Precision Medication 2 (2025) 100029

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

Biologic therapy for immune-mediated inflammatory diseases during pregnancy and lactation: Efficacy, safety, and challenges

Lin Han[a], Zhenyan Hou[b,c], Jun Li[d], Yan Wang[a,*], Huibo Li[b,c,*]

[a] Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China
[b] Department of Pharmacy, Peking University Third Hospital, Beijing 100191, China
[c] Institute for Drug Evaluation, Peking University Health Science Center, Beijing 100191, China
[d] Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China

ARTICLE INFO

Keywords:
Immune-mediated inflammatory diseases
Pregnancy
Lactation
Biologics
Safety

ABSTRACT

Immune-mediated inflammatory diseases (IMIDs) commonly affect women of reproductive age, and concerns regarding the impact of therapeutic drugs on pregnancy outcomes, fetal development, and infant health complicate medication decision-making during pregnancy and lactation. This article reviews the latest practice guidelines and clinical studies, analyzing the impact of IMIDs disease activity on pregnancy outcomes from the perspective of immune balance. It also explains drug exposure to biologics during pregnancy based on placental transport mechanisms and maternal physiological changes. We summarize recent advances and safety data regarding the use of biologics in pregnant and lactating IMIDs patients, compare and analyze guideline recommendations for the use of different biologics during pregnancy and lactation, and propose optimal suggestions regarding the timing of drug discontinuation during pregnancy and neonatal vaccination strategies. Multidisciplinary collaboration is believed to provide effective and safe therapeutic strategies for IMIDs patients in the peri-pregnancy period to safeguard maternal and infant health.

Introduction

Immune-mediated inflammatory diseases (IMIDs) refer to a group of common clinical conditions, including rheumatoid arthritis (RA), spondyloarthritis (SpA), connective tissue diseases, psoriasis, atopic dermatitis, inflammatory bowel disease (IBD), asthma, and multiple sclerosis, among others.[1] Some IMIDs have a peak incidence during reproductive age, necessitating long-term pharmacologic therapy to maintain disease stability. However, the special physiological stages of pregnancy and lactation complicate treatment decision-making. Therefore, it is recommended that fertility planning be guided by multidisciplinary experts in rheumatology, gastroenterology, dermatology, obstetrics and gynecology when disease activity is well controlled. During the peri-pregnancy period, individualized treatment strategies should be formulated by clinical pharmacists based on multiple factors to balance maternal disease control and fetal safety. During delivery, neonatal care plans should be jointly developed with neonatology specialists. This study reviews national and international clinical guidelines and evidence from clinical studies, providing an in-depth analysis of advances and safety considerations in biologic therapy for IMIDs during pregnancy and lactation, aiming to offer effective and safe therapeutic strategies through multidisciplinary management.

Impact of IMIDs disease activity on pregnancy outcomes

During pregnancy, the maternal immune system undergoes complex and delicate adaptations while maintains its own immune defense function. In early pregnancy, a pro-inflammatory environment induces immune tolerance, ensuring proper placental formation and fetal development. The cytokine milieu is maintained in a delicate balance between pro-inflammatory and anti-inflammatory states, which significantly affects patients with immune-mediated inflammatory diseases.[2] The changes in immune system dynamics, as well as the balance of pro-inflammatory and anti-inflammatory factors during pregnancy, are illustrated in Fig. 1.

Disease control status of IMIDs patients in early pregnancy is closely associated with disease activity during pregnancy. If disease activity

* Corresponding authors.
E-mail addresses: wjgqhn@263.net (Y. Wang), lihuibo@bjmu.edu.cn (H. Li).

https://doi.org/10.1016/j.prmedi.2025.100029
Received 11 February 2025; Received in revised form 1 March 2025; Accepted 20 March 2025
Available online 16 June 2025

