

Pregnancy Outcomes in Women with Multiple Sclerosis Who Had Exposure to Ocrelizumab: a Systematic Review of the Literature

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ABSTRACT

Objective: To estimate the pooled prevalence of pregnancy-related issues in women who were exposed to Ocrelizumab before or during pregnancy.

Methods: PubMed, Scopus, EMBASE, Web of Science, Google Scholar, references and conference abstracts were comprehensively searched by two independent researchers. The search was conducted on 1 June 2023.

Results: A literature search revealed 320 records, of which 44 full-texts were evaluated and only five studies remained for the systematic review, among which one study was conducted in Australia, one in the United States, one in Canada and one in the United Kingdom. All eligible studies were conducted between 2017 and 2022. They included a number of patients ranging from 12 to 608, and totaled 1 305 participants and 1 306 pregnancies. The pooled prevalence of term delivery was 46% (95% CI 31-61%) ($I^2=94.5\%$, $P<0.001$). The pooled prevalence of abortion was 9% (95% CI 4-14%) ($I^2=80\%$, $P<0.001$). Three studies reported on the number of ectopic pregnancies. The pooled prevalence of ectopic pregnancies was 5% (95% CI 2-4%) ($I^2=60\%$, $P<0.001$). The pooled prevalence of major congenital malformations was 2% (95% CI 1-3%) ($I^2=0$).

Conclusions: The results of this systematic review show that exposure to Ocrelizumab during conception is not associated with a higher frequency of preterm deliveries or major malformations.

Keywords: Ocrelizumab, pregnancy, multiple sclerosis, abortion, delivery, ectopic pregnancy, congenital malformation.

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INTRODUCTION

Demyelinating plaques of the central nervous system (CNS) are characteristic of multiple sclerosis (MS), an autoimmune inflammatory disease that affects women more than men, with a wide range of physical and psychological complications (1).

B cells and T cells play a role in the development of MS and new treatments target B cells to control disease activity and progression (2). The role of B cells in disease pathogenesis highlights the role of antibodies and complements, which is confirmed by the presence of B cell-related chemokines in the CNS and intrathecal immunoglobulins (3, 4). Presentation of CD-20 antigen on the surface of B cells makes it possible to differentiate and proliferate (5).

Ocrelizumab is a humanized monoclonal anti-CD20 antibody which has been proven to be administered for relapsing-remitting MS (RRMS) and primary progressive MS (PPMS), which is associated with progression and activity reduction (6, 7). The mean half-life of ocrelizumab is 26 days and it takes 4.5 to be eliminated from the body (8). It is recommended to avoid pregnancy at least six months after the last infusion of Ocrelizumab (9, 10).

Ocrelizumab administration during pregnancy leads to prolonged B-cell depletion, which can cause infections, miscarriages, preterm birth and stillbirths (11).

Animal studies have shown that Ocrelizumab exposure during pregnancy was leading to perinatal death, neonatal B-cell depletion as well as bone marrow, renal and testicular toxicity (9).

There are studies regarding the effects of Ocrelizumab on fetuses and pregnancy outcomes, but there is no specific systematic review in this field. Therefore, this study aimed to estimate the pooled prevalence of pregnancy-related issues in women exposed to Ocrelizumab before or during pregnancy. □

MATERIALS AND METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (12).

Eligibility criteria

We included retrospective or prospective cohort studies or case series reports on pregnancy outcomes in women with MS who were treated with Ocrelizumab. Letters to the editor, case reports and case-control studies were all excluded.

Information sources

PubMed, Scopus, EMBASE, Web of Science, Google Scholar, references and conference abstracts were comprehensively searched by two independent researchers. The search was conducted on 1 June 2023.

