Original Article

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Abortion adverse events associated with adalimumab, etanercept, ustekinumab, and dupilumab during pregnancy: A pharmacovigilance study based on FDA adverse event reporting system

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SUMMARY: Biologics are essential for managing immune-related inflammatory diseases during pregnancy to prevent disease progression and adverse pregnancy outcomes. However, data on the safety of biologics in a broader population are limited. This study aims to evaluate abortion-related adverse events (AEs) associated with adalimumab, etanercept, ustekinumab, and dupilumab, using data from the FDA Adverse Event Reporting System (FAERS) database. A disproportionality analysis was performed using the Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) to identify signals of abortion-related AEs. The time-to-onset profiles were assessed by analyzing the description and Weibull shape parameters (WSPs) for these events. Sensitivity analyses were also conducted, including drug–drug interaction studies, logistic regression, and a similar retrospective analysis using data from the Japanese Adverse Drug Event Report (JADER) database. Disproportionality analysis revealed specific signals for abortion-related AEs associated with adalimumab, etanercept, and ustekinumab. The drug–drug interaction analysis indicated that these biologics, particularly without methotrexate or prednisolone, increase the risk of abortion-related AEs. Logistic regression identified several factors influencing outcomes. The time-to-onset analysis revealed that dupilumab had an earlier onset of 62.5 days, while etanercept had a later onset at 184 days. WSPs analysis revealed that signals for adalimumab, ustekinumab, and dupilumab exhibited early failure-type features, indicating a decreasing risk of abortion-related AEs over time. In conclusion, adalimumab, etanercept, and ustekinumab are associated with an increased risk of abortion-related adverse pregnancy outcomes, though the signals remain relatively weak. Further large-scale studies are needed to provide more definitive evidence.

Keywords: disproportionality analysis, spontaneous abortion, FAERS, biologics, pharmacovigilance

1. Introduction

Immune-related inflammatory disorders impose significant challenges on pregnant populations. In 2019, the age-standardized rates of autoimmune diseases were 89.51 (95% CI: 71.94 to 110.35) per 100,000 women of childbearing age and 85.78 (95% CI: 68.72 to 106.37) per 100,000 in sexually mature adults (*1*). Biologic therapies, including anti-tumor necrosis factor (anti-TNF) agents and anti-interleukin (IL)-12/23 or IL-4/IL-13 antibodies, are widely used to treat immune-mediated inflammatory diseases. Biologics targeting tumor necrosis factor (TNF), such as adalimumab and etanercept, have shown significant promise in managing autoimmune inflammatory diseases (*2*). Patients with spontaneous abortion and preeclampsia/eclampsia exhibit markedly elevated levels of inflammatory cytokines like TNF-α and IL-4 (*3*). These immune-related inflammatory diseases upregulate immunomodulatory and anti-inflammatory factors, which can disrupt syncytialization, adhesion, and hormonal functions of the trophectoderm (*4*). Since the embryo functions as a semi-allograft to the mother, maternal immune tolerance is crucial for sustaining pregnancy. Among the various factors, the balance between Th1 and Th2 cytokines plays a critical role in maintaining immune equilibrium at the maternal-fetal interface (*5-7*). This raises the question of whether biologics targeting T Helper Cells 1 (Th1) (TNF, IL-12/23, IFN-γ) or T Helper Cells 2 (Th2) (IL-4, IL-13, IL-5) cytokines affect the immune balance at this interface during pregnancy. These biologics, which vary in their ability to cross the placental barrier (*8*), may have distinct impacts on pregnancy outcomes, warranting further investigation.

Intrauterine growth restriction, spontaneous abortion, and preterm birth are common adverse outcomes

associated with anti-TNF-α drugs during pregnancy (*9*). Until 2007, the use of etanercept was advised against during pregnancy (*10*); however, its use has since been approved up to gestational weeks 30-32 and throughout pregnancy from 2016 onward (*11*). A recent systematic review of 13 clinical studies involving 68 pregnant patients indicated that dupilumab has demonstrated efficacy in treating atopic dermatitis without clear evidence of adverse pregnancy or neonatal outcomes (*12*). Ustekinumab, which crosses the placental barrier in mid to late pregnancy (*13*), has fetal concentrations higher than maternal levels. However, there is currently no definitive evidence linking ustekinumab to increased risks of adverse pregnancy or neonatal outcomes (*13,14*). Continued use of biologics during pregnancy is recommended for patients with inflammatory bowel disease (IBD) or inflammatory rheumatic diseases to prevent relapse, control symptoms, and minimize complications and disease progression (*15*). Discontinuation of ustekinumab or vedolizumab in these patients may lead to IBD relapse (*16*).

The long-term safety of biotherapy remains a topic of ongoing debate. Antibodies do not cross the placental barrier until mid-gestation (*17*). However, medication withdrawal typically occurs during the first trimester or as soon as pregnancy is confirmed. Pregnant patients with immune-mediated chronic inflammatory diseases face the dilemma of whether the benefits of biological therapy outweigh potential harms to pregnancy outcomes.

The FAERS database contains spontaneous adverse event reports submitted to the FDA, supporting post-marketing safety monitoring and providing insights into the real-world usage of drugs and biologics (*18*). Currently, there is a lack of extensive, comprehensive, and systematic research on the association between biologics and miscarriage, largely due to the high-risk nature of pregnant women. Therefore, a pharmacovigilance study was conducted to examine the relationship between various biological agents and pregnancy loss by analyzing real-world data from the FDA's FAERS. Specifically, this study focused on pregnant women using different biologics, systematically evaluating adverse event signals through descriptive statistics, disproportionality analysis, adverse reaction induction time, logistic regression, and other methods. In summary, this study provides further evidence for the use of biologics in pregnant women with chronic immune-inflammatory diseases, aiming to control disease progression and improve pregnancy outcomes.

2. Materials and Methods

2.1. Data sources

FAERS (the FDA Adverse Event Reporting System) is a database maintained by the FDA that collects and analyzes reports of adverse events associated with drugs and therapeutic biologics. Data for several biologics (adalimumab, etanercept, ustekinumab, and dupilumab) were extracted from the FAERS database for the period from January 2004 to December 2024. This retrospective pharmacovigilance study utilized disproportionality analysis to assess adverse events related to these biologics. Each reported adverse event in the database was mapped to a Preferred Term (PT). The PTs associated with abortion or pregnancy loss were identified from the following categories: "Termination of pregnancy and risk of abortion" (SMQ, Standardized MedDRA Query), "Pregnancy, puerperium and perinatal conditions" (SOC, System Organ Class), "Abortions and stillbirth" (HLGT, High-Level Group Term), and "Abortion-related conditions and complications" (HLT, High-Level Term), based on the Medical Dictionary for Regulatory Activities (MedDRA/J 26.1) English version. Initially, all drugs linked to these adverse events were identified, with several biologics, excluding contraceptive medications or devices, ranking among the top. Following this, abortion-related adverse events (AEs) caused by TNF inhibitors, IL12/23 inhibitors, or IL4 inhibitors were analyzed within a specific population (pregnant women (*19*) aged 15-55 years) from the FAERS database.

