Biologics Therapy for Immune-Mediated Inflammatory Diseases During Pregnancy and Lactation: Efficacy, Safety, and Challenges Postprint

Authors: Han Lin, Hou Zhenyan, Jun Li, Wang Yan, Li Huibo, Wang Yan, Huibo Li

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Abstract

Immune-mediated inflammatory diseases (IMIDs) frequently affect women of reproductive age, and the effects of therapeutic agents on pregnancy outcomes, fetal development, and infants complicate pharmacotherapeutic decision-making during pregnancy and lactation. This review examines the latest domestic and international diagnostic and therapeutic guidelines and clinical studies, analyzes the impact of IMIDs disease activity on pregnancy outcomes from an immune balance perspective, elucidates biologic drug exposure during pregnancy through placental transfer mechanisms and maternal physiological changes, summarizes recent advances and safety data on biologic therapy for IMIDs patients during pregnancy and lactation, comparatively analyzes guideline recommendations for various biologics in pregnancy and lactation, and proposes optimal recommendations regarding the timing of biologic discontinuation during pregnancy and neonatal vaccination. Through multidisciplinary collaboration, we aim to provide effective and safe treatment strategies for peripregnancy IMIDs patients, thereby safeguarding maternal and infant health.

Full Text

Biologic Therapy for Immune-Mediated Inflammatory Diseases during Pregnancy and Lactation: Efficacy, Safety, and Challenges

Han Lin[1], Hou Zhenyan[2,3], Li Jun[4], Wang Yan[1], *Li Huibo*[2,3]

[1]Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China
[2]Department of Pharmacy, Peking University Third Hospital, Beijing 100191,

China
[3]Institute for Drug Evaluation, Peking University Health Science Center, Beijing 100191, China
[4]Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China

Corresponding authors: Wang Yan, Chief Physician/Doctoral Supervisor; E-mail: wjgqhn@263.net
Li Huibo, Associate Chief Pharmacist; E-mail: lihuibo@bjmu.edu.cn

Abstract

Immune-mediated inflammatory diseases (IMIDs) frequently affect women of reproductive age, posing complex challenges for pharmacotherapy decisions during pregnancy and lactation due to potential impacts on pregnancy outcomes, fetal development, and infant health. This article comprehensively reviews the latest national and international diagnostic and treatment guidelines alongside recent clinical research. We analyze the influence of IMIDs disease activity on pregnancy outcomes from an immunological balance perspective and elucidate drug exposure mechanisms of biologics during pregnancy based on placental transport and maternal physiological changes. Additionally, we integrate the most recent advancements and safety data for biological therapies in IMID patients during pregnancy and lactation, present a comparative analysis of guideline recommendations for various biologic agents, and propose optimal strategies for discontinuation timing and neonatal vaccination. Through multidisciplinary collaboration, this work aims to promote the development of effective and safe treatment strategies for IMID patients during the perinatal period, thereby safeguarding the health of both mothers and infants.

Keywords: Immune-mediated inflammatory diseases; Pregnancy; Lactation; Biological agents; Safety

1. Impact of IMIDs Disease Activity on Pregnancy Outcomes

During pregnancy, the maternal immune system undergoes complex and finely-tuned adaptive adjustments while maintaining autoimmune defense functions. In early pregnancy, a pro-inflammatory microenvironment induces an immunotolerant environment to ensure normal placental formation and fetal growth. The cytokine environment exists in a delicate balance between pro-inflammatory and anti-inflammatory states, and these changes significantly impact patients with immune-mediated inflammatory diseases [2].

Pregnancy outcomes are closely associated with pre-pregnancy disease control in IMIDs patients. Once disease becomes active during pregnancy, it may adversely affect both mother and infant. Clinical studies have shown that increased

rheumatoid arthritis (RA) disease activity during pregnancy is associated with low birth weight in offspring [3], and inflammatory bowel disease (IBD) activity before and during pregnancy increases risks of maternal infection, preterm birth, low birth weight, small-for-gestational-age infants, and neurodevelopmental abnormalities [4]. Therefore, maintaining effective and safe pharmacotherapy during pregnancy is recommended for IMIDs patients.