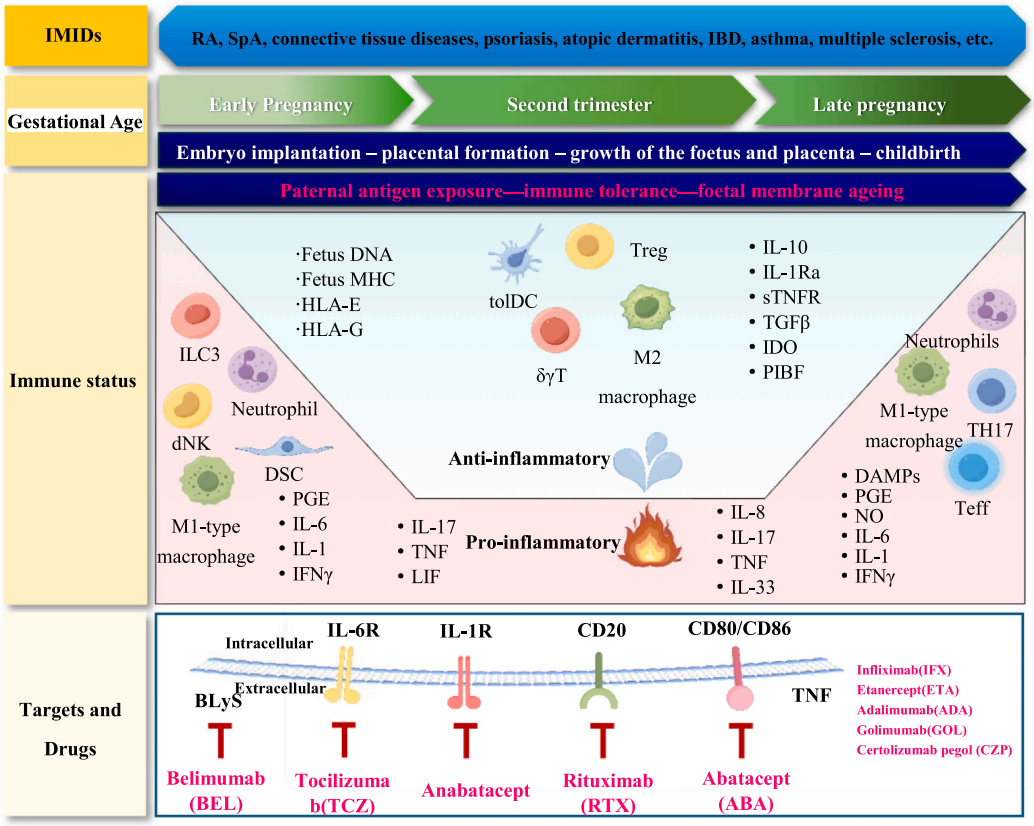

Fig. 1. Changes in the immune system and drug therapy for IMIDs during pregnancy. Note: In innate immune cells, gene activity of peripheral blood mononuclear cells is higher during pregnancy compared to the postpartum period. Subsets of innate immune cells exhibiting immune tolerance are active within the placenta, while an early increase in decidual natural killer (dNK) cells supports placental formation. In the adaptive immune compartment, although Th2 cells do not completely dominate, effector T cell activity is downregulated, regulatory T cells (Tregs) are expanded, and changes in B cell function lead to increased galactosylation of IgG. Abbreviations: DAMP, damage-associated molecular patterns; dNK cells, decidual natural killer cells; DSC, decidual stromal cells; IDO, indoleamine 2,3-dioxygenase; IL-1Ra, interleukin-1 receptor antagonist; ILC3, type 3 innate lymphoid cells; LIF, leukemia inhibitory factor; NK, natural killer; NO, nitric oxide; PGE, prostaglandin E; PIBF, progesterone-induced blocking factor; sTNFR, soluble TNF receptor; TGF-β, transforming growth factor beta; Teff cells, effector T cells; Th17 cells, T helper 17 cells; tolDC, tolerogenic dendritic cells; Treg, regulatory T cells; γδT cells, gamma-delta T cells; Blys, B lymphocyte stimulator, also referred to as B cell-activating factor (anti-BAFF).

flares, it may have adverse effects on both the mother and the fetus. Clinical studies have shown that exacerbation of RA during pregnancy is associated with lower birth weight in offspring.[3] Additionally, preconception and gestational activity of IBD increases the risk of maternal infections, preterm birth, low birth weight, small-for-gestational-age infants, and neuronal and developmental abnormalities in the newborn.[4] Thus, it is recommended that IMIDs patients continue maintenance therapy with effective and safe medications throughout pregnancy.

In the late 20th century, treatment of IMIDs primarily relied on broad-spectrum immunomodulators, such as glucocorticoids and azathioprine. These agents lacked high immune specificity, typically only partially alleviated symptoms, and were associated with numerous adverse effects, with many limitations during pregnancy and lactation. The advent of biologic therapies marked the beginning of targeted immunotherapy.[1] Currently, commonly used biologics for IMIDs include tumor necrosis factor inhibitors (TNFi) such as infliximab (IFX), anti-B cell agents such as rituximab (RTX), interleukin-6 receptor inhibitors such as tocilizumab (TCZ), interleukin-1 receptor inhibitors such as anakinra, costimulatory molecule inhibitors such as abatacept (ABA), and belimumab (BEL), with their therapeutic targets shown in Fig. 1. Compared to traditional drugs, biologics provide more effective disease control. However, concerns about the safety of these large-molecule monoclonal antibodies during pregnancy, lactation, and the postpartum period remain important.

Drug exposure to biologics during pregnancy

Drug exposure levels during pregnancy differ significantly from those in the general population, primarily due to the placental barrier, fetal Fc receptor (Neonatal Fc Receptor, FcRn)-mediated drug transport, and maternal physiological changes. FcRn is expressed in the human placenta, particularly in syncytiotrophoblast cells,[5] and facilitates the active transport of IgG-type antibodies (Fig. 2). Most biologic agents are IgG antibodies, and under physiological conditions, IgG antibodies are actively transported across the placenta into the fetal circulation via FcRn located on the placental surface. However, certolizumab pegol (CZP), which lacks the Fc region of IgG1, is hardly transports across the placenta, allowing its continued use throughout pregnancy.[6] The human embryo is referred to as an “embryo” within the first 10 weeks of pregnancy, a critical period for organogenesis and differentiation. Other TNF inhibitors are thought to gradually begin placental transfer from around 13 weeks of gestation, and the very low transfer rate of TNFi agents may explain the relatively low incidence of congenital malformations associated with TNFi exposure during pregnancy.[7]

As the fetus develops, Fc receptors become widely expressed across various tissues, including epithelial cells, endothelial cells, and other parenchymal and hematopoietic cells, and their recycling function can prolong the half-life of drugs. Meanwhile, the fetal reticuloendothelial system is still immature, and the expression of FcRn can be regulated by cytokines or infection, thereby affecting drug transport and clearance.[5] BITTER and colleagues[8] uncovered that BEL can undergo placental transfer in pregnant patients and that its serum half-life is prolonged. Notably, a single BEL exposure near the end of the second trimester could still be detected in neonatal cord blood. Since the clearance time of different biologics can range from an average of 6–12 months,[6] the potential effects of these agents should still be considered even one year after drug discontinuation.

