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Pregnancy and Infant Outcomes in Women With Multiple Sclerosis Treated With Ocrelizumab

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Abstract

Background and Objectives

Ocrelizumab labeling advises contraception for women during treatment and for 6–12 months thereafter. Because pregnancies may occur during this time, it is critical to understand pregnancy and infant outcomes in women with multiple sclerosis (MS) after ocrelizumab exposure.

Methods

Pregnancy cases reported to Roche global pharmacovigilance until 12 July 2023 were analyzed. In utero exposure was defined if the last ocrelizumab infusion occurred in the 3 months before the last menstrual period or during pregnancy. Breastfeeding exposure was defined if at least one infusion occurred while breastfeeding. Fetal death was termed spontaneous abortion (SA) if < 22 complete gestational weeks (GWs) and stillbirth if later. Live births (LBs) were preterm if < 37 complete GWs. Major congenital anomalies (MCAs), infant outcomes, and maternal complications were also analyzed.

Results

In total, 3,244 pregnancies were reported in women with MS receiving ocrelizumab. The median maternal age was 32 years (Q1-Q3: 29–35 years), and most women had relapsing MS (65.6%). Of 2,444 prospectively reported pregnancies, 855 were exposed to ocrelizumab in utero (512 with a known outcome), 574 were nonexposed, and the remaining 1,015 had unknown timing of exposure. Most (83.6%; 956/1,144) of the pregnancies with a known outcome resulted in LBs (exposed, 84.2%; nonexposed, 88.3%). The exposed and nonexposed groups had similar proportions of other important pregnancy outcomes (preterm births, 9.5% vs 8.7%; SA, 7.4% vs 9.1%). Elective abortions were more frequent in the exposed group (7.4%, vs 1.7% in the nonexposed group). The proportion of LBs with MCAs was similar between the exposed and nonexposed groups (2.1% vs 1.9%) and within epidemiologic background rates. In the exposed group, one stillbirth and one neonatal death were prospectively reported.

Discussion

In this analysis of a large pregnancy outcome dataset for an anti-CD20 in MS, in utero exposure to ocrelizumab was not associated with an increased risk of adverse pregnancy or infant outcomes. These data will enable neurologists and women with MS to make more informed decisions around family planning, balancing safety risks to the fetus/infant against the importance of disease control in the mother.

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Glossary

AE = adverse event; **APGAR** = appearance, pulse, grimace, activity, and respiration; **DMT** = disease-modifying therapy; **EUROCAT** = European Surveillance of Congenital Anomalies; **LMP** = last menstrual period; **MCA** = major congenital anomaly; **MS** = multiple sclerosis; **PPMS** = primary progressive multiple sclerosis; **PT** = preferred term; **PV** = pharmacovigilance; **RMS** = relapsing multiple sclerosis.

Introduction

A large proportion of persons with multiple sclerosis (MS) are women of childbearing age.[1] Family planning is, therefore, a critical aspect in the management of women with MS, and the benefits of using disease-modifying therapies (DMTs) in pregnant and breastfeeding women must be balanced against the potential for adverse pregnancy outcomes or harm to infants.[2]

To avoid poor long-term disease outcomes, maintaining control of MS disease activity through treatment should be prioritized, particularly during and after pregnancy, because discontinuing certain DMTs before or during pregnancy can increase relapse risk[3-6] and relapse risk peaks immediately after pregnancy.[4,7] While the introduction of newer DMTs has increased options, product labeling generally mandates DMT discontinuation before pregnancy and recommends against use while breastfeeding. Such label restrictions potentially limit access to effective medications[2,8] and are also variably interpreted in clinical practice.[2,9,10]

For ocrelizumab, an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS, labeling recommends discontinuation 6 months before conception in the United States[11] and 12 months before in the EU.[12] In addition, discontinuation of breastfeeding is recommended during treatment in the EU[12] while a "benefit-risk" approach is advised in the United States.[11] Considering its prolonged immunomodulatory activity and the low likelihood of placental transfer in the first trimester,[13,14] ocrelizumab might be an appropriate option for women planning pregnancy because fetal exposure is unlikely even if the last infusion is scheduled relatively late, e.g., 3 months before the last menstrual period (LMP). This is currently not permitted by product labeling, although recommended by some national MS societies and MS experts.[2,8,10] Shortening the treatment-free window might allow greater disease control without increasing risks to the pregnancy and the fetus. Recent real-world data suggest that preconception ocrelizumab use controls disease activity throughout the pregnancy and postpartum period.[15-18]

Published data on ocrelizumab in pregnancy and lactation from case series and single-center studies (n = 1 to 39 cases) have not identified an increased risk of adverse outcomes.[18-22] However, to better characterize such risks, especially those such as congenital anomalies that are relatively rare, more data are needed. In this study, we present an integrated analysis of cumulative data in the Roche global pharmacovigilance (PV) database on pregnancy and maternal outcomes in women with MS treated with ocrelizumab and 1-year outcomes in infants potentially exposed to ocrelizumab in utero or through breastfeeding.

Methods

Participants and Data Collection

Pregnancy cases were extracted between November 5, 2008 (database inception), and July 12, 2023, from the Roche global PV database, which collects safety information from interventional and noninterventional clinical studies, spontaneous reports, noninterventional programs (including the OCREVUS Pregnancy Registry and market access programs), and published literature. Cases (women with MS who received at least one ocrelizumab infusion before the LMP and/or during pregnancy, including where the exact timing of the last ocrelizumab dose was unknown or unavailable) were validated by structured medical review and duplicates removed based on patient initials and date of birth, reported events, and pregnancy and birth outcomes. Given the known bias toward retrospective reporting,[23] we have focused our interpretations on prospectively reported cases.

In Utero Exposure

For comparison, cases were classified as having in utero exposure (hereafter referred to as "exposed") when the last ocrelizumab infusion occurred at any time from 3 months before the LMP until the end of the pregnancy (outcomes were also compared between cases exposed before pregnancy, i.e., in the 3 months before the LMP, and those exposed during pregnancy, i.e., in the first, second, or third trimester). Cases where the last infusion occurred >3 months before the LMP were classified as having no in utero exposure (referred to as "nonexposed"). Where exposure timing could not be determined or was missing, cases were defined as having "unknown exposure." The scientific rationale underlying this exposure classification is based on the average terminal half-life of ocrelizumab of 26 days, which implies that full elimination from the body is expected by approximately 4.5 months and the fact that no relevant placental transfer of IgG1 antibodies occurs before 12 weeks of gestation.[13,14]

Pregnancy Outcomes

Pregnancies were categorized as prospective if first reported while ongoing and the final outcomes of interest

were not yet known at the time of notification and, conversely, as retrospective if outcomes were known at initial notification.