2.2. Analysis procedures

The sample range was determined based on relevant literature (*20,21*), with the age range (15-55 years) selected to focus on the reproductive age group of pregnant women. Only drugs identified as "PS" (Primary Suspect Drug) were included in the analysis. Disproportionality analysis, a validated method in pharmacovigilance databases, was employed for this research (*22*). The primary statistical tools used for signal detection were the Reporting Odds Ratio (ROR) (*23*) and Bayesian Confidence Propagation Neural Network (BCPNN) (*24*), with Information Component (IC) values to identify adverse reaction signals. A signal was deemed present if the number of AEs exceeded three and the lower boundary of the 95% Confidence Interval (CI) for the ROR (ROR_{025}) was > 1 or the lower boundary of the 95% CI for the IC (IC_{025}) was > 0 (*25*). The equations and parameters are listed in Table S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=264*).

Time to onset was defined as the period between the start of treatment and the occurrence of abortion events (Event onset date (EVENT_DT) – Therapy start date (START_DT)). To prevent distortion of results, list-wise deletion was applied to missing data and instances where the treatment start date exceeded the AE onset date. The analysis of time-to-onset data included the use of median duration, quartiles, and Weibull shape parameters (WSPs) (*26*). The differences in time to onset for abortion-related

AEs compared to non-abortion-related AEs for each biologic were assessed simultaneously.

2.3. Sensitivity analysis

To account for potential confounding factors, adjustments were made for age, weight, time-to-onset, and different medications in both univariate and multivariate logistic regression analyses. Potential covariates were screened as well. Additionally, drug-drug interactions (DDI) between methotrexate and biologics were used as a positive control, while DDI between prednisolone and biologics served as a negative control, to mitigate signal bias caused by polypharmacy. The Ω-shrinkage model, in combination with the BCPNN method, was employed to analyze DDI signals (*27*). The Japanese Adverse Drug Event Report (JADER) database, a pharmacovigilance database managed by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, has been publicly accessible since 2012. It is used to collect and analyze AEs occurring in clinical settings post-marketing of drugs (*28*). To further validate the reliability of the findings, the same analysis was performed using the JADER database for verification purposes.

2.4. Ethical approval of studies and informed consent

Ethical review is not required as the study analyzed de-identified and publicly available FAERS or JADER data. These databases serve as the primary global system for spontaneous reporting of adverse drug events and are freely accessible to the public. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki).

2.5. Statistical analysis

Statistical analyses were conducted using Microsoft Excel 2019 and R statistical software version 4.3.0. The Mann-Whitney *U* test was employed to compare AEs related to miscarriage with other AEs caused by biologics. Logistic regression was used for sensitivity analyses.

3. Results

3.1. Clinical characteristics

From Q1 2004 to Q4 2024, after data cleaning and deduplication in the FAERS database, a total of 18,627,667 cases were included (Figure 1). Among these, 124,927 cases occurred in pregnant women of childbearing age. Among biologics targeting Th1 or Th2 type cytokines, positive signals for abortion-related AEs were observed with adalimumab, etanercept, ustekinumab, and dupilumab. A total of 5,076 abortion-related AEs were reported, with adalimumab, etanercept, ustekinumab, and dupilumab identified as the "primary suspect" (PS) in 151, 225, 3, and 6 cases, respectively. Descriptive statistics regarding age, weight, reporting country, and outcomes of these cases are provided in Table 1. The number of reported cases for adalimumab (39.2%) and etanercept (58.4%) was significantly higher. This can be attributed to the time of their market approval: Adalimumab was approved in the US in 2002, and etanercept in 1998, while ustekinumab and dupilumab were launched in 2009 and 2017, respectively. Most of patients with abortion-related AEs were between 25 and 45 years old: Adalimumab (89.4%), etanercept (88%), ustekinumab (100%), and dupilumab (66.6%). The majority of patients had a weight between 45 and 65 kg: Adalimumab (23.1%), etanercept (12.4%), ustekinumab (66.7%), and dupilumab (16.7%). The top three reporting countries were the US, France, the UK, and Germany. In terms of outcomes, aside from other outcomes (OT), hospitalization (HO) was the most common, with rates of adalimumab (8.6%), etanercept (4.4%), and dupilumab (66.6%). Excluding "NA" values, the top 20 diseases treated with these drugs are presented in Figure 2.

3.2. Disproportionality analysis for biologics-related abortion AEs

The total number of abortion-related AEs involving adalimumab and etanercept was the highest, with adalimumab (1,077 cases), etanercept (455 cases), ustekinumab (91 cases), and dupilumab (131 cases). The signal values and associations between each drug and abortion-related AEs are shown in Figure 3: Adalimumab (ROR (95% CI) = 1.32 (1.24–1.42), IC (IC_{025}) = 0.37 (0.28)), etanercept (ROR (95% CI) = 1.13 (1.03–1.24), IC (IC_{025}) = 0.17 (0.03)), and ustekinumab (ROR (95% CI) = 1.29 (1.05–1.60), IC (IC_{025}) = 0.35 (0.04)) exhibited positive signal values, while dupilumab (ROR (95% CI) = 1.13 (0.95–1.35), IC (IC_{025}) = – 0.08) displayed a negative signal. At the PT level, all drugs showed positive signal values for the term "Abortion spontaneous": Adalimumab (ROR (95% CI) = 1.49 (1.39–1.59), IC (IC_{025}) = 0.53 (0.43)), etanercept (ROR (95% CI) = 1.32 (1.19–1.46), IC (IC_{025}) = 0.38 (0.23)), ustekinumab (ROR (95% CI) = 1.54 (1.23–1.92), IC (IC_{025}) = 0.59 (0.27)), and dupilumab (ROR (95% CI) = 1.35 (1.12–1.62), IC (IC_{025}) = 0.41 (0.14)). Furthermore, adalimumab showed positive signals for several additional abortion-related AEs: Abortion (ROR (95% CI) = 1.46 (1.14–1.88), IC (IC_{025}) = 0.53 (0.16)), Hemorrhage in pregnancy (ROR (95% CI) = 1.73 (1.31–2.29), IC (IC_{025}) = 0.76 (0.35)), and Post-abortion hemorrhage (ROR (95% CI) = 2.28 (1.11–4.69), IC (IC_{025}) = 1.13 (0.13)). These results suggest that different biologics are associated with positive signals for a limited number of AEs, as depicted in Figures 4A and 4B.

