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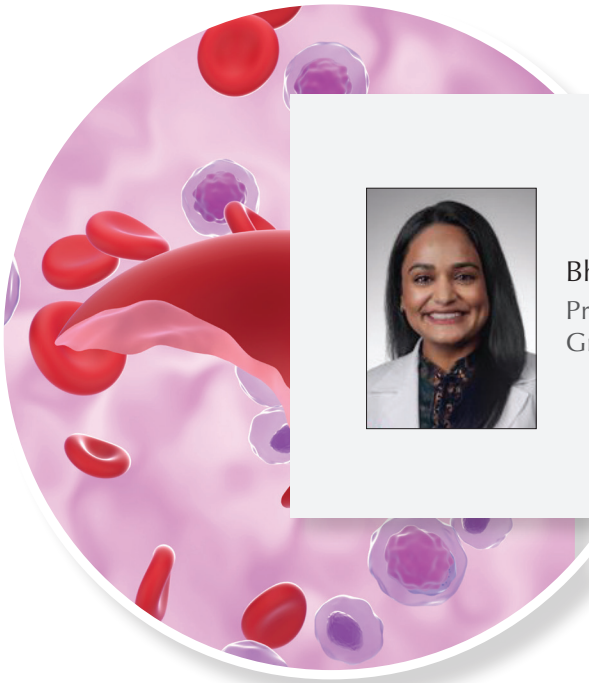
Use of Ravulizumab in a Pregnant Patient With PNH: Case-Based Insights



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Use of Ravulizumab in a Pregnant Patient With PNH: Case-Based Insights

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About the Patient

AK has been under the care of my practice for several years, and her case is notably complex (Table). This case demonstrates that, even in the setting of significant comorbidities, a patient with paroxysmal nocturnal hemoglobinuria (PNH) can achieve a successful pregnancy when supported by intensive monitoring and coordinated management from a multidisciplinary team. *(Note that this patient case was previously published as an abstract and was also part of a recently published international multicenter retrospective analysis.)*[1,2]

Diagnosis

In 2016, 29-year-old AK presented with progressive severe nausea, vomiting, and epigastric pain radiating to the right shoulder and lower abdomen. Initial evaluation revealed mild hepatomegaly (19 cm) and *Helicobacter pylori* infection, for which she received antibiotics without symptomatic improvement. A hepatobiliary iminodiacetic acid scan subsequently demonstrated biliary dyskinesia with sludge and a markedly reduced ejection fraction (12%). Laboratory studies showed persistent leukocytosis with neutrophilia and elevated alkaline phosphatase. Her hepatomegaly persisted, and she developed symptomatic splenomegaly (16.5 cm) accompanied by abdominal pain, nausea, fatigue, diarrhea, bloating, and dark urine.

Further workup established a diagnosis of Budd-Chiari syndrome with splenomegaly. She was started on rivaroxaban and discontinued oral contraception. In 2017, flow cytometry and genetic testing confirmed a dual diagnosis of *JAK2* V617F–positive polycythemia vera (PV) and PNH. As ascites progressed, spironolactone was initiated.

By this stage, the complexity of AK's presentation was evident. She carried 2 highly thrombogenic diagnoses, PNH and *JAK2*-positive PV, along with Budd-Chiari syndrome and a superior sagittal sinus thrombosis. Management of these overlapping conditions needed to address not only PNH but also the interplay between the 2 blood disorders, with her PNH appearing relatively compensated, likely as a consequence of the PV.

Management and Progression

One week after her diagnosis, AK developed head pain accompanied by asymmetric sinus signal and right jugular vein/sigmoid sinus enhancement, raising concern for superior sagittal sinus thrombosis. Eculizumab was initiated promptly. AK received the meningococcal B vaccine, *Haemophilus influenzae* type b (Hib) polysaccharide–tetanus toxoid conjugate vaccine, pneumococcal conjugate 13-valent vaccine, and meningococcal polysaccharide

On the Cover
Illustration of red blood cells affected by hemolytic anemia.