Search strategy

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(((((Ocrelizumab[Supplementary Concept]
OR (ocrelizumab[Text Word])) OR (ocrevus[Text
Word])) OR (R1594[Text Word])) OR (R1594[Text
Word])) OR (R-1594[Text Word])) OR (RG-
1594[Text Word])) OR (PR 070769[Text Word]))
OR (PR070769[Text Word])) OR (PR-070769[Text
Word])) AND (((((((((((((((((((((((((((((((
Live birth[MeSH Terms]) OR (Live birth*[Text Word])
OR (Parturition[MeSH Terms])) OR
(Parturition*[Text Word])) OR (Birth*[Text
Word])) OR (Childbirth*[Text Word])) OR
(Stillbirth[MeSH Terms])) OR (Stillbirth*[Text
Word])) OR (Pregnancy[MeSH Terms])) OR
(Pregnanc*[Text Word])) OR (Gestation[Text
Word])) OR (Abortion, Spontaneous[MeSH
Terms])) OR (Abortion, Spontaneous[Text Word]))
OR (Abortions, Spontaneous[Text Word])) OR
(Spontaneous Abortion*[Text Word])) OR (Early
Pregnancy Loss*[Text Word])) OR (Loss, Early
Pregnancy[Text Word])) OR (Losses, Early
Pregnancy[Text Word])) OR (Pregnancy Loss,
Early[Text Word])) OR (Pregnancy Losses,
Early[Text Word])) OR (Miscarriage*[Text Word]))
OR (Abortion, Tubal[Text Word])) OR (Abortions,
Tubal[Text Word])) OR (Tubal Abortion*[Text
Word])) OR (Congenital Abnormalities[MeSH
Terms])) OR (Congenital Abnormalit*[Text
Word])) OR (Abnormality, Congenital[Text
Word])) OR (Deformit*[Text Word])) OR (Con-
genital Defect*[Text Word])) OR (Defect,
Congenital[Text Word])) OR (Defects,
Congenital[Text Word])) OR (Abnormalities,
Congenital[Text Word])) OR (Birth Defect*[Text
Word])) OR (Defect, Birth[Text Word])) OR (Fetal
Malformation*[Text Word])) OR (Malformation,
Fetal[Text Word])) OR (Fetal Anomal*[Text
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Word])) OR (Anomaly, Fetal[Text Word])) OR (Neonatal outcome*[Text Word]))).

Selection process

Two independent researchers did a comprehensive search in desired databases. EndNote software was used to transfer the search results to the reference manager software and duplicates were deleted.

Two researchers screened the title/abstract of probable studies.

The full texts of potential studies were evaluated, and data were extracted and entered into Excel data sheets. In the case of a discrepancy, a third party solved the conflict.

Data items

We extracted data regarding the total number of patients, name of the first author, publication year, country of origin, mean age, number of term deliveries, abortions, ongoing pregnancies, neonatal deaths, preterm delivery, small for gestational age and major congenital malformations.

Risk of bias assessment

We evaluated the risk of potential bias using the Newcastle-Ottawa Scale (NOS) developed for cohort studies (13).

All statistical analyses were performed using STATA (version 14.0; StataCorp LP, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

Heterogeneity was also assessed using the I-square index (12). A random-effects model was used.

Certainty assessment

For all estimated effect sizes, we reported 95% CI. 

RESULTS

A literature search revealed 320 records, of which 44 full-texts were evaluated, and finally, five studies remained for the systematic review (Figure 1). Three studies were abstracts of conferences. One study was conducted in Australia, one in the United States, one in Canada and one in the United Kingdom. All eligible studies were conducted between 2017–2022. They included a number of patients ranging from 12

