REVIEW OPEN ACCESS

# Use of B-Cell–Depleting Therapy in Women of Childbearing Potential With Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

Alexandra Galati, MD, Thomas McElrath, MD, and Riley Bove, MD

**Correspondence**
Dr. Bove
riley.bove@ucsf.edu

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## Abstract

### Purpose of Review

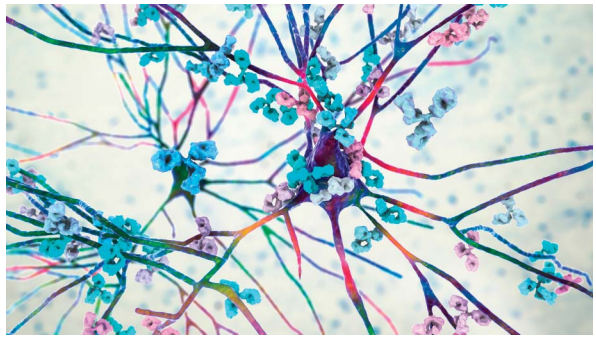
There is considerable heterogeneity in the use of B-cell depletion in women of childbearing age, likely driven at least in part by the discrepancy between the product labels and what is known about the physiology of IgG1, including breastmilk and placental transfer.

### Recent Findings

We provide practical considerations on the use of this medication class in women of childbearing potential. We discuss prepregnancy planning including vaccinations, safety of B-cell depletion during pregnancy, and postpartum considerations including breastfeeding.

### Summary

B-cell–depleting monoclonal antibodies have shown to be effective for prepregnancy and postpartum prevention of inflammatory activity in MS and neuromyelitis optica spectrum disorder. B-cell–depleting therapies are large IgG1 monoclonal antibodies, which have minimal transfer across the placenta and into breastmilk. Consideration of risks and benefits of these therapies should be considered in counseling women planning pregnancy and postpartum.



MS and neuromyelitis optica spectrum disorder (NMOSD) are inflammatory CNS disorders mediated in part by demyelinating attacks. Both conditions have typical onset in women, with the female:male sex ratio in NMOSD (9:1) even higher than that in MS (3:1), and onset slightly later. The use of B-cell–depleting therapies to treat MS and NMOSD is becoming increasingly common, and there is a need for updated guidance on the management of women with these conditions who plan to conceive.

This narrative review is intended to provide evidence-based guidance to neurologists regarding optimal use of B-cell–depleting therapies in women with NMO and NMOSD of childbearing age, particularly those who are planning pregnancy, pregnant, or lactating. This review was conducted via PubMed, Google Scholar, and Cochrane database from May 15, 2021, to October 9, 2021. The search strategy included the following keywords: "multiple sclerosis," "neuromyelitis optica spectrum disorder," "pregnancy," "breastfeeding," "CD20," and "B cell depletion." Titles and abstracts were screened based on study design and patient population and were searched for

Division of Neuroimmunology and Glial Biology (A.G., R.B.), Department of Neurology, University of California, San Francisco, UCSF Weill Institute for the Neurosciences, San Francisco, CA; and Brigham & Women's Hospital, Harvard Medical School, Boston, MA.

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additional references as well. Topics covered include conception planning, vaccination timing, management during pregnancy, and postpartum and breastfeeding considerations.

## Overview of MS and NMOSD and Pregnancy

Studies to date have been largely reassuring that MS is not associated with difficulty with fertility/fecundity, with gestational complications, or with adverse pregnancy outcomes including early pregnancy loss, stillbirth, fetal malformations, low birthweight, and low gestational age.[1] Notably, pregnancy is felt to play a modulatory role on neuroinflammatory function. Pregnancy itself is considered an immunotolerant state, promoting tolerance to placental proteins, with a shift from Th1 to Th2 response. Perhaps as a result, relapse rates in MS have been reported across numerous studies to decrease during pregnancy and then rise postpartum. Up to about a third of women have been reported to experience an MS relapse in the first 3 months postpartum. Increased postpartum activity is evidenced by both increased rate of clinical relapse as well as new radiographic activity including new T2 hyperintense lesions or gadolinium-enhancing lesions.[2]