Credit: Nemes Laszlo/Science Source

Table. About the Patient

Initial presentation and follow-ups (2016-2017)	
Age at first presentation	29 years
Clinical symptoms at presentation	• Nausea and vomiting • Epigastric pain
Liver and spleen	• Hepatomegaly (19 cm) and splenomegaly (16.5 cm) • Biliary dyskinesia with low ejection fraction (12%)
CBC with differential	• Leukocytosis (WBC 11,000-16,000/μL) • Neutrophilia
CMP	Elevated alkaline phosphatase (244 U/L; 1.7×ULN)
Flow cytometry	PNH RBCs • Type I: Normal CD59 level (3.61%) • Type II: Partial CD59 deficiency (96.45%) • Type III: Complete CD59 deficiency (0.11%) PNH granulocytes • FLAER/CD24 deficiency (62.31%) PNH monocytes • FLAER/CD14 deficiency (4.66%)
Genetic testing	*JAK2* V617F (50% variant allele frequency)
Diagnoses	• Budd-Chiari • Polycythemia vera • PNH
Treatments prior to pregnancy (2017-2022)	
Anticoagulation	Enoxaparin, then switched to rivaroxaban, then apixaban
Diuretic	Spironolactone
Complement inhibitor	Eculizumab, then switched to ravulizumab (owing to breakthrough hemolysis with eculizumab)
Chemotherapy	Hydroxyurea, then discontinued
JAK inhibitor	Ruxolitinib
Surgery	Liver transplant
Immunosuppression	Tacrolimus

Pregnancy (2022)	
Initial treatment adjustment	• Continue ravulizumab and tacrolimus • Discontinue ruxolitinib and apixaban • Initiate enoxaparin
Monitoring	Hematologic and obstetric monitoring, including serial CBCs and frequent clinical assessments
Trimester 1 and 2	Clinically stable without transfusion requirements or breakthrough hemolysis, likely aided by weight-based ravulizumab dosing
Mid-pregnancy	Splenomegaly progressed to 30 cm, causing significant abdominal discomfort
20 weeks	Ruxolitinib reintroduced
21 weeks	Hospitalization for intensive monitoring Multiple complications • Malnutrition • Hemoptysis • Splenic infarcts • Hemorrhagic pleural effusion requiring thoracentesis • Acute renal failure necessitating temporary dialysis • Decompensated cirrhosis requiring paracentesis • Near-complete inferior vena cava occlusion, attributed to interruptions in anticoagulation during acute events
28 weeks + 2 days	• Unplanned cesarean section • Viable infant (1.09 kg; Apgar 3/4/4)
Postpartum	• AK's organ function improved postpartum • Prepregnancy regimen resumed • AK discharged 2.5 weeks later with close follow-up • Infant in the NICU for nutritional and respiratory support for 8 weeks

CBC, complete blood count; CMP, comprehensive metabolic panel; FLAER, fluorescein-labeled proaerolysin; NICU, neonatal intensive care unit; PNH, paroxysmal nocturnal hemoglobinuria; RBCs, red blood cells.

vaccine 2 weeks prior to starting therapy with eculizumab. *(Note that patients should be vaccinated against meningococcal infection [serogroups A, C, W, Y, and B] according to current Advisory Committee on Immunization Practices [ACIP] recommendations at least 2 weeks prior to initiation of a complement inhibitor. If urgent therapy with a complement inhibitor is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, the patient should be given antibacterial drug prophylaxis and these vaccines should be administered as soon as possible. Refer to the specific product prescribing information for more information.)*

Over the following 9 months, AK experienced progressive hepatic dysfunction. Erythrocytosis led to initiation of hydroxyurea, which was discontinued owing to thrombocytopenia, and she required multiple therapeutic phlebotomies. By 2019, continued hepatic decline prompted a switch from rivaroxaban to apixaban, and ultimately, she underwent liver transplant followed by tacrolimus-based immunosuppression.

In 2021 and 2022, breakthrough hemolysis manifested by dark urine and fatigue led to a transition from eculizumab to ravulizumab, with subsequent symptomatic improvement. By 2022, worsening splenomegaly (28 cm) necessitated initiation of ruxolitinib.

