



Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines

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ABSTRACT

Neurologists increasingly use anti-CD20 therapies, including for women of childbearing age, despite these medications being unlicensed for use in pregnancy. Current evidence suggests that women can safely conceive while taking anti-CD20 therapy. Women should not be denied treatment during pregnancy when it is clinically indicated, although they should be counselled regarding live vaccinations for their infant. Women receiving regular ocrelizumab for multiple sclerosis should preferably wait 3 months before trying to conceive. There are few data around ofatumumab in pregnancy, and while there is probably a class effect across all anti-CD20 therapies, ofatumumab may need to be continued during pregnancy to maintain efficacy. We recommend that anti-CD20 therapies can be safely given while breast feeding. It is important to make time to discuss treatments with women of childbearing age to help them choose their most suitable treatment. Outcomes should be monitored in pregnancy registries.

INTRODUCTION

Anti-CD20 therapies are increasingly used to treat neurological diseases. The National Institute for Health and Care Excellence has approved regular fixed-dose ocrelizumab (2018; TA533¹) and more recently ofatumumab (2021; TA699²) to treat active relapsing–remitting multiple sclerosis (RRMS). Rituximab is used for other inflammatory or autoimmune neurological diseases, including myasthenia gravis, autoimmune encephalitis, and neuromyelitis optica spectrum disorders, although its treatment frequency is less standardised and may be shorter term, focusing on inducing disease remission. Ocrelizumab

and rituximab are given intravenously, dosing at least 6 months apart (or based on peripheral CD19 counts in selected cases), whereas ofatumumab is a monthly self-administered subcutaneous injection.

Many of the women eligible for these treatments are of childbearing age. Real-world evidence shows the importance of achieving disease control in RRMS around pregnancy.³ This needs to be balanced against potential harm to the baby either from direct fetal exposure to the drug, or from gestation in an immunocompromised mother. Clinicians must consider early effects on the pregnancy, including miscarriages, stillbirths, congenital malformations and longer-term effects on the child, including impaired intellectual and behavioural development.

Because contraception use is essential for inclusion in most clinical trials, there are only limited high quality data in RRMS informing the use of disease-modifying therapies in and around pregnancy.⁴ This absence of evidence led to the development of UK MS Pregnancy consensus guidelines,⁵ published before anti-CD20 drugs were as widely used. Here we review the evidence for using these drugs in pregnancy and while breast feeding, and provide consensus recommendations.

All current anti-CD20 monoclonal antibodies are IgG₁. Fetal IgG originates from the mother. Data regarding materno-fetal IgG transfer come from measuring the concentrations of endogenous antibodies in maternal and fetal sera at different gestational ages. While total IgG, IgG subclasses and antigen-specific antibodies have been examined,⁶ there are fewer studies on the transport of exogenous antibodies. Placental transfer of IgG₁ is negligible in the first trimester but rises



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throughout the second and third trimesters.⁷ IgG₁ is preferentially transferred to the fetus,⁷ and at 17–22 weeks' gestation, fetal IgG is only 5%–10% of the maternal concentration, while at term it exceeds the maternal concentration. This knowledge has informed guidelines to limit dosing of the IgG₁ anti-TNF α monoclonal antibodies during pregnancy in inflammatory bowel disease⁸ and in inflammatory arthritis.⁹

There is still limited understanding of fetal immune system development, and the interplay between maternal and fetal immune systems. While the fetus needs to remain tolerogenic in the foreign environment of the mother's uterus, neonates require a rapid switch to a protective immune repertoire with heightened local activation when microbially colonised at birth.¹⁰ The full impact of immunomodulatory agents on this delicate balance is not yet known.

Fetal exposure to a drug during pregnancy is at least partly informed by its pharmacokinetics. The mean half-life of ocrelizumab is 26 days,¹¹ rituximab 21 days¹² and ofatumumab, once in a steady state (ie, with regular administration), 16 days.¹³ Drugs are considered to have fully cleared after five half lives: approximately 18.5 weeks for both ocrelizumab and rituximab, and around 11.5 weeks for ofatumumab. Thus, even with exposure around the time of conception, these monoclonal antibodies will have cleared from the maternal system by the time placental transfer is established at 17–20 weeks gestation.

In this review, we examine the available evidence around the use of anti-CD20 therapies in and around pregnancy. We searched Medline (PubMed) using terms related to MS, anti-CD20 therapies and pregnancy with no time constraints. We reviewed references of papers and used expert opinion within the group to ensure that we considered all available literature. We cover evidence for safety in pregnancy from both the neurological and wider literature, and examine the available data for breast feeding. We also consider available literature addressing the safety of suspending treatment, and apply this to develop practical guidelines to aid discussion with women on anti-CD20 agents considering pregnancy.