In recent years, national and international specialty societies, including the Chinese Medical Association of Rheumatology (CMAR),[9] the Inflammatory Bowel Disease Group of the Chinese Medical Association of Gastroenterology,[10] the European Alliance of Associations for Rheumatology (EULAR),[7] the British Society for Rheumatology (BSR),[6] the British Association of Dermatologists,[11] and the American College of

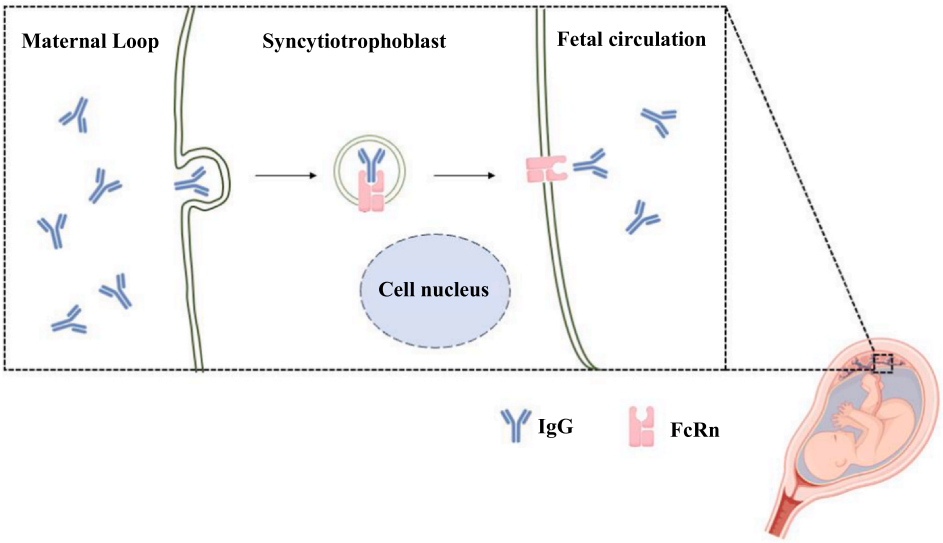

Fig. 2. The mechanism of TNFi-associated IgG placental transport.

Rheumatology (ACR),[12] have successively issued guidelines regarding the safe use of biologics during the peripregnancy period. However, due to differences in the evidence evaluation systems employed by these guidelines, their recommendations and the strength of those recommendations vary. The guideline recommendations for the use of biologics during pregnancy and lactation are summarized in Table 1.

Use of biologics and clinical outcomes

TNF inhibitors

Currently, internationally used TNF inhibitors for IMIDs treatment include infliximab, etanercept (ETA), adalimumab (ADA), certolizumab pegol, and golimumab (GOL). TNFi have demonstrated significant efficacy in maintaining low disease activity during pregnancy. A prospective study found that patients with axial spondyloarthritis who had not used TNFi before pregnancy exhibited persistently high disease activity from preconception to postpartum; discontinuation of TNFi after positive pregnancy testing led to increased disease activity (OR = 3.08, 95 % CI = 1.2–7.9), particularly during the second trimester.[13]

The association between TNFi use and increased risk of pregnancy complications remains controversial. A retrospective cohort study by LUU et al.[14] found that maintenance treatment of TNFi after 24 weeks of gestation did not increase the risk of maternal complications, while interruption of TNFi therapy increased the risk of disease relapse. In contrast, a population-based study by BRÖMS et al.[15] reported that compared with non-biologic therapies, TNFi use during pregnancy was associated with higher 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 (SGA) infants (aOR = 1.36, 95 % CI = 0.96–1.92). Moreover, among pregnant women with RA, AS, PsA, or psoriasis, IFX use was associated with greater risks of preterm birth and severe SGA compared to ETA, but no differences were observed between IFX and ADA in patients with IBD. However, due to the lack of detailed information on disease activity, it remains unclear whether the observed outcomes are related to disease severity and whether biologic therapy are the only decisive factor.

Current studies generally hold that TNFi use during pregnancy is essentially safe for the fetus. A systematic review of 143 studies found no significant differences in birth defect rates or miscarriage rates between TNFi-exposed pregnancies and the general population.[16] Considering the potential for placental transfer of TNFi and its possible effects on neonatal infection risk and vaccination schedules, expert consensus generally recommends discontinuing TNFi in the second or third trimester, with continued therapy during late pregnancy reserved only for patients with active disease.

Anti-B cell therapy (CD20): rituximab

Rituximab is typically used for the treatment of refractory RA, SLE, and vasculitis. Its safety during pregnancy and lactation remains controversial, and most guidelines[6,9] recommend discontinuation six months prior to conception. Reports on RTX use during pregnancy are limited. A systematic review involving 102 pregnant women treated with RTX within six months of conception found that RTX use did not appear to increase the risk of congenital malformations, with a reported miscarriage rate of 12 %, comparable to that of the general population.[17] Two additional studies also supported these findings.[18,19] However, a population-based study by SMITH et al.[20] involving 74 pregnant women with multiple sclerosis found a slightly higher risk of miscarriage following RTX exposure, with 15 patients (27 %) experiencing 23 early pregnancy losses. Results regarding the association between RTX exposure and pregnancy complications are inconsistent. CHAKRAVARTY et al.[19] observed that the preterm birth rate among 153 RTX-exposed pregnancies was similar to that reported for women with chronic medical diseases. Conversely, a prospective cohort study by KÜMPFEL et al.[18] involving 68 pregnancies found that patients treated with anti-CD20 antibodies during pregnancy had a higher risk of preterm birth compared to those treated prior to pregnancy (9.76 % vs. 45.45 %, P = 0.019), although confounding by underlying disease or concurrent autoimmune conditions could not be excluded. Overall, limited studies suggest that RTX exposure within six months of conception does not increase the risk of congenital malformations, but the potential risks of miscarriage and preterm birth remain controversial.

