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SAFETY AND EFFICACY OF RITUXIMAB IN NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) DURING PREGNANCY: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Neuromyelitis Optica Spectrum Disorder (NMOSD) is known to present an elevated risk of disease recurrence during pregnancy and in the postnatal phase. Rituximab, an anti-CD20 monoclonal antibody, is frequently employed to mitigate relapse risk, yet its safety profile during gestation is not well established.

Methods: We conducted a systematic literature search in PubMed using the terms "Rituximab," "Neuromyelitis Optica," and "Pregnancy." Of 16 records identified, seven studies—including one systematic review, one cohort analysis, two case series, and three individual case reports—met inclusion criteria. Data on rituximab exposure timing, disease stability, and maternal and fetal outcomes were extracted and evaluated.

Results: Most reports indicated a reduction in disease relapse during pregnancy with rituximab use. The majority did not demonstrate increased risk of miscarriage or preterm labor compared to general population rates, though one series noted more adverse fetal events. Limitations included small sample sizes and retrospective design with potential confounding factors.

Conclusions: Rituximab administered prior to conception may provide a favorable balance of benefits and risks in NMOSD management during pregnancy. Further research—especially prospective trials —is necessary to validate its safety profile.

KEYWORDS: Rituximab, NMOSD, Pregnancy, Safety, Systematic Review, Relapse

INTRODUCTION

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an uncommon autoimmune condition marked by recurrent episodes that predominantly impact the optic nerves and spinal cord, often resulting in severe disability including blindness and paralysis. The disease disproportionately affects women of reproductive age, which makes its clinical management during pregnancy particularly challenging. Unlike multiple sclerosis (MS), NMOSD is associated with increased disease activity during pregnancy and a heightened risk of relapse in the postpartum period, often leaving lasting deficits [1].

The disease is mediated by pathogenic autoantibodies, especially those directed against aquaporin-4 (AQP4), a channel protein located on astrocytic membranes. These antibodies play a central role in triggering immune-mediated damage [2]. Immunotherapies that suppress the immune system, such as rituximab which depletes B-cells by targeting CD20 antigens, have been effective in reducing relapses and slowing disease progression [3].

Rituximab is widely used as a maintenance therapy for NMOSD due to its established role in preventing relapses. However, its use during pregnancy remains controversial, largely due to uncertainties about fetal exposure, potential teratogenicity, and neonatal immune suppression. Consequently, treatment decisions in pregnant NMOSD patients must carefully balance the benefits of preventing maternal relapses against potential fetal harm [4,5].

This systematic review aims to summarize existing data on rituximab use during pregnancy in NMOSD patients, evaluating maternal disease activity, obstetric outcomes, and fetal safety [3–7].

METHODS

1.Protocol and Registration

This systematic review adhered to the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Although a structured protocol was formulated prior to commencing the review, it was not registered on PROSPERO or similar registries due to constraints in time and resources. Nevertheless, PRISMA methodology was rigorously followed to ensure transparency, reproducibility, and methodological rigor throughout the review process.

2. Inclusion and Exclusion Criteria

Inclusion Criteria:

Studies were considered eligible if they met the following parameters:

- Population: Pregnant individuals with a confirmed diagnosis of NMOSD.
- Intervention: Rituximab exposure either during pregnancy or within six months prior to conception.
- Outcomes: Studies that reported maternal outcomes (e.g., relapse control) and/or fetal outcomes such as miscarriage, preterm birth, stillbirth, or congenital anomalies.
- Study Designs: Systematic reviews, cohort studies, case series, and case reports that included human subjects.
- Language and Availability: Articles published in English, available in full text, and indexed in PubMed.

Exclusion Criteria:

The following studies were excluded:

- Research conducted on animals or in vitro models.
- Pharmacokinetic-only investigations.
- Articles not focusing on rituximab exposure in pregnancy.
- Reviews without original clinical data or those presenting duplicate patient datasets.

