P061

Pregnancy and Infant Outcomes in Women Receiving Ocrelizumab for the Treatment of Multiple Sclerosis: Analysis of the Largest Available Outcomes Database

K Hellwig,[1] C Oreja-Guevara,[2] S Vukusic,[3] C Pietrasanta,[4] T McElrath,[5] R Dobson,[6] L Craveiro,[7] G Ferreira,[7] D Goncalves Pereira Alves,[7] CJ Lin,[8] N Pasquarelli,[7] D Zecevic,[7] R Bove[9]

[1]Katholisches Klinikum Bochum, St. Josef Hospital, Universitätsklinikum, Bochum, Germany; [2]Neurology, Hospital Clínico San Carlos, Idissc, Madrid, Spain; [3]Service de Neurologie et Sclérose en Plaques, Fondation Eugène Devic EDMUS contre la Sclérose en Plaques, Hôpital Neurologique Pierre Wertheimer, Lyon, France; [4]NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Division of Maternal-Fetal Medicine, Brigham and Women's Hospital, Boston, MA, USA; [6]Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [8]Roche Products Ltd, Welwyn Garden City, UK; [9]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA.

OBJECTIVE

To report on pregnancy and infant outcomes among women with MS exposed to ocrelizumab before or during pregnancy up to July 2023

CONCLUSIONS

- *In utero* exposure to ocrelizumab did not increase the risk of adverse pregnancy or infant outcomes compared with epidemiological background of both MS and general population[1–6]
- This is the largest dataset of pregnancy outcomes for an anti-CD20 therapy in MS[7]
- Reports of infant outcomes throughout the first year of life are very limited; continuous improvement of reporting by healthcare professionals remains a critical component to increase available evidence
- Pregnancy and infant outcomes are important to women with MS. Patients and data continue to be collected through post-marketing commitments (OCREVUS pregnancy registry)[8] and two prospective Phase IV studies examining infant B cell levels and ocrelizumab pharmacokinetics across the placenta (MINORE, MN42988) and breastmilk (SOPRANINO, MN42989)[9]

METHODS

Sources, Reporting Period and Type, and Definition of *In Utero* Exposure

Sources

- Reports from the Roche Global Safety Database: (1) interventional or non-interventional clinical studies, (2) spontaneous reports, (3) non-interventional programme, (4) published literature

Reporting type

- **Prospective:** Final outcomes were unknown at initial notification
- **Retrospective:** Final outcomes were known at initial notification

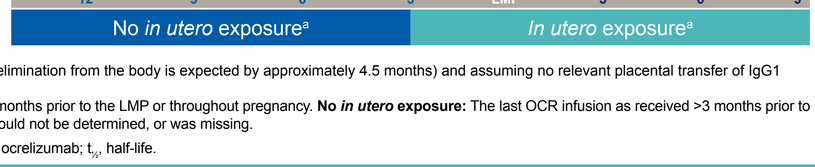
Reporting period

- Cumulative pregnancies reported from

November 2008 to **12 July 2023**

Exposure

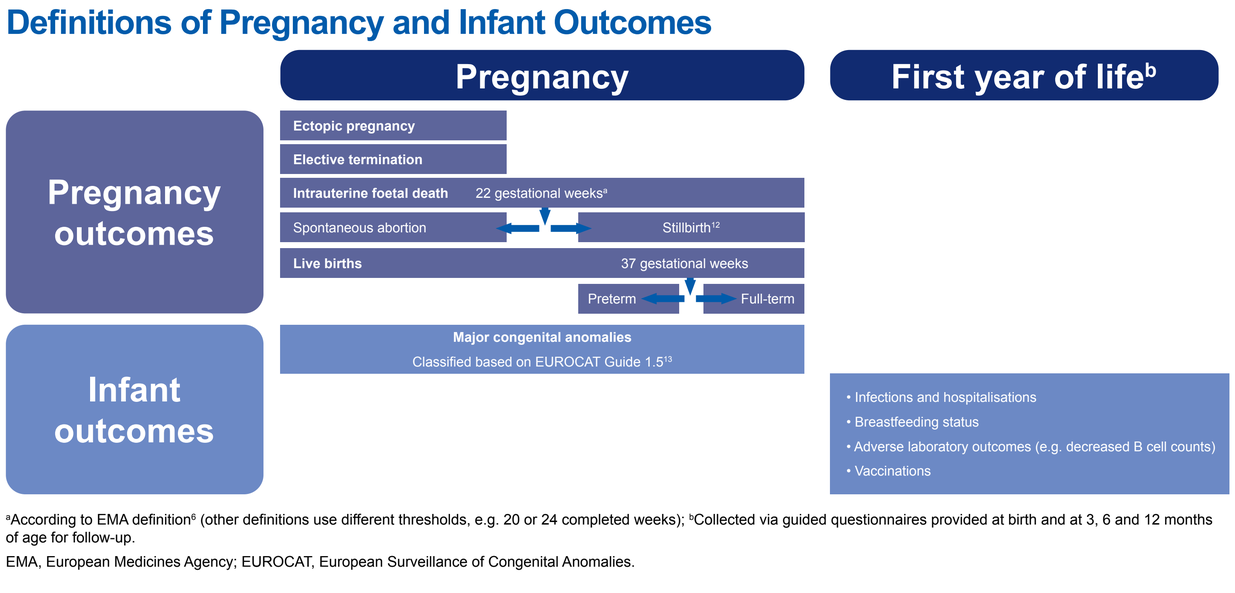
Timing of last OCR dose in relation to date of LMP (months)



[a]Exposure classification is based on OCR t½=26 days (full elimination from the body is expected by approximately 4.5 months) and assuming no relevant placental transfer of IgG1 antibodies occurs prior to 12 weeks of gestation.[10,11]
***In utero* exposure:** The last OCR infusion was received ≤3 months prior to the LMP or throughout pregnancy. **No *in utero* exposure:** The last OCR infusion as received >3 months prior to the LMP. **Unknown exposure:** Where the exposure timing could not be determined, or was missing.