IL-6 receptor inhibitor: tocilizumab

Tocilizumab is approved for the treatment of RA and giant cell arteritis and has been considered a second-line therapy for controlling inflammation in SARS-CoV-2 infections. The safety of TCZ use during pregnancy remains uncertain, and it is recommended that TCZ be discontinued at least three months prior to conception.[6,9] Small-sample studies during pregnancy suggest that TCZ does not increase teratogenic risk but may be associated with certain adverse outcomes. A retrospective study by JIMÉNEZ-LOZANO et al.[21] involving 12 pregnant women with severe COVID-19 found that all pregnancies resulted

Table 1
Recommendations for the use of biological agents during pregnancy and lactation.

Biological agents	Structure	Pregnancy safety				Neonatal vaccination schedule	Lactation safety	Paternal exposure safety
		CMAR (2021)	EULAR (2016)	BSR (2023)	ACR (2020)			
TNF inhibitor								
Infliximab (IFX)	Anti-TNF-α monoclonal antibody	Discontinue in late pregnancy	Discontinue by 20 weeks' gestation	Discontinue by 16 weeks' gestation	Use before conception, early and mid-pregnancy permitted; discontinue a few half-lives before delivery in late pregnancy	Discontinue by 20 weeks; term infants follow standard vaccination schedule	Breastfeeding permitted	Yes
Etanercept (ETA)	Fusion protein linking TNF receptor to IgG1 Fc domain		Discontinue by 30–32 weeks' gestation	Discontinue by the end of the second trimester		Discontinue by 32 weeks; term infants follow standard vaccination schedule		
Adalimumab (ADA)	Anti-TNF-α monoclonal antibody		Discontinue by 20 weeks' gestation	Discontinue by the end of the second trimester		Discontinue by 28 weeks; term infants follow standard vaccination schedule		
Golimumab (GOL)	Anti-TNF-α monoclonal antibody		Insufficient data support	Early pregnancy exposure unlikely to be harmful		Discontinue by 28 weeks; term infants may follow standard vaccination schedule		
Certolizumab pegol (CZP)	Antigen-binding fragment of anti-TNF-α monoclonal antibody without Fc region	Can be used throughout pregnancy				Yes, no adjustment to vaccination schedule required		
Anti-B cell therapy (CD20)								
Rituximab (RTX)	Chimeric human-mouse monoclonal antibody	Discontinue 6 months before conception; avoid use in middle and late pregnancy	Early pregnancy use possible under special conditions; late pregnancy use requires attention to neonatal B-cell depletion and risk of other blood cell reductions	Discontinue 6 months before conception	Early pregnancy use permitted for life-threatening rheumatic and musculoskeletal diseases	If used in late pregnancy, avoid live vaccines until 6 months of age	Limited data; very low RTX levels in breast milk; breastfeeding may be considered	Limited data
IL−6 receptor inhibitor								
Tocilizumab (TCZ)	Recombinant humanized monoclonal antibody against human IL−6 receptor	Discontinue 3 months before conception; not recommended during pregnancy	Insufficient data support; avoid use	Discontinue 3 months before conception; early pregnancy exposure unlikely to be harmful	Discontinue after conception	If used in late pregnancy, avoid live vaccines until 6 months of age	Limited data; no adverse reactions reported	Limited data
IL−1 receptor antagonist								
Anakinra	Recombinant human IL−1 receptor antagonist (IL−1Ra)	None	May be used before and during pregnancy under special circumstances	Early pregnancy exposure unlikely to be harmful	Discontinue after conception	If used in late pregnancy, avoid live vaccines until 6 months of age	Limited data	Limited data
Costimulatory factor inhibitor								
Abatacept (ABA)	Soluble fusion protein composed of the extracellular domain of CTLA−4 linked to humanized IgG1 Fc region	Discontinue 14 weeks before conception; not recommended during pregnancy	Insufficient data support; avoid use	Early pregnancy exposure unlikely to be harmful	Discontinue after conception	If used in late pregnancy, avoid live vaccines until 6 months of age	Limited data; breastfeeding should be stopped during therapy; breastfeeding may be resumed at least 14 weeks after the last dose	Limited data
Belimumab (BEL)	Humanized monoclonal antibody	Discontinue 4 months before conception	Insufficient data support; avoid use				Limited data; breastfeeding is recommended to be suspended	

Note: CMAR, the Chinese Medical Association of Rheumatology; EULAR, the European Alliance of Associations for Rheumatology; BSR, the British Society for Rheumatology; BSR, the British Association of Dermatologists; ACR, the American College of Rheumatology.

