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Original Article
Immunology, Allergic Disorders & Rheumatology

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Pregnancy Outcomes Associated With Biologic Agent Exposure in Patients With Several Rheumatic Diseases and Inflammatory Bowel Diseases

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ABSTRACT

Background: This study aimed to analyze pregnancy outcomes based on biologic agents use in women using the nationwide population-based database.
Methods: The study used the claims database to identify women of childbearing age with several rheumatic (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis) and inflammatory bowel diseases (Crohn's disease and ulcerative colitis) who had pregnancy-related codes between January 2010 and December 2019. We analyzed live births and adverse pregnancy outcomes based on the previous use of biologics. We also stratified the patients according to duration of biologic agent exposure before pregnancy and the use of biologics during pregnancy to analyze the pregnancy outcomes by subgroups.
Results: We identified 4,787 patients with pregnancy events. Among them, 1,034 (21.6%) used biologics before pregnancy. Live birth rate was not different between the biologics group and biologics naïve group (75.0% vs. 75.2%). Multivariate analyses showed that biologics use was associated with higher risk of intrauterine growth retardation (odds ratio [OR], 1.780) and lower risk of gestational diabetes mellitus (OR, 0.776) compared with biologics naïve. Biologics use during pregnancy was associated with higher risk of preterm delivery (OR, 1.859), preeclampsia/eclampsia (OR, 1.762), intrauterine growth retardation (OR, 3.487), and cesarean section (OR, 1.831), but lower risk of fetal loss (OR, 0.274) compared with biologics naïve.
Conclusions: Although there was no difference in live birth rate between the biologics group and biologics naïve group, biologics use seems to be associated with several adverse pregnancy outcomes, especially in patients with biologics during pregnancy. Therefore, patients with biologics during pregnancy need to be carefully observed for adverse pregnancy outcomes.

Keywords: Biologics; Pregnancy; Rheumatoid Arthritis; Ankylosing Spondylitis; Psoriatic Arthritis; Inflammatory Bowel Diseases

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Disclosure
The authors have no potential conflicts of interest to disclose.

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Conceptualization: Ahn SM, Joo YB, Lee HS. Data curation: Ahn SM, Kim YJ. Formal analysis: Kim YJ. Funding acquisition: Lee HS. Investigation: Ahn SM, Joo YB. Methodology: Joo YB, Bang SY. Project administration: Lee HS. Resources: Ahn SM, Joo YB, Bang SY, Lee HS. Software: Joo YB. Supervision: Bang SY. Validation: Joo YB, Kim YJ. Visualization: Ahn SM. Writing - original draft: Ahn SM. Writing - review & editing: Ahn SM, Joo YB, Bang SY, Lee HS.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are a group of conditions with complex and multifactorial etiology and common inflammatory pathways.[1,2] The IMIDs include several rheumatic and gastroenteologic diseases, comprising rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus, Crohn's disease (CD), and ulcerative colitis (UC).[2] These diseases, especially RA and inflammatory bowel disease (IBD), are prevalent in reproductive-aged women.[3-6] Therefore, reproductive health concerns are critical for female patients with IMIDs. Female patients with IMIDs, particularly those with high disease activities, might have higher maternal and perinatal adverse outcomes than healthy populations. Various medications to treat IMIDs could affect these outcomes.[4,7] Self-discontinuing therapies before or during pregnancy due to fear of fetal harm could increase the risk of disease flares and lead to adverse pregnancy outcomes.[8-10] Biologic agents, including anti-tumor necrosis factor-alpha (TNF-α) agents, non-TNF-α biologics, and Janus kinases inhibitors, are widely used effective therapeutics for various IMIDs such as RA, JIA, AS, PsA, CD, and UC.[11-13] While several guidelines on the use and safety of biologic agents in women of reproductive age and pregnant women are available for these IMIDs, certainty remains unclear.[9,14-16]

As perinatal care is managed by obstetricians, rheumatologists or gastroenterologists (who prescribe biologic agents) may be unable to detect maternal or perinatal complications. Therefore, it would be challenging to conduct a study investigating the effects of biologic agents on pregnancy outcomes in patients with rheumatic diseases and IBD using a hospital-based cohort. Moreover, due to the inadequate sample size in single-center hospital-based approaches, different study methods, such as an approach using a nationwide population database, would be necessary.

Therefore, this study aimed to investigate whether biologic agent exposure was associated with an increase in adverse pregnancy outcomes in patients with rheumatic diseases and IBD using the National Health Insurance Service (NHIS) claims database of South Korea.

METHODS

Data source
This study was a retrospective population-based nationwide study using patient records extracted from the Korean NHIS claims database. The NHIS is the primary social insurance administered by the Korean government, a health insurance system covering 97% of the 50 million Korean population, and a medical aid program covering 3%.[17] The NHIS database contains information on patient demographics, diagnosis, medical procedures, operations, and prescriptions.

Study population
The study population selection process is presented in **Fig. 1**. The recorded diagnoses were based on the version of the International Classification of Disease 10th revision (ICD-10) modified for the Korean healthcare system and the Korean rare intractable disease (RID) registration code for each disease. In the RID registration program, rare diseases including some rheumatic diseases and IBD, are diagnosed by qualified physicians according to the unified diagnostic criteria distributed by the National Health Insurance. The study cohort
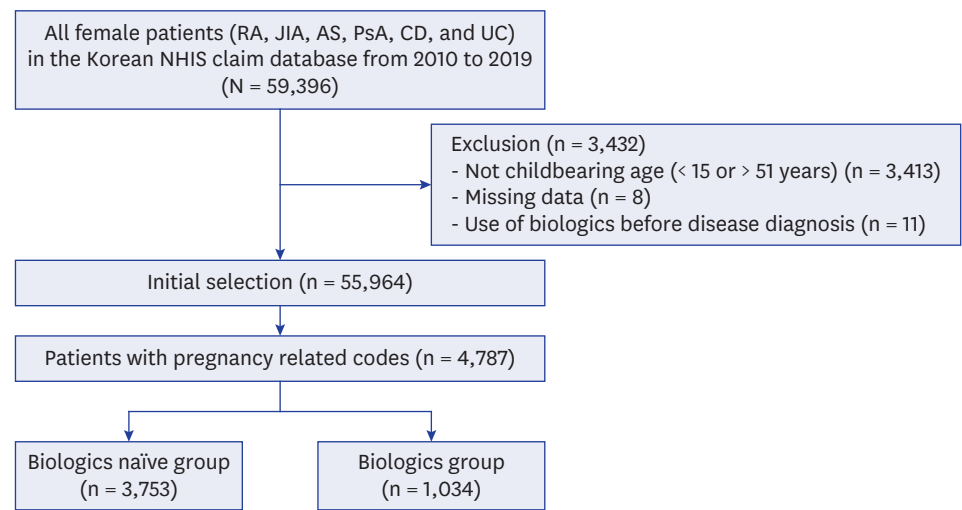
Fig. 1. Flow diagram of the study population.
AS = ankylosing spondylitis, CD = Crohn's disease, JIA = juvenile idiopathic arthritis, NHIS = National Health Insurance Service, PsA = psoriatic arthritis, RA = rheumatoid arthritis, UC = ulcerative colitis.