TABLE 1. Characteristics of included studies

ID	Author	Year	Country	Study design	Participants	Age	Drug exposure	Term	Ongoing pregnancy	Still birth	Preterm birth	Miscarriage	Elective/therapeutic abortion	Ectopic pregnancy	Major congenital malformation	Quality assessment
1	Bove <i>et al</i>	2020	United States	Cohort	608		Before or during pregnancy	156 (live birth)	134	3		42	37	5		Conference abstract
2	Shin Yee Chey <i>et al</i>	2022	Australia	Retrospective cohort	14 pregnancies of 12 MS patients	34.8 years (2.9)	Six months prior to conception or during pregnancy	13					1			7/9
3	Dobson R <i>et al</i>	2021	UK	Retrospective cohort	604		Before pregnancy or during pregnancy	202	130	5	47		54	13	8	Conference abstract
4	Victor Gitman <i>et al</i>	2022	Canada	Cohort	65	30 (20-45) Mean (range)	Before or during pregnancy	21			4	13	2	3	1	9/9
5	Vukusic <i>et al</i>	2017	Not mentioned (conference abstract)	Retrospective cohort	15		Before or during pregnancy	3	4				6		1	Conference abstract

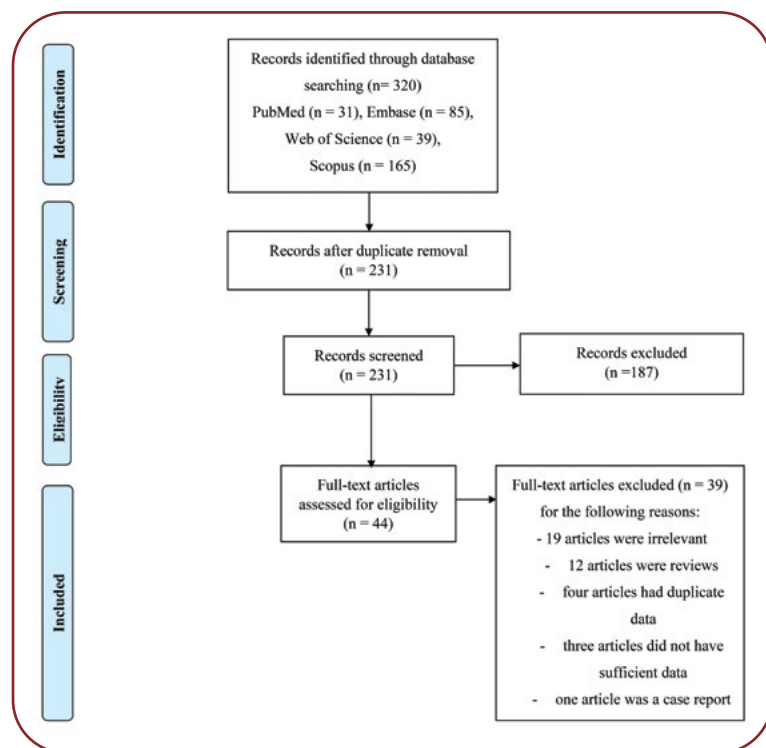


FIGURE 1. Flow chart of included studies

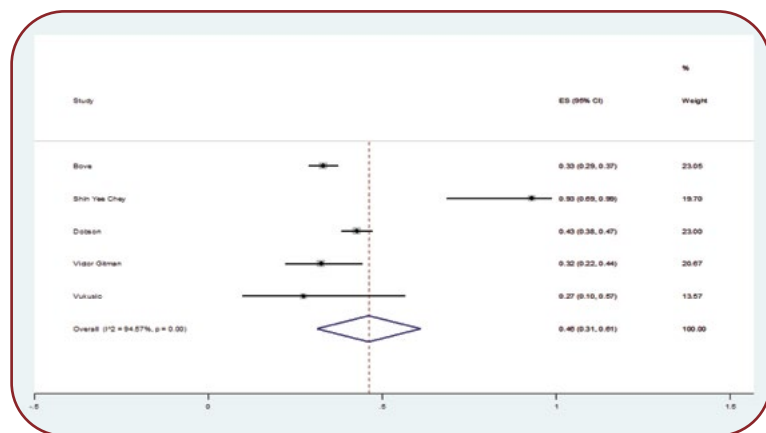


FIGURE 2. Pooled prevalence of term delivery

to 608 and totalized 1 305 participants and 1 306 pregnancies.