Pregnancy loss is closely related to abnormal

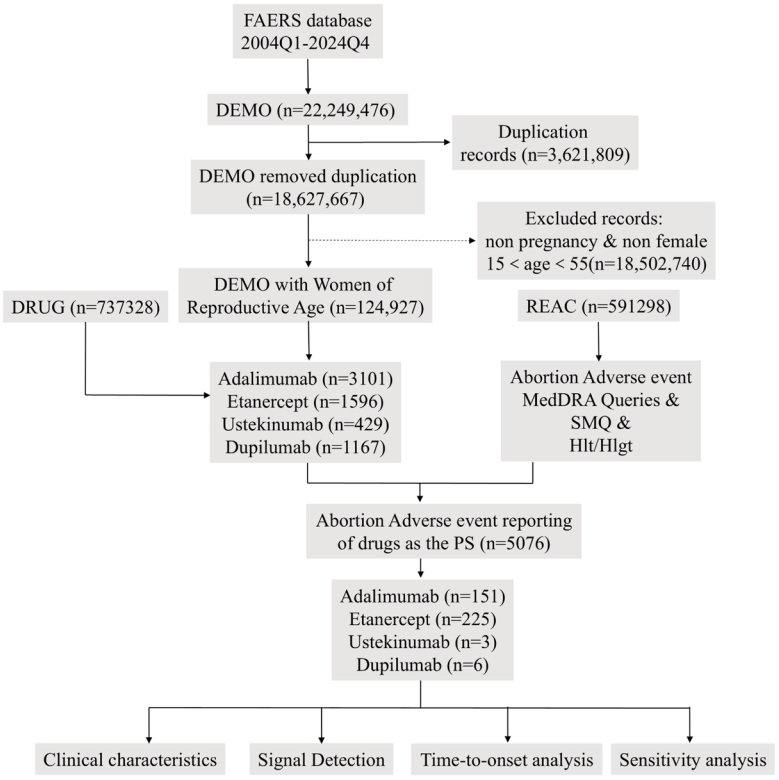

Figure 1. The flow chart of the study.

embryonic development, with the elimination of such embryos often manifesting as miscarriage. While this study focused on miscarriage-related AEs, the top 10 most frequently reported adverse reactions during pregnancy were also examined for the biologics in question. These included: Spontaneous abortion (1,519 cases), live birth (531 cases), pregnancy (456 cases), fetal death (332 cases), premature delivery (206 cases), preeclampsia (174 cases), premature labor (158 cases), gestational diabetes (149 cases), normal newborn (145 cases), and ectopic pregnancy (128 cases) (Figure 5A). Etanercept had the highest number and proportion of reports for abortion-related AEs (225 cases, 14.11%), followed by adalimumab (151 cases, 4.87%), dupilumab (6 cases, 0.51%), and ustekinumab (3 cases, 0.7%) (Figure 5B). This distribution may be influenced by the differing market availability timelines of the drugs, which could affect the baseline number of reports. The number of AEs caused by biologics in women of childbearing age during pregnancy, with a focus on death as the outcome indicator, is shown in Figure 5C. The proportion of death with the outcome of "live birth" was the highest, at 6.59%, while the proportion of death with the outcome of "abortion spontaneous" was 0.13%. The pregnancy process inherently carries risks to both the mother and fetus. Although the likelihood of maternal death due to abortion-related AEs is low, it highlights the potential risks of embryonic loss, endometrial dysfunction, and broader maternal health complications.

3.3. Time to onset of abortion-related adverse event

The time to onset of abortion-related AEs induced by these biologics was analyzed and presented in Figure 6. It was found that dupilumab had the earliest median time for inducing abortion-related AEs, whereas etanercept had the latest median time, with the broadest range. The median time to onset and interquartile range were as follows: Adalimumab: 460 days (146–1,150 days), etanercept: 558 days (184–1,432 days), ustekinumab: 281 days (120–953 days), and dupilumab: 185 days (62.5–324 days).

The WSP analysis was conducted to assess the change ratio in the incidence rate of AEs. As shown in Table 2, based on the shape parameter values, the Weibull distribution types for each drug were as follows: Adalimumab, ustekinumab, and dupilumab were categorized as "Early failure," indicating that the incidence rate of abortion-related AEs induced by these drugs decreases over time. In contrast, etanercept had a shape parameter β of 0.93, which, although classified within the "Random failure" model, still showed tendencies towards the "Early failure" pattern. A comparative analysis of the time to onset of abortion-related and non-abortion-related AEs induced by these biologics revealed that the time to onset of abortion-related AEs induced by adalimumab was significantly longer than that for non-abortion-related AEs, with a significant difference ($p = 0.009$). Conversely, the time to onset of abortion-related AEs induced by etanercept was

Table 1. Characteristics of abortion-related AEs associated with biologics

FAERS	Cases, N (%)			
Characteristic	Adalimumab	Etanercept	Ustekinumab	Dupilumab
Total cases	151 (39.2%)	225 (58.4%)	3 (0.8%)	6 (1.6%)
Gender				
Female	151 (100%)	225 (100%)	3 (100%)	6 (100%)
Age				
≥15&<25	15 (10%)	23 (10.2%)	0	1 (16.7%)
≥25&<45	135 (89.4%)	198 (88%)	3 (100%)	4 (66.6%)
≥45&≤55	1 (0.6%)	4 (1.8%)	0	1 (16.7%)
Reported countries (Top3)				
1	US 33 (21.8%)	US 102 (45.3%)	FRA 2 (66.6%)	US 2 (33.3%)
2	GER 12 (7.9%)	UK 21 (9.3%)	US 1 (33.3%)	FRA 1 (16.6%)
3	UK 10 (6.6%)	GER 15 (6.6%)	-	GER 1 (16.6%)
Outcomes				
OT	137 (90.7%)	208 (92.4%)	3 (100%)	4 (66.6%)
HO	13 (8.6%)	10 (4.4%)	-	2 (33.3%)
CA		4 (1.7%)		-
DS		1 (0.4%)		
LT		1 (0.4%)		
Weight				
<45	2 (1.3%)	1 (0.4%)	0	0
≥45&<65	35 (23.1%)	28 (12.4%)	2 (66.7%)	1 (16.7%)
≥65&<80	17 (11.3%)	9 (4%)	1 (33.3%)	0
≥80	10 (6.6%)	9 (4%)	0	1 (16.7%)
JADER	Cases, N (%)			
Characteristic	Adalimumab	Etanercept	Ustekinumab	Dupilumab
Total cases	9 (32.1%)	13 (46.4%)	5 (17.9%)	1 (3.6%)
Gender/Female	9 (100%)	13 (100%)	5 (100%)	1 (100%)
Reported person				-
Physician	5 (55.6%)	10 (76.9%)	3	
consumer	1 (11.1%)	0	0	
pharmacist	2 (22.2%)	0	2	
Medical professionals	1 (11.1%)	3 (33.1%)	0	
Outcomes				
recovery	4 (44.4%)	4 (30.8%)	1 (20.0%)	
sequela	0		2 (40.0%)	
unknow	5 (55.6%)	9 (69.2%)	2 (40.0%)	

FAERS: FDA Adverse Event Reporting System, JADER: Japanese Adverse Drug Event Report, OT: Other, HO: Hospitalization - Initial or prolonged, CA: Congenital Anomaly, DS: Disability, LT: Life - Threatening.

significantly shorter than for non-abortion-related AEs ($p < 0.01$). For the other two biologics, the differences were not statistically significant.

