Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria

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BACKGROUND
Eculizumab, a humanized monoclonal antibody against complement protein C5 that inhibits terminal complement activation, has been shown to prevent complications of paroxysmal nocturnal hemoglobinuria (PNH) and improve quality of life and overall survival, but data on the use of eculizumab in women during pregnancy are scarce.

METHODS
We designed a questionnaire to solicit data on pregnancies in women with PNH and sent it to the members of the International PNH Interest Group and to the physicians participating in the International PNH Registry. We assessed the safety and efficacy of eculizumab in pregnant patients with PNH by examining the birth and developmental records of the children born and adverse events in the mothers.

RESULTS
Of the 94 questionnaires that were sent out, 75 were returned, representing a response rate of 80%. Data on 75 pregnancies in 61 women with PNH were evaluated. There were no maternal deaths and three fetal deaths (4%). Six miscarriages (8%) occurred during the first trimester. Requirements for transfusion of red cells increased during pregnancy, from a mean of 0.14 units per month in the 6 months before pregnancy to 0.92 units per month during pregnancy. Platelet transfusions were given in 16 pregnancies. In 54% of pregnancies that progressed past the first trimester, the dose or the frequency of use of eculizumab had to be increased. Low-molecular-weight heparin was used in 88% of the pregnancies. Ten hemorrhagic events and 2 thrombotic events were documented; both thrombotic events occurred during the postpartum period. A total of 22 births (29%) were premature. Twenty cord-blood samples were examined for the presence of eculizumab; the drug was detected in 7 of the samples. A total of 25 babies were breast-fed, and in 10 of these cases, breast milk was examined for the presence of eculizumab; the drug was not detected in any of the 10 breast-milk samples.

CONCLUSIONS
Eculizumab provided benefit for women with PNH during pregnancy, as evidenced by a high rate of fetal survival and a low rate of maternal complications. (ClinicalTrials.gov number, NCT01374360.)
ECULIZUMAB IN PREGNANT PATIENTS WITH PNH

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) is a rare, acquired stem-cell disorder that is characterized by chronic hemolysis, bone marrow failure, and venous thromboembolism. Manifestations of the disease are related primarily to complement-mediated hemolysis. Patients with PNH present with a wide range of clinical symptoms, and if they do not receive specific treatment for the disorder, they can have a chronic, progressive illness and an increasing risk of death, primarily from thrombosis, over time (the median survival from the time of diagnosis ranges from 10 to 32 years).1-3

Historically, the management of PNH during pregnancy has been challenging, and pregnancy has been discouraged in patients with PNH.4-6 Intravascular hemolysis and anemia are frequently more severe during pregnancy, with greater transfusion requirements, than in the nonpregnant state.7-9 Morbidity and mortality are higher among pregnant women with PNH than among nonpregnant women with PNH, and the risks continue to be high during the postpartum period. Fetal morbidity and mortality are higher among pregnant women with PNH than among pregnant women without PNH.5,8,9 Maternal mortality has been reported to be between 8% and 20.8%, with thromboembolism as the primary cause of death; the majority of thrombotic events occur during the postpartum period.5,6,8,10 Fetal mortality has been reported to be between 4% and 9%.6,8,10 This high fetal mortality associated with pregnancies in patients with PNH is related to premature births, with only half the pregnancies progressing to term in one study.8

Terminal complement formation increases during pregnancy, and in cases of preeclampsia, terminal complement activation is even more pronounced.11,12 Eculizumab is a humanized monoclonal antibody that binds to the complement protein C5 and blocks terminal complement activation.13 Clinical trials involving patients with PNH have shown that eculizumab prevents disease complications and improves quality of life and overall survival.14-17 Because young women with PNH who have received treatment with eculizumab have a reduction in their symptoms, they are more likely to consider pregnancy.