Three studies reported the presence of major malformation. For studies conducted by Bove *et al*, Dobson *et al* and Vukusic *et al* we subtracted the number of ongoing pregnancies from the total number of pregnancies to perform a meta-analysis.

The characteristics of eligible studies are summarised in Table 1.

The pooled prevalence of term delivery was 46% (95% CI 31-61%) (I²=94.5%, P<0.001) (Figure 2).

The pooled prevalence of abortion was 9% (95% CI 4-14%) (I²=80%, P<0.001) (Figure 3).

Three studies reported on the number of ectopic pregnancies. The pooled prevalence of ectopic pregnancy was 5% (95% CI 2-4%) (I²=60%, P<0.001) (Figure 4).

The pooled prevalence of major congenital malformations was 2% (95% CI 1-3%) (I²=0) (Figure 5). □

DISCUSSION

To our knowledge, this is the first systematic review in this field. Our results showed that in completed pregnancies, the pooled prevalence of term delivery and abortion was 46% and 9%, respectively. We also found that the pooled prevalence of ectopic pregnancy and major congenital malformations was 5% and 2%, respectively. These findings could help physicians who are involved in treating MS-cases.

Chen *et al* retrospectively reviewed the results of 14 pregnancies in 12 patients with MS and reported 13 live births, and one pregnancy was terminated due to the detection of a chromosomal defect. They reported no serious maternal infections and most patients were relapse-free. They recorded no major congenital anomalies, preterm births, stillbirths (11).

Gitman *et al* identified 65 Canadian pregnant women exposed to Ocrelizumab. They reported 47 live births, of which 21 were term deliveries and four preterms. Three ectopic pregnancies have been reported (14).

Another cohort study conducted by Kumpfel in Germany (we did not include this study as patients who were exposed to Rituximab or Ocrelizumab were all evaluated totally, not separately), followed women with MS, neuromyelitis optica spectrum disorders (NMOSDs) and other neuroimmunologic diseases (ONID) after treatment with rituximab (RTX)/ocrelizumab (OCR) 12 months before or during pregnancy. They were divided into three groups: RTX/OCR >6 but ≤12 months before the last menstrual period (LMP), RTX/OCR< six months before the LMP and pregnant group = RTX/OCR after LMP. The authors found that the number of preterm births was higher in the third group. They also found that gestational age was significantly lower in the third group, and only two major congenital abnormalities were observed in the third