IgG1, immunoglobulin G1; LMP, last menstrual period; OCR, ocrelizumab; $t_{½}$, half-life.

Definitions of Pregnancy and Infant Outcomes

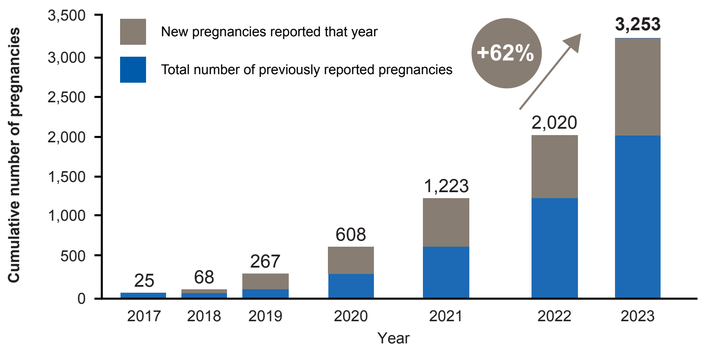


[a]According to EMA definition[6] (other definitions use different thresholds, e.g. 20 or 24 completed weeks); [b]Collected via guided questionnaires provided at birth and at 3, 6 and 12 months of age for follow-up.

EMA, European Medicines Agency; EUROCAT, European Surveillance of Congenital Anomalies.

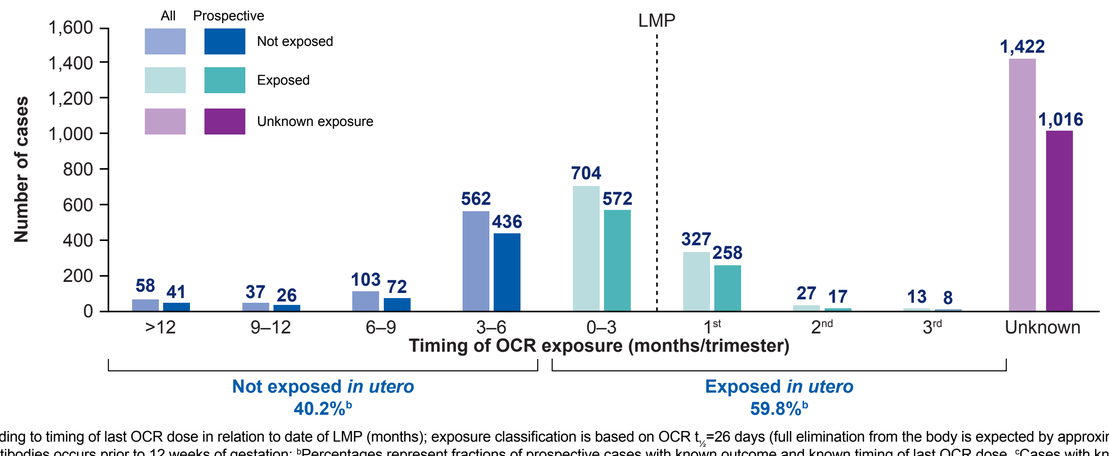
RESULTS

The cumulative number of pregnancies reported among women with MS treated with OCR continues to grow[7]



There was a 62% increase in the number of cases from 2022 to 2023

MS Pregnancies by *In Utero* Exposure:[a] All Cases and Prospective Cases



- **Median age at LMP (range) was 32.0 (16–60) years[c]**
- **Timing of last OCR dose in relation to LMP was known for 58% of all or prospective cases**
- **Where exposure was known, most cases were reported as exposed *in utero* and most exposed to the last OCR dose 0–3 months before LMP followed by 1st trimester of pregnancy**
- **For cases with no exposure *in utero*, most were reported in mothers exposed to the last OCR dose 3–6 months before LMP**

[a]Determined according to timing of last OCR dose in relation to date of LMP (months); exposure classification is based on OCR $t_{½}$=26 days (full elimination from the body is expected by approximately 4.5 months) and assuming no relevant placental transfer of IgG1 antibodies occurs prior to 12 weeks of gestation; [b]Percentages represent fractions of prospective cases with known outcome and known timing of last OCR dose. [c]Cases with known age: n=2,676 (82.3%).

MS, multiple sclerosis; OCR, ocrelizumab.

IgG1, immunoglobulin G1; LMP, last menstrual period; OCR, ocrelizumab; $t_{½}$, half-life.

