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Pregnancy outcome following exposure to ocrelizumab in multiple sclerosis

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Abstract

Background: Ocrelizumab is a monoclonal antibody targeting CD20-expressing B cells used in the treatment of multiple sclerosis (MS). Currently, there is limited safety data in pregnancy.

Objectives: To report the pregnancy outcome following exposure to ocrelizumab in MS.

Methods: We retrospectively identified 14 pregnancies of 12 MS patients who had been exposed to ocrelizumab within 6 months prior to conception or during pregnancy from a specialty clinic in Western Australia.

Results: 13 of 14 pregnancies resulted in live births. One pregnancy was electively terminated following detection of a chromosomal defect. One pregnancy was complicated with placental insufficiency and the infant developed hyaline membrane disease which was complicated by sepsis. There were no observed major congenital anomalies, preterm births, stillbirths or low birthweight. We did not observe any serious maternal infections. All patients were relapse-free despite a mean ocrelizumab-free interval of 65.1 weeks.

Conclusions: We did not identify any major safety signals among the patients who received ocrelizumab prior to conception or during the first trimester of pregnancy. Our patients appeared to have a stable disease course despite a prolonged period of treatment interruption during pregnancy.

Keywords: Multiple sclerosis, pregnancy outcome, ocrelizumab, anti-CD20 therapy

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1. Introduction

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that selectively targets CD20-expressing B cells which has been increasingly used in the treatment of multiple sclerosis (MS).[1] Whilst it is a highly efficacious disease modifying drug, the data regarding its safety in pregnancy is very limited.

Ocrelizumab is administered intravenously every six months. The average terminal half-life of ocrelizumab is 26 days.[2] The drug is estimated to be eliminated from the body by approximately 4.5 months following the last administration.[3] It is important to note that IgG1 antibodies such as ocrelizumab do not cross the placenta in first trimester of pregnancy.[4]

In animal studies, the drug has been shown to cause neonatal B cell depletion, bone marrow, renal and testicular toxicity as well as perinatal deaths at doses similar to or greater than those used clinically.[2] The current recommendation is to avoid pregnancy for 6 months (Food and Drug Administration) to 12 months (European Medicine Agency) following the last ocrelizumab infusion.[2,5] However, these recommendations do little to address the arguably greater risk of significant and potentially disabling MS relapse in some patients without disease modifying therapy during pregnancy.

The use of ocrelizumab in pregnancy carries a potential risk of prolonged B-cell depletion, thereby possibly increasing the risk of maternal systemic infections or chorioamnionitis, leading to miscarriages, preterm birth, or stillbirths. As transient reduction in neonatal B-cells and lymphocytes has been reported in another anti-CD20, rituximab in pregnancy,[6] this has also become a concern with ocrelizumab. This is

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Table 1. Patients' demographics.

Demographics		
Age at conception, mean (SD)		34.8 years (2.9)
Duration of disease, mean (SD)		65.2 months (54.3)
Number of ocrelizumab infusions at conception, mean (SD)		1.9 (0.9)
Number of previous DMTs, N (%)	0	4 (33.3%)
	1–2	4 (33.3%)
	3 or more	4 (33.3%)
Ocrelizumab exposure, N (%)	Preconception	13 (92.9%)
	First trimester	3 (21.4%)
	Second/third trimester	0

especially true when the fetus is exposed to ocrelizumab after transplacental transfer of IgG1 takes place at around 16th week of gestation.[4]

Data from 267 pregnancies in patients with MS treated with ocrelizumab did not suggest an increased risk of adverse outcomes.[3] However, a recent study reported an increased risk of preterm births in a group of patient with neuroimmunologic disorders who were exposed to either ocrelizumab or rituximab after conception.[7]

The objective of our study is to report the pregnancy outcome in a group of MS patients exposed to ocrelizumab during pregnancy.

2. Methods

We retrospectively identified 14 pregnancies of 12 MS patients from a specialty clinic in Western Australia, who had been exposed to ocrelizumab within 6 months prior to conception or at any time during pregnancy between 2018 and 2020.

We reviewed the medical records of our patients and their infants. Details of adverse pregnancy outcomes were recorded. This included low birthweight (less than 2500 g), stillbirths (death or loss of baby after 20 weeks completed pregnancy weeks), preterm delivery (less than 37 weeks gestational age) and major malformations as well as maternal complications such as chorioamnionitis or systemic infections. We were also interested in the risks of relapse in the cohort as evidenced by development of new neurotological symptoms or MRI lesions throughout pregnancy and within 3 months postpartum.