included female patients with several rheumatic diseases and IBD between January 2010 and December 2019. The cohort consisted of seropositive RA (ICD-10 code: M05, RID code: V223), JIA (ICD-10 code: M08, RID code: V133), AS (ICD-10 code: M45, RID code: V140), PsA (ICD-10 code: M07, RID code: V237), CD (ICD-10 code: K50, RID code: V130), and UC (ICD-10 code: K51, RID code: V131). We only included patients hospitalized at least once or those who had three or more outpatient visits in 2 years with the corresponding diagnosis. The age of patients was limited to the reproductive age (15–50 years) during the study period.

Among the selected patients, we identified pregnant women using the ICD-10 codes associated with pregnancy (codes for labor, abortions or confirmed pregnancies) and procedure codes associated with delivery and abortion (Health Insurance Review and Assessment Service [HIRA] procedure codes for delivery and abortion) (**Supplementary Table 1**). If a patient had more than one pregnancy during the study period, we only evaluated the first pregnancy to avoid potential bias associated with multiple outcomes from the same patient. The index date was defined as the date of conception, which was defined as the earliest of 38 weeks (266 days) before the delivery date and 14 days before a clinic visit with an ICD-10 code for abortion or confirmed pregnancy.[18]

The study population was allocated to two groups based on the use of biologic agents before pregnancy-related code records. Biologic agents included etanercept, infliximab, adalimumab, golimumab, tocilizumab, secukinumab, ixekizumab, ustekinumab, vedolizumab, tofacitinib, baricitinib, rituximab, and abatacept.

Additional clinical data were collected from patients, including age, the use of IMIDs-related medications, comorbidities, and the Charlson Comorbidity Index.[19,20] IMID-related medications include oral non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, and immune-modulating agents. The drug exposure of IMID-related medication from rheumatic diseases or IBD diagnosis to the index date was investigated. Long-term glucocorticoid use was defined as using of oral glucocorticoids for 3 months or longer.[21] Among these drugs, methotrexate and leflunomide are classified as Federal

Drug Administration (FDA) pregnancy category X drugs. Biologic agents and IMIDs-related medications used by the study population were investigated by searching for HIRA formulary codes in the database (**Supplementary Table 2**).

Study outcomes

The primary endpoint was the impact of prior use of biologic agents on pregnancy outcomes. The secondary endpoints were the effect of the duration of biologic agent exposure and the biologic agent administration during pregnancy on adverse pregnancy outcomes.

Pregnancy outcomes were divided into two categories: 1) live births rate ([total labors minus total abortions or stillbirths]/[total confirmed pregnancies, labors, or abortions]), and 2) adverse pregnancy outcomes. Adverse pregnancy outcomes included six sub-classifications: 2-1) fetal loss (including spontaneous abortion, induced abortion or medical abortion, stillbirth, and ectopic pregnancy), 2-2) preterm delivery, 2-3) preeclampsia/eclampsia, 2-4) gestational diabetes mellitus, excluding those whose condition was diagnosed before pregnancy, 2-5) intrauterine growth retardation, and 2-6) cesarean section. The details of codes for pregnancy outcomes are shown in **Supplementary Table 1**.

Statistical analysis

Continuous variables were presented as median (interquartile range [IQR]). Categorical variables were presented as frequencies and percentages as assessed using the χ^2 and Fisher's exact tests. We examined the risk of each pregnancy outcome between the biologics and non-biologics groups using multivariate logistic regression models adjusted for recorded diagnosis, age, comorbidities (including Charlson Comorbidity Index, infertility, and previous abortion history), and use of medications (long-term glucocorticoids, NSAIDs, and FDA category X drugs). Adjusted odds ratio (OR) with the 95% confidence interval (CI) were calculated. Statistical significance was determined using two-sided tests, and a *P* value less than 0.05 was considered significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board owing to the retrospective nature of the study using a database, and the study was certified by Hanyang University Guri Hospital (No. 2021-04-014-001).

RESULTS

Study population

The Korean NHIS database consisted of 59,396 women with RA, JIA, AS, PsA, CD, and UC diagnostic codes between 2010 and 2019 (**Fig. 1**). Of these women, 55,964 (94.2%) of childbearing age (15–50 years) were identified. Among them, we identified 4,787 (26.8%) women with records of pregnancy-related claims. Finally, we identified 1,034 (21.6%) women who used biologic agents before pregnancy and 3,753 (78.4%) without biologic agent exposure before pregnancy.

Characteristics of the study population

Among the 4,787 participants in the study population, 2,941 (61.4%) were diagnosed with rheumatic diseases (including RA [n = 1,940, 40.5%], JIA [n = 65, 1.4%], AS [n = 900, 18.8%], and PsA [n = 36, 0.8%]) and 1,846 (38.6%) with IBD (CD [n = 582, 12.2%] and UC [n = 1,264, 26.4%]) (**Table 1**).The individual proportion of use of biologic agents among each disease was 17.9% (348 of 1,940 RA patients), 32.3% (21 of 65 JIA patients), 33.7% (303 of 900 AS patients), 55.6% (20 of 36 PsA patients), 39.9% (232 of 582 CD patients), and 8.7% (110 of 1,264 UC patients). The disease duration was significantly longer in the biologics group than in the biologics naïve group (45.6 vs. 29.1 months, *P* < 0.001). The median Charlson Comorbidity Index, the proportion of underlying diabetes mellitus and previous history of abortion, was also higher in the biologics group. Long-term glucocorticoid use (≥ 3 months) was more common in the biologics group (57.4% vs. 35.7%, *P* < 0.001). The rate of exposure to FDA category X drugs (methotrexate and leflunomide) and the rate of other IMID-related drugs use, including NSAIDs and immunosuppressants, was significantly higher in the biologics than in the biologics naïve group (**Table 1**).

