REVIEW CPD

The use and impact of monoclonal antibody biologics during pregnancy

Anne Pham-Huy MD, Karina A. Top MD, Cora Constantinescu MD, Cynthia H. Seow MBBS, Darine El-Chaâr MD

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Monoclonal antibody biologics, also known as biologics, have revolutionized the treatment and quality of life of many patients with inflammatory and autoimmune conditions.[1] Women of reproductive age are increasingly using these agents to maintain disease remission because of emerging evidence of safety before conception, during pregnancy and lactation.

Biologic drugs contain an immunoglobulin G (IgG) structure. They bind to receptors or key inflammatory molecules and may modulate inflammation by inhibiting cytokine production, lymphocyte trafficking, costimulation signal blockade or B-cell depletion. The use of biologics has become standard treatment for many conditions, including inflammatory bowel disease (IBD), systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis and psoriasis, for which they have revolutionized clinical care. More biologics with broader indications are now available for clinical use, making it challenging to keep up with each drug's characteristics and effects on the immune system (Table 1).

Most monoclonal antibody biologics readily cross the placenta,[2,3] leading to concerns regarding their use during pregnancy and their impact on the fetus and infant, and historical avoidance of their use during pregnancy. However, the last decade has seen a shift in disease management toward tight disease control in pregnant patients and a goal of improving both maternal and fetal outcomes. Achieving clinical remission is recognized as one of the best predictors of favourable pregnancy outcomes,[4–7] and a stable disease course, especially in the 6 months before conception, has been associated with improved maternal and fetal outcomes.[8–10] This has resulted in an increased use of biologics before conception, during pregnancy and postpartum, with treat-to-target objectives varying for each disease.[11–14] Increasingly, cohort studies, clinical registries and systematic reviews have reported safety with the use of anti-tumour necrosis factor (TNF) biologics during pregnancy, mostly reported among patients with IBD.[3,15–17] Confusingly, subspecialty societies provide different guidance on which drugs may be used and when they should be discontinued.[4–6,18,19]

We discuss care for patients taking biologics during pregnancy and their exposed infants, drawing on emerging evidence regarding the potential or reported effects of biologics on the fetus and infant (Box 1).

KEY POINTS

- Increasingly, pregnant patients with inflammatory or autoimmune diseases use monoclonal antibody biologics before conception, during pregnancy and while breastfeeding.
- A minority of biologics may lead to immunological and hematological abnormalities in the exposed infant.
- For infants exposed to biologics, most clinical guidelines recommend avoiding live vaccines in the first 6–12 months of life, but emerging evidence suggests that the live rotavirus vaccine may be provided safely to exposed infants if normal immune function can be documented.
- Minimal transfer of biologics in breast milk means breastfeeding appears to be safe.
- Increasingly, management of the pregnant patient and the infant exposed to biologics is undertaken in specialist multidisciplinary clinics.

What evidence and guidance exists to support prescriptions of biologics during pregnancy?

Insufficient evidence exists to support the routine prescribing of biologics other than anti-TNF agents during pregnancy despite emerging data. Although some prospective studies of 100–200 pregnant patients with stable IBD disease activity have reported that anti-TNFα therapy can be stopped safely without adverse complications,[20–22] others have reported that stopping therapy during pregnancy increases the risk of disease relapse,[23,24] with associated poor outcomes for the infant, such as preterm delivery and low birth weight.[25]

Potential risks of fetal exposure should be weighed against the risk of disease flare in the pregnant patient, which differs depending on the severity and risk of complications and hospitalization from the underlying disease, as well as the type of biologic. Currently, some societies suggest stopping certain biologics during pregnancy, typically in the late second or early third trimester, with the goal of minimizing drug transfer to the fetus.[5,6,18,19] The Toronto consensus statements for the management of IBD in pregnancy,[4] the IBD in pregnancy clinical care pathway[26] and the multicentre Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry[15] have

Table 1: Characteristics of monoclonal antibody biologics and indications for use