3.Search Strategy

A comprehensive literature search was conducted using the PubMed database. The following Medical Subject Headings (MeSH) and keywords were employed:

- "Rituximab"
- "Neuromyelitis Optica"
- "Pregnancy"

Filters were applied to restrict results to human studies published in English. All available literature up to the time of manuscript drafting was considered. Relevant citations from included studies were also screened to identify additional eligible sources.

4.Selection Process

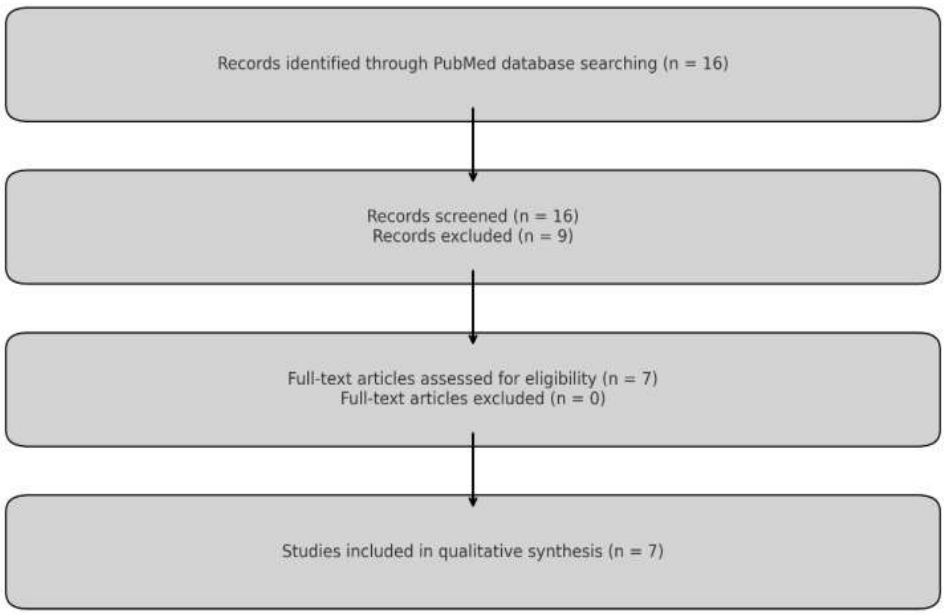
Two reviewers independently performed title and abstract screening, followed by full-text review of potentially relevant articles. Any disagreements regarding eligibility were resolved through discussion and consensus. Out of 16 initially identified publications, 7 met all criteria and were included in the final review. The PRISMA flow diagram illustrates the selection process.

5.Data Collection

A standardized and pilot-tested data extraction sheet was used to ensure consistency. The following information was systematically extracted from each study:

- Lead author, year, and study location
- Type of study design (e.g., case report, cohort analysis)
- Number and clinical characteristics of patients
- Rituximab dosing and timing relative to conception or pregnancy
- Maternal outcomes (e.g., relapse frequency, disease stability)
- Fetal outcomes (e.g., miscarriage, stillbirth, prematurity, congenital issues)

Two authors independently conducted the data extraction, and discrepancies were resolved through mutual review. In cases of unclear or missing data, corresponding study authors were contacted to obtain clarification.



RESULTS

Study Selection

A total of 16 articles were retrieved from the PubMed search. After screening abstracts and titles for eligibility, 9 studies were excluded for not meeting the predefined criteria. The remaining 7 articles were selected for detailed analysis. These consisted of a variety of study types: one systematic review, one prospective cohort study, two case series, and three individual case reports. The flow of study selection is outlined in the accompanying PRISMA diagram.

Study Characteristics

Table 1 summarizes the characteristics of included studies, including study design, number of patients, rituximab exposure timing, and reported outcomes.