The effects of NMOSD on fertility are not clearly understood, possibly in part because of the more recent discovery of the anti–aquaporin-4 antibody, or because of its less common presentation in western populations. In a recent study, 8% of patients with NMOSD reported infertility of unknown etiology, and 6% reported infertility due to known causes including structural problems and hormonal dysregulation.[3] As is the case with MS, women with NMOSD face an increased risk of postpartum relapse[4]; however, data on relapse rate during pregnancy are mixed. Prior studies have demonstrated stable or increased rate of relapse during pregnancy,[4,5] whereas a 2021 study of 46 women with aquaporin-4–seropositive NMOSD, 30 with MOG-associated disease, and 13 with double-negative NMOSD[6] demonstrated a lower relapse rate during pregnancy compared with the prepregnancy period. In this study, only the patients with aquaporin-4–seropositive NMOSD demonstrated increased postpartum relapse compared with the prepregnancy period, but numbers were small. Unlike MS, women with NMOSD have an increased rate of pregnancy complications.[7] One study demonstrated that NMOSD increases the risk of miscarriage, with 43% of pregnancies occurring after the onset of NMOSD ending in miscarriage compared with 7% before NMOSD onset. The risk of miscarriage was found to be independent of comorbid autoimmune conditions including antiphospholipid syndrome.[7] NMOSD has also been associated with preeclampsia, at rates of 11.5% after disease onset compared with 3.1% in obstetric controls. Comorbid autoimmune diseases were noted to be a risk factor for preeclampsia in NMOSD.[7]

## Use of B-Cell Depletion in MS and NMOSD

CD20 is a cell surface molecule expressed on B-cell subsets including pre-B, immature, mature, and memory B cells. The therapeutic efficacy of anti-CD20 therapies stems from significant depletion of circulating $CD20^+$ B cells in the periphery.

Traditionally, the postulated pathophysiologic mechanism underlying MS was felt to be direct cytotoxicity mediated by T lymphocytes. Increasingly, however, the role of B cells has also been recognized. B cells function as antigen-presenting cells, thereby recruiting inflammatory cells and stimulating myelin-reactive T cells. They also produce antibodies, including IgG oligoclonal bands detectable in the spinal fluid of a majority of patients with MS. The high efficacy of B-cell–depleting therapy in MS further demonstrates that B cells are significant contributors to its pathophysiology. In comparison, monoclonal antibody treatment approaches targeting T cells uniquely have not demonstrated efficacy, although other T-cell treatment approaches have been efficacious. To date, for the treatment of MS, several monoclonal antibodies targeting $CD20^+$ B cells have been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency for treatment of MS including ocrelizumab and ofatumumab; rituximab has been used off-label for MS therapy for many years as well.

Aquaporin-4–seropositive NMOSD is mediated primarily by the humoral immune system leading to complement activation and resulting in CNS demyelination and axonal loss within the gray and white matter. For the treatment of NMOSD, inebilizumab, a B-cell–depleting monoclonal antibody targeting CD19, has been FDA approved; rituximab is also often used off-label for NMOSD.

### General Safety Considerations of B-Cell–Depleting Therapies

In addition to their efficacy and convenient dosing (either intravenously every 6 months or subcutaneously monthly), B-cell–depleting therapies are well tolerated. The most common side effects are infusion reactions, most of which are mild. For ofatumumab, postinjection systemic inflammatory reactions can occur but are very mild and generally do not require pretreatment. The depletion of circulating B cells also leads to risk of infection, and some studies,[8] though not all,[9] suggest that this can arise particularly in the setting of hypogammaglobulinemia. In addition to IgG depletion, depletion of IgM and IgA can also occur[10] (vide infra, section on breastfeeding). Infections associated with B-cell–depleting therapy include upper respiratory tract infections and nasopharyngitis, as well as more serious infections including herpes virus and hepatitis B reactivation. Of particular importance in the setting of SARS CoV-2 pandemic, these therapies may increase the risk of severe COVID infection characterized by the need for admission to the intensive care unit or death, with level of disability and patient comorbidities further influencing this risk.[11]

Pregnancy and postpartum state have been identified as risk factors for severe COVID compared with nonpregnant women, emphasizing the consequence of infection in this patient population.[12,13]

As highlighted in the wake of the SARS CoV-2 pandemic, another consideration of the use of B-cell–depleting monoclonal antibodies is attenuated immune response to vaccination. A study of antigen response demonstrated decreased immunization responses and lower titers in patients with type 1 diabetes mellitus on rituximab during B-cell depletion compared with those whose B-cell population had reconstituted.[14] Another study in patients with rheumatoid arthritis demonstrated a partial response to vaccination when immunization was administered 6–10 months after the last rituximab infusion, even if B lymphocytes had not yet repopulated on serum assay.[15] Patients with MS demonstrated impaired humoral response to nonlive vaccines in B-cell–depleted patients on ocrelizumab compared with untreated patients or those on interferon-beta.[16] A recent study of patients with MS receiving anti-CD20 therapy demonstrated decreased humoral response after CoV-2 mRNA vaccination, with 36.7% of patients mounting a positive spike antibody response, and of those patients, only 8.3% developed sufficient antibody levels above 254 BAU/mL.[17] In contrast to impaired humoral response, studies have demonstrated that CD4 and CD8 T-cell responses to CoV-2 vaccinations in the setting of B-cell depletion remain strong.[18] Given attenuated vaccine efficacy, a general recommendation is that patients obtain any age-appropriate vaccinations at least 6 weeks before initiating treatment, and the use of attenuated or live vaccines should be avoided until B-cell repopulation.