Characteristics of the biologics group

Table 2 shows the details of the biologics group. Anti-TNF-α agents (n = 994, 96.1%) were the most frequently used biologic agents, of which infliximab (n = 373, 36.1%) was the most common, followed by adalimumab (n = 341, 33.0%), etanercept (n = 228, 22.1%), and golimumab (n = 52, 5.0%). No patients received ixekizumab, vedolizumab, tofacitinib, or baricitinib. The median duration of biologic agent exposure was 17.8 months. In addition, 633 patients (61.2%) used biologic agents for more than one year and 312 (30.2%) were administered their last biologic agent during pregnancy. Among the patients who used biologics during pregnancy, 304 (97.4%) were anti-TNF-α agents users and 8 were non-TNF biologics users (tocilizumab [n = 4], ustekinumab [n = 2], abatacept [n = 1], and secukinumab [n = 1]). The median duration of use of biologics during pregnancy and the postpartum period in these patients was 154 days (IQR, 33–238 days).

Pregnancy outcomes

The total live birth rates for the biologics and biologics naïve groups were 75.0% and 75.2%, respectively (**Table 3**). No statistically significant differences were observed in the rates of fetal loss (including spontaneous abortion, induced abortion, stillbirth, and ectopic pregnancy) between the two groups (**Table 3**). Preterm delivery was observed in 539 patients (11.3%), with no significant difference between the two groups. However, the rate of gestational diabetes mellitus in the biologics naïve group was significantly higher than that in the biologics group (35.3% vs. 29.1%, *P* < 0.001). Intrauterine growth retardation was observed in 131 patients (2.7%), significantly higher in patients exposed to biologic agents (4.2% vs. 2.3%, *P* = 0.002). In addition, the rate of cesarean section in patients with delivery codes (vaginal delivery codes plus cesarean delivery codes) was significantly higher in the biologics group than in the biologics naïve group (58.8% vs. 48.3%, *P* < 0.001). To define the factors associated with adverse pregnancy outcomes, multivariate analyses (adjusted for possible confounding factors [recorded diagnosis, Charlson Comorbidity Index, long-term glucocorticoid use, NSAIDs use, FDA X drugs exposure, age, and history of infertility and abortion]) showed that biologic agents use was associated with a higher risk of intrauterine growth retardation (OR, 1.780; 95% CI, 1.182–2.680) and lower risk of gestational diabetes mellitus (OR, 0.776; 95% CI, 0.658–0.914) compared with the biologics naïve group. However, the risk of fetal loss, preterm delivery, preeclampsia/eclampsia, and cesarean section were not significantly different between the biologics and biologics naïve groups in

Table 1. Baseline characteristics of the study population

Characteristics	Total (N = 4,787)	Biologics naïve group (n = 3,753)	Biologics group (n = 1,034)	P
Diagnosis[a]				< 0.001
Rheumatic diseases	2,941 (61.4)	2,249 (59.9)	692 (66.9)	
Rheumatoid arthritis	1,940 (40.5)	1,592 (42.4)	348 (33.4)	
Juvenile idiopathic arthritis	65 (1.4)	44 (1.2)	21 (2.0)	
Ankylosing spondylitis	900 (18.8)	597 (15.9)	303 (29.3)	
Psoriatic arthritis	36 (0.8)	16 (0.4)	20 (1.9)	
Inflammatory bowel diseases	1,846 (38.6)	1,504 (40.1)	342 (33.1)	
Crohn's disease	582 (12.2)	350 (9.3)	232 (22.4)	
Ulcerative colitis	1,264 (26.4)	1,154 (30.8)	110 (10.6)	
Age at disease diagnosis, yr	30 (27–33)	30 (27–33)	29 (25–32)	< 0.001
Age at conception, yr	32 (30–36)	32 (30–36)	32 (30–36)	0.963
Disease duration, mon	32.6 (14.0–58.3)	29.1 (12.3–53.7)	45.6 (24.9–72.8)	< 0.001
Charlson Comorbidity Index	1 (1–2)	1 (1–2)	2 (1–2)	0.002
0	949 (19.8)	779 (20.8)	170 (16.4)	0.008
1 to 2	2,791 (58.3)	2,165 (57.7)	626 (60.5)	
3 to 4	1,047 (21.9)	809 (21.6)	238 (23.0)	
Comorbidities (2 years before index date[b])				
Hypertension	83 (1.7)	59 (1.6)	24 (2.3)	0.107
Dyslipidemia	344 (7.2)	256 (6.8)	88 (8.5)	0.066
Renal failure	4 (0.1)	2 (0.1)	2 (0.2)	0.206
Diabetes mellitus	87 (1.8)	57 (1.5)	30 (2.9)	0.005
Cancer	74 (1.6)	53 (1.4)	21 (2.0)	0.156
Infertility	303 (6.3)	240 (6.4)	63 (6.1)	0.773
Previous abortion history	234 (4.9)	129 (3.4)	105 (10.2)	< 0.001
Drug exposure				
Long-term glucocorticoid (≥ 90 days)	1,934 (40.4)	1,341 (35.7)	593 (57.4)	< 0.001
Use of NSAIDs (≥ 0.7 PDC)	605 (12.6)	411 (11.0)	194 (18.8)	< 0.001
FDA category X drugs[c]	153 (3.2)	64 (1.7)	89 (8.6)	< 0.001
Methotrexate	148 (3.1)	62 (1.7)	86 (8.3)	< 0.001
Leflunomide	19 (0.4)	7 (0.2)	12 (1.2)	< 0.001
Azathioprine	206 (4.3)	64 (1.7)	142 (13.7)	< 0.001
Mercaptopurine	18 (0.4)	7 (0.2)	11 (1.1)	< 0.001
Sulfasalazine	137 (2.9)	60 (1.6)	77 (7.5)	< 0.001
Mesalazine	423 (8.8)	214 (5.7)	209 (20.2)	< 0.001
Basalazide	29 (0.6)	12 (0.3)	17 (1.6)	< 0.001
Hydroxychloroquine	83 (1.7)	56 (1.5)	27 (2.6)	0.021
Tacrolimus	8 (0.2)	3 (0.1)	5 (0.5)	0.015

Values are presented as number (%) or median (interquartile range).
FDA = Federal Drug Administration, NSAIDs = non-steroidal anti-inflammatory drugs, PDC = proportion of days covered.
[a]The proportion of the use of biologics was 17.9% (348 of 1,940) in rheumatoid arthritis), 32.3% (21 of 65) in juvenile inflammatory arthritis, 33.7% (303 of 900) in ankylosing spondylitis, 55.6% (20 of 36) in psoriatic arthritis, 39.9% (232 of 582) in Crohn's disease, and 8.7% (110 of 1,264) in ulcerative colitis.
[b]Index date was defined as the date of conception.
[c]FDA category X drugs including methotrexate and/or leflunomide.

the multivariate analysis (**Table 4**). In a subgroup analysis targeting only the anti-TNF-α agent group (n = 994), preterm delivery, intrauterine growth retardation, and cesarean section were significantly higher and gestational diabetes mellitus was lower in the anti-TNF-α agent group than in the biologics naïve group (**Supplementary Table 3**). Also, anti-TNF-α agent use was associated with a higher risk of intrauterine growth retardation, cesarean section, and lower risk of gestational diabetes mellitus (**Supplementary Table 4**). Furthermore, a subgroup analysis was conducted to exclude unintended pregnancy from fetal loss, excluding 'induced abortion' or 'medical abortion' from fetal loss. In this subgroup analysis, the use of biologics also increased the risks of intrauterine growth retardation, and cesarean section, and decreased the risk of gestational diabetes mellitus (**Supplementary Table 5**).