Pregnancy outcomes were ectopic pregnancy (extrauterine pregnancy, most often in the fallopian tube); intrauterine/fetal death (a category including spontaneous abortions, i.e., noninduced embryonic or fetal death at or before 22 complete weeks of gestation, or stillbirth, i.e., death of a fetus after 22 weeks of gestation and before birth; note that, however, these outcomes were individually reported); elective abortion (any induced or voluntary fetal loss during pregnancy); live birth; and preterm live birth (live birth before 37 complete weeks of gestation). Pregnancy status definitions followed those used by Roche Safety for processing of cases for regulatory reporting; pregnancies were classified as "ongoing" (pregnancy outcome reported as ongoing at the time of the report/notification, as of the data cutoff date) and "unknown/lost to follow-up" (pregnancy outcome reported as "unknown" or "lost to follow-up/no follow-up possible" or "no response received after multiple follow-up attempts", as of the data cutoff date). Pregnancy outcomes are presented as a proportion relative to known pregnancy outcomes, except where noted otherwise, e.g., for the gestational age category at birth, where the denominator is the number of live births, and for MCAs, where the denominator is the number of live births or of live births, stillbirths, and intrauterine/fetal deaths of unknown gestational age.

Demographics, Breastfeeding Exposure, Major Congenital Anomalies, Infant Outcomes, and Maternal Complications

MCAs were classified according to definitions in the European Surveillance of Congenital Anomalies (EUROCAT) Guide Version 1.5,[24] and maternal complications were identified by reviewing individual case narratives against a predefined list of preferred terms (PTs; eTable 1). Complete methods related to demographics and baseline characteristics, breastfeeding exposure, major congenital anomalies (MCAs), infant outcomes and 1-year follow-up, and maternal complications are available in the eMethods.

Standard Protocol Approvals, Registrations, and Patient Consents

Clinical protocols, collection of data in clinical studies, and follow-up of postmarketing cases met the requirements of International Conference on Harmonisation guidelines, Good Pharmacovigilance Practices guidelines,[25] FDA guidance,[26] and the principles of the Declaration of Helsinki. All AEs analyzed were spontaneously reported in the postmarketing setting and solicited as per the protocol for clinical trial cases.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Over a period of approximately 15 years, 3,244 pregnancies were reported in women with MS receiving ocrelizumab, with 2,977 (91.8%) reported over a period of 4 years (March 2019 to July 2023) (Figure 1). In most cases, pregnancies were reported prospectively (75.3%) rather than retrospectively (793/3,244; 24.4%). Outcomes of pregnancies were known for over half of the cases (58.0%) and unknown/not reported/lost to follow-up for 33.8% while the remaining (8.2%) were ongoing as of July 2023. Cases originated from noninterventional studies/programs (77.3%), spontaneous reports (13.7%), clinical studies (6.5%), and literature reports (2.5%). The largest proportion of pregnancies was reported from the United States (55.1%), followed by Germany (13.5%) and Canada (12.3%); the remainder (19.1%) were reported from various other countries (listed in Table 1 and the table footnotes; also in eFigure 1).

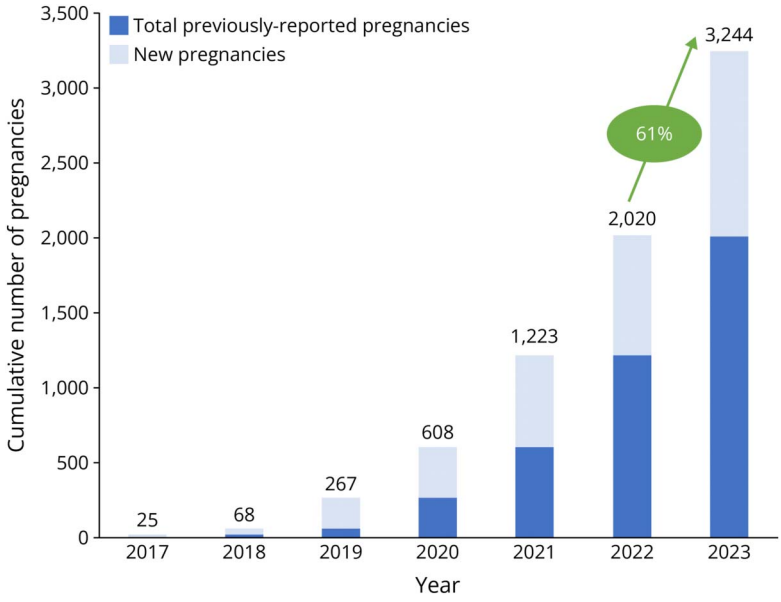
Among 2,671 pregnancies with age reported, the median maternal age was 32 years (Q1–Q3: 29–35 years); 68.9% of pregnancies (n = 1841/2,671) were reported in women younger than 35 years. Most women had relapsing MS (65.6%), and small proportions had PPMS (2.8%) or SPMS (0.2%); for almost a third of patients (31.4%), the type of MS was unspecified or nondeterminable (Table 1).

For pregnancies where exposure timing could be determined (n = 1830/3,244, 56.4%), most cases were classified as having in utero exposure ("exposed"; n = 1,071), of which 855 were reported prospectively. In the exposed group (n = 1,071), the last ocrelizumab infusion was mostly recorded in the 3 months before the LMP (65.7%, n = 704 [prospective, n = 572]), followed by in the first trimester of pregnancy (30.5%; n = 327 [prospective, n = 258]) (Figure 2). Exposure to ocrelizumab in the second and third trimesters of pregnancy was infrequent (n = 27 [2.5%] and n = 13 [1.2%], respectively [prospective, n = 17 and 8, respectively]). No notable differences in demographics, disease characteristics, source, and country of reporting were observed between exposed and nonexposed groups (Table 1).

Pregnancy Outcomes Prospective

Most pregnancies (Table 2) resulted in live births (83.6% [n = 956]), with similar proportions among exposed (84.2%) and nonexposed (88.3%) groups (note that the proportion of live births was 76.6% in the group with unknown exposure timing; outcomes for this group are not discussed in detail). Gestational age could only be determined in approximately two-thirds of pregnancies with live births; among these (n = 668), 87.7% (n = 586/668) of babies were reported as born full-term and 12.3% (n = 82/668) as preterm. The proportion of full-term and preterm pregnancies was similar for exposed (65.7% and 9.5%) and nonexposed (70.9% and 8.7%) groups. The median (Q1, Q3) gestational age was 39 (38, 40) weeks for live births and 10 (7, 12) weeks for terminated

Figure 1 Pregnancies Reported in Women With Multiple Sclerosis Exposed to Ocrelizumab, by Year



Columns represent the cumulative number of pregnancies in women with MS exposed to ocrelizumab in each year of analysis (numbers in bold above each column). For each year, the cumulative previously reported pregnancies are shaded dark blue and those newly reported in that year are shaded light blue. The analysis period for each year extended from the day after the previous clinical cutoff date (CCOD) up to that year's CCOD, as follows: *2017* (no previous CCOD), till 31 January 2017; 2018, till 31 March 2018; 2019, till 31 March 2019; 2020, till 27 March 2020; 2021, till 31 March 2021; 2022, till 31 March 2022; 2023, till 12 July 2023. Note that of the cumulative total of 3,244, 91% (3,244-267 = 2,977) of cases were reported after the 2019 CCOD, i.e., after 31 March 2019.

pregnancies; values were similar across exposure groups (data not shown).

