RESEARCH ARTICLE OPEN ACCESS

Pregnancy Exposure to Anti-CD20 Monoclonal Antibodies in Patients With Multiple Sclerosis

Results From an Italian Multicenter Registry Study

Irene Gattuso,[1] Angela Genchi,[1] Girolama Alessandra Marfia,[2] Doriana Landi,[2] Assunta Bianco,[3] Massimiliano Mirabella,[3,4] Giovanna Borriello,[5] Antonio Gallo,[6,7] Laura Brambilla,[8] Valentina Gasparini,[9] Lorena Lorefice,[10] Maria Pia Amato,[11,12] Francesca Rinaldi,[13] Roberta Lanzillo,[14] Elisabetta Signoriello,[15] Maria Cellerino,[16] Clara Grazia Chisari,[17] Paola Cavalla,[18] Carla Tortorella,[19] Giovanna De Luca,[20] Albulena Bajrami,[21] Roberta Fantozzi,[22] Damiano Paolicelli,[23] Cristina Montomoli,[24] Massimo Filippi,[1,25,26,27,28] and Lucia Moiola,[1] for the CD20-Pregnancy Study Group

Correspondence
Dr. Moiola
moiola.lucia@hsr.it

Neurol Neuroimmunol Neuroinflamm 2026;13:e200650. doi:10.1212/NXI.0000000000200650

Abstract

Background and Objectives

Although anti-CD20 monoclonal antibodies (anti-CD20s) theoretically represent an ideal treatment option for women with multiple sclerosis (wwMS) planning a pregnancy, the paucity of real-world data still limits their use in this context. Through our Italian registry "CD20-PREGNANCY," we aim to report pregnancy, infant, and maternal outcomes in wwMS treated with anti-CD20s.

Methods

In this observational study, wwMS having received rituximab (RTX), ocrelizumab (OCR), or ofatumumab (OFA) before and/or during pregnancy (≤12 months for RTX/OCR, ≤6 months for OFA) were included. Considering drug pharmacokinetics and timings of immunoglobulin placental transfer, pregnancies were classified as "exposed" (last administration pre-pregnancy ≤2.3 months for RTX, ≤3 for OCR, ≤1.8 for OFA) and "not-exposed" (last administration beyond these intervals) for comparative analysis.

Results

A total of 153 pregnancies (85 "not-exposed," 68 "exposed") across 27 Italian MS centers were collected. The median age at conception was 33.9 years (interquartile range 30.0–37.6) with 39.9% of women older than 35 years. Most pregnancies occurred in patients treated with OCR (77.1%). 80.4% of pregnancies ended in livebirth and 13.1% in spontaneous abortions (SA), without stillbirths/neonatal deaths. There was a significantly higher percentage of SA in "exposed" pregnancies than "not-exposed" (20.6% vs 7.1%, $p = 0.014$), but with values similar to those reported in general population. One serious perinatal infection ("exposed" group) and 2 major congenital anomalies (MCA) (one per group) were reported. Compared with the

MORE ONLINE

Supplementary Material

[1]Neurology Unit and Multiple Sclerosis Center, IRCCS San Raffaele Scientific Institute, Milan, Italy; [2]Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, Rome, Italy; [3]Multiple Sclerosis Center, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; [4]Centro di Ricerca per la Sclerosi Multipla "Anna Paola Batocchi", Università Cattolica del Sacro Cuore, Rome, Italy; [5]MS Center, S.Pietro Fatebenefratelli Hospital, Rome, Italy; [6]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [7]First Division of Neurology and Neurophysiopathology, AOU Luigi Vanvitelli, Naples, Italy; [8]Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [9]S.C. Neurologia ad indirizzo Neuroimmunologico - Centro Sclerosi Multipla Ospedale di Gallarate - ASST Valle Olona, Gallarate, Italy; [10]Multiple Sclerosis Center, Binaghi Hospital, ASL Cagliari, Italy; [11]Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Italy; [12]Department of Neurorehabilitation, IRCCS Don Carlo Gnocchi Foundation, Florence, Italy; [13]Multiple Sclerosis Centre, Azienda Ospedaliera di Padova, Padua, Italy; [14]Dipartimento Neuroscienze, Scienze Riproduttive e Odontostomatologiche, Università Federico II di Napoli, Naples, Italy; [15]UOSD Second Neurology, University of Campania "Luigi Vanvitelli", Naples, Italy; [16]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI), University of Genoa, Italy; [17]Department "GF Ingrassia", Section of Neurosciences, University of Catania, Italy; [18]Department of Neuroscience, University of Turin & Multiple Sclerosis Centre, AOU City of Health & Science University Hospital, Turin, Italy; [19]Department of Neurosciences, Multiple Sclerosis Centre - San Camillo Forlanini Hospital, Rome, Italy; [20]Multiple Sclerosis Centre, Neurology Unit, SS Annunziata Hospital, University "G. d'Annunzio", Chieti-Pescara, Italy; [21]Neurology Unit, Santa Chiara Hospital, Trento, Italy; [22]Neurology Unit, IRCCS Neuromed, Pozzilli, Italy; [23]Department of Translational Biomedicine and Neurosciences, University of Bari 'Aldo Moro', Italy; [24]Department of Public Health, experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, University of Pavia, Italy; [25]Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy; [26]Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [27]Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy; and [28]Vita-Salute San Raffaele University, Milan, Italy.

Coinvestigators are listed in Appendix at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

anti-CD20s = anti-CD20 monoclonal antibodies; **ARR** = annualized relapse rate; **ART** = assisted reproductive technology; **CDW** = confirmed disability worsening; **CRP** = C-reactive protein; **CUA** = combined unique active; **DA** = disease activity; **DMD** = disease-modifying drug; **EDC** = expected date of conception; **EDSS** = Expanded Disability Status Scale; **ET** = elective terminations; **FU** = follow-up; **GA** = gestational age; **IQR** = interquartile range; **LB** = livebirths; **LBW** = low birth weight; **MCA** = major congenital anomalies; **ND** = neonatal deaths; **OCR** = ocrelizumab; **OFA** = ofatumumab; **OR** = odds ratio; **RTX** = rituximab; **SA** = spontaneous abortions; **SB** = stillbirths; **WHO** = World Health Organization; **wwMS** = women with multiple sclerosis.

12 months pre-pregnancy, annualized relapse rate remained stable during pregnancy but slightly increased postpregnancy (0.00 vs +0.09) in "not-exposed." Conversely, it decreased in both periods (−0.02 vs −0.13) among "exposed". Compared with pre-pregnancy, postpregnancy combined unique active lesions decreased in both groups (−0.15 in "not-exposed", −0.38 in "exposed"), while 2 confirmed disability worsening were observed ("not-exposed").

Discussion

In conclusion, a good control of disease activity was observed without an increased risk of MCA or perinatal infections. Percentages of SA were overall in line with those of general population, although with a higher proportion in the "exposed" group. These findings support the use of anti-CD20 therapies in wwMS planning pregnancy, although further data are needed to better define their safety profile in this setting.