Table 2. Characteristics of the biologics group

Characteristics	Biologics group (N = 1,034)
Biologics agents	
Anti-TNF-α agents	994 (96.1)
Infliximab	373 (36.1)
Adalimumab	341 (33.0)
Etanercept	228 (22.1)
Golimumab	52 (5.0)
Non-TNF-α targeted biologics	40 (3.9)
Tocilizumab	16 (1.6)
Ustekinumab	10 (1.0)
Abatacept	9 (0.9)
Rituximab	4 (0.4)
Secukinumab	1 (0.1)
Duration of biologics exposure, mon	17.8 (6.3–37.5)
Duration of biologics exposure, group	
Biologics use for less than one year	401 (38.8)
Biologics use for more than one year	633 (61.2)
The time of last biologics administration	
One year prior to conception	155 (15.0)
Six months to one year prior to conception	96 (9.3)
Six months prior to conception	471 (45.6)
During pregnancy	312 (30.2)

Values are presented as number (%) or median (interquartile range).
TNF-α = tumor necrosis factor-alpha.

Table 3. Pregnancy outcomes

Pregnancy outcomes	Total (N = 4,787)	Biologics naïve group (n = 3,753)	Biologics group (n = 1,034)	P
Live birth	3,590 (75.0)	2,813 (75.0)	777 (75.2)	0.935
Fetal loss	1,197 (25.0)	940 (25.0)	257 (24.9)	0.935
Spontaneous abortion	820 (17.1)	641 (17.1)	179 (17.3)	0.852
Induced abortion	20 (0.4)	16 (0.4)	4 (0.5)	1.000
Stillbirth	17 (0.4)	12 (0.3)	5 (0.5)	0.388
Ectopic pregnancy	340 (7.1)	271 (7.2)	69 (6.7)	0.585
Preterm delivery	539 (11.3)	405 (10.8)	134 (13.0)	0.052
Preeclampsia/eclampsia	177 (3.7)	141 (3.8)	36 (3.5)	0.780
Gestational diabetes mellitus	1,624 (33.9)	1,323 (35.3)	301 (29.1)	< 0.001
Intrauterine growth retardation	131 (2.7)	88 (2.3)	43 (4.2)	0.002
Cesarean section[a]	1,485 (50.5)	1,118 (48.3)	367 (58.8)	< 0.001

Values are presented as number (%).
[a]Percentage of patients with delivery-procedure codes.

The risk of adverse pregnancy outcomes according to the duration of biologic agent exposure before pregnancy and administration of biologics during pregnancy

We performed the subgroup analysis according to the duration of biologic agent exposure whether it was used for more than one year or less than one year, by logistic regression analysis. In both groups who used biologics for more than 1 year or less than 1 year prior to pregnancy, the risk of cesarean section was increased, the risk of gestational diabetes was decreased, and fetal loss and preeclampsia/eclampsia were not significant compared to the biologics naïve group. Also, compared with the biologics naïve group, the risk of preterm delivery and intrauterine growth retardation was significantly higher only in the group that used the biologic agents for more than one year but not in the group for less than one year (**Table 5**). In multivariate analysis adjusted for possible confounding factors, only intrauterine growth retardation was significantly increased in the group that used biologic agents for more than one year compared with the biologics naïve group (OR, 2.053; 95% CI, 1.291–3.265), whereas the significance of the increased risk of preterm delivery and cesarean section

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Table 4. Effects of biologics on adverse pregnancy outcomes

Outcomes	No.	Univariate analysis	Multivariate analysis
		Unadjusted OR (95% CIs)	Adjusted OR[a] (95% CIs)
Fetal loss			
Biologics naïve group	940	Reference	Reference
Biologics group	257	0.990 (0.844–1.161)	0.888 (0.743–1.061)
Preterm delivery			
Biologics naïve group	405	Reference	Reference
Biologics group	134	1.231 (0.999–1.517)	1.124 (0.894–1.415)
Preeclampsia/eclampsia			
Biologics naïve group	141	Reference	Reference
Biologics group	36	0.924 (0.637–1.341)	1.017 (0.679–1.524)
Gestational diabetes mellitus			
Biologics naïve group	1,323	Reference	Reference
Biologics group	301	0.754 (0.649–0.876)	0.776 (0.658–0.914)
Intrauterine growth retardation			
Biologics naïve group	88	Reference	Reference
Biologics group	43	1.807 (1.247–2.620)	1.780 (1.182–2.680)
Cesarean section			
Biologics naïve group	1,118	Reference	Reference
Biologics group	367	1.297 (1.121–1.500)	1.167 (0.994–1.370)[b]

CI = confidence interval, OR = odds ratio, FDA = Federal Drug Administration.
[a]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term use of glucocorticoids, non-steroid anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, and abortion.
[b]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term glucocorticoid use, non-steroidal anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, abortion, and cesarean section.

disappeared. In addition, the risk of gestational diabetes mellitus was still significantly lower in multivariate analysis (biologics use for less than one year: OR, 0.772; 95% CI, 0.610–0.977, biologics use for more than one year: OR, 0.778; 95% CI, 0.638–0.949) (**Table 5**). **Table 6** shows the effect of the biologic agent administration during pregnancy on adverse pregnancy outcomes. The multivariate analysis adjusted for possible confounding factors showed that the patients who received biologic agents during pregnancy were significantly associated with increased risk of preterm delivery (OR, 1.859; 95% CI, 1.535–2.554), preeclampsia/eclampsia (OR, 1.762; 95% CI, 1.003–3.006), intrauterine growth retardation (OR, 3.487; 95% CI, 2.109–5.767), and cesarean section (OR, 1.831; 95% CI, 1.430–2.344), but decreased risk of fetal loss (OR, 0.274; 95% CI, 0.183–0.411). The results of the subgroup analysis excluding unintended pregnancy also showed no significant difference from previous results (**Supplementary Tables 6** and **7**).