Biologic type	Drug name	Structure	Indication for use*
Anti-TNFα	Infliximab	Chimeric anti-TNFα IgG1	Rheumatoid arthritis, ankylosing spondylitis, Crohn disease, ulcerative colitis, plaque psoriasis
	Adalimumab	Recombinant humanized anti-TNFα IgG1	Rheumatoid arthritis, polyarticular JIA, psoriatic arthritis, ankylosing spondylitis, Crohn disease, ulcerative colitis, hidradenitis suppurativa, plaque psoriasis, uveitis
	Golimumab	Humanized anti-TNFα IgG1	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, ulcerative colitis
	Certolizumab pegol	Recombinant, humanized antibody to the antigen-binding fragment to anti-TNFα	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis
	Etanercept	Human recombinant TNFα receptor/IgG1-Fc fusion protein	Ankylosing spondylitis, rheumatoid arthritis, polyarticular JIA, psoriatic arthritis, plaque psoriasis
Anticytokine	Ustekinumab	Anti-IL-12 and IL-23 humanized IgG1	Plaque psoriasis, psoriatic arthritis, Crohn disease, ulcerative colitis
	Tocilizumab	Anti-IL-6 receptor humanized IgG1	Rheumatoid arthritis, polyarticular and systemic JIA, giant cell arteritis
	Canakinumab	Anti-IL-1β human IgG1	CAPS, TRAPS, HIDS, MKD, FMF, systemic JIA
Anti-integrin	Vedolizumab	Humanized anti- α4β7 integrin IgG1	Ulcerative colitis, Crohn disease
	Natalizumab	Anti-integrin α4 subunit humanized IgG4	Multiple sclerosis
Anti-B cell	Rituximab	Anti-CD20 IgG1	Rheumatoid arthritis, non-Hodgkin lymphoma, chronic lymphocytic leukemia, granulomatosis with polyangiitis
	Belimumab	Anti-B-cell activating factor human IgG1	Systemic lupus erythematosus

Note: CAPS = cryopyrin-associated periodic syndromes, FMF = familial Mediterranean fever, HIDS = hyperimmunoglobulin D syndrome, Ig = immunoglobulin, IL = interleukin, JIA = juvenile idiopathic arthritis, MKD = mevalonate kinase deficiency, TNF = tumour necrosis factor, TRAPS = tumour necrosis factor receptor associated periodic syndrome.
*Off-label use not listed.

suggested continuing anti-TNFα therapy throughout pregnancy, as the risks associated with poor maternal and fetal outcomes and potential future loss of response to effective medication (i.e., formation of antibodies against the drug related to a drug hiatus)[27,28] appear to outweigh the potential risks to the exposed fetus.[4,15,16,26,29] This is different from older guidelines from the European Crohn's and Colitis Organization, which recommended that anti-TNF agents be discontinued between 24–26 weeks' gestation, when possible.[18]

Box 1: Evidence used in this narrative review

We conducted a literature review of preclinical and clinical studies in PubMed, published from January 2005 to February 2021. We searched for articles relevant to the use of monoclonal antibody biologics during pregnancy using the following search terms: biologics, monoclonal antibody biologics, pregnancy, infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, rituximab and neonatal outcomes. Given the rapid emergence of data pertaining to this topic, we also reviewed selected abstracts, published expert guidelines and case reports. In addition, we reviewed the bibliographies of articles from high-impact journals in the fields of gastroenterology, rheumatology and dermatology. Recently published articles were preferred to reflect the most up-to-date evidence for this review.

The American College of Rheumatology guideline conditionally recommends the continuation of anti-TNF agents during pregnancy, but recommends stopping other biologic agents, such as tocilizumab, ustekinumab and belimumab.[19] The European League Against Rheumatism suggests that infliximab and adalimumab be stopped at 20 weeks and that etanercept be stopped at 30–32 weeks gestation, but that therapy could also be continued throughout pregnancy, if indicated.[6]

To what degree are biologics transferred to the fetus and which are detectable at birth?

The degree to which biologic drugs transfer to the fetus is variable and depends on several factors, such as the specific drug structure, the drug half-life, the dose and the timing of the last dose in relation to the gestational age. Transfer is minimal during the first trimester and occurs mainly by simple diffusion across the placenta.[30] After this period, maternal IgG antibodies are increasingly and actively transferred across the placenta, mediated by the neonatal Fc receptor found in the placental syncytiotrophoblast. The highest rate of transfer occurs after 36 weeks of gestation[30,31] and with the following IgG subclass order of transfer efficiency: IgG1 > IgG4 > IgG3 > IgG2.[32] The time since the last maternal dose of biologic is inversely correlated with cord blood concentration.[33]

Table 2: Drug transfer, estimated drug clearance and clinical experience of monoclonal antibody biologics in pregnancy