Study	Design	Patients	Exposure	Key Findings	Limitations
Das et al.	Systematic review + case series	102 pregnancies	≤6 months before/during pregnancy	No major safety concerns; confounded by methotrexate use	Heterogeneous data, confounders
Das et al. (subset)	Case series	11 (6 MS, 3 NMOSD)	≤6 months before pregnancy	No relapses during pregnancy, 1 postpartum relapse	No Rtx during pregnancy, no B-cell monitoring
Kümpfel et al.	Cohort study	13	≥6 months, ≤6 months, and during pregnancy	Only 1 relapse; more preterm births with during-pregnancy use	Small size, short follow-up
Ahadi et al.	Case series	8	During pregnancy	3 adverse outcomes (2 abortions, 1 stillbirth)	No efficacy data, small sample
Kim et al.	Registry case series	14	≤6 months before conception	1 relapse, 3 spontaneous abortions	Retrospective design
Munger & Samkoff	Case report	1	During pregnancy	Initiation of Rituximab during pregnancy	Single case
Study	Design	Patients	Exposure	Key Findings	Limitations
Pellkofer et al.	Case report	1	During pregnancy	Stable disease course	Single case
Ringelstein et al.	Case report	1	During pregnancy	Low-dose Rituximab postpartum prevented rebound	Single case

Summary of Included Studies

- Das et al. (2018) conducted a systematic review of 102 pregnancies exposed to rituximab across multiple indications. Although most patients tolerated the drug without major adverse effects, interpretation was limited due to concurrent use of other immunosuppressants (notably methotrexate), which are known teratogens. A subset case series within the same study reported 11 patients (6 patients with Multiple sclerosis, 3 with NMOSD) who received rituximab within 6 months before conception. None experienced relapses during pregnancy, and there were no miscarriages or preterm births. However, no patients in this subset received rituximab during pregnancy.
- Kümpfel et al. (2020) presented a prospective cohort study comparing pregnancy outcomes in patients receiving rituximab before vs. during pregnancy. Among 13 NMOSD patients, only one relapse occurred during pregnancy. Notably, a higher rate of preterm births was observed in the group exposed during pregnancy, suggesting timing of exposure may influence fetal outcomes. Small sample size and short follow-up limited conclusions.
- Ahadi et al. (2021) described 8 NMOSD patients in a case series who were treated with rituximab during pregnancy. Three adverse fetal outcomes were reported: two spontaneous abortions and one stillbirth. The study lacked data on disease activity and relapse, limiting its assessment of efficacy.
- Kim et al. (2020) analyzed registry-based data of 14 patients who received rituximab within 6 months before conception. Only one maternal relapse occurred during pregnancy. There were three spontaneous abortions and one

elective abortion. This study reinforced the potential benefit of rituximab in controlling disease activity during gestation, although the exact contribution of rituximab to fetal outcomes remains uncertain.

- Munger and Samkoff (2020) reported a single case of initiating rituximab during early pregnancy for newly diagnosed NMOSD. The patient remained relapse-free, and pregnancy progressed without complications.
- Pellkofer et al. (2009) described an inadvertent pregnancy during rituximab therapy. Despite ongoing exposure, the patient had no relapses, and fetal outcome was uneventful.
- Ringelstein et al. (2013) reported a case involving therapeutic B-cell depletion during pregnancy, followed by low-dose rituximab postpartum to prevent rebound relapses. No relapses or fetal complications were noted, and neonatal anti-AQP4() antibody levels were monitored.

Key Findings

- Relapse Suppression: Across most studies, rituximab given before pregnancy was associated with a notable reduction in disease relapses during both pregnancy and the postpartum period.
- Pregnancy and Fetal Outcomes: Most studies reported miscarriage and preterm birth rates within the expected range for the general population. However, Ahadi et al.'s case series stood out with a higher number of adverse fetal outcomes.
- Impact of Exposure Timing: Evidence suggests that rituximab use during pregnancy—especially in early trimesters—may be linked to an increased risk of preterm birth. Nonetheless, the limited sample size restricts the ability to draw definitive conclusions.