## Vaccine Considerations in Women of Childbearing Age

Although, ideally, neurologic and obstetrical clinicians regularly communicate once a woman with MS or NMOSD has decided to conceive or become pregnant, many times the decision to start B-cell–depleting therapy precedes—sometimes by years—the decision to conceive. Furthermore, women may also accidently become pregnant, even when counseled to avoid pregnancy; rates of unplanned pregnancy, representing almost half of pregnancies in the general US population, are unknown in MS and NMOSD. Therefore, before initiating anti-CD20 therapy, neurologists should broach the subject of vaccination, including vaccines relevant to pregnancy management, in women of childbearing potential with MS and NMOSD because they may not mount as effective a response once therapy is initiated.

There are general guidelines surrounding the vaccination of women of childbearing potential against preventable diseases before conception. Vaccination during pregnancy is considered appropriate when the vaccine is safe and when infection confers an increased risk to the mother and/or fetus. Immunization is reported to be equally effective in pregnant and nonpregnant women.[19]

Although patients should be up to date on appropriate vaccinations before starting B-cell–depleting therapy, some vaccinations may be needed once on treatment, including annual influenza vaccination and COVID-19 vaccination and booster series. In patients on B-cell–depleting infusion therapy, there is evolving guidance on the timing of immunization relative to treatment in an effort to optimize appropriate response to vaccination.[16] There are no clear data on the optimal timing of vaccination in the setting of monthly ofatumumab injections; however, in our practice, we recommend obtaining immunization at least 4 weeks after the last injection and resuming ofatumumab 2–4 weeks thereafter. The timing of immunizations with B-cell–depleting therapies can be challenging, and as such, assessment of the patient's individualized risk is important when guiding patients with ongoing vaccination requirements.

Current vaccination guidelines from both the American College of Obstetricians and Gynecologists (ACOG) and the Infectious Diseases Society of America (IDSA) are summarized in Table 1. This table includes a list of vaccinations, which are considered safe during pregnancy for a woman of childbearing age and which ones should be considered before conception and/or before B-cell–depleting therapy, and the optimal timing of vaccinations in patients currently on B-cell–depleting therapy.

Because the live attenuated measles-mumps-rubella and varicella vaccinations are to be avoided both after B-cell depletion and during pregnancy, they should be considered in all women of childbearing potential at least 4 weeks before the initiation of B-cell–depleting therapy. The Gardasil vaccine, protecting against certain strands of human papillomavirus, is an important consideration in women of childbearing age given the risk of cervical dysplasia in women on highly effective disease-modifying therapies.[20] Guidelines about age eligibility have evolved, and Gardasil is now approved up to age 45 years. Finally, though not routinely recommended in women of childbearing age, according to the IDSA guidelines, the zoster and pneumococcal vaccines should also be administered for all immunocompromised patients regardless of age, including those on or planning to initiate B-cell–depleting therapies.

## Safety of B-Cell–Depleting Therapy During Pregnancy

To evaluate the safety of B-cell depletion exposures during pregnancy, consideration of physiology of placental transfer, possible impacts of B-cell depletion, and data from clinical series can be helpful. Overall, there are several mechanisms for the transport of both small and large molecules across the placenta, including passive transport, simple diffusion, active transport through ATPase channels, facilitated diffusion, and receptor-mediated endocytosis. Although many medications are small molecules that passively diffuse across the placenta, monoclonal antibodies (including anti-CD20 and CD19 therapies) are larger and do not efficiently passively diffuse