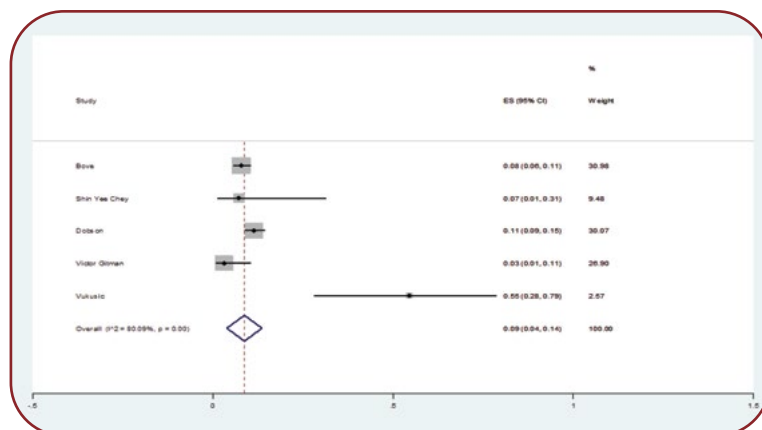


FIGURE 3. Pooled prevalence of abortion

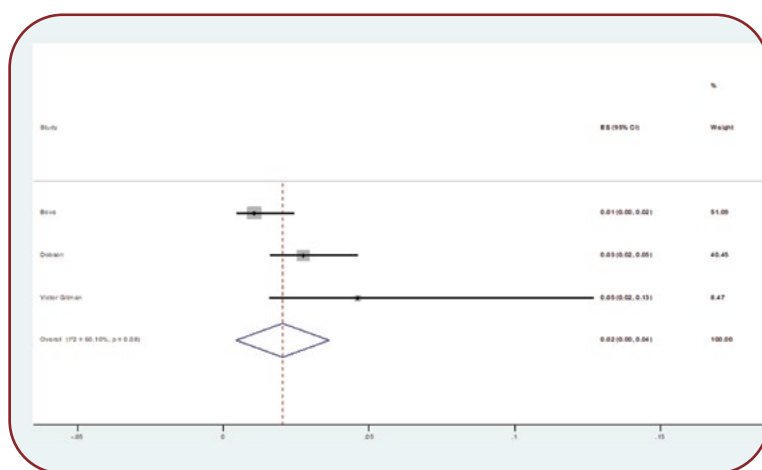


FIGURE 4. Pooled prevalence of ectopic pregnancy

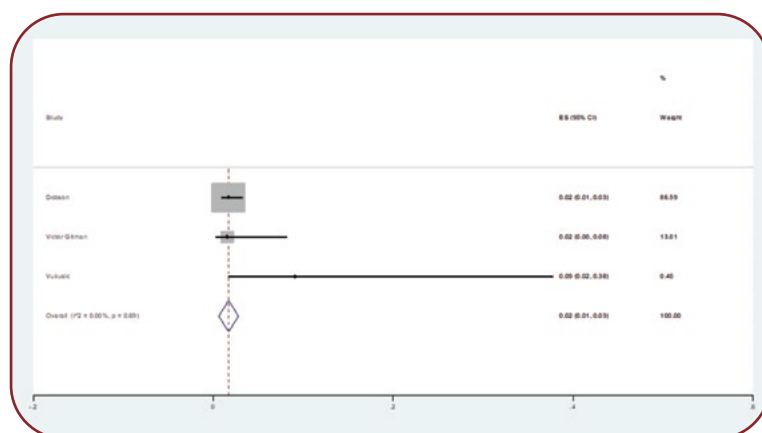


FIGURE 5. Pooled prevalence of major congenital malformations

group (both in women who had exposure to Ocrelizumab) (15).

It has been shown that exposure to anti CD20 monoclonal antibodies such as Rituximab or Ocrelizumab was not associated with teratogenicity (16, 17).

Before the introduction of high-efficacy disease-modifying therapies (DMTs), women with MS should wait for disease activity stabilization to attempt pregnancy, and reports show rebound of the disease after discontinuation of Fingolimod and Natalizumab (18-22).

Pregnancy and childbearing are important issues in many couples. There is no consensus regarding the administration of high-efficacy DMTs such as Ocrelizumab.

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that depletes B cells by targeting CD20-expressing B cells (23). The antibody-dependent cytotoxicity of Ocrelizumab is greater than that of Rituximab, whereas complement-dependent cytotoxicity is less (23).

Gingele *et al* show that administration of 300 mg Ocrelizumab for two weeks leads to the depletion of both CD20-expressing T cells and B cells (24). The depletion of CD-20 presenting B cells causes a reduction in antibody production, antigen presentation and suppression of pro-inflammatory cytokine production (25). On the other hand, depletion of T cells presenting with 20 results in the reduction of TNF α , IL-1 β and IL-17, which have roles in MS development. Decreased disease activity on MRI evaluation occurs during four weeks of Rituximab or Ocrelizumab treatment (26, 27).

It could be a good treatment option for women with pregnancy plans as its immunomodulatory effects last long (14). It does not cross the placenta during the first trimester (27). In most women, B cells are depleted and they need no dose because of the relapse-free period during pregnancy and after delivery (11).

This systematic review had some limitations. First, the number of eligible studies was limited. Second, the sample size was small.

Therefore, more longitudinal observational studies with larger sample sizes from different nations are further needed. $\square$

CONCLUSION

The results of this systematic review shows that exposure to Ocrelizumab during conception is not associated with a higher frequency of pre-term deliveries or major malformations. $\square$

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