DISCUSSION

This population-based study using the Korean NHIS claims database found that there was no significant difference in live births between the biologics user and biologics naïve groups in patients with several rheumatic diseases and IBD. The risk of intrauterine growth retardation was higher in the biologics group than in the biologics naïve group; however, the risk of gestational diabetes mellitus was lower. In addition, patients treated with biologic agents for longer than one year showed an increased risk of intrauterine growth retardation but not those treated for less than one year. Patients who received biologic agents during pregnancy were significantly associated with increased risk of preterm delivery, preeclampsia/eclampsia, intrauterine growth retardation, and cesarean section but decreased risk of fetal loss.

Table 5. Effects of biologics duration on adverse pregnancy outcomes

Outcomes	No.	Univariate analysis	Multivariate analysis
		Unadjusted OR (95% CIs)	Adjusted OR[a] (95% CIs)
Fetal loss			
Biologics naïve group	940	Reference	Reference
Biologics use for less than one year	104	1.048 (0.828–1.326)	0.964 (0.749–1.239)
Biologics use for more than one year	153	0.954 (0.784–1.161)	0.840 (0.676–1.043)
Preterm delivery			
Biologics naïve group	405	Reference	Reference
Biologics use for less than one year	47	1.098 (0.796–1.513)	1.043 (0.747–1.458)
Biologics use for more than one year	87	1.317 (1.027–1.689)	1.177 (0.898–1.542)
Preeclampsia/eclampsia			
Biologics naïve group	141	Reference	Reference
Biologics use for less than one year	21	1.416 (0.884–2.266)	1.518 (0.926–2.488)
Biologics use for more than one year	15	0.622 (0.363–1.066)	0.690 (0.392–1.213)
Gestational diabetes mellitus			
Biologics naïve group	1,323	Reference	Reference
Biologics use for less than one year	117	0.757 (0.604–0.948)	0.772 (0.610–0.977)
Biologics use for more than one year	184	0.753 (0.626–0.905)	0.778 (0.638–0.949)
Intrauterine growth retardation			
Biologics naïve group	88	Reference	Reference
Biologics use for less than one year	13	1.395 (0.772–2.522)	1.381 (0.747–2.552)
Biologics use for more than one year	30	2.072 (1.357–3.164)	2.053 (1.291–3.265)
Cesarean section			
Biologics naïve group	1,118	Reference	Reference
Biologics use for less than one year	141	1.278 (1.029–1.587)	1.146 (0.912–1.441)[b]
Biologics use for more than one year	226	1.309 (1.096–1.562)	1.180 (0.974–1.431)[b]

CI = confidence interval, OR = odds ratio, FDA = Federal Drug Administration.
[a]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term glucocorticoids use, non-steroidal anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, and abortion.
[b]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term glucocorticoid use, non-steroidal anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, abortion, and cesarean section.

Table 6. Effects of the biologics administration during pregnancy on adverse pregnancy outcomes

Outcomes	No.	Univariate analysis	Multivariate analysis
		Unadjusted OR (95% CIs)	Adjusted OR[a] (95% CIs)
Fetal loss			
Biologics naïve group	940	Reference	Reference
Biologics use during pregnancy	29	0.307 (0.208–0.453)	0.274 (0.183–0.411)
Preterm delivery			
Biologics naïve group	405	Reference	Reference
Biologics use during pregnancy	60	1.968 (1.458–2.656)	1.859 (1.353–2.554)
Preeclampsia/eclampsia			
Biologics naïve group	141	Reference	Reference
Biologics use during pregnancy	18	1.568 (0.947–2.598)	1.762 (1.033–3.006)
Gestational diabetes mellitus			
Biologics naïve group	1,323	Reference	Reference
Biologics use during pregnancy	101	0.879 (0.687–1.125)	0.903 (0.697–1.169)
Intrauterine growth retardation			
Biologics naïve group	88	Reference	Reference
Biologics use during pregnancy	24	3.471 (2.176–5.537)	3.487 (2.109–5.767)
Cesarean section			
Biologics naïve group	1,118	Reference	Reference
Biologics use during pregnancy	145	2.047 (1.621–2.584)	1.831 (1.430–2.344)[b]

CI = confidence interval, OR = odds ratio, FDA = Federal Drug Administration.
[a]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term use of glucocorticoids, non-steroid anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, and abortion.
[b]Adjusted for recorded diagnosis, age, Charlson Comorbidity Index, previous long-term glucocorticoids use, non-steroidal anti-inflammatory drugs, and FDA category X drugs, previous history of infertility, abortion, and cesarean section.

In the study, the proportion of patients who used biologic agents before and/or during pregnancy was approximately 22% among the female patients of childbearing age with. This proportion was ten times more than that in the previous study using British Columbia population data, which reported that 2.1% of women with autoimmune diseases were exposed to biologic agents during preconception and pregnancy between 2002 and 2012.[22] Furthermore, compared with previous studies on female patients with AS and IBD using the Korean nationwide claims database, the proportion of patients using biologics was approximately twice as high in this study.[23,24] These findings may be due to several reasons: the recent trend of more frequent prescription of biologics, increasing number of biologic agents, expansion of indications for each biologic agent as a result of proven efficacy, and the different operational definitions of the patient groups between studies.[11,12,25] Moreover, recently published treatment guidelines for some IMIDs are more favorable for biologic agents use, such as anti-TNF-α agents than the previous guidelines. For example, in 2020, the American College of Rheumatology released guidelines recommending conditional continuation of anti-TNF-α agents before and during pregnancy.[16] In addition, recent treatment guidelines for IBD also recommend continued anti-TNF-α agents during pregnancy.[14,15] Moreover, in a recent small hospital-based study of patients with AS in Korea, 28.6% (6 of 21) of patients had a history of biologic agent use before pregnancy, similar to the findings in our study (1,034 of 4,787 patients, 21.6%).[26]

Intrauterine growth retardation is a heterogeneous condition that results in small babies for their gestational age due to several causes, including congenital malformations, infections, or placental insufficiency.[27] The level of TNF-α was significantly higher in the intrauterine growth retardation group with placental insufficiency than in the healthy control group; however, no difference was observed in the intrauterine growth retardation group with the other causes.[27] Previous studies from Denmark, Finland, and Sweden population cohorts reported that the anti-TNF-α agent was significantly associated with a higher OR for small for gestational age (1.36) compared with biologics naïve.[28] In a meta-analysis of eight prospective studies, anti-TNF-α agents had a significantly higher risk of small for gestational age (OR, 1.43).[29] Corroborating these previous results, our study also showed that intrauterine growth retardation was associated with biologic agent use (OR, 1.780). In particular, the risk of intrauterine growth retardation was significantly higher in the groups that used the biologic agents for more than one year (OR, 2.053) and during pregnancy (OR, 3.487) than in the biologics naïve group. Furthermore, the risk of preterm delivery was significantly higher in the group that used biologic agents during pregnancy (OR, 1.859) than in the biologics naïve group. While immunosuppression due to biologic agents might increase peripartum infection, further studies to explore underlying basic mechanisms for the association of biologics during pregnancy with preterm delivery and intrauterine growth retardation are needed.[28]