**Table 1** Age-Appropriate Vaccines for Consideration in Women of Childbearing Potential

| | Timing | Mechanism | ACOG and IDSA recommendations before pregnancy[49,50] | Consider during pregnancy[49,50] | Consider before B-cell–depleting therapy | Consider during B-cell–depleting therapy |
|---|---|---|---|---|---|---|
| **Routinely recommended during pregnancy** | | | | | | |
| **Influenza inactivated (IIV) or influenza recombinant (RIV)** | 1 dose annually | Inactivated | Yes | Yes, recommended for maternal and fetal protection, regardless of gestational age | Yes | Yes |
| **COVID-19** | 1 or 2 doses depending on vaccine, plus booster | mRNA, adenovirus | Yes | Yes | Yes | Yes |
| **Tetanus, diphtheria, acellular pertussis (Tdap) or tetanus, diphtheria (Td)** | 1 dose Tdap, then Tdap or Td booster every 10 y | Toxoid, inactivated | Yes | Yes, recommended during 27–36 wk gestation to provide passive immunity to the fetus. | Yes | Yes, if indicated |
| **Not routinely recommended during pregnancy** | | | | | | |
| **Pneumococcal polysaccharide (PPSV23)[a]** | 1 or 2 doses | Inactivated | Yes, if indicated | Yes, if indicated | Yes, if indicated | Yes, if indicated |
| **Pneumococcal conjugate (PCV13)[a]** | 1 dose | Inactivated | Yes, if indicated | Yes, if indicated | Yes, if indicated | Yes, if indicated |
| **Hepatitis A (HepA)** | 2 or 3 doses depending on vaccine | Inactivated | Yes, if indicated | Yes, if at risk for infection | Yes, if indicated | Yes, if indicated |
| **Hepatitis B (HepB)** | 2 or 3 doses depending on vaccine | Recombinant | Yes, if indicated | Yes, if at risk for infection | Yes, if indicated | Yes, if indicated |
| **Meningococcal A, C, W, Y (MenACWY)** | 1 or 2 doses | Inactivated | Yes, if indicated | Yes, if indicated | Yes, if indicated | Yes, if indicated |
| **Human papillomavirus (Gardasil)** | 2 or 3 doses depending on age | Recombinant | Yes, if indicated, for women aged 13–26 years not previously vaccinated, and formally approved up to age 45 years in the United States | No | Yes, if indicated | Yes, if indicated |
| **Measles, mumps, rubella (MMR)** | 1 dose | Live | Yes, if indicated, avoid conception for 4 wk | No | Yes, if indicated | No |
| **Influenza live, attenuated (LAIV)** | 1 dose annually | Live attenuated | Yes | No | Yes | No |

[a] For adults aged less than 65 years with immunocompromising conditions including immunosuppression.

across the placenta.[21] Although few studies focus on placental transfer of large biomolecules including monoclonal antibodies, research on placental transfer of human immunoglobulin (Ig) is a useful model. The fetus itself synthesizes minimal immunoglobulin, and thus, the majority of fetal Ig before birth is obtained from the mother. Ig molecules are large (~150 kDa), and placental transport occurs via receptor-mediated active transport, predominantly via Fc receptors.[22] Other subclasses of immunoglobulins including IgM, IgE, and antibody fragments do not contain the Fc domain and are thus minimally transported across the placenta. One exception to this is IgA, which does have some minimal transfer from mother to fetus, but not via Fc-mediated active transport.[22] Maternal transfer of IgG is minimal during the first trimester, increases significantly around gestational weeks 13–18, and peaks around gestational weeks 22–26.[21] IgG1 transfers through the placenta most efficiently, followed by IgG3 and IgG4; IgG2 transfers only minimally through the placenta.[22] Maternal transfer of immunoglobulin subclasses is summarized in Table 2.

The physiology of human IgGs suggests that the highest exposure to IgG1-based monoclonal antibodies, including B-cell–depleting therapies, is during the second and third trimesters, particularly after 32 weeks gestation, but is minimal during the first trimester.[23] The molecular weights of rituximab and ocrelizumab are ~143 kDa, of ofatumumab ~146

**Table 2** Placental and Breastmilk Transfer of Human Immunoglobulin Subclasses

| | Placental transfer[21] | Presence in breastmilk[41] |
|---|---|---|
| **IgG** | Yes, minimal in the first trimester, peak in weeks 22–26 gestation | Minimal |
| **IgM** | Minimal | Minimal |
| **IgA** | Minimal | Yes, majority of Ig in breastmilk |
| **IgE** | Minimal | Minimal |

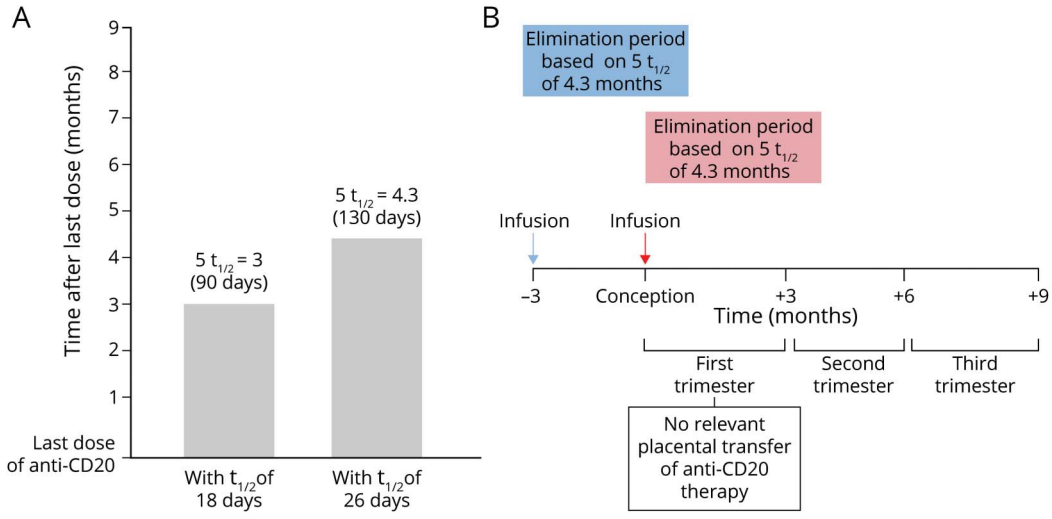
kDa, and of inebilizumab ~149 kDa.[24-26] These molecular weights are similar to human IgG, and the large molecular size prevents significant placental transfer during the first trimester of organogenesis.[27]