Pregnancy Outcomes by Exposure in Prospective Cases[a]

- **Most pregnancies resulted in live births** (83.6%), and proportions were similar in the exposed and non-exposed groups
- **Most live births were full term** (61.4%) and a smaller proportion were preterm (8.5%)
  - Proportions were similar in the exposed and non-exposed groups
  - **Gestational age was unknown** in 30.2% of cases
- **A higher proportion of elective terminations** occurred in the exposed group, but the overall cumulative proportion of elective abortions is decreasing (5.1% in 2023 vs 11.5% in 2022 and 15.7% in 2021)[7]
- **A smaller proportion of spontaneous abortions** occurred in the exposed group (**7.4%**) compared with the non-exposed group (**9.1%**)
- The overall rate of **stillbirths** (<0.1%) remained low

Number of MS pregnancies	Non-exposed (N=575)	Exposed (N=855)	Unknown (N=1,016)	Total (N=2,446)	Epidemiological rates	
					MS background rate	General population background rate
Known outcomes	**n=351**	**n=512**	**n=282**	**n=1,145**		
Live births[b]	**88.3%**	**84.2%**	**76.6%**	**83.6%**	**70.2–77.2[1]**	**70.2[1]**
Full term (≥37 weeks)[c]	**70.9%**	**65.7%**	**39.1%**	**61.4%**	–	–
Preterm (<37 weeks)[c]	**8.4%**	**9.5%**	**6.5%**	**8.5%**	**7.2–15.4[1–4]**	**6.5–10.4[1-2, 4]**
Unknown gestational age[c]	**20.7%**	**24.8%**	**54.4%**	**30.2%**	–	–
Ectopic pregnancy[b]	**0.9%**	**0.8%**	**2.5%**	**1.2%**	**0.6–1.3[1,2]**	**1.1–2.0[1,2]**
Elective termination[b]	**1.7%**	**7.4%**	**5.0%**	**5.1%**	**10.7–18.1[1]**	**18.2[1]**
Intrauterine foetal death[b]						
Spontaneous abortion, ≤22 weeks[b]	**9.1%**	**7.4%**	**16.0%**	**10.0%**	**10.5–11.6[1–3]**	**10.0–20.0[1,2]**
Stillbirth, >22 weeks[b]	–	**0.2%**	–	**<0.1%**	**0.3–0.6[1,4]**	**0.2–0.7[1,4]**

The dash indicates that no cases were reported; Please see Supplementary Materials for details on all cases, pregnancy outcomes by more granular timings of OCR exposure and listing of stillbirths.
[a]*In utero* exposure based on timing of last OCR dose relative to LMP; [b]Percentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero,* unknown exposure, total); [c]Percentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero,* unknown exposure, total).
LMP, last menstrual cycle; MS, multiple sclerosis; OCR, ocrelizumab.

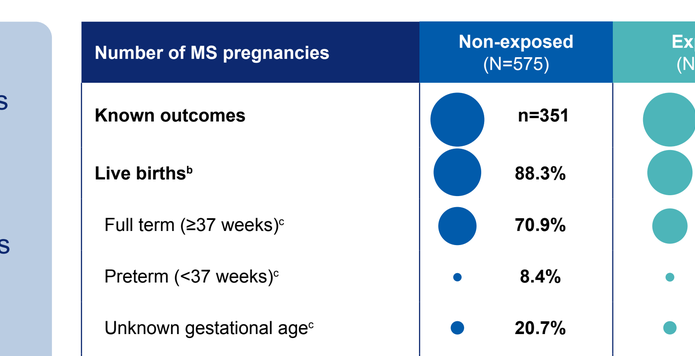
Major Congenital Anomalies in Pregnancies with Known Outcomes

Proportions and types are consistent with epidemiological background[1-6]

	Non-exposed	Exposed	Unknown exposure	Total
Live births	**N=310**	**N=431**	**N=216**	**N=957**
Live birth with MCA, n (%)[a]	4 (1.3%)	7 (1.6%)	1 (0.5%)	12 (1.3%)
Full term with MCA, n	3	4	1	8
Preterm with MCA, n	1	3	–	4
Unknown GA with MCA, n	–	–	–	–
Stillbirths >22 weeks	**N=0**	**N=1**	**N=0**	**N=1**
Stillbirth with MCA, n	–	1	–	1
Live birth/stillbirth with MCA, n (%)[b]	4 (1.3%)	8 (1.9%)	1 (0.5%)	13 (1.4%)

Around 2–4% of all children born every year will have a MCA[1–5]

Distribution of Major Congenital Anomalies by EUROCAT[13] Category, n (%)[c]



Please see Supplementary Materials for details on the listing of major congenital anomalies. The dash indicates that no cases were reported.
[a]Percentages represent fractions of total live births for the respective exposure category; [b]Percentages represent fractions of the total stillbirths/live births for the respective exposure category; [c]The number of major congenital anomalies prospectively reported is 14, as one live birth reported two MCAs; see Supplementary Materials for all cases.
EUROCAT, European Surveillance of Congenital Anomalies; GA, gestational age; MCA, major congenital anomaly.

Reports of Infant Outcomes Throughout the First Year of Life are Very Limited[a]

1,888 known pregnancy outcomes[b]

226 Infants with 1-year follow-up data

127 infants were exposed *in utero*
54 infants were not exposed *in utero*
45 infants had unknown exposure

80 infants were also exposed *in utero*
46 infants exposed via breastfeeding only

Infants with exposure via breastfeeding **126**

[a]For further details, see the Supplementary Materials. [b]Includes all known outcomes, either prospectively or retrospectively reported.