Currently, there are few data on the use of eculizumab during pregnancy, with only four cases reported18-21 and one small case series involving seven patients.22 In addition, one report on two pregnancies specifically examined whether eculizumab crosses the placenta.23 Here we present data gleaned from the international PNH community on 75 pregnancies in 61 women that were documented after eculizumab became available for use in 2007.

METHODS

STUDY DESIGN AND OVERSIGHT
We designed a questionnaire to solicit data on pregnancies in women with PNH (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The work was performed in association with the International PNH Registry. The questionnaire was sent to the members of the International PNH Interest Group and to physicians participating in the International PNH Registry.24

The data were collected by the authors and the collaborators listed in the Supplementary Appendix. The first, second, third, and last authors interpreted the data and wrote the manuscript. The registry sponsor had no role in the study. Written informed consent by the patients was obtained for the International PNH Registry (www.pnregistry.com) and the Italian PNH registry (Registro EPN–Emoglobinuria Parossistica Notturna; www.iss.it/cnmr/index.php?lang=1&id=2325&tipo=14). The collection of the data for the registries was not restricted for a specific purpose; therefore, no additional approval for analysis was necessary. Approval for the registries was granted by institutional review boards or the equivalent of the centers at which the participating physicians work. The study was performed in accordance with the principles of the Declaration of Helsinki.

DIAGNOSIS AND TREATMENT OF PNH
A diagnosis of PNH was established by means of flow cytometry. Information was collected on the dates of diagnosis, history of thrombosis and aplasia, and outcomes of pregnancies before eculizumab was available for use. Transfusion history and medication use were evaluated.

MATERNAL AND FETAL COMPLICATIONS AND CHILDHOOD DEVELOPMENT
Obstetrical data included the number of pregnancies, miscarriages, and deliveries, as well as the term and mode of delivery. Premature delivery
was defined as delivery before 37 weeks of gestation, which was determined by means of ultrasonography. Newborn vital status and birth weight were recorded. The postpartum period was defined as the period between delivery and 6 months after delivery, because the delayed postpartum phase can last for 6 months. Maternal and fetal complications during pregnancy, at delivery, and during the postpartum period were recorded.

**Eculizumab Therapy**

Therapy with eculizumab was commenced at the discretion of the treating physician. Eculizumab was administered as a weekly intravenous infusion at a dose of 600 mg for 4 weeks, followed by 900 mg every 14 days. The dose or the frequency of use of eculizumab was increased when there was evidence of breakthrough intravascular hemolysis. We obtained maternal and cord-blood samples in the case of some pregnancies, as well as breast-milk samples from some mothers, to evaluate whether levels of eculizumab were detectable (assay lower limit of detection, 5 μg per milliliter). The decision to initiate anticoagulation therapy in a patient was made at the discretion of the treating physician.

**RESULTS**

**CHARACTERISTICS OF THE PATIENTS**

We identified 75 pregnancies in 61 women with PNH, who were followed up at 31 centers in 9 countries during the period from June 2006 through November 2014. Three patients had 3 pregnancies each, and 8 patients had 2 pregnancies each. Three pregnancies involved twins, and among these pregnancies a fetal loss of 1 twin occurred in utero. One patient discontinued eculizumab therapy at 12 weeks of gestation. Overall, there were 69 live births, 6 spontaneous abortions during the first trimester, and 3 stillbirths.

The characteristics of the patients and the history of pregnancies in these patients before they began to receive eculizumab are shown in Table 1. The median age of the patients at the time of diagnosis of PNH was 23 years (range, 13 to 37), and the median age at the start of their pregnancies was 29 years (range, 18 to 40). In most cases, pregnancy occurred in patients who had previously received a diagnosis of PNH; in 46 of the 75 pregnancies (61%) included in this analysis, the patients had been using eculizumab before conception. The median time from the diagnosis of PNH to pregnancy was 70 months (range, 0 to 192), and the mean duration of eculizumab use before conception was 34 months (range, 3 to 115). In 9 women (15%), the diagnosis of PNH was made during pregnancy. In 29 of the 69 pregnancies (42%) that progressed past the first trimester, eculizumab therapy was started during the second or third trimester. One patient in the study discontinued eculizumab therapy at 12 weeks of gestation. All the other patients continued therapy with eculizumab throughout the entire postpartum period.