To weigh the likelihood of exposure, it is important to consider the kinetics of elimination of a compound. After an initial dose, assuming first-order pharmacokinetics, 94%–97% of a drug is eliminated after 4–5 half-lives. The elimination half-life of rituximab is about 18–22 days, and thus, by about 110 days, the drug has been effectively eliminated in a majority of cases, although the maximal half-life of up to 77 days has been reported.[24] Similarly, the elimination half-lives of ocrelizumab, inebilizumab, and ofatumumab are 26, 18, and 15 days, respectively.[25,26] In a study of patients with rheumatoid arthritis on rituximab, reconstitution of peripheral B cells was variable and did not necessarily correlate with disease relapse.[28]

Given that the elimination of B-cell–depleting therapy occurs within 3–6 months after exposure and that these drugs transfer minimally across the placenta during the first trimester, it could be hypothesized that minimal IgG1 might be transferred across the placenta if conception coincides with the timing of B-cell–depleting infusion or self-injection. In this same vein, if conception occurs 3 months after the most recent exposure of B-cell–depleting therapy, even less IgG1 might be transferred across the placenta. The fetal exposure based on the terminal half-life and IgG1 placental transfer characteristics is summarized in Figure 1. Importantly, these considerations are based on 4-5 mean, and not maximal, half-lives. To date, studies of reproductive risk have considered any treatment within 6 months of conception as exposed pregnancies.

In a systematic review of 102 pregnancies in women who became pregnant within 6 months of exposure to rituximab used for a range of neurologic and nonneurologic maternal indications, 78 resulted in live births and 12 in spontaneous abortions, similar to that seen in the general population.[27] That article also reported on a case series of a further 10 women with MS or NMOSD treated with rituximab. Altogether, in the 63 live births with reported gestational age, 40 (63%) occurred at term (37 + weeks), and 2 (3%) occurred before 32 weeks. The primary adverse effect was low neonatal B-cell count, occurring in 39% of newborns, with the lymphopenia normalizing within 6 months in all cases. Notably, the specific timing between the patient's last infusion and conception was variable. Among the studies included in this review was 1 large study that included 153 pregnancies that occurred at a variable timeframe after maternal exposure to rituximab, of which 90 (59.0%) resulted in live births.[29] In this study, first trimester pregnancy loss occurred in 21% of these pregnancies, slightly higher than the general population (10–15%), though similar to rates in women with chronic disease. Of the live births, 19% were premature, similar to the rate of prematurity in women with certain chronic medical conditions. Two congenital malformations were reported, consistent with the rate in the general

**Figure** Fetal Exposure to B-Cell–Depleting Therapy Based on Terminal Half-Lives as Well as IgG1 Placental Transfer Characteristics




(A) Schema illustrating elimination of B-cell–depleting therapy. Average $t_{1/2}$ of anti-CD20: 18–26 days. Of note, this schema is based on usual half-lives of 18 (rituximab) to 26 (ocrelizumab) days; maximal half-lives of up to 77 days have been reported. (B) Schema illustrating fetal exposure to B-cell–depleting therapy.

population.[29] Adverse events in neonates included hematologic abnormalities (lymphopenia) and neonatal infection. Further reviews have also described reassuring outcomes in women treated at more variable intervals before conception for both MS and other conditions.[30,31] These data provide some guidance regarding the possible implications for women with refractory disease who may need to be treated during pregnancy.

In as-yet unpublished data from ocrelizumab postmarketing surveillance,[32] a total of 608 pregnancies were reported in women with MS exposed to ocrelizumab; 104 of these both were defined as likely fetal exposure in utero (defined in this case as conception occurring within 3 months of the last ocrelizumab infusion) and had known pregnancy outcomes. These outcomes included 62 (59.6%) live births, of which 90.3% were healthy, and 3 (4.8%) were preterm with an abnormal findings. Elective termination/therapeutic abortion occurred in 24 (23.1%), spontaneous abortion occurred in 15 (14.4%), 1 pregnancy (1%) was ectopic, and 2 were still births (1.9%). The published epidemiologic range for these outcomes is as follows: therapeutic abortion (2.9%–36.1%), spontaneous abortion (9.1%–17.2%), ectopic pregnancy (0%–1.5%), and still birth (0%–1.3%).[33,34] Of all 156 live births reported among the 608 women (regardless of exposure), 6 congenital malformations and 1 adverse pregnancy outcome were reported. There were very limited data on infant outcomes according to maternal treatment or potential breastmilk exposure.

