Original Article

DOI: 10.14235/bas.galenos.2025.44227
Bezmialem Science

The Effects of Medications Used in the Treatment of Rheumatological Diseases on Pregnancy and Fertilization: A Single-center Experience

Romatolojik Hastalıkların Tedavisinde Kullanılan İlaçların Gebelik ve Fertilizasyon Üzerine Olan Etkileri: Tek Merkez Deneyimi

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ABSTRACT

Objective: Considering that the group of rheumatological patients generally consists of women in their reproductive period due to hormonal effects, we aimed to investigate the effects of the treatments given to prevent joint and organ damage caused by these diseases on pregnancy and fertilization.

Methods: This study included 1,000 female patients who were followed up due to rheumatological diseases at the rheumatology

ÖZ

Amaç: Romatolojik hasta grubunun hormonal etkiler nedeniyle genellikle üreme çağındaki kadınlardan oluştuğu düşünüldüğünde, bu hastalıkların neden olduğu eklem ve organ hasarlarını önlemek için verilen tedavilerin gebelik ve döllenme üzerine etkilerini araştırmayı amaçladık.

Yöntemler: Bu çalışmaya Ocak 2014-2021 tarihleri arasında hastanemiz iç hastalıkları anabilim dalı romatoloji kliniğinde

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Cite this article as: Karataş B, Çabuk Çelik N, Karakaş B, Yalçın İ, Pire G, Eren HŞ, Şenol Kuzu M, Yıldırım M, Özdamar BN, Aşkın MF, Şahin A. The effects of medications used in the treatment of rheumatological diseases on pregnancy and fertilization: a single-center experience. Bezmialem Science. [Epub Ahead of Print]

***This study was presented as written posters at the EULAR European Congress of Rheumatology from June 1-4, 2022, and as an oral presentation at the 3rd Sivas Cumhuriyet University Rheumatology Days from June 2-4, 2023.**

Received: 16.03.2025
Accepted: 20.08.2025
Epub: 08.01.2026

ABSTRACT

department of the internal medicine department of our hospital between January 2014 and January 2021. The patients' ages, rheumatological disease diagnoses, pregnancy status, abortion status, curettage status, medications used, medications used during pregnancy, pregnancy complications, infertility data were retrospectively analyzed.

Results: The number of patients who became pregnant after diagnosis increased with the use of colchicine and anakinra, while it decreased with the use of methotrexate and leflunomide. It was observed that the number of abortions before diagnosis increased in the presence of antiphospholipid antibody syndrome (APS) and systemic lupus erythematosus. It was determined that the number of patients giving live births decreased in the presence of an APS diagnosis. It was determined that the number of patients who had live births with the use of colchicine and hydroxychloroquine during pregnancy increased.

Conclusion: It should be considered that women of reproductive age with rheumatic diseases may desire pregnancy and may present to the clinic with either planned or unplanned pregnancies during their follow-ups, and accordingly, efforts should be made to avoid medications that could cause infertility as much as possible.

Keywords: Antiphospholipid antibody syndrome, colchicine, pregnancy

ÖZ

romatolojik hastalıklar nedeniyle takip edilen 1.000 kadın hasta dahil edildi. Hastaların yaşları, romatolojik hastalık tanıları, gebelik durumları, düşük durumları, küretaj durumları, kullanılan ilaçlar, gebelikte kullanılan ilaçlar, gebelik komplikasyonları, infertilite verileri retrospektif olarak analiz edildi.

Bulgular: Tanı sonrası gebe kalan hasta sayısı kolşisin ve anakinra kullanımı ile artarken, leflunomid kullanımı ile azaldı. Metotreksat kullanımı ile tanı sonrası gebelik sayısı azalmıştır. Antifosfolipid antikor sendromu (AFAS) ve sistemik lupus eritematozus varlığında tanı öncesi düşük sayısının arttığı görüldü. AFAS tanısı varlığında canlı doğum yapan hasta sayısının azaldığı belirlendi. Gebelikte kolşisin ve hidroksiklorokin kullanımı ile canlı doğum yapan hasta sayısının arttığı belirlendi.

Sonuç: Üreme çağındaki romatizmal hastalığı olan kadınların gebelik isteğinde bulunabilecekleri ve takipleri sırasında planlı veya plansız gebeliklerle kliniğe başvurabilecekleri göz önünde bulundurulmalı ve buna göre kısırlığa neden olabilecek ilaçlardan mümkün olduğunca uzak durulmalıdır.