In this study, the proportion of patients who underwent cesarean section was 50.5%, which was significantly higher in the group using biologic agents than in the group without biologic agents (58.8% vs. 48.3%, $P < 0.001$). The cesarean section rate in Korea is the highest worldwide, maintained at over 35% since the 2000s.[30] Previous studies have shown that women with IBD/AS have a higher cesarean section rate than the general population.[23,31-33] In a study using Korean claim data between 2007 and 2017, the cesarean section rate was highest among women with AS (50.8%), followed by RA (44.1%) and the general population (38.0%).[33] In another study using the Korean NHIS claim database, cesarean sections were performed more often in women with CD (46.5%) or moderate to severe IBD patients (46.4%) than in the general population (38.8%).[23] In a hospital-based study in Korea, the

cesarean section rate was twice as high in AS compared with that in women without any autoimmune disease.[26] In a study in Norway, women with inflammatory rheumatic diseases (RA, JIA, and AS) had significantly higher rates of cesarean section than those without rheumatic diseases.[34] Results from Denmark, Finland, and Sweden population-based studies showed that women with IMIDs treated with anti-TNF-α agents had a higher risk of cesarean section (OR, 1.57) than biologics non-users.[28] In particular, in our study, the cesarean section was significantly higher with the use of biologic agents during pregnancy compared with the biologics naïve group. Therefore, consistent with this study and the previous ones, the biologic agents seem to affect the implementation of the cesarean section in IMID patients. However, it should be cautioned that these findings might have been influenced by the severity of the IMID disease requiring biologic agents.

The risk of gestational diabetes mellitus was lower (OR, 0.776) in the biologics group than in the biologics naïve group in this study, suggesting the possibility that anti-TNF-α agents prevent the progression to gestational diabetes mellitus. No previous study has shown that biologic agent use might reduce the risk of gestational diabetes in patients with rheumatic diseases and IBD. Patients with RA and IBD might be at risk of insulin resistance.[35,36] Several studies have shown that pro-inflammatory cytokines, such as TNF-α and interleukin-6, are associated with insulin resistance; biologic agents that inhibit these cytokines could decrease the risk of diabetes mellitus by increasing insulin sensitivity.[37-39] Notably, anti-TNF-α agents were associated with a significant reduction in the risk of diabetes mellitus in patients with RA, and showed a favorable effect on insulin sensitivity in IBD patients.[36,40] Moreover, a study showed that increased TNF-α levels are associated with gestational diabetes mellitus.[41] While the previous studies could explain the underlying mechanisms of reduced risk of gestational diabetes mellitus in the biologics group in the present study, the other possibilities such as concomitant glucocorticoid use and disease activity of this association should be addressed, which could not be addressed due to lack of data in the current study. Though the use of biologics during pregnancy showed a tendency to lower the risk of gestational diabetes compared to the non-use of biologics, no statistical significance was obtained (OR, 0.903; 95% CI, 0.697–1.169).

In the study, fetal loss and preeclampsia/eclampsia showed no association with ever-exposure to biologic agents. TNF-α affects hormone synthesis, placental structure, and embryonic development during pregnancy.[42] Studies have shown that increased TNF-α levels are associated with fetal loss.[43] In addition, some anti-TNF-α agents (adalimumab and etanercept) have effectively treated women with recurrent miscarriages or repeated in vitro fertilization failure.[44] In 2004, Katz et al.[45] reported no increase in spontaneous abortion rates in a group of 96 pregnant women with RA and CD treated with infliximab compared with the general population. A meta-analysis study showed that fetal loss (including therapeutic abortion and spontaneous abortion) was not significantly different between anti-TNF-α agent users and non-users during pregnancy.[29] Another recent meta-analysis study reported no difference in the rates of miscarriage or preeclampsia with the use of biologic agents during pregnancy.[46] These previous studies are consistent with the present study regarding biologic agent use not affecting overall fetal loss. Interestingly, we found that the risk of fetal loss in the patients who used biologics during pregnancy was significantly decreased, which needs to be confirmed in further studies with larger sample sizes.

Notably, in our study, biologics use during pregnancy was associated with an increased risk of adverse pregnancy outcomes including preterm delivery, preeclampsia/eclampsia,

intrauterine growth retardation, and cesarean section. While, in a small hospital-based study of 18 patients with IBD, there were no pregnancy-related complications such as premature or stillbirths among patients who used biologics during pregnancy.[47] Although disease activity decreases during pregnancy in patients with IMIDs, especially RA and IBD, active disease during pregnancy can lead to adverse pregnancy outcomes such as fetal loss, stillbirth, preterm delivery, and cesarean section.[48-51] Also, in a meta-analysis, women with IMIDs treated with anti-TNF-α agents showed a significantly increased risk of preterm delivery, spontaneous abortion, and low birth weight than the general population; however, anti-TNF-α non-users also showed similar results, suggesting the contribution of disease itself to the adverse pregnancy outcomes.[52] The increase in pregnancy complications in patients who used biologics during pregnancy may be attributed to the patient's high disease activity rather than biologics.

This study had some limitations. First, the NHIS claims database lacks detailed clinical information on individual patients, such as laboratory findings, disease activities, radiological findings, and lifestyle factors. Since the biologics group is estimated to have higher disease activity than the biologics naïve group, many patients with severe disease activity might be included in the biologics group, which may have resulted in poor pregnancy outcomes such as intrauterine growth retardation. Second, the results of neonatal complications, including congenital anomalies and low birth weight, were unknown because mother-infant pairs were not established. Therefore, further hospital-based studies are needed to confirm the effect of disease activity on pregnancy and fetal outcomes in the biologics group. Third, the precise gestational weeks at the time of delivery and abortion were unknown. Therefore, since the exact exposure time of biologic agents was unclear, we defined the conception date using the operational definition according to the previous literature, which defined it as the earliest of 38 weeks (266 days) before the date of delivery and 14 days before a clinic visit with an ICD-10 code for abortion or confirmed pregnancy.[18] However, in cases of extremely preterm birth, the index date may be significantly earlier than the actual conception date. Fourth, most participants used anti-TNF-α agents, and few used non-TNF agents. Therefore, further research should examine the association of pregnancy outcomes with non-TNF biologics. Fifth, the biologics group included patients who used the biologic agent even once in the study. Sixth, it is not possible to obtain drug compliance from the claim data, and prescription itself alone may not accurately reflect the actual individual patient's biologics use. Therefore, further hospital-based studies are needed to verify that the prescribed biologics have actually been administered. To compensate for this limitation, arbitrary criteria for the duration of the biologics use for more than one year or less than one year were set to perform the subgroup analysis for adverse pregnancy outcomes in the present study. However, further studies are needed to analyze more details about the duration of drug exposure and the time points of administration prior to pregnancy, considering the half-life of the biologic agents. Despite these limitations, a major strength of this study was that it used the largest possible population data, a nationwide claims database, to investigate the impact of exposure to biologic agents on pregnancy outcomes in patients with rheumatic diseases and IBD.