Introduction

Multiple sclerosis (MS) mainly affects women of childbearing potential. In the past years, a better knowledge of the disease and the development of effective therapies have dramatically changed the approach to family planning in MS. Relapse rate typically decreases during pregnancy, to increase again in the first 3 months after delivery.[1] Although exposure to disease-modifying drugs (DMDs) in the 2 years before pregnancy has proven protective for disease activity (DA) in postpartum,[2] discontinuing a DMD can lead to disease reactivation, underscoring the importance of continuing treatment as long as safely possible. Nevertheless, a well-defined therapeutic planning is also crucial to minimize potential risks for the offspring. Anti-CD20 monoclonal antibodies (anti-CD20s), namely rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OFA), could represent a convenient therapeutic option in women with MS (wwMS) planning a pregnancy. In fact, they are very efficacious in controlling DA with long-lasting effect after withdrawal, in the absence of rebound risk.[3] However, robust evidence of their safety for both mother and fetus is still lacking, and labeling indications remain conservative with the exception of recent modifications for OCR in Europe.[4]

From a biologic perspective, maternal drug exposure does not necessarily imply concomitant fetal exposure. RTX, OCR, and OFA are all IgG1 type monoclonal antibodies, with their capability to cross the placenta depending on the presence of neonatal Fc receptor, which is expressed from the second trimester on. Therefore, IgG levels are undetectable in fetal circulation during first trimester.[5] To estimate the timings of fetal exposure during pregnancy, the pharmacokinetic properties of each drug must be considered. In particular, RTX (off-label) has an elimination time of approximately 100 days, OCR of 130 days, and OFA of 80 days.[6]

Existing literature about the topic, comprising case series, single-center studies,[7,8] and a large multicenter study,[9] has shown no increased risk of adverse pregnancy or infant outcomes in women exposed to anti-CD20s while seeking or during pregnancy. However, because of the rarity of events like congenital malformations, additional data are needed. Here, we present data collected through the Italian, multicenter registry, CD20-PREGNANCY, with the aim to expand current evidences about the use of anti-CD20s in wwMS planning a pregnancy. Our objective is to describe pregnancy and infant outcomes, including spontaneous abortions (SA), major congenital anomalies (MCA), perinatal infections, and hematologic abnormalities, and to assess maternal DA, to better understand whether the use of anti-CD20s in this setting is safe for the offspring and provides advantages in maternal disease control.

Methods

Study Population and Data Collection

Our study included 27 Italian MS centers. Each involved MS expert neurologist spontaneously reported all known pregnancies in wwMS under treatment with RTX/OCR/OFA. For this analysis, data were collected both retrospectively and prospectively between December 2023 and November 2025. To ensure an adequate postpregnancy observation period, only pregnancies ended by August 31, 2025, were included. Cases were defined as pregnancies in women who had

received at least one dose of RTX/OCR/OFA, either before last menstrual period (LMP) or during pregnancy. Main inclusion criteria were diagnosis of MS according to 2017 revision of McDonald criteria[10]; last RTX/OCR administration up to 12 months before LMP or during pregnancy or last OFA administration up to 6 months before LMP or during pregnancy; and RTX/OCR/OFA as last DMD before delivery/abortion. Abovementioned timings were decided on the basis of drugs European Summary of Product characteristics (SmPC) (withdrawal timings according to European SmPCs: 12 months before seeking pregnancy for RTX; recently shortened from 12 to 4 months for OCR; 6 months for OFA).[4,11,12] The whole cohort was divided into "not-exposed" and "exposed" pregnancies, by considering the different elimination times of each drug and the timings of placental Fc neonatal receptor expression. In previous studies,[7,9] pregnancies in OCR were considered exposed when occurred within 3 months from last administration. We maintained this timing for OCR and scaled it to elimination times of RTX and OFA, so that pregnancies were considered exposed when last RTX had been administered up to 2.3 months, when last OCR had been administered up to 3 months, and when last OFA had been administered up to 1.8 months before LMP or during pregnancy.

Outcomes

Pregnancy outcomes were livebirths (LB); spontaneous abortions (any fetal death occurred at a gestational age [GA] ≤ 22 weeks); elective terminations (ET); stillbirths ([SB]—any fetal death occurred at a GA > 22 weeks); neonatal deaths ([ND]—any death of a LB occurred before 28 days of age[13,14]). Among LB, preterm were defined as infants born at a GA ≤ 37 weeks.

Maternal infections during pregnancy were recorded. Congenital anomalies were collected both in case of LB and fetal deaths and categorized as "major" or "minor" according to epidemiologic surveillance of congenital anomalies (EUROCAT) definitions.

Anthropometric measurements (weight, length, and cranial circumference) at birth, APGAR 5′, as well as any known hematologic abnormalities and serious perinatal infections, were collected for LB. Given the observational design of the study, any clinical examinations and laboratory tests in the infants were performed per clinical practice. Among LB, infants were defined as low birth weight (LBW) when weight at birth was ≤2,500 gr. Finally, infant general health status (absence of major health concerns, including recurrent infections, developmental disturbances, or need for additional clinical evaluations beyond routine care) at last follow-up (FU) was collected.

As regards maternal disease outcomes, number of clinical relapses before pregnancy (previous 12 months), during pregnancy (interval between LMP and delivery date), and in the postpregnancy (3 months after delivery/abortion) were collected. A relapse was defined as occurrence of new neurologic signs/symptoms reflecting a CNS demyelinating event, lasting at least 24 hours, in the absence of fever/infections.[10] Individual annualized relapse rate (ARR) for each patient was calculated as "number of relapses/observation time in years". Global ARR for each period was then calculated as a mean of individual ARR with 95% confidence interval (CI). Expanded Disability Status Scale (EDSS) at the beginning of pregnancy and 6 and 12 months after delivery was collected. The number of patients with 12-month confirmed disability worsening (CDW), compared with the prepregnancy period, were assessed. CDW was defined as an increase of 2 points in the EDSS for patients with EDSS 0.0, of 1 point for patients with EDSS lower than 5.5, and of 0.5 points for patients with an EDSS higher than 5.5.[15] Finally, number of new/enlarging T2 lesions, gadolinium-enhancing lesions, and combined unique active (CUA) lesions at last MRI before pregnancy and at first MRI postpartum were collected.

Standard Protocol Approvals, Registrations, and Patient Consents

Data collection was approved by local ethic committees, and all enrolled patients signed a written informed consent, in accordance with the Declaration of Helsinki.