A higher proportion of elective abortions were seen in the exposed group (7.4% [n = 38]) compared with the nonexposed group (1.7% [n = 6]) (Table 2). Notably, in our periodic analyses of the Roche global PV database, the proportion of elective abortions in the exposed group has decreased over time (cumulative rates: 43% in 2017, 22% in 2018, 14% in 2019, 23% in 2020, 13% in 2021,[27] and 10% in 2022[28]). The proportion of pregnancies resulting in spontaneous abortion was similar between the exposed (7.4%) and nonexposed (9.1%) groups (note that a higher proportion (16.0% [n = 45]) was reported in the group with unknown exposure). For pregnancies where maternal age was known (n = 1,051), the percentage of spontaneous abortions increased with increasing age: 8.9% (64/716) in women younger than 35 years, 10.4% (28/268) in women aged 35–40 years, and 23.9% (16/67) in women aged 40 years and older (data not shown). Ectopic pregnancies were infrequently reported (0.8% [n = 4] for exposed and 0.9% [n = 3] for nonexposed). One stillbirth (0.2%) was reported in the exposed group (last ocrelizumab infusion 3 months before the LMP) and none in the nonexposed group (Table 2). For this stillbirth, noninvasive prenatal testing in the first trimester estimated a 9/10 chance of trisomy 21 and the mother had potential confounding risk factors, including a history of miscarriage and premature birth and of cannabis use (eTable 2).

Retrospective

Five additional stillbirths (4 in the exposed group and 1 in the nonexposed group) and 3 intrauterine/fetal deaths of unknown or nondeterminable gestational age (1 in the nonexposed group, 2 in the unknown exposure group) were reported. These cases presented with potentially confounding comorbidities and/or concomitant medications (additional details in eTable 2).

Altogether, among prospective pregnancies with known outcomes and considered exposed to ocrelizumab (n = 512), no differences were observed in pregnancy outcomes between the group with infusions in the 3 months before LMP and the group with infusions during pregnancy, except for spontaneous abortions, which were more common in the former group (9.3%, vs 3.6% in the group with infusions during pregnancy). Additional details are given in Table 3.

Major Congenital Anomalies

Prospective

Among the live births, stillbirths, and intrauterine/fetal deaths of unknown gestational age (n = 957), 17 cases with MCAs (1.8%) were reported (Table 2), 16 in live births and 1 in a stillbirth; one case had 2 MCAs. The relative risk of EUROCAT-adjudicated congenital anomalies in this group, compared with the general population (EUROCAT data[29]), was 0.67 (95% CI 0.42–1.07) for all pregnancies, 0.87 (95% CI 0.47–1.61) for exposed pregnancies and 0.73 (95% CI 0.33–1.61) for nonexposed pregnancies (more details in eTable 3). Congenital heart defects and urinary defects (each 27.8% [n = 5]) were the most common EUROCAT 1.5 anomaly classes (Figure 3). Fifteen cases had potentially confounding risk factors, including concomitant medications with teratogenic potential or relevant medical or family history (listing of MCAs in eTable 4). The proportion of live births with at least one MCA was similar between the exposed and nonexposed groups (2.1% [n = 9] vs 1.9% [n = 6]; Table 2).

Table 1 Overview of Case Distribution, Demographics, and Baseline Conditions (Prospective Cases and All Cases)

Category	Prospective cases				All cases[a]			
	Nonexposed (N = 574)	Exposed (N = 855)	Unknown exposure (N = 1,015)	Total (N = 2,444)	Nonexposed (N = 759)	Exposed (N = 1,071)	Unknown exposure (N = 1,414)	Total (N = 3,244)
Case distribution								
Outcome status, n (%)								
Known outcome	350 (61.0)	512 (59.9)	282 (27.8)	1,144 (46.8)	527 (69.4)	715 (66.8)	638 (45.1)	1880 (58.0)
Unknown outcome, not reported, or lost to follow-up	171 (29.8)	274 (32.0)	594 (58.5)	1,039 (42.5)	176 (23.2)	286 (26.7)	636 (45.0)	1,098 (33.8)
Pregnancy ongoing[b]	53 (9.2)	69 (8.1)	139 (13.7)	261 (10.7)	56 (7.4)	70 (6.5)	140 (9.9)	266 (8.2)
Source, n (%)								
Noninterventional study/program	462 (80.5)	656 (76.7)	840 (82.8)	1958 (80.1)	603 (79.4)	784 (73.2)	1,121 (79.3)	2,508 (77.3)
Spontaneous report	43 (7.5)	120 (14.0)	151 (14.9)	314 (12.8)	61 (8.0)	161 (15.0)	224 (15.8)	446 (13.7)
Clinical study	69 (12.0)	78 (9.1)	17 (1.7)	164 (6.7)	86 (11.3)	96 (9.0)	28 (2.0)	210 (6.5)
Literature (noninterventional study/program and spontaneous)	0 (0.0)	1 (0.1)	7 (0.7)	8 (0.3)	9 (1.2)	30 (2.8)	41 (2.9)	80 (2.5)
Country, n (%)								
United States	286 (49.8)	445 (52.0)	603 (59.4)	1,334 (54.6)	389 (51.3)	558 (52.1)	840 (59.4)	1787 (55.1)
Germany	118 (20.6)	180 (21.1)	70 (6.9)	368 (15.1)	138 (18.2)	193 (18.0)	108 (7.6)	439 (13.5)
Canada	46 (8.0)	75 (8.8)	195 (19.2)	316 (12.9)	65 (8.6)	85 (7.9)	249 (17.6)	399 (12.3)
Australia	17 (3.0)	13 (1.5)	18 (1.8)	48 (2.0)	15 (2.0)	25 (2.3)	29 (2.1)	69 (2.1)
Italy	9 (1.6)	13 (1.5)	17 (1.7)	39 (1.6)	18 (2.4)	16 (1.5)	30 (2.1)	64 (2.0)
Israel	13 (2.3)	10 (1.2)	13 (1.3)	36 (1.5)	19 (2.5)	12 (1.1)	18 (1.3)	49 (1.5)
United Kingdom	4 (0.7)	10 (1.2)	17 (1.7)	31 (1.3)	6 (0.8)	12 (1.1)	27 (1.9)	45 (1.4)
France	10 (1.7)	11 (1.3)	6 (0.6)	27 (1.1)	11 (1.4)	15 (1.4)	10 (0.7)	36 (1.1)
Egypt	3 (0.5)	6 (0.7)	11 (1.1)	20 (0.8)	4 (0.5)	9 (0.8)	15 (1.1)	28 (0.9)
Switzerland	6 (1.0)	7 (0.8)	5 (0.5)	18 (0.7)	10 (1.3)	6 (0.6)	11 (0.8)	27 (0.8)
Other[c]	62 (10.8)	85 (9.9)	60 (5.9)	207 (8.5)	84 (11.1)	140 (13.1)	77 (5.4)	301 (9.3)
Demographics and disease characteristics								
Maternal age								
Reported, n (%)	529 (92.2)	766 (89.6)	760 (74.9)	2055 (84.1)	690 (90.9)	957 (89.4)	1,024 (72.4)	2,671 (82.3)
Median (Q1; Q3), y	32 (29; 35)	32 (29; 35)	32 (29; 35)	32 (29; 35)	32 (29; 35)	32 (29; 35)	32 (29; 35)	32 (29; 35)
<35 y, n (%)	369 (64.3)	520 (60.8)	549 (54.1)	1,438 (58.8)	480 (63.2)	647 (60.4)	714 (50.5)	1841 (56.8)
35–40 y, n (%)	146 (25.4)	217 (25.4)	174 (17.1)	537 (22.0)	188 (24.8)	267 (24.9)	256 (18.1)	711 (21.9)
>40 y, n (%)	14 (2.4)	29 (3.4)	37 (3.6)	80 (3.3)	22 (2.9)	43 (4.0)	54 (3.8)	119 (3.7)
BMI								
Reported, n (%)	297 (51.7)	408 (47.7)	196 (19.3)	901 (36.9)	392 (51.6)	498 (46.5)	312 (22.1)	1,202 (37.1)
Median (Q1; Q3), kg/m^2	25 (22; 29)	26 (22; 31)	27 (23; 32)	26 (22; 31)	25 (22; 29)	26 (23; 31)	27 (23; 33)	26 (23; 31)
MS type								
Relapsing forms of MS, including RRMS	406 (70.7)	559 (65.4)	677 (66.7)	1,642 (67.2)	533 (70.2)	680 (63.5)	914 (64.6)	2,127 (65.6)