During this period, AK expressed a strong desire for pregnancy. This prompted multiple in-depth discussions with her multidisciplinary team and with senior experts in PNH, all of whom strongly advised against pregnancy given the exceptionally high maternal and fetal risks. This consensus was communicated clearly to the patient.

Pregnancy

In 2022, AK became pregnant despite repeated counseling against it. At her return visit, we had a discussion outlining the substantial maternal and fetal risks, the absence of pregnancy-specific safety data for ravulizumab, and the fact that she had conceived while taking multiple medications not approved for use in pregnancy. She understood that a successful outcome could not be assured.

I sought input from colleagues with extensive experience in PNH and despite the absence of robust pregnancy-specific data for ravulizumab, there was consensus that maintaining therapy and prioritizing disease stability offered the safest course.

AK's treatment plan was adjusted to continue ravulizumab and tacrolimus, discontinue ruxolitinib and apixaban, and initiate enoxaparin. She underwent close hematologic and obstetric monitoring, including serial laboratory and clinical assessments. Throughout the first 2 trimesters, she remained clinically stable without transfusion requirements or breakthrough hemolysis, likely aided by weight-based ravulizumab dosing. *(Note that the half-life of ravulizumab [49.7 days] is longer than that of eculizumab [11.3 days].)*

By mid-pregnancy, her splenomegaly progressed to 30 cm, causing significant abdominal discomfort. At 20 weeks, ruxolitinib was reintroduced after she provided informed consent acknowledging the unknown fetal risks. At 21 weeks, she required hospitalization for intensive monitoring. During this period, she developed multiple complications, including malnutrition, hemoptysis, splenic infarcts, hemorrhagic pleural effusion requiring thoracentesis, acute renal failure necessitating temporary dialysis, and decompensated cirrhosis requiring paracentesis. Imaging also revealed near-complete inferior vena cava occlusion, attributed to interruptions in anticoagulation during her acute events.

Given the escalating maternal risk, repeated discussions were held regarding preterm delivery and the possibility of pregnancy termination. As her condition worsened, the multidisciplinary team determined that delivery was necessary. At 28 weeks + 2 days, she underwent an unplanned cesarean section, delivering a viable infant (1.09 kg; Apgar 3/4/4), after receiving her scheduled ravulizumab dose to mitigate the risk of breakthrough hemolysis. Postpartum, AK's organ function improved, and she resumed her prepregnancy regimen. She was discharged 2.5 weeks later with close follow-up. The infant required approximately 8 weeks in the neonatal intensive care unit for nutritional and respiratory support.

In the Clinic: Complications Associated With Pregnancy in PNH[8,9,13,15]

Fetal complications
- Miscarriage
- Stillbirth
- Premature birth

Causes of preterm delivery
- Planned cesarean section
- Preeclampsia
- Intrauterine growth restriction
- Falling platelet count

Maternal complications
- Worsening hemolysis
- Thrombotic complications
- Obstetric morbidity
- Organ dysfunction

The child, who was formula-fed, is now a healthy 2-year-old. AK continues on ravulizumab every 8 weeks, tacrolimus, and oral anticoagulation, and has had no subsequent thrombotic or hemolytic events.

Clinical context of this case will be discussed in the following sections through:

- A concise overview of PNH
- Key challenges associated with pregnancy in PNH
- Current experience with complement inhibitors in pregnant patients with PNH
- The critical role of multidisciplinary coordination and close monitoring throughout pregnancy