Statistical Analysis

Pregnancy outcomes, congenital anomalies, and categorical infant outcomes were reported as percentages relative to the total number of known outcomes for that variable. Given the small sample size, continuous variables were assumed to be not normally distributed and reported as median and interquartile range (IQR), except for ARR and MRI lesions. Comparisons between the 2 study groups, "not-exposed" and "exposed," were conducted using the Wilcoxon test for continuous variables and the Chi square or Fisher exact test for categorical variables as appropriate, with 0.05 significance level. As regards MCA, hematologic abnormalities, and perinatal infections, given the small number of events, no statistical comparisons between "not-exposed" and "exposed" pregnancies, were performed. Odds ratios (OR) and their corresponding 95% CI were estimated using Firth logistic regression to assess the association between the risk of SA and preterm births and factors including drug exposure, disease duration, EDSS before pregnancy, duration of therapy before pregnancy, and time to expected date of conception (EDC). This approach was used to provide reliable estimates in the context of rare events like SA. ARR and MRI lesion counts were compared between "not-exposed" and "exposed" groups using adjusted Poisson or negative binomial regression models, depending on data dispersion, including age at conception and EDSS as covariates. Analyses were performed with R version 4.5.0.

Data Availability

Pseudonymized data will be shared upon any reasonable request from qualified investigators.

Results

Baseline Characteristics

Baseline characteristics of women before each pregnancy are summarized in Table 1. A total of 153 pregnancies (85 "not-exposed" and 68 "exposed") in 136 women were collected.

The median age at conception was 33.9 years (IQR 30.0-37.6), with 39.9% of women older than 35 years and a median disease duration of 7.9 years (IQR 4.4–11.7). In the whole cohort, 94.1% (n = 144) of patients had relapsing-remitting MS, 3.3% (n = 5) secondary progressive MS, and 2.6% (n = 4) primary progressive MS. Overall, 3.3% (n = 5) of patients were on treatment with RTX, 77.1% (n = 118) with OCR, and 19.6% (n = 30) with OFA. The median EDSS at conception was 2.0 (IQR 1.0–2.5). The median duration of therapy before conception was 1.5 years (IQR 0.9–2.6), with a median FU postpregnancy of 1.9 years (IQR 1.2–3.1). The 2 study groups, "not-exposed" and "exposed" pregnancies, significantly differed in terms of percentage of women older than 35 (31.8% in "not-exposed" vs 50.0% in "exposed", $p = 0.034$), a known risk factor for unfavorable pregnancy outcomes. They also significantly differed in terms of type of anti-CD20 ("not-exposed": RTX 2.4%, OCR 95.2%, OFA 2.4%; "exposed": RTX 4.4%, OCR 54.4%, OFA 41.2%; $p < 0.001$), duration of therapy with anti-CD20 before pregnancy (2.0 in "not-exposed" vs 1.2 years in "exposed," $p < 0.001$), and duration of FU after pregnancy (2.4 in "not-exposed" vs 1.6 years in "exposed," $p = 0.040$). As expected, time to EDC was significantly higher in "not-exposed" than "exposed" pregnancies (164.0 in "not-exposed" vs 12.0 days in "exposed", $p < 0.001$).

Pregnancy Outcomes

Pregnancy outcomes are summarized in Table 2. In the whole cohort, 80.4% (n = 123) of pregnancies ended in LB, 13.1% (n = 20) in SA, and 6.5% (n = 10) in ET, in the absence of SB or ND. There was a significantly higher percentage of SA in "exposed" group compared with "not-exposed" [20.6% (n = 14) vs 7.1% (n = 6), $p = 0.014$]. Most LB were full-term, with a preterm birth rate of 11.4% (n = 14) across the entire cohort, and a significantly higher percentage of preterm in "exposed" group than "not-exposed" [19.2% (n = 10) vs 5.6% (n = 4), $p = 0.023$]. Despite the small number of events, exploratory univariate analyses were conducted to assess factors associated with SA and preterm (see eTables 1 and 2). Drug exposure and age at conception were significantly associated with higher risk of SA (OR = 3.41, 95% CI 1.28–10.15, $p = 0.018$ and OR = 1.14, 95% CI 1.03–1.27, $p = 0.017$ respectively), with exposure remaining significant after adjusting for age at conception (OR = 2.83, 95% CI 1.04–7.74, $p = 0.042$). Other variables including disease duration, EDSS before pregnancy, duration of therapy before pregnancy, and time to EDC, were not significantly associated with SA risk. Even in the case of preterm, exposure was significantly associated with higher risk (OR = 3.71, 95% CI 1.21–13.21, $p = 0.021$), together with EDSS before pregnancy (OR = 1.47,

Table 1 Baseline Characteristics of Women at Each Pregnancy

	Whole cohort	Not exposed	Exposed	*p* Value
Pregnancies	N = 153	N = 85	N = 68	—
Women	N = 136	N = 78	N = 66	—
Age at conception (y), median (Q1; Q3)	33.9 (30.0; 37.6)	33.8 (29.5; 35.9)	35.0 (30.6; 39.3)	0.072[a]
Age ≥35, N (%)	61 (39.9)	27 (31.8)	34 (50.0)	0.034[c]
Disease duration (y), median (Q1; Q3)	7.9 (4.4; 11.7)	8.4 (5.2; 11.8)	7.4 (3.1; 11.5)	0.198[a]
MS subtype, N (%)				0.149[b]
RR	144 (94.1)	83 (97.6)	61 (89.7)	
SP	5 (3.3)	1 (1.2)	4 (5.9)	
PP	4 (2.6)	1 (1.2)	3 (4.4)	
Type of anti-CD20, N (%)				<0.001[b]
RTX	5 (3.3)	2 (2.4)	3 (4.4)	
OCR	118 (77.1)	81 (95.2)	37 (54.4)	
OFA	30 (19.6)	2 (2.4)	28 (41.2)	
EDSS, median (Q1; Q3)	2.0 (1.0; 2.5)	1.5 (1.0; 2.1)	2.0 (1.4; 3.0)	0.085[a]
Duration of therapy with anti-CD20 before conception (y), median (Q1; Q3)	1.5 (0.9; 2.6)	2.0 (1.1; 2.9)	1.2 (0.6; 1.8)	<0.001[a]
Time to EDC (d), median (Q1; Q3)	109.0 (17.0; 171.0)	164.0 (129.0; 215.0)	12.0 (−12.3; 42.3)	<0.001[a]
Post-pregnancy follow-up duration (y), median (Q1; Q3)	1.9 (1.2; 3.1)	2.4 (1.4; 3.3)	1.6 (1.0; 2.8)	0.040[a]

Abbreviations: d = days; EDC = expected date of conception; EDSS = Expanded Disability Status Scale; MS = multiple Sclerosis; N = number; OCR = ocrelizumab; OFA = ofatumumab; PP = primary progressive; Q = quartile; RR = relapsing-remitting; RTX = rituximab; SP = secondary progressive; y = years.
[a]Comparison with the Wilcoxon test between the 2 groups.
[b]Comparison with the Fisher exact test between the 2 groups.
[c]Comparison with the χ^2 test between the 2 groups.

