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ORIGINAL RESEARCH

Medication utilisation trends during pregnancy and factors influencing adverse pregnancy outcomes in patients with rheumatoid arthritis

Yeo-Jin Song ,[1,2] Soo-Kyung Cho ,[1,2] Yu-Seon Jung,[3] Sun-Young Jung,[3] Jihyun Keum,[4] Eunwoo Nam,[2] Yoon-Kyoung Sung ,[1,2] Dae Hyun Yoo[1,2]

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[1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea
[2]Hanyang University Institute for Rheumatology Research, Seoul, Korea
[3]College of Pharmacy, Chung-Ang University, Seoul, Korea
[4]Department of Obstetrics and Gynecology, College of Medicine, Hanyang University, Seoul, Korea

Correspondence to
Dr Yoon-Kyoung Sung; sungyk@hanyang.ac.kr

Dr Dae Hyun Yoo; dhyoo@hanyang.ac.kr

ABSTRACT

Objectives We aimed to investigate medication utilisation trends during pregnancy and identify factors associated with adverse pregnancy outcomes (APOs) in patients with rheumatoid arthritis (RA).

Methods Female patients with RA aged 20–50 years were identified from the Korean national health insurance database between 2010 and 2020. Pregnancy episodes were divided into two groups according to pregnancy outcome: the delivery group and the APO group (abortion and stillbirth). The characteristics and medication utilisation patterns were compared between the two groups, and multivariable logistic regression analysis was conducted to identify the factors associated with APOs.

Results A total of 5728 pregnancy episodes were included, comprising 4576 delivery episodes and 1152 APO episodes. The mean maternal age for all pregnancy episodes was 33.7 years; 33.3 years in the delivery group and 33.7 years in the APO group. Hydroxychloroquine was the most commonly used conventional synthetic disease-modifying antirheumatic drug (DMARD) during the preconception period and pregnancy in both groups. The prescription rate of all DMARDs decreased rapidly during pregnancy. In the multivariable analysis, use of methotrexate (adjusted OR (aOR): 2.14, 95% CI 1.57 to 2.92) and leflunomide (aOR: 2.68, 95% CI 1.39 to 5.15) within 3 months before conception was associated with APOs.

Conclusion Methotrexate and leflunomide are associated with an increased possibility of APOs, emphasising the importance of appropriate medication adjustment when planning for pregnancy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis (RA) have less favourable pregnancy outcomes compared with the general population.
⇒ Female patients with RA who are planning for pregnancy and lactation have limited treatment options, such as avoiding methotrexate and leflunomide.

WHAT THIS STUDY ADDS

⇒ Differences in drug use patterns were observed between patients who experienced delivery and those who experienced abortion and stillbirth.
⇒ Methotrexate and leflunomide treatment within the 3 months prior to conception was associated with a higher possibility of abortion and stillbirth.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with RA should consult their physicians to plan for pregnancy, including by discontinuing teratogenic drugs, and continue medical supervision to monitor and control disease activity during pregnancy.

INTRODUCTION

Rheumatoid arthritis (RA) is more common in female patients, with a female-to-male ratio ranging from approximately 2:1 to 4:1, while the prevalence of RA among women of childbearing age reaches approximately 0.5%–1.0%.[1–3] Therefore, pregnancy and childbirth naturally require attention during treatment for female patients with RA.

Compared with healthy controls, patients with RA have been reported to experience difficulty in conceiving and a lower number of births.[4–6] Factors associated with prolonged time to pregnancy include older age, nulliparity, high RA disease activity, use of non-steroidal anti-inflammatory drugs (NSAIDs) and daily use of prednisone >7.5 mg.[7] Prostaglandins play a crucial role in ovulation and blastocyst implantation, both of which may be disrupted by NSAIDs through inhibition of prostaglandin production.[8 9] Glucocorticoids are known to suppress the hypothalamic–pituitary–ovarian axis and affect ovarian physiology and periconceptual uterine growth.[8 10]

