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REVIEW



From mother to baby: antenatal exposure to monoclonal antibody biologics

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ABSTRACT

Introduction: More women with autoimmune and inflammatory conditions are being treated with monoclonal antibody biologics (mAbs) during their pregnancy, to maintain clinical remission. The use of anti-tumor necrosis factor alpha agents in pregnancy appears to be safe but less is known regarding other mAbs, such as anti-integrins and anti-cytokine agents. There are currently no comprehensive guidelines on how to manage the exposed infants.

Areas covered: We review recent literature to assess the impact of mAbs on birth and early infant outcomes, including what is currently known about maternal and infant drug levels at birth and drug clearance in the infant. We describe the potential risks of infections and reported hematological and immunological effects of antenatal mAbs exposure on the infant and provide guidance on the management of the exposed infant.

Expert opinion: Exposed infants should be monitored closely. Certain mAb exposures require specific testing and management. Safety monitoring should be done in a multidisciplinary approach and should include pediatric care providers. The current clinical experience with anti-tumor necrosis factor agents in pregnancy cannot be extrapolated to other mAbs. Long-term observational studies and a multicenter international registry are needed to better appreciate the impact of exposure, especially to newer mAbs.

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1. Introduction

Autoimmune and inflammatory conditions affect a large number of patients globally, many of whom are women of reproductive age. Control of maternal disease activity prior to and during pregnancy is recognized as the strongest predictor of a successful pregnancy and neonatal outcome [1]. As a result, experts may choose to continue immunosuppressive therapy during pregnancy, including monoclonal antibody biologics (mAbs), such as anti-tumor necrosis factor alpha (anti-TNF α) agents, anti-integrin agents, and various other cytokine inhibitors. Here, we perform a comprehensive review of the current literature and provide guidance on the management and evaluation of infants with antenatal exposure to mAbs. Recommendations in this document are based on currently available literature and expert opinion and the term 'biologics' refers only to mAbs drugs.

2. Biologics use in pregnancy and early birth outcomes

Collective experience from thousands of pregnancies in patients with inflammatory arthritis and inflammatory bowel

disease (IBD) suggests that exposure to biologics, mainly anti-TNF α agents, during pregnancy does not result in an increased risk of adverse pregnancy or fetal outcomes, including congenital malformations, preterm delivery, and early pregnancy loss [2–9]. In a report from the PIANO registry (Patient Prospective Registry of Pregnancy Outcomes in Women with IBD Exposed to Immunomodulators and Biologic Therapy), 1115 women were followed throughout pregnancy and during their infant's first year of life, and analyzed according to whether they received; (a) immunosuppression, such as azathioprine or 6-mercaptopurine (6-MP), (b) anti-TNF α agents, (c) combination therapy or (d) no medication during pregnancy. In this cohort, the use of thiopurines (e.g. 6-MP) and anti-TNF α agents were not associated with an increase in pregnancy loss, congenital anomalies, preterm birth, intrauterine growth restriction, caesarean section, or neonatal intensive care unit stays [10]. More recently, French investigators published the results of a study using the French national health system database to link 11,275 pregnancies, in 8726 women with IBD, and infant complications following anti-TNF exposure (mainly infliximab and adalimumab) during pregnancy.

Article highlights

- (1) Increasing infants are being exposed to biologics *in utero* due to maternal immunosuppressive treatment.
- (2) Antenatal exposure to mAbs can lead to immunological and hematological abnormalities in certain infants.
- (3) Overall, antenatal exposure to infliximab and adalimumab does not appear to have significant adverse outcomes in the infant, but counseling and close monitoring of exposed infant is warranted.
- (4) Less data is available for other mAbs such as tocilizumab, ustekinumab, natalizumab, vedolizumab, rituximab, and other biologics.
- (5) Opportunistic infections should be considered in exposed infants presenting with acute illnesses.
- (6) Exposed infants should be monitored for clinical and immunological impact, especially in the first few months of life where effect is thought to be greatest.

