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CASE REPORT

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# Eculizumab for paroxysmal nocturnal hemoglobinuria: Two cases of successful pregnancy outcomes

**Jovanka Ilic**[1] | **Borislava Pujic**[2] | **Branislava Jakovljevic**[3] | **Borivoj Sekulic**[1,4] | **Danijela Agic**[1,4] | **Amir El Farra**[1,4] | **Branimir Micanovic**[1] | **Tihomir Vejnovic**[3,5] | **Ivana Urosevic**[1,4] | **Aleksandar Savic**[1,4]

[1]Clinic of Hematology, Clinical Center of Vojvodina, Novi Sad, Serbia

[2]Clinic of Anesthesia, Intensive Care and Pain Therapy, Clinical Center of Vojvodina, Novi Sad, Serbia

[3]Clinic of Gynecology and Obstetrics, Clinical Center of Vojvodina, Novi Sad, Serbia

[4]Department of Internal Medicine, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[5]Department of Gynecology and Obstetrics, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

**Correspondence**
Aleksandar Savic, Clinic of Hematology, Clinical Centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 1-9, 21137 Novi Sad, Serbia.
Email: aleksandar.savic@mf.uns.ac.rs

**Key Clinical Message**

Paroxysmal nocturnal hemoglobinuria is a rare disease with the incidence ranging from 0.08 to 0.57 per 100,000 person-years. Up to 25% of cases in women are detected during pregnancy. We report two cases of successful pregnancy outcomes in patients treated with eculizumab, pointing out the importance of interdisciplinary approach in these high-risk pregnancies.

**KEYWORDS**

eculizumab, paroxysmal nocturnal hemoglobinuria, PNH, pregnancy

## 1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder caused by somatic mutations in phosphatidylinositol glycan class A (PIGA), leading to deficiency of the glycosyl phosphatidylinositol (GPI)-anchored proteins like complement inhibitory proteins, CD55 and CD59. This results in chronic complement-mediated hemolysis, as well as activation of platelets, monocytes, and granulocytes. Consequently, hemolytic anemia, thrombophilia, and bone marrow failure develop, making the hallmarks of PNH.[1] With the prevalence estimated at approximately 38 per million individuals, PNH is considered a rare disease.[2] Its incidence ranges from 0.08 to 0.57 per 100,000 person-years worldwide.[2,3]

Up to 25% of PNH cases in women are detected during pregnancy.[4–6] However, not many case series/case reports on pregnancy with PNH have been reported so far, with <100 patients in total,[7] and not a single case from Serbia thus far. As pregnancy tends to worsen hemolysis, aggravate risk of thrombotic complications, and increase transfusion requirements, pregnancy among these women had generally been discouraged.[8,9] However, since the

development of eculizumab, a humanized monoclonal antibody against protein C5 that inhibits terminal complement activation, safe pregnancies for many women with complement-mediated diseases have been enabled.[9–11] Whatever the mode of delivery, anesthesia should be administered to prevent exacerbation of hemolysis triggered by stress and pain.[12]

## 2 | METHODS

At the Clinical Centre of Vojvodina, two women with PNH were treated with eculizumab during pregnancy and postpartum in 2021 and 2022. This mini case series study was based on a detailed analysis of patients' medical records. Patients' characteristics are shown in Table 1.

## 3 | CASE HISTORY

### 3.1 | Case 1

A 38-year-old primipara was hospitalized during the 30th week of pregnancy for further examination of anemia. For several years, she had been treated for iron-deficiency anemia due to severe menorrhagia caused by leiomyoma. Three years before the pregnancy was confirmed, a myomectomy had been performed, thus achieving stable red blood cell counts. A few months before the pregnancy was confirmed, another drop in the red blood cell count had been documented. This time, elements of combined anemia were observed and vitamin B12 supplementation was initiated.

During the abovementioned hospitalization, laboratory findings showed possible hemolysis with direct and indirect antiglobulin tests both being negative. As the Ham test was positive, immunophenotyping using flow cytometry was performed. PNH clone size on neutrophils was 59%. Low molecular weight heparin (LMWH) prophylaxis was initiated.