Continued

Table 1 Overview of Case Distribution, Demographics, and Baseline Conditions (Prospective Cases and All Cases) *(continued)*

Category	Prospective cases				All cases[a]			
	Nonexposed (N = 574)	Exposed (N = 855)	Unknown exposure (N = 1,015)	Total (N = 2,444)	Nonexposed (N = 759)	Exposed (N = 1,071)	Unknown exposure (N = 1,414)	Total (N = 3,244)
MS unspecified or nondeterminable	158 (27.5)	270 (31.6)	299 (29.5)	727 (29.7)	210 (27.7)	358 (33.4)	451 (31.9)	1,019 (31.4)
PPMS	9 (1.6)	22 (2.6)	37 (3.6)	68 (2.8)	14 (1.8)	29 (2.7)	47 (3.3)	90 (2.8)
SPMS	1 (0.2)	4 (0.5)	2 (0.2)	7 (0.3)	2 (0.3)	4 (0.4)	2 (0.1)	8 (0.2)

Abbreviations: MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
[a] 'All cases' include 7 cases for which the reporting type was unknown; i.e., it was not known whether they were prospectively or retrospectively reported.
[b] 'All cases' include 5 additional cases with the status 'pregnancy ongoing' than 'Prospective cases'. These 5 cases, classified as 'retrospectively reported,' had their status updated: one had a known outcome (live birth), and the other 4 were reclassified as prospectively reported with the status 'pregnancy ongoing.' Because these updates were made after the cutoff date for the analyses reported here, the table does not reflect the updated information.
[c] Includes Albania, Algeria, Argentina, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Estonia, Finland, Greece, Hungary, Ireland, Jordan, Korea, Republic of Kuwait, Latvia, Lebanon, Mexico, Morocco, Netherlands, New Zealand, Northern Ireland, Norway, Pakistan, Peru, Poland, Portugal, Puerto Rico, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia, Slovakia, South Africa, Spain, Sweden, Turkey, Ukraine, and United Arab Emirates.

Retrospective

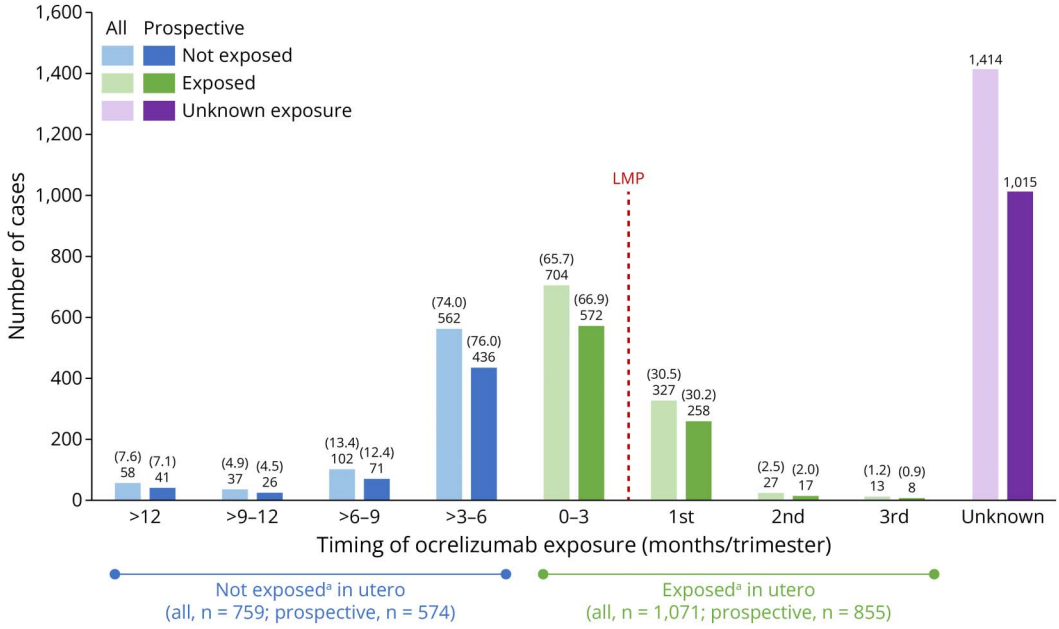
Five additional pregnancies (4 live births and 1 intrauterine/fetal death) with MCA were reported; 3 were in the exposed group and 2 had unknown exposure (eTable 4).

Infant Outcomes at Birth

Prospective

Birth outcomes were available for a total of 671 infants (male 50.7%, female 40.8%, not reported 8.5%). The median (Q1, Q3) weight (reported for n = 397 infants) was 3.4 (3.0, 3.9) kg; the median (Q1, Q3) length (n = 327) was 51 (49; 54) cm; and the median (Q1, Q3) head circumference (n = 218) was 35 (34; 36) cm. Overall, the median APGAR scores at 1, 5, and 10 minutes were normal. All infant outcomes were comparable between ocrelizumab-exposed and nonexposed infants (Table 4 provides more details). There were substantial missing data for some parameters; as discussed later, this is a known limitation with spontaneous reports (in addition, some parameters such as 10-minute APGAR scores are not routinely collected in all countries).

Figure 2 Multiple Sclerosis Pregnancies by In Utero Exposure: All Cases and Prospective Cases



IgG1 = immunoglobulin G1; LMP = last menstrual period; OCR, ocrelizumab; t½, half-life. [a]Determined according to timing of the last OCR dose in relation to the date of LMP (months); exposure classification is based on OCR t½ = 26 days (full elimination from the body is expected by approximately 4.5 months) and assuming that no relevant placental transfer of IgG1 antibodies occurs before 12 weeks of gestation. Percentages displayed in parentheses above the bars are proportions of the total exposed or nonexposed cases (for all cases or prospective cases, as applicable; 'n's are shown at the bottom of the figure).