In the late 20th century, IMIDs treatment primarily relied on broad-spectrum immunomodulators such as corticosteroids and azathioprine. These drugs had low immunological specificity, provided only partial symptom relief, and had numerous adverse effects with significant restrictions for use during pregnancy and lactation. The advent of biologics marked the beginning of immune-targeted therapy [1]. Currently, commonly used biologics for IMIDs include TNF inhibitors (TNFi) such as infliximab (IFX), anti-B cell agents like rituximab (RTX), IL-6 receptor inhibitors such as tocilizumab (TCZ), IL-1 receptor inhibitors like anakinra, costimulatory factor inhibitors such as abatacept (ABA) and belimumab (BEL), with their targets illustrated in Figure 1 [Figure 1: see original paper]. Compared to conventional drugs, biologics more effectively control disease activity, but safety concerns regarding these large-molecule monoclonal antibodies during pregnancy, lactation, and postpartum periods warrant careful attention.

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2. Drug Exposure of Biologics During Pregnancy

Due to placental barrier function, fetal Fc receptor (Neonatal Fc Receptor, FcRn)-mediated drug transport, and maternal physiological changes, drug exposure levels during pregnancy differ significantly from the general population. FcRn is expressed in human placenta, particularly in syncytiotrophoblast cells [5], facilitating active transport of IgG-type antibodies (Figure 2 [Figure 2: see original paper]). Most biologics are IgG antibodies that cross the placenta into fetal circulation via FcRn-mediated active transport under physiological conditions. However, certolizumab (CZP) lacks the IgG1 Fc region and therefore crosses the placenta minimally, enabling its continuous use throughout pregnancy [6]. The human embryo during the first 10 weeks of gestation is termed an embryo—the period of organ differentiation and formation. Other TNFi agents are believed to begin crossing the placenta gradually from 13 weeks gestation, though the transfer rate is extremely low, which may explain the low rate of congenital malformations associated with TNFi exposure during pregnancy [7].

As fetal development progresses, Fc receptors become widely distributed across various tissues, including epithelial cells, endothelial cells, parenchymal cells, and hematopoietic cells. Their recycling function can prolong drug half-life. Meanwhile, the fetal reticuloendothelial system remains immature, and FcRn expression is regulated by cytokines or infectious stimuli, thereby affecting drug transport and clearance [5]. Bitter et al. [8] first confirmed that BEL can cross

the placenta in pregnant patients, with the drug still detectable in neonatal cord blood when the last BEL exposure occurred at the end of the second trimester. Due to its extended half-life in serum and the prolonged clearance time averaging 6–12 months after discontinuation [6], drug effects should be considered for up to one year post-discontinuation.

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3. Guideline Recommendations and Clinical Evidence for Biologic Use During Pregnancy

In recent years, numerous professional societies—including the Chinese Rheumatology Association [9], Chinese Society of Gastroenterology IBD Group [10], European Alliance of Associations for Rheumatology (EULAR) [7], British Society for Rheumatology (BSR) [6], British Association of Dermatologists [11], and American College of Rheumatology (ACR) [12]—have issued guidelines on the safe use of biologics during the perinatal period. However, recommendations and strength of evidence vary due to different evidence evaluation systems employed by these guidelines. The recommendations for biologic use during pregnancy and lactation across guidelines are summarized in Table 1 .

3.1 TNF Inhibitors (TNFi)

Currently available TNFi agents for IMIDs include infliximab (IFX), etanercept (ETA), adalimumab (ADA), certolizumab (CZP), and golimumab (GOL). TNFi demonstrates significant efficacy in maintaining low disease activity during pregnancy. A prospective study found that patients with axial spondyloarthritis who discontinued TNFi upon positive pregnancy testing showed increased disease activity (OR=3.08, 95%CI=1.2–7.9), particularly during the second trimester, compared to those who continued therapy [13].