In the 36th gestational week, the patient was hospitalized again due to high-risk pregnancy. Laboratory findings correlated with an increased hemolysis. A consilium of physicians, comprising a hematologist, obstetrician-gynecologists, an anesthesiologist, and an internist, made a decision regarding further treatment. As the most serious potential complication of terminal complex inhibition is associated with meningococcal infections, the patient got vaccinated with quadrivalent conjugated meningococcal vaccine (serogroups A, C, Y, W-135) according to general recommendations. The first dose of eculizumab was administered the day before delivery. Laboratory findings before the eculizumab initiation and periodically during the treatment are shown in Table 2. Since it had been 3 years since myomectomy with cystectomy had been performed, the pregnancy was terminated via cesarean section at 39 weeks of gestation, with no maternal nor fetal complications.

### 3.2 | Case 2

The second patient was diagnosed with PNH at the age of 25. She was treated symptomatically, using oral iron and folic acid formulations, with periodic filtered erythrocyte and platelet transfusions. Occasionally, small doses of oral corticosteroids were administered to control hemolytic crises. The last one occurred 3 years prior to conception. Two years before pregnancy, hysteroscopy with polypectomy had been performed, as well as transvaginal laparoscopy, as part of the infertility testing.

Ten years after the PNH diagnosis, in vitro fertilization and embryo transfer procedures were conducted resulting in pregnancy. The PNH neutrophil clone size at that time was 98%. Prophylactic LMWH was initiated along with folic acid and oral iron supplementation. Laboratory controls were conducted regularly, and worsening trends of anemia and thrombocytopenia were observed. LMWH dose was reduced in the 32nd gestational week due to more pronounced thrombocytopenia (platelet count: 106...75...42 $\times 10^9$/L). Regular eculizumab therapy was introduced in the 35th week of gestation. After the second dose of eculizumab had been administered, the pregnancy was complicated by preeclampsia. Therefore, an elective cesarean section was performed upon completion of 37 weeks of gestation, following the third dose. Operative blood loss was replaced by transfusion of one unit of filtered erythrocytes and a platelet separate.

During the maintenance therapy, the values of hemoglobin and platelets increased up to 128 g/L and $110\times 10^9$/L, accordingly. One mild bacterial upper respiratory tract infection was noted during that period.

## 4 | CONCLUSION AND RESULTS

In both patients, eculizumab was administered in accordance with the standard dosing regimen: 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter. Eculizumab was continued 3 months after delivery and LMWH thromboprophylaxis was continued during puerperium. Both babies were born without congenital or developmental anomalies. Neither of the patients experienced thrombotic complications

**TABLE 1** Basic characteristics of the presented patients.

| | Case 1. | Case 2. |
|---|---|---|
| Age at PNH diagnosis (years) | 38 | 25 |
| Age at pregnancy (years) | 38 | 35 |
| Clone size detected by flow cytometry in pregnancy | 59% PNH+ neutrophils | 98% PNH+ neutrophils |
| Immunophenotype of the PNH clone | $CD45^{+}$, $CD15^{+}$, $CD24^{neg}$, CD66b $^{neg}$, $CD16^{+low}$, $CD55^{+low/neg}$, $CD59^{+low/neg}$ | $CD45^{+}$, $CD15^{+}$, CD24 $^{neg}$, CD66b $^{neg}$, $FLAER^{neg}$, CD157 $^{neg}$, $CD16^{+low}$, $CD55^{+low}$, $CD59^{+low}$ |
| Initial manifestation | Hemolytic anemia | Pancytopenia (hemolytic anemia), low haptoglobin, LDH > 1000, and abdominal pain |
| Time of PNH diagnosis in relation to pregnancy | During pregnancy | Before pregnancy |
| Previous hematological disorders | Iron-deficiency anemia | None |
| Therapy before eculizumab | Oral iron, folic acid and vitamin B12 supplementation, and transsfusions of filtered erythrocytes | Oral iron, folic acid, filtered erythrocyte and platelet transfusions, and small doses of corticosteroids occasionally |
| Meningococcal vaccine | 37. GW | 32. GW |
| Start of eculizumab | 39. GW | 35. GW |
| Number of doses before delivery | 1 | 3 |
| Concomitant hematological therapy during pregnancy | Oral iron, folic acid, and vitamin B12 supplementation | Oral iron and folic acid supplementation, and filtered erythrocytes transfusions |
| Number of earlier pregnancies | 0 | 0 |
| Mean of conception | Natural | IVF |
| Thromboprophylaxis during pregnancy and puerperium | LMWH: nadroparin | LMWH: nadroparin |
| Filtered erythrocyte transfusions during pregnancy | None | In 25th, 26th, and 33rd GW |
| Maternal complications | None | Preeclampsia |
| Fetal complications | None | None |
| Time and method of delivery | 39 + 1 GW, *SC* | 37 + 1 GW, *SC* |
| Type of anesthesia | GA | GA |
| Surgical or anesthetic complications | None | None |
| Outcome | A healthy female newborn, BW 3120 g, BL 48 cm, AS 10/10 | A healthy male newborn, BW 3240 g, BL 50 cm, AS 10/10 |
| Breastfeeding | 6 months | 1 month |