Table 2 Pregnancy Outcomes (Prospective and All Cases) by Exposure Category

Outcome	Prospective cases				All cases				Epidemiologic rates (%)	
	Nonexposed (N = 574)	Exposed (N = 855)	Unknown exposure (N = 1,015)	Total (N = 2,444)	Nonexposed (N = 759)	Exposed (N = 1,071)	Unknown exposure (N = 1,414)	Total (N = 3,244)	MS population	General population
Known outcomes	350	512	282	1,144	527	715	638	1880	—	—
Live births, n (%)[a]	309 (88.3)	431 (84.2)	216 (76.6)	956 (83.6)	445 (84.4)	589 (82.4)	447 (70.1)	1,481 (78.8)	70.2–77.2[c]	70.2[c]
Full term (≥37 wk), n (%)[b]	219 (70.9)	283 (65.7)	84 (38.9)	586 (61.3)	299 (67.2)	360 (61.1)	125 (28.0)	784 (52.9)	—	—
Preterm (<37 wk)[b]	27 (8.7)	41 (9.5)	14 (6.5)	82 (8.6)	33 (7.4)	54 (9.2)	25 (5.6)	112 (7.6)	7.2–15.4[c,d,f]	6.5–10.4[c,d,f]
Unknown gestational age[b]	63 (20.4)	107 (24.8)	118 (54.6)	288 (30.1)	113 (25.4)	175 (29.7)	297 (66.4)	585 (39.5)	—	—
Ectopic pregnancy, n (%)[a]	3 (0.9)	4 (0.8)	7 (2.5)	14 (1.2)	5 (0.9)	4 (0.6)	13 (2.0)	22 (1.2)	0.6-1.3[c,d]	1.1–2.0[c,d]
Elective abortion, n (%)[a,e]	6 (1.7)	38 (7.4)	14 (5.0)	58 (5.1)	15 (2.8)	50 (7.0)	32 (5.0)	97 (5.2)	10.7–18.1[c]	18.2[c]
Intrauterine/fetal death, n (%)										
Spontaneous abortion (≤22 wk)[a]	32 (9.1)	38 (7.4)	45 (16.0)	115 (10.1)	60 (11.4)	67 (9.4)	144 (22.6)	271 (14.4)	10.5–11.6[c,d,f]	10.0–20.0[c,d]
Stillbirth (>22 wk)[a,f]	0	1 (0.2)	0	1 (<0.1)	1 (0.2)	5 (0.7)	0	6 (0.3)	0.3-0.6[c,g]	0.2-0.7[c,g]
Unknown or nondeterminable gestational age[a]	—	—	—	—	1 (0.2)	0	2 (0.3)	3 (0.2)	—	—
Live birth with at least one MCA, n (%)[h]	6 (1.9)	9 (2.1)	1 (0.5)	16 (1.7)	6 (1.3)	12 (2.0)	2 (0.4)	20 (1.4)	2.2–4.2[i]	2.0–4.4[j]
Full term with MCA, n	4 (1.3)	6 (1.4)	1 (0.5)	11 (1.2)	4 (0.9)	9 (1.5)	1 (0.2)	14 (1.0)	—	—
Preterm with MCA, n	2 (0.7)	3 (0.7)	0	5 (0.5)	2 (0.5)	3 (0.5)	0	5 (0.3)	—	—
Unknown GA with MCA, n	0	0	0	0	0	0	1 (0.2)	1 (0.1)	—	—
Live births/stillbirths/intrauterine or fetal deaths of unknown GA with MCA, n (%)[k]	6 (1.9)	10 (2.3)	1 (0.5)	17 (1.8)	6 (1.3)	13 (2.2)	3 (0.7)	22 (1.5)	—	—

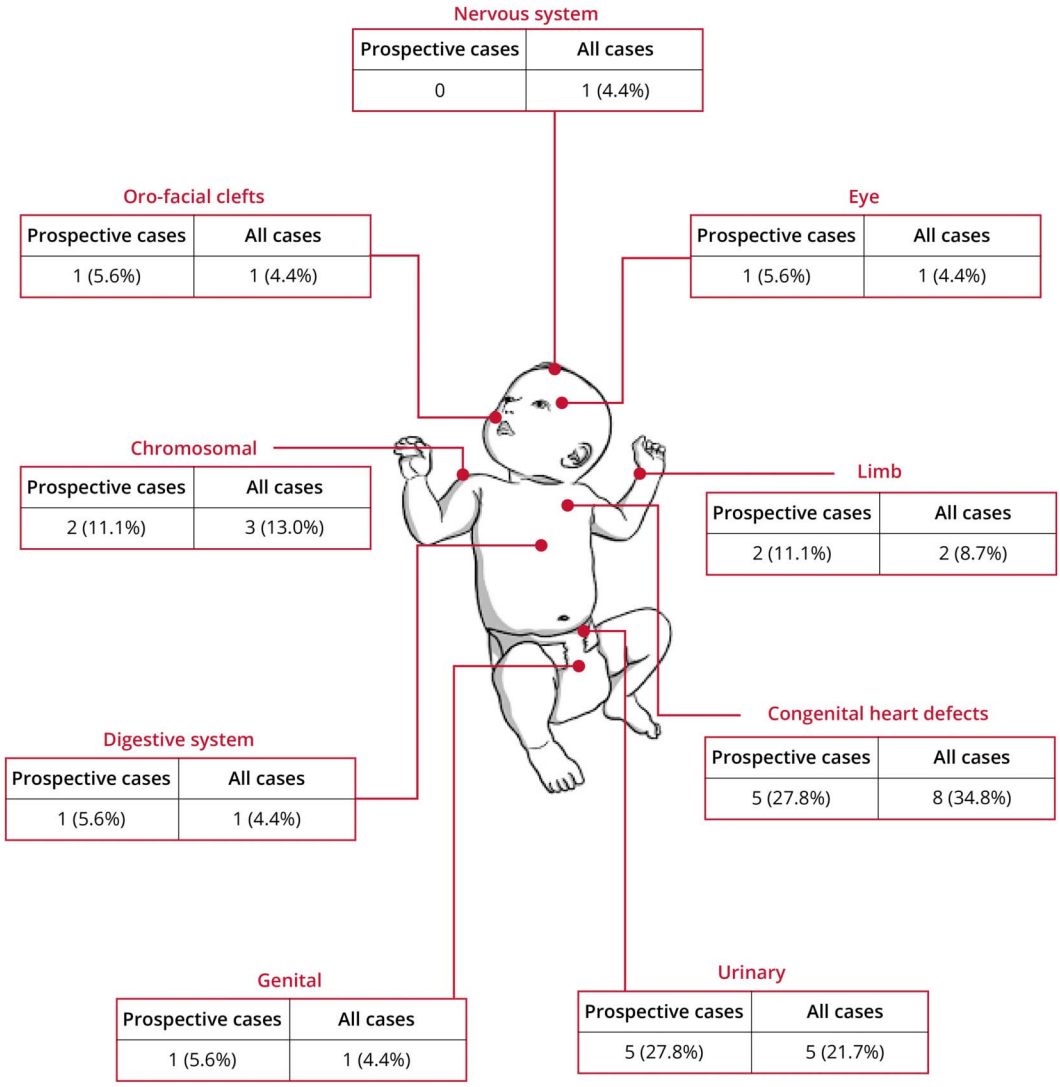
Abbreviations: GA = gestational age; LMP = last menstrual period; MCA = major congenital anomaly.
Note: exposure category based on timing of the last ocrelizumab dose relative to LMP. Cases were classified as having in utero exposure when the last ocrelizumab infusion was received at any time from 3 mo before the LMP until the end of the pregnancy.
[a] Percentages represent fractions of the total known outcomes of the respective exposure category (not exposed in utero, exposed in utero, unknown exposure, total).
[b] Percentages represent fractions of live births.
[c] Ref. 35.
[d] Ref. 36.
[e] Cumulative rates of elective abortions in women with MS considered to have in utero exposure to ocrelizumab, in each year for which data are available, are as follows: 43% in 2017, 22% in 2018, 14% in 2019, 23% in 2020, 13% in 2021, and 10% in 2022.
[f] Ref. 34.
[g] Ref. 33.
[h] Percentages represent fractions of total live births for each exposure category.
[i] Truven Health MarketScan Commercial Claims and Encounters Database; n = 1,439 with MS and 1,101,165 without MS; DMT information not collected[33]; meta-analysis of 10 studies; n ranged from 28 to 2016; DMTs were mainly IFN, glatiramer acetate, and natalizumab[34]; n = 1009 DMT-exposed MS pregnancies; n = 1,073 unexposed; DMTs were dimethyl fumarate and natalizumab[35]; meta-analysis of 44 studies; n ranged from 11 to 3,000 [total = 15,986]; DMTs were interferon, natalizumab, glatiramer acetate, fingolimod, dimethyl fumarate, cladribine, and teriflunomide.[36]
[j] Refs. 25, 33-37.
[k] Percentages represent fractions of the total stillbirths/deaths of unknown GA/live births (n = 957) for the respective exposure category.