3.4. Sensitivity analysis

To mitigate potential confounding factors, logistic regression analyses were performed, with age, weight, time to onset, and each drug as independent variables and the occurrence of the target AEs as the dependent variable. The variables were categorized as follows: AGE (age) into four groups: < 23 years, 23-35 years, 35-45 years, and > 45 years; WT (weight) into three groups: < 50 kg, 50-80 kg, and > 80 kg; TIME (time of onset) into three groups: < 1 year, 1-2 years, and > 2 years; and each drug: Adalimumab, etanercept, ustekinumab, and dupilumab. Using the "< 23 years old" group as the reference for age, the risk of abortion-related AEs was significantly increased in the 23-35 years old group (OR = 1.62 [1.12-2.38, $p = 0.012$]), increased but not significantly in the 35-45 years old group (OR = 1.28 [0.87-1.92, $p = 0.228$]), and decreased but not significantly in the > 45 years old group (OR = 0.49 [0.11-1.51, $p = 0.269$]). For time to onset, the risk of abortion was significantly increased in the 1-2 years group (OR = 1.65 [1.24-2.18, $p < 0.001$]) and even more so in the > 2 years group (OR = 2.26 [1.84-2.77, $p < 0.001$]). Compared to the adalimumab group (reference), the risk of abortion was significantly lower in the ustekinumab group (OR = 0.73 [0.57-0.92, $p = 0.010$]), while no significant differences were observed in the other two groups (Figure 7A). After adjusting for other risk factors (Figure 7B), the risk of abortion in the 23-35 years age group was significantly higher than in the reference group (< 23 years old) (OR = 0.73 [0.57-0.92, $p = 0.010$]), while no significant differences

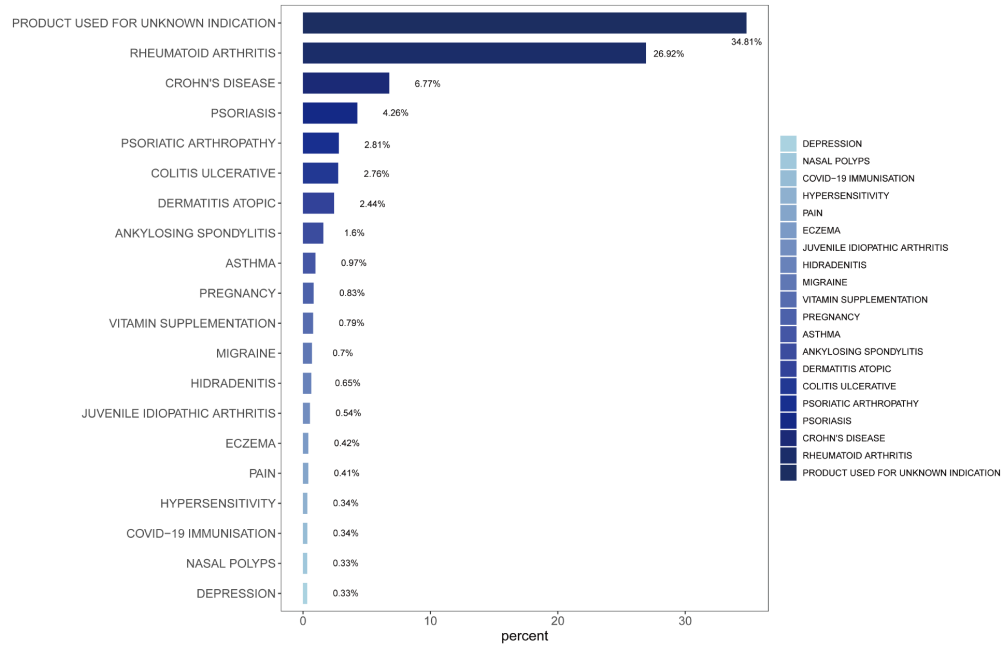

Figure 2. Top 20 diseases treated with these biologics as reported in the FAERS database.

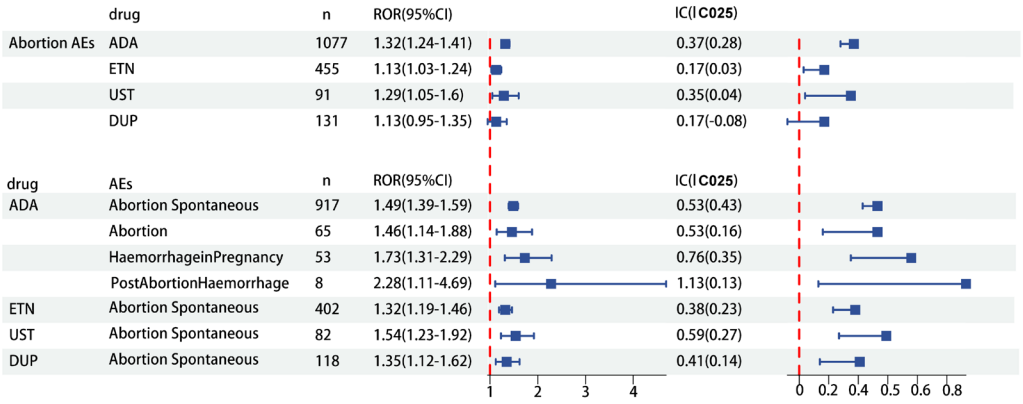

Figure 3. Abortion-related AEs among different biologics.

were observed in the 35-45 and > 45 years age groups compared to the reference group. Weight differences did not significantly influence the outcome. The risk of abortion was significantly higher in the 1-2 years group (OR = 1.65 [1.24-2.19, $p = 0.001$]) and even more so in the > 2 years group (OR = 2.30 [1.86-2.83, $p < 0.001$]). Compared to the adalimumab group, the risk of abortion was significantly lower in the ustekinumab group (OR = 0.72 [0.56-0.92, $p = 0.011$]) and significantly higher in the dupilumab group (OR = 1.97 [1.23-3.13, $p = 0.004$]). The covariates selected by on the stepwise method are presented in Table S2 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=264*). The covariates that have a notably influence on the model include AGE ≥ 23 years and < 35 years, time to onset ≥ 1 year, and the two drugs ustekinumab and dupilumab.