Biologic	Drug transfer to fetus	Estimated drug clearance in the infant	Level of clinical experience*	Reference
Infliximab	High	3–7 mo	++++	2,15,33,36,44
Adalimumab	Moderate	3–5 mo	++++	2,15,33,44
Golimumab	Moderate	Unknown	+	38
Certolizumab pegol	Minimal (passive diffusion)	NA	+++	2,15,41,42,45–47
Etanercept	Low	0–3 mo	+++	39,40
Ustekinumab	Moderate	Unknown	+	15,37,38
Vedolizumab	Low-moderate	Likely < 3 mo	+	15,38,43,44
Natalizumab	Low-moderate	Unknown	+	15,38,48,49
Rituximab	Moderate-high	Unknown	+	50,51
Belimumab	Unknown	Unknown	+	52

Note: NA = not applicable.
*We categorized the amount of clinical experience into 4 levels depending on size and quality of studies: + = least clinical experience (i.e., small case reports and case series only) to ++++ = largest clinical experience (i.e., large prospective cohort studies with > 1000 participants enrolled).

Consistent with studies on maternal–fetal transfer of antibodies,[34] biologic drug levels at birth can often be higher in the infant than the mother.[2,33,35–38] Infliximab levels have been reported to be twofold higher at birth in the infant than in the mother, but are generally undetectable by 3–7 months of age.[2,33] Infant adalimumab levels are typically 1–1.5 times higher than maternal levels at birth, with most studies showing undetectable levels by 3–5 months of age.[3,33,38,39] Etanercept is a fusion protein, consisting of a dimeric TNF receptor fused to a fragment of IgG1-Fc molecule. A few case reports measuring etanercept levels in exposed infants reported low levels at birth and no detectable levels at 12 weeks of age.[39,40] Certolizumab pegol, which only contains the Fab portion of IgG and lacks the Fc portion, does not undergo active transplacental transport and drug levels at birth are negligible.[41,42] Vedolizumab appears to be cleared from the blood within 3 months, based on very small case reports.[16,43,44] Very little has been reported on drug transfer and clearance of newer biologics and further studies are needed in this area. The differential drug transfer has led the American College of Rheumatology to strongly recommend continuation of certolizumab therapy during pregnancy, but to recommend continuation of the other anti-TNF agents only conditionally.[19] Table 2 provides a comparison of reported biologic drug transfer and clearance in the infant.

What are the potential adverse outcomes associated with the use of biologics during pregnancy?

Over 20 years of post-marketing surveillance for infliximab use during pregnancy has not shown any teratogenic or serious adverse pregnancy outcomes.[53–57] Retrospective observational cohort studies[24,58,59] and some prospective studies[15,60] also report a lack of associated increased risk of miscarriages, preterm delivery and congenital malformations. The large prospective cohort PIANO study, which followed 1490 pregnancies that led to 1431 live births, recently reported 1-year outcome data for 1010 infants exposed to monoclonal antibody biologics.[15] Participants were women with IBD who received thiopurines (azathioprine, 6-mercaptopurine), biologics (infliximab, adalimumab, certolizumab, golimumab, vedolizumab, natalizumab and ustekinumab) or both during pregnancy (n = 1111) and participants who were unexposed to those drugs (n = 379). Rates of congenital malformation, spontaneous abortion, preterm birth, low birth weight and infant infection were not increased compared with the nonexposed group. However, preterm birth was associated with a higher rate of infections in infants.

Studies looking at the impact of exposure to anti-TNF agents during pregnancy on infections have shown an increased risk for the mother but not the infant,[24] that the risk of infection was associated with preterm delivery rather than the medication,[58] and that combination therapy (anti-TNF and thiopurines) may increase the risk of infection during the infant's first year of life.[33] A systematic review and meta-analysis, including 6963 patients, showed that adverse pregnancy outcomes among patients with IBD using biologics were similar to those of the general population.[61]

Studies of women with autoimmune diseases in British Columbia, using linked administrative health data and a perinatal registry, did not find associations between exposure to various biologics during pregnancy and infant outcomes, including risk of preterm birth, infections and congenital anomalies.[62–64] No serious safety signals have yet been reported with other biologics, such as tocilizumab,[65] canakinumab,[66] ustekinumab,[67] vedolizumab[59] or belimumab,[68] but the evidence is mainly from small retrospective observational studies and is of low quality.[3,16]

Can a patient taking biologics receive immunizations during pregnancy?

