Pregnancy and Infant Outcomes in Women Receiving Ocrelizumab for the Treatment of Multiple Sclerosis

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BACKGROUND AND OBJECTIVE

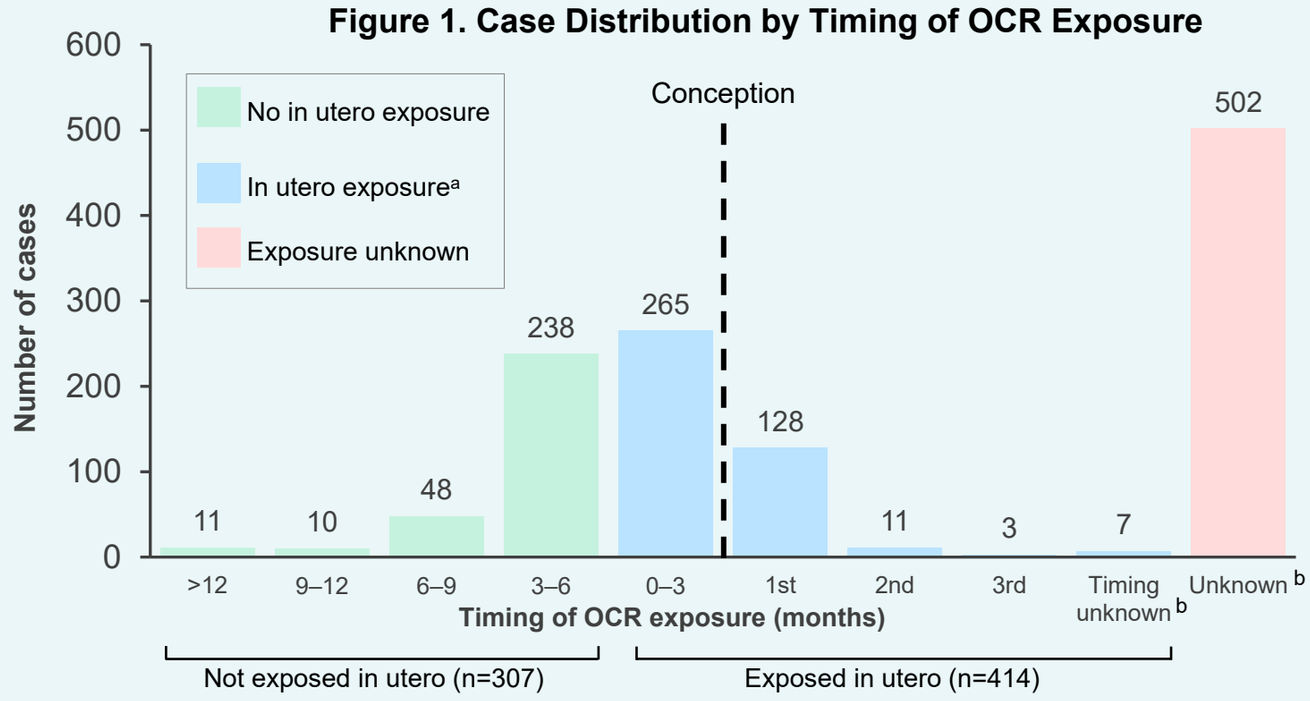
- As of December 2020, >200,000 people had been treated with ocrelizumab (OCR) globally,[1] including women with MS of childbearing potential
- Although women with MS are advised to use contraception while receiving treatment with OCR and for 6–12 months afterwards,[2,3] an increasing number of pregnancy cases in this time frame have been reported in clinical trials and real-world settings[4] (see **Supplemental Figure 1**)
- **Objective:** To report updated cumulative pregnancy and infant outcomes in pregnant or lactating women with MS receiving OCR up to 31 March 2021

RESULTS

Overview of Cases

- As of March 2021, 1223 pregnancies had been reported in women with MS treated with OCR, an increase of approximately 100% relative to the previous data cut (n=608; March 2020)[5]
- Of 1223 cumulative MS pregnancies, 414 (33.9%) had in utero exposure (128 in the first trimester), 307 (25.1%) had no in utero exposure and 502 (41.0%) had unknown exposure (**Figure 1**)
- For women whose age was reported (70.6%), mean age (SD) was 31.8 (5.2) years and median age (range) was 32.0 (18-55) years
- The countries reporting the most frequent pregnancies were the US (733 cases [59.9%]), Germany (136 cases [11.1%]) and Canada (121 cases [9.9%]) (**Supplemental Table 1** and **Supplemental Figure 2)**

Figure 1. Case Distribution by Timing of OCR Exposure



[a]An embryo/foetus was considered to have exposure to OCR in utero if the last infusion occurred within 3 months of conception, during pregnancy or in utero with timing unknown.
[b]Timing unknown: exposed in utero, but timing of exposure unclear from available information; Unknown: not known whether exposed or not exposed *in utero*.
Also see **Methods** in **Supplementary Information.**
Reporting: Prospective: 898/retrospective: 314/unknown: 11
Source: Clinical trials: 144/postmarketing: 1079 (31 of which were from Ocrevus pregnancy registry)