DISCUSSION

This systematic review brings together current evidence on the maternal and fetal outcomes associated with rituximab use in pregnant individuals diagnosed with Neuromyelitis Optica Spectrum Disorder (NMOSD). Despite inherent variability across study designs and relatively small patient populations, the findings indicate that rituximab, when administered before conception, may provide substantial disease control without significantly increasing risks to the fetus.

Disease Activity and Relapse Control

One consistent observation across the reviewed studies was the notable reduction in disease relapses when rituximab was used prior to pregnancy. Given NMOSD's high risk for severe and potentially disabling relapses—especially in the postpartum period—ensuring disease quiescence before conception is critical. Rituximab, by targeting CD20-positive B-cells, effectively dampens the autoimmune activity responsible for relapses [3,4]. Most patients receiving rituximab within six months before conception remained relapse-free during gestation, underscoring the importance of pre-pregnancy disease stabilization

Fetal Outcomes and Timing of Exposure

Fetal complications associated with rituximab exposure were generally in line with expected rates in the general population. Spontaneous abortion rates (approximately 18–25%) reported across several studies were comparable to baseline epidemiological data [1,4,6]. The case series by Ahadi et al. showed a higher-than-expected number of adverse fetal events, but the study lacked detailed control for maternal health status, co-morbidities, or concurrent medications, making causality difficult to establish [5].

Importantly, while pre-conceptional rituximab did not appear to increase fetal risk, data from several reports hinted at a possible rise in preterm delivery when rituximab was administered during pregnancy. The underlying mechanism remains unclear but may involve immune modulation affecting placental development or fetal immune function.

Comparisons with Other Autoimmune Disorders

Rituximab has also been used in other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. In these conditions, outcomes have generally supported its safety during pregnancy, especially when exposure is confined to the pre-conception phase. The parallels observed in NMOSD lend additional reassurance to its cautious use in similar patient populations.

Immunologic Considerations and Neonatal Outcomes

Since rituximab can cross the placenta—especially during the second and third trimesters
—concerns about neonatal B-cell depletion and subsequent immune suppression are valid. However, existing data do not suggest long-term immune dysfunction in neonates exposed in utero. In most reported cases, B-cell counts normalized within a few months post-delivery, and no serious infections were attributed to rituximab exposure [3,7].

Despite these reassuring findings, neonatal B-cell monitoring was infrequently reported, pointing to a gap in postnatal care and research follow-up.

Clinical Implications

The available evidence suggests that pre-conception rituximab offers a strategic advantage in reducing relapse risk without substantial fetal compromise. In light of the disabling nature of NMOSD attacks, the benefits of relapse prevention may outweigh the theoretical risks of fetal exposure—particularly when the medication is timed prior to organogenesis. Nevertheless, patients should be thoroughly counseled regarding the limited nature of current safety data. Collaborative management involving neurology, obstetrics, and neonatology teams is essential for optimal outcomes.

CONCLUSION

his systematic review indicates that rituximab, when administered before conception, may be both effective in controlling disease activity and generally safe for use in pregnant individuals with Neuromyelitis Optica Spectrum Disorder (NMOSD). A consistent trend across studies showed a reduction in relapse rates during gestation and after childbirth, which is particularly relevant given the disabling consequences of NMOSD relapses.

Most fetal outcomes—including rates of miscarriage and preterm birth—did not deviate significantly from those observed in the general population, particularly when exposure occurred before pregnancy. These findings suggest that rituximab is unlikely to be a major contributor to adverse obstetric events when appropriately timed.

However, the overall strength of evidence is limited by several factors, including small sample sizes, retrospective study designs, and inconsistent neonatal follow-up. In particular, prospective studies with robust maternal-fetal monitoring and long-term neonatal immune surveillance are critically needed to establish a more definitive safety profile.

Until such data are available, clinicians should approach rituximab use in pregnancy with caution. For women with high disease activity who are planning pregnancy, administering rituximab prior to conception—combined with multidisciplinary oversight throughout pregnancy—may offer the most favorable balance between maternal disease control and fetal safety.

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