SAFETY IN PREGNANCY: EVIDENCE FROM RRMS AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

Anti-CD20 therapies have no known impact on fertility, either in males or females. There have been many reported pregnancies potentially exposed either to ocrelizumab or rituximab (table 1). The largest reported pregnancy dataset is the ocrelizumab pregnancy register¹⁴ with 1223 recorded pregnancies in women with RRMS treated with ocrelizumab before pregnancy, of whom 414 (34%) had exposure within 3 months of pregnancy, and 128 (10%) exposure in the first trimester. There were seven major congenital anomalies reported from 604 pregnancies with

known outcomes (1.6% of 427 live births), similar to the 2017 background rate of reported major congenital anomalies in the UK of 2.1%.¹⁵ The outcomes were not known in the remaining 619 pregnancies. Of those pregnancies where ocrelizumab was used within 3 months of conception or during pregnancy and outcomes were available, there were 171 (72.5%) live births, 30 (12.7%) terminations of pregnancy, 29 (12.3%) spontaneous miscarriages, 4 (1.7%) stillbirths and 2 (0.8%) ectopic pregnancies. The rate of spontaneous miscarriage was actually lower in women with potential in utero exposure than in those without (12.3% vs 19.0%). However, miscarriage rates are greatly affected by maternal age (8.7% at age 22% and 84.1% aged 48); therefore this difference must be interpreted with caution in the absence of age-adjustment of these outcomes.¹⁶

These data are supplemented by real-world data from pregnancy registries. A case series¹⁷ identified 74 pregnancies in 55 women after exposure to at least one dose of rituximab. Eighty per cent of these pregnancies occurred within 6 months of rituximab administration, and nine had accidental first trimester exposure. Notably, 15 women (27.3%) were aged over 35, and 33 (60.0%) were overweight or obese, both risk factors for adverse pregnancy outcomes. During the study period, eight women had one first-trimester miscarriage, six women had two and one woman had three (overall miscarriage rate 23/74, 31.1%). There were no miscarriages after 12 weeks and no stillbirths. Three pregnancies ended in preterm deliveries of four babies, including one set of 27-gestational-week twins—the overall preterm birth rate was 4/38 (10.5%), similar to background rates for the same population (9.0%).¹⁸

A cohort study from Germany reported 88 pregnancies in 81 women with neuroinflammatory disorders treated with rituximab or ocrelizumab within the 12 months before pregnancy; 10 were exposed more than 6 months before conception, 64 within 6 months of conception and 14 after their last menstrual period (LMP).¹⁹ Pregnancy outcomes were available for 67 pregnancies, including 1 twin pregnancy. There were only a few spontaneous miscarriages before 22 gestational weeks (5/68, 7.4%), in contrast to the case series above¹⁷ and nationally reported miscarriage rates.¹⁸ Preterm birth (defined as live birth before 37 gestational weeks) occurred in 15%, significantly more often in those exposed after their LMP (9.8% vs 45.5%, $p=0.019$). Two out of 60 (3.3%) live births were associated with major congenital anomalies (ventricular septal defect and atrial septal defect with pulmonary stenosis), both exposed after LMP. Severe infection during pregnancy occurred in three mothers (two with decreased/depleted B-cells) and infections leading to hospitalisation occurred in three newborns. B cell counts were available in 14 neonates; they were borderline in 4 and depleted in 1 (where the mother was treated with azathioprine until week

Table 1 Summary of case series/cohort studies in neurological disorders containing a minimum of five patients