The retrospective study showed an increased risk of maternal complications, but no increased risk in the exposed infants compared to an unexposed group. The study also suggests that discontinuation of anti-TNF α prior to 24 weeks gestation led to an increase in disease flare [11]. The European League against Rheumatism (EULAR) conducted a systematic review of the use of anti-TNF α agent use in pregnant patients with rheumatological disorders. There were 10 cohorts reviewed, comprising nearly 2500 patients. Again, there was no difference in miscarriages or congenital malformation in pregnancies exposed to anti-TNF α compared with controls [12]. At this time, less data is available for other mAbs being used during pregnancy.

3. Drug levels at birth and time to drug clearance

Active placental transfer of maternal immunoglobulins is mediated by the neonatal Fc receptor (FcRn) expressed on syncytiotrophoblast cells and begins during the second trimester, peaking towards the last weeks of gestation with term newborn levels of Immunoglobulin G (IgG) around 120–130% of maternal levels [13]. Transfer during the first trimester is by passive diffusion and low [14]. IgG is most efficiently transported in the rank order of IgG1, IgG4, IgG3, and IgG2 [15]. Therefore, mAbs with an IgG1 molecule, such as infliximab or adalimumab, will have more efficient transport as opposed to drugs like eculizumab (IgG2/4k molecule). Studies have consistently demonstrated detectable levels of biologic agents in the exposed newborn (Table 1) [16–20]. In general, there is an inverse correlation between the time since the last maternal dose of biologic and cord blood concentrations [16,19,21]. Levels at birth are lower if drugs were given before 30 weeks' gestation. However, despite discontinuing drugs prior to 30 weeks, certain mAbs remain detectable at birth [21,22]. Mechanisms suggested for the prolonged half-life of biologics in infants include the ineffective clearance of antibodies within the immature reticuloendothelial system and increased expression of FcRn in the first few months of life [20,23]. In a study of 80 women with IBD, 44 received infliximab, and 36 received adalimumab during pregnancy. In the adalimumab exposed infants, 8 (22%) had undetectable

concentrations at birth. For those with detectable levels, the median ratio of infant to maternal drug concentration at birth was 1.21 (95% CI, 0.94–1.49), and mean time to clearance was 4.0 months (95% CI, 2.9–5.0 months). In the infliximab exposed newborns, all had detectable drug levels at birth with a median ratio of infant to maternal drug concentration at birth of 1.97 (95% CI, 1.50–2.43). Mean time to drug clearance was 7.3 months (95% CI, 6.2–8.3 months) with five infants noted to have detectable concentrations at 9 months of age [19]. In another study comparing maternal and infant drug levels at birth, infliximab ($n = 51$) had a ratio of infant/maternal level of 2.2 (0.7–4.7) and adalimumab ($n = 35$) was 1.5 (0.4–3.5) [24]. In contrast, etanercept, a fusion protein consisting of the extracellular ligand-binding TNF receptor linked to Fc portion of IgG1, has been detected in very low levels in cord blood [25]. Certolizumab pegol (CZP), which only contains the Fragment antigen binding (Fab) portion of IgG is not thought to undergo active transplacental transport [77,78]. In a study of 14 infants born to mothers treated with CZP throughout pregnancy, 13 had undetectable levels at birth and one infant only had minimal CZP levels [26]. Vedolizumab (VDZ) is an anti- $\alpha 4\beta 7$ integrin humanized IgG1 mAb. Serum levels of VDZ in four exposed infants at birth were approximately half that detected in the maternal serum (infant/maternal level = 0.5 range 0.4–0.8) [24]. Additionally, three infant/mother pairs had a ratio of infant/maternal drug level of 1.4 following exposure to ustekinumab (USK), a humanized IgG1 mAb against the p40 subunit of IL-12 and IL-23 [27]. There are no data on USK or VDZ drug clearance for infants. Natalizumab (NAT) is a humanized IgG4 mAb to the $\alpha 4$ subunit of integrin molecules, important in the adhesion and migration of lymphocytes [28]. In a study of 11 infant-mother pairs, NAT was only detectable when the last infusion was given less than 75 days before delivery. Free NAT was detectable in the serum of 6 out of 11 mother/infant pairs [29]. Rituximab is a mAb against CD20 found on B cells, leading to CD20+ B cell depletion. In one report, a mother with Burkitt's lymphoma received rituximab throughout her pregnancy. Drug levels at birth were 3-fold higher in the infant compared to the mother. B cells were absent in both mother and newborn [30]. Canakinumab is an IL-1 inhibitor IgG1 mAb. In one report, drug levels at birth were 2-fold higher in the newborn compared to the mother [31]. Eculizumab is a humanized mAb IgG2/4k directed against the terminal complement protein C5, preventing the formation of the membrane attack complex. Based on a few studies, eculizumab is thought to have poor transfer to the newborn with undetectable or very low levels at birth [32,33]. There are very few studies looking at drug clearance in infants exposed to mAbs. At this time, availability of drug level measurement is limited, and generally only available for infliximab and adalimumab levels.