Overview of PNH

PNH is a rare, acquired, nonmalignant clonal hematopoietic stem cell disorder characterized primarily by the clinical triad of complement-mediated intravascular hemolysis, bone marrow failure, and thrombosis.[3] It arises from a somatic mutation in the *PIGA* gene that disrupts synthesis of the glycosylphosphatidylinositol (GPI) anchor required to tether several protective proteins—most notably CD55 and CD59—to the cell surface. Loss of these complement regulatory proteins renders red blood cells (RBC) exquisitely sensitive to terminal complement activation. As a result, patients with PNH develop chronic hemolysis and hemoglobinuria, with downstream consequences including fatigue, smooth muscle dysfunction, and renal impairment. Thrombosis is the leading cause of mortality and may occur in atypical sites (eg, hepatic, cerebral, or abdominal veins), driven by complex interactions between complement activation, hemolysis, platelet activation, and endothelial dysfunction.[4] Patients with PNH tend to be female and young at diagnosis, with initial clinical symptoms including fatigue, shortness of breath, abdominal pain, thrombosis, and infections, as well as peripheral blood abnormalities (anemia, thrombocytopenia, and/or neutropenia).[5]

Challenges With Pregnancy in PNH

Pregnancy in patients with PNH is considered high risk for both maternal and fetal complications, primarily owing to markedly increased thrombotic risk and the potential for worsening intravascular breakthrough hemolysis against a background of rising complement activity.[6-9] Historically, pregnancy outcomes in PNH were poor; however, the advent of targeted complement inhibition has substantially improved maternal survival, reduced hemolysis, and enabled successful pregnancies in many patients.[7,9]

A retrospective review of 27 pregnancies among 22 women across a number of French centers between 1978 and 2008 provides a window into outcomes prior to the era of disease-modifying therapies in PNH.[10] None of these patients were treated with eculizumab or ravulizumab. Minor maternal complications were frequent (95% of cases), owing primarily to cytopenias such as anemia (74%) and thrombocytopenia (80%). Two patients experienced a major complication, both related to onset of severe aplastic anemia during pregnancy. No thrombotic events were reported during pregnancy, but 4 thromboses occurred postpartum, 2 of which were fatal. Overall, maternal mortality was 8% and the fetal mortality rate was 4%.

Experience With Complement Inhibitors in Pregnant Patients With PNH

Complement inhibitors have transformed pregnancy outcomes in PNH, reducing maternal mortality, improving fetal survival, and enabling successful pregnancies even in medically complex cases such as that of AK. Of the available complement inhibitors, case reports regarding managing PNH in pregnant patients are predominantly available for eculizumab and ravulizumab (Figure).[11-31] There is a single case report published using pegcetacoplan

In the Clinic: Importance of Early Counseling

Note that PNH is often diagnosed during peak reproductive years; our patient AK was 29 years old at diagnosis. For any newly diagnosed patient, whether with classical PNH or PNH secondary to aplastic anemia, the conversation can begin with a straightforward question about pregnancy plans. Early counseling about pregnancy is essential for women with PNH. Given the substantial maternal and fetal risks associated with PNH in pregnancy, clinicians should ensure patients understand both the evidence and the uncertainties associated with pregnancy in PNH.

This dialogue enables informed planning and timely initiation of optimal therapy should pregnancy occur. Although no controlled studies are available to guide best management practices for pregnancy in PNH, emerging data from case series provide important insights into outcomes and guide current practice.