Although the underlying physiology of IgGs and clinical experiences to date are reassuring, evidence remains limited, and there is a notable dearth of prospectively designed pharmacy-sponsored studies in this arena to guide care. The product labels remain cautious. FDA labels of ocrelizumab and ofatumumab state that these therapies may cause fetal harm based on animal studies and thus recommend that contraception be used during treatment and for 6 months after medication discontinuation.[25,26] Though not approved for MS or NMOSD, rituximab is commonly used off-label to treat these conditions. The FDA label for rituximab states that based on the limited human data available, rituximab can cause fetal harm from B-cell lymphocytopenia in infants exposed to the drug in utero. It advises females of reproductive potential to use effective contraception for at least 12 months after the last dose.[24] The European Medical Agency offers similar guidance, with recommendations to use contraception during and through 12 months after exposure to these monoclonal antibody therapies[35]; this would de facto place some patients (e.g., with NMOSD or active MS) to elevated risk of inflammatory activity with B-cell repopulation.

## Clinical Efficacy of B-Cell–Depleting Treatment Before and During Pregnancy

Several case series of women with MS and NMOSD have suggested that B-cell–depleting therapy before pregnancy is associated with clinical stability both before conception and during pregnancy. A systematic literature review including case series documented that in 10 pregnant women (7 with MS and 3 with NMOSD) treated with rituximab within 6 months of conception, no maternal relapses occurred before or during pregnancy.[27] Additional studies have corroborated these findings.[36] In fact, in the general MS population, discontinuation of rituximab therapy for reasons including pregnancy is associated with a very low risk of rebound activity, suggesting that this can be a stabilizing approach when planning a pregnancy.[36]

Because B-cell reconstitution is variable and may occur more than 6 months after the last infusion, it may be reasonable to trend lymphocyte subsets in women attempting conception and delay infusion if CD19 levels remain undetectable. These could be monitored prospectively (e.g., every 6 weeks). As inflammatory attacks in NMOSD tend to be more severe with less recovery than in MS, we recommend close attention to maintaining undetectable CD19 levels in NMOSD to prevent disease relapse. There may be less urgency in maintaining undetectable CD19 levels in MS during a period of attempting conception, particularly in those patients with mild disease. Areas of notable uncertainty include lack of knowledge about the long-term effect of a lack of maternal B cells, as well as lack of maternal immunoglobulins—particularly IgA—in long-term B-cell–depleted mothers, on the developing fetus' immune system.

## Postpartum Considerations

### Postpartum Relapse and B-Cell–Depleting Therapy

A number of emerging case series suggest that B-cell–depleting therapy can successfully abrogate the risk of postpartum relapse activity in both MS and NMOSD.[37] A recent study demonstrated that in addition to reduced clinical relapse, anti-CD20 therapy is associated with fewer radiographic changes including gadolinium-enhancing lesions postpartum.[2] It is important to note that to date, these observational series were inherently biased toward women with higher disease activity (possibly including relapse rate, radiologic activity, and disease severity) because they would be most likely to be treated with more effective treatments.

Ideally, B-cell–depleting therapy would occur soon after delivery to prevent these postpartum relapses, but also allowing for a few weeks for maternal postpartum recovery and milk maturation from early colostrum to mature milk. In our practice, we typically consider infusion of B-cell–depleting therapy 2–4 weeks postpartum. Delaying infusion past this time period may leave the patient unprotected during the at-risk postpartum period, particularly given that complete B-cell depletion takes some time after treatment administration. Monitoring CD19 levels could be used to help guide resumption of B-cell depletion. If resuming treatment soon after delivery, concerns arise regarding how best to reduce the risk of postpartum disease activity in women who wish to breastfeed.

## Breastfeeding and B-Cell–Depleting Therapy

Breastfeeding has proven benefits for both mother and child, and is recommended by the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, and the World Health Organization. Infant benefits include neurobehavioral development, gut development and microbiota regulation, and decreased risk of infections and chronic diseases. Maternal benefits include short-term gynecologic recovery and longer-term risks of chronic diseases and malignancy.[38] In women with MS, breastfeeding also has likely direct benefits for their MS. In fact, breastfeeding is associated with 37% lower odds of postpartum relapse compared with nonbreastfeeding, and exclusive breastfeeding has demonstrated even greater benefit (48% reduced odds).[39] A recent study also suggested decreased risk of gadolinium-enhancing lesions associated with breastfeeding.[2] In NMOSD, unlike in MS, breastfeeding does not appear to be protective against postpartum disease activity.[40] Regardless of this, women with NMOSD should be encouraged to breastfeed if they desire to do so, given both maternal and fetal general benefits of breastfeeding.