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Supplementary Materials

Contents

Background

As of March 2023, more than 300,000 people with MS had initiated ocrelizumab globally[1]

Women with MS of childbearing potential represent a significant number of people with MS[2]

The number of women with MS exposed to ocrelizumab before, during and after pregnancy is increasing[3]

MS, multiple sclerosis.

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Methods

Definitions of pregnancy and infant outcomes[1,2]

Pregnancy outcome[1]	Definition		
Ectopic pregnancies	Extrauterine pregnancy, most often in the fallopian tube.		
Elective or therapeutic terminations	Induced or voluntary foetal loss during pregnancy due to medical or any other reasons.		
Intrauterine foetal death[a]	Death prior to complete expulsion or extraction from the mother of a foetus, irrespective of the duration of pregnancy:		
	Spontaneous abortion* Loss of a foetus before 22 completed weeks of gestation.	**Stillbirth*** Loss of a foetus after 22 completed weeks of gestation and prior to birth.	**Intrauterine foetal death** If gestational age unknown, not reported or could not be determined.
	*For cases of spontaneous abortion or stillbirth where the exact gestational age was not reported or could not be calculated, a definition of gestational age ≤22 or >22 completed weeks was assumed if there was reliable and objective documentation that confirmed the spontaneous abortion or stillbirth, respectively (this includes an autopsy report, results of prenatal tests [e.g. ultrasound] or a well-document clinical diagnosis recorded in the healthcare records).		
Live birth	Complete expulsion or extraction from the mother of a foetus, irrespective of the duration of the pregnancy, that, after such separation, breathes or shows any evidence of life.		
	Pre-term live birth Birth at less than 37 completed weeks (less than 259 days) of gestation.	**Full-term birth** Birth at any time from 37 completed weeks (more than 259 days) of gestation.	**Unknown** Gestational age at birth unknown or not reported.
Infant outcome[2]	**Definition**		
Major congenital anomaly	Congenital anomalies (birth defects) are defined as any morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities (structural birth defect, sometimes congenital malformation, foetal defect), foetopathies, genetic diseases with early onset or developmental delay. Congenital anomalies are classified as major according to the EUROCAT Classification System Version 1.5.		

[a]Threshold of 22 weeks according to the EMA definition; global variations in the definition of spontaneous abortion versus stillbirths exist (FDA 20 weeks, UK 24 weeks, WHO 28 weeks).[3]

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EMA, European Medicines Agency; EUROCAT, European Surveillance of Congenital Anomalies; FDA, Food and Drug Administration; WHO, World Health Organization.

MS pregnancies by outcome status, data source, and reporting type

- Of 3,253 cumulative MS pregnancies, 1888 (58.0%) had a known outcome
- 2,515 (77.3%) cases were from non-interventional studies, of which 231 from the OCREVUS pregnancy registry (WA40063)
- 2,446 (75.2%) cases were prospectively reported

Distribution of cases, n (%)[a]	N=3,253
By outcome status (%)	
Known outcome	**1,888 (58.0)**
Unknown, not reported or lost to follow-up	1,098 (33.8)
Pregnancy ongoing	267 (8.2)
By data source (%)	
Non-interventional study/program	**2,515 (77.3)**
Ocrevus pregnancy registry	231 (7.1)
Spontaneous report	448 (13.8)
Clinical studies	210 (6.5)
Literature review (case reports, case series)	80 (2.5)
By reporting type (%)	
Prospective	**2,446 (75.2)**
Retrospective	800 (24.6)
Unknown	7 (0.2)

MS, multiple sclerosis.

Pregnancy outcomes by exposure[a]: prospective cases and all cases

Number of MS pregnancies	Prospective cases				All cases			
	Non-exposed, % (N=575)	Exposed, % (N=855)	Unknown, % (N=1,016)	Total, % (N=2,446)	Non-exposed, %(N=760)	Exposed, % (N=1,071)	Unknown, % (N=1,422)	Total, % (N=3,253)
Known outcomes	n=351	n=512	n=282	n=1,145	n=528	n=715	n=645	n=1,888
Live births[b]	88.3	84.2	76.6	83.6	84.5	82.4	70.4	78.9
Full term (≥37 weeks)[c]	70.9	65.7	39.1	61.4	67.2	61.1	27.9	52.9
Pre-term (<37 weeks)[c]	8.4	9.5	6.5	8.5	7.2	9.2	5.6	7.5
Unknown gestational age[c]	20.7	24.8	54.4	30.2	25.6	29.7	66.5	39.6
Live birth with MCA	1.3	1.6	0.5	1.3	0.9	1.5	0.4	1.0
Ectopic pregnancy[b]	0.9	0.8	2.5	1.2	0.9	0.6	2.0	1.2
Elective/therapeutic termination[b]	1.7	7.4	5.0	5.1	2.8	7.0	5.0	5.1
Intrauterine foetal death[b]								
Spontaneous abortion, ≤22 weeks	9.1	7.4	16.0	10.0	11.4	9.4	22.3	14.4
Stillbirth, >22 weeks	-	0.2	-	<0.1	0.2	0.7	-	0.3
Unknown gestational age	-	-	-	-	0.4	-	0.3	0.2
Live/still births/ unknown gestational age with MCA[d]	1.3	1.9	0.5	1.4	0.9	1.7	0.7	1.1

[a]*In utero* exposure based on timing of last OCR dose relative to the last menstrual period; [b]Percentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); [c]Percentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); [d]Percentages represent fractions of total live births and still births.
MCA, major congenital anomaly; MS, multiple sclerosis; OCR, ocrelizumab.