Whether TNFi increases pregnancy complication risks remains controversial. A retrospective cohort study by Luu et al. [14] found that maintaining TNFi treatment after 24 weeks gestation did not increase maternal complication risk, while interrupting anti-TNF therapy increased relapse risk. Conversely, a population-based study by Bröms et al. [15] found that TNFi-treated pregnant women had increased risks of preterm birth (aOR=1.61, 95%CI=1.29–2.02), cesarean delivery (aOR=1.57, 95%CI=1.35–1.82), and small-for-gestational-age infants (aOR=1.36, 95%CI=0.96–1.92) compared to non-biologic treatments. Additionally, IFX was associated with greater risks of preterm birth and severe SGA than ETA in pregnant women with RA, AS, PsA, or psoriasis, though no difference was observed between IFX and ADA in IBD patients. However, detailed information on disease activity was lacking, making it difficult to determine whether disease severity rather than biologics was the decisive factor.

Current research generally considers TNFi use during pregnancy to be safe for the fetus. A systematic review of 143 studies found no difference in birth defect

or miscarriage rates between TNFi-treated pregnant women and the general population [16]. However, due to placental transfer potentially increasing neonatal infection risk and affecting vaccination, expert consensus generally recommends discontinuing TNFi in the second or third trimester, with continuation in the third trimester reserved only for patients with active disease.

3.2 Anti-B Cell (CD20): Rituximab (RTX)

RTX is commonly used for refractory RA, SLE, and vasculitis, though its safety during pregnancy and lactation remains controversial. Most guidelines [6,9] recommend discontinuation 6 months before conception.

A systematic review of 102 pregnant women treated with RTX within 6 months of pregnancy found no increased risk of congenital malformations, with a spontaneous abortion rate of 12%, similar to the general population [17]. Two additional studies supported these findings [18-19]. However, Smith et al. [20] reported a slightly higher miscarriage risk in a population-based study of 74 pregnant women with multiple sclerosis, with 15 (27%) experiencing spontaneous abortion after RTX exposure.

Research on whether RTX exposure increases pregnancy complications has yielded mixed results. Chakravarty et al. [19] found preterm birth rates similar to those reported in women with chronic medical conditions among 153 RTX-exposed pregnancies. In contrast, Kümpfel et al. [18] found higher preterm birth risk in a prospective cohort of 68 patients (9.76% vs 45.45%, P=0.019) compared to those receiving anti-CD20 monoclonal antibodies before pregnancy, though this could not exclude associations with underlying disease or concomitant autoimmune conditions. Limited studies suggest RTX use within 6 months of pregnancy does not increase teratogenic risk, but whether it increases miscarriage and preterm birth risk remains controversial.

3.3 IL-6 Receptor Inhibitor: Tocilizumab (TCZ)

TCZ is approved for RA and giant cell arteritis and serves as second-line therapy for the inflammatory phase of SARS-CoV-2 infection. Safety during pregnancy remains uncertain, with recommendations to discontinue 3 months before conception [6,9].

Small-scale pregnancy studies show TCZ does not increase teratogenic risk but may have adverse effects. A retrospective study by Jiménez-Lozano et al. [21] of 12 pregnant women with severe COVID-19 reported live births in all cases, with 2 cases of hepatotoxicity and 1 case of cytomegalovirus reactivation and congenital infection possibly related to TCZ use. Nakajima et al. [22] found no increased miscarriage or congenital malformation rates in a retrospective analysis of 61 patients. However, Hoeltzenbein et al. [23] reported high miscarriage rates in both prospective (21.7%) and retrospective (28.7%) cohorts of 180 and 108 patients, respectively. The study also observed 7 major congenital malformations among 88 live births: 3 cardiovascular diseases, and 1 each of cleft

lip/palate, meningocele, pyloric stenosis, and skull deformity. The malformation rate (7.9%) was slightly higher than the general population (3–5%), though concomitant methotrexate use and high disease activity could not be excluded as confounders. Additionally, 6 preterm births and 4 low-birth-weight infants (<2,500 g) were observed among 17 neonates exposed during the second and third trimesters.