Table 3 Pregnancy Outcomes in Prospectively Reported Cases According to the Timing of the Last Ocrelizumab Dose Relative to the Last Menstrual Period

	Nonexposed			Exposed			Unknown		Epidemiologic rates (%)	
Outcome, n (%)	>6 mo before (N = 138)	3–6 mo before (N = 436)	Total (N = 574)	0–3 mo before (N = 572)	During pregnancy (N = 283)	Total (N = 855)	Total (N = 1,015)	Total prospective cases (N = 2,444)	MS population	General population
Known outcomes	80	270	350	343	169	512	282	1,144		
Live births, n (%)[a]	73 (91.3)	236 (87.4)	309 (88.3)	283 (82.5)	148 (87.6)	431 (84.2)	216 (76.6)	956 (83.6)	70.2–77.2[e]	70.2[e]
Full term (≥37 wk)[b]	50 (68.5)	169 (71.6)	219 (70.9)	190 (67.1)	93 (62.8)	283 (65.7)	84 (38.9)	586 (61.3)		
Preterm (<37 wk)[b]	5 (6.8)	22 (9.3)	27 (8.7)	28 (9.9)	13 (8.8)	41 (9.5)	14 (6.5)	82 (8.6)	7.2–15.4[e,f,g,h]	6.5–10.4[e,f,h]
Unknown GA week[b]	18 (24.7)	45 (19.1)	63 (20.4)	65 (23.0)	42 (28.4)	107 (24.8)	118 (54.6)	288 (30.1)		
MCA[c]	0	6 (2.5)	6 (1.9)	6 (2.1)	3 (2.0)	9 (2.1)	1 (0.5)	16 (1.7)	2.2–4.2[i]	2.0–4.4[j]
Ectopic pregnancy, n (%)[a]	0	3 (1.1)	3 (0.9)	4 (1.2)	0	4 (0.8)	7 (2.5)	14 (1.2)	0.6–1.3[e,f]	1.1–2.0[e,f]
Elective abortion, n (%)[a]	0	6 (2.2)	6 (1.7)	23 (6.7)	15 (8.9)	38 (7.4)	14 (5.0)	58 (5.1)	10.7–18.1[e]	18.2[e]
Intrauterine/fetal death, n (%)										
Spontaneous abortion (≤22 wk)[a]	7 (8.8)	25 (9.3)	32 (9.1)	32 (9.3)	6 (3.6)	38 (7.4)	45 (16.0)	115 (10.1)	10.5–11.6 [e–g]	10.0–20.0[e,f]
Stillbirth (>22 wk)[a]	0	0	0	1 (0.3)	0	1 (0.2)	0	1 (<0.1)	0.3–0.6[e,h]	0.2–0.7[e,h]
Live births/stillbirths with MCA, n (%)[d]	0	6 (2.5)	6 (1.9)	7 (2.5)	3 (2.0)	10 (2.3)	1 (0.5)	17 (1.8)		

Abbreviations: GA = gestational age; MCA = major congenital anomaly.
[a] Percentages represent fractions of cases with a known outcome in each column.
[b] Percentages represent fractions of live births.
[c] Percentages represent fractions of live births in each column.
[d] Percentages represent the fraction of total births (stillbirths + live births) for each column.
[e] Ref. 35.
[f] Ref. 36.
[g] Ref. 34.
[h] Ref. 33.
[i] Refs. 33-36.
[j] Refs. 25,33,35-37.

Figure 3 Incidence of Major Congenital Anomalies by EUROCAT 1.5 Anomaly Class



The graphic represents the reported number of major congenital anomalies in each EUROCAT 1.5 anomaly class, for prospectively reported cases and for all cases. Percentages are proportions of the total number of anomalies reported in each class.

Infant Outcomes During the First Year of Life

Attempts to follow up pregnancies resulting in live births were made using guided questionnaires at birth, 3 months, 6 months, and 12 months of age. For 400 (21%) of the 1,880 infants with known pregnancy outcomes, some follow-up information for up to 1 year was available. Full details are available in eTable 5. Breastfeeding exposure was reported for 122 infants.

Infection status was reported (i.e., yes or no) for only 31.5% (126/400) of infants: infections were reported to occur in 43 of these (10.8%), and no clinically significant infections were reported in 83 (20.8%). When infants were categorized based on possible in utero exposure to ocrelizumab, infections were reported in 5.5% (5/91) of infants not exposed to ocrelizumab in utero and in 13.5% (23/170) of those with in utero exposure; infections were reported in 12.7% (14/110) of those with unknown exposure. The most frequently reported were "unspecified infection" (n = 9), respiratory syncytial virus infection (n = 7), COVID-19 (n = 7), urinary tract infection (n = 4), ear infection including otitis media (n = 4), and sepsis (n = 3).

B-cell levels were reported for only 62 (15.5%) of 400 infants and either not reported, unknown, or not determinable in 84.5% (338/400; eTable 5). Levels were defined as abnormal if reported as such or if actual B-cell levels were available and were below the defined reference range.[30] A total of 56 infants (14.0%) were reported as having 'normal' B-cell levels and 6 infants (1.5%) as having 'abnormal.' All infants with abnormal B-cell levels (n = 6) were reported as being exposed to ocrelizumab in utero (2 within 0–3 months before the LMP, 3 in the first trimester, and one in the second trimester). The timing of B-cell measurement in these infants was at birth (n =