Patients with RA who are planning for pregnancy or lactation have limited treatment

options. Methotrexate (MTX) is teratogenic in humans, and MTX treatment in the 3 months prior to conception is associated with a high risk of pregnancy loss.[11] According to the European Alliance of Associations for Rheumatology recommendations and the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines, MTX should be stopped 3 months before conception.[12 13] Leflunomide (LEF) should also be avoided during pregnancy, and cholestyramine washout is recommended.[12] Other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including hydroxychloroquine (HCQ), sulfasalazine (SSZ), and tacrolimus (TAC), are not inhibited throughout pregnancy.[12] Glucocorticoids can also be continued at the lowest effective dose throughout pregnancy. However, the use of NSAIDs is not recommended in the third trimester of pregnancy.[8 14] Regarding biological DMARDs, the recommended timing of drug discontinuation varies across the literature. According to BSR and BHPR guidelines, infliximab should be stopped at 16 weeks, and etanercept and adalimumab should be stopped before the third trimester, while certolizumab can be administered throughout the entire pregnancy.[12] According to the recently published American College of Rheumatology Guideline in 2020, tumour necrosis factor (TNF) inhibitor therapy with infliximab, etanercept, adalimumab or golimumab prior to and during pregnancy is conditionally recommended.[15] Currently, there are insufficient data regarding the safety of abatacept, tocilizumab and Janus kinase (JAK) inhibitors during pregnancy.[8 12 13]

In Korea, there is a lack of studies on pregnant patients with RA. A nationwide population-based study of Korean women with rheumatic diseases reported an increased risk of pregnancy complications, but there has been no large study of patients with RA.[16] Therefore, in this study, we investigated medication utilisation patterns during pregnancy and identified factors associated with adverse pregnancy outcomes (APOs) in patients with RA in Korea.

METHODS

Data source and study population

In Korea, the National Health Insurance (NHI) system covers 97% of the population, and the remaining population consists of Medical Aid recipients, as well as temporary or illegal residents.[17] The NHI database includes sociodemographic information, healthcare utilisation and national health examination results.[18] Using the NHI database, we extracted data on female patients with RA who claimed insurance between 2010 and 2020. Patients with RA were defined as having diagnostic codes for RA and prescription codes for any DMARDs, an operational definition of RA validated by a previous study.[19] Female patients aged between 20 and 50 years were selected, among whom, those diagnosed with ankylosing spondylitis, psoriasis, psoriatic arthritis, inflammatory bowel disease, juvenile idiopathic arthritis, or systemic lupus erythematosus were excluded.

Definitions of pregnancy episodes and outcomes

Patients with at least one code related to pregnancy between 2010 and 2020 were selected, and each pregnancy episode was considered for eligibility. Pregnancy episodes were defined by the presence of both diagnostic codes of pregnancy confirmation and procedure or diagnostic codes of pregnancy outcomes, including delivery and APOs (abortion and stillbirth). Delivery was defined using procedure codes, and both abortion and stillbirth were defined using diagnostic codes (online supplemental table 1).

Study design

Because an accurate conception date could not be identified from the NHI data, we estimated the conception date inversely from the date of pregnancy outcome. For delivery episodes, the conception date was defined as 39 weeks (273 days) before the procedure code of delivery or 35 weeks (245 days) before the diagnostic codes of preterm delivery.[20] For APO episodes, the conception date was defined as the date 10 weeks (70 days) before the diagnostic code of abortion, or the date 28 weeks (196 days) before the diagnostic codes of stillbirth. The process of defining the conception date was conducted in consultation with an obstetrician. To validate the estimated conception date, we calculated the mean interval between the conception date and the diagnostic code of pregnancy confirmation.

We excluded invalid pregnancy episodes, such as episodes with maternal age <20 or >50 years, with calculated pregnancy lasting longer than 42 weeks, and without diagnostic codes of pregnancy confirmation. Pregnancy episodes before RA diagnosis were also excluded, as were episodes with insufficient data before and after pregnancy.

Pregnancy episodes were divided into delivery and APO groups according to pregnancy outcome. The assumed conception date was defined as the index date. We compared the demographic and clinical characteristics of the two groups. Demographics included age, type of insurance, institution and household income. The type of institution indicates where insurance claims for RA were filed closest before and after pregnancy. Clinical characteristics included the period from RA diagnosis to pregnancy, comorbidities, Charlson Comorbidity Index score and healthcare utilisation. Comorbidities and healthcare utilisation were investigated using data obtained within a year before the conception date.

The pattern of medication use, including csDMARDs, targeted therapies (TNF inhibitors, non-TNF inhibitors and JAK inhibitors), NSAIDs and oral glucocorticoids, was investigated in both groups. The usage of DMARDs and oral glucocorticoids was defined as cases with more than one prescription of each drug from the NHI data. The NSAID usage was defined by cases with prescriptions

lasting more than 7 consecutive days since NSAIDs are frequently prescribed for purposes other than RA. The analysis period was 1 year before conception, during pregnancy and 1 year after pregnancy (online supplemental figure 1). We considered medication use before pregnancy to be the most important, so the year before conception was divided into 4 groups of 3 months and investigated in detail. The changes in drug use for each period in the two groups are presented as graphs, as are the annual changes in drug use for the delivery group.