Methotrexate and prednisolone are commonly used to treat autoimmune inflammatory diseases. Methotrexate is associated with pregnancy loss and teratogenicity (*29*), while prednisolone is used to support pregnancy, particularly in patients with recurrent miscarriages (*30*). A sensitivity analysis was conducted to assess the combination of biologics with methotrexate or prednisolone. The association between the combination of adalimumab and methotrexate and abortion was statistically significant, with the combination potentially reducing the risk of abortion (IC: -2.65 (-2.97 to -2.30), Ω: 0.02) (Table 3). Adalimumab alone was associated with an increased risk of abortion (IC: 0.74 (0.65 to 0.84)). Methotrexate alone may reduce the risk of abortion (IC:

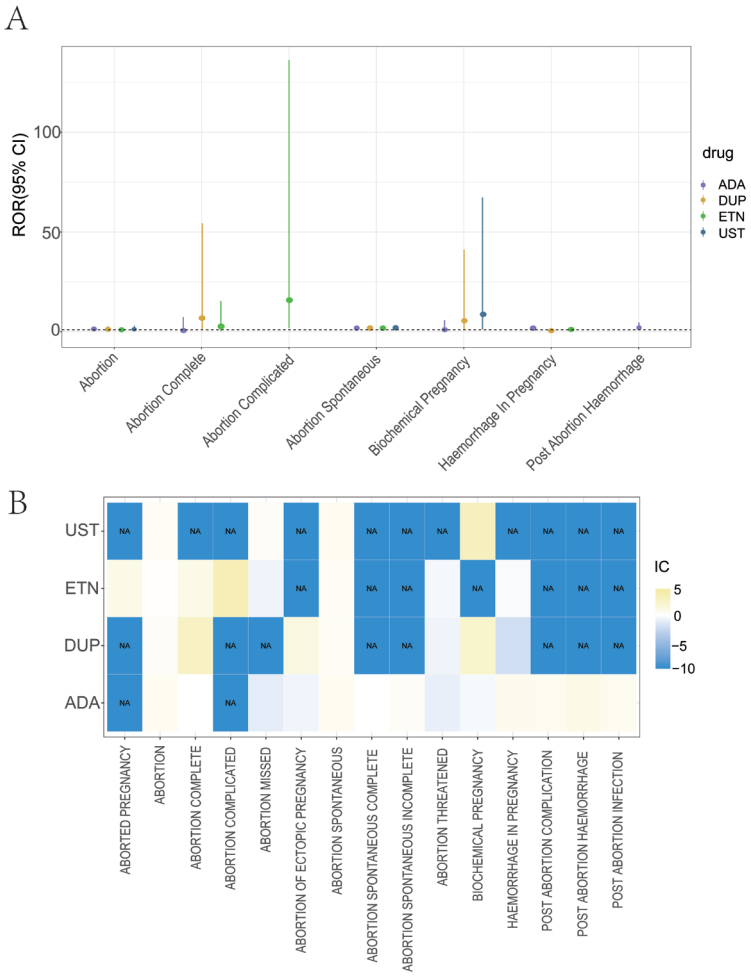

Figure 4. The associations between Abortion-related AEs and different biologics. (A) Forest plots of RORs of different biologics. **(B)** Heatmap showing the associations between biologics and abortion-related AEs. ADA, Adalimumab; ETN, Etanercept; UST, Ustekinumab; DUP, Dupilumab.

-1.01 (-1.29 to -0.71)), though not to the extent observed with the combination of both drugs. A disproportionality analysis of methotrexate in the FAERS database at the PT level for pregnant women is shown in Table S3 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=264*). Among the AEs related to abortion, "INDUCED ABORTION FAILED" was the only positive event (ROR: 13.67 (7.92 to 23.61)). Given its known teratogenic risks, the use of methotrexate in pregnant populations is highly cautioned. Even so, the analysis in the FAERS database is inconsistent with existing literature. In summary, adalimumab is significantly associated with abortion-related AEs. The combination of adalimumab and prednisolone may reduce the risk of abortion (IC: -2.51 (-2.89 to -2.07), Ω: 0.02), whereas the use of prednisolone alone is associated with abortion-related AEs (IC: 0.79 (0.69 to 0.88)). For other biologics, the risk of abortion is higher in non-combined use with prednisolone compared to combination therapy, except for dupilumab. Additionally, there is insufficient data on the combination of ustekinumab and dupilumab with prednisolone and methotrexate. These findings support the reliability of the association between the studied biologics and abortion-related AEs.

A similar investigation was conducted on abortion-related AEs reports in pregnant women of childbearing age from the post-marketing period of these drugs through Q2 2024 in the JADER database (Figure 7C). The number of cases involved was relatively small, including adalimumab (9 cases), etanercept (13 cases), ustekinumab (5 cases), and dupilumab (1 case). The risk assessment results were as follows: Adalimumab: ROR (95% CI) = 2.48 (1.28–4.79), IC (IC025) = 1.29 (– 0.38); Etanercept: ROR (95% CI) = 2.22 (1.28–3.85), IC (IC025) = 1.14 (– 0.53); Ustekinumab: ROR (95% CI) = 10.09 (4.14–24.58), IC (IC025) = 3.29 (1.61). The signal values for adalimumab, etanercept, and ustekinumab were positive. However, only adalimumab and etanercept had sufficient sample sizes for further analysis. Positive signal values for the PT "Abortion spontaneous " were observed: Adalimumab: ROR (95% CI) = 4.7 (2.09–10.57), IC (IC025) = 2.2 (0.52); Etanercept: ROR (95% CI) = 3.98 (1.97–8.05), IC (IC025) = 1.96 (0.28). These results are generally consistent with the findings from the

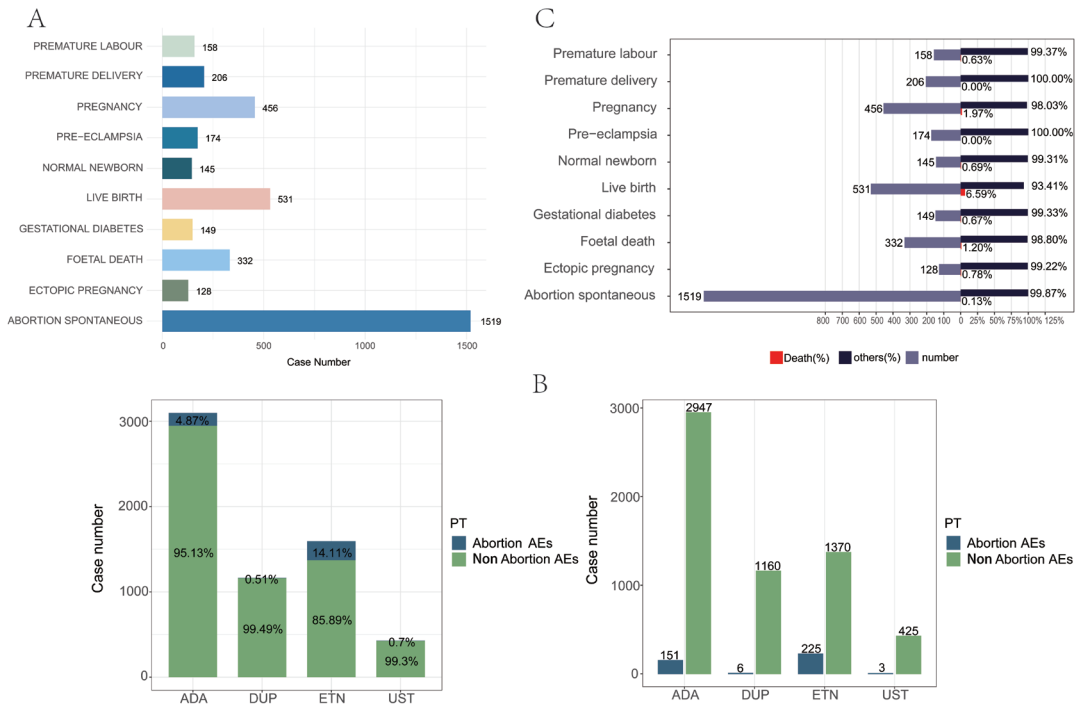

Figure 5. Comparison and outcomes of Abortion-related AEs caused by biologics versus other adverse events. (A) The number of reported cases of the first ten types of these biologics related abortion- AEs. **(B)** The bar chart shows the percentage and number of different biologics abortion AEs and non-abortion-related AEs of different biologics in the FAERS database from Q1 2004 to Q4 2024. **(C)** Death cases and their proportion in biologics concomitantly with abortion AEs. ADA, Adalimumab; ETN, Etanercept; UST, Ustekinumab; DUP, Dupilumab. The vertical axis represents PT. PT, preferred term.

