot be ignored. Disease should be controlled for more than 3 to 6 month before conception (Firestein et al., 2012: 1321-1322).

Another aspect is that the patients suffering from SLE, SSc, or polymyositis were more counseled regarding drug teratogenicity than the patients of RA. The reason behind this aspect is unidentified. A recent study conducted by Birru Talabi M and colleagues showed that only 32.1% patients are using prescribed contraceptive as compared to

others and contraception usage is more when patients with rheumatic diseases are under treatment with a gynecologist (Birru Talabi et al., 2018: 169-174). A survey of reproductive-age women with SLE reported that 59% had not received any contraceptive counseling in the prior year, 12% never used contraception, and 10% used contraception inconsistently. Women using potentially teratogenic medications were no more likely to have received contraceptive counseling or use contraception than women using nonteratogenic medications (Yazdany et al., 2011: 358-365). Similarly, nearly half of reproductive-age women with SLE in another survey reported having had unprotected sex, with 23% of respondents having had unprotected sex most of the time, in the prior 3 months (Schwarz and Manzi, 2008: 863-866). Another survey reported that 33% of women with SLE did not receive contraceptive counseling when starting new medications, and individuals with the highest disease activity were least likely of all patients to receive contraceptive counseling (Ferguson et al., 2016: 12-17). A study by Chakravarty et al. reported that a majority of European and US women with SLE, RA, and inflammatory bowel diseases (IBD) felt that family planning concerns were inadequately addressed by their providers (Chakravarty et al., 2014).

Only 56% patients received contraceptive counseling when they started receiving new teratogeinc drugs. The situation is even more alarming in our study, and only 34% were counseled about contraception usage with teratogenic potential drugs.

So rapid actions are needed to provide awareness and easy access to contraception for every patient with rheumatological diseases.

The selection of contraceptive method is best guided by an individual woman's preferences, with considerations of reversibility, safety, noncontraceptive benefits, side effects, costs and convenience. Progestin-only subdermal implants are the most effective contraceptives available (first year failure rate 0.05%) (Birru Talabi et al., 2018: 169-174).

But in our study results very few patients are taking oral contraceptive pills(OCP) for contraception in rheumatic diseases. The reason behind may be the fear of using more pills or the gynecologists lack of confidence in prescribing OCP to a patient with any rheumatic disease. Barrier method is the most common contraceptive method used by rheumatic diseases. According to research, progestin-only subdermal implants are the most effective contraceptives available (first-year failure rate 0.05%) (Birru Talabi et al., 2018: 169-174). But long-acting reversible contraceptives, such as intrauterine devices (IUDs), are also highly effective for preventing pregnancy (Yazdany et al., 2011: 358-365). A study conducted in Srilanka by Galappatthy and colleagues showed that fetal outcomes (fetal loss, pre-maturity, low birth weight) in SLE. Unplanned pregnancies were significantly higher in SLE (80%) compared to RA (25%). Contraceptive usage was lower in patients with SLE (25.6%) and RA (33%) in this study the use of modern contraceptive methods by patients with SLE and related conditions was significantly lower than in patients with RA andWNCI of the same age (25.6% vs. 33% vs.56.4%, respectively; $P<0.01$ (Galappatthy et al., 2017: 746-754).

In a study, patients with SLE with negative or positive APS profile, Copper-bearing IUD (A) or levonorgestrel-releasing IUD are the first line contraception methods along with condoms while in disease like juvenile idiopathic arthritis, juvenile dermatomyositis Combined oral contraceptive or other combined hormonal contraceptive (NS) are recommened as first line. In SLE with APS, COC are not recommended. Instead, progestin only pills or depot medroxyprogestrone should be used. COC are strictly prohibited in patients with SLE and APS due to increased risk of deep venous thrombosis and chances of lupus flare (Lourenço et al., 2017).

Among 206 women, 86 were at risk for unplanned pregnancy. Most (59%) had not received contraceptive counseling in the last year, 22% reported inconsistent contraceptive use, and 53% depended solely on barrier methods. Intrauterine device contraceptives (IUDs) were used by 13%. Women using potentially teratogenic medications were no more likely to have received contraceptive counseling, to have used contraception consistently, or to have used more effective contraceptives (Yazdany et al., 2011: 358-365).

Another aspect is that many patients are using some mode of contraception inspite of not being counseled by their primary physician as to avoid pregnancy. This may be due to the fear that pregnancy may adversely effect their chronic rheumatic disease or they have already completed their families. This aspect should be studied in detail in future studies. By default, usage of contraception is about 21.2% who are using any form of contraception by themselves without being counseled by the health care professionals.

The presented study is the first local study of such type but it has certain limitations. The limitation of our study are a small sample size, single center study, not assessing the reasons of not counselling the patients and assessing the causes of not using contraception even if patients are counseled about the risk. More number of patients including who are taking biologic DMARDS should be included in the study. Contraception and pregnancy is a topic which most of the patient's female are reluctant to discuss with their male doctor. No male patients are included in the study, the study can be expanded to include male patients, number of children they have, any difficulty in having children, their fertility issues and the effects of teratogenic medicines on their married life.

The importance of this study is to create awareness amongst the physicians especially rheumatologists and medical specialists directly treating rheumatic diseases, to counsel their patients about the possible teratogenicity with the drugs. There should be no communication gap between the patient and the physician regarding the drugs teratogenicity as this is the right of the patient to know the drug she is taking and responsibility of the doctor to explain all important adverse effect of the drug to the patient. This is not the responsibility of gynecologists but it is the responsibility of the treating physician to counsel about teratogenic drugs, when to get pregnant when the disease is inactive. The talk about family planning, contraception use and planning for pregnancy should be a part of management plan of the treating rheumatologist and he or she should initiate this talk with the patient and his partner at the time of starting the teratogenic treatment.13 The use of contraception should also be addressed by the treating physicians. Interdepartmental 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. Liaison should also be done regarding proper mode of contraception use by the patient.

This is a pilot study of its type and needs more studies needed with large sample size and multicenter studies to see the exact percentages.

Conclusion

Awareness regarding drug teratogenicity, contraception and mode of contraception used by patients with rheumatologic diseases is an under addressed topic and it should be dealt properly by treating rheumatologists.

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