We then identified associated factors for APOs in patients with RA. Demographic and clinical characteristics on the index date were included as variables. The use of drugs in the 3 months prior to conception, that were considered to have the greatest impact on pregnancy, was also included in the analysis. Additionally, the presence of any hospital visit for RA during pregnancy was included as a variable to assess whether the patient was under a doctor's care for RA during pregnancy. This variable was determined based on the presence of insurance claims for the diagnostic code of RA during pregnancy at least once during the first 12 weeks from conception. Whether the pregnancy episode was one of multiple pregnancies or a single pregnancy was also included as a variable.

Statistical analysis

To compare the baseline characteristics between the two groups, we performed the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Additionally, the χ^2 test or Fisher's exact test was used to compare the pattern of medication use within the 3 months before conception. We used a multivariable logistic regression model adjusting for age, economic status, healthcare utilisation, seropositivity, comorbidities, multiple pregnancy status and drug usage to identify the factors associated with APOs. We excluded missing data from the multivariable analysis, but we also conducted a sensitivity analysis that included them.

All analyses were performed using SAS V.9.4 (SAS Institute), and p values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 5728 pregnancy episodes were included in the study, comprising 4576 delivery episodes and 1152 APO episodes (figure 1). The mean interval between the conception date and the diagnostic code of pregnancy confirmation was 37.7 days. The mean maternal age of total pregnancy episodes was 33.7±4.1 years, which was higher in the APO group than that in the delivery group (33.7±4.5 vs 33.3±3.8 years, p<0.001) (table 1). The proportion of Medicaid was higher in the APO group (1.5% vs 0.7%, p=0.011). The period from RA diagnosis to pregnancy was 3.2±2.3 years in all pregnancies and was similar between the two groups. Several comorbidities,

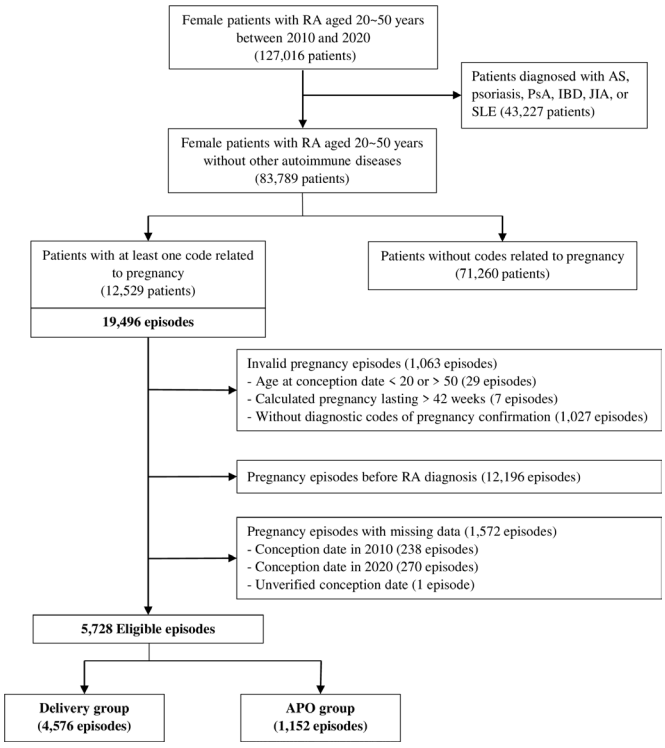

Figure 1 Flow chart of patient selection. APO, adverse pregnancy outcome; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

including cerebrovascular disease, chronic pulmonary disease, and diabetes mellitus, were more frequent in the APO group than in the delivery group. Additionally, there was no significant difference in the frequency of healthcare utilisation within a year before conception. Additional information on baseline characteristics is presented in online supplemental table 2.

Pattern of medication use according to pregnancy outcome

The pattern of medication use from 1 year before the conception date to a year after pregnancy termination in the delivery and APO groups is presented in figure 2. In the delivery group, use of MTX and LEF was stopped earlier before pregnancy than in the APO group, and the prescription rates of both drugs during pregnancy were nearly zero in the delivery group. The prescription of other csDMARDs, NSAIDs and oral glucocorticoids also decreased near the conception date. All medication use increased rapidly in the year after delivery or termination of pregnancy.