Paper	Population	Patient details	Pregnancy outcomes	MS/NMO outcomes
Seyed Ahadi <i>et al</i> ⁴⁸	NMOSD; RTX only	8 patients, exposure within 6M 2 treated during pregnancy (17/40, 30/40)	2 elective terminations (5/40 and 8/40) 1 stillbirth at 36/40 (nuchal cord)	Relapse free
Seyed Ahadi <i>et al</i> ⁴⁹	MS; RTX only	21 patients, median time from RTX to pregnancy 7M (SD 5M) 1 treated in pregnancy, 2 ongoing	10 live births–1 preterm birth 7 elective terminations, 2T1 miscarriages	Relapse free
Kim <i>et al</i> ⁵⁰	NMOSD; RTX only	11 women/15 pregnancies; median time from RTX to pregnancy 3M ; 1 T1 exposure	11 live births 1 elective abortion, 3 T1 miscarriages	1 relapse in pregnancy, same patient had PP relapse
Kümpfel <i>et al</i> ¹⁹	MS, NMOSD, other neuroinflammation; RTX and OCR	81 women/88 pregnancies/67 included All treated within 12M of pregnancy	60/68 - live birth (1 twin), 9 premature 5 miscarriages; 2 MCM- VSD, ASD with pulmonary stenosis	Relapse free in pregnancy 5/29 relapse PP
Das <i>et al</i> ²²	MS and NMOSD; RTX only	11 pregnancies, 10 within 6M RTX	All term births, healthy children	Relapse free in pregnancy 1 relapse PP
Dobson <i>et al</i> ¹⁴	MS; OCR only	1223 pregnancies, 414 exposure within 3M, 128 with T1 exposure 604 known outcomes	Where OCR used within 3M of conception: 171 live births 20 elective terminations, 29 miscarriages 4 stillbirths, 2 ectopic pregnancies; 7/604 MCM	Not reported
Hellwig <i>et al</i>	MS; Ofatumumab	32 pregnancies, 4 exposure within 6M 12 with T1 exposure	23 known outcomes: 11 live births, 6 miscarriages, 6 elective terminations	Not reported
Razaz <i>et al</i> ⁵¹	MS; RTX only	76 suspended RTX for pregnancy	Not reported	1 pregnancy relapse in T1 1 patient with gad lesion PP
Smith <i>et al</i> ¹⁷	MS; RTX only	55 women/74 pregnancies 50 within 6M of RTX, 9T1 exposure	38 live births (37 pregnancies); 4 preterm births (1 twins) 23T1 miscarriages, 1 neonatal death (27/40 twin), 1 perinatal stroke	1 relapse in pregnancy 1 relapse PP

ASD, atrial septal defect ; MCM, Major congenital malformation ; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder ; OCR, ocrelizumab; PP, post partum ; RTX, Rituximab ; VSD, Ventricular septal defect .

7 of pregnancy and with rituximab 141 days after the LMP).¹⁹

Pregnancy data following ofatumumab exposure has been collected following treatment as part of clinical trials and in a postmarketing surveillance programme.²⁰ Pregnancy outcome data were collected for women who received at least one dose of ofatumumab within 6 months of their LMP, although the precise timing of exposure for these pregnancies is not reported. There were 32 reported pregnancies, with outcomes known in 23. Eleven ended in live births, with six terminations and six miscarriages. There were no reported cases of neonatal B cell depletion, immunoglobulin, haematological or fetal abnormalities, or serious infantile infections. Thus is little information to guide ofatumumab use in pregnancy; however the findings above probably represent a class effect across all anti-CD20 therapies.

SAFETY IN PREGNANCY: EVIDENCE FROM NON-NEUROLOGICAL ILLNESSES

In 2011, the rituximab global safety database reported 231 anti-CD20 exposed pregnancies,²¹ probably only a fraction of overall global exposure. Maternal

indications for rituximab use included lymphoma, autoimmune cytopenias and other autoimmune diseases. Most cases were confounded by concomitant use of potentially teratogenic medications and severe underlying disease. Eleven infants had haematological abnormalities at birth (peripheral B-cell depletion, neutropenia, lymphopenia, thrombocytopenia and anaemia); in three of these, rituximab had been given during the second trimester. Neonatal thrombocytopenia occurred in three cases. One infant had a cerebral haemorrhage attributed to thrombocytopenia (mother was treated at 7 months of gestation for immune thrombocytopenic purpura). In most cases, cytopenias were transient and recovered spontaneously within weeks to months. Three reports included data on rituximab concentrations in cord or infant blood, with maternal rituximab administered <12 weeks before delivery in each case.²¹ In each case rituximab was detected in cord or infant blood at birth with corresponding undetectable peripheral B-cell counts. A further 9 of the 23 infants had neonatal B-cell depletion. None of these neonates experienced any infective complications, and none experienced adverse reactions to vaccinations.

Box 1 Summary of consensus recommendations

Anti-CD20 therapies can be used in women wishing to get pregnant.

Current evidence suggests that women can safely start trying to conceive without delay following anti-CD20 therapy.

Where clinically indicated, women can potentially receive anti-CD20 therapies during pregnancy; this is particularly relevant in women with myasthenia or neuromyelitis optica spectrum disorder.

Women with relapsing-remitting multiple sclerosis are at increased risk of relapsing in the postpartum period, and so prompt treatment post partum is recommended.

Where women wish to breastfeed, they should be encouraged to do so alongside therapy resumption where their treatment of choice is an anti-CD20 monoclonal antibody.