Anahtar Kelimeler: Antifosfolipid antikor sendromu, kolşisin, gebelik

Introduction

The birth of a healthy baby is related to how the mother and/or expectant mother experience their reproductive cycle, pregnancy, and childbirth process. The dominance of immune-mediated pathophysiology in rheumatological diseases also affects the fertilization and pregnancy periods. Considering that the group of rheumatological patients often consists of women in their reproductive period due to the influence of hormones, the effects of joint and organ damage caused by these diseases, as well as the impact of treatments given to prevent them on pregnancy and fertilization, should be taken into account (1).

For example, in systemic lupus erythematosus (SLE), it has been noted that women with active lupus nephritis experience life-threatening pregnancy complications such as eclampsia more frequently, and in antiphospholipid antibody syndrome (APS), recurrent abortions occur (2). In a patient with Sjogren's syndrome, it has been reported that anti-Ro/SSA and anti-La/SSB antibodies (anti-SSA/SSB) can cause neonatal heart block in the fetus during pregnancy (3). In a pregnant woman diagnosed with ankylosing spondylitis (AS), in addition to the growth of the uterus, the change in the structure of the pelvic bones and ligaments can increase inflammatory back and hip pain, and the patient's mobility can be severely impaired. Additionally, this condition can also affect the management of childbirth (4). In cases of Familial Mediterranean fever (FMF), infertility due to amyloidosis can develop (5). These examples can be further increased. When these are considered, it is difficult for mothers and/or expectant mothers with rheumatological diseases to avoid using medication before or during pregnancy. Not all medications are safe (3). Drugs that inhibit DNA synthesis, such as methotrexate and leflunomide, are teratogenic; it is recommended to discontinue them before pregnancy (6). It is also known that cyclophosphamide treatment leads to infertility. Although most of the data on drug safety are obtained from case reports, small series, and observational studies, certain drugs are still used during pregnancy due to the dangerous consequences of uncontrolled systemic inflammatory disease and the patients' vulnerability to postpartum disease flare-ups (3).

Therefore, knowing the effects of rheumatological diseases and the medications used in their treatment on pregnancy and fertilization will be guiding for patient management and medication choices.

Methods

Ethics Statement

In this study, 1,000 female patients with rheumatological diseases, either outpatient or inpatient, who were followed up in the rheumatology department of the internal medicine department of our hospital between January 2014 and January 2021, were included. The inclusion criteria for the study were determined as being anatomically and physiologically female patients in the reproductive period from birth, aged 18-45, having at least one rheumatological disease, and using at least one rheumatological medication. The breastfeeding status of the patients included in the study was disregarded. Ethics approval for the study was obtained from the Sivas Cumhuriyet University Non-

Interventional Clinical Research Ethics Committee (decision no: 2021-10/16, date: 20.10.2021). Informed consent was obtained in writing from the patients.

The patients' ages, rheumatological disease diagnoses, disease durations, pregnancy status and numbers before and after diagnosis, abortion status and numbers before and after diagnosis, curettage status and numbers, live birth status and numbers, comorbid conditions, medications used, medications used during pregnancy, pregnancy complications (eclampsia and pre-eclampsia), pregnancy-related hypertension and thyroid diseases, gestational diabetes mellitus status, organ damage status related to rheumatological diseases, and infertility data were analyzed retrospectively. Conditions where hypertension (systolic 140 mm/Hg, diastolic 90 mm/Hg and above) was detected during pregnancy and accompanied by proteinuria (300 mg/24 hours and above) were classified as pre-eclampsia; if convulsions accompanied the condition in the last trimester of pregnancy, it was classified as eclampsia (7). In our study, patients who had never achieved pregnancy despite 12 months of regular and unprotected sexual intercourse, those who had previously achieved pregnancy but had not been able to conceive despite regular unprotected intercourse in the last year, those who experienced recurrent abortions despite achieving pregnancy, and those who had never had a live birth due to stillbirth were included under the definition of infertility (8). Cases where a live fetus was born after completing the 28th week of pregnancy were recorded as live births (9). Pregnancies terminated voluntarily before the 20th week of gestation or for medical reasons after the 20th week of gestation were classified as curettage (10). The event of the complete or partial expulsion of an embryo or fetus weighing less than 500 grams and its appendages outside the uterine cavity within the first 20 weeks of pregnancy was classified as an abortion (miscarriage) (11). The drugs used were evaluated independently of the dose. The patient was examined based on whether they took the medication, even if it was not at an effective dose. The use of medication during pregnancy was recorded as the period from the first trimester of pregnancy until the birth resulting in either a live or stillbirth, or until an abortion occurred.