The PNH granulocyte clone size at the time eculizumab therapy was initiated was greater than 20% in all but one patient who had a granulocyte clone size of 4%. In this patient, there was

<table>
<thead>
<tr>
<th>Presenting Features</th>
<th>Value</th>
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<tbody>
<tr>
<td>At diagnosis</td>
<td></td>
</tr>
<tr>
<td>Median age (range) — yr</td>
<td>23 (13–37)</td>
</tr>
<tr>
<td>Mean PNH granulocyte clone size (range) — %</td>
<td>63.7 (1.6–100)*</td>
</tr>
<tr>
<td>Mean hemoglobin level (range) — g/dl</td>
<td>8.5 (4.0–12.7)*</td>
</tr>
<tr>
<td>Mean granulocyte count (range) — ×10^9 per liter</td>
<td>2.38 (0.4–8.9)*</td>
</tr>
<tr>
<td>Mean platelet count (range) — ×10^9 per liter</td>
<td>129 (9–413)*</td>
</tr>
<tr>
<td>PNH history — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Documented history of aplastic anemia</td>
<td>21/61 (34)</td>
</tr>
<tr>
<td>Documented history of thrombotic events</td>
<td>8/61 (13)</td>
</tr>
<tr>
<td>Pregnancy before eculizumab treatment</td>
<td></td>
</tr>
<tr>
<td>Overall no.</td>
<td>31/31 (100)</td>
</tr>
<tr>
<td>Live births</td>
<td>12/31 (39)</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>8/31 (26)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3/31 (10)</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>8/31 (26)</td>
</tr>
<tr>
<td>Medication at the time of conception — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>21/61 (34)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4/61 (7)</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>32/61 (53)</td>
</tr>
</tbody>
</table>

* Data on paroxysmal nocturnal hemoglobinuria (PNH) granulocyte clone size, hemoglobin level, granulocyte counts, and platelet counts at diagnosis were not available for 8, 7, 13, and 6 of the mothers, respectively.
a discrepancy between the granulocyte clone size and the monocyte clone size (4% vs. 20%) at the start of eculizumab therapy. In addition to anticoagulants and eculizumab, other medications that were used included aspirin in 4 pregnancies (5%), folic acid in 67 pregnancies (89%), and iron supplements in 26 pregnancies (35%). Four patients were treated with cyclosporine before conception and continued to use cyclosporine during their pregnancy.

MATERNAL COMPLICATIONS

Breakthrough intravascular hemolysis, which required more frequent use or higher doses of eculizumab or both, was observed in 36 of 67 pregnancies (54%) that progressed to delivery. One patient in whom intravascular hemolysis developed was treated with prednisolone for a period of 7 days. Transfusion of red cells increased during pregnancy, from a mean of 0.14 units per month in the 6 months before pregnancy to 0.92 units per month during pregnancy. Transfusions returned to prepregnancy levels after delivery. Platelet transfusions were not given in any patient before pregnancy, but they were given in seven patients during pregnancy and in nine additional patients just before and up to 48 hours after the time of delivery. Hematologic status and evolution of hematologic variables during and after pregnancy are shown in Figure 1.