Where breastfeeding women receive anti-CD20 therapy before infant vaccinations, the Medicine and Healthcare product Regulatory Agency advises deferring live-attenuated vaccinations whilst there is any remaining influence on the immune status of the infant. In the case of anti-CD20 treatment, we believe any risk of the infant being significantly immunosuppressed by exposure via breast feeding is low and the pros and cons of vaccination should be discussed with the parents.

Clinicians should use these guidelines to discuss potential risks and benefits of treatment with anti-CD20 therapies close to and during pregnancy as part of shared decision making.

All B-cell levels normalised within 6 months, sometimes sooner.

A systematic review²² identified 102 women who became pregnant within 6 months of exposure to rituximab or who were treated with rituximab while pregnant. Of these, 38 were described in case reports or small case series, and 64 in a meta-analysis (which included many women receiving methotrexate alongside rituximab). Live births were reported in 73/104 (70.2%) babies, with 1 stillbirth attributed to placental insufficiency, 14 miscarriages and 16 terminations of pregnancy.

The Organization of Teratology Information Specialists identified 21 women who became pregnant following rituximab treatment, 19 of whom had known outcomes.²³ Two women received their last infusion shortly after conception, and one reported using rituximab through the second trimester, receiving her last infusion at 25 weeks of gestation. There were no reported miscarriages or stillbirths. One woman with an infusion less than a week before conception delivered an infant with multiple haemangiomas. There were no serious or opportunistic infections in any infant. A further 20 pregnancy outcomes following rituximab use more than 6 months before pregnancy

are described in the British Society for Rheumatology Biologics Register.²⁴ Fifteen babies were liveborn, two were stillborn (one of whom was from a twin pregnancy), two babies miscarried and there was one termination of pregnancy. For women receiving rituximab at any point before pregnancy in the whole cohort, the gestational age at birth was reported for 18 pregnancies, of which four delivered preterm (22.2%).

Studies in rheumatoid arthritis provide limited evidence around ofatumumab use in pregnancy. One unplanned pregnancy was reported in OFA110635 and two were reported in OFA110634.²⁵ The outcomes were a miscarriage in OFA110635, a termination of pregnancy and a live birth in OFA110634.

CASE SERIES AND REPORTS OF TREATMENT DURING PREGNANCY

There are several small case series of anti-CD20 treatment for neuroinflammatory disease during pregnancy. However, the experience of treating women with anti-CD20 monoclonal antibodies for both autoimmune disease and lymphoma during pregnancy extends beyond the published literature, with most cases having no significant adverse sequelae for the infants and not being published (personal communication, Catherine Nelson-Piercy).

One woman with RRMS was treated with ocrelizumab at 19 weeks gestation,²⁶ resulting in maternal disease remission and B cell depletion for the remainder of pregnancy. This pregnancy was complex, with several maternal risk factors. Neonatal lymphocyte subsets at birth were normal, and at 3 months of age, the baby had a normal neurological examination and met all early developmental milestones. Examination was normal at 7 months haematology follow-up.

Additional cases describe rituximab use for severe, refractory neuroinflammatory disease. There were two reported RRMS cases where rituximab was given during pregnancy (13 weeks and 21 weeks gestation) with no adverse medical or developmental outcomes in either the baby or mother to 12 months of life, although neonatal CD19 counts were not measured.²⁷ An infant born to a mother with neuromyelitis optica spectrum disorder treated with rituximab at 24 weeks gestation and CD19 <1% throughout pregnancy had a CD19 count of 1% at birth, rising to 23% at 2 months. At 6-month follow-up, there had been no infections, with normal development, and normal B-cell counts.²⁸

There are also small case series from the oncological and haematological literature. In one of these,²⁹ rituximab was given during the first (two patients) or the second trimester (two patients), at a median of 21 weeks (range, 19–33 weeks) before delivery. One of these also received intravenous cyclophosphamide 6 weeks before delivery. There is also a single case report of rituximab administered in the first trimester for the treatment of autoimmune haemolytic anaemia.³⁰ All

Clinical Consensus recommendations

<p>Conception Can safely start trying to conceive immediately following anti-CD20 therapy</p> <p>Dosing interval In women with MS taking ocrelizumab or rituximab, if no pregnancy at 6 months, consider increasing dose interval to 9-12 months</p> <p>No evidence to adjust ofatumumab dosing interval</p>	<p>Treatment during pregnancy Proceed if clinically indicated (NMOSD relapse, myasthenic crisis)</p> <p>Safety If treatment is given during pregnancy, women can be relatively reassured regarding safety</p> <p>Vaccination Defer BCG and other live vaccinations until 6 months of life where exposure during pregnancy has occurred</p>	<p>Timing of infusion Avoid treatment during first week of life if breast feeding</p> <p>Breast feeding MHRA advise that live vaccinations be deferred for 6 months following potential exposure via breastmilk. For anti-CD20 therapy, we believe risk of infant exposure is low, and the pros and cons of vaccination should be discussed with parents</p>
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Figure 1 Rationale underlying recommendations. MHRA, Medicine and Healthcare product Regulatory Agency; NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis.

babies were healthy without malformations, hypogammaglobulinaemia or leucopenia.