Approval for data collection was granted from the ethics committee. Written informed consent was obtained from all patients.

3. Results

3.1 Baseline characteristics

Mean age was 34.8 years. Mean disease duration was 65.2 months. 4 patients received at least 3 disease modifying therapies (DMTs) prior to ocrelizumab therapy, 4 patients received 1 to 2 DMTs while 4 patients had ocrelizumab as their first line treatment. The mean number of cycles of ocrelizumab infusions at the onset of pregnancy was 1.9 (range: 1–4). See Table 1.

3.2 Ocrelizumab exposure and dose

13 of 14 pregnancies were exposed to ocrelizumab within 6 months prior to conception. Mean preconceptive exposure was 14.2 weeks (range: 0.4–24 weeks). 3 patients were also inadvertently given ocrelizumab during the first trimester prior to the discovery of their pregnancies. Mean first trimester exposure was 5.7 weeks of gestation (range: 2–9 weeks). None of the patients had second or third trimester exposure. Table 2 provides a summary of the clinical characteristics of the pregnancies.

With the exception of one patient (M10), all patients received a standard dosing of 600mg of ocrelizumab (either as a single dose or given as two 300mg doses administered two weeks apart for those receiving ocrelizumab for the first time). M10 received only a single dose of 300mg ocrelizumab and was scheduled to have the second 300mg ocrelizumab 2 weeks later, but was found to be pregnant prior to the infusion being due (Table 2).

3.3 Pregnancy and infant outcome

Of the 14 pregnancies, 13 resulted in live births. One patient (M1, first pregnancy) underwent termination of pregnancy due to detection of fetal alobar holoprosencephaly, nuchal thickening, facial abnormalities

Table 2. Clinical characteristics of the pregnancies.

		At Conception			*OCR Infusions*						
Mother	*Newborn*	*Age*	*Duration of disease (weeks)*	*No. of cycles of OCR infusions*	*Before conception (weeks)*	*During pregnancy (weeks)*	*Postpartum (weeks)*	*Duration of treatment interruption (weeks)*	*Pregnancy complications*	*B-cell repopulation during pregnancy*	*Relapse*
M1	TOP *	32	120	1	13	No	2	No	Fetal anomalies, triploidy	No	No
	NB1	33	132	2	18	No	48	105	No	No	No
M2	NB2	38	132	1	18	6	21	57	No	No	No
M3	NB3	34	156	2	22	9	31	64	No	No	No
M4	NB4	34	12	1	2	No	30	72	No	No	No
	NB5	36	48	3	17	No	9	66	No	No	No
M5	NB6	40	120	2	11	No	7	56	Breech presentation	No	No
M6	NB7	39	48	1	24	No	24	88	No	No	No
M7	NB8	30	48	2	8	No	1	46	Placental insufficiency, oligohydramnios, breech presentation	Yes (At 35w of gestation)	No
M8	NB9	32	12	2	21	No †	Switched to NTZ during pregnancy	Switched to NTZ during pregnancy	No	Yes (At 2w of gestation)	No
M9	NB10	35	12	2	18	No	29	85	GDM, primary PPH	No	No
M10	NB11	33	1	1 (only a single dose of 300mg of OCR)	No	2 ¶	4	40	No	No	No
M11	NB12	37	36	4	13	No	8	61	No	No	No
M12	NB13	34	36	2	0.4	No	1	41	No	No	No

Legend: OCR: ocrelizumab, w: weeks, M: male, F: female, SVD: spontaneous vaginal delivery, LSCS: lower segment Caesarean Section, GDM: gestational diabetes, PPH: postpartum haemorrhage, NTZ: natalizumab, TOP: termination of pregnancy.

* Fetal alobar holoprosencephaly and nuchal thickening, facial abnormalities and exomphalos, resulting in termination of pregnancy with cytogenetics confirming triploidy 69 XXY which occurs de novo.

† Mother received Natalizumab infusions throughout pregnancy as a bridging therapy in view of B cells repopulation during early stage of pregnancy.

¶ Only received a single 300mg dose of IV ocrelizumab. Was due for the second 300mg dose of ocrelizumab but fell pregnant before the scheduled infusion.

and exomphalos in the first trimester with the subsequent cytogenetics confirming triploidy 69 XXY (Table 2). There were no reported serious infections or chorioamnionitis among the mothers in our cohort.