Table 2 Pregnancy Outcomes

	Whole cohort	Not exposed	Exposed	*p* Value
Pregnancies	N = 153	N = 85	N = 68	—
Pregnancy outcomes				
Spontaneous abortions, N (%)	20 (13.1)	6 (7.1)	14 (20.6)	0.014[a]
Elective terminations, N (%)	10 (6.5)	8 (9.4)	2 (2.9)	0.186[b]
Stillbirths, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	—
Neonatal deaths, N (%)	0 (0.0)	0 (0.0)	0.0	—
Livebirth, N (%)	123 (80.4)	71 (83.5)	52 (76.5)	0.274[a]
Preterm	14 (11.4)	4 (5.6)	10 (19.2)	0.023[b]
Full-term	109 (88.6)	67 (94.4)	42 (80.8)	0.023[b]

Abbreviation: N = number.
[a]Comparison with the χ^2 test between the 2 groups.
[b]Comparison with the Fisher exact test between the 2 groups.

95% CI 1.02–2.12, $p = 0.038$) and duration of therapy before pregnancy (OR = 1.34, 95% CI 1.02–1.76, $p = 0.038$), while age at conception was not significant. After adjustment for EDSS and duration of therapy before pregnancy, exposure remained significantly associated with an increased risk of preterm birth (OR = 7.04, 95% CI 1.60–30.87; $p = 0.01$).

Congenital Anomalies and Infant Outcomes

Congenital anomalies and infant outcomes are summarized in Table 3. Infant follow-up was aligned with maternal follow-up (see Table 1). A detailed description of all malformations can be found in eTable 3. The rate of MCA was 1.7% (n = 2/117) in the whole cohort, 1.5% (n = 1/67) in "not-exposed" and 2.0% (n = 1/50) in "exposed" group. In not-exposed pregnancy (last OCR 4.6 months before LMP), MCA consisted of encephalocele, bringing to ET because of the severity of malformation; the mother was in her late 30s at conception, and she had recurred to assisted reproductive technology (ART) because of infertility; a subsequent pregnancy in the same woman brought to a healthy LB (not-exposed pregnancy). The other case occurred in "exposed" group (last OFA 6 days before LMP) and resulted in a LB with slight aortic isthmus narrowing associated with a minor malformation (renal pelvis ectasia); the infant was precautionary monitored in intensive care unit for 1 day but was otherwise healthy and had no perinatal infections (412 days FU after delivery). A further pregnancy in the "exposed" group (last OCR 1.7 months before LMP) ended in a SA because of trisomy 16; a previous pregnancy in the same patient ("not-exposed") had similarly brought to SA.

As regards hematologic abnormalities, 2 events were reported, both in "exposed" group. One case, in which OCR was firstly prescribed during pregnancy as rescue therapy, involved a late-term birth with isolated IgA deficiency, persisting at 1-year FU and not associated to B-cell depletion; the infant's general health status at FU (more than 1 year) was good. Maternal IgA levels were within the normal range both before

Table 3 Congenital Anomalies and Infant Outcomes

	Whole cohort	Not exposed	Exposed
Congenital malformations, N (%)	7 (6.0)	4 (6.0)	3 (6.0)
Reported, N/total of livebirths	117/153	67/85	50/68
Major, N (%)	2 (1.7)	1 (1.5)	1 (2.0)
Minor, N (%)	5 (4.3)	3 (4.5)	2 (4.0)
Infections, N (%)	1 (1.0)	0 (0.0)	1 (2.4)
Reported, N/total of livebirths	96/123	55/71	41/52
General good health status at FU, N (%)	92 (100)	52 (100)	42 (100)
Reported, N/total of livebirths	92/123	52/71	42/52

Abbreviations: FU = follow up; N = number.

Table 4 Anthropometric Measurements and APGAR

	Whole cohort	Not exposed	Exposed	*p* Value
N of livebirths	123	71	52	—
Weight at birth (gr), median (Q1; Q3)	3,140.0 (2,900.0; 3,450.0)	3,160.0 (2,900.0; 3,360.0)	3,102.5 (2,790.0; 3,500.0)	0.721[a]
Reported, N/total of livebirths	113/123	65/71	48/52	—
Low birth weight, N (%)	7 (6.2)	1 (1.5)	6 (12.5)	0.041[b]
Length at birth (cm), median (Q1; Q3)	50.0 (49.0; 51.0)	50.0 (49.0; 51.0)	49.6 (48.0; 51.0)	0.329[a]
Reported, N/total of livebirths	105/123	61/71	44/52	—
Cranial circumference (cm), median (Q1; Q3)	34.0 (33.0; 35.0)	34.0 (33.5; 36.0)	34.0 (33.0; 35.0)	0.117[a]
Reported, N/total of livebirths	81/123	48/71	33/52	—
APGAR 5′ normal, N (%)	96 (96.0)	51 (94.4)	45 (97.8)	0.621[b]
Reported, N/total of livebirths	100/123	54/71	46/52	—

Abbreviations: N = number; gr = grams; cm = centimeters.
[a]Comparison with the Wilcoxon test between the 2 groups.
[b]Comparison with the Fisher exact test between the 2 groups.

and after delivery. The second case involved a new-born of a woman treated with OCR, delivered at 38 + 5 weeks, with thrombocytopenia and C-reactive protein (CRP) increase; the infant remained clinically stable and FU beyond 1 year showed no health concerns. Only one serious perinatal infection was reported ("exposed" group), in a woman treated with OCR, and consisted of bronchiolitis and blood cultures positivity for staphylococcus and enterococcus faecalis. General health status of the infant at FU was good.

A detailed report of anthropometric measurements of infants at birth can be found in Table 4. Overall, 6.2% (n = 7) LB turned to be LBW, with a significantly higher percentage in "exposed" group [12.5% (n = 6) vs 1.5% (n = 1), $p = 0.041$]; however, 5/7 LBW infants were preterm. A detailed description can be found in eTable 4. As regards weight, length, and cranial circumference at birth, all values were between fifth and ninety-fifth percentile according to World Health Organization (WHO), and no significant differences between

Table 5 Maternal Disease Activity

	Whole cohort	Not exposed	Exposed	IRR	CI	*p* Value
ARR before pregnancy (95% CI)	0.10 (0.04–0.16)	0.05 (0.00–0.09)	0.16 (0.05–0.28)	3.44[a]	1.09–10.80	0.034
ARR during pregnancy (95% CI)	0.04 (0.00–0.08)	0.05 (0.00–0.12)	0.14 (0.02–0.26)	1.45[a]	0.28–7.53	0.661
ARR after pregnancy (95% CI)	0.13 (0.00–0.31)	0.14 (0.00–0.31)	0.03 (0.00–0.08)	0.89[b]	0.36–2.18	0.803
New/enlarging T2 lesions before pregnancy, mean (±SD)	0.35 (±1.35)	0.15 (±0.55)	0.61 (±1.93)	3.94[a]	2.10–7.38	1.873
Gd enhancing lesions before pregnancy, mean (±SD)	0.08 (±0.31)	0.04 (±0.19)	0.13 (±0.42)	3.51[a]	0.93–13.24	0.063
CUA lesions before pregnancy, Mean (±SD)	0.32 (±1.41)	0.19 (±0.95)	0.50 (±1.86)	2.66[a]	1.46–4.84	0.322
New/enlarging T2 lesions after pregnancy, mean (±SD)	0.20 (±1.09)	0.14 (±0.95)	0.29 (±1.26)	2.09[b]	0.37–11.73	0.205
Gd enhancing lesions before pregnancy after pregnancy, mean (±SD)	0.03 (±0.18)	0.04 (±0.20)	0.02 (0.13)	0.42[b]	0.04–4.0	0.458
CUA lesions after pregnancy, mean (±SD)	0.07 (±0.26)	0.04 (±0.20)	0.12 (±0.33)	2.74[b]	0.69–11.0	0.153
12mo CDW, N/N of reported outcome	4/81	3/50	1/31	—	—	—