A further report details the infant of a mother diagnosed with pre-B-cell acute lymphoblastic leukaemia during her 18th week of pregnancy.³¹ The mother received three cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone and five cycles of rituximab, with the last dose of rituximab at 27 weeks gestation and a planned caesarean section at 30 weeks gestational age. Having had a normal blood count at delivery, the baby developed severe neutropenia at 10 weeks (absolute neutrophil count 0.0) with severe hypogammaglobulinaemia. The baby's neutrophil count recovered by 9 months, but she developed persistent severe hypogammaglobulinaemia requiring intravenous immunoglobulin every 4–8 weeks. Her B-cell population consisted of IgM-only memory B cells, with no evidence of IgG antibody secreting, class switched B cells at 24 months. The authors comment that given the 50 years of documented experience with doxorubicin, cyclophosphamide and corticosteroid exposure in utero the cytotoxic chemotherapy probably played only a supporting role and the prolonged

immune dysfunction was most likely primarily due to the rituximab exposure.

SAFETY IN BREAST FEEDING

There are few data regarding anti-CD20 monoclonal antibody transfer into breast milk. A single case study with repeated breast milk sampling found a maximum breast milk rituximab concentration of 0.6 µg/mL (in the context of peak maternal concentration of 130 µg/mL).³² A second case had a maximum breast milk concentration of 0.004 µg/mL, with undetectable concentrations in infant serum.³³ A review of the transfer of monoclonal antibodies into breast-milk included 10 women treated with rituximab, 9 of whom had RRMS.³⁴ Thirty-four samples collected from 8 hours to 90 days postinfusion were identified; five patients provided serial samples. Rituximab was detected at a low concentration in all samples, with a maximum concentration of 0.6 µg/mL 8 days post-infusion. The maximum relative infant dose observed was 0.33% 11 days postinfusion, although in women with serial samples, the median relative infant dose was 0.08% (range 0.06%–0.10%) and estimated

