Ocrevus and Pregnancy and Lactation in Women with Multiple Sclerosis

This article responds to your request for information on Ocrevus® (ocrelizumab) and pregnancy and lactation in women with multiple sclerosis.

In brief

- There is limited data on the use of Ocrevus in pregnant women or women who are breastfeeding.
- As of July 2023, 3,244 pregnancies had been reported in women with multiple sclerosis treated with Ocrevus.
    - Available data do not suggest an increased risk of adverse pregnancy or infant outcomes with Ocrevus use.
- The ongoing SOPRANINO and MINORE studies are evaluating the placental transfer of Ocrevus from mother to baby.
- The SOPRANINO study is also evaluating the transfer of Ocrevus into breastmilk.

Abbreviations

CIS=clinically isolated syndrome
DMT=disease modifying therapy
GA=gestational age
LLN=lower limit of normal
LMP=last menstrual period
MCA=major congenital abnormality
MS=multiple sclerosis

Ocrevus use in pregnancy product label information

Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.[1] There are no adequate and well-controlled data from studies in pregnant women. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

Please refer to the locally approved prescribing information for further information on Ocrevus.

Pregnancy outcomes in clinical trials and the post-marketing setting

Bove et al. described pregnancy outcomes of women who were exposed to Ocrevus in clinical trials in MS and post-marketing experience up to July 2023.[2] As of March 2023, more than 300,000 patients have been treated with Ocrevus globally.[3]

Maternal-exposure pregnancies in patients treated with Ocrevus

There were 3,244 maternal-exposure pregnancies in patients treated with Ocrevus for MS as of July 2023.[2] Of these pregnancies, 2,444 were prospective in nature (i.e., final outcomes were unknown at initial notification). Of the 1,144 cases with known outcomes, 956 (83.6%) resulted in live births:[2]

- 61.3% of pregnancies were full term

- 8.6% were pre-term
- 30.1% had an unknown gestational week

Details of the outcomes among prospective cases are shown in Table 1. Across exposure categories, data were in line with expected epidemiological ranges.[4,5]

Table 1. Summary of pregnancies with known outcomes[2]

Pregnancies with known outcomes	Not exposed in utero (n=350)	Exposed in utero (n=512)	Unknown timing of exposure (n=282)	Total cases (n=1144)
Live births, %†	**88.3%**	**84.2%**	**76.6%**	**83.6%**
Full term (≥37 weeks)‡	70.9%	65.7%	38.9%	61.3%
Pre-term (<37 weeks)‡	8.7%	9.5%	6.5%	8.6%
Unknown GA‡	20.4%	24.8%	54.^%	30.1%
Ectopic pregnancy, n (%)†	0.9%	0.8%	2.5%	1.2%
Therapeutic/elective termination, n (%)†	1.7%	7.4%	5.0%	5.1%
Intrauterine foetal death n (%)†				
Spontaneous abortion (≤22 weeks)	9.1%	7.4%	16%	10.1%
Stillbirth (>22 weeks)	-	0.2%	-	<0.1%

†Percentages represent fractions of the total known outcomes of the respective exposure category (not exposed in utero, exposed in utero unknown exposure, total). ‡Percentages represent fractions of the total live births for the respective exposure category (not exposed in utero, exposed in utero unknown exposure, total). The dash indicated that no cases were reported.

Major congenitial abnormalities in pregnancies with known outcomes

Fourteen major congenital abnormalities were reported among the pregnancies with known outcomes (Table 2). One live birth reported two MCAs.[2] Similar background rates of congenital abnormalities have been reported in both MS and the general population (approximately 2-4%).[4-7]

Table 2. Major congenital abnormalities[2]

Pregnancies with known outcomes	Not exposed in utero	Exposed in utero	Unknown timing of exposure	Total cases
Live births	**309**	**431**	**216**	**956**
Live births with MCA, n (%)	6 (1.9)	9 (2.1)	1 (0.5)	16 (1.7)
Full term with MCA), n	4	6	1	11
Pre-term with MCA, n	2	3	-	5
Unknown GA with MCA, n	-	-	-	-
Stillbirths >22 weeks	0	1	0	1
Stillbirths with MCA, n	-	1	-	1
Live birth/ stillbirth with MCA n (%)	6 (1.9)	10 (2.3)	1 (0.5)	17 (1.8)

†Percentages represent fractions of the total known outcomes of the respective exposure category (not exposed in utero, exposed in utero unknown exposure, total). ‡Percentages represent fractions of the total live births for the respective exposure category (not exposed in utero, exposed in utero unknown exposure, total). §The dash indicated that no cases were reported.

Infant exposure to Ocrevus through breastfeeding

As of July 2023, 400 babies had 1-year follow-up data available.[2] One hundred twenty-two babies were exposed to Ocrevus through breastfeeding, while 278 babies had no exposure through breastfeeding. Among the babies with breastfeeding exposure to Ocrevus, 29 (7%) were exclusively exposed via breastfeeding.

Five babies who were exposed through breastfeeding were vaccinated. Forty-three babies experienced adverse events (9 exposed and 34 non-exposed through breastfeeding), primarily infections. B cell levels were available in 7 exposed infants and the levels were within normal limits of age-specific ranges.

Ocrevus exposure reported in registries,observational studies and case reports

Additional reports of Ocrevus exposure during pregnancy and lactation have been described in a number of registries, observational studies and case reports.[8-20] We refer the interested reader to the publications for more information.

Ongoing clinical trials evaluating Ocrevus in pregnancy and lactation

Women planning pregnancies are usually excluded from clinical trials and therefore there is little evidence on the safety of DMTs during pregnancy and lactation. Available data on Ocrevus suggest no increased

risk in terms of pregnancy or infant outcomes. However, there are a number of uncertainties such as whether Ocrevus crosses the placenta or is excreted in breastmilk; and if so, whether infant B cell development, immune responses or growth and development are affected. The ongoing SOPRANINO and MINORE studies are designed to address these uncertainties.[21]

SOPRANINO study (NCT04998851)

SOPRANINO is a prospective, multicenter, open-label study in women with CIS or MS, evaluating the pharmacokinetics of Ocrevus in the breast milk of lactating women and the resultant exposure and pharmacodynamic effects in the infant.[21,22] The study will enrol at least 20 women who delivered a term infant and plan to breastfeed for at least 60 days after the first postpartum Ocrevus infusion.

The co-primary endpoints of the study are

- proportion of infants with B-cell levels below the LLN, measured 30 days after the mother's first postpartum Ocrevus infusion, and
- estimated average daily infant dose over 60 days after the mother's first postpartum Ocrevus infusion.

Additional endpoints will assess

- immune responses
- infant growth and development, and
- adverse events in the mother and infant.

MINORE study (NCT04998812)

MINORE is a Phase 4, prospective, multicenter, open-label study in women with CIS or MS, evaluating the placental transfer of Ocrevus, and the corresponding pharmacodynamic effects in infants.[21,23] The study will enrol approximately 44 women between GWk 22–26, whose last Ocrevus dose occurred at any time from 6 months before the LMP until the end of the first trimester.

The primary endpoint of the study is the proportion of infants with B-cell levels below LLN at Week 6 of life. Key secondary endpoints are

- serum Ocrevus levels in umbilical cord blood, and
- infant humoral immune responses to vaccinations.

Additionally, infant growth and development will be followed over the first year, and infant immune responses to vaccines will be assessed. The rate and nature of adverse events in the mother and infant will also be evaluated.

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