Statistical Analysis

Data were processed in SPSS version 23, Pearson chi-square, Mann-Whitney U test, Wilcoxon test were performed. In our study, there was no control group because the patients were compared within themselves. Since we evaluated the patients within themselves, the comorbid conditions, lifestyle changes, and other factors affecting pregnancy, such as the course of the disease, were the same. This also allowed us to understand the effectiveness of the medications.

The reason for not having a control group is that we only conducted research on patients with rheumatological diseases, so there were no cases that did not use medication. Even if we did not give it, there was a history of medication use from another center.

Results

Demographic Data

In our study, the median age of the patients was 37 years (min 19-max 45). Two hundred twenty-four patients (22.4%) had FMF, 197 patients (19.7%) had rheumatoid arthritis (RA), 274 patients (27.4%) had AS, 59 patients (5.9%) had psoriatic arthritis, 1 patient (0.1%) had sarcoidosis, 1 patient (0.1%) had mastitis, 1 patient (0.1%) had polymyositis, 7 patients (0.7%) had vasculitis, 169 patients (16.9%) had Behçet's disease, 3 patients (0.3%) had Still's disease, 2 patients (0.2%) had gout, 146 patients (14.6%) had fibromyalgia, 105 patients (10.5%) had SLE, 60 patients (6%) had Sjogren's syndrome, 37 patients (3.7%) had systemic sclerosis and Raynaud's phenomenon, and 29 patients (2.9%) had APS. 127 patients (12.7%) used sulfasalazine, 426 patients (42.6%) used colchicine, 340 patients (34%) used hydroxychloroquine (HCQ), 144 patients (14.4%) used methotrexate, 54 patients (5.4%) used leflunomide, 259 patients (25.9%) used corticosteroid preparations, 103 patients (10.3%) used azathioprine, 14 patients (1.4%) used mycophenolate mofetil, 127 patients (12.7%) used duloxetine, 757 patients (75.7%) used non-steroidal anti-inflammatory drugs (NSAIDs), 58 patients (5.8%) used infliximab, 88 patients (8.8%) used adalimumab, 8 patients (0.8%) used tocilizumab, 3 patients (0.3%) used tofacitinib, 42 patients (4.2%) used etanercept, 18 patients (1.8%) used rituximab, 53 patients (5.3%) used certolizumab, 3 patients (0.3%) used abatacept, 12 patients (1.2%) used secukinumab, 2 patients (0.2%) used ustekinumab, 10 patients (1%) used cyclophosphamide, 19 patients (1.9%) used golimumab, 16 patients (1.6%) used anakinra, and 8 patients (0.8%) used canakinumab. Two hundred patients (20%) used colchicine during pregnancy, 174 patients (17.4%) used HCQ during pregnancy, 2 patients (0.2%) used methotrexate during pregnancy, 13 patients (1.3%) used sulfasalazine during pregnancy, 27 patients (2.7%) used steroid preparations during pregnancy, 55 patients (5.5%) used azathioprine during pregnancy, 279 patients (27.9%) used NSAIDs during pregnancy, 31 patients (3.1%) used adalimumab during pregnancy, 14 patients (1.4%) used etanercept during pregnancy, 38 patients (3.8%) used certolizumab during pregnancy, and 17 patients (1.7%) used anakinra during pregnancy (Table 1).

Seven hundred twenty patients (72%) had experienced pregnancy before diagnosis; the median number of pregnancies was 2 (min 1-max 11). Five hundred seventeen patients (51.7%) had pregnancies after diagnosis; the median number of pregnancies was 1 (min 1-max 6). Eighty eight patients had abortus before diagnosis; the median abortus was 2 (min 1-max 7). Thirty nine patients had abortus after diagnosis; the median abortus was 1 (min 1-max 4). Nine hundred fifty seven patients had live births; the median birth was 2 (min 1-max 5). Sixty nine patients underwent curettage; the median number of curettages was 1 (min 1-max 3). Fourty three patients (4.3%) were unable to have children (Table 2).