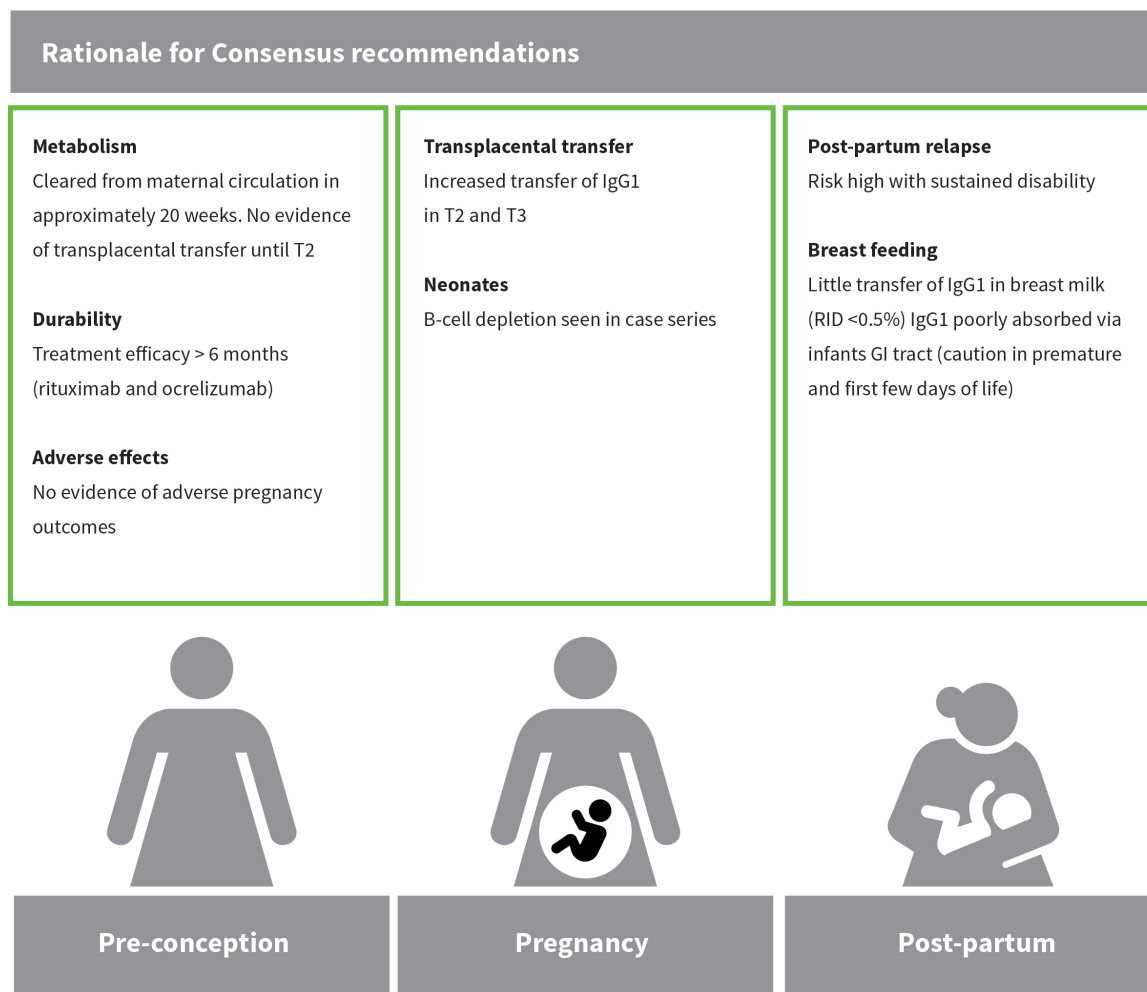


Figure 2 Recommendations for an approach to anti-CD20 use pre-pregnancy, intrapartum and during breast feeding. GI, gastrointestinal; RID, relative infant dose.

24-hour infant dose was $9.4 \mu\text{g}/\text{kg}/\text{day}$. In general, relative infant doses (which are corrected for body size) of <10% are considered safe,³⁵ although this depends on the mechanism of action of the drug in question.

The German Pregnancy Registry identified six RRMS breastfeeding exposures,³⁶ of whom three women received rituximab, two ocrelizumab, and one both rituximab and ocrelizumab. Across the whole study (pregnancy and breast milk exposure), physical growth and infant development were normal with no significant infections. An American dataset showed similar findings, with detailed information on four women who continued to breastfeed after receiving rituximab.³⁷ The infant exposed to rituximab through breast milk earliest and with a higher total dose to the mother had more infections, although all were common infections seen in infancy and none were serious. There were no preliminary concerns identified with growth or development up to 8–12 months, and routine vaccinations were given with no adverse events. Five further infants breastfed after maternal treatment with rituximab were followed for between

8 and 18 months, again with normal development, no serious infections and routine vaccinations.³⁴

IMPACT OF STOPPING OR SUSPENDING ANTI-CD20 THERAPIES

The impact on maternal disease of stopping or suspending monoclonal antibodies around pregnancy must be considered alongside any potential neonatal benefit of continuing treatment. In RRMS, this is most clearly seen with disease reactivation or rebound following natalizumab cessation⁵; outside of RRMS, the impact of undertreated myasthenia gravis during pregnancy has potential adverse impact on the developing fetus and neonate.³⁸ There is a high risk of postpartum relapse in people with neuromyelitis optica³⁹ and stopping rituximab in pregnancy is often complemented by additional immunosuppression like steroids, which carry potential risks of their own.

Rituximab and ocrelizumab have a duration of action that exceeds the routine 6-monthly dosing schedule, particularly in RRMS. In the initial trials in RRMS, ocrelizumab was administered for 48–72

months before treatment suspension.⁴⁰ Follow-up data found no substantial increase in relapse rate for at least 12–18 months following treatment suspension.⁴¹ Real-world evidence in RRMS, where treatment was delayed or suspended for safety reasons during periods of high COVID-19 community transmission, showed efficacy apparently maintained despite prolonged intervals between infusions,¹⁴ with support for personalised dosing strategies with ocrelizumab⁴¹ without loss of efficacy. Outside of RRMS, personalised dosing strategies are well established for rituximab as a treatment for neuromyelitis optica spectrum disorder,⁹ and treatment based on CD19 levels is commonly used. In myasthenia gravis, however, treatment intervals are often based on the clinical response and rather than purely on CD19 levels.⁴²

This clinical evidence is supported by laboratory evidence from real-world studies and clinical trials showing that B cell repopulation is both highly variable between recipients, and also delayed on average beyond 6 months in people with RRMS who have received 48–72 months of ocrelizumab.⁴¹ Furthermore, laboratory evidence suggests that the phenotype of repopulated B-cell after anti-CD20 treatment differs from the pretreatment phenotype. Reemergent B-cells are more likely to be naïve, whereas the more biologically relevant memory B-cells appear to undergo a more durable depletion.