Abbreviations: ARR = annualized relapse rate; CDW = confirmed disability worsening; CI = confidence interval; CUA = combined unique active; Gd = gadolinium; IRR = incidence rate ratio; mo = months; N = number.
IRR were obtained with
[a]Poisson regression or
[b]Negative binomial regression, by considering "not-exposed" the reference group.

the 2 study groups were observed. Most infants [96.0% (n = 96) in the whole cohort; 94.4% (n = 51) "not-exposed"; 97.8% (n = 45) "exposed"] had normal APGAR 5".

Maternal Disease Outcomes

MS outcomes are summarized in Table 5. In the year before pregnancy, ARR was 0.10 (95% CI 0.04–0.16) in the whole cohort, significantly lower in the "not-exposed" group (0.05, 95% CI 0.00–0.09) than in the "exposed" group (0.16, 95% CI 0.05–0.28; $p = 0.034$). ARR remained low during pregnancy and postpregnancy, with no significant differences between groups. During pregnancy, ARR was 0.04 (95% CI 0.00–0.08) in the whole cohort, 0.05 (95% CI 0.00–0.12) in "not-exposed," and 0.14 (95% CI 0.02–0.26) in "exposed" ($p = 0.661$). Postpregnancy ARR was 0.13 (95% CI 0.00–0.31), 0.14 (95% CI 0.00–0.31), and 0.03 (95% CI 0.00–0.08), respectively ($p = 0.803$).

Three relapses occurred during pregnancy (one "exposed" and 2 "not-exposed"). The "exposed" patient (7 cycles of OCR), had high pre-pregnancy disease activity (2 relapses in the 12 months before pregnancy). As regards "not-exposed" cases, one patient had only received titration and one more cycle of OFA before LMP; the other had been in treatment with OCR for approximately 3 years with no history of DA before pregnancy. All remained clinically and radiologically stable postpartum. An additional patient experienced a relapse during pregnancy, but occurred before initiating anti-CD20 (OCR administered as rescue therapy in second trimester). Five postpregnancy relapses were recorded (3 "not-exposed", 2 "exposed"). Women in the "not-exposed" group were clinically and radiologically stable before pregnancy. One had been treated with 4 cycles of OCR before conception (time to LMP 4.9 months), remained stable during pregnancy and delayed therapy resumption for breastfeeding. She had the relapse 75 days after delivery, and OCR was restarted 17 days after the relapse (OCR-free-interval 16 months); EDSS progressed from 2.0 to 3.5. Another, previously treated with 5 cycles of OCR (time to LMP 11.1 months), remained stable during pregnancy and also delayed therapy resumption; she had the relapse 20 days after delivery, and OCR was resumed 30 days after the relapse (OCR-free interval 21.8 months); EDSS before pregnancy was 1.5 and increased to 2.0 after the relapse. The third patient, who had received only 2 cycles of OCR before conception (time to LMP 6.4 months), remained stable during pregnancy but had a relapse the day after delivery; she restarted OCR 20 days after the relapse (OCR-free interval 15.6 months); EDSS before pregnancy was 2.0 and improved to 1.5 postpartum. The 2 women in "exposed" group were clinically and radiologically stable both before and during pregnancy. One had been treated with 9 cycles of OFA before conception (time to LMP-9 days) and resumed therapy the day after abortion; she had the relapse 30 days after therapy resumption. The other one had received 18 cycles of OFA before conception (time to LMP -50 days) and resumed therapy 13 days after abortion; she had a relapse 70 days after therapy resumption.

At last MRI before pregnancy, mean numbers of new/enlarging T2 lesions were 0.35 ± 1.35 (whole cohort), 0.15 ± 0.55 ("not-exposed"), and 0.61 ± 1.93 ("exposed"; $p = 1.873$). Mean Gd-enhancing lesions were 0.08 ± 0.31, 0.04 ± 0.19, and 0.13 ± 0.42 ($p = 0.063$), while CUA lesions were 0.32 ± 1.41, 0.19 ± 0.95, and 0.50 ± 1.86 ($p = 0.322$), respectively. Post-pregnancy MRI activity remained low. Mean new/enlarging T2 lesions were 0.20 ± 1.09 overall, 0.14 ± 0.95 in "not-exposed," and 0.29 ± 1.26 in "exposed" ($p = 0.205$). Mean Gd-enhancing lesions were 0.03 ± 0.18, 0.04 ± 0.20, and 0.02 ± 0.13 ($p = 0.458$), while mean CUA lesions were 0.07 ± 0.26, 0.04 ± 0.20, and 0.12 ± 0.33 ($p = 0.153$), respectively.

CDW was observed in 2 patients, both in "not-exposed" group: one patient progressed from an EDSS of 2.0–3.5 because of a relapse in the postpartum; the other one progressed from an EDSS of 1.0–2.0 in the absence of clinical relapses.

Discussion

MS is a potentially disabling disease that predominantly affects young women, often before completion of their family planning. Anti-CD20s are large molecules, requiring neonatal Fc receptor to cross the placenta, which is expressed from the 20th–21st gestational week.[5,6,16] With these premises and given their unique characteristics (high efficacy in controlling DA, pharmacodynamic effect persisting long after drug elimination, no rebound risk at withdrawal), anti-CD20s could represent an optimal therapeutic strategy for wwMS who wish to become pregnant. Until recently, real-world data were scarce, and drugs labelling indications reported excessively long discontinuation timings, potentially compromising patient safety and/or leading to the abandonment of pregnancy plans. Today, with the emergence of real-life studies, we are witnessing an initial update of labelling information.