Table 4 Infant Characteristics at Birth

	Prospective cases				All cases			
	Nonexposed (N = 232)	Exposed (N = 314)	Unknown exposure (N = 125)	Total (N = 671)	Nonexposed (N = 483)	Exposed (N = 668)	Unknown exposure (N = 476)	Total (N = 1,627)
Sex of child								
Male	119 (51.3)	173 (55.1)	48 (38.4)	340 (50.7)	168 (50.5)	216 (51.6)	75 (35.2)	459 (47.6)
Female	99 (42.7)	114 (36.3)	61 (48.8)	274 (40.8)	145 (43.5)	156 (37.2)	103 (48.4)	404 (41.9)
Not reported	14 (6.0)	27 (8.6)	16 (12.8)	57 (8.5)	20 (6.0)	47 (11.2)	35 (16.4)	102 (10.6)
Weight								
Reported, n (%)	152 (65.5)	196 (62.4)	49 (39.2)	397 (59.2)	204 (61.3)	237 (56.6)	77 (36.2)	518 (53.7)
Median (Q1; Q3), kg	3.3 (2.9; 3.7)	3.4 (3.0; 4.0)	3.4 (3.0; 3.9)	3.4 (3.0; 3.9)	3.3 (2.9; 3.7)	3.4 (3.0; 3.9)	3.4 (3.1; 3.8)	3.3 (3.0; 3.8)
Length								
Reported, n (%)	123 (53.0)	171 (54.5)	33 (26.4)	327 (48.7)	153 (45.9)	195 (46.5)	49 (23.0)	397 (41.1)
Median (Q1; Q3), cm	51 (49; 53)	51 (49; 54)	51 (50; 54)	51 (49; 54)	51 (49; 53)	51 (49; 54)	51 (49; 53)	51 (49; 53)
Head circumference								
Reported, n (%)	79 (34.1)	119 (37.9)	20 (16.0)	218 (32.5)	92 (27.6)	132 (31.5)	31 (14.6)	255 (26.4)
Median (Q1; Q3), cm	34 (34; 36)	35 (34; 37)	35 (33; 36)	35 (34; 36)	34 (33; 36)	35 (34; 37)	35 (34; 36)	35 (34; 36)
APGAR score (1 min)								
Reported, n (%)	86 (37.1)	88 (28.0)	20 (16.0)	194 (28.9)	109 (32.7)	104 (24.8)	31 (14.6)	244 (25.3)
Median (Q1; Q3)	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (8; 9)
APGAR score (5 min)								
Reported, n (%)	93 (40.1)	116 (36.9)	20 (16.0)	229 (34.1)	115 (34.5)	133 (31.7)	31 (14.6)	279 (28.9)
Median (Q1; Q3)	10 (9; 10)	10 (9; 10)	9 (9; 10)	10 (9; 10)	9 (9; 10)	10 (9; 10)	9 (9; 10)	10 (9; 10)
APGAR score (10 min)								
Reported, n (%)	72 (31.0)	102 (32.5)	15 (12.0)	189 (28.2)	83 (24.9)	109 (26.0)	22 (10.3)	214 (22.2)
Median (Q1; Q3	10 (9; 10)	10 (10; 10)	10 (9; 10)	10 (9; 10)	10 (9; 10)	10 (10; 10)	10 (9; 10)	10 (9; 10)

Note: percentage calculations are based on the number of pregnancies with live births reported for each case where child data were captured.

3), at 2 weeks (n = 1), at 17 days (n = 1), and not specified (n = 1). Of the infants with 'normal' B-cell levels, 39 were exposed in utero (29 within 0–3 months before the LMP, 7 in the first trimester, and 3 in the second), 2 had postpartum exposure only, 10 had unknown exposure, and 5 had no exposure.

Three neonatal deaths were reported. All 3 cases had in utero exposure to ocrelizumab; one infusion occurred within 3 months before the LMP and 2 in the first trimester (more details in eTable 6). In one case (prospectively reported), the mother had been admitted to the hospital for cervical shortening requiring cerclage at week 20. The infant was delivered preterm (gestational age, 25 weeks) by induced vaginal delivery because of suspected chorioamnionitis and died 2 hours after delivery because of extreme prematurity. In the second case (retrospectively reported), the mother was hospitalized during her fifth month of pregnancy for COVID-19 pneumonia and died after 25 days of hospitalization; the infant was delivered live preterm through induced labor (unknown gestational age) and died 48 hours after delivery. In the third case (retrospectively reported), the infant was delivered live preterm (gestational age, 31 weeks) and died a few days after birth from sepsis secondary to a pulmonary infection.

Maternal Complications

Complications were reported for 95 women (2.9%) in total (outcomes were 81 live births, 5 spontaneous abortions, 2 intrauterine/fetal deaths, 1 stillbirth, and 6 unknown; data not shown). The 81 pregnancies that resulted in live births had reasonably complete information available, summarized in eTable 7. Among these, most complications were classified as obstetric complications during pregnancy (4.3% of all live births). Hypertension (n = 24; 1.6% of all live births), gestational diabetes (n = 17, 1.1%), and pre-eclampsia (n = 16, 1.1%) were the most common individual maternal complications (eFigure 2).

In total, 3 maternal deaths were reported (listed in eTable 8), all from retrospectively reported pregnancies. Two received ocrelizumab during the first trimester and one 3–6 months before the LMP. In one case, the mother died of bacterial pneumonia and the outcome of the pregnancy was reported as intrauterine/fetal death. In the second case, the mother died of COVID-19 pneumonia; the outcome was a premature live birth at unknown gestational week, followed by neonatal death (described earlier). Relevant medical history included asthma and obesity. In the third case, the mother died of COVID-19; the infant was delivered at 32 weeks through C-section and discharged after 3 weeks in intensive care.

Discussion

We analyzed a large dataset of pregnancy outcomes in women with MS treated with ocrelizumab. This database has grown from 25 pregnancies reported in 2017 to a cumulative number of 3,244 pregnancies by July 12, 2023. Of total cases, 1,071 had in utero exposure, of which 715 (512 prospectively reported) had known outcomes. Similar increases in DMT-exposed MS pregnancies over time have been reported elsewhere.[31,32] Notably, despite the label restrictions, more exposed than nonexposed pregnancies were reported, with most women having received the last ocrelizumab infusion within the 3 months before their LMP or in the first trimester of pregnancy. This likely reflects cases of accidental exposure during pregnancy and unplanned pregnancies, as well as potentially evolving clinical practices in relation to anti-CD20 use in family planning.[2,8-10,14] Still, it is important that clinicians consider potential pregnancy at the time of infusion to avoid unintended exposures during the first trimester.

The findings suggest that in utero exposure to ocrelizumab is not associated with an increased risk of adverse pregnancy or infant outcomes compared with other MS cohorts[33-36] or the general population.[25,33-37]

Most pregnancies with known outcomes resulted in live births. Among prospective cases, similar proportions of live births were observed in exposed and nonexposed pregnancies, and among exposed pregnancies, the proportion of live births with exposure before or during pregnancy was also similar. Most live births were full-term (gestational age ≥37 weeks); there were no differences in the rate of live births and in the proportion of preterm live births between exposed and nonexposed groups and between in utero exposure subgroups (i.e., before or after LMP). It is important to note that rates of preterm births are consistent with those reported for other MS cohorts (7.2%–15.4%), as well as for the general population (6.5%–10.4%).[34-36] In a smaller cohort treated with anti-CD20, a significantly higher rate of preterm births was reported in women exposed during pregnancy (45.5% [5/13]) than in those exposed >6 months before the LMP (0/8) and those exposed <6 months before the LMP (9.8% [4/47]; $p = 0.019$). Reasons for the difference from our study are not clear; however, the cohort was relatively small (n = 88 pregnancies) and included women with conditions other than MS (neuromyelitis optica spectrum disorder, 17; other neuroimmunologic conditions, 7). The authors suggested that underlying disease, concomitant autoimmune diseases, previous DMT exposure, and concomitant steroids may have been partially responsible for the higher rate.

