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

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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 pre-pregnancy planning including vaccinations, safety of B cell depletion during pregnancy as well as postpartum considerations including breastfeeding.

Summary:

B cell depleting monoclonal antibodies have shown to be effective for pre-pregnancy and postpartum prevention of inflammatory activity in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). 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.

Introduction

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are inflammatory central nervous system 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 additional references as well. Topics covered include conception planning, vaccination timing, management during pregnancy, as well as postpartum and breastfeeding considerations.

Overview of Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder and Pregnancy

Studies to date have been largely reassuring that MS is not associated with difficulty either 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 three months postpartum. Increased postpartum activity is evidenced both by increased rate of clinical relapse as well as 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-aquaporin4 antibody, or to 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 is 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 lower relapse rate during pregnancy as compared to the pre-pregnancy period. In this study, only the aquaporin-4 seropositive NMOSD patients demonstrated increased postpartum relapse compared to pre-pregnancy 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 onset of NMOSD ending in miscarriage as compared to 7% prior to 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 as compared to 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 Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

CD20 is a cell surface molecule expressed on B cell subsets including pre-B cells, 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 pathophysiological 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, though 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 FDA and EMA for treatment of MS including ocrelizumab and ofatumumab; rituximab has been utilized 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 central nervous system 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, post-injection systemic inflammatory reactions can occur but are very mild and generally do not require pre-treatment. 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 risk of more serious infections including herpesvirus and hepatitis B reactivation. Of particular importance in setting of SARS CoV-2 pandemic, these therapies may increase risk of severe COVID infection characterized by need for ICU admission 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 as compared to non-pregnant 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 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 as compared to 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 six to ten

months after last rituximab infusion, even if B lymphocytes had not yet repopulated on serum assay.[15] Patients with MS demonstrated impaired humoral response to non-live vaccines in B cell depleted patients on ocrelizumab as compared to 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 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 six weeks prior to initiating treatment, and use of attenuated or live vaccines should be avoided until B cell repopulation.

Vaccine Considerations in Women of Childbearing Age

Even though, 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 accidentally 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 since 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 prior to conception. Vaccination during pregnancy is considered appropriate when the vaccine is safe, and when infection confers increased risk to mother and/or fetus. Immunization is reported to be equally effective in pregnant and nonpregnant women.[19]

While patients should be up to date on appropriate vaccinations prior to starting B cell depleting therapy, some vaccinations may be needed once on treatment, including annual influenza vaccination as well as Covid-19 vaccination and booster series. In patients on B cell depleting infusion therapy, there is evolving guidance on timing of immunization relative to treatment, in an effort to optimize appropriate response to vaccination.[16] There are no clear data on optimal timing of vaccination in the setting of monthly ofatumumab injections, however in our practice we recommend obtaining immunization at least 4 weeks after last injection, and resuming ofatumumab 2-4 weeks thereafter. 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 prior to conception and/or prior to B cell depleting therapy, as well as optimal timing of vaccinations in patients currently on B cell depleting therapy.

Because the live attenuated MMR 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 four weeks prior to 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 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. Finally, though not routinely recommended in women of childbearing age, according to 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. While 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 across the placenta.[21] Though 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 prior to 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 as well as 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 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 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 to 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, though maximal half-life of up to 77 days has been reported.[24] Similarly, the elimination half-lives of ocrelizumab, inebilizumab and ofatumumab are 26 days, 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**. 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 six months of exposure to rituximab used for a range of neurological and non-neurological maternal indications, 78 resulted in live births and 12 in spontaneous abortions, similar to that seen in the general population.[27] That manuscript 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 six 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 one large study which 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 population.[29] Adverse events in neonates included hematologic abnormalities (lymphopenia) as well as 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 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 pre-term with an abnormal findings. Elective termination/therapeutic abortion occurred in 24 (23.1%), spontaneous abortion in 15 (14.4%), 1 pregnancy (1%) was ectopic, and 2 were still births (1.9%). The published epidemiologic range for these outcomes is: therapeutic abortion (2.9–36.1%); spontaneous abortion (9.1–17.2%); ectopic pregnancy (0–1.5%); 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.