The relationship between patients' pregnancy, abortion, curettage, live birth status and numbers before and after diagnosis,

Table 1. Demographic characteristics of patients

Age (year), Mean±*SD, (min-max)	37±6.16 (19-45)
Methotrexate using, (n %)	144 (14.4%)
Duloxetine using, (n %)	127 (12.7%)
Hydroxychloroquine using, (n %)	340 (34%)
Sulfasalazine using, (n %)	127 (12.7%)
Colchicine using, (n %)	426 (42.6%)
**NSAID using, (n %)	757 (75.7%)
Leflunomid using, (n %)	54 (5.4%)
Glukokortikoid using, (n %)	259 (25.9%)
Azatiopurin using, (n %)	103 (10.3%)
***MMF using, (n %)	14 (1.4%)
Adalimumab using, (n %)	88 (8.8%)
Infliximab using, (n %)	58 (5.8%)
Certolizumab using, (n %)	53 (5.3%)
Golimumab using, (n %)	19 (1.9%)
Etanercept using, (n %)	42 (4.2%)
Secukinumab using, (n %)	12 (1.2%)
Tocilizumab using, (n %)	8 (0.8%)
Tofacitinib using, (n %)	3 (0.3%)
Rituximab using, (n %)	18 (1.8%)
Abatacept using, (n %)	3 (0.3%)
Ustekinumab using, (n %)	2 (0.2%)
Kanakinumab using, (n %)	8 (0.8%)
Anakinra using, (n %)	16 (1.6%)
Cyclophosphamide using, (n %)	10 (1%)
‡FMF, (n %)	224 (22.4%)
Behcet's disease, (n %)	169 (16.9%)
‡‡RA, (n %)	197 (19.7%)
¶AS, (n %)	274 (27.4%)
¶¶SLE, (n %)	105 (10.5%)
†PSA, (n %)	59 (5.9%)
Sjogren syndrome, (n %)	60 (6%)
††APS, (n %)	29 (2.9%)
Fibromyalgia, (n %)	146 (14.6%)
Vasculitis (large vessel and small vessel), (n %)	7 (0.7%)
Systemic sclerosis, (n %)	37 (3.7%)
Gout, (n %)	2 (0.2%)
Mastitis, (n %)	1 (0.1%)
Still's disease, (n %)	3 (0.3%)
Sarcoidosis, (n %)	1 (0.1%)
Myositis, (n %)	1 (0.1%)
Using sulfasalazine during pregnancy, (n %)	13 (1.3%)
Using colchicine during pregnancy, (n %)	200 (20%)
Using hydroxychloroquine during pregnancy, (n %)	174 (17.4%)
Using methotrexate during pregnancy, (n %)	2 (0.2%)
Glucocorticoids during pregnancy using, (n %)	27 (2.7%)
Using azathioprine during pregnancy, (n %)	55 (5.5%)
Using **NSAIDs during pregnancy, (n %)	279 (27.9%)
Using etanercept during pregnancy, (n %)	14 (1.4%)
Using adalimumab during pregnancy, (n %)	31 (3.1%)
Using certolizumab during pregnancy, (n %)	38 (3.8%)
Using anakinra during pregnancy, (n %)	17 (1.7%)

*: Standard deviation, **: Non-steroidal anti-inflammatory drugs, ***: Mycophenolate mofetil, ‡: Familial Mediterranean fever, ‡‡: Rheumatoid arthritis, ¶: Ankylosing sponylitis, ¶¶: Systemic lupus erythematosus, †: Psoriatic arthritis, ††: Antiphospholipid antibody syndrome

and their rheumatological diseases and medications used. It was determined that the number of pregnancies in patients decreased after the use of colchicine, HCQ, sulfasalazine, methotrexate, leflunomide, glucocorticoids, NSAIDs, adalimumab, infliximab, golimumab, and anakinra (Table 3). The abortions in the cases were observed after discontinuation of colchicine, HCQ, acetylsalicylic acid, and low molecular weight heparin (Table 4). The number of patients who became pregnant after diagnosis increased by 0.76 times [95% confidence interval (CI): 0.66-0.89] with the use of colchicine, and by 0.153 times (95% CI: 0.035-0.66) with the use of anakinra; it decreased by 1.82 times (95% CI: 1.06-3.11) with the use of leflunomide. It was observed that the number of pregnancies after diagnosis decreased with the use of methotrexate. In patients with APS and SLE, the number of pregnancies after diagnosis was lower compared to before diagnosis. It was observed that the number of abortions before diagnosis increased in the presence of APS and SLE diagnoses. The likelihood of developing eclampsia among pregnancy complications was found to be 0.016 times higher in APS cases (95% CI: 0.005-0.051) and 0.087 times higher in SLE cases (95% CI: 0.061-0.122). It was determined that the number of curettages increased in the presence of an APS diagnosis, while the number of patients giving live births decreased by 3.56 times (95% CI: 1.29-9.78). Among those using methotrexate, the number of patients undergoing curettage was found to have increased by 0.63 times (95% CI: 0.39-0.99). In all cases using colchicine, an increase in the number of live births was recorded with the use of colchicine during pregnancy. It was determined that the number of patients who had live births with the use of HCQ during pregnancy increased by 0.39 times (95% CI: 0.13-0.99) (Table 5).