There are no data in the public domain at present about disease reactivation following treatment with ofatumumab, which cannot be assumed to have the same prolonged impact as ocrelizumab or rituximab.

CONCLUSIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

Based on the available current evidence, the European SmPC recommendation seems overly conservative, advising to continue using contraception for at least 12 months after the last infusion of ocrelizumab and rituximab, and for at least 6 months after the last injection of ofatumumab. We recommend that women and their clinicians should have the option to continue anti-CD20 therapies closer to, and potentially during, pregnancy. **Box 1** and **figure 1** summarise the consensus recommendations; **figure 2** provides the underlying rationale.

PRECONCEPTION ADVICE

We recommend that anti-CD20 therapies can be used in women wishing to become pregnant, even when there is an alternative, less effective treatment that is licensed for use in pregnancy, such as interferon beta or glatiramer acetate in RRMS. Current evidence suggests that women can safely start trying to conceive without delay following anti-CD20 therapy, and potentially to receive treatment during pregnancy when clinically indicated—particularly in those women receiving

anti-CD20 therapies for myasthenia gravis or neuromyelitis optica spectrum disorder.

All women considering pregnancy should be advised to start daily folic acid supplementation as standard, and to ensure full vaccination. If they have recurrent or severe infections during pregnancy or in the postpartum period, clinicians should consider the possibility of hypogammaglobulinaemia.

ANTI-CD20 THERAPY DURING PREGNANCY

Anti-CD20 use during pregnancy can lead to B cell depletion in the neonate. While this appears to be transient in the relatively few cases where there are available longitudinal measurements, clinicians must consider the potential for longer-term impact on immunological development and response to vaccination. The UK Medicine and Healthcare product Regulatory Agency (MHRA) advice is that where infants have been exposed to immunosuppressive treatments from the mother in pregnancy or via breast feeding, live-attenuated vaccines should be deferred for as long as a post-natal influence on the immune status of the infant remains possible.⁴³ Babies born to women who have received anti-CD20 therapies during pregnancy should therefore not receive the rotavirus vaccine, and should delay the BCG vaccination (in areas where it is offered) until aged 6 months.⁴³ They should receive other infant vaccinations according to schedule.⁴⁴ Mothers should be encouraged to receive the COVID-19, influenza and whooping cough vaccinations during pregnancy, and if considered for redosing during pregnancy then they should receive vaccines before starting treatment wherever possible. Everyone receiving anti-CD20 therapies should be counselled regarding the risk of reduced vaccine efficacy with these treatments.⁴⁵

There is potential for pregnancy unexposed to medication, given the clinical trials data supporting the safety and efficacy of extending the dose interval in RRMS, and the knowledge of reduced relapse rate during pregnancy. In women with RRMS receiving regular treatment, it may be preferable to wait 3 months after rituximab or ocrelizumab treatment before trying to conceive, given emerging knowledge around extending dose intervals. Following conception, treatment for RRMS should be suspended during pregnancy unless there is clinical evidence of disease activity in which case they should be offered the option of further treatment. Women should be considered for re-treatment if they do not conceive within 9–12 months of their previous dose. While the shorter half-life of ofatumumab may be advantageous in minimising fetal drug exposure, at present there is insufficient evidence to advise increasing the dose interval should pregnancy occur; however, we anticipate that evidence will accrue over the next few years. Patients with neuromyelitis optica may need bridging therapy

Further reading

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(usually corticosteroids) if rituximab is withheld during pregnancy, although clinicians and patients can choose to treat with rituximab during pregnancy given the evidence presented above. Patients with refractory myasthenia gravis should be individually counselled given the substantial risk of fetal complications purely due to uncontrolled myasthenia (including arthrogyrposis and neonatal myasthenia) and the relative safety of rituximab.

Key points

- ▶ Following anti-CD20 therapy, women can safely start trying to conceive without delay.
- ▶ Women may receive anti-CD20 therapies during pregnancy if clinically indicated, for example with myasthenia gravis or neuromyelitis optica spectrum disorder.
- ▶ Women wishing to breastfeed should be encouraged to do so alongside resuming therapy where their treatment of choice is an anti-CD20 monoclonal antibody.
- ▶ Where breastfeeding women receive anti-CD20 therapy during pregnancy, the Medicine and Healthcare product Regulatory Agency advises deferring live-attenuated vaccinations, for example, BCG and rotavirus vaccine, for as long as the infant's immune status may possibly be influenced by the treatment; the pros and cons of vaccination should be discussed with the parents.
- ▶ There is only a low risk to the infant from a breastfeeding mother taking anti-CD20 treatment.