The two groups showed differences in medication use in the 3 months before conception (table 2). MTX and LEF treatment were more frequent in the APO group, as was the use of NSAIDs. Targeted therapies were prescribed for only 2.8% and 3.6% in the delivery and APO groups, respectively, and the rate of csDMARD use combined with targeted therapy was 40.7%. The two groups showed no significant differences in targeted therapies. Oral glucocorticoid use was similar between the delivery and APO

Table 1 Baseline characteristics of the study population at the date of conception

Variables	All pregnancies (n=5728)	Delivery (n=4576)	APO (n=1152)	P value
Age, years	33.7±4.1	33.3±3.8	33.7±4.5	<0.001
Type of insurance				0.011
National Health Insurance	5679 (99.1)	4544 (99.3)	1135 (98.5)	
Medicaid	49 (0.9)	32 (0.7)	17 (1.5)	
Type of institution*				<0.001
Tertiary referral hospital	2408 (42.1)	1958 (42.8)	450 (39.1)	
General hospital	1281 (22.4)	1056 (23.1)	225 (19.5)	
Community hospital/clinic	2039 (35.6)	1562 (34.1)	477 (41.4)	
Income (n=5672, 4530, 1142)				0.03
First quartile	942 (16.4)	723 (15.8)	219 (19.0)	
Second quartile	1318 (23.0)	1081 (23.6)	237 (20.6)	
Third quartile	2123 (37.1)	1708 (37.3)	415 (36.0)	
Fourth quartile	1289 (22.5)	1018 (22.2)	271 (23.5)	
Seopositivity				0.798
Seropositive	2616 (45.7)	2086 (45.6)	530 (46.0)	
Seronegative	3112 (54.3)	2490 (54.4)	622 (54.0)	
Period from RA diagnosis to pregnancy, years	3.2±2.3	3.2±2.3	3.3±2.4	0.539
Type of APO				N/A
Abortion			1122 (97.4)	
Stillbirth			30 (2.6)	
Comorbidities†				
Peripheral vascular disease	160 (2.8)	131 (2.9)	29 (2.5)	0.534
Cerebrovascular disease	34 (0.6)	20 (0.4)	14 (1.2)	0.002
Chronic pulmonary disease	1348 (23.5)	1046 (22.9)	302 (26.2)	0.014
Peptic ulcer disease	1121 (19.6)	885 (19.3)	236 (20.5)	0.358
Mild liver disease	779 (13.6)	617 (13.5)	162 (14.1)	0.584
Diabetes mellitus without complication	161 (2.8)	112 (2.4)	49 (4.3)	<0.001
Diabetes mellitus with complication	19 (0.3)	10 (0.2)	9 (0.8)	0.003
Any malignancy	85 (1.5)	64 (1.4)	21 (1.8)	0.282
CCI score	0.6±0.9	0.6±0.9	0.6±0.9	0.062
Healthcare utilisation†				
Hospitalisation	1174 (20.5)	914 (20.0)	259 (22.5)	0.062
Rheumatologist visits	2077 (36.3)	1654 (36.1)	423 (36.7)	0.542
Emergency department visits	842 (14.7)	658 (14.4)	184 (16.0)	0.172
Medication†				
Not used any DMARDs	3256 (56.8)	2620 (57.3)	636 (55.2)	0.21
Conventional synthetic DMARDs				
Methotrexate	1011 (17.7)	784 (17.1)	227 (19.7)	0.041
Leflunomide	159 (2.8)	112 (2.5)	47 (4.1)	0.003
Hydroxychloroquine	1660 (29.0)	1318 (28.8)	342 (29.7)	0.554
Sulfasalazine	807 (14.1)	673 (14.7)	134 (11.6)	0.007
Tacrolimus	173 (3.0)	132 (2.9)	41 (3.6)	0.232
Targeted therapies	217 (3.8)	168 (3.7)	49 (4.3)	0.355

Data are presented as numbers with percentages (%) or mean±SD.
*The institution of claims for RA closest to the conception date.
†Data within a year before the conception date were used.
APO, adverse pregnancy outcome; CCI, Charlson Comorbidity Index; DMARD, disease-modifying antirheumatic drug; N/A, not applicable; RA, rheumatoid arthritis.