With respect to transfer of drugs into breastmilk, however, until recently, this was a relatively neglected topic for women with demyelinating diseases. Drug transfer depends on a variety of factors including the molecular weight of the drug, its protein binding and lipid solubility, and the volume of distribution and transport mechanisms. There is less transfer of drugs into mature milk than into colostrum (during the initial 7–14 days postpartum).[41] IgA is the primary immunoglobulin in human breastmilk, and in general, maternal IgG does not transfer into the breastmilk. Table 2 summarizes the transfer of immunoglobulin subclasses into breastmilk.

In a recent systematic review of 19 monoclonal antibodies including anti-CD20 therapies used for a range of maternal indications (neurologic, gastrointestinal, oncologic, and rheumatologic), drug concentration in breastmilk was low.[42] The relative infant dose (RID) is the percent of weight-adjusted maternal dose consumed in breastmilk over a 24-hour period and is used to determine the safety of medication use during breastfeeding. The acceptable RID of a medication is generally less than 10%. A study of 9 breastfeeding women exposed to rituximab for MS, included in the systematic review, reported a minimal concentration of rituximab in all samples, with maximum concentration up to 8 days postinfusion, and nearly undetectable rituximab levels in breastmilk by 90 days postinfusion; mean RID was 0.08% (and maximal RID was <0.4%).[43]

In addition to the minimal transfer of IgG1 antibodies into the milk, exposure in the infant is also limited by the large molecular size and low oral bioavailability of IgG monoclonal antibodies. Gastrointestinal absorption of IgG1 by breastfeeding infants is less than 25%.[44] In the systematic review of monoclonal antibodies, none of the 368 infants were reported to have developmental delay or serious infections over a follow-up period of at least 6 months.[42] In the study of infants breastfed by mothers on rituximab, 5 of the 6 infants followed up to 18 months of age demonstrated no developmental delay and no serious infections, and they underwent routine vaccination.[27] Another study reported no signals of harm in 6 infants breastfed by mothers who received ocrelizumab or rituximab; in 5 of the 6 infants exposed during breastfeeding only, B cell levels were checked and normal.

In addition to immunoglobulins, breastmilk contains other biologically active components including stem cells, oligosaccharides with antimicrobial actions, and growth factors and factors promoting gut health. Many are particularly concentrated in colostrum but persist in mature milk (after 2 weeks). As noted above, B-cell–depleting therapies deplete not only IgG and IgM but also IgA over time.[8] Therefore, because IgA is the primary immunoglobulin in human breastmilk, it is possible that in some postpartum women previously treated with these agents, IgA levels may be reduced. Theoretically, this could be associated with a secondary reduction in the immunoprotective effects of breastmilk.

Breastfeeding is considered safe while on rituximab by both the American Gastrointestinal Association and the American College of Rheumatology, and both subspecialties recommend that this class of monoclonal antibodies can be continued during lactation. In addition to rituximab, other B-cell–depleting IgG1 monoclonal antibodies may be considered safe, given their low RID (well below the theoretically acceptable cutoff of 10%) and low oral bioavailability. Given the safety data and low biological risk of adverse neonatal outcomes with exposure to B-cell–depleting therapies during lactation, it may be reasonable to restart monoclonal antibody therapies in the early postpartum period in women who plan to breastfeed, once their mature milk has come in (i.e., after 2 weeks postpartum). Women who had highly active disease before conception or had a relapse during pregnancy would be particularly encouraged to reinitiate B-cell–depleting therapy postpartum. Infusion of B-cell–depleting therapy using standard premedications (acetaminophen, diphenhydramine, and methylprednisolone) is appropriate in breastfeeding women.[46]

# Summary: Practical Guidance for Use of B-Cell–Depleting Monoclonal Antibodies in Women of Childbearing Potential

The use of B-cell–depleting monoclonal antibodies as highly effective therapy for MS, NMOSD, and other neuroinflammatory conditions is becoming increasingly common. To date, clinical experience has suggested that these can be effective agents to prevent relapses both while awaiting conception (including when discontinuing therapies with risk of discontinuation rebound) and during the period of heightened postpartum risk. Counseling around risk is always individualized and can be informed based on several considerations.

For all women of childbearing potential, regardless of their current family planning goals, it is important to counsel on both age-appropriate vaccinations and those usually recommended by obstetricians peripregnancy—before starting B-cell–depleting therapy because its potential for attenuating the immune response to vaccination could have implications for both the mother and her future offspring.