No studies have looked at vaccine immunogenicity for pregnant patients on biologics. The immunogenicity of both the pertussis and influenza vaccines have been shown during pregnancy. In nonpregnant patients with IBD, some vaccines have shown decreased immunogenicity with concomitant use of biologics.[69] Regardless, clinicians are strongly encouraged to follow routine guidance for immunization during pregnancy for patients receiving biologics. Both the Canadian National Advisory Committee on Immunization and the United States Advisory Committee on Immunization Practices recommend pertussis vaccination during each pregnancy, irrespective of previous pertussis vaccination history.[70,71] Live vaccines are contraindicated during pregnancy, regardless of biologic use. During the influenza season, inactivated seasonal influenza vaccine is recommended.[72] Emerging clinical evidence supports the use of SARS-CoV-2 vaccines during pregnancy, particularly mRNA vaccines. Many societies (e.g., the Society of Obstetricians and Gynecologists of Canada, the American College of Obstetricians and Gynecologists) have suggested that SARS-CoV-2 vaccines be offered to pregnant patients, as pregnancy has been shown to be a risk factor for severe COVID-19 and hospitalization, including admission to the intensive care unit.[73,74]

What are the effects on the infant of in utero exposure to biologics?

Biologics may have different distribution and elimination processes in infants compared with adults.[75] No biologics are currently licensed for use in infants. Understandably, providers are concerned about the potential impact of exposure to biologics on the infant's developing immune system and response to infections and immunizations. One prospective cohort study of 80 patients with IBD reported a threefold increased risk of infection (mostly mild and self-limited upper respiratory tract infections) in infants exposed to concomitant biologics and thiopurines, compared with biologic monotherapy.[33] These results differ from those from the larger PIANO cohort, which did not show increased risk of infections for the infants exposed to combination therapy.[15] A variety of infections, mostly uncomplicated and self-limited, have also been reported in small case series of infants exposed to monoclonal antibody biologics, although infections requiring hospitalizations are rare.[76–78] Severe cytopenias (e.g., neutropenia, lymphopenia and anemia) at birth have been reported in infants exposed to natalizumab,[48,79] rituximab[80] and, on rare occasions, infliximab.[81] In some cases, screening of exposed infants with a complete blood count may be considered. One study of immune responses in infants exposed to anti-TNFα showed a more immature phenotype of T- and B-helper cells that normalized by 12 months of age.[82] B-cell depletion has been well documented in infants exposed to rituximab and belimumab.[50,51,83]

Should patients taking biologics continue breastfeeding?

All societies agree that use of anti-TNF agents during breastfeeding presents a low risk given minimal IgG1 secretion and biologic transfer in breast milk. In general, the use of biologics should not influence the decision to breastfeed, and breastfeeding should not influence the decision to use these medications.[4,15,18,84] Many studies, including multicentre prospective studies, have documented the presence of detectable, albeit very low, amounts of biologics in breastmilk.[52,56,85,86] Even with continued maternal use of biologics and breastfeeding, serum levels in exposed infants steadily decrease after birth until they become undetectable.[87] Any small amount of drug that might be ingested is likely further degraded and denatured by proteolytic enzymes in the infant's gastrointestinal tract; the amount that is subsequently absorbed by the infant is estimated to be very low and not clinically important.[87,88] For other agents, such as belimumab, abatacept, tocilizumab, rituximab and ustekinumab, some societies recommend caution[19,89] or avoidance during breastfeeding until further safety data are reported.[6]

Should infants exposed to biologics be immunized?

All exposed infants should receive inactivated immunizations according to the routine schedule. A few small studies have evaluated the immunogenicity of vaccines and have reported normal and protective antibody titers in exposed infants, similar to nonexposed infants.[36] Two studies showed lower antibody levels to *Hemophilus influenzae* type B (Hib) after Hib-conjugate vaccination in exposed infants compared with nonexposed infants.[90,91] Most guidelines recommend avoiding all live vaccines for the first 6–12 months of life.[4,5,18,33,92] A single case of disseminated bacille Calmette–Guerin (BCG) disease was reported in an infant exposed to infliximab following the live, attenuated BCG vaccine.[93] However, cohort studies of infants receiving BCG have reported no serious adverse outcomes.[74,94,95] In Canada, the only live vaccine that is routinely administered before 6 months of age is the rotavirus vaccine. Accumulating clinical experience suggests that the rotavirus vaccine may be given safely to certain infants exposed to biologics, even if the drug is still detectable in serum. Case series[65,82] and more recently, cohort studies[59,76,96] have described exposed infants who received this vaccine without serious complications, such as vaccine-associated rotavirus disease.[83,97–99] Rotavirus infection from the live-attenuated vaccine has been limited primarily to patients with severe combined immune deficiency,[100–102] suggesting that this adverse event is mostly observed in children with severe T- and B-cell immunodeficiency and not with other immune defects or mild immunosuppression.[103–105] Specialist assessment of immune function is recommended before considering administration of rotavirus vaccination, with careful review of the specific drug exposure. This information should then guide a risk–benefit discussion about whether or not to proceed with this

vaccine.[103,106] If the exposed infant cannot be evaluated, then live vaccines should be avoided for the first 6–12 months of life. In certain situations (e.g., travel or local outbreak), the theoretical risk of providing live vaccines before 12 months of age should be weighed against the risks of exposure to natural infection. Live vaccines are generally permitted after 12 months of age, when all types of biologics would be cleared from the infant's circulation.