Current expert groups provide different restrictions and recommendations for the use of mAb during pregnancy. If used during pregnancy, there is a debate on whether to discontinue mAb at a specific gestational week or to continue throughout. For example, the Toronto consensus statements for the management of IBD in pregnancy recommends to continue anti-TNF α maintenance therapy throughout pregnancy in most patients [34]. In contrast, the British Society for

Table 1. List of monoclonal antibody biologics that can be transferred to the fetus during pregnancy.

Drug	Monoclonal antibody structure	Route	Half-life adults (days)	Indications and clinical Use*	Infant/maternal ratio at birth	Infant drug clearance	References
Anti-TNF alpha agent							
Infliximab	Anti-TNFα chimeric IgG1	IV	7.7–9.5	RA, AS, CD, UC	Typically, 2 fold maternal levels at birth	Most studies show undetectable by 7 months	[19,22,24,74]
Adalimumab	Anti-TNFα humanized IgG1	SC	10–20	RA, Polyarticular juvenile idiopathic arthritis, Psoriatic arthritis, AS, CD, UC, Hidradenitis Suppurativa, Plaque psoriasis, Uveitis	Typically, 1.5 fold maternal levels	Most studies show undetectable by 3–5 months.	[6,17,19]
Golimumab	Anti-TNFα humanized IgG1	IV/SC	7–20	RA, Psoriatic arthritis, AS, Non-radiographic Axial Spondyloarthritis, UC	No data	Unknown	
Etanercept	Human recombinant TNFα receptor/IgG1-Fc fusion protein	SC	3–5	AS, RA, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis	Thought to cross placenta due to structure		
Certolizumab pegol	Anti-TNFα PEGylated human Fab antigen binding	SC	11–14	RA, Psoriatic Arthritis, AS	Minimal levels at birth or undetectable	In one case, reported undetectable by 12 weeks of age	[18,24,25]
Anti-cytokine agent							
Tocilizumab	Anti-IL-6 receptor humanized IgG1	IV/SC	8–14	RA, giant cell arteritis, polyarticular JIA, systemic juvenile idiopathic arthritis	Thought to cross placenta due to structure	Unknown	
Ustekinumab	Anti-IL-12 and IL-23 humanized IgG1	IV/SC	20–24	Plaque psoriasis, Psoriatic Arthritis, CD	Limited data 1.4–2 fold levels at birth	Unknown	[24,27]
Canakinumab	Anti-IL1β human IgG1	SC	16–26	CAPS, Tumor Necrosis Factor Receptor Associated Periodic Syndrome, HyperIgD syndrome, Familial Mediterranean Fever, Systemic, JIA	Limited data 1 case shows 2 fold newborn levels at birth	Unknown	[31]
Secukinumab	Anti-IL-17A human IgG1	SC	22–31	Plaque psoriasis Psoriatic arthritis AS	Thought to cross placenta due to structure	Unknown	
Anti-integrin agent							
Natalizumab	Anti-integrin α4 subunit humanized IgG4	IV	10–17	Multiple sclerosis	Likely efficient transfer 0.4–4.4 fold	Unknown	[24,62]
Vedolizumab	Anti-α4β7 integrin humanized IgG1	IV	15–22	UC, CD	Estimated to be about half of maternal serum level	Unknown	[24]
B cell targeted agent							
Rituximab	Anti-CD20 IgG1	IV	14–62	RA, Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Granulomatosis with Polyangiitis	Some studies show 1.5–3 fold levels at birth	Prolonged effect even once drug is undetectable	[60]
Belimumab	Anti-B cell activating Factor human IgG1	IV/SC	8–14	Systemic lupus erythematosus	Thought to cross placenta due to structure	Unknown	
Costimulation blockade agent							
Abatacept	Anti-CTLA-4 IgG1 (Fusion protein with Fc regions of IgG1)	IV/SC	8–25	RA, JIA	Likely efficient transfer	Unknown	
Other mAb							
Omalizumab	Anti-IgE Humanized IgG1	SC	26	Asthma, Chronic idiopathic urticaria	Thought to cross placenta due to structure	Unknown	
Eculizumab	Anti-C5 Humanized IgG2/4	IV	8–15	PNH, Atypical uremic syndrome	Reported poor transfer	Unknown	[33]