Pregnancy outcomes by exposure[a]: different ocrelizumab washout periods

Exposure based on last ocrelizumab dose	Not exposed *in utero*, prospective cases			Exposed *in utero*, prospective cases			Total prospective cases (n=2,446)
Number of MS pregnancies	**<6 months (n=139)**	**<3-6 months (n=436)**	**Total not exposed *in utero* (n=575)**	**0-3 months (n=572)**	**During pregnancy (n=283)**	**Total exposed *in utero* (n=855)**	
Known outcomes	n=81	n=270	n=351	n=343	n=169	512	1,145
Live births[b]	91.4%	87.4%	88.3%	82.5%	87.6%	84.2%	83.6%
Full term (≥37 weeks) [c]	68.5%	71.6%	70.9%)	67.1%	62.8%	65.7%	61.4%
Preterm (<37 weeks) [c]	6.8%	8.9%	8.4%	9.9%	8.8%	9.5%	8.5%
Unknown gestational week[c]	24.7%	19.5%	20.7%	23.0%	28.4%	24.8%	30.2%
Major congenital anomalies[c]	-	1.7%	1.3%	1.8%	1.4%	1.6%	1.3%
Ectopic pregnancy[b]	-	1.1%	0.9%	1.2%	-	0.8%	1.2%
Therapeutic/elective abortion	-	2.2%	1.7%	6.7%	8.9%	7.4%	5.1%
***Intrauterine/foetal death*[b]**							
Spontaneous abortion (≤22 weeks)	8.6%	9.3%	9.1%	9.3%	3.6%	7.4%	10.0%
Stillbirth (>22 weeks)	-	-	-	0.3%	-	0.2%	<0.1%
Live births/stillbirths with MCA[d]	-	1.7%	1.3%	2.1%	1.4%	1.9%	1.4%

Data as of 12 July 2023. Dash indicates a data value of 0. [a]*In utero* exposure based on timing of last OCR dose relative to the last menstrual period; [b]Percentages represent fractions of the total known outcomes of the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total); [c]Percentages represent fractions of the total live births for the respective exposure categories (not exposed *in utero*, exposed *in utero*, unknown exposure, total). [d]Percentages represent fractions of total live births and still births
MCA, major congenital anomaly; MS, multiple sclerosis; OCR, ocrelizumab

Stillbirths/Intrauterine foetal deaths: case characteristics (n=9)

- As of July 2023, one prospectively reported stillbirth occurred
- No new prospective cases have been reported since the 2022 datacut
- The majority of cases presented with comorbidities and/or concomitant medications as potential confounders

Type[1]	Case description	Maternal age, years	**Gestational age,** weeks	Time of last OCR infusion	Medical history including medication	Reporting
Stillbirth	First trimester screening, non-invasive prenatal testing 9/10 estimated risk of trisomy 21 (amniocentesis declined)	35	30	0-3 months before LMP	History of miscarriage and premature birth, family history of diabetes C: docosahexaenoic acid, eicosapentanoic acid, bupropion, gabapentin, calcium, macrogol, baclofen, vitamin D, cannabis oil	**Prospective**
Stillbirth	NR	25	Unknown	0-3 months before LMP	Blood clots in legs, stroke and unable to walk P: warfarin; C: enoxaparin and apixaban for thrombosis	Retrospective
Stillbirth	Mother hospitalized for mild COVID-19 pneumonia during pregnancy (recovered)	24	27	0-3 months before LMP	D: enoxaparin and corticosteroids for COVID-19 pneumonia	Retrospective
Stillbirth	Short-term inhalation of fluid, retroplacental hematoma and multiple infarctions with the placenta (autopsy confirmed). No infections.	28	Unknown	1st trimester	No previous history of spontaneous or therapeutic abortions P: interferon-beta-1a/1b; C: fexofenadine, paracetamol, sertraline, bromazepam, etilefrine, ascorbic acid, quetiapine fumarate	Retrospective
Stillbirth	True knot in umbilical cord confirmed upon autopsy	32	39	1st trimester	Obesity, wheelchair-bound and venous stasis in lower extremities	Retrospective
Intrauterine foetal death	Foetal encephalocele and retrognathia. Unknown if autopsy performed	Unknown	Unknown	Unknown	NR	Retrospective
Intrauterine foetal death (maternal death)	Maternal death due to acute bacterial pneumonia (autopsy confirmed, 11 weeks post-mortem)	36	21-24 weeks (reported as 6 months)	3-6 months before LMP	Mother was healthy with no clinical symptoms (e.g. cough, trouble breathing, problem exercising)	Retrospective
Stillbirth	NR	Unknown	24	>12 months before LMP	Obesity	Retrospective
Intrauterine foetal death	Mother experienced oligohydramnios	29	Unknown	Unknown	NR	Retrospective

[1]**Stillbirth** refers to the death of a foetus after 22 completed weeks of gestation and prior to birth. For cases of stillbirth where the exact gestational age is not reported or cannot be calculated, a definition of gestational age >22 completed weeks was assumed if there was reliable and objective documentation that confirms the stillbirth (this includes an autopsy report, results of prenatal tests [e.g., ultrasound], or a well-document clinical diagnosis recorded in the healthcare records. If gestational age unknown, not reported or could not be determined case was simply defined as intrauterine foetal death.