in live births, but two cases of hepatotoxicity and one case of cytomegalovirus reactivation and congenital infection were reported, possibly related to TCZ use. A retrospective study by NAKAJIMA et al.[22] involving 61 pregnancies found no increase in miscarriage or congenital malformation rates. However, a prospective cohort study and a retrospective cohort study by HOELTZENBEIN et al.[23] involving 180 and 108 pregnancies, respectively, reported no significant increase in congenital malformations with TCZ exposure but found elevated miscarriage rates of 21.7 % and 28.7 %. Moreover, TCZ exposure was associated with a slightly higher preterm birth rate compared to the general population. Among 17 neonates exposed during mid-to-late pregnancy, there were six cases of preterm birth and four cases of low birth weight (< 2500 g), although concurrent methotrexate use and high disease activity could not be ruled out as contributing factors.[23]

IL-1 receptor antagonist: anakinra

Anakinra has been used to treat RA and certain autoinflammatory diseases. Due to its homology with natural IL-1Ra and its short elimination half-life, it is considered a safe alternative for treating febrile conditions during pregnancy,[24] and it may also mitigate cytokine storms triggered by severe COVID-19 infection in pregnant women.[25] In a mouse model of IL-1β-induced inflammation, anakinra was found to protect placental function, improve fetal survival, and mitigate offspring neurobehavioral deficits, thereby improving perinatal outcomes.[26] A study by CHANG et al.[27] involving 24 pregnancies with cryopyrin-associated periodic syndromes (CAPS) found that the miscarriage rate was lower among women who received anakinra compared to those who did not (11 % vs. 27 %). YOUNGSTEIN et al.[24] reported no infections or fetal malformations among 10 infants breastfed for up to 10 months after maternal anakinra exposure and 6 infants with paternal exposure.

However, the safety of anakinra during pregnancy remains uncertain, and discontinuation upon pregnancy confirmation is recommended. Use during the second or third trimester may increase the risk of neonatal malformations and maternal complications.[24,27–29] Although most neonates were normal, maternal anakinra exposure was associated with an increased risk of musculoskeletal malformations (ROR = 7.18, 95 % CI = 3.50–14.73).[29] Other adverse pregnancy outcomes have also been reported. In a study of 69 pregnancies exposed to anakinra, BRIEN et al.[28] found that 26.1 % of women experienced pregnancy complications such as preterm birth, vaginal bleeding, hypertension, or oligohydramnios. Among neonates, 13.6 % had mild complications, including five cases diagnosed with CAPS, one case suffered from malnutrition, respiratory distress syndrome, and hyperbilirubinemia, one case with right hydrocele with cardiac murmur, and one case with unilateral renal agenesis with ectopic neurohypophysis. Additionally, CHANG et al.[27] reported a case of twin pregnancy with one case of renal dysplasia and intrauterine death; the surviving twin had no abnormalities. It remains unclear whether the renal abnormalities were associated with anakinra exposure or underlying maternal disease.

CTLA4-Ig: abatacept

Abatacept is approved for the treatment of RA, PsA, and juvenile idiopathic arthritis (JIA). Due to a lack of sufficient data in pregnant women, its use during pregnancy is not recommended. Women of childbearing potential should use effective contraception during ABA therapy and for 14 weeks after the last dose.[30] Several studies have reported adverse outcomes associated with ABA exposure during pregnancy. Dernoncourt et al.[29] found a significant association between fetal musculoskeletal malformations and maternal ABA exposure (ROR = 5.09, 95 % CI = 2.77–9.33). A systematic review by Ghalandari et al.[16] involving 153 ABA-exposed pregnancies reported a miscarriage rate of 26.1 %, higher than that of the general population (10–20 %). Among 88 live births, seven major congenital malformations were observed: three cardiovascular malformations, and one each of cleft lip and palate, meningocele, pyloric stenosis, and cranial malformation. The congenital malformation rate (7.9 %) was slightly higher than that of the general population (3–5 %), although the potential confounding effect of concomitant methotrexate or other teratogenic drugs cannot be ruled out.

Anti-BAFF: belimumab

Belimumab is the only biologic approved for the treatment of SLE. However, due to a lack of supporting data, it should be avoided during pregnancy. A study by GHALANDARI et al.[31] found that persistent BEL exposure during pregnancy (for at least three months preconception) was associated with a fetal mortality rate of 52.4 %, higher than the 46.4 % fetal mortality rate among those who discontinued BEL early in pregnancy (OR = 1.27, 95 % CI = 0.48–3.32), although the difference was not statistically significant. Both groups exhibited high fetal mortality rates, likely influenced by high disease activity and reporting bias. PETRI et al.[32] analyzed 18 clinical trials and found that the birth defect rate was higher in the BEL exposure group than in the placebo group (5.6 % vs. 0 %), although no consistent pattern of defects was identified. Two case series involving a total of 26 SLE patients exposed to BEL during pregnancy reported high preterm birth rates among live births (52.2 %, 12/23), with five cases of SGA and one case of intrauterine growth restriction.[33,34] The pregnant women had higher average maternal ages and histories of recurrent miscarriage. Additionally, studies have shown that pregnant women with SLE have higher risks of congenital malformations and pregnancy complications compared to the general or non-SLE populations.[35] Overall, these studies did not identify any adverse pregnancy outcomes directly attributable to BEL exposure. Although cautious consideration and further research are necessary, BEL may be a reasonable therapeutic option for pregnant SLE patients requiring treatment.