Abbreviations: AS, Apgar score; BL, body length; BW, birth weight; CD, cluster of differentiation; GA, general anesthesia; GW, gestational week; IVF, in vitro fertilization; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; *low*, low expression; *neg*, no expression; *SC*, *sectio cesarea*.

nor serious infections. However, in Case 1, laboratory signs of hemolysis reappeared within 2 months after the drug discontinuation. Due to aggravation of hemolysis with occasional abdominal pain and appearance of dark urine in the following months, eculizumab was reintroduced 18 months after the discontinuation (in February 2023). The treatment is still being administered to the patient with the disease being kept under control most of the time. Increased hemolytic activity has been noted seldom, following a few cases of mild infections. The second patient has stable red blood cell counts with no observed exacerbations and no therapy needed to this day.

## 5 | DISCUSSION

Eculizumab seems to be generally safe in pregnancy for both mother and fetus. Along with anticoagulant prophylaxis, eculizumab shows significant effectiveness in

**TABLE 2** Laboratory values before the eculizumab initiation, after the fourth dose and 3 months after the therapy initiation.

| | Case 1 | | | Case 2 | | | Reference range |
|---|---|---|---|---|---|---|---|
| | Before therapy | 4 w | 3 m | Before therapy | 4 w | 3 m | |
| RBC ($\times 10^{12}$/L) | 3.0 | 3.36 | 3.41 | 2.55 | 2.67 | 3.27 | 3.9–5.4 |
| HT | 0.32 | 0.36 | 0.349 | 0.28 | 0.29 | 0.345 | 0.37–0.47 |
| HGB (g/L) | 104 | 119 | 115 | 93 | 94 | 109 | 120–160 |
| WBC ($\times 10^{9}$/L) | 5.79 | 4.17 | 4.05 | 3.07 | 3.04 | 2.12 | 4–10 |
| ANC ($\times 10^{9}$/L) | 4 | 2.23 | 2.86 | [#] | 1.74 | 1.53 | 2–7.5 |
| PLT ($\times 10^{9}$/L) | 205 | 273 | 249 | 41 | 61 | 74 | 140–400 |
| TB (μmol/L) | 8.4 | 16 | 28 | 14.2 | 29 | 87 | 3–21 |
| DB (μmol/L) | 2.2 | 5.4 | 10 | 4.2 | 8.3 | 6.6 | <5.2 |
| LDH (U/L) | 1531 | 270 | 236 | 1436 | 436 | 392 | 125–220 |
| Haptoglobin (g/L) | <0.08 | <0.08 | <0.08 | <0.08 | <0.08 | <0.08 | 0.35–2.5 |
| RET (%) | 6.19 | 7.51 | 6.7 | [#] | [#] | 10.99 | 0.6–2.6 |

Abbreviations: 3 m, after 3 months; 4 w, after 4 weeks; ANC, absolute neutrophil count; DB, direct bilirubin; HGB, hemoglobin; HT, hematocrit; LDH, lactate dehydrogenase; PLT, platelets; RBC, red blood cells; RET, reticulocytes; TB, total bilirubin; WBC, white blood cells.