Pregnancy Outcomes by Exposure Category

- Of 604 pregnancies with known outcomes (**Table 1**), 427 (70.7%) resulted in live births. Of these, most pregnancies were full term (47.3%) and a smaller proportion were preterm (11.0%). Rates of full-term live births were similar in the group exposed in utero (55.0%) and the group not exposed in utero (59.1%)
- The overall cumulative rate of therapeutic/elective abortions decreased from 15.2% in the 2020 data cut[5] to 8.9% in the current (2021) data cut
- Rates of spontaneous abortions were lower in the group exposed in utero (12.3%) than in the group not exposed in utero (19.0%)
- Five **stillbirths** (0.8%) were reported, three of which presented with comorbidities as potential confounders (**Supplemental Table 2**). All were retrospectively reported cases and no increase in rate was observed since the 2020 data cut[5]
- Seven **major congenital anomalies** (1.6% of known outcomes) were reported, four of which were potentially confounded by risk factors (concomitant medications, medical/family history) (**Supplemental Table 3)**. Similar background rates have been reported in patients with MS (untreated, 2.7%-6.1%; treated, 1.8%-4.4%)[6] and in the general population (≈3%)[7]
- Infant exposure through lactation and infant 1-year follow-up data remain limited (see **Supplemental Figure 3** and **Supplemental Infant Outcomes Results**)

Table 1. Summary of Pregnancy Outcomes by Exposure Category

Exposure based on last ocrelizumab dose	Not exposed in utero (n=307)			Exposed in utero (n=414)			Unknown timing of exposure (n=502)	Total cases (N=1223)
Outcome, n (%)[a]	**<6 months (n=69)**	**<3 to 6 months (n=238)**	**Total not exposed in utero (n=307)**	**0 to 3 months (n=265)**	**During pregnancy (n=142)**	**Total exposed in utero[b] (n=414)**		
Known outcomes	45 (100.0)	134 (100.0)	179 (100.0)	158 (100.0)	75 (100.0)	236 (100.0)	189 (100.0)	604 (100.0)
Live births[c]	29 (64.4)	98 (73.1)	127 (70.9)	114 (72.2)	56 (74.7)	171 (72.5)	129 (68.3)	427 (70.7)
Full term (≥37 weeks)	21 (72.4)	54 (55.1)	75 (59.1)	65 (57.0)	28 (50.0)	94 (55.0)	33 (25.6)	202 (47.3)
Preterm (<37 weeks)	2 (6.9)	11 (11.2)	13 (10.2)	18 (15.8)	8 (14.3)	26 (15.2)	8 (6.2)	47 (11.0)
Unknown gestational week	6 (20.7)	33 (33.7)	39 (30.7)	31 (27.2)	20 (35.7)	51 (29.8)	88 (68.2)	178 (41.7)
Major congenital anomalies	0	0	0	1 (0.9)	4 (7.1)	5 (2.9)	2 (1.6)	7 (1.6)
Ectopic pregnancy	4 (8.9)	2 (1.5)	6 (3.4)	1 (0.6)	1 (1.3)	2 (0.8)	5 (2.6)	13 (2.2)
Therapeutic/elective abortion	1 (2.2)	11 (8.2)	12 (6.7)	23 (14.6)	7 (9.3)	30 (12.7)	12 (6.3)	54 (8.9)
Spontaneous abortion (≤22 weeks)	11 (24.4)	23 (17.2)	34 (19.0)	17 (10.8)	10 (13.3)	29 (12.3)	42 (22.2)	105 (17.4)
Stillbirth (>22 weeks)	0	0	0	3 (1.9)	1 (1.3)	4 (1.7)	1 (0.5)	5 (0.8)

[a]Proportions of live births, ectopic pregnancies, therapeutic/elective abortions, spontaneous abortions and stillbirths were calculated using known outcomes of the respective exposure category as the denominator.
[b]Total exposed *in utero* includes 7 *in utero* exposure cases for which exact timing of exposure could not be determined.
[c]Proportions of live birth gestational age and anomalies were calculated using live births in the respective exposure category as the denominator.

CONCLUSIONS

- Over the past 12 months, there has been a substantial increase in newly reported pregnancies with OCR in women with MS
- Updated data do not suggest an increased risk of adverse pregnancy outcomes with OCR use with or without in utero exposure and remain in line with previous reports and expected epidemiological ranges[6,7]
- Although this report extends the knowledge base on OCR and pregnancy, the number of known outcomes remains small, limiting the ability to draw conclusions between subgroups with different timing of in utero exposure
- Data continue to be collected through postauthorization commitments (the Ocrevus pregnancy registry) and two prospective phase IV pregnancy/lactation studies examining infant B-cell levels and OCR pharmacokinetics (MINORE [NCT04998812; placental transfer], poster **P655**; SOPRANINO [NCT04998851; breast milk transfer], poster **P686**)

Abbreviations: MS, multiple sclerosis; OCR, ocrelizumab.

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