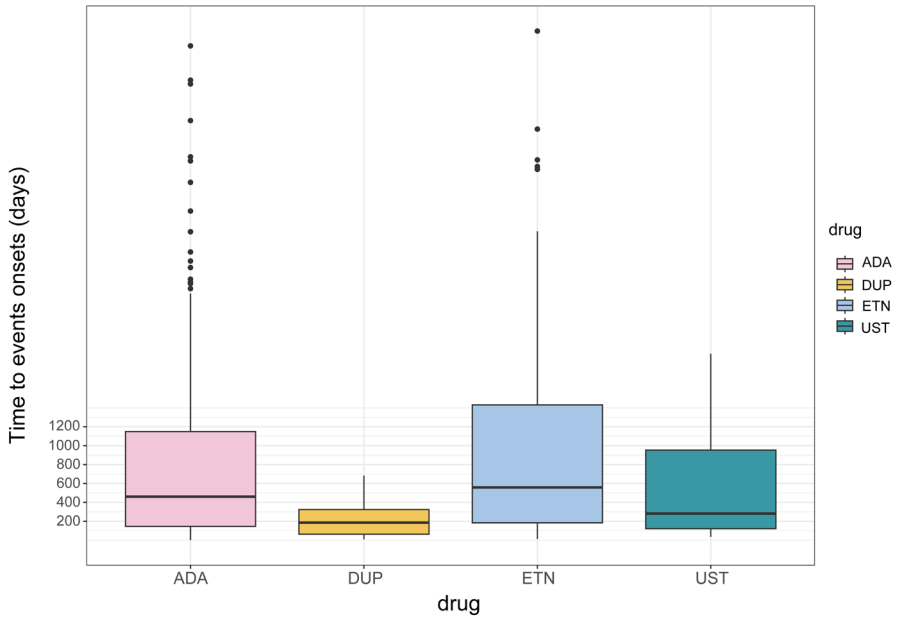

Figure 6. Time to onset of abortion-related AEs. ADA, Adalimumab; ETN, Etanercept; UST, Ustekinumab; DUP, Dupilumab.

FAERS database study.

4. Discussion

The pregnancy represents a high-risk period for pharmacological treatments, particularly for women with chronic inflammatory rheumatic, gastroenterological, or dermatological diseases. During this time, pharmacokinetics and pharmacodynamics undergo significant alterations, presenting potential risks to fetal development. This poses a crucial concern in treatment decisions. Pregnant women often face the challenge of balancing the benefits and risks of pharmacotherapy, which necessitates collaborative decision-making with

Table 2. The WSP analysis for Time-to-onset of different biologics

Database	Adalimumab		Etanercept		Ustekinumab		Dupilumab	
	Abortion AEs	Non Abortion AEs	Abortion AEs	Non Abortion AEs	Abortion AEs	Non Abortion AEs	Abortion AEs	Non Abortion AEs
case reports	622	1036	276	500	48	138	40	162
Median(d)	460	394	558	920	281	395	185	119
(25%-75%)	(146-1150)	(140-809)	(184-1432)	(374-1425)	(120-953)	(133-924)	(62.5-324)	(46-330)
p	0.009		< 0.001		0.408		0.708	
Scale parameter:α	752.57	615.20	868.52	1323.81	597.43	667.58	229.355867	240.53
(95% CI)	(680.35-824.79)	(572.72-657.68)	(750.43-986.61)	(1207.32-1440.30)	(389.73-769.13)	(533.34-801.82)	(158.77-299.94)	(193.63-287.43)
Shape parameter:β	0.86	0.93	0.91	1.04	0.91	0.87	1.05	0.84
(95% CI)	(0.81-0.92)	(0.86-0.94)	(0.83-1.00)	(0.98-1.12)	(0.71-1.12)	(0.76-0.99)	(0.79-1.32)	(0.74-0.93)
Type	Early failure	Early failure	Random failure	Random failure	Random failure	Early failure	Random failure	Early failure

physicians and pharmacists(*31*). This study employed the ROR and BPCNN methods to investigate abortion-related adverse signals linked to adalimumab, etanercept, ustekinumab, and dupilumab in pregnant populations, utilizing data from the FAERS and JADER databases. Among the reported conditions, rheumatoid arthritis (RA, 26.92%), Crohn's disease (6.77%), psoriasis (4.46%), psoriatic arthropathy (2.81%), ulcerative colitis (2.76%), atopic dermatitis (2.44%), ankylosing spondylitis (1.6%), and asthma (0.97%) comprised nearly half of the cases. Notably, "Abortion spontaneous" was the most frequently reported AE across all AEs in pregnant women using these biologics.

Adalimumab and etanercept had a higher number of reported cases due to their earlier release compared to other biologics. Studies have shown that 88.3% of patients with RA are aged between 25 and 45 years, which aligns with the typical childbearing age. Women are more likely to develop RA than men, with conditions such as menopause, postpartum status, and anti-estrogen therapy potentially increasing the risk for RA (*32*). RA also tends to peak between the ages of 50 and 54 years (*33*). The age distribution for IBDs like Crohn's disease and ulcerative colitis follows a bimodal pattern, peaking around ages 20-30 and 50-70 (*34,35*). Atopic dermatitis typically begins in early childhood (*36*) and has a higher incidence in women (10.2%) than men (5.8%) (*37*). The onset of psoriasis is concentrated in two age brackets: 30-39 and 60-69 years, with women tending to develop it slightly earlier than men (*38*). Ankylosing spondylitis is more common in men, particularly between the ages of 18 and 35 (*39*), though it often experiences diagnostic delays in women. The age distribution of these immune-related inflammatory disorders aligns with the age group of women under study. In the sensitivity analysis, both univariate and multivariate logistic regression revealed that compared to the < 23 age group, the signals for abortion-related AEs were more pronounced in the 23-35 age group. Women aged 25 to 45 years, a group with higher fertility demands, may be more exposed to biological treatments, which raises the question of whether the age distribution of cases correlates with active drug interventions in women with strong fertility desires. Factors such as the sensitivity of the reproductive system, the placental barrier's permeability to drugs, and the combined effects of drugs and diseases on pregnancy were considered in relation to the age distribution of cases (*40*).