In conclusion, the present study using nationwide population data may improve the understanding of the impact of biologics on the pregnancy prognosis of patients with rheumatic diseases and IBD. This study showed that patients treated with biologic agents had live births and fetal loss comparable to the biologics naïve group and lower risk of gestational diabetes mellitus than the biologics naïve group. However, biologics use seems

to increase the risk of intrauterine growth retardation and cesarean delivery, especially patients with biologics use during pregnancy. Therefore, clinicians who prescribe biologics during pregnancy need to collaborate with obstetricians for screening and management of pregnancy complications.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Operational definitions of inclusion criteria, outcome, and comorbidities

Click here to view

Supplementary Table 2

Standardized codes of the Korean National Health Insurance claims database for medical treatments used in this study

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Supplementary Table 3

Pregnancy outcomes in patients on an anti-TNF-α agent

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Supplementary Table 4

Effect of biologics on adverse pregnancy outcomes in patients on an anti-TNF-α agent

Click here to view

Supplementary Table 5

Effects of biologics on adverse pregnancy outcomes excluding induced abortion

Click here to view

Supplementary Table 6

Effects of biologics duration on adverse pregnancy outcomes excluding induced abortion

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Supplementary Table 7

Effects of the biologics administration during pregnancy on adverse pregnancy outcomes excluding induced abortion

Click here to view

REFERENCES

1. Agrawal M, Shah S, Patel A, Pinotti R, Colombel JF, Burisch J. Changing epidemiology of immune-mediated inflammatory diseases in immigrants: a systematic review of population-based studies. *J Autoimmun* 2019;105:102303.
   PUBMED | **CROSSREF**

2. El-Gabalawy H, Guenther LC, Bernstein CN. Epidemiology of immune-mediated inflammatory diseases: incidence, prevalence, natural history, and comorbidities. *J Rheumatol Suppl* 2010;85(0):2-10.
   PUBMED | **CROSSREF**

3. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis* 2006;12 Suppl 1:S3-9.
   PUBMED | **CROSSREF**

4. Littlejohn EA. Pregnancy and rheumatoid arthritis. *Best Pract Res Clin Obstet Gynaecol* 2020;64:52-8.
   PUBMED | **CROSSREF**

5. Barenbrug L, Groen MT, Hoentjen F, van Drongelen J, Reek JM, Joosten I, et al. Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor-α during pregnancy: a systemic review and meta-analysis. *J Autoimmun* 2021;122:102676.
   PUBMED | **CROSSREF**

6. Kim H, Sung YK. Epidemiology of rheumatoid arthritis in Korea. *J Rheum Dis* 2021;28(2):60-7.
   CROSSREF

7. Palomba S, Sereni G, Falbo A, Beltrami M, Lombardini S, Boni MC, et al. Inflammatory bowel diseases and human reproduction: a comprehensive evidence-based review. *World J Gastroenterol* 2014;20(23):7123-36.
   PUBMED | **CROSSREF**

8. Tincani A, Taylor P, Fischer-Betz R, Ecoffet C, Chakravarty E. FRI0693 Fears and misconceptions of women with chronic rheumatic diseases on their journey to motherhood. *Ann Rheum Dis* 2018;77 Suppl 2:866.
   CROSSREF

9. Allen KD, Kiefer MK, Butnariu M, Afzali A. Pregnant women with immune mediated inflammatory diseases who discontinue biologics have higher rates of disease flare. *Arch Gynecol Obstet* 2022;306(6):1929-37.
   PUBMED | **CROSSREF**

10. Ghalandari N, Dolhain RJ, Hazes JM, van Puijenbroek EP, Kapur M, Crijns HJ. Intrauterine exposure to biologics in inflammatory autoimmune diseases: a systematic review. *Drugs* 2020;80(16):1699-722.
    PUBMED | **CROSSREF**

11. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis* 2018;77(2):175-87.
    PUBMED | **CROSSREF**

12. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. *Postgrad Med J* 2007;83(978):251-60.
    PUBMED | **CROSSREF**

13. Kim J, Koh JH, Choi SJ, Jeon CH, Kwok SK, Kim SK, et al. KOBIO, the first web-based Korean biologics registry operated with a unified platform among distinct disease entities. *J Rheum Dis* 2021;28(4):176-82.
    CROSSREF

14. Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016;150(3):734-757.e1.
    PUBMED | **CROSSREF**

15. Mahadevan U, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, et al. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD Parenthood Project Working Group. *Gastroenterology* 2019;156(5):1508-24.
    PUBMED | **CROSSREF**

16. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse ME, Lockshin MD, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;72(4):529-56.
    PUBMED | **CROSSREF**

17. Park JS, Lee CH. Clinical study using healthcare claims database. *J Rheum Dis* 2021;28(3):119-25.
    CROSSREF

18. Kim HO, Lee K, Lee SM, Seo GH. Association between pregnancy outcomes and radioactive iodine treatment after thyroidectomy among women with thyroid cancer. *JAMA Intern Med* 2020;180(1):54-61.
    PUBMED | **CROSSREF**

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
   PUBMED | CROSSREF

20. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43(11):1130-9.
   PUBMED | CROSSREF

21. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68(1):1-26.
   PUBMED | CROSSREF

22. Tsao NW, Lynd LD, Sadatsafavi M, Hanley G, De Vera MA. Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune diseases: a population-based cohort study. *Arthritis Care Res (Hoboken)* 2018;70(7):979-86.
   PUBMED | CROSSREF

23. Lee HH, Bae JM, Lee BI, Lee KM, Wie JH, Kim JS, et al. Pregnancy outcomes in women with inflammatory bowel disease: a 10-year nationwide population-based cohort study. *Aliment Pharmacol Ther* 2020;51(9):861-9.
   PUBMED | CROSSREF

24. Lee JS, Oh JS, Kim YJ, Hong S, Lee CK, Yoo B, et al. Effects of pregnancy and delivery methods on change in ankylosing spondylitis treatment using the Korean health insurance review and assessment service claims database. *J Korean Med Sci* 2019;34(37):e238.
   PUBMED | CROSSREF

25. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological therapies in immune-mediated inflammatory diseases: can biosimilars reduce access inequities? *Front Pharmacol* 2019;10:279.
   PUBMED | CROSSREF