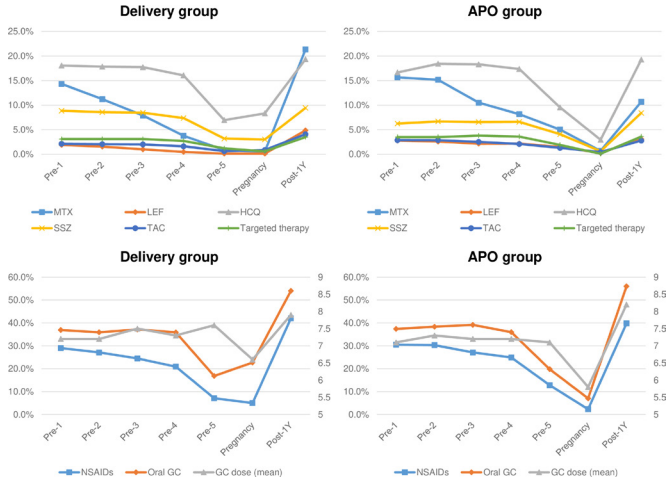

Figure 2 Pattern of medication use according to pregnancy outcome. GC doses are presented as prednisolone-equivalent dose (mg). (Pre-1: from 12 to 9 months before conception, Pre-2: from 9 to 6 months before conception, Pre-3: from 6–3 months before conception, Pre-4: in the 3 months prior to conception, Pre-5: from conception to pregnancy recognition, Pregnancy: during pregnancy, Post-1Y: in the year following pregnancy outcome.) APO, adverse pregnancy outcome; GC, glucocorticoid; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; SSZ, sulfasalazine; TAC, tacrolimus.

groups, but the mean dose of glucocorticoid was higher in the delivery group.

Pattern of medication use in the delivery group by year

The changes in drug use in the delivery group from 2011 to 2019 are presented in figure 3. During the preconception period, the rate of MTX use decreased, and the rate of LEF use was consistently low. The most commonly used csDMARDs were HCQ and SSZ, both of which showed decreasing prescription rates, as did NSAIDs and oral glucocorticoids, while both TAC and targeted therapy showed increasing prescription rates in the preconception period.

During pregnancy, HCQ was still the most commonly used csDMARD, followed by TAC and SSZ. Since 2018, targeted therapy has been more actively prescribed during pregnancy. NSAIDs and oral glucocorticoid use have been decreasing during pregnancy, but changes in the mean dose of oral glucocorticoids were irregular. After delivery, the use of all medications increased, including csDMARDs and targeted therapy. Changes in MTX and HCQ use were most prominent before and after delivery, but the prescription rates of both drugs have been decreasing by year.

Associated factors of APOs

In the multivariable analysis, patients aged 30–39 years (adjusted OR (aOR): 1.33, 95% CI 1.07 to 1.66) and 40–49 years (aOR: 5.35, 95% CI 4.16 to 6.89) were at higher odds of APOs than those aged 20–29 years (table 3). Additionally, patients who were being treated for RA in a community hospital or clinic had slightly higher odds of APOs compared with those in tertiary referral hospital (aOR: 1.33, 95% CI 1.13 to 1.56). MTX (aOR: 2.14, 95% CI 1.57 to 2.92) and LEF (aOR: 2.68, 95% CI 1.39 to 5.15) use in the 3 months prior to conception was associated with APOs. The other medications, including targeted therapy in the 3 months prior to conception, were unrelated to the risk of APOs. Multiple pregnancy status was not associated with APO in the multivariable model. The significant factors associated with APOs were similar in the sensitivity analysis focusing solely on first pregnancies, though the effect of LEF use became marginally significant (online supplemental table 3). The income variable was the only one with missing data, and the sensitivity analysis that included missing data is presented in online supplemental table 4.

DISCUSSION

According to our findings, HCQ was the most commonly used csDMARD before and during pregnancy in both groups, and the use of TAC has been increasing recently. The delivery and APO groups exhibited differences in the pattern of medication use. MTX and LEF treatment was significantly associated with APOs in the multivariable analysis.

Safety is the most important factor in determining drug use during pregnancy. The guidelines suggest the safety of csDMARDs, except MTX and LEF, and recommend that these safe csDMARDs can be continued throughout pregnancy.[12 13] Our study showed that MTX and LEF were stopped appropriately in advance in the delivery group, with decreasing prescriptions of them within 3 months before conception in the real world. HCQ and SSZ were the most frequently prescribed csDMARDs, and there may be a perception among physicians that these drugs are most well known to be safe. Although even the use of HCQ and SSZ has decreased over the years before and after pregnancy, TAC use has been increasing in recent years. TAC is prescribed for RA treatment mainly in the Asia-Pacific region, and it is suggested that it can be continued at the lowest effective dose throughout pregnancy.[12 13 21] In this study, there was no significant association between TAC use in the 3 months prior to conception and APOs in the multivariable analysis.