Use of biologics during pregnancy and neonatal vaccination

The metabolic half-life of a drug determines the duration of its immunosuppressive effect on the fetus, which directly influences the timing of neonatal vaccination. Most biologic agents do not significantly increase the risk of infections.[36,37] Demortiere et al.[38] analyzed cord blood samples from fetuses of five pregnant women with multiple sclerosis who had discontinued anti-CD20 therapy prior to pregnancy and found no abnormalities in B-cell counts. Among 23 pregnancies exposed to RTX in which neonatal B-cell counts were measured,[17] nine cases of neonatal B-cell depletion were reported; however, none of these neonates experienced infectious complications or adverse reactions to vaccination, and all B-cell counts normalized within six months. Some studies have reported contrasting findings. DERNONCOURT et al.[29] found that, after excluding the confounding effects of corticosteroid use, BEL exposure was significantly associated with neonatal infections (ROR = 28.49, 95 % CI = 5.75–141.25). A prospective cohort study by JULIAO et al.[35] involving 55 cases reported that six out of 46 infants (13 %) experienced at least one episode of unexplained infection or fever within the first four months after birth. Other studies have shown that fetuses exposed in utero to RTX often exhibit hypogammaglobulinemia, resulting in transient lymphopenia and reduced IgG levels on the first day after birth.[29] Therefore, for neonates born to mothers treated with RTX or BEL during pregnancy, close monitoring of B-cell counts after birth is recommended to ensure early detection and management of potential infections.

EULAR[7] recommends that infants exposed to biologic agents only before 22 weeks of gestation can follow the standard vaccination schedule, including live vaccines. For infants exposed to biologics during the second and third trimesters, it is advised to avoid administration of live vaccines within the first six months of life. Where

available, measurement of serum biologic levels in infants may assist in guiding decisions regarding live vaccine administration.

The Bacillus Calmette-Guérin (BCG) vaccine, rotavirus vaccine, and measles-mumps-rubella (MMR) vaccine are all live attenuated vaccines. The rotavirus vaccination series must be completed by 24 weeks of age to avoid the risk of intussusception.

In a systematic review by GOULDEN et al.,[39] the safety of vaccinations during the first year of life in infants exposed to biologics in utero was comprehensively analyzed. Following BCG vaccination, some adverse events were reported, including one death, two cases of local skin reactions, and one case of axillary lymphadenopathy. Additionally, four cases of fatal disseminated BCG infection were observed in infants who had been exposed to different TNFi agents (including IFX, ADA, and unspecified TNFi) in utero. In contrast, adverse events following rotavirus vaccination were generally mild and similar to those observed in infants not exposed to biologics. No complications were reported in infants vaccinated with the MMR vaccine. Overall, evidence of harm to infants was found after BCG vaccination within the first three months of life, and among those exposed to IFX in utero. However, most rotavirus vaccines are administered within six months after birth, and MMR vaccines are administered after one year, with reassuring safety outcomes following vaccination.

Use of biologics during lactation

Most biologic agents are large-molecule proteins that are secreted into breast milk in minimal amounts, resulting in relatively low infant exposure and making their use during lactation relatively safe.[6,40,41] A study by ANDERSON et al.[42] showed that the median concentration of RTX in breast milk was only 0.03 μg/mL, with a negligible amount entering the infant's circulation. Moreover, there were no significant differences in growth and development between breastfed and non-breastfed infants. SAITO et al.[43] reported two cases of infants exposed to TCZ via breast milk, neither of whom developed any serious complications. TADA et al.[44] found that the placental transfer rate of TCZ was relatively high at 11 %, possibly due to the high concentration of proteins and antibodies in colostrum; however, the use of TCZ during lactation is still considered relatively safe. Case reports on ABA have also indicated that even when infants are exposed to ABA through breastfeeding, no adverse events were observed, and the amount of ABA secreted into breast milk was only about 1/200–1/300 of the maternal serum concentration.[40]

However, due to limited data, some researchers have suggested that, to avoid potential risks to the newborn, women receiving RTX therapy should avoid breastfeeding during treatment and for six months after therapy completion,[45] and those receiving ABA therapy should avoid breastfeeding for 14 weeks.[30] Overall, although the use of these biologics during lactation appears to be safe, clinical decisions should still be made cautiously, with careful assessment of the patient's individual therapeutic needs and potential risks.

Conclusion

The treatment of immune-mediated inflammatory diseases during pregnancy and lactation must balance maternal disease control with fetal and infant safety. Certolizumab pegol, which barely crosses the placenta, can be used throughout pregnancy and is considered the safest biologic agent during this period. In contrast, biologics such as rituximab and tocilizumab, due to insufficient evidence, should be discontinued prior to conception. During lactation, most biologic agents (such as TNF inhibitors) are present in breast milk at extremely low concentrations and are relatively safe; however, caution should be exercised when using other biologics due to limited data. For neonates born to mothers treated with rituximab or belimumab during pregnancy, close monitoring of B-cell counts after birth is recommended. If neonates were exposed to biologic agents during the second or third trimester, administration of live vaccines should be delayed until six months of age. This review comprehensively summarizes and critically analyzes the latest advancements and breakthroughs in the use of biologics for IMIDs patients during pregnancy and lactation, based on authoritative clinical guidelines and abundant research evidence from both domestic and international sources. Particular attention is given to evaluating the safety of these therapies during these special periods. However, current research still has notable gaps, including the long-term safety of offspring, disease-specific differences, and pregnancy data on new biologic agents such as JAK inhibitors. Future prospective studies are needed to optimize individualized therapeutic strategies and ensure maternal and infant safety.