During the postpartum period, two women required antibiotics for sepsis. Low-molecular-weight heparin was used in 66 pregnancies (88%) and fondaparinux in 1 pregnancy (1%). Therapeutic doses of low-molecular-weight heparin were used in 27 pregnancies, whereas intermediate doses were used in 7 pregnancies and prophylactic doses in 32 pregnancies. Ten bleeding episodes that were considered by the clinicians overseeing the patients to be clinically significant were documented: 1 episode of recurrent epistaxis, 1 of antepartum hemorrhage, and 8 of postpartum hemorrhage. Among the patients in whom these 10 bleeding episodes occurred, one patient had a postpartum hemorrhage that required uterine-artery embolization and an infusion of a prothrombin complex concentrate, and another patient received treatment with pooled plasma. Among the patients who had bleeding events, two had been receiving therapeutic doses of low-molecular-weight heparin, seven had been receiving prophylactic doses of low-molecular-weight heparin, and one had not been receiving treatment with an anticoagulant.

No thrombotic events were observed during pregnancy. During the postpartum period, a thrombotic complication occurred in 2 of the 75 pregnancies (3%): one involved a deep-vein thrombosis in the leg and the other involved a mesenteric thrombosis. The mean duration of

Figure 1. Laboratory Values during and after Pregnancy.
follow-up after delivery was 19 months (range, 1 to 72) for all pregnancies.

In addition, 2 other patients who had stopped receiving eculizumab 12 weeks after delivery had a thrombosis; 1 patient who had continued to receive therapeutic doses of low-molecular-weight heparin had a mesenteric thrombosis 4 weeks after stopping eculizumab therapy, and the other patient had Budd–Chiari syndrome 8 weeks after stopping eculizumab therapy. Both patients recommenced eculizumab therapy — one on the day that the thrombosis was radiologically detected and the other a few days after the thrombosis was detected — and neither patient had a further complication. Overall, eculizumab therapy was discontinued in 10 patients 12 weeks after delivery, because there had not been a clinical need for this treatment before pregnancy. There were no reports of maternal death in this study.

### Factors Affecting the Fetus

Six spontaneous abortions occurred during the first trimester; in addition, two stillbirths occurred in one patient, at 30 and 32 weeks of gestation, and there was one fetal loss at 33 weeks of gestation in a dichorionic and diamniotic twin pregnancy. In the case of all three stillbirths, a histologic examination of the placentas revealed hypotrophy with intervillous fibrosis. In the patient who had the twin pregnancy, a histologic examination of the placenta confirmed hypotrophy with intervillous fibrin and placental abruption. The rate of premature deliveries (defined as delivery before 37 weeks of gestation) was high, at 29% (Table 2). The reason for these early deliveries included pre eclampsia in six pregnancies, concern over possible intrauterine growth retardation in five pregnancies, falling maternal platelet counts in three pregnancies, and reduced fetal movements in one pregnancy. The methods of delivery varied, with 19 natural deliveries, 16 induced deliveries (15 resulted in vaginal deliveries and 1 resulted in a cesarean delivery because of failure of progression to natural labor), and 32 cesarean deliveries.

### Table 2. Fetal Complications and Causes of Premature Delivery in 75 Pregnancies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preganacies no. (%)</th>
</tr>
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<tbody>
<tr>
<td>Fetal complication</td>
<td></td>
</tr>
<tr>
<td>Miscarriage during first trimester</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Premature birth</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cause of premature delivery</td>
<td></td>
</tr>
<tr>
<td>Planned cesarean delivery</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Growth retardation†</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Falling platelet count</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Reduced fetal movements</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Premature delivery was defined as delivery before 37 weeks of gestation.
†Growth retardation was defined as fetal size below the 10th percentile.

### Characteristics of the Children and Complications

Information on birth weight, gestational age, neonatal complications, and developmental milestones is shown in Table 3. Neonatal complications were due mainly to prematurity; six children required a prolonged stay in the hospital after delivery and one baby had the meconium-plug syndrome, a functional immaturity of the colon associated with prematurity, that required a temporary ileostomy. Tests for cystic fibrosis in this child were negative.