C, concurrent medication; D, disease treatment; P, previous medication; LMP, last menstrual period; NR, not reported; OCR, ocrelizumab.

Major congenital anomalies: summary of data

18 total MCA in 17 live births and stillbirths were reported, of which 13 are prospective (compared to a total of 10 MCA in 10 newborns in 2022)

Three cases originally reported as minor anomaly were reclassified as major due to the EUROCAT 1.5 update[1,2]

Some cases were potentially confounded by risk factors (concomitant medications, medical/family history)

Similar background rates have been reported in both MS (2.2-4.2)[3,4,5] and general population (2.0-4.4)[3,5,6]

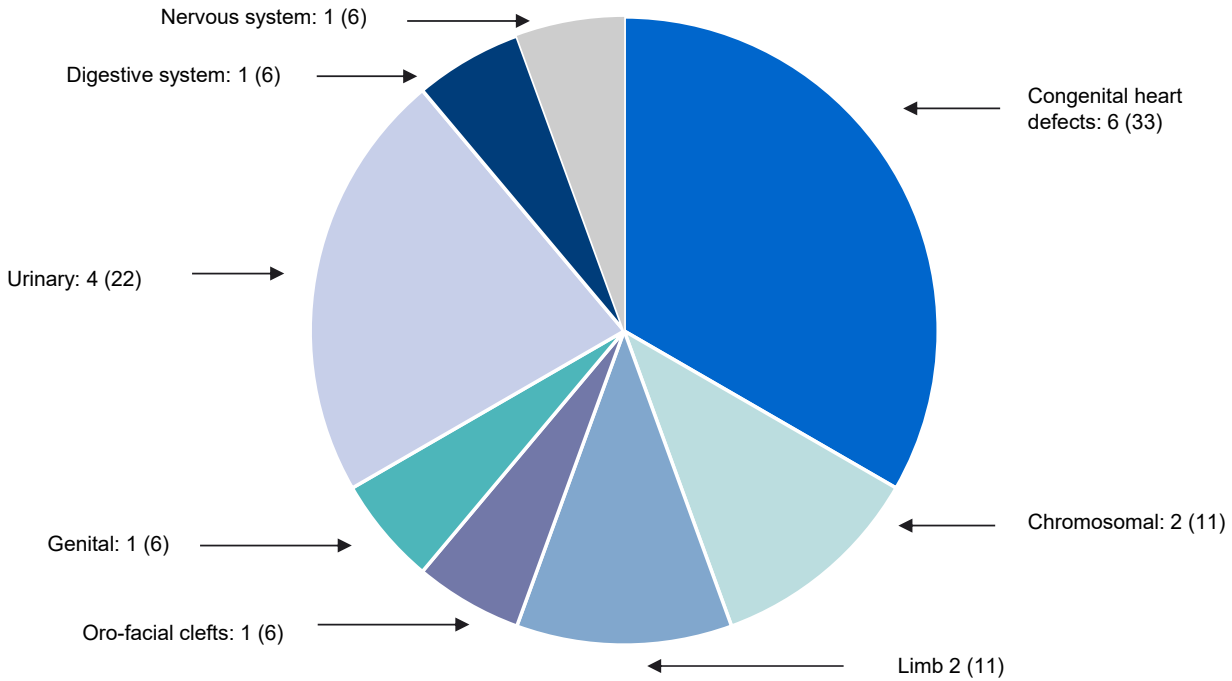
EUROCAT, European Surveillance of Congenital Anomalies; MCA, major congenital anomalies; MS, multiple sclerosis.

1. Oreja-Guevara C, et al. *ECTRIMS* 2022; P O038; 2. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en. Accessed September 2023; 3. Anderson JB, *et al. Eur J Neurol* 2023;30:162–171. 4. Lopez-Leon S, *et al. J Neurol* 2020;267:2721–2731; 5. MacDonald SC, *et al. Am J Epidemiol* 2019;188:57–66; 6. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5.

Results
Major Congenital Anomalies in Pregnancies with Known Outcomes in all cases

Proportions and type are consistent with epidemiological background[1-6]

Distribution of Major Congenital Anomalies by EUROCAT[7] Category, n (%)[c]



[c]The number of major congenital anomalies reported in all cases is 18, as one live birth reported two MCAs.

EUROCAT, European Surveillance of Congenital Anomalies; MCA, major congenital anomaly.

1. Anderson JB, et al. *Eur J Neurol* 2022; 30 (1): 162–171; 2. Khan E, et al. *J Neuroimmunol* 2023; 24; 383: 578178; 3. Lopez-Leon S, et al. *J Neurol* 2020; 267(9): 2721–2731; 4. MacDonald SC, et al. *Am J Epidemiol* 2019; 1;188 (1): 57–66; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2008;57:1–5. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm. Accessed: September 2023; 6. European Medicines Agency (EMA). Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data. November 2005. Available from: https://www.ema.europa.eu/en/documents/regulatoryprocedural-guideline/guideline-exposure-medicinal-productsduring-pregnancy-need-post-authorisation-data_en.pdf. 7. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rdplatform.jrc.ec.europa.eu/eurocat/data-collection/guidelinesfor-data-registration_en Accessed September 2023.