Pregnant women with chronic autoimmune inflammatory diseases may face significant challenges in controlling active disease, ensuring endometrial receptivity, and weighing the benefits and risks of pharmacological treatment. The impact of diseases such as RA and Crohn's disease on pregnancy outcomes is largely determined by the loss of disease control, a concern also applicable to atopic diseases (*32,40,41*). Adequate disease control before and during pregnancy is

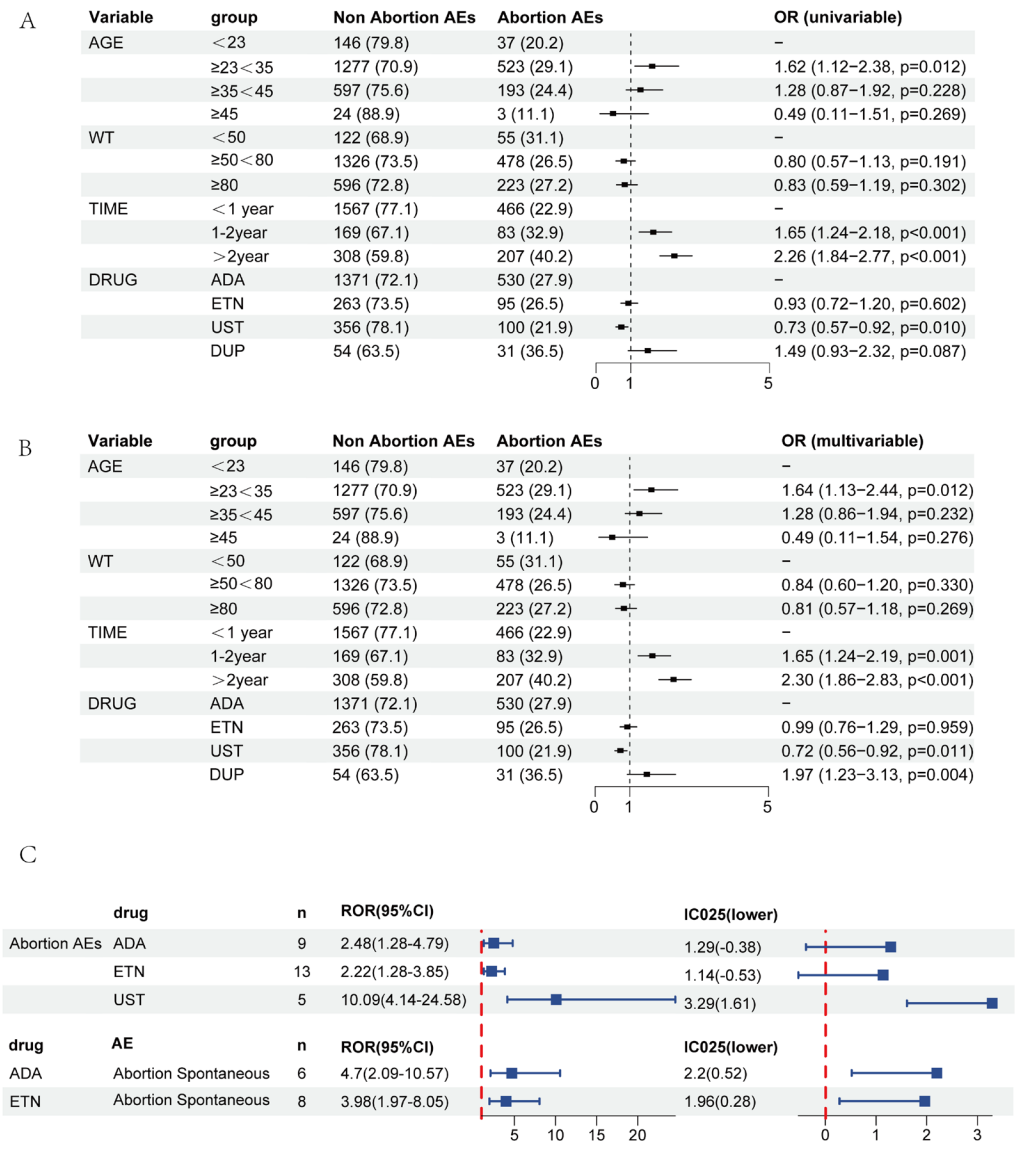

Figure 7. Logistic regression model for detecting influences on the results of outcomes and analysis of JADER databases. (A) Univariate logistic regression for age, weight, time-to-onset, and the effects of different drugs on AEs. **(B)** Multivariate logistic regression for age, weight, time-to-onset, and the effects of different drugs on abortion-related AEs. WT, weight; ADA, Adalimumab; ETN, Etanercept; UST, Ustekinumab; DUP, Dupilumab. **(C)** Abortion-related AEs among different biologics in the JADER database.

crucial. Inflammatory responses undergo distinct phases during pregnancy (*42*). Early pregnancy inflammation, at mild levels, supports endometrial decidualization, trophoblast invasion, and the formation of placental and embryonic structures (*43,44*). However, chronic autoimmune inflammatory diseases like RA, IBD, psoriasis, and ankylosing spondylitis can disrupt cytokine and chemokine signaling in embryonic trophoblast cells. Adalimumab, ustekinumab, and dupilumab are fully human monoclonal antibodies that exert their effects by neutralizing tumor necrosis factor-alpha (TNF-α), blocking the signaling of IL-12 and IL-23, and dual-blocking the signaling of IL-4 and IL-13, respectively (*16,40*). Etanercept, a fusion protein, inhibits TNF-α activity and signaling by preventing its interaction with natural receptors (*4*). These biologics target different cytokines or receptors to modulate inflammatory responses and treat a variety of autoimmune and inflammatory diseases. In the preliminary screening results of biologics associated with abortion-related AEs, these drugs ranked among the top, but relevant research on their safety during pregnancy remains limited.

As research advances, the use of biologics during pregnancy has shifted from cautious hesitation (*45*) to more optimistic support (*16*). This is based on the conclusions derived from subsequent research that reported the safety and lower risk of spontaneous abortion associated with the use of the evoked above biologics during pregnancy. Respectively, a case studies have supported the therapeutic benefits of adalimumab in patients with potential spontaneous abortions (*46*); During pregnancy, the use of etanercept relatively safe