*Off-label use not listed. AS: ankylosing spondylitis; CAPS: Cryopyrin-Associated Periodic Syndromes; CD: Crohn's disease; JIA: Juvenile Idiopathic Arthritis; RA: rheumatoid arthritis; PNH: paroxysmal nocturnal hemoglobinuria; UC: ulcerative colitis.

Rheumatology and British Health Professionals in Rheumatology have been more cautious and given specific guidance on mAb use and discontinuation during pregnancy. For instance, they recommend discontinuing infliximab by 16 weeks gestation and by the third trimester for etanercept and adalimumab. They also advocate to completely avoiding mAbs such as rituximab, tocilizumab, and belimumab during peri-conception and pregnancy [35].

4. Biologics and risk of infections

A common host response to infection is to generate a regulated and effective immune-mediated inflammatory response. If a specific component of the host response is inhibited, the inflammatory response may be impaired, dampened, or dysregulated. This may lead to increased susceptibility to infection or inability to control infection. In both adult and pediatric patients with inflammatory conditions, biologics have been associated with an increased risk of infections including tuberculosis (reactivation and disseminated disease), invasive fungal infections, severe bacterial and viral infections and more rarely opportunistic infections [36–47]. Biologics are often given concomitantly with other immunosuppressive agents, which, in combination with the underlying inflammatory condition, add to the cumulative risk of infection. The increased risk also varies depending on the specific immune modulatory effects of the drug. For example, increased susceptibility to mucocutaneous candidiasis has been reported with IL-17 blockade [38].

In a retrospective study of 388 anti-TNF α exposed infants, severe infections were not increased compared with 453 non-exposed children over a median follow-up of 47 months (range, 9–202 months) [48]. Similar results were noted in a cohort of 72 anti-TNF α exposed infants compared with 69 un-exposed children. There were no significant differences in the frequency of infections requiring antibiotics or hospitalization between the two groups [49]. Bortlik *et al.* reviewed 25 children with antenatal exposure to anti-TNF α agents, of whom 80% experienced at least one infection (mainly respiratory) and 60% received antibiotics over a median of 34 months of follow up. Four infections required hospitalization including pyelonephritis, pneumonia, laryngitis and obstructive bronchitis. The significance of these findings is unclear since there was no control group [50]. Two other studies suggested that the combination of an anti-TNF α agent with thiopurines during pregnancy may lead to a 1.5–3 fold increased relative risk for infection in the infant [10,19]. Other infections in infants exposed to anti-TNF α agents have been reported, including varicella infection and recurrent upper respiratory infections [51,52]. In a cohort of 90 infants exposed to rituximab during pregnancy, four neonatal infections were reported (fever, bronchiolitis, cytomegalovirus hepatitis and chorioamnionitis) [53]. At this time, there is insufficient data to assess the short and long-term consequences of VDZ on fetal and infant development or the potential impact of altering gut lymphocyte trafficking [54].