First data about the use of anti-CD20s during pregnancy in MS derive from case series on the use of RTX as rescue therapy in women with DA during pregnancy.[17,18] In a study of 2020 about RTX (74 pregnancies)[19], no serious infectious or obstetric complications were reported, although a relatively high rate of SA was observed, attributed to pre-existing fertility issues. Another study of 2021 about OCR and RTX[8], evaluated 67 pregnancies and found outcomes consistent with those observed in the general population, except for a higher rate of preterm births and 2 MCA in the group exposed during pregnancy. Both studies showed good disease control during and after pregnancy. In 2022, another study[7] analyzed data about OCR from a Canadian cohort, categorizing pregnancies as "in utero exposure" or "not in utero exposure" (cutoff 3 months after last OCR). Of 65 pregnancies, 72.3% resulted in LB and 20% in SA (21.2% in exposed group vs 15.4% in not-exposed). Preterm births were similar between groups, and only one MCA was reported. In 2025, data from over 3,200 pregnancies (outcome known for 1880) - collected in the OCR global pharmacovigilance database and categorized

similarly - were published, leading to modification of OCR labelling indications in Europe. The majority of pregnancies resulted in LB (84.4% in "not-exposed", 82.4% in "exposed" group and 70.1% in "unknown exposure" group), with comparable preterm birth (7.4%, 9.2% and 5.6%, respectively) and SA rates (11.4%, 9.4% and 22.6%, respectively) among groups. A total of 22 MCA was reported, with percentages comparable with those reported by EUROCAT. Three neonatal deaths were reported, all in the "exposed" group, attributed to extreme prematurity and associated conditions. Overall, the study found no increased risk of adverse outcomes for pregnancies or offspring exposed to OCR. No data about maternal disease outcomes were reported.[9] To date, data on OFA exposure during pregnancy are limited to a few abstracts.[20] Last update was presented at the 2025 Annual Meeting of the Consortium of MS Centers. Over a total of 275 pregnancies occurred within 180 days from last OFA administration, the outcome was known for 103: 70.9% LB, 12.6% ET, 12.6% SA, 1.9% ectopic pregnancies, 1.0% SB, and 1.0% abortion not otherwise specified. No MCA were reported.[21]

Our study provides, on a national multicenter basis, valuable insights into the efficacy and safety, for both mother and offspring, of anti-CD20s in wwMS with pregnancy desire. In our population, in the whole cohort, the majority of pregnancies (80.4%) ended in LB. The rate of SA was 13.1%. A significantly higher percentage of SA was observed in the "exposed" group compared with "not-exposed" group (20.6% vs 7.1%, p = 0.014), which is in line with the study of 2020 about RTX.[19] SA is a phenomenon normally occurring in the general population, with many possible etiologies (i.e., infertility, nulliparity, advanced maternal age). A review of 2021 reported a pooled miscarriage risk of 15.3% (95% CI, 12.5–18.7) in the general population, with a maximum of 21.6% (95% CI, 21.2–22.0),[14] which is not different from that observed in our study in the "exposed" group, as well as in aforementioned studies about RTX,[19] OCR,[7] and OCR global pharmacovigilance database (pregnancies with unknown exposure).[9]

At univariate exploratory analysis, pregnancy exposure and age at conception were significantly associated with an increased risk of SA (OR = 3.41 and 1.14, respectively). As maternal age is a known risk factor for miscarriage,[14] and the "exposed" group included a higher proportion of women older than 35 years (50.0% vs 31.8%, p = 0.034), analyses were adjusted for age. Even after adjustment, exposure remained independently associated with SA (OR = 2.83). In light of these findings, we cannot exclude that immunosuppression in first trimester could have played a role in increasing SA risk, given that a good inflammatory response is fundamental for implantation and placentation.[22] Among LB, the preterm delivery rate was 11.4%, significantly higher in the "exposed" group (20.6% vs 7.1%, p = 0.023). Even in this case, exposure was significantly associated with a higher risk (OR = 3.71), together with EDSS and therapy duration before pregnancy (OR = 1.47 and 1.34, respectively). After adjustment for these 2 factors, exposure remained independently associated (OR = 7.04). Notably, preterm cases included intercurrent infections, premature rupture of membranes, and relapse requiring steroid treatment, highlighting the importance of disease stability before conception. Nevertheless, it is worth noting that abovementioned associations should be interpreted cautiously, as the wide CI indicates limited precision, likely because of the small sample size and the low number of SA and preterm birth events. Moreover, given the observational nature of our study—partially prospective but predominantly retrospective—a degree of selection bias cannot be excluded. In particular, pregnancies exposed to anti-CD20s may have been subject to closer clinical attention, potentially increasing the likelihood of identifying and reporting adverse outcomes.

Only 2 MCA were reported, one per group (1.5% vs 2.0%), with proportions similar to those reported in the study of 2025 from OCR pharmacovigilance database[9]: One case involved encephalocele ("not-exposed") and led to ET of pregnancy because of severity; the other consisted of mild aortic arch narrowing ("exposed") in association with a minor malformation. Encephalocele is a neural tube defect with multifactorial and incompletely understood aetiology.[23] In our cohort, it occurred in a woman in her late 30s who conceived through ART, a context associated with increased risks of chromosomal abnormalities, congenital malformations, and adverse pregnancy outcomes. Aortic isthmus narrowing is a relatively common congenital defect (≈5/1,000 births), which may present early with cardiac symptoms or remain asymptomatic and be diagnosed later in life.[24] In our case, it was incidentally detected during routine evaluation of the child and to date had no impact on his healthy status.

As regards hematologic abnormalities, only 2 events were reported. One was IgA deficiency, the most common primary antibody deficit in the general population.[25] Anti-CD20s are associated with a risk of hypogammaglobulinemia, which typically develops after several treatment cycles, with available data suggesting that IgA reduction is relatively uncommon and typically mild, even after repeated dosing. In this case, pregnancy was exposed to OCR during second trimester, with certain fetal exposure. However, the patient received only a single OCR cycle, making a causal association between the abnormality and drug exposure unlikely. This affirmation is also supported by the observation that IgA levels in the mother at delivery were normal.[26,27] The other case was characterized by transient thrombocytopenia and CRP increase, without perinatal infections. General health status of the child at FU was good. Finally, only one serious perinatal infection was reported: a case of bronchiolitis in an "exposed" pregnancy, without consequences on long-term health status of the infant and which could still be due to chance.

All anthropometric measurements of the infants at birth were between fifth and ninety-fifth percentile of the same variable reported by WHO. There was a significantly higher percentage of LBW in the "exposed" group compared with "not-exposed" (12.5% vs 1.5%, p = 0.041), but 5/7 infants were

preterm, which could explain this finding, together with other associated conditions, unrelated to drug exposure.

Finally, as regards maternal disease outcomes, although the number of patients is relatively low to provide robust data, we can affirm that overall, DA remained low in our study population, both during and after pregnancy. Baseline ARR was slightly higher in the "exposed" group (0.16 vs 0.05) and decreased both during and after pregnancy (−0.02 and −0.13 compared with pre-pregnancy, respectively). A slight increase in the ARR was observed in the "not-exposed" group (0.00 and +0.09 compared with pre-pregnancy, respectively), together with the evidence of 2 CDW. MRI activity was well-controlled after pregnancy, without relevant differences between groups (Table 5).

To conclude, in January 2025, the results of the largest pregnancy registry about anti-CD20 OCR for MS have been published.[9] Despite some differences, our study displays results which are in line with those of the Roche registry and of previously published literature.