A total of 25 babies were breast-fed, and in 10 of these cases, breast milk was examined for the presence of eculizumab. The drug was not detected in any of the 10 breast-milk samples. Cord-blood samples from 20 deliveries were examined for the presence of eculizumab; the drug was detected in 7 of the 20 samples, with levels ranging from 11.8 to 21.2 μg per milliliter.

At the time of this study, the mean age of the 69 children who survived was 31 months (range, 4 to 94). Formal developmental assessments were available for 64 of the 69 children. There were no concerns by the parents with regard to childhood development in the 5 children for whom information could be obtained only orally, rather than by formal assessment, and documented. Only 1 mother and child were lost to follow-up. One child was found to have neutropenia after delivery, and the condition persisted during the first year of life. This child was asymptomatic, and the number of neutrophils returned...
to normal by the time the child was 12 months of age. One child was referred to a speech and language therapist because of slightly delayed speech.

**DISCUSSION**

The introduction of eculizumab for the treatment of patients with PNH has improved the management of this illness in that it has reduced the mortality and morbidity associated with PNH and has allowed patients who were previously severely affected to lead a relatively normal life. PNH tends to manifest in early adulthood, and as the symptoms of PNH are reduced with the use of eculizumab in young women, it can be anticipated that they may consider starting a family. Before the use of eculizumab, mortality among pregnant women with PNH was unacceptably high (8 to 20%). In the current study, no maternal deaths were reported, and only two thrombotic events were reported among the patients who were receiving eculizumab, with both events occurring soon after delivery. One of the thrombotic events occurred after a plasma infusion was administered to treat a postpartum hemorrhage. Plasma contains high levels of complement and can overcome the effects of eculizumab and thereby render the patient susceptible to complications of PNH. The use of plasma should thus be avoided if possible. The other thrombotic event was a deep-vein thrombosis in a patient’s leg.

Most of the patients (88%) were treated with low-molecular-weight heparin from the time of confirmation of pregnancy to the end of the postpartum period. Because of the low rate of maternal thrombosis and maternal mortality, we could not determine from the findings in this study whether a therapeutic or a prophylactic strategy is preferable; however, heparin was a part of the routine care in patients with PNH during this high-risk period.

Blood products were administered at the discretion of the treating clinicians. Transfusion of red cells increased during the pregnancy but returned to the prepregnancy levels after delivery. In a previous study, thrombocytopenia was reported to be a notable issue; in our study, 16 pregnancies (21%) involved platelet transfusions, most of which were administered at the time of delivery. Granulocyte levels tended to increase during the course of the pregnancy; no patient had an acute decrease in the number of granulocytes (Fig. 1).

In 36 of 67 pregnancies (54%) that progressed to delivery, the dose of eculizumab, the frequency of use of eculizumab, or both were increased for the treatment of symptomatic intravascular hemolysis. Alterations in the dose or frequency of use of eculizumab were made at the discretion of the treating physician. The dose of eculizumab was increased in 23 pregnancies, the frequency of use was increased in 9 pregnancies, and both the dose and the frequency of use were increased in 4 pregnancies. The hemolytic episodes tended to occur during the third trimester — probably related to the increased terminal complement activation at this stage of pregnancy. Eculizumab is metabolized by lysosomal enzymes into small peptides and amino acids. The increased activity of lysosomal enzyme activation, as well as the physiologic changes that occur during pregnancy, such as the increase in fat and water content, may account for the higher doses required.

Three fetal deaths (4%) were documented: two stillbirths from the same mother (at 30 and

<table>
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<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean birth weight (range) — g</td>
<td>2692 (450–4290)</td>
</tr>
<tr>
<td>Mean gestational age (range) — wk</td>
<td>37 (28–41)</td>
</tr>
<tr>
<td>Neonatal complication — no./total no.</td>
<td>6/69</td>
</tr>
<tr>
<td>Prolonged hospital stay</td>
<td>3/69</td>
</tr>
<tr>
<td>Initial poor growth</td>
<td>1/69</td>
</tr>
<tr>
<td>Meconium-plug syndrome</td>
<td>63/64</td>
</tr>
</tbody>
</table>