Data on Medication Use During Pregnancy

The average dose of colchicine used during pregnancy was 1.37 mg/day, 1 g/day for sulfasalazine, 400 mg/day for HCQ, 6 mg/day for prednisolone, and 130 mg/day for azathioprine. The average dose of adalimumab used during pregnancy was 40 mg/2 weeks, 50 mg/week for etanercept, 100 mg/day for anakinra, and 200 mg/2 weeks for certolizumab pegol. The average duration of colchicine used during pregnancy was 18.5 years (222 months), 2.5 years (30 months) for sulfasalazine, 6 years (72 months) for HCQ, 3.5 months for prednisolone, and 2 years (24 months) for azathioprine. The average duration of adalimumab used during

Table 2. Pregnancy, abortus, curettage and live birth status of the patients and the number of pregnancies, abortus and curettages

	Pregnant before diagnosis	Getting pregnant after diagnosis	Abortus before diagnosis	Abortus after diagnosis	Live birth	Curettage	Never having a pregnancy (infertility)
Number of patients	720	517	88	39	957	69	43
(%n)	72%	51.7%	8.8%	3.9%	95.7%	6.9%	4.3%
Median (min-max)	2 (1-11)	1 (1-6)	2 (1-7)	1 (1-4)	2 (1-5)	1 (1-3)	0

Table 3. Difference between the number of pregnancies of patients before and after the medication

	Number of pregnancies after medication-number of pregnancies before medication z-score	p-value*
Colchicine	-3.74	0.000
Hydroxychloroquine	-6.97	0.000
Sulfasalazine	-3.43	0.000
Methotrexate	-5.09	0.000
Leflunomide	-3.56	0.000
Glucocorticoid	-4.93	0.000
**NSAID	-8.5	0.000
Adalimumab	-2.6	0.000
Infliximab	-2.24	0.0025
Golimumab	-2.77	0.005
Anakinra	-2.39	0.017

*:<0.05 significant, **: Non-steroidal anti-inflammatory drugs

Table 4. Difference between the number of abortus of patients before and after the medication

	Post-medication abortus counts-pre-medication abortus counts z-score	p-value*
Colchicine	-14.2	0.000
Hydroxychloroquine	-12.1	0.000
Acetylsalicylic acid	-10.8	0.000
****LMWH**	-2	0.046

*: 0.05 and below is significant, **: Low molecular weight heparin

pregnancy was 1.5 years (18 months), 2 years (24 months) for etanercept, 10 months for anakinra, and 6 months for certolizumab pegol (Table 6).

Since the patients informed us of their desire for pregnancy, all biological agents except adalimumab, etanercept, certolizumab, and anakinra were discontinued 3 months prior. For leflunomide, this period was 2 years, and for methotrexate, it was 6 months. NSAIDs were discontinued in the 32nd week of pregnancy.

Data on Infertility

We had 10 cases who were treated with cyclophosphamide due to vital organ involvement, and all of these patients were in the infertility group. Four patients had SLE-related nephritis and central nervous system involvement, 2 patients had Behçet's disease with pulmonary artery involvement, 2 patients had anti-neutrophil cytoplasmic antibody-negative small vessel vasculitis (Henoch-Schonlein purpura with gastrointestinal and renal involvement), and 2 patients had catastrophic antiphospholipid syndrome. SLE cases received a total of 6 doses of 500 mg intravenous (IV) cyclophosphamide every 2 weeks, while the vasculitis cases received IV cyclophosphamide at a dose of 15 mg/kg (between 500-1000 mg) once a month for 6 months. Patients were informed about the matter, consent was obtained, and the option of egg preservation was offered.

Discussion

In this article, where we investigate the impact of pregnancy and fertility on medication use and preferences in rheumatological diseases, we should mention the colchicine used by women of childbearing age who are frequently monitored in our clinic, due to our country being in the FMF belt and our city of Sivas being one of the cities where FMF is most commonly seen (12).