Our study has some limitations: low sample size, not allowing the detection of rare events, and limiting the statistical power of some analyses. Most cases were reported retrospectively, with possible reporting bias. A contribution of selection bias to the higher percentage of unfavorable outcomes in "exposed" group cannot be excluded. Nevertheless, some strengths of our work can also be highlighted: all currently used anti-CD20s are considered (ublituximab not approved at the time of our registry start), the small sample size has allowed an accurate collection of relevant information, and maternal DA outcomes have also been analyzed. Data collection through the CD20-PREGANCY registry is still ongoing to further expand sample size and to explore additional aspects such as lactation and physical and psychological development of the infant. Despite its limitations, our study highlights how pregnancy is possible in wwMS with active disease, who are in treatment with anti-CD20s. The long-lasting effect of anti-CD20s can allow us to achieve full disease control and prevent disability accumulation, enabling patients to plan their families, which is particularly significant when considering a disease affecting young adults at the height of their social and personal lives.

Author Contributions

I. Gattuso: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Genchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G.A. Marfia: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Landi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Bianco: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Mirabella: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Borriello: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Gallo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Brambilla: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Gasparini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Lorefice: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.P. Amato: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Rinaldi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Lanzillo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Signoriello: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Cellerino: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.G. Chisari: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Cavalla: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Tortorella: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. De Luca: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Bajrami: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Fantozzi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Paolicelli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Montomoli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Filippi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L. Moiola: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

I. Gattuso received honoraria from Novartis, Roche, Biogen and Merck. A. Genchi received compensation for speaking

activities from Novartis. G.A. Marfia is an advisory board member of Amgen, Alexion, Behering, Sanofi-Genzyme, Merck-Serono, Neauraxpharm, Novartis, Roche, and Takeda; and received honoraria for speaking and consultation fees from Alexion, Almirall, Bayer Schering, Biogen Idec, Merck Serono, Neauraxpharm, Novartis, Sanofi-Genzyme, Roche, and BMS. D. Landi received travel funding from Roche, Biogen, Merck Serono, and Sanofi-Genzyme; and received honoraria for speaking and consultation fees from Alexion, Merck Serono, Roche, and Neuraxpharm. A. Bianco has received honoraria for speaking and advisory board participation from Biogen, Novartis, Merck Serono, Roche, Sanofi Genzyme, Bristol-Myers Squibb, and Alexion. M. Mirabella has received honoraria for speaking and for advisory board/consulting from Biogen, Novartis, Merck Serono, Roche, Sanofi Genzyme, Janssen, Bristol-Myers Squibb, Viatris, and Alexion. G. Borriello has received fees for consulting and advisory board participation from Alexion, Almirall, Amgen, Biogen, Merck, Novartis, Roche, and Sanofi. A. Gallo has nothing to disclose. L. Brambilla has received honoraria for speaking activities from Novartis, Roche, and Horizon; has received honoraria for traveling from Sanofi-Genzyme, Merck-Serono, Novartis, Horizon, and Roche; and acted as an advisory board member of Sanofi-Genzyme, Novartis, and Merck-Serono. V. Gasparini has received honoraria for participation in advisory boards and/or travel expenses for attending congresses and meetings from Merck, Novartis, and Roche. L. Lorefice received honoraria for consultancy or speaking from Biogen, Bristol, Merck, Novartis, Roche, Sanofi, Amgen, Alexion, and Neuraxpharm. M.P. Amato has received research grants from the National MS Society, Canadian MS Society, Italian Health Ministry, Regione Toscana, Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Teva, Almirall, and Roche; and has received honoraria as a speaker and member of advisory boards from Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Teva, Almirall, Roche, Celgene BMS, and Sandoz. F. Rinaldi reports grants from Sanofi Genzyme, Merck Serono, Biogen Italy, and Novartis; and reports consultancy for Novartis, Biogen Italy, and Sanofi Genzyme. R. Lanzillo received personal compensations for speaking or consultancy from Biogen, Alexion, Amgen, Sanofi, Merck, Bristol Myers Squibb, Jansenn, Novartis, and Roche. E. Signoriello received honoraria from Biogen, Alexion, Sanofi, Merck, Bristol-Meyer-Squibb, Jannsen, Novartis, Amgen, and Roche. M. Cellerino received personal compensation from Novartis, Sanofi Genzyme, Teva, Merk, and Roche; and consulting fees from Zambon. C.G. Chisari received honoraria from Sanofi, Almiral, Biogen, Merck Serono, Novartis, Roche, and TEVA. P. Cavalla received compensation for travel grants and for participation on advisory boards and/or speaking activities from Alexion, Biogen, BMS Celgene, Merck Serono, Neuraxpharm, Novartis, Sanofi-Genzyme, Roche, and Janssen. C. Tortorella reports personal fees from Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Amgen, and Alexion. G. De Luca received honoraria from Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Lundbeck. A. Bajrami has nothing to disclose. R. Fantozzi received travel support, consultation fees, and honoraria for advisory boards from Novartis, Merck-Serono, Biogen, Roche, Neuraxpharm, Alexion, and Sanofi-Genzyme. D. Paolicelli received advisory board membership, speaker's honoraria, travel support, research grants, consulting fees, or clinical trial support from Alexion, Amgen, BMS-Celgene, Biogen, Merck, Neuraxpharm, Novartis, Roche, Sandoz, and Sanofi-Genzyme. C. Montomoli has nothing to disclose. M. Filippi is Editor-in-Chief of the *Journal of Neurology* is an associate editor of *Human Brain Mapping, Neurologic Sciences*, and *Radiology*; received compensation for consulting services from Almirall, Biogen, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Roche, and Sanofi; for speaking activities from Amgen, Bayer, Biogen, Bristol-Myers Squibb, Celgene, Chiesi Italia SpA, Eisai, Eli Lilly, Fujirebio, Genzyme, Janssen, Merck, Neopharmed Gentili, Neuraxpharm, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda; for participation in advisory boards for Alexion, Biogen, Bristol-Myers Squibb, Eli Lilly, GE Healthcare Ltd., Merck, Neuraxpharm, Novartis, Roche, Sandoz, Sanofi, and Takeda; for scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. L. Moiola received honoraria from Merck, Celgene, Biogen, Sanofi, Novartis, Roche, Alexion, Neuraxpharm, and Amgen. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* February 19, 2026. Accepted in final form July 2, 2026. Submitted and externally peer reviewed. The handling editor was Deputy Editor Anne-Katrin Pröbstel, MD.