* Included are data from the 69 live births among the 75 pregnancies in 61 women.
† Formal developmental information was not available for 3 of the 69 children. The assessments took place at different time points depending on the country in which the children were being assessed.
32 weeks of gestation) and the loss of a twin in another pregnancy. Fetal mortality was similar to that in previous reports (4 to 9%) of data obtained before the availability of eculizumab. There were six miscarriages during the first trimester, representing a rate of miscarriage of 8%, which is lower than the estimated rate of miscarriage of 17% among pregnancies in women without PNH in the United Kingdom.26 The lower rate of miscarriage in our study than that in the general population in the United Kingdom is probably due to ascertainment bias, because 29 of the patients did not start eculizumab therapy until the second or third trimester.

We found a high rate of premature birth (22 of 75 pregnancies [29%]), which has been a feature in previous reports on pregnancy in women with PNH; the corresponding rate among women without PNH in the United Kingdom in 2012 was 7.3%.27 Reasons for premature delivery included a planned cesarean delivery (in 2 of the twin pregnancies and in 5 other pregnancies), preeclampsia, intrauterine growth retardation, and falling maternal platelet counts. The high rates of hemolysis and premature births highlight the importance of careful monitoring in these patients. Because terminal complement activation is elevated in women during the third trimester and in women with preeclampsia, eculizumab may be a useful agent in other high-risk situations, such as the HELLP syndrome (which is characterized by hemolysis, elevated liver-enzyme levels, and low platelet counts), or in the case of preeclampsia itself, in which complement dysregulation has been reported.28,29

Different methods of delivery were observed among the pregnancies that were evaluated, but a tendency toward induced labor, to allow the delivery to take place in a more controlled manner, was noted in the more recent deliveries. Care should be taken after pregnancy if eculizumab therapy is to be discontinued, because there may be an increased risk of thrombotic complications.

Eculizumab was detected in 7 of 20 cord-blood samples, which suggests that eculizumab may cross the placenta at low levels. In another study, two patients with PNH were evaluated at delivery, and the mother had no detectable terminal complement activity and both newborns had normal complement activity.23 That study supports the findings of our study that suggest that if eculizumab crosses the placenta, the level is not high enough to affect complement activation.

A total of 25 babies were breast-fed, and in 10 of these cases, breast milk was examined for the presence of eculizumab; the drug was not detected in any of the 10 breast-milk samples. In a previous case report, eculizumab was detected in the first breast-milk sample in a patient but was not detected in subsequent samples, a finding that differs from that in our study.21 We interpret our findings to show that the drug is not excreted into breast milk in measurable amounts and that breast-feeding by patients receiving eculizumab is safe.

A comparison of maternal and fetal mortality among the pregnancies in our study with maternal and fetal mortality among pregnancies that were described before eculizumab was available is difficult and is subject to potential selection bias because the patients were studied retrospectively. However, it is not feasible to conduct a study comparing patients with PNH who receive eculizumab during pregnancy with those who do not receive eculizumab during pregnancy, partly because of the rarity of the condition but also because pregnancy has been discouraged in women who are not receiving eculizumab. A contemporary randomized study would not be ethical.

Overall, our findings showed acceptable outcomes when eculizumab treatment was used in the management of PNH in patients during pregnancy. Both hematologists and obstetrical care specialists participated in the delivered care to achieve the outcomes reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the personnel who gave us access to the global PNH registry, which allowed the identification of physicians caring for women with PNH during pregnancy, Deborah Meyran (pediatrician, clinical hematology, Hôpital Robert Debré, Paris, France) for constructive discussions regarding developmental milestones, and the other collaborators involved in this study, whose names are listed in the Supplementary Appendix.

APPENDIX

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ECULIZUMAB IN PREGNANT PATIENTS WITH PNH

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REFERENCES


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