The outcome data of the newborns are summarized in Table 3. The median gestational age at birth was 38.7 weeks (range: 38–40 weeks) and the median birth weight was 3364.5 grams (range: 2620–4018 grams). We did not observe any babies who were born preterm or had low birth weights.

Only 1 of 13 (7.7%) newborns (NB2) had a minor congenital anomaly (tongue tie). One infant (NB6) was born with mild transient respiratory distress which resolved spontaneously without specific treatment. Another infant (NB8) developed oligohydramnios in utero secondary to placental insufficiency and was born with hyaline membrane disease, requiring non-invasive ventilation soon after birth and intubation on day 3 of life, complicated with sepsis and hypoglycaemia, requiring treatment with antibiotics. The full blood count showed leukocytosis with no evidence of lymphopenia noted.

We did not observe any miscarriage or stillbirth in our cohort.

3.4 Duration of ocrelizumab treatment interruption during pregnancy, intrapartum B-cell monitoring and relapse of disease

All patients ceased ocrelizumab upon finding out about their pregnancy status. We monitored the B-cell subsets of all mothers during and after pregnancy, and used CD19 to predict the need for an additional therapy as well as the timing to re-dose ocrelizumab postpartum.

Most of the patients' B-cells remained suppressed and did not require any additional therapy except for one patient (M8) who required a bridging therapy with natalizumab throughout her pregnancy due to repopulation of B cells during an early stage of her pregnancy. Another patient (M7) showed reconstitution of B cells during the third trimester of pregnancy, 2 weeks prior to delivery, and required administration of ocrelizumab one week postpartum (Table 2).

For those who did not require an additional therapy during pregnancy, the mean duration of treatment interruption was 65.1 weeks (Range: 40–105 weeks) (Table 2).

There was no reported MS relapse in our cohort (Table 2). All MRI performed postpartum showed stable appearances despite treatment interruption during pregnancy.

3.5 Breastfeeding

Of the 8 (61.5%) patients of breastfed their infants, only 4 (30.8%) patients received ocrelizumab during breastfeeding, with the remainder completed breastfeeding for at least 6 months prior to resuming ocrelizumab therapy. There were no reported adverse effects in the infants exposed to ocrelizumab during breastfeeding.

4. Discussion

We did not identify any concerning major safety signals among the patients who were exposed to ocrelizumab prior to conception or during the first trimester of pregnancy. There was no report of serious maternal infection or chorioamnionitis during pregnancy.

In contrast to a recently published study which reported an increased risk of premature births in a group of patients with neuroimmunologic disorders including MS who were exposed to either ocrelizumab or rituximab, we have not found such an association.[7]

One patient (M1, Pregnancy 1) had an elective termination of pregnancy following detection of fetal anomalies related to triploidy 69 XXY. Triploidy is a chromosomal abnormality which occurs sporadically in 1% to 3% of pregnancies[8,9] and cannot be attributed to the use of ocrelizumab.

M7 developed placental insufficiency during pregnancy without any identifiable risk factors. The cause of placental insufficiency in this case was unclear, and it remained uncertain as to whether ocrelizumab could have any direct effect on the placenta. To our knowledge, there is no report of ocrelizumab causing placental insufficiency to date, but a larger scale study is required to further investigate this.

We believe that the neonatal sepsis in M7's infant was not related to the use of ocrelizumab as the mother received ocrelizumab 8 weeks prior to conception, and the drug would have been eliminated from the body before it could cross the placenta after the 16th week of gestation.

Importantly, our study found that six-monthly ocrelizumab prior to pregnancy and withholding the infusion during the pregnancy can result in a stable

Table 3. Pregnancy and infant outcomes.

	OCR Infusion		*Complications*		*Infants' data*				*APGAR*	
Newborn	*Preconception (weeks)*	*During pregnancy (weeks)*	*Pregnancy complications*	*Infant complications*	*Mode of delivery*	*Gender*	*BW (g)*	*Gestation (weeks)*	*1min*	*5min*
NB1	18	No	No	No	LSCS	M	3185	38	9	9
NB2	18	5	No	Posterior tongue tie	SVD	M	3452	39	9	9
NB3	22	9	No	No	LSCS	F	3425	38	NA	NA
NB4	2	No	No	No	LSCS	M	3620	40	9	9
NB5	17	No	No	No	LSCS	M	3430	40	7	9
NB6	11	No	Breech presentation	Mild and transient respiratory distress at birth	LSCS	F	3220	38	9	9
NB7	24	No	No	No	LSCS	M	3608	40	NA	NA
NB8	8	No	Placental insufficiency, oligohydramnios, breech presentation	Hyaline membrane disease, neonatal sepsis, hypoglycaemia	LSCS	M	3180	38	7	9
NB9	21	No†	No	No	SVD, Forceps	M	3900	38	6	9
NB10	18	No	GDM, primary PPH	No	LSCS	M	2620	38	9	9
NB11	No	2¶	No	No	LSCS	F	2930	38	9	10
NB12	13	No	No	No	SVD	F	4018	40	9	9
NB13	0.4	No	No	No	LSCS	F	3150	38	9	9