Declarations

Not applicable

Authors' contributions

L. Han, study conception, literature review, manuscript drafting; Z. Hou, manuscript revision, figure design; J. Li, feasibility analysis, supervision and quality control; H. Li, research protocol design, figure creation, funding acquisition; H. Li and Y. Wang, final version revision, responsibility for work integrity.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This study was supported by the Peking University Medicine Youth Science and Technology Innovation "Yangfan Program" Project (BMU2024YFJHPY040), Key Clinical Project of Peking University Third Hospital (BYSYZD2022022), Startup Research Fund for Returned Scholars of Peking University Third Hospital (BYSYLXHG2024010), and National Multidisciplinary Collaborative Diagnosis and Treatment Capacity Building Project for Major Diseases.

Declarations of Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable

Authors' other information

Not applicable.

References

1. McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol.* 2021;21(10):680–686. https://doi.org/10.1038/s41577-021-00603-1
2. Förger F, Villiger PM. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. *Nat Rev Rheumatol.* 2020;16(2):113–122. https://doi.org/10.1038/s41584-019-0351-2

3. Romanowska-Próchnicka K, Felis-Giemza A, Olesińska M, et al. The role of TNF-α and Anti-TNF-α agents during preconception, pregnancy, and breastfeeding. *Int J Mol Sci.* 2021;22(6):2922. https://doi.org/10.3390/ijms22062922
4. Guerrero Vinsard D, Kane SV. Biologics and pregnancy: a clinician's guide to the management of IBD in pregnant women. *Expert Rev Gastroenterol Hepatol.* 2021;15(6):633–641. https://doi.org/10.1080/17474124.2021.1876562
5. Pyzik M, Kozicky LK, Gandhi AK, et al. The therapeutic age of the neonatal Fc receptor. *Nat Rev Immunol.* 2023;23(7):415–432. https://doi.org/10.1038/s41577-022-00821-1
6. Russell MD, Dey M, Flint J, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. *Rheumatology.* 2023;62(4):e48–e88. https://doi.org/10.1093/rheumatology/keac551
7. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75(5):795–810. https://doi.org/10.1136/annrheumdis-2015-208840
8. Bitter H, Warren DJ, Bolstad N, et al. Transplacental passage of belimumab during pregnancy and follow-up of a child exposed in utero. *Ann Rheum Dis.* 2023;82(4):577–579. https://doi.org/10.1136/ard-2022-223684
9. Hu JH, Zhou XY, Yu F, et al. Clinical characteristics analysis of adult eosinophilic esophagitis patients in China. *Chin J Intern Med.* 2025;64(3):212–219. https://doi.org/10.3760/cma.j.cn112138-20241010-00670
10. He Y, Li Y, Tan B, et al. Expert consensus on the management of inflammatory bowel disease during pregnancy. *Med J Peking Union Med Coll.* 2019;10(5):465–475.
11. Smith CH, Yiu Z, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *Br J Dermatol.* 2020;183(4):628–637. https://doi.org/10.1111/bjd.19039
12. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American college of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Care Res (Hoboken).* 2020;72(4):461–488. https://doi.org/10.1002/acr.24130
13. van den Brandt S, Zbinden A, Baeten D, et al. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. *Arthritis Res Ther.* 2017;19(1):64. https://doi.org/10.1186/s13075-017-1269-1
14. Luu M, Benzenine E, Doret M, et al. Continuous anti-TNFα use throughout pregnancy: possible complications for the mother but not for the fetus. a retrospective cohort on the french national health insurance database (EVASION). *Am J Gastroenterol.* 2018;113(11):1669–1677. https://doi.org/10.1038/s41395-018-0176-7
15. Bröms G, Kieler H, Ekbom A, 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):316–327. https://doi.org/10.1002/pds.4930
16. Ghalandari N, Dolhain R, Hazes J, et al. Intrauterine exposure to biologics in inflammatory autoimmune diseases: a systematic review. *Drugs.* 2020;80(16):1699–1722. https://doi.org/10.1007/s40265-020-01376-y
17. Das G, Damotte V, Gelfand JM, et al. Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. *Neurol Neuroimmunol Neuroinflamm.* 2018;5(3):e453. https://doi.org/10.1212/NXI.0000000000000453
18. Kümpfel T, Thiel S, Meinl I, et al. Anti-CD20 therapies and pregnancy in neuroimmunologic disorders: a cohort study from Germany. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(1):e913. https://doi.org/10.1212/NXI.0000000000000913
19. Chakravarty EF, Murray ER, Kelman A, et al. Pregnancy outcomes after maternal exposure to rituximab. *Blood.* 2011;117(5):1499–1506. https://doi.org/10.1182/blood-2010-07-295444
20. Smith JB, Hellwig K, Fink K, et al. Rituximab, MS, and pregnancy. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(4):e734. https://doi.org/10.1212/NXI.0000000000000734
21. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: a retrospective study. *J Clin Pharm Ther.* 2021;46(4):1062–1070. https://doi.org/10.1111/jcpt.13394
22. Nakajima K, Watanabe O, Mochizuki M, et al. Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. *Mod Rheumatol.* 2016;26(5):667–671. https://doi.org/10.3109/14397595.2016.1147405
23. Hoeltzenbein M, Beck E, Rajwanshi R, et al. Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum.* 2016;46(2):238–245. https://doi.org/10.1016/j.semarthrit.2016.05.004