5. Immunological and hematological effects

In contrast to the mother, the baby is typically not receiving other concomitant immunosuppressive drugs or affected by

the mother's underlying condition. However, newborns have a relatively immature immune system and in the first few months of life, infants are especially dependent on passive humoral immunity and innate immune responses. Targeting specific cytokine pathways in the mother may affect the fetal immune system and subsequent developing infant immune system. One can speculate that if a newborn with anti-TNF α blockade was to be exposed to a serious infection, the infant's potentially dampened immune response could lead to a more severe course of illness. A study looking specifically at immunological changes in newborns exposed *in utero* to anti-TNF α therapy showed that exposed infants had a more immature T and B helper cell phenotype than unexposed infants in the first few months of life which normalized within 12 months as well as a decreased number of Treg cells at birth that inversely correlated with the mother's peripartum anti-TNF α levels. The authors documented normal T cell proliferation to mitogens, immunoglobulin production and humoral response to inactivated vaccines. Exposure to anti-TNF α during pregnancy was associated with reduced anti-mycobacterial responses based on cell surface activation markers and cytokine secretion in whole blood culture after mycobacterial challenge [55]. Cytopenias have been reported in anti-TNF α agent exposed newborns with cases of profound neutropenia leading to skin infections requiring IV antibiotics and granulocyte colony-stimulating factor [56]. Extended lymphocyte immunophenotyping was performed in 22 infants exposed to various anti-TNF α agents or thiopurines. No significant differences in the main subsets were observed; however, trends in reductions of switched memory B cells and plasmablasts in the exposed infants were observed at one year of age [57]. Rituximab leads to targeted CD20+ B cell depletion typically lasting 6 months after infusion. It is known that B-cell reconstitution can be variable and resultant hypogammaglobulinemia and B cell lymphopenia can persist for years in some patients [58,59]. There have been reports of infants exposed to rituximab *in utero* with B cell depletion, neutropenia, lymphopenia, thrombocytopenia and anemia at birth [53,60]. Thus far, reported cytopenias were generally transient and resolved spontaneously within weeks to months [30]. Natalizumab (NAT), an anti-integrin leads to decreased T lymphocyte migration. Schneider *et al.* studied T lymphocyte chemotaxis in 2 infants exposed to NAT *in utero*; both infants showed impaired CXCL12 induced T lymphocyte chemotaxis rates at 2 weeks of age that resolved at 2 months. The clinical significance of these findings remains unknown [61]. A high incidence of hematological abnormalities was reported in a series of 13 infants exposed to NAT during the third trimester. Ten of the 13 infants had hematological abnormalities such as anemia, thrombocytopenia, and leukocytosis, with most normalizing by 4 months of age without specific treatment [62]. Three pregnant women, who received ecilizumab during pregnancy lacked terminal complement pathway activity when measured at birth but their newborns had normal complement activity [32]. Belimumab is a fully humanized mAb against B cell activating factor (BAFF). One infant exposed to belimumab *in utero* had marked B cell depletion and

reduced T cell lymphocyte subsets at birth which normalized by 4 months of age [63]. In summary, broad and specific immunological and hematological abnormalities have been reported in infants exposed to a variety of mAbs. In general, reported abnormalities resolved spontaneously within the first few months of life.

6. Vaccine responses after *in utero* exposure to biologics

In a study of infants exposed to anti-TNF α agents *in utero*, 15 children were given hepatitis B vaccine at 6 weeks, 3, 4 and 11 months of age. All children developed protective antibody levels (anti-HB ≥ 10 IU/L) [64]. A study from the PIANO registry measured infant responses to tetanus toxoid and *Haemophilus influenzae type B* (Hib) vaccines and drug levels to assess the effect of maternal use of biologics and/or immunomodulatory drugs on vaccine responses [65]. There were 42 infants with antenatal exposure to biologics: infliximab ($n = 27$), adalimumab ($n = 7$), certolizumab ($n = 3$), natalizumab ($n = 2$), ustekinumab ($n = 2$), and vedolizumab ($n = 1$). Eight infants exposed to drugs other than biologics (e.g. steroids, thiopurines) formed the comparison group. No significant differences were observed in proportions of mAb-exposed versus unexposed infants with protective antibody titers against Hib or tetanus. However, the overall rates of protective response to Hib and tetanus in this cohort, 67% and 80%, respectively, were lower than what is reported historically among healthy infants [66]. In this same cohort, 43 infants exposed to biologics *in utero* received the rotavirus (RV) vaccine, a live attenuated viral vaccine. Seven of 40 infants with available data reported only minor expected reactions (fever, diarrhea) and no severe adverse events. Other small observational studies of 4–18 infants exposed to infliximab, adalimumab or VDZ who received RV similarly reported no significant adverse events [55,67]. Bacillus Calmette-Guérin (BCG) is a live attenuated bacterial vaccine that is given routinely at birth in regions with high tuberculosis prevalence. There is a single case report of a fatal outcome in an infant, born to a mother taking infliximab throughout pregnancy for IBD, who received BCG vaccination at 3 months of age. He subsequently developed poor weight gain, head lag, and died at 4.5 months of age from presumed disseminated BCG disease [68]. In another study, 15 infliximab exposed infants received BCG vaccine. Of those infants, three developed large local reactions with one child developing axillary lymphadenopathy. No serious complications were reported in this group [50]. At this time, all guidelines recommend proceeding with routine inactivated vaccines. Most experts recommend avoiding live attenuated vaccines in infants with prenatal exposure to biologics varying between 6 and 12 months of age or until serum drug levels in the infant are undetectable given the potential for serious adverse events [19,34,69,70].