Legend: w: weeks, BW: birth weight, M: male, F: female, SVD: spontaneous vaginal delivery, LSCS: lower segment Caesarean Section, GDM: gestational diabetes, PPH: postpartum haemorrhage, NTZ: natalizumab, NA: not available.

† Mother received Natalizumab infusions throughout pregnancy as a bridging therapy in view of B cells repopulation during early stage of pregnancy.

¶ Only received a single 300mg dose of IV ocrelizumab. Was due for a second 300mg dose of ocrelizumab but fell pregnant before the scheduled infusion.

disease course. As the suppression of CD19 B cells has been shown to correlate with therapeutic response of anti-CD20 monoclonal antibody therapy such as rituximab,[10] we monitored CD19 B cells in these patients to predict the need for a bridging therapy during pregnancy and to determine the timing to restart ocrelizumab post-delivery. A majority of our patients did not require any additional therapy as their B cells remained suppressed throughout pregnancy. We did not observe any relapses despite a prolonged ocrelizumab treatment-free interval of up to 105 weeks. Some patients even managed to complete breastfeeding for at least 6 months before ocrelizumab therapy was re-commenced. Studies investigating extended-interval dosing of ocrelizumab is scarce, but the median time to B-cell repopulation for ocrelizumab had been suggested to take approximately 62 weeks after 3 treatment cycles and 72 weeks after 4 treatment cycles.[11] Interestingly, one MS treatment-naïve patient (M10) who received only a half-dose (300mg) of ocrelizumab pre-pregnancy remained protected from disease activity throughout pregnancy despite a treatment interruption interval of 40 weeks. Her CD19 B lymphocytes taken one week postpartum remained suppressed with no evidence of relapse despite being given only a single half-dose of ocrelizumab.

In patients like M7 who developed repopulation of B cells as the pregnancy approached term, we suggest for timely re-dosing of ocrelizumab soon after delivery to prevent a relapse. On the other hand, if reconstitution of B cells occurs at an early stage of pregnancy, our approach is to transition to an alternative high efficacy DMT which is considered safe in pregnancy. We chose to switch M8 to natalizumab after considering the significant risk of an MS relapse in this patient. There have been reports suggesting that the use of natalizumab in the first trimester of pregnancy is safe.[12–16] We continued M8 on natalizumab until the 32nd week of gestation, according to our own experience,[17] and in line with the UK consensus on pregnancy in MS[18] to reduce the risk of transient fetal haematological abnormalities with third trimester exposure to the drug.[13]

With regard to the potential risk of neonatal B-cell depletion, none of our patients were exposed to ocrelizumab after the second trimester when transplacental ocrelizumab transfer occurs, and hence we did not anticipate any of our neonates to have B cell depletion.

Only minimal amounts of ocrelizumab are detectable in breastmilk,[2] and there is no published evidence that has demonstrated significant risk to the infant. Only four of our patients received ocrelizumab during breastfeeding, and there were no reported adverse effects in the infants.

The main limitation of our study was the retrospective nature which predisposes to a number of potential confounders and the small number of participants included. With the potential ethical implications, prospective studies or randomized controlled trials in MS patients during pregnancy will be difficult.

5. Conclusion

We did not observe increased adverse events in our cohort of patients who were exposed to ocrelizumab prior to conception or during the first trimester of pregnancy. Our data suggests that patients with MS who had been treated with ocrelizumab before pregnancy experienced a stable MS disease course throughout pregnancy and during postpartum period despite a prolonged period of treatment interruption. Future observational studies incorporating larger patient cohorts will be required to provide more robust data.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Shin Yee Chey has no disclosures. Allan Kermode has in recent times received speaker honoraria and Scientific Advisory Board fees from Bayer, BioCSL, Biogen-Idec, Merck, Novartis, Roche, Sanofi-Aventis, Sanofi-Genzyme, Teva, NeuroScientific Biopharmaceuticals, Innate Immunotherapeutics, and Mitsubishi Tanabe Pharma.

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