In women planning conception, optimal timing of B-cell–depleting infusions is informed by both maternal risk and preference. The biologic effects of B-cell depletion are long lasting and persist beyond the drug's pharmacokinetic elimination, allowing for a period of attempting conception during which there is no detectable drug and theoretical risk to fetus. Ideally, there would be a period of 3 months between the last infusion and conception to ensure that by the second trimester, when placental transfer of IgG1 is expected, there has been near complete elimination of the product based on maximal half-lives reported.[47] However, some women with a higher risk of relapse or fertility concerns may prefer to attempt conception immediately following infusion given the low likelihood of transfer of the product in the first trimester when organogenesis occurs and when levels would be detectable. If there are delays in conception, CD19 levels should be monitored beginning at 6 months postinfusion to evaluate for peripheral B-cell reconstitution, and a pregnancy test should be obtained before each infusion in patients attempting conception.[47] Notably, in contrast to the B-cell–depleting infusion therapies timed every 6 months, the cumulative effect of monthly ofatumumab injections is unknown, raising concerns about whether women will stay protected during pregnancy with prenatal ofatumumab exposure.

In neonates born to mothers exposed to B-cell–depleting therapy either before conception or during pregnancy, we recommend evaluating lymphocytes and B-cell subsets in newborn cord blood. Some newborns have been reported to have a reduction in B cells during the first few weeks of life, with normalization of circulating B cells by 6 months. The cord blood can be sent clinically by the delivery team; counseling the patient to request this, and recommending to the delivery team that order sets and tubes be prepared in advance, can reduce delays and thereby the likelihood that this blood is clotted once it reaches the laboratory. In the event of transient neonatal B-cell depletion, vaccines could be delayed until peripheral B-cell reconstitution is observed.[48] Once vaccination efforts are initiated, pediatricians could consider evaluating vaccine titers during the first year of the infant's life to ensure that an optimal immune response to vaccination has been mounted.

In the postpartum period, women on B-cell–depleting therapies could be encouraged to breastfeed if they desire because breastfeeding has numerous established advantages for mothers and infants and can also reduce the risk of postpartum relapses in MS in particular. Because these IgG-based monoclonal antibodies have a large molecular size, B-cell–depleting therapies are transferred minimally into breastmilk and can safely be continued during this period.

A number of questions remain for the care of pregnant and postpartum patients with MS and NMOSD on B-cell–depleting therapies. Although the literature available suggests the safety and efficacy of these therapies in women of childbearing age, there are limitations to the data, particularly as the studies available use small sample sizes with a considerable number of biases. Long-term safety data of maternal B-cell depletion during pregnancy, long-term outcomes of infants born to women exposed to this class of monoclonal antibody therapy, and the impact of prepregnancy maternal B-cell depletion on postpartum immunoglobulin levels, including IgA, in maternal circulation and breastmilk are not fully known. Future studies elucidating these clinical queries are needed for the optimal care of women of childbearing potential with MS and NMOSD.

## TAKE-HOME POINTS

- All women of childbearing age should become up to date on appropriate vaccinations, including those recommended before conception and those for immunocompromised hosts, before starting B-cell–depleting therapy given attenuated vaccination response during B-cell depletion and contraindications to use of live vaccines after treatment initiation.
- B-cell–depleting therapies have demonstrated efficacy during pregnancy and postpartum by reducing the risk of inflammatory activity. Given the need for a cautious approach toward use in women of childbearing age, as advised by the FDA, clinicians should review FDA guidance and real-life experience with their patients to decide on the appropriate course of action on a case-by-case basis.
- B-cell–depleting therapies are large IgG1 monoclonal antibodies, which are minimally transferred across the placenta. Maternal transfer of immunoglobulin is negligible during the first trimester throughout organogenesis, whereas highest exposure occurs after week 32, during fetal growth.
- Evaluation of lymphocytes and B-cell subsets in newborn cord blood can be useful in informing whether modified vaccination timing is warranted for infants exposed to maternal B-cell–depleting therapy during pregnancy.
- Concentration of anti-CD20 and anti-CD19 antibodies is low in breastmilk, well under the acceptable relative infant dose. Use of these therapies can be considered in the breastfeeding mother.

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## Appendix Authors

| Name | Location | Contribution |
|---|---|---|
| **Alexandra Galati, MD** | UCSF Weill Institute for the Neurosciences, Division of Neuroimmunology and Glial Biology, Department of Neurology, University of California, San Francisco | Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design |
| **Thomas McElrath, MD** | Brigham & Women's Hospital, Harvard Medical School, Boston, MA | Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data |
| **Riley Bove, MD** | UCSF Weill Institute for the Neurosciences, Division of Neuroimmunology and Glial Biology, Department of Neurology, University of California, San Francisco | Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data |

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