Colchicine is widely used in the treatment of rheumatological diseases, especially FMF. There are studies in the literature regarding the effects of colchicine on fertilization and pregnancy. As an example, in the review by Both et al. (13), who examined 83 articles, it was concluded that colchicine did not have an adverse effect on reproductive functions; on the contrary, it was found that untreated FMF could lead to infertility due to amyloid accumulation in the testes and ovaries. In addition, it was reported that no serious complications developed with the use of colchicine during pregnancy. In the meta-analysis conducted by Indraratna et al. (14) in Australia, it was shown that the use of colchicine during pregnancy was not associated with an increased risk of abortus, and due to the high likelihood of recurrence of FMF, which could lead to teratogenicity and systemic amyloidosis during pregnancy if left untreated, colchicine should not be discontinued. Additionally, among pregnant women diagnosed with FMF, those who used the medication were compared to those who did not; it was found that the incidence of abortus was significantly lower in those who used the medication. However, although the incidence of preterm birth and low birth weight was found to be increased in pregnant women with FMF who used colchicine, this situation was attributed to the disease itself. In our study, the number of pregnancies and fertilization status before and after colchicine treatment were evaluated in patients diagnosed with rheumatological diseases who were using colchicine. A significant increase was observed in the number of

Table 5. Chi-square, Wilcoxon, Mann-Whitney U analysis of the number of patients who became pregnant before and after diagnosis, the number of pregnancies, abortus, curettages, the number of patients who performed curettage, the number of patients who experienced eclampsia complications during pregnancy, and the number of patients who gave birth live, according to rheumatological diseases and drugs

Chi-square	Colchicine use *OR %95 confidence range, **p-value	Anakinra use *OR %95 confidence range, **p-value	Leflunomide use *OR %95 confidence range, **p value	Mann-Whitney U test	Methotrexate use *z-score, **p-value
Number of patients who became pregnant after diagnosis	***OR:0.768 (0.66-0.89) **p<0.000**	***OR:0.153 (0.035-0.66) **p<0.004**	***OR:-1.82 (1.06-3.11) **p=0.035**	**Number of pregnancies after diagnosis**	***z=-1.813 **p=0.05**
Wilcoxon	**#APS **p-value**		**††SLE **p-value**		
Number of pregnancies after medication-number of pregnancies before medication (z-score)	**z=-3.20 **p=0.000**		**z=-3.24 **p=0.001**		
Mann-Whitney U test	**#APS *z-score, **p-value**		**††SLE *z-score, **p-value**		
Number of abortus before diagnosis	***z=14.5 **p<0.000**		***z=12.9 **p=0.000**		
Chi-square	**#APS *OR %95 confidence range **p-value**		**††SLE *OR %95 confidence range **p-value**		
Number of patients developing eclampsia complications during pregnancy	***OR: 0.016 (0.005-0.051) **p=0.000**		***OR: 0.087 (0.061-0.122) **p=0.00**		
Mann-Whitney U test	**#APS, *z-score, **p-value**				
Number of curettage	***Z:-3.74 **p=0.000**				
Chi-square	**#APS, *OR %95 confidence range, **p-value**				
Number of patients giving live birth	***OR: -3.56 (1.29-9.78), **p=0.032**				
Chi-square	**Methotrexate use, *OR %95 confidence range, **p-value**				
Number of patients who had curettage	***OR: 0.63 (0.39-0.99), **p=0.05**				
Mann-Whitney U	**Use of colchicine during pregnancy in all cases using colchicine**				
Number of live births	****p-value: 0.047**				
Cox regression	**Hydroxychloroquine use in pregnancy *OR %95 confidence range, **p-value**				
Number of patients giving live birth	***OR: 0.39 (0.13-0.99), **p=0.05**				

*: Odds ratio, **: 0.05 and below is significant, ††: Systemic lupus erythematosus, #: Antiphospholipid antibody syndrome

patients who became pregnant after treatment. However, in cases using colchicine, the number of pregnancies after colchicine use was lower than the number of pregnancies before colchicine use. The reason for this may be that the cases, after becoming aware of their disease and considering the challenging process, had a desire to experience fewer pregnancies, or it may be due to our recommendation to the patients to postpone pregnancy until FMF remission is expected. However, among the cases using colchicine, there was a significant difference in the number of live births between those who used colchicine during pregnancy and those who did not; the number was higher in the pregnant women who used colchicine. Again, a significant decrease in the number of abortions was observed in cases using colchicine. These results were indicative of colchicine's positive effect on fertilization and supported the necessity of continuing treatment in pregnant women diagnosed with FMF.