26. Park EH, Lee JS, Kim YJ, Lee SM, Jun JK, Lee EB, et al. Pregnancy outcomes in Korean women with ankylosing spondylitis. *Korean J Intern Med* 2021;36(3):721-30.
   PUBMED | CROSSREF

27. Bartha JL, Romero-Carmona R, Comino-Delgado R. Inflammatory cytokines in intrauterine growth retardation. *Acta Obstet Gynecol Scand* 2003;82(12):1099-102.
   PUBMED | CROSSREF

28. Bröms G, Kieler H, Ekbom A, Gissler M, Hellgren K, Lahesmaa-Korpinen AM, et al. Anti-TNF treatment during pregnancy and birth outcomes: A population-based study from Denmark, Finland, and Sweden. *Pharmacoepidemiol Drug Saf* 2020;29(3):316-27.
   PUBMED | CROSSREF

29. Mirdamadi K, Salinas T, Vali R, Papadimitropoulos M, Piquette-Miller M. Meta-analysis of pregnancy outcomes after exposure to TNF-α inhibitors during pregnancy for the treatment of arthritic diseases. *J Popul Ther Clin Pharmacol* 2018;25(1):e53-6.
   PUBMED | CROSSREF

30. Kim AM, Park JH, Kang S, Yoon TH, Kim Y. An ecological study of geographic variation and factors associated with cesarean section rates in South Korea. *BMC Pregnancy Childbirth* 2019;19(1):162.
   PUBMED | CROSSREF

31. Shand AW, Chen JS, Selby W, Solomon M, Roberts CL. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. *BJOG* 2016;123(11):1862-70.
   PUBMED | CROSSREF

32. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KA, Nordvåg BY, Koldingsnes W, et al. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. *Arthritis Rheum* 2011;63(6):1534-42.
   PUBMED | CROSSREF

33. Lee JS, Oh JS, Kim YJ, Hong S, Lee CK, Yoo B, et al. Reasons for the high cesarean delivery rate among women with ankylosing spondylitis: using the Korean National Health Insurance database. *J Rheumatol* 2020;47(5):668-73.
   PUBMED | CROSSREF

34. Skomsvoll JF, Ostensen M, Irgens LM, Baste V. Pregnancy complications and delivery practice in women with connective tissue disease and inflammatory rheumatic disease in Norway. *Acta Obstet Gynecol Scand* 2000;79(6):490-5.
   PUBMED

35. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. *Arthritis Rheum* 2006;54(9):2765-75.
   PUBMED | CROSSREF

36. Paschou SA, Kothonas F, Lafkas A, Myroforidis A, Loi V, Terzi T, et al. Favorable effect of anti-TNF therapy on insulin sensitivity in nonobese, nondiabetic patients with inflammatory bowel disease. *Int J Endocrinol* 2018;2018:6712901.
   PUBMED | CROSSREF

37. Nam SH, Kim M, Kim YJ, Ahn SM, Hong S, Lee CK, et al. Risk of new-onset diabetes mellitus associated with antirheumatic drugs in patients with rheumatoid arthritis: a nationwide population study. *J Clin Med* 2022;11(8):2109.
   PUBMED | CROSSREF

38. Baker JF, England BR, George M, Cannon G, Sauer B, Ogdie A, et al. Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis. *Ann Rheum Dis* 2021;80(5):566-72.
   PUBMED | CROSSREF

39. Antohe JL, Bili A, Sartorius JA, Kirchner HL, Morris SJ, Dancea S, et al. Diabetes mellitus risk in rheumatoid arthritis: reduced incidence with anti-tumor necrosis factor α therapy. *Arthritis Care Res (Hoboken)* 2012;64(2):215-21.
   PUBMED | CROSSREF

40. Lin C, Ji H, Cai X, Yang W, Lv F, Ji L. The association between the biological disease-modifying anti-rheumatic drugs and the incidence of diabetes: a systematic review and meta-analysis. *Pharmacol Res* 2020;161:105216.
   PUBMED | CROSSREF

41. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta* 2015;36(7):709-15.
   PUBMED | CROSSREF

42. Hunt JS, Chen HL, Miller L. Tumor necrosis factors: pivotal components of pregnancy? *Biol Reprod* 1996;54(3):554-62.
   PUBMED | CROSSREF

43. Romanowska-Próchnicka K, Felis-Giemza A, Olesińska M, Wojdasiewicz P, Paradowska-Gorycka A, Szukiewicz D. The role of TNF-α and anti-TNF-α agents during preconception, pregnancy, and breastfeeding. *Int J Mol Sci* 2021;22(6):2922.
   PUBMED | CROSSREF

44. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, Llurba E, Gris JM. Tumor necrosis factor-alpha and pregnancy: focus on biologics. an updated and comprehensive review. *Clin Rev Allergy Immunol* 2017;53(1):40-53.
   PUBMED | CROSSREF

45. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004;99(12):2385-92.
   PUBMED | CROSSREF

46. O'Byrne LJ, Alqatari SG, Maher GM, O'Sullivan AM, Khashan AS, Murphy GP, et al. Fetal and maternal outcomes after maternal biologic use during conception and pregnancy: a systematic review and meta-analysis. *BJOG* 2022;129(8):1236-46.
   PUBMED | CROSSREF

47. Lee KE, Jung SA, Park SH, Moon CM, Shim SY, Kim ES, et al. Influence of anti-tumor necrosis factor-alpha therapy to pregnant inflammatory bowel disease women and their children's immunity. *Intest Res* 2019;17(2):237-43.
   PUBMED | CROSSREF

48. Agret F, Cosnes J, Hassani Z, Gornet JM, Gendre JP, Lémann M, et al. Impact of pregnancy on the clinical activity of Crohn's disease. *Aliment Pharmacol Ther* 2005;21(5):509-13.
   PUBMED | CROSSREF

49. Hazes JM, Coulie PG, Geenen V, Vermeire S, Carbonnel F, Louis E, et al. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. *Rheumatology (Oxford)* 2011;50(11):1955-68.
   PUBMED | CROSSREF

50. Andreoli L, García-Fernández A, Chiara Gerardi M, Tincani A. The course of rheumatic diseases during pregnancy. *Isr Med Assoc J* 2019;21(7):464-70.
   PUBMED

51. Restellini S, Biedermann L, Hruz P, Mottet C, Moens A, Ferrante M, et al. Update on the management of inflammatory bowel disease during pregnancy and breastfeeding. *Digestion* 2020;101 Suppl 1:27-42.
   PUBMED | CROSSREF

52. Komaki F, Komaki Y, Micic D, Ido A, Sakuraba A. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-α use in females with immune mediated diseases; a systematic review and meta-analysis. *J Autoimmun* 2017;76:38-52.
   PUBMED | CROSSREF