While 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 these therapies may cause fetal harm based on animal studies, and thus recommend contraception be used during treatment and for six 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 twelve 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 prior to 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 six months after 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 towards women with higher disease activity (possibly including relapse rate, radiologic activity, and disease severity), since 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 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 both the American Academy of Pediatrics and American College of Obstetrics and Gynecology, as well as 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 gynecological 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 as compared to non-breastfeeding, 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, as well as 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 rheumatological), 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 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, and RID of 0.08%, with maximum concentration up to 8 days post infusion, and nearly undetectable rituximab levels in breastmilk by 90 days post-infusion.[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, no serious infections, and they underwent routine vaccination.[27] Another study reported no adverse outcomes in one infant exposed to breastmilk from a mother treated with ocrelizumab.[45]

In addition to immunoglobulins, breastmilk contains other biologically active components including stem cells, oligosaccharides with antimicrobial actions as well as 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 since 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 the

immunoprotective effects of breastmilk. To our knowledge, this has not yet been evaluated scientifically.

Breastfeeding is considered safe while on rituximab by both the American Gastrointestinal Association as well as 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 prior to conception, or had a relapse during pregnancy, would be particularly encouraged to reinstitute B cell depleting therapy postpartum. Infusion of B cell depleting therapy utilizing standard pre-medications (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 peri-pregnancy -- prior to starting B cell depleting therapy, since its potential for attenuating the immune response to vaccination could have implications for both 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 last infusion and conception to ensure that by the second trimester, when placental transfer of IgG1 is expected, there has been complete elimination of the product based on maximal half lives reported.[47] However, some women with 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 post-infusion to evaluate for peripheral B cell reconstitution, and a pregnancy test should be obtained prior to each infusion in patients attempting conception.[47] Notably, in contrast to the B cell depleting infusion therapies timed every six 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 prior to 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 six 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 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, since breastfeeding has numerous established advantages for mothers and infants, and can also reduce risk of postpartum relapses in MS in particular. Since 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. While the literature available suggests safety and efficacy of these therapies in women of childbearing age, there are limitations to the data, particularly as the studies available utilize 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, as well as the impact of pre-pregnancy 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 optimal care of women of childbearing potential with MS and NMOSD.

Five New Things in Anti-CD20 Therapy for Women of Childbearing Age

- 1) All women of childbearing age should become up to date on appropriate vaccinations, including those recommended prior to conception as well as those for immunocompromised hosts, prior to starting B cell depleting therapy given attenuated vaccination response during B cell depletion and contraindications to use of live vaccines after treatment initiation.
- 2) B cell depleting therapies have demonstrated efficacy during pregnancy and postpartum by reducing 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.
- 3) 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.
- 4) 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.
- 5) 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.

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 Prior to 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 years	Toxoid, inactivated	Yes	Yes, recommended during 27 to 36 weeks gestation to provide passive immunity to fetus.	Yes	Yes, if indicated
Not routinely recommended during pregnancy						
Pneumococcal polysaccharide (PPSV23)*	1 or 2 doses	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated	Yes, if indicated
Pneumococcal conjugate (PCV13)*	1 dose	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated	Yes, if indicated
Hepatitis A (HepA)	2 or 3	Inactivated	Yes, if indicated	Yes, if at risk for	Yes, if indicated	Yes, if indicated

	doses depending on vaccine			infection		
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 13 to 26 years old not previously vaccinated; and formally approved up to age 45 in US	No	Yes, if indicated	Yes, if indicated
Measles, mumps, rubella (MMR)	1 dose	Live	Yes, if indicated, avoid conception for 4 weeks	No	Yes, if indicated	No
Influenza live, attenuated (LAIV)	1 dose annually	Live attenuated	Yes	No	Yes	No

* For adults less than 65 years old with immunocompromising conditions including immunosuppression

Table 2: Placental and breastmilk transfer of human immunoglobulin subclasses

	Placental Transfer [21]	Presence in Breastmilk [41]
IgG	Yes, minimal in first trimester, peak in weeks 22-26 gestation	Minimal
IgM	Minimal	Minimal
IgA	Minimal	Yes, majority of Ig in breastmilk
IgE	Minimal	Minimal

Figure 1a. Schema illustrating Elimination of B Cell Depleting Therapy.

Average $t_{1/2}$ of anti-CD20: 18-26 days

Figure 1b. Schema illustrating Fetal Exposure to B Cell Depleting Therapy.

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