Appendix Coinvestigators

Name	Location	Role(s)	Contribution(s)
Francesca Napoli	Multiple Sclerosis Clinical and Research Unit, Tor Vergata University, Rome	PhD Student in Neuroscience	Data acquisition
Maria Triassi	Department of Public Health University Federico II, Naples	Full Professor of Public Health and Hygiene	Data acquisition
Elena Colombo	IRCCS Fondazione Mondino, Pavia	MS Center Director	Data acquisition
Daniela Cargnelutti	Azienda Sanitaria Universitaria Friuli Centrale	MS Center Director	Data acquisition
Vanessa Ziccone	P.O. Muscatello, Augusta	Neurologist	Data acquisition
Emanuela Laura Susani	ASST Grande Ospedale Matropolitano Niguarda, Milan	Neurologist	Data acquisition
Laura Ghezzi	Ospedale Maggiore Policlinico, Milan	Neurologist	Data acquisition
Maria Teresa Infante	Sanremo Hospital	Neurologist	Data acquisition

Continued

Appendix *(continued)*

Name	Location	Role(s)	Contribution(s)
Isabella Righini	UO Neurologia, University of Pisa	Neurologist	Data acquisition
Marco Vercellino	Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino	Neurologist	Data acquisition
Carmine Esilio	Azienda Ospedaliera Universitaria Luigi Vanvitelli, Naples	Neurology Resident	Data acquisition
Marco Zoccarato	Azienda Ospedaliera di Padova	Neurologist	Data acquisition
Sebastiano Crisafulli	Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan	Neurologist	Data acquisition
Pietro Annovazzi	Centro Sclerosi Multipla Ospedale di Gallarate (VA) - ASST Valle Olona	MS Center Director	Data acquisition
Eleonora Cocco	Binaghi Hospital, ASL Cagliari	Full Professor of Neurology, MS Center Director	Data acquisition
Giacomo Lus	AOU Luigi Vanvitelli, Naples	MS Center Director	Data acquisition
Matilde Inglese	University of Genoa	Full Professor of Neurology, MS Center Director	Data acquisition
Emilio Portaccio	Azienda ospedaliera Universitaria Careggi, Florence	Associate Professor of Neurology, Neurologist	Data acquisition
Vincenzo Brescia Morra	Department of Public Health University Federico II Naples	Professor of Neurology, MS Center Director	Data acquisition
Francesco Patti	Department "GF Ingrassia", section of Neurosciences, University of Catania	Full professor of Neurology, MS Center Director	Data acquisition
Paola Perini	Azienda Ospedaliera di Padova	MS Center Director	Data acquisition
Maria Assunta Rocca	IRCCS Ospedale San Raffaele, Milan; Vita-Salute San Raffaele University, Milan	Associate Professor of Neurology, Neurologist	Data acquisition

References

1. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. *N Engl J Med*. 1998;339(5):285-291. doi:10.1056/NEJM199807303390501
2. Hughes SE, Spelman T, Gray OM, et al.; MSBase Study Group. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mult Scler*. 2014;20(6):739-746. doi:10.1177/1352458513507816
3. Juto A, Fink K, Al Nimer F, Piehl F. Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity. *Mult Scler Relat Disord*. 2020;37:101468. doi:10.1016/j.msard.2019.101468
4. European Medicinals Agency. *European Summary of Product Carachteristics (SmPC) for Ocrevus [Internet]*. EMA; Accessed April 29, 2026. ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf
5. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol*. 1996;36(5):248-255. doi:10.1111/j.1600-0897.1996.tb00172.x
6. Krajnc N, Bsteh G, Berger T, Mares J, Hartung HP. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. *Neurotherapeutics*. 2022;19(3):753-773. doi:10.1007/s13311-022-01224-9
7. Gitman V, Stavropoulos A, Saenz V, Pasquarelli N, Zecevic D, Devonshire V. Pregnancy outcomes of women with multiple sclerosis treated with ocrelizumab in Canada: a descriptive analysis of real-world data. *Mult Scler Relat Disord*. 2022;62:103792. doi:10.1016/j.msard.2022.103792
8. Kümpfel T, Thiel S, Meinl I, et al. Anti-CD20 therapies and pregnancy in neuroimmunologic disorders: a cohort study from Germany. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(1):e913. doi:10.1212/NXI.0000000000000913
9. Vukusic S, Bove R, Dobson R, et al. Pregnancy and infant outcomes in women with multiple sclerosis treated with ocrelizumab. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(1):e200349. doi:10.1212/NXI.0000000000200349
10. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2
11. European Medicinals Agency. European Summary of Product Characteristics (SmPC) for Kesimpta (Ofatumumab) [Internet]. EMA; Accessed January 19, 2025. ema.europa.eu/en/medicines/human/EPAR/kesimpta
12. Mabthera. *Summary of Characteristics of Product*. Roche; 2023.
13. Barfield WD, Committee On Fetus And Newborn. Standard terminology for fetal, infant, and perinatal deaths. *Pediatrics*. 2016;137(5):e20160551. doi:10.1542/peds.2016-0551
14. Quenby S, Gallos ID, Dhillon-Smith RK, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397(10285):1658-1667. doi:10.1016/S0140-6736(21)00682-6
15. Kurtzke JF. Historical and clinical perspectives of the expanded disability status Scale. *Neuroepidemiology*. 2008;31(1):1-9. doi:10.1159/000136645
16. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646. doi:10.1155/2012/985646
17. Canibaño B, Ali M, Mesraoua B, et al. Severe rebound disease activity after fingolimod withdrawal in a pregnant woman with multiple sclerosis managed with rituximab: a case study. *Case Rep Women's Health*. 2020;25:e00162. doi:10.1016/j.crwh.2019.e00162
18. Hollen C, Rice J, Park M, Yadav V. Rituximab for treatment of refractory multiple sclerosis relapses during pregnancy. *Mult Scler*. 2021;27(10):1620-1623. doi:10.1177/1352458521998937
19. Smith JB, Hellwig K, Fink K, et al. And pregnancy. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(4):e734. doi:10.1212/NXI.0000000000000734
20. Bove R, Amato MP, Dobson R, et al. Pregnancy outcomes in patients with MS following exposure to ofatumumab: updated results from the novartis safety database (P9-3.014). *Neurology*. 2023;100(17_supplement_2):2985. doi:10.1212/WNL.0000000000202940
21. Bove Ri, Stoll S, Dobson R, et al. Pregnancy and infant outcomes in women with relapsing multiple sclerosis following exposure to ofatumumab: update from the Prim Study. *Poster LBA14 originally presented in Phoenix, AZ, USA*. Consortium of Multiple Sclerosis Centers (CMSC); May 28-31, 2025.
22. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. *Nat Rev Immunol*. 2017;17(8):469-482. doi:10.1038/nri.2017.64
23. Markovic I, Bosnjakovic P, Milenkovic Z. Occipital encephalocele: cause, incidence, neuroimaging and surgical management. *Curr Pediatr Rev*. 2020;16(3):200-205. doi:10.2174/1573396315666191018161535
24. Ezzahi M, Bijbij A, Akammar A, et al. Incidental finding of undiagnosed aortic coarctation in an elderly patient with a rare association with thymic carcinoma: a case report with review of the literature. *Radiol Case Rep*. 2023;18(9):3317-3322. doi:10.1016/j.radcr.2023.07.003
25. Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Scand J Immunol*. 2017;85(1):3-12. doi:10.1111/sji.12499
26. Mancinelli CR, Rossi ND, Capra R. Ocrelizumab for the treatment of multiple sclerosis: safety, efficacy, and pharmacology. *Ther Clin Risk Manag*. 2021;17:765-776. doi:10.2147/TCRM.S282390
27. Sacta MA, Jacobs K, Sun D, Lee J. Ocrelizumab-induced B-cell depletion in a newborn. *Pediatrics*. 2025;156(3):e2025070891. doi:10.1542/peds.2025-070891