Table 3. DDI interactions between biologics and methotrexate/prednisolone

Durg1	Drug2	N of Abortion with Drug1&Drug2/N of all AEs with Drug1&Drug2	Drug1&Drug2 IC(IC025-IC975)	Ω(Ω025-Ω075)	N of Abortion with Drug1/N of all AEs with Drug1	Drug1 IC (IC025-IC975)	N of Abortion with Drug2/N of all AEs with Drug2	Drug2 IC (IC025-IC975)
Adalimumab	Methotrexate	75/11092	-2.65 (-2.97–-2.3)	0.02 (-0.04-0.08)	984/13851	0.74 (0.65-0.84)	100/4746	-1.01 (-1.29–-0.71)
Adalimumab	Prednisone	49/6567	-2.51 (-2.89–-2.07)	0.02 (-0.057-0.104)	1002/13685	0.79 (0.69-0.88)	44/1873	-0.85 (-1.27–-0.4)
Etanercept	Methotrexate	59/10208	-2.88 (-3.23–-2.48)	-3.88 (-4.72–-3.03)	413/4831	1.01 (0.86-1.16)	89/4767	-1.18 (-1.48–-0.87)
Etanercept	Prednisone	26/5283	-3.11 (-3.62–-2.5)	-4.08 (-5.35–-2.80)	427/5051	0.99 (0.84-1.14)	44/1908	-0.88 (-1.3–-0.43)
Ustekinumab	Methotrexate	1/4913	-7.7 (-8.75–-4.67)	0.03 (-0.07-0.12)	90/1265	0.75 (0.42-1.05)	108/5773	-1.18 (-1.45–-0.89)
Dupilumab	Prednisone	3/13	2.44 (-0.31-2.96)	1.66 (-2.09-5.42)	127/2726	0.13 (-0.13-0.39)	108/10270	-2.01 (-2.28–-1.72)

(*47*); it has also identified that the safety of ustekinumab during pregnancy is higher than that of TNF-α inhibitors (*48*). A review and meta-analysis estimated that among patients with psoriasis using adalimumab, etanercept, ustekinumab, and other biologics during early pregnancy, the prevalence of abortion was 15.3%, and the rate of congenital malformations in live births was approximately 3.0%. This suggests that the pregnancy risks associated with biologic treatment in patients with psoriasis are not significant (*49*). However, spontaneous abortion remains one of the most common adverse pregnancy outcomes associated with TNF-α inhibitors (*9*). Additionally, there have been recommendations to prohibit the clinical use of etanercept and adalimumab from the mid-pregnancy period to the end of pregnancy (*15*). A multicenter retrospective cohort study indicated that exposure to dupilumab during 2–24 weeks of gestation may be linked to an increased risk of adverse pregnancy outcomes, including abortion or embryonic abnormalities, although no statistically significant effects were found. Dupilumab use during pregnancy was also associated with improved atopic dermatitis and a very low risk of adverse pregnancy outcomes (*50*). Fully human monoclonal antibodies like adalimumab, dupilumab, and ustekinumab have half-lives ranging from 9 to 23 days, while Fc fusion proteins such as etanercept have shorter half-lives of 4 to 13 days (*11*). These biologics cross the placenta, with transfer rates gradually increasing from mid-pregnancy through to after 30 weeks of gestation, when fetal or cord serum levels may match or exceed maternal levels (*4*). Previous studies may generate bias in their results due to different kinds of Immune-related inflammatory diseases, limitations in sample size, and variations in administration methods. The present study selectively included women of childbearing age who were pregnant, excluding those with abortion-related AEs. The overall signal for all abortion-related AEs induced by each drug, along with signals for individual PTs, was within the positive range. However, the ROR and IC values indicated a weak association between the drugs and abortion-related AEs. These findings are consistent with previous research. Despite this, the unique characteristics of the pregnant population necessitate a thorough assessment, rational medication use, and vigilant monitoring. Forest plots and heatmaps were employed to depict the degree of association between the drugs and abortion-related AEs. Both "abortion" and "Abortion spontaneous" were observed with each drug. Ustekinumab and dupilumab showed relatively stronger associations with "biochemical pregnancy," whereas etanercept and adalimumab were more strongly associated with "abortion complicated" or "abortion complete". While the overall number of abortion-related AEs was highest in the pregnant population, severe outcomes such as death were rare. Time-to-onset analysis revealed that adalimumab and etanercept

had relatively longer durations, while ustekinumab and dupilumab had shorter ones. Weibull analysis indicated that the incidence of abortion-related AEs generally declined over time, suggesting that prolonged treatment may correlate with reduced risk. Logistic regression in the sensitivity analysis revealed that the risk of AEs increased for events occurring between 1 and 2 years, or after 2 years, compared to those occurring within 1 year. Long-term drug use may lead to cumulative effects, heightening the risk of AEs. These findings offer insights into the latency period of drug-induced AEs in clinical practice, but further long-term prospective observational data are needed for confirmation.

The positive signal strength of abortion-related AEs associated with the same biologics in women of childbearing age, as observed in the JADER database, aligns closely with findings from the FAERS database and prior literature. However, small sample sizes continue to introduce significant confounding factors and biases. Treatment guidelines for RA caution against the use of methotrexate during pregnancy, regardless of dose, recommending its discontinuation at least three months prior to conception (*15*). The therapeutic benefits of prednisolone in recurrent miscarriages or spontaneous abortions primarily pertain to antiphospholipid syndrome treatment, and its effects on pregnancy outcomes and embryonic development are complex and not universally applicable (*51,52*). During the data mining process, these drugs are often administered in combination. The signal for abortion-related AEs from methotrexate in the FAERS database does not align with literature findings, likely due to the explicit prohibition of its use in pregnant populations. However, adalimumab, etanercept, ustekinumab, and dupilumab still exhibit a positive association with abortion-related AEs, independent of their use alongside methotrexate or prednisolone.

Several limitations are inherent in this retrospective database study. Both the FAERS and Open FDA databases are subject to natural reporting bias, with significant information loss in spontaneous anonymous reporting systems. As such, causality between biologics and pregnancy loss cannot be definitively established through pharmacovigilance studies alone (*53*). Furthermore, most of the studies referenced in this analysis were conducted in the US and Europe, while the JADER database has a limited sample size and lacks global representation. With the limitations of the database information exceptions, clinical studies on the association between biologics and spontaneous abortions are extremely rare currently. Most of existing research has expressed doubts and uncertainties regarding their safety during pregnancy. However, in recent years, their reputation has improved somewhat. The last limitation is whether the biologics or the disease itself is the "culprit" of spontaneous abortion. Clinical research on different biologics for treating various diseases has yielded different conclusions. For example, some studies have found that conditions such as RA (*4,54*), psoriasis (*55,56*), ankylosing spondylitis (*57*), and atopic dermatitis (*58*) basically do not increase the risk of miscarriage. The positive results of another study on psoriasis may be related to the older age of the sample population (*59*). However, Crohn's disease and ulcerative colitis may increase the risk of miscarriage (*60,61*). In summary, this overview is consistent with the findings of a recent registry linkage study in Norway (*62*). Therefore, the key issue we need to address in subsequent research is to further clarify the complex interactions between drugs, diseases during pregnancy. Larger, prospective, randomized clinical trials are necessary to validate these findings and support these hypotheses. In clinical studies, efforts should be made to standardize disease activity and treatment duration as much as possible, while also establishing comprehensive control groups.

In conclusion, the study performed a disproportionality analysis of four biologics used during pregnancy and their association with abortion-related AEs. The results are consistent with existing literature: biologics are linked to an increased risk of adverse pregnancy outcomes such as miscarriage, although the association remains relatively weak. This conclusion necessitates confirmation through large-scale, prospective studies.

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