Major congenital anomalies: case characteristics (n=17)

EUROCAT v1.5 Anomaly class	Anomaly type	Maternal age, years	**Pregnancy outcome**	GA, weeks	Time of last OCR infusion	Pregnancy history	Medical history including current and past medication	Reporting
Congenital heart defects	Unclear if ASD, VSD or PFO	35	Live birth Full-term	38	2nd trimester	3 full-term LB	Current Grave's disease C: Carbimazole; P: Alemtuzumab, Dimethyl Fumarate, Fingolimod	Retrospective
Congenital heart defects	*Aortic valve dysfunction, "two holes in the heart"*	32	Live birth	Unknown	Unknown	NR	NR	Retrospective
Congenital heart defects	Ventricular septal defect	31	Live birth Full-term	Term	2nd trimester	NR	Diabetes type I P: alemtuzumab; C: insulin	Retrospective
Congenital heart defects	Atrial and ventricular septal defect	35	Live birth Full-term	40	3-6 months before LMP	No SA or TA	Obesity, hypertension, anxiety, thyroid disorder, fatigue, peripheral venous disease, malnutrition, pre-eclampsia, oedema, nasopharyngitis, anemia, vitamin D deficiency; partial placenta previa C: Folic Acid, Venlafaxine, Levothyroxine, Methyldopa, Acetylsalicylic Acid, Ferrous Sulfate, Candesartan, Dimetindene, Cortisone, tobacco and alcohol, COVID-19 and pertussis vaccine	Prospective
Congenital heart defects	Atrial septal defect	33	Live birth Full-term	40	0-3 months before LMP	Primigravida	No maternal complications, maternal medical history and risk factors	Prospective
Congenital heart defects **Urinary**	Ventricular septal defect Hydronephrosis, bilateral, stage III, with ureteric dilatation	36	Live birth Full-term	40	3-6 months before LMP	1 SA	Anxiety disorder, Thyroid disorder, Fructose/Sorbitol intolerance, Vitamin B12 deficiency/malnutrition, Urinary tract infection, Influenza, Caffeine consumption (<TID) C: Naproxen, Cyanocobalamin, Levothyroxine, Cortisone Acetate, Paracetamol, Cefuroxime, Caffeine	Prospective
Urinary	Renal agenesis, unilateral	30	Live birth Full-term	37	Unknown	NR	Affective disorder P: Rituximab, Oseltamivir, Interferon beta-1b, Natalizumab, Glatiramer Acetate, Fingolimod, Dimethyl Fumarate; C: vitamins, Bupropion	Prospective
Urinary	Renal agenesis, unilateral	33	Live birth Pre-term	36	0-3 months before LMP	NR	NR P: Natalizumab; C: alcohol (occasionally during pregnancy), marijuana (daily)	Prospective
Urinary	Ectopic kidney, unilateral	30	Live birth Pre-term	30	3-6 months before LMP	NR	fetofetal transfusion syndrome (FFTS), twin pregnancy P: dimentidene, cortisone, proprionate, cannabis; C: DHA, EHA	Prospective
Genital	Hypospadia (non-confirmed)	32	Live birth Full-term	40	3-6 months before LMP	Primigravida	Migraine, Hyperthyroidism, COVID-19, no personal/family history of birth defects C: vitamins, colecalciferol, iron, ibuprofen, paracetamol, dalteparin, amoxicillin, phenylephrine, carbetocin, bupivacaine	Prospective

Major congenital anomalies: case characteristics (n=17)

EUROCAT v1.5 Anomaly class	Anomaly type	Maternal age, years	**Pregnancy outcome**	GA, weeks	Time of last OCR infusion	Pregnancy history	Medical history including current and past medication	Reporting
Chromosomal	Down Syndrome	36	Live birth Pre-term	34	0-3 months before LMP	1 full-term LB	NR	Prospective
Chromosomal	Down Syndrome	35	Stillbirth	30	0-3 months before LMP	1 SA, 1 pre-term LB	Family history of diabetes C: DHA, EPA, bupropion, gabapentin, calcium. macrogol, baclofen for neuralgia, vitamin D, cannabis oil	Prospective
Limb	Polydactyly	35	Live birth Full-term	37	1st trimester	1 LB	Father had polydactyly C: Paclitaxel, cannabidiol	Prospective
Limb	Polydactyly	18	Live birth Pre-term	35	2nd trimester	NR	Smoking, diplopia, dysarthria, ataxia C/P: Natalizumab; unknown if C: marijuana (THC) [started at 16.5 years]	Prospective
Oro-facial clefts	Cleft lip and palate	22	Live birth Full-term	38	0-3 months before LMP	NR	Concurrent depression, anxiety C: clonazepam, escitalopram, bupropion	Prospective
Nervous system	Encephalocele	Unknown	Intrauterine foetal death	Unknown	Unknown	NR	NR	Retrospective
Digestive system	Atresia of small intestine	29	Live birth Full-term	41	0-3 months before LMP	1 full-term LB	Ichthyosis; no previous pregnancy complications P: Glatiramer Acetate	Prospective

C, concurrent; DHA, docosahexaenoic acid; DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale; EPA: eicosapentanoic acid; GA, gestational age; LMP, last menstrual period; NR, not reported; P, previous; SA, spontaneous abortion; THC, tetrahydrocannabinol.