[#]Missing value.

reducing the risk of thrombotic complications in the postpartum period, which were the leading cause of maternal mortality in women with PNH in the pre-eculizumab era.[13–17]

There are variations between cases reported in the literature when it comes to time of therapy initiation, drug doses, intervals between infusions, and therapy duration.[18] As eculizumab has not been registered in Serbia, there was a special procedure for its procurement, which caused delay in the commencement of the treatment. Consequently, the drug was introduced during the third trimester in both patients we presented. However, according to the available literature, eculizumab seems to be safe for use in the first or second trimester as well. Mostly favorable outcomes have been noted in patients treated during the entire pregnancy, resulting in a low rate of maternal complications and a high rate of fetal survival.[18,19] Most authors do not provide information on whether the therapy was continued after delivery and for how long.[18]

Hemolysis often worsens during pregnancy, so there is a need for drug dose and/or dosing interval adjustment, all of which could be explained by the physiological expansion of the circulating volume in the second and third trimesters of pregnancy.[6,9,18,20] A group of authors in a review paper concerning the pharmacological, pharmacokinetic, and pharmacodynamic properties of the drug mentions several factors affecting the concentration of eculizumab, such as age, body mass, concentrations of the C5 component and the C5b-C9 complex, presence of human antihuman antibodies (HAHAs), as well as pregnancy. Drug dose monitoring is suggested, as well as individualized therapeutic approach.[21] These would also reduce costs, and, in some cases, the excessive use of this very expensive innovative drug.

Patients treated with eculizumab are not spared the risks of developing preeclampsia.[9,16] The question arises whether the drug dose was adequate in Case 2, taking into account that the patient was an obese person in an advanced pregnancy. Also, it should be borne in mind that this patient had previously received only two doses of the abovementioned drug.

In extremely rare cases, as described in a Japanese study, a poor therapeutic response to eculizumab can be determined by genetic variants of the gene encoding complement component C5.[22]

Both pregnancies ended at term, despite the elevated risk of prematurity in PNH-positive pregnant women, which is around 30% even with the use of eculizumab.[19]

According to general recommendations,[4] LMWH administration was continued during puerperium in both of our cases. No thrombotic complications were noted during the follow-up, despite the fact that the 10-year risk for thrombosis in individuals with >50% of PNH-positive granulocytes is estimated to be around 44%.[4] In pregnancy, which is a prothrombogenic state itself, we can assume that such risk is even higher. As a reminder, in both of our patients the proportion of PNH-positive neutrophils was >50%, and in the second case it even accounted for 98%.

PNH should be suspected whenever faced with unexplained hemolytic anemia in pregnancy. Given that it is a rare disease, unrecognized and without adequate supportive treatment, it carries a high risk for maternal and fetal morbidity and mortality. Even with appropriate monitoring and prophylactic therapy, the outcomes had often

been poor. Today, with targeted therapy available, such high-risk pregnancies, if adequately monitored and managed by an expert team of physicians, have a much better chance of a favorable outcome. In our cases, the importance of interdisciplinary approach to a patient was confirmed once again.

Having in mind well-known ethical reasons and the concerns about performing clinical trials in pregnancy, it is unlikely that randomized trials regarding this topic will ever be conducted. Although insufficient for general conclusions, case reports and case series still present a valuable source of information, contributing to building knowledge and potentially generating new research questions regarding rare diseases and new therapeutic options. A step forward to gain a better understanding and help to improve outcomes for patients with PNH would be establishment of well-designed and regularly updated international registries. More clinical data and a long-term follow up of infants from mothers who were treated with eculizumab during pregnancy are needed.

## AUTHOR CONTRIBUTIONS

**Jovanka Ilic:** Conceptualization; data curation; formal analysis; investigation; writing – original draft; writing – review and editing. **Borislava Pujic:** Data curation; supervision; writing – review and editing. **Branislava Jakovljevic:** Data curation; supervision; writing – review and editing. **Borivoj Sekulic:** Data curation; validation; writing – review and editing. **Danijela Agic:** Data curation; validation; writing – review and editing. **Amir El Farra:** Data curation; validation; writing – review and editing. **Branimir Micanovic:** Data curation; investigation; writing – review and editing. **Tihomir Vejnovic:** Supervision; validation; writing – review and editing. **Ivana Urosevic:** Supervision; validation; writing – review and editing. **Aleksandar Savic:** Conceptualization; data curation; formal analysis; investigation; project administration; supervision; validation; writing – review and editing.

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None.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT

The approval of the local Ethics Committee was obtained.

## CONSENT

Written informed consents were obtained from the two patients to publish this report in accordance with the journal's patient consent policy.

## ORCID

*Jovanka Ilic* https://orcid.org/0009-0000-3001-8664
*Ivana Urosevic* https://orcid.org/0000-0003-0672-3739
*Aleksandar Savic* https://orcid.org/0000-0002-5619-3724

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