How should the biologic-exposed infant be cared for?

The dearth of reported adverse events in the exposed infant does not mean that there is no risk of harm. Infants exposed to monoclonal antibody biologics may benefit from follow-up with a health care provider familiar with the potential impact of in utero exposure. Counselling should be individualized for each infant, depending on the characteristics of the drug exposure, concomitant maternal immunosuppressive therapy and potential postnatal exposures to infectious diseases. Specialty pediatric clinics are available in select tertiary care centres, where infants exposed to biologics in utero can be assessed for additional aspects of care, such as documenting adequate protective response to vaccines received (e.g., after rituximab exposure) or to evaluate the safety of administering the rotavirus vaccine after a review of the drug exposure, immunologic testing and a risk–benefit discussion with the caregivers. Guidance on the potential risk of infectious diseases and altered host immune response is also provided in these specialty clinics. One example is the Canadian Immunization Research Network's Special Immunization Clinic Network, which has clinics in 11 pediatric tertiary care centres to provide expertise in the clinical care of children with underlying conditions that complicate immunization, including infants exposed to biologics.[107,108]

What are current knowledge gaps?

Although no clinically important safety signal has been noted in infants exposed to monoclonal antibody biologics, a subtler impact on immune development may be apparent only with continued broad use of biologics in pregnancy. Many questions remain regarding drug-specific effects and long-term impact of exposure to biologics. For example, vedolizumab, a gut-specific inhibitor of lymphocyte trafficking, is not thought to have a systemic impact on immune function, but its effect on the developing fetus and infant gut is unknown. Rituximab, a B-cell depleting agent, can lead to prolonged hypogammaglobulinemia in some patients with poor B-cell recovery, despite undetectable levels in serum; it is unclear what the impact may be on the infant. Drug clearance remains unknown for many drugs. Finally, very few studies have looked at the long-term (> 1 yr) impact of in utero exposure to biologics on the child. A Canadian registry that collects data on the safety of biologic use during pregnancy and in newborns would provide important information to guide practice, especially for drugs that have not been well studied to date.

Conclusion

Current evidence suggests that anti-TNFα agents are safe for use during pregnancy, without significant adverse effects reported for mothers or babies. Further, the benefits of ongoing disease control in mothers result in favourable maternal and fetal outcomes. Given very different mechanisms of action, the experience with anti-TNFα agents cannot be generalized to other biologics. Less is known about the effects of other agents in pregnancy, such as anti-integrins, anticytokines and anti-costimulatory blockade agents, and the potential risk of neonatal infections, immune responses and adverse events after immunization. National and international research and surveillance is needed to monitor the use of newer biologics in pregnancy and their impact on the exposed newborn. Exposed infants should be monitored closely.

Clinics specializing in the care of pregnant patients with chronic conditions are being established, with a focus on counselling before conception and determining the safety of medications during pregnancy and breastfeeding. Clinical care pathways can be used for additional guidance. Each patient's disease history should be reviewed carefully, weighing the maternal–fetal benefit of medical treatment, including the use of biologics during pregnancy, against potential maternal or fetal risks.

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Affiliations: Division of Infectious Diseases, Immunology and Allergy (Pham-Huy), Children's Hospital of Eastern Ontario; Faculty of Medicine (Pham-Huy), University of Ottawa, Ottawa, Ont.; IWK Health Centre, Division of Infectious Diseases, Canadian Center for Vaccinology (Top), Halifax, NS; University of Calgary Faculty of Medicine, Division of Pediatric Infectious Diseases (Constantinescu); Division of Gastroenterology and Hepatology (Seow), Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alta.; OHRI OMNI Research Group (El-Chaâr), Clinical Epidemiology Program; Department of Obstetrics, Gynecology and Newborn Care (El-Chaâr), Ottawa Hospital, Ottawa, Ont.

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Correspondence to: Anne Pham-Huy, aphamhuy@cheo.on.ca