3.4 IL-1 Receptor Inhibitor: Anakinra

Anakinra is used for RA and certain autoinflammatory diseases. Due to its homology with natural IL-1Ra and short elimination half-life, it is considered a safe alternative for treating pregnant women with periodic fever syndromes [24] and can alleviate cytokine storms induced by viral infections in severe COVID-19 pregnant patients [25]. Mouse model studies of IL-1β elevation found that anakinra protected placental function, increased fetal survival, and reduced neurobehavioral deficits in offspring to improve perinatal outcomes [26]. Chang et al. [27] included 24 pregnancies with cryopyrin-associated periodic syndromes (CAPS) and found lower miscarriage rates in women using anakinra compared to untreated women (11% vs 27%). Youngstein et al. [24] reported no infections or fetal malformations in 10 infants exposed to anakinra through breastfeeding up to 10 months and 6 infants with paternal exposure.

However, anakinra's safety during pregnancy remains uncertain, with recommendations to discontinue upon pregnancy detection due to risks of increased neonatal malformations and maternal complications in the second and third trimesters [24,27-29]. Although most neonates were normal, fetal musculoskeletal malformations increased with maternal anakinra exposure (OR=7.18, 95%CI=3.50–14.73) [29]. Other adverse pregnancy outcomes have been reported. Brien et al. [28] found 26.1% of 69 anakinra-exposed pregnant women experienced complications including preterm labor, vaginal bleeding, hypertension, or oligohydramnios. Among neonates, 13.6% had mild complications, including 5 diagnosed with CAPS, 1 with malnutrition, respiratory distress syndrome, and hyperbilirubinemia, and 1 with right hydrocele. Chang et al. [27] also reported a twin pregnancy with fetal renal agenesis and intrauterine fetal demise, though the surviving twin was normal. Whether renal abnormalities are related to anakinra use or maternal underlying disease remains unclear.

3.5 CTLA4-Ig: Abatacept (ABA)

ABA is approved for RA, psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), and other rheumatic diseases. Due to limited data in pregnant women, its use during pregnancy is not recommended. Women of childbearing potential should use effective contraception throughout treatment and for 14 weeks after the last ABA dose [30]. Studies have reported adverse outcomes with ABA use during pregnancy. Dernoncourt et al. [29] found a significant association between fetal musculoskeletal malformations and maternal ABA exposure (OR=5.09, 95%CI=2.77–9.33). Ghalandari et al. [16] observed a 26.1% mis-

carriage rate in a systematic review of 153 ABA-exposed pregnancies, higher than the general population (10–20%). Among 88 live births, 7 major congenital malformations were observed: 3 cardiovascular diseases, and 1 each of cleft lip/palate, meningocele, pyloric stenosis, and skull deformity. The malformation rate (7.9%) was slightly higher than the general population (3–5%), though concomitant methotrexate use and high disease activity could not be excluded.

3.6 Anti-BAFF: Belimumab (BEL)

BEL is the only biologic approved for systemic lupus erythematosus (SLE), but its use should be avoided during pregnancy due to insufficient data. Ghalandari et al. [31] found a fetal mortality rate of 52.4% with continuous BEL exposure (at least 3 months before pregnancy), higher than the rate with BEL discontinued in the first trimester or earlier (46.4%, OR=1.27, 95%CI=0.48–3.32), though the difference was not statistically significant, possibly due to high disease activity and reporting bias. Petri et al. [32] analyzed 18 clinical trials and found higher birth defect rates in the BEL exposure group versus placebo (5.6% vs 0%), though no consistent pattern of defects was identified. Two case series totaling 26 SLE patients with BEL exposure during pregnancy reported high preterm birth rates (52.2%, 12/23) among live births, with 5 SGA infants and 1 with fetal growth restriction [33-34]. These studies found no pregnancy adverse events directly attributable to BEL, though caution and further research are warranted. For SLE patients requiring treatment during pregnancy, BEL may be a reasonable option.

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4. Biologic Use During Pregnancy and Neonatal Vaccination

Drug half-life determines the duration of immunosuppression in the fetus, directly affecting neonatal vaccination timing. Most biologics do not significantly increase infection risk [36-37]. Demortiere et al. [38] analyzed cord blood from 5 MS patients who discontinued anti-CD20 therapy before pregnancy and found no abnormal B cell counts. Among 23 RTX-exposed pregnancies with B cell count assessments [17], 9 showed neonatal B cell depletion, though none experienced infectious complications or adverse vaccination reactions, with all B cell levels normalizing within 6 months.