Among the studies in the literature on the use of anakinra and kanakinumab during pregnancy, which are the main biological agents used in the treatment of FMF, the study conducted

Table 6. Doses and durations of medications used by patients during pregnancy

	Doses (mean)	Usage period (mean) (months)
Colchicine	1.37 mg/day	222
Hydroxychloroquine	400 mg/day	72
Sulfasalazine	1 g/day	30
Prednisolone	6 mg/day	3.5
Azathioprine	130 mg/day	24
Adalimumab	40 mg/2 weeks	18
Etanercept	50 mg/week	24
Certolizumab pegol	200 mg/2 weeks	6
Anakinra	100 mg/day	10

by Youngstein et al. (15) with 31 pregnant women with autoinflammatory diseases from seven countries stands out. In this study, due to autoinflammatory diseases such as FMF, adult-onset Still's disease, and tumor necrosis factor receptor-associated periodic syndrome, no serious infections were observed in either the mother or the fetus during pregnancy or after childbirth in pregnant women using either anakinra or canakinumab. In addition, although unilateral renal agenesis and ectopic neurohypophysis were detected in the fetus of a pregnant woman who used anakinra, the other pregnancies resulted in the birth of healthy fetuses without any complications. However, in terms of anakinra, this is the second case of renal agenesis in the literature. Therefore, they reported that this should be taken into consideration and that this patient had used a high dose of anakinra. In pregnancies exposed to canakinumab, no complications were noted. Nevertheless, Youngstein et al. (15) preferred anakinra over canakinumab for use during pregnancy due to its greater evidence and shorter half-life. They argued that kanakinumab should not be used from the 22nd week of pregnancy onwards due to concerns that it could lead to infections in newborns. They emphasized that in pregnant women with autoinflammatory diseases, the cessation of interleukin-1 (IL-1) inhibitors would lead to increased chronic inflammation, resulting in a rise in pregnancy complications, and that infertility could develop before pregnancy due to the effects of cytokines and amyloidosis (15). In a review prepared by Brien et al. (16) in Canada, 69 pregnancies in which anakinra was used were examined, and live births occurred without any complications in 63.8% of them. In contrast, 17.4% resulted in premature birth, while the others experienced vaginal bleeding, hypertension, and oligohydramnios. In one case, stillbirth occurred. While 90.9% of the 11 pregnancies using canakinumab resulted in term births, gestational diabetes mellitus was reported in only one case. Brien et al. (16) noted that the rate of preterm births among these cases was lower than reported in the literature, and they did not attribute this solely to the existing condition. However, they reported that the mechanisms explaining the causation of premature birth by IL-1 inhibitors were open to research. In our study, an increase in the number of patients who became pregnant with the use of anakinra was detected; this was interpreted as increased fertilization due to decreased inflammation. Despite this, similar to colchicine, the number of pregnancies after anakinra in patients using anakinra was lower than the number of pregnancies before the use of the drug. In our study, it was found that only one out of 17 pregnant women using anakinra experienced a abortus in the first trimester. It was observed that this patient with FMF was in remission during pregnancy. However, the fetal anomaly was not known. In addition, it was determined that 4 cases had preterm births due to eclampsia, and these cases were found to have proteinuria and hypertension due to FMF renal involvement. In one case, gestational hypertension was found. Although these data were supportive of the literature, they were not statistically significant. The reason for this may be the small number of patients using anakinra during pregnancy. We did not have any patients using canakinumab during pregnancy. Our recommendation of planned pregnancy for female patients using canakinumab during the reproductive period and our transition to anakinra for patients who wished to become pregnant contributed to the occurrence of this situation.

If we examine methotrexate and leflunomide, which are among the most commonly used drugs in the treatment of RA, the review by Janssen and Genta (17) suggests that methotrexate does not have a negative effect on fertilization, but due to its embryotoxic effects, contraception is recommended. The effects of methotrexate on the fetus are described as craniofacial malformations, anencephaly, limb defects, hydrocephalus, and meningomyelocele (17). In the review by Bilgen et al. (6), it is stated that methotrexate should be discontinued 3 months before conception. In Germany, Weber-Schoendorfer et al. (18) observed an increase in spontaneous abortions in a study conducted with 65 pregnant women who were exposed to leflunomide. Therefore, they emphasized that in female patients using leflunomide, the drug plasma concentration should be below 0.02 mg/L before pregnancy; for this, pregnancy should be postponed until 2 years after stopping leflunomide, and in cases where this period is not met, drug elimination with cholestyramine should be performed. In our study, a decrease in the number of pregnancies among patients using methotrexate and leflunomide was observed. The reason for this may be the long duration of 2 years that women using leflunomide need to wait before becoming pregnant. In our study, there were 2 patients who used methotrexate during pregnancy. While one patient experienced a spontaneous abortus, it was learned that the other patient underwent a curettage. Besides this, it was found that the incidence of curettage increased in pregnant women who had a break of less than 3 months from methotrexate before becoming pregnant. We did not have any patients using leflunomide during pregnancy. The reason for this was seen as the interruption of the medication due to the desire for pregnancy among patients using leflunomide during the reproductive period.