Targeted therapy appears to be increasing, but the prescription rate remains low. For targeted therapies, evidence for safety during pregnancy has yet to be partially presented. Recommendations are relatively well established for TNF inhibitors and are similar between the guidelines.[12 13] Reflecting on the guidelines, TNF inhibitors were the most commonly prescribed targeted therapy in the real world, with a prescription rate more than 10 times higher than non-TNF inhibitors during pregnancy. Rituximab and JAK inhibitors were not prescribed during pregnancy in either group, as recommended. However, even the prescription rate of TNF inhibitors during pregnancy was very low compared with that in the

Table 2 Pattern of medication use in the 3 months prior to conception

Variables	Delivery (n=4576)	APO (n=1152)	P value
Not used any DMARDs	3514 (76.8)	839 (72.8)	0.005
Conventional synthetic DMARDs			
Methotrexate	172 (3.8)	94 (8.2)	<0.001
Leflunomide	22 (0.5)	25 (2.2)	<0.001
Hydroxychloroquine	735 (16.1)	200 (17.4)	0.286
Sulfasalazine	337 (7.4)	76 (6.6)	0.368
Tacrolimus	74 (1.6)	24 (2.1)	0.275
Targeted therapies	126 (2.8)	41 (3.6)	0.146
TNF inhibitor	104 (2.3)	32 (2.8)	0.314
Adalimumab	31 (0.7)	11 (1.0)	0.324
Infliximab	8 (0.2)	2 (0.2)	1.000
Etanercept	62 (1.4)	18 (1.6)	0.592
Golimumab	5 (0.1)	2 (0.2)	0.634
Non-TNF inhibitor	20 (0.4)	10 (0.9)	0.070
Abatacept	4 (0.1)	4 (0.3)	0.057
Tocilizumab	16 (0.3)	6 (0.5)	0.423
JAK inhibitor	1 (0.0)	0 (0.0)	1.000
Tofacitinib	1 (0.0)	0 (0.0)	1.000
Baricitinib	0 (0.0)	0 (0.0)	–
Rituximab	1 (0.0)	0 (0.0)	1.000
Other medications			
NSAIDs	957 (20.9)	287 (24.9)	0.003
Oral glucocorticoids	1642 (35.9)	414 (35.9)	0.972
Prednisolone-equivalent dose, mg	7.3 ± 5.3	7.2 ± 4.5	<0.001

Data are presented as numbers with percentages (%) or mean±SD.
APO, adverse pregnancy outcome; DMARD, disease-modifying antirheumatic drug; JAK, Janus kinase; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

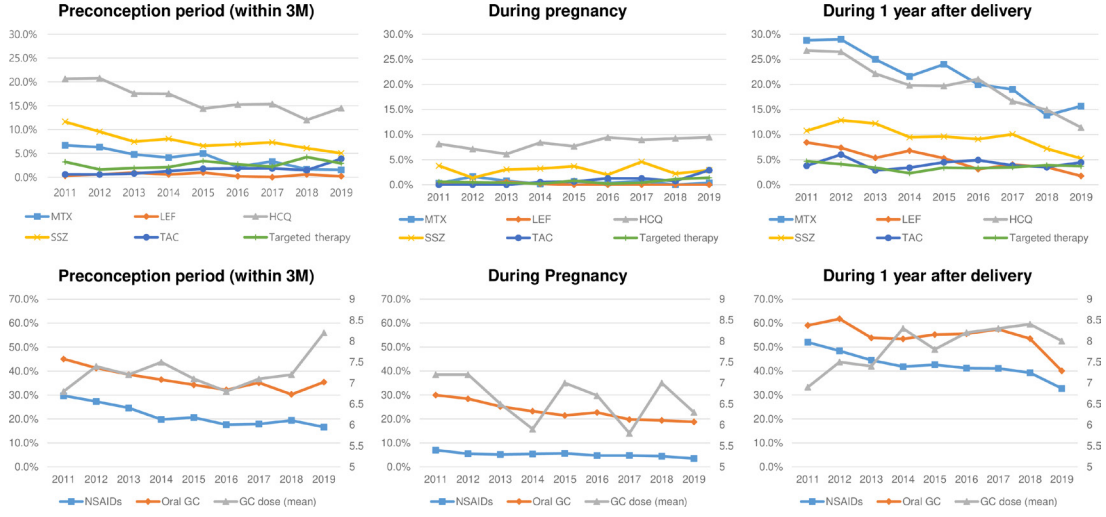

Figure 3 Pattern of medication use in the delivery group by year. GC doses are presented as prednisolone-equivalent dose (mg). GC, glucocorticoid; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; SSZ, sulfasalazine; TAC, tacrolimus.