Some studies report contradictory findings. Dernoncourt et al. [29] found BEL exposure significantly increased neonatal infection risk (OR=28.49, 95%CI=5.75–141.25) after controlling for steroid use. Juliao et al. [35] reported 6 of 46 infants (13%) experienced at least one unexplained infection or fever within the first 4 months after birth. Other researchers found infants exposed to RTX in utero often had hypogammaglobulinemia, leading to transient lymphopenia and reduced IgG levels on day 1 of life [29]. Therefore, neonates born to mothers treated with RTX or BEL during pregnancy should undergo

close monitoring of B cell levels to enable timely detection and management of potential infections.

EULAR [7] recommends that infants exposed to biologics only before 22 weeks gestation can follow standard vaccination schedules, including live vaccines. For infants exposed during the second and third trimesters, live vaccines should be avoided for the first 6 months after birth. When feasible, measuring biologic drug levels in infant serum can help guide live vaccine administration.

BCG, rotavirus, and measles-mumps-rubella vaccines are live attenuated vaccines. Rotavirus vaccination must be completed before 24 weeks of age to avoid intussusception risk. A systematic review by Goulden et al. [39] analyzed vaccination safety in infants exposed to biologics in utero during the first year of life, reporting adverse reactions after BCG vaccination including 1 death, 2 local skin reactions, and 1 axillary lymphadenopathy. Additionally, 4 cases of fatal disseminated BCG infection were observed due to in utero exposure to various TNFi (including IFX, ADA, and unspecified TNFi). In contrast, infants receiving rotavirus vaccine had milder adverse reactions similar to unexposed infants, while no complications were reported with measles-mumps-rubella vaccination. Overall, BCG vaccination before 3 months of age and in utero IFX exposure were found to be harmful to infants. Rotavirus vaccine is mostly administered within 6 months of birth, and measles-mumps-rubella vaccine after 1 year, with reassuring post-vaccination outcomes.

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5. Biologic Use During Lactation

Most biologics are large-molecule proteins that are minimally secreted into breast milk, resulting in low relative infant doses and relative safety during lactation [6,40-41]. Anderson et al. [42] showed median RTX concentration in breast milk was only 0.03 g/mL, with minimal transfer to infant circulation. Additionally, breastfed infants showed no significant differences in growth and development compared to non-breastfed infants. Saito et al. [43] reported no serious complications in 2 infants exposed to TCZ through breast milk. Tada et al. [44] found TCZ transfer rate in breast milk was 11%, relatively high, possibly due to high protein and antibody concentrations in colostrum, though TCZ use during lactation is still considered relatively safe. Case reports for ABA also indicated no adverse effects in breastfed infants, with ABA secretion in breast milk only 1/200 to 1/300 of serum levels [40].

However, due to limited data, some scholars recommend that lactating women avoid breastfeeding during RTX treatment and for 6 months after treatment completion [45], and extend this to 14 weeks after ABA treatment [30]. Overall, although biologic use during lactation appears safe, clinical practice still requires careful consideration with thorough evaluation of individual maternal treatment needs and potential risks before decision-making.

Conclusion

Treatment of immune-mediated inflammatory diseases during pregnancy and lactation requires balancing maternal disease control with fetal/infant safety. Certolizumab can be used throughout pregnancy due to minimal placental transfer, representing the safest option during gestation, while rituximab and tocilizumab require pre-pregnancy discontinuation due to insufficient evidence. Most biologics (such as TNF inhibitors) are present at extremely low concentrations in breast milk and are relatively safe during lactation, though other agents require caution due to limited data. Neonates exposed to rituximab or belimumab during pregnancy should have B cell levels closely monitored after birth. Live vaccines should be delayed until 6 months of age for infants exposed to biologics during the second and third trimesters.

This review comprehensively examines authoritative guidelines and clinical evidence, systematically analyzing cutting-edge advances and safety evaluations for biologic therapy in pregnant and lactating IMIDs patients. However, current research remains limited regarding long-term offspring safety, disease-specific differences, and pregnancy data for novel biologics (such as JAK inhibitors). Future prospective studies are needed to optimize individualized treatment strategies and ensure maternal-infant safety.

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