Among the drugs used in the treatment of rheumatological diseases, cyclophosphamide stands out as an agent proven to cause infertility. In the literature, as noted by Mok (19), the use of cyclophosphamide was associated with premature ovarian insufficiency. In addition, Gajjar et al. (20) pointed out that due

to the determination of oocyte count during fetal life, the use of cyclophosphamide in women at higher doses and older ages might lead to irreversible infertility. In our study, there were 10 patients who used cyclophosphamide, and all of these patients were infertile.

Among rheumatic diseases, the conditions where pregnancy complications (for both the mother and fetus) are most frequently encountered are SLE and APS (2). It is known that recurrent abortus are included in the diagnostic criteria for APS (21). In women with SLE (with or without APS), the rates of prematurity, pre-eclampsia and eclampsia, hemolysis, elevated liver enzyme levels, low platelet count (hemolysis, elevated liver enzymes, low platelet count syndrome), maternal hypertension, and nephritis are increasing (2). In accordance with the literature, our study found that in patients diagnosed with APS and SLE, there was a decrease in the number of pregnancies, along with an increase in the rates of eclampsia, abortus and curettages in pregnancies before the diagnosis. In addition, we found that the number of patients with a primary diagnosis of APS who had live births decreased. However, in these cases, lower numbers of abortions were observed in pregnancies that developed after the diagnosis. With the thought that the agents used in treatment might be the reason for this difference, we specifically focused on HCQ. The discontinuation of HCQ treatment in pregnant women diagnosed with SLE and APS is associated with an increased risk of SLE flares during pregnancy. It was suggested that HCQ had a beneficial effect on maternal disease activity during pregnancy (2). In the review published by Abarientos et al. (22), it was argued that the use of HCQ during pregnancy was not associated with the risks of spontaneous abortions, congenital defects, fetal death, prematurity, and decreased live birth rates. However, in a cohort study conducted by Huybrechts et al. (23) in England, which investigated 2,045 pregnant women exposed to HCQ, it was reported that exposure to the drug in the first trimester caused a slight increase in malformations, including cleft palate, cleft lip, pulmonary hypoplasia, and urinary tract anomalies, independent of the presence of underlying rheumatological diseases or concurrent steroid use. Nevertheless, they concluded that in pregnant women diagnosed with SLE and RA, the benefits of treatment would outweigh these outcomes, the drug's half-life would be more than a month even if discontinued, and due to the risk of encountering pre-eclampsia, heart defects, fetal distress, and fetal deaths associated with increased disease activity, HCQ treatment should not be altered. In our study, it was observed that the use of HCQ before pregnancy was associated with a decrease in the number of pregnancies and the number of abortions among patients. The reason for the decrease in the number of pregnancies may be that the patients avoided becoming pregnant due to medication use or that we recommended delaying pregnancy to the patients to wait for SLE remission. In our study, it was found that the use of HCQ during pregnancy reduced spontaneous abortions and increased the number of patients who had live births.

In conclusion, we observed that the number of patients who became pregnant increased after the use of colchicine and anakinra in those diagnosed with rheumatological diseases, the number of patients who became pregnant decreased with the use of leflunomide, and the number of pregnancies decreased after the use of methotrexate. We found that the number of abortions and curettages before diagnosis increased in patients with diagnoses of APS and SLE, while the number of live births decreased.

Study Limitations

The positive aspects of our study are that there are more reviews than research articles in the literature on this topic, and we are among the few who have conducted such articles; however, the weaknesses may include not recording postnatal fetal anomalies and not examining the pathological diagnoses involved in the etiology of abortions. Although it was a single-center study, we avoided practices that could be considered biases, such as excluding patients who had abortus or underwent curettage from the study.

Conclusion

It should be considered that women of reproductive age with rheumatic diseases may desire pregnancy and may present to the clinic with either planned or unplanned pregnancies during their follow-ups, and accordingly, efforts should be made to avoid medications that could potentially cause infertility as much as possible. Patients should be thoroughly informed about the effects of their disease and the medications they are using.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval no: 2021-10/16, date: 20.10.2021).

Informed Consent: Informed consent was obtained in writing from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., Concept: B.K., B.N.Ö., M.F.A., Design: B.K., İ.Y., A.Ş., Data Collection or Processing: B.K., N.Ç.Ç., Bu.K., İ.Y., G.P., H.Ş.E., M.Ş.K., M.Y., B.N.Ö., M.F.A., Analysis or Interpretation: B.K., M.F.A., A.Ş., Literature Search: B.K., G.P., H.Ş.E., Writing: B.K., Bu.K., M.F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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