Table 3 Factors associated with APOs versus delivery in patients with RA

	Univariable analysis (n=5728)		Multivariable analysis (n=5672)	
Variables	**OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Age group, years (ref: 20–29)				
30–39	1.34 (1.08 to 1.65)	0.008	1.33 (1.07 to 1.66)	0.010
40–49	5.46 (4.27 to 6.97)	<0.001	5.35 (4.16 to 6.89)	<0.001
Type of insurance (ref: NHI)	2.13 (1.18 to 3.84)	0.012	1.39 (0.72 to 2.69)	0.328
Type of institution (ref: tertiary referral hospital)				
General hospital	1.05 (0.88 to 1.26)	0.567	0.93 (0.77 to 1.13)	0.474
Community hospital/clinic	3.26 (2.77 to 3.83)	<0.001	1.33 (1.13 to 1.56)	<0.001
Income group (ref: first quartile) (n=5672)				
Second quartile	0.72 (0.59 to 0.89)	0.002	0.78 (0.63 to 0.97)	0.026
Third quartile	0.80 (0.67 to 0.97)	0.020	0.87 (0.71 to 1.06)	0.152
Fourth quartile	0.88 (0.72 to 1.08)	0.210	0.84 (0.68 to 1.04)	0.116
Seropositivity (ref: seronegative)	1.02 (0.89 to 1.16)	0.797	0.95 (0.81 to 1.11)	0.49
CCI score	1.07 (1.00 to 1.14)	0.070	1.04 (0.97 to 1.12)	0.246
Any hospital visit for RA during early pregnancy*	0.98 (0.85 to 1.14)	0.826	0.95 (0.78 to 1.17)	0.638
Conventional synthetic DMARD†				
Methotrexate use (ref: not use)	2.28 (0.72 to 2.95)	<0.001	2.14 (1.57 to 2.92)	<0.001
Leflunomide use (ref: not use)	4.59 (2.58 to 8.17)	<0.001	2.68 (1.39 to 5.15)	0.003
Hydroxychloroquine use (ref: not use)	1.10 (0.93 to 1.30)	0.286	1.12 (0.91 to 1.39)	0.292
Sulfasalazine use (ref: not use)	0.89 (0.69 to 1.15)	0.368	0.86 (0.64 to 1.15)	0.303
Tacrolimus use (ref: not use)	1.30 (0.81 to 2.06)	0.277	0.95 (0.57 to 1.59)	0.856
NSAIDs use† (ref: not use)	1.20 (1.06 to 1.37)	0.006	1.15 (0.95 to 1.40)	0.140
Oral GC use† (ref: not use)	1.00 (0.88 to 1.15)	0.972	0.95 (0.81 to 1.11)	0.507
Targeted therapy† (ref: not use)	1.30 (0.91 to 1.87)	0.147	1.21 (0.81 to 1.81)	0.355
Multiple pregnancies (ref: single pregnancy)	1.15 (1.01 to 1.31)	0.036	1.10 (0.96 to 1.26)	0.179

*The first 12 weeks from conception.
†Medication use in the 3 months prior to conception.
APO, adverse pregnancy outcome; CCI, Charlson Comorbidity Index; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; NHI, National Health Insurance; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis.

year after delivery. One possible explanation for this is that pregnant women are still concerned about the use of targeted therapies during pregnancy, while strict reimbursement criteria for targeted therapy in patients with RA in Korea may be another reason. To initiate targeted therapy, patients with RA must have been treated with at least two types of csDMARDs, including MTX, for more than 3 months each.[22] MTX must be included if a patient does not have any serious adverse event after MTX treatment, and planning for pregnancy is not admitted as an appropriate reason for skipping MTX. Because MTX is stopped in advance of preparing for pregnancy, it is inevitably more difficult for young female patients to initiate targeted therapy. Therefore, even if a patient needs targeted therapy before or during pregnancy, the reimbursement criteria may interfere with this. It is necessary to revise the reimbursement criteria for targeted therapy to reflect real practice.