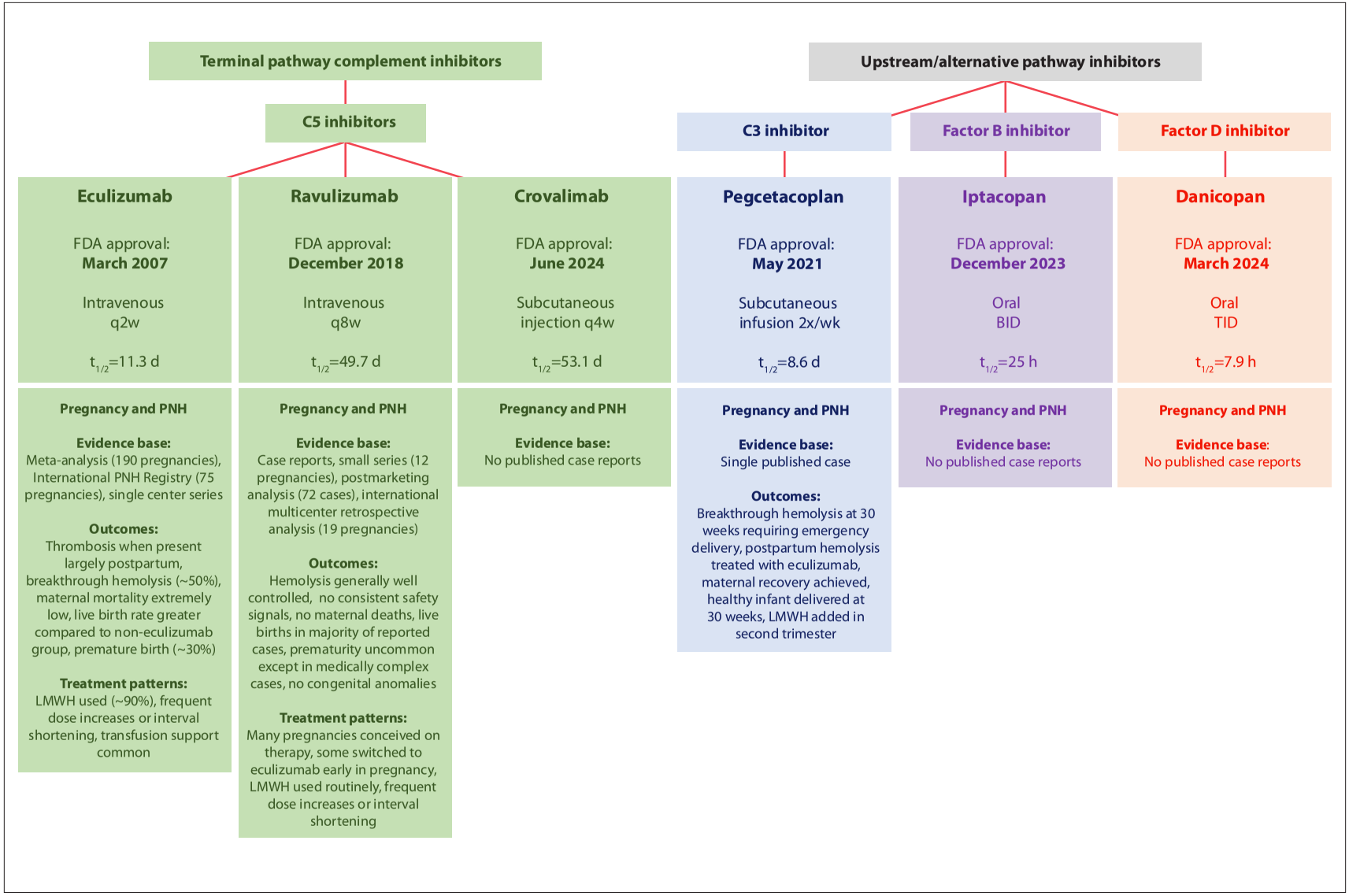

Figure. Reported pregnancy outcomes in PNH across complement inhibitors.
BID, twice daily; d, days; FDA, US Food and Drug Administration; h, hours; PNH, paroxysmal nocturnal hemoglobinuria; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; $t_{½}$, half-life; TID, 3 times daily; wk, week.

and none regarding the use of crovalimab, iptacopan, and danicopan.

Eculizumab

By inhibiting terminal complement–mediated intravascular hemolysis, eculizumab reduces hemoglobinuria, transfusion requirements, thrombotic risk, and PNH-related morbidity, while improving quality of life and survival. Its safety and efficacy in PNH were established in the phase 3 TRIUMPH study, which led to its US Food and Drug Administration (FDA) approval in 2007.[11,12]

Because it has been on the market now for nearly 2 decades, the majority of clinical experience and published case reports of PNH in pregnancy involve the use of eculizumab. These collectively demonstrate low maternal mortality, manageable hemolysis, and generally favorable fetal outcomes.