USE IN THE POSTPARTUM PERIOD AND DURING BREAST FEEDING

In the postpartum period, women with RRMS are at increased risk of relapsing and so treatment early in the postpartum period is recommended, with no need to suspend breast feeding for treatment. Even with the small amounts potentially transferred in breast milk, IgG₁ molecules are likely to be at least partially destroyed within the infant's gastrointestinal tract.⁴⁶ It must be noted that IgG, IgA and IgM concentrations are higher in colostrum (produced during the first week of infant life) than established breast milk⁴⁷; this, combined with the lower acidity of the newborn gastrointestinal tract mean that clinicians should be cautious about potential antibody transfer if mothers are treated in the first few days post partum.

We recommend that where women wish to breast-feed, they should be encouraged to do so alongside therapy resumption where their treatment of choice is an anti-CD20 monoclonal antibody. The UK's MHRA advises women who have been exposed to immunosuppressive treatment during pregnancy or via breast feeding to have live-attenuated vaccinations, for example, BCG, rotavirus and MMR vaccinations, deferred for as long as postnatal influence on the immune status of the infant remains possible.⁴³ This is usually taken to be 6 months after last possible exposure. In the case of anti-CD20 treatment, we believe the risk of the infant being significantly immunosuppressed by exposure via breast feeding is low and the pros and cons of vaccination should be discussed with the parents.

Despite RRMS affecting mainly women, and being diagnosed at an increasingly younger age, there are relatively few studies examining drug safety in pregnancy and breast feeding. There is similarly limited evidence in other neuroinflammatory disorders; however, use of anti-CD20 medications during pregnancy in non-neurological inflammatory disease is increasingly widespread. Women are potentially being denied effective treatment based on their reproductive choices, in the absence of evidence to support this. There is evidence for the relative safety of anti-CD20 medications used around pregnancy, and recent evidence suggests that with adaptive dosing, women have the potential for medication-free pregnancy with effective disease control, with safe resumption of therapy in the postpartum period. There remain areas of uncertainty, particularly with long-term outcomes. It is important to make time to counsel women and involve them in treatment choice.

As the use of these treatments around the time of pregnancy increases it is important to monitor outcomes and update these guidelines as appropriate. We still need to gather more data around the use of medications in pregnancy, in order to ensure that women and their families have access to the highest quality data. The UK MS Pregnancy Register has been

developed for this purpose, and all women with MS who are pregnant should be encouraged to register via www.ukmsregister.org/pregnancy.

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Contributors RD, DR, KM, SH, ORP, HLF, NB, SW and PB conceived the idea of these guidelines. They were initially drafted by RD, who performed the initial literature search. PB and KM provided additional literature searches. All authors reviewed the guidelines and commented on the consensus recommendations. RD, DR, KM, SH, HLF, ORP and PB are neurologists with a special interest in MS and pregnancy SW and NB are MS Specialist Nurses with an interest in MS and pregnancy JM is a neuro-pharmacist CO is an obstetrician with a special interest in medical disorders in pregnancy CN-P is an obstetric physician.

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Competing interests RD, DR, KM, SH, ORP, HLF, NB-M, SW and PB are on the steering committee for the UK MS Pregnancy Register, which seeks to improve our understanding of the safety of DMT in pregnancy. RD has received honoraria for sitting on advisory boards from Roche and Novartis. She sits on the steering committee for the MINORE and SOPRANINO studies, which are examining the safety of ocrelizumab in pregnancy and breastfeeding. She receives grant support from the UK MS Society, BMA foundation, NIHR, MRC, NMSS, Horne Family Charitable Trust, Biogen, Celgene, and Merck. She has received honoraria for advisory boards and/or educational activities from Biogen, Teva, Sanofi, Merck, Janssen, Novartis, and Roche. DR has received honoraria for sitting on advisory boards and/or speaker fees from Biogen, Celgene, Hikma, Janssen, MedDay, Merck Serono, Novartis, Roche, Sanofi, Teva Neuroscience. He is the UK Coordinating Investigator for Tecfidera, Aubagio and Lemtrada pregnancy registries. He has received research support, paid to his institution, from Actelion, Biogen, Janssen, Merck Serono, Mitsubishi, Novartis, Sanofi, Teva Neuroscience, TG Therapeutics. CO consults for Mirum Pharmaceuticals. KM reports honoraria for advisory boards/educational activities from Biogen, Roche, Merck, Teva, Novartis, Sanofi. ORP has received honoraria for advisory boards and/or educational activities from Biogen, Teva, Sanofi, Merck, Janssen, Novartis, and Roche. SH has received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche and Sanofi Genzyme. NB-M has nothing to declare SW

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