Approximately 10% of prospective cases had an outcome of spontaneous abortion, with rates similar between the exposed and nonexposed groups, consistent with epidemiology in MS cohorts (10.5%–11.6%[34-36]). Furthermore, the increase in spontaneous abortions with increasing maternal age (the strongest known risk factor) was also consistent with data for the general population.[38] The rate of stillbirths, in prospectively reported cases and overall, was similarly consistent with reported rates.[33,35] No obstetric infections (e.g., chorioamnionitis) were reported with the outcome of stillbirth. In addition, several stillbirths presented with risk factors (one case had multiple obstetric risk factors, one had thrombotic

comorbidities, and another occurred after recovery of a COVID-19 infection).

A higher proportion of elective abortions were observed in the exposed group, although the rate was still less than those reported for MS (10.7%–18.1%) and for the general population (18.2%).[35] This may indicate underreporting to the pharmacovigilance database. However, the fact that elective terminations (likely after unintended pregnancies) in the exposed group declined over time (from 43% in 2017 to 23% in 2020 and 7.4% in 2023) suggests an evolution in the perception of risk by neurologists with accruing clinical experience and evolving expert consensus recommendations.[2,8-10,14]

In this analysis, the overall frequency of MCAs in prospective cases was within the range reported for other MS cohorts (2.2%–4.2%[33-36]) and for the general population (2.0%–4.4%[25,33-37]). It is important to note that the rates in exposed and nonexposed pregnancies were similar (2.1% vs 1.9%). When including retrospective cases, the rate in exposed pregnancies was slightly higher (2.0% vs 1.3%), although this may reflect a reporting bias toward off-label exposure, i.e., exposure <6 months before the LMP. Among exposed pregnancies, rates were similar whether the last ocrelizumab infusion occurred before the LMP or after (mostly in the first trimester). There is no increased risk of congenital anomalies in pregnancies with in utero exposure to ocrelizumab, when compared with EUROCAT prevalence rates. The frequency of congenital anomalies in ocrelizumab-exposed pregnancies was not expected to exceed the rates in the general population, given the negligible transplacental crossing of ocrelizumab in the first trimester, the most critical period for organogenesis.[13] However, intrauterine infections are another putative mechanism for congenital anomalies[39] that may be associated with exposure to ocrelizumab; therefore, additional data are needed to reach firm conclusions on the risk of MCAs after ocrelizumab exposure. Reassuringly, the pattern of reported MCAs was consistent with the distribution observed in EUROCAT prevalence data,[29] with cardiac defects, urinary/renal defects, and chromosomal disorders (i.e., Down syndrome) being the most common categories. Potentially contributing factors such as teratogenic concomitant medications (e.g., carbimazole and anticoagulants) and relevant family history (e.g., familial polydactyly) were also present in some cases. Fetal outcomes at birth, including weight, length, and body weight, were consistent with data reported for the general population.[40,41]

One-year follow-up data in infants with potential in utero exposure were limited, likely because reports are voluntary and missing data are more likely with longer follow-up. Therefore, while the proportion of reported infections was slightly higher in infants potentially exposed to ocrelizumab in utero compared with those not exposed, a reporting bias cannot be excluded. Moreover, the rate of reported infections in the first year of life seems low compared with rates expected in children,[42] which further reinforces the likelihood of missing information. Similar biases may be observed in the reporting of B-cell levels. All infants with abnormal B-cell levels (n = 6) were reported as being exposed to ocrelizumab in utero, but in most cases, the actual level was not known. Because normative data on B-cell levels adjusted for week of age in the first year of life have only recently become available,[30] some results could also have been interpreted incorrectly by reporting physicians. Higher quality, systematically collected evidence is, therefore, needed on potential effect of maternal ocrelizumab treatment on B-cell levels and immune system functionality in infants, as measured by humoral responses to vaccinations or susceptibility to infection. To that end, 2 ongoing prospective studies are currently assessing whether ocrelizumab is transferred across the placenta or into breastmilk and potential pharmacodynamic effects in developing infants (MINORE [NCT04998812] and SOPRANINO [NCT04998851][43]).

The 3 neonatal deaths all occurred in the context of extreme prematurity, potentially complicated by pre-existing maternal conditions (cervical shortening) and concomitant diseases such as COVID-19 infection. One was associated with chorioamnionitis, possibly related to cervical cerclage (a known risk factor of chorioamnionitis[44]). Regarding the 3 maternal deaths (2 from COVID-19 infection and one from bacterial pneumonia), it is important to note that COVID-19 infection in pregnant women with MS is known to significantly increase the risk of maternal complications[45] and bacterial infection is the most common fatal nonobstetric infection in pregnancy.[46] However, more data are needed to determine the risks of infections in mothers and children exposed to anti-CD20 antibodies during pregnancy.

This study has some limitations. The definition of potential in utero exposure is based on previous studies[13] and the known pharmacokinetics of ocrelizumab,[11,12] but it is arbitrary, given that the pharmacokinetics may vary widely across individuals. It is hoped that data from the MINORE study ([43] described earlier) will allow more accurate assessments in the future. In addition, some exposure subgroups had very low case numbers. Similarly, the low rates of maternal complications in our data set limit the interpretability of maternal complication data. Moreover, a substantial fraction of cases had incomplete information; for example, approximately 34% had unknown outcomes, and the timing of exposure was unknown in approximately 44%. Missing data are a known limitation of spontaneous reports, as mentioned earlier. One-year infant outcomes and breastfeeding cases had particularly sparse data; this may occur because clinicians do not always respond to follow-up requests. In addition, there may have been a selection bias toward reporting of 'exposed' cases, as acknowledged elsewhere.[47] Initiatives are underway to improve the quality of spontaneous reporting; e.g., in a pilot training and education program in Italy, both the total pregnancy/lactation reports and the proportion of prospective reports in women with MS receiving ocrelizumab increased over a 1-year period.[48]

In summary, our analysis, expanding on existing evidence from smaller cohorts and cases series,[18-22] suggests that in utero exposure to ocrelizumab is not associated with an increased risk of adverse pregnancy or infant outcomes, with event rates remaining consistent with epidemiologic background rates. Our data also build on previous experience with rituximab,[21,49,50] which has informed clinical practice around anti-CD20 use in MS. Therefore, ocrelizumab may be a suitable option for maintaining disease control in women with MS who wish to become pregnant, adding to the list of therapeutic options (IFN-beta, glatiramer acetate, and natalizumab) that are considered to pose very low risk to the fetus.[2,8] These findings may also inform physicians' decisions regarding other anti-CD20 agents such as ofatumumab, for which such extensive pregnancy data are not yet available,[51,52] although the influence of differences in posology and route of administration are unknown.[14]

These data represent an important step in enabling neurologists and women with MS to make more informed decisions around family planning and ocrelizumab, balancing safety risks to the fetus/infant against the importance of MS disease control in mothers.

Author Contributions

S. Vukusic: 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. R. Bove: 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. R. Dobson: 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. T. McElrath: 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. C. Oreja-Guevara: 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. C. Pietrasanta: 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. C.-J. Lin: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Ferreira: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L. Craveiro: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. D. Zecevic: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. N. Pasquarelli: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K. Hellwig: 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.

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