7. Biologics and risk of malignancy

Hepatosplenic T cell lymphomas have been reported in adolescent and adult patients treated with anti-TNF α blockers. It is

difficult to determine the true risk attributable to biologics as patients with inflammatory and autoimmune diseases may also be at higher risk of malignancy when compared with the general population. There is currently no data on the risk of malignancy for infants exposed to biologics *in utero*.

8. Exposure to biologics and breastfeeding

IgA is the predominant immunoglobulin in human milk and IgG secretion in breast milk is limited. Many studies have documented the presence of detectable but clinically insignificant amounts of biologics in breastmilk [71–74]. Even if biologics are ingested by the infant, there is likely degradation by proteolytic enzymes in the infant intestine and the amount subsequently absorbed by the infant is thought to be very low and of no clinical significance [74]. At this time, most expert panels state that the use of biologics should not influence the decision to breastfeed, and breastfeeding should not influence the decision to use these medications [12,34,70].

9. Guidance

At this time, studies on the use of biologics in pregnancy have not reported significant adverse events except for a single infant death following *in utero* infliximab and post-natal BCG vaccine exposures [68]. Subsequently, a growing number of infants are exposed to biologics *in utero*. Most of the monitoring occurs during pregnancy and at birth. In general, maternal health-care providers simply recommend routine infant care for the exposed infant. There is currently a paucity of high-quality evidence to guide management of these children. Based on the literature described above and discussion among the authors, we developed guiding principles for management of mAb exposed infants based on available published clinical guidelines from the IBD and inflammatory rheumatic diseases literature. We propose general recommendations for the evaluation and management of infants exposed to mAbs *in Utero* (Table 2) as well as specific guidance depending on the drug used (Table 3).

10. Expert opinion

Increasing women with autoimmune and inflammatory conditions are being treated with monoclonal antibody biologics during their pregnancy to maintain clinical remission. There are increasing studies showing that the use of anti-TNF α agents appears to be safe during pregnancy, due to lack of significant reported effects in the exposed infant in terms of infections, growth, development, vaccine responses or immunological abnormalities. However, prescribers should still be very cautious, especially when anti-TNF α is used in late pregnancy. Each patient's particular disease should be reviewed carefully, weighing potential maternal, fetal and infant risks versus maternal benefit of mAb treatment. Additionally, due to very different mechanisms of action, one cannot and should not generalize the experience with anti-TNF α agents to other mAbs. There is much less known about the effects of other biologics, such as anti-integrins, anti-cytokines and anti-costimulatory blockade agent's use in pregnancy. The current

Table 2. General recommendations for the evaluation and management of all infants exposed to mAbs *in utero*.