The rate of drug use before and after pregnancy is also noteworthy. During pregnancy, the overall drug use was significantly reduced in both delivery and APO groups, while all drug use increased rapidly after the pregnancy outcome. This may be a result of immunological tolerance in pregnancy related to a decrease in RA activity during pregnancy and an increase after pregnancy termination.[23] The trend in oral glucocorticoid use clearly shows that the prescription of oral glucocorticoids decreased during pregnancy and rapidly increased with higher dosages after pregnancy outcome. Some patients may not take drugs during pregnancy despite the high disease activity of RA. Indeed, according to a recent study of Asian-Pacific female patients with rheumatic diseases, 94% responded that they stopped treatment around pregnancy due to fear of fetal harm.[24] The increase in MTX prescription after pregnancy outcome, especially in the delivery group, indicates that the discontinued regular

treatment was necessary again. However, DMARD use in the year following delivery, especially MTX and HCQ, has been shown to decrease over the years. This has two possible explanations. First, the number of patients with well-regulated disease activity may have increased in recent years with the introduction of targeted therapy. Second, as the advantages of breast feeding became widely known, the breastfeeding rate has increased in Korea.[25] Moreover, patients may be concerned about the impact of drugs on breast feeding. A previous study using the German claims database also showed that women with inflammatory rheumatic diseases did not return to prepregnancy treatments after delivery despite signs of worsening disease activity.[26] Many patients express a lack of sufficient information regarding the impact of their disease and treatment on pregnancy.[24] Therefore, it is essential for rheumatologists to address this concern and provide comprehensive support to alleviate patient anxiety.

In terms of pregnancy outcome, patients with active RA are known to have less-favourable outcomes compared with the general population.[27 28] Moreover, several large studies have revealed that pregnant women with RA are more likely to have APOs, such as preterm deliveries, caesarean deliveries and babies with lower birth weights.[4 14 29] High disease activity of RA is an important factor associated with an increased risk of APOs.[14 30 31] The disease activity of RA has been reported to improve in 60% of patients with RA during pregnancy, and flare in 46.7% during the postpartum period.[32] Improved RA activity may be attributed to the maternal anti-inflammatory state induced by various fetal factors and hormones to maintain fetomaternal tolerance.[23] However, controlling RA activity in pregnant patients remains challenging in some cases.

The factors associated with APOs were old age, MTX and LEF treatment within 3 months before conception. Visiting a tertiary hospital was associated with a lower probability of APOs relative to visiting a community hospital/clinic. Previous studies have reported that previous miscarriages, antinuclear antibody positivity and high activity of RA were risk factors for APOs.[33 34] Overall, this suggests that patients with RA should consult their physician about planning for pregnancy, including the discontinuation of teratogenic drugs.

In our study, abortion was defined according to diagnostic codes for both spontaneous and induced abortion. During the study period (2010–2020), induced abortion was illegal in Korea and was permitted only under a few limited circumstances, such as severe genetic, mental or physical disorders of the fetus, or infectious diseases of the parents. Exposure to teratogenic agents may have been the reason for induced abortion, but we also considered it an APO. Furthermore, induced abortions accounted for only 1.0% of all abortions in our study, so the impact of including induced abortion was small.

Our study has several strengths. First, this study was a nationwide population-based study including all pregnant patients with RA during the observation period. We investigated the drug use of the study population by year and pregnancy period in detail and presented the results as graphs showing the trends.Second, we investigated the pattern of medication use in detail, considering the time sections before, during and after pregnancy. Additionally, we examined changes in drug use patterns by year. Consequently, we summarised the medication use patterns in Korean women with RA using graphs for easy comprehension at a glance.

Our study has several limitations that warrant discussion. First, RA activity may have influenced APOs, but information about RA disease activity was not available from the NHI data. Nonetheless, the use of drugs, such as oral glucocorticoids and NSAIDs, may have partially indicated disease activity. Second, the conception date could not be precisely identified from the NHI data, so we had to estimate the conception date indirectly from the date of pregnancy outcome. However, we attempted to improve the accuracy of the estimated conception date by including only episodes with the diagnostic code of pregnancy confirmation. We validated the conception date by calculating the interval using the diagnostic code for pregnancy confirmation, and the resulting mean interval was reasonably estimated to be approximately 1 month. Third, the rate of biological DMARD use was too low to be analysed separately. The low prescription rate could have several explanations, including patient refusal and reimbursement criteria. However, as the rate has been increasing by year, further study would be informative. Fourth, other factors associated with APOs, such as smoking and body mass index, were not included in the study because health examination data were not available for the study population.

In conclusion, patients who experienced delivery and APOs showed differences in drug use patterns. MTX and LEF treatment in the 3 months prior to conception were associated with increased odds of APOs in patients with RA. Therefore, it is crucial for patients with RA to engage in thorough consultations with their physicians regarding pregnancy planning, and to maintain medical supervision throughout pregnancy to effectively monitor and control disease activity.

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ORCID iDs
Yeo-Jin Song http://orcid.org/0000-0001-9420-2129
Soo-Kyung Cho http://orcid.org/0000-0003-4493-8837
Yoon-Kyoung Sung http://orcid.org/0000-0001-6691-8939

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