Infants with follow-up in the first year of life (n=226)

Vaccinations, infections and B-cell level data remain limited

		Not exposed *in utero* (N=54)	Exposed *in utero* (N=127)	Unknown exposure (N=45)	Total (N=226)	Additional information reported
Live or live-attenuated vaccines administered, n(%)	**Yes**	14 (25.9%)	29 (22.8%)	7 (15.6%)	50 (22.1%)	As of July 2023, there have been no reports of breakthrough infections following administration of common childhood vaccines in infants born to mothers receiving ocrelizumab within 6 months prior to the LMP and/or during pregnancy, enrolled in WA40063 (OCREVUS pregnancy registry).
	No	–	–	–	–	
	NR/Unk/NA	40 (74.1%)	98 (77.2%)	38 (84.4%)	176 (77.9%)	
Infections and other adverse events reported, n(%)	**Yes**	9 (16.7%)[c]	33 (26.0%)[b]	17 (37.8%)[d]	59 (26.1%)	[b]Asphyxia (n=1), common cold (n=1), COVID-19 (n=3), COVID-19, influenza and hand-foot-mouth disease (n=1), hyperbilirubinemia and anemia (n=1), acidosis (n=1), Kawasaki disaese (n=1), nasopharyngitis (n=1), non-specified infection (n=5), prematurity (n=1), respiratory distress (n=6), respiratory syncytial virus (n=5), sepsis (n=2), URTI (n=1), UTI and ear infection (n=1), volvulus (n=1), vomiting/swelling (n=1) [c]cold (n=1), COVID-19 (n=1), ear infection (n=1), hyperbilirubinemia (n=2), UTI (n=1), respiratory syncytial virus (n=1), vomiting and fever after 6-month vaccine (n=1), non-specified infection (n=1) [d]bradycardia (n=1), COVID-19 (n=1), COVID-19, enterococcus faecalis, staphylococcus and respiratory syncytial virus (n=1), neye infection (n=1), gastrointestinal infection and otitis (n=1), group B streptococcus (n=2), non-specified infection (n=3), oral candidiasis and UTI (n=1), oral candidiasis (n=1), nephritis (n=1), respiratory distress (n=1), sepsis and pneumonia (n=1), pneumonia (n=1), UTI (n=1)
	No	21 (38.9%)	34 (26.8%)	17 (37.8%)	72 (31.9%)	
	NR/Unk	24 (44.4%)	60 (47.2%)	11 (24.4%)	95 (42.0%)	
B-cell levels reported, n(%)[a]	**Normal**	4 (7.4%)	39 (30.7%)	12 (26.7%)	55 (24.3%)	[e]lower B cell levels at birth, not further specified (n=3); at 2 weeks, CD19 of 0 (n=1); at 17 days of age, B cell levels were 85/ul (n=1); lower B cell levels with timing and levels not specified (n=1)
	Abnormal	–	6 (4.7%)[e]	–	6 (2.65%)	
	NR/Unk/ indeterminable	50 (92.6%)	82 (64.6%)	33 (73.3%)	165 (73.0%)	

CD19, cluster of differentiation 19; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; Unk, unknown; UTI, urinary tract infection.
[a]Where actual B-cell levels were reported, adjudication on whether results were below the lower limit of normal was made according to Borriello *et al.*, 2022[1].

1. Borriello F, *et al. J Allergy Clin Immunol* 2022;18:S0091-6749(22)00835-1.

Infants with potential exposure to OCR through breastfeeding (n=126)

Vaccinations, infections and B-cell level data remain limited

	Live or live-attenuated vaccines administered, n(%)	Infections and other adverse events reported, n(%)	B-cell levels reported, n(%)[a,b]	Also exposure *in utero*, n(%)	Additional information reported
Yes	5 (4.0%)	11 (8.7%)[b]	Normal 7 (5.6%) Abnormal -	80 (63.5%)	[b]Conjunctivitis and otitis media (n=1); eye infection (n=1); pelvic inflammation/nephritis (n=1); excessive vomiting/swelling due to potential dairy allergies (n=1) live-threatening breathing disorder and mild neurodermatitis (n=1); vomiting and fever after 6-month vaccine (n=1); unspecified neonatal infection (n=2); respiratory syncytial virus infection (n=2); upper respiratory tract infection (n=1)
No	–	4 (3.2%)	–	46 (36.5%)	
NR/Unk/NA	121 (96.0%)	111 (88.1%)	119 (94.4%)	–	

NA, not applicable; NR, not reported; Unk, unknown; OCR, ocrelizumab

[a]Percentages represent fractions of the total reports of potential infant OCR exposure through breastfeeding for the respective outcomes (vaccines administered, infections/adverse events reported, B cell levels reported, also exposed in utero). [b]Where actual B-cell levels were reported, adjudication on whether results were below the lower limit of normal was made according to Borriello *et al*., 2022[1].

1. Borriello F, *et al*. *J Allergy Clin Immunol* 2022;18:S0091-6749(22)00835-1.