24. Youngstein T, Hoffmann P, Gül A, et al. International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. *Rheumatology.* 2017;56(12):2102–2108. https://doi.org/10.1093/rheumatology/kex305
25. Karakaş Ö, Erden A, Ünlü S, et al. Can Anakinra and corticosteroid treatment be an effective option in pregnant women with severe Covid-19. *Women Health.* 2021;61(9):872–879. https://doi.org/10.1080/03630242.2021.1981517
26. Lei J, Vermillion MS, Jia B, et al. IL-1 receptor antagonist therapy mitigates placental dysfunction and perinatal injury following Zika virus infection. *JCI Insight.* 2019;4(7):e122678. https://doi.org/10.1172/jci.insight.122678
27. Chang Z, Spong CY, Jesus AA, et al. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). *Arthritis Rheumatol.* 2014;66(11):3227–3232. https://doi.org/10.1002/art.38811
28. Brien ME, Gaudreault V, Hughes K, et al. A systematic review of the safety of blocking the IL-1 system in human pregnancy. *J Clin Med.* 2021;11(1):225. https://doi.org/10.3390/jcm11010225
29. Dernoncourt A, Liabeuf S, Bennis Y, et al. Fetal and neonatal adverse drug reactions associated with biologics taken during pregnancy by women with autoimmune diseases: insights from an analysis of the world health organization pharmacovigilance database (VigiBase(. *BioDrugs.* 2023;37(1):73–87. https://doi.org/10.1007/s40259-022-00564-4
30. Puchner A, Gröchenig HP, Sautner J, et al. Immunosuppressives and biologics during pregnancy and lactation: a consensus report issued by the Austrian Societies of Gastroenterology and Hepatology and Rheumatology and Rehabilitation. *Wien Klin Woche.* 2019;131(1-2):29–44. https://doi.org/10.1007/s00508-019-1448-y
31. Ghalandari N, Crijns HJ, Dolhain RJ, et al. Dilemma of belimumab therapy (dis) continuation during pregnancy: results of a retrospective study in eudravigilance. *Lupus.* 2023;32(2):189–197. https://doi.org/10.1177/09612033221143286
32. Petri M, Landy H, Clowse M, et al. Belimumab use during pregnancy: a summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry and postmarketing reports. *Ann Rheum Dis.* 2023;82(2):217–225. https://doi.org/10.1136/ard-2022-222505
33. Kao JH, Lan TY, Lu CH, et al. Pregnancy outcomes in patients treated with belimumab: report from real-world experience. *Semin Arthritis Rheum.* 2021;51(5):963–968. https://doi.org/10.1016/j.semarthrit.2021.06.005
34. Crisafulli F, Gerardi MC, Moschetti L, et al. POS0702: Pregnancy in SLE patients treated with belimumab: Experience from 3 Italian centers. *Ann Rheum Dis.* 2021;80(1):600–601. https://doi.org/10.1136/annrheumdis-2021-eular.2862
35. Juliao P, Wurst K, Pimenta JM, et al. Belimumab use during pregnancy: Interim results of the belimumab pregnancy registry. *Birth Defects Res.* 2023;115(2):188–204. https://doi.org/10.1002/bdr2.2091
36. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. *Am J Gastroenterol.* 2018;113(3):396–403. https://doi.org/10.1038/ajg.2017.501
37. Vinet É, De Moura C, Pineau CA, et al. Serious infections in rheumatoid arthritis offspring exposed to tumor necrosis factor inhibitors: a cohort study. *Arthritis Rheuma.* 2018;70(10):1565–1571. https://doi.org/10.1002/art.40536
38. Demortiere S, Maarouf A, Rico A, et al. Disease evolution in women with highly active MS who suspended natalizumab during pregnancy vs rituximab/ocrelizumab before conception. *Neurol Neuroimmunol Neuroinflamm.* 2023;10(5):e200161. https://doi.org/10.1212/NXI.0000000000200161
39. Goulden B, Chua N, Parker E, et al. Administering live vaccines to infants exposed to biologic and targeted synthetic DMARDs in utero for maternal treatment of rheumatic disease: a systematic review of the literature. *Rheumatology.* 2021;60(1):keab247.197. https://doi.org/10.1093/rheumatology/keab247.197
40. Saito J, Yakuwa N, Takai C, et al. Abatacept concentrations in maternal serum and breast milk during breastfeeding and an infant safety assessment: a case study. *Rheumatology.* 2019;58(9):1692–1694. https://doi.org/10.1093/rheumatology/kez135
41. Saito J, Yakuwa N, Ishizuka T, et al. Belimumab concentrations in maternal serum and breast milk during breastfeeding and the safety assessment of the infant: a case study. *Breast Med.* 2020;15(7):475–477. https://doi.org/10.1089/bfm.2020.0068
42. Anderson A, Rowles W, Poole S, et al. Anti-CD20 monoclonal antibody therapy in postpartum women with neurological conditions. *Ann Clin Transl Neurol.* 2023;10(11):2053–2064. https://doi.org/10.1002/acn3.51893
43. Saito J, Yakuwa N, Takai C, et al. Tocilizumab concentrations in maternal serum and breast milk during breastfeeding and a safety assessment in infants: a case study. *Rheumatology.* 2018;57(8):1499–1501. https://doi.org/10.1093/rheumatology/key091
44. Tada Y, Sakai M, Nakao Y, et al. Placental transfer of tocilizumab in a patient with rheumatoid arthritis. *Rheumatology.* 2019;58(9):1694–1695. https://doi.org/10.1093/rheumatology/kez155
45. Krajnc N, Bsteh G, Berger T, et al. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. *Neurotherapeutics.* 2022;19(3):753–773. https://doi.org/10.1007/s13311-022-01224-9