	Recommendations
Prenatal counseling	Women of reproductive age should be counseled regarding potential impact of their medication, including biologics on pregnancy and fetal/infant outcomes. In general, women with IBD and inflammatory conditions have an increased rate of adverse pregnancy outcomes compared with the general population. Consideration should be made to refer these patients to high risk obstetrics during pregnancy. Consider enrolling patient in applicable pregnancy registry [76]
Breastfeeding	There are no contraindications to breastfeeding for any of the biologics known to be transferred across the placenta [12,34,70]
Vaccines	Proceed with routine inactivated immunizations as per local schedule. In general, avoid live vaccines until 6–12 months of age in infants exposed to biologics that may cross the placenta at clinically significant levels. If testing available, consideration may be given to giving the vaccine earlier if biologic clearance has been documented [34,70,79–81] although some drugs such as rituximab may have prolonged effects. A discussion regarding risks and benefits of live vaccines in the context of specific local epidemiology (e.g. rotavirus) or potential travel exposure (e.g. measles and yellow fever vaccine) is recommended [80] Measles Immunoglobulin may be considered for pre-exposure prophylaxis in case of travel to endemic area [79] Given serious adverse event reported with the use of BCG vaccine in infliximab exposed infant, most experts would strongly recommend against giving BCG vaccine during the first year of life [68]
Infectious Diseases	Review potential epidemiologic infant exposures (e.g. endemic mycoses, tuberculosis) A broader differential to include opportunistic, invasive fungal and mycobacterial diseases should be kept in mind for the exposed infant that presents with an acute illness.
Follow-up	Exposed infants should be monitored closely, especially in the first 6 months of life, when most potential reported immunological and hematological effects occur. Health care providers should be aware of potential long-term impact of antenatal exposure to mAbs. Long-term follow up of exposed children beyond infancy should monitor for evidence of infectious, autoimmune or malignant diseases that may be associated with antenatal mAb exposure.

Table 3. Specific recommendations according to monoclonal antibody biologic exposure *in utero*.

Monoclonal antibody biologic	Additional testing and specific guidance
Infliximab Adalimumab Golimumab	Consider complete blood count (CBC) with differential at birth [56] If testing available, consider measurement of drug levels every 3 months until clearance.
Rituximab Belimumab	Consider CBC with differential at birth Consider T, B, NK cell subsets at 6–12 months of age [30,82] Avoid live vaccines until 12 months of age [69] Consider documenting vaccine responses at 12–18 months (e.g. tetanus, diphtheria and pneumococcus) to ensure adequate response.
Natalizumab	Consider CBC with differential, bilirubin, lactate dehydrogenase, liver enzymes at birth if last natalizumab infusion was within 75 days of birth. [62]
Canakinumab	Consider CBC with differential at birth [83]

lack of reports of severe clinical outcomes may be due to a lack of infectious diseases exposure and the small sample sizes of the studies conducted to date. For example, infliximab was approved for use in the United States in 1998. Serious infections, especially granulomatous infections were not as well recognized during initial clinical trials. Within a few years of broader use, the infectious diseases susceptibility became more apparent [75]. In the general population, the use of biologics is uncommon; therefore adverse events in infants would be rare occurrences. Thus, monitoring for these events will require the follow up of large numbers of infants to reliably assess the true impact of *in utero* exposure to biologics on immunologic development, the risk of infectious diseases, autoimmunity and lymphoid malignancies. Pregnancy exposure registries exist for patients with autoimmune and inflammatory conditions. Registries collect important health information on exposure to various drugs, including mAbs. Prescribers should be encouraged to participate and submit information to those registries such as the ‘MotherToBaby’ pregnancy studies conducted by the Organization of Teratology Information Specialists (OTIS) [76]. In summary, expert knowledge of biologics and their effects on the pregnant patient, the developing fetus and infant is

needed to inform patients and help guide management decisions.

11. Five-year view

The use of monoclonal antibody biologics has enabled a greater number of women with autoimmune and inflammatory conditions to achieve successful and healthy pregnancies. We expect that there will be increasing liberal use of mAbs during pregnancy, especially in the context where the maternal benefit is deemed to outweigh the potential risks to the infant. Pediatric health-care providers should be familiar with this emerging population of infants exposed to mAb *in utero*. Effort should be made to develop accessible and standardized laboratory tests to measure the different biologics levels in infants in order to guide management. Safety monitoring and management require a multidisciplinary approach with a comprehensive focus on the exposed infant. The creation of a multicenter international registry for long-term follow up could potentially optimize the assessment of the impact of antenatal exposure to biologics.

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