In 2025, Manning and colleagues published a systemic review and meta-analysis of outcomes in 190 pregnancies (135 patients with PNH, with eculizumab used in 131 patients).[13] A total of 45% of the patients on eculizumab required dose up-titration to control breakthrough hemolysis and 90% received antenatal thromboprophylaxis (most frequently low-molecular-weight heparin [LMWH]). Thrombosis complicated 6% of pregnancies, but none of those in women receiving anticoagulation. Among patients treated with eculizumab, 7 cases of thrombosis occurred, all during the early postpartum period. Bleeding complicated 14% of pregnancies, and was relatively similar between patients who did and did not receive eculizumab. One maternal death occurred in a woman not treated with eculizumab. Eculizumab was associated with a higher rate of fetal survival (82% vs 68%), lower miscarriage rate (first 23 weeks; 9.7% vs 18.6%), and lower premature birth rate (earlier than 37 weeks; 32% vs 44%). Eculizumab was detectable in 8 of 23 cord blood samples but was not detected in 14 breast milk samples.

A survey of the International PNH Interest Group members and the International PNH Registry physicians by Kelly and colleagues provided data on 75 pregnancies involving eculizumab in 61 women with PNH (31 centers across 9 countries; June 2006 to November 2014).[14] There were no maternal deaths, 3 fetal deaths, and 6 miscarriages during the first trimester. A total of 61% of the patients were already receiving eculizumab at the time of pregnancy and the remaining patients started eculizumab in the second or third trimester. Eculizumab dose or frequency was increased owing to breakthrough intravascular hemolysis in 54% of the pregnancies that progressed beyond the first trimester. RBC transfusion requirement increased during pregnancy and platelet transfusions occurred in 16 pregnancies. LMWH was used in 88% of pregnancies. A total of 10 hemorrhagic events and 2 postpartum thrombotic events occurred. A total of 29% of infants were premature. Fetal complications included miscarriage during the first trimester (8%), stillbirth (4%), premature birth (29%), and toxic megacolon (1%). Causes of preterm delivery included planned cesarean delivery (9%), preeclampsia (8%), growth retardation (7%), falling platelet count (4%), and reduced fetal movement (1%). After birth, eculizumab was detected in 7 of 20 cord blood samples evaluated.

Alashkar and colleagues reported outcomes from 16 pregnancies in 9 patients with classical PNH (Germany; May 2009 to January 2020).[15] One ended in spontaneous abortion before PNH diagnosis, 11 were conceived during eculizumab treatment (1 discontinued), 3 initiated eculizumab during the first trimester owing to increasing hemolysis, and 1 had no indication for eculizumab therefore it was not initiated. Of the 13 pregnancies supported by eculizumab, 8 were successful, with no maternal mortality. Breakthrough hemolysis occurred in 6 pregnancies, requiring a stepwise dosage increase; RBC transfusions were required in 8 pregnancies; and complications such as cholecystitis and Budd-Chiari syndrome, occurring in 2 pregnancies, were managed by antibiotics and anticoagulation, respectively. There were no bleeding complications. Preterm deliveries (5) were due to premature labor, cholecystitis, fetal distress, or premature rupture of membranes (twin pregnancy).

Czyz and colleagues reported on 3 patients with PNH treated with eculizumab (Polish National Health Fund program; 2017-2020).[16] One (with a previous successful pregnancy) initiated eculizumab at week 20 during her second pregnancy as her PNH clone increased; platelet transfusion was required at the time of her vaginal delivery (week 39). The second, who had been on eculizumab for 1 year prior to becoming pregnant, continued eculizumab throughout her pregnancy and delivered via artificial labor induction owing to premature rupture of the fetal membranes (week 36). The third (with a previous successful pregnancy) became pregnant with her second child while on eculizumab and underwent cesarean section owing to a falling platelet count (week 34). No fetal defects were reported.

Ilic and colleagues described 2 pregnancies in women with PNH treated with eculizumab.[17] The first involved a 38-year-old diagnosed with PNH at 30 weeks after presenting with anemia. She received LMWH prophylaxis and was readmitted at 36 weeks for high-risk pregnancy and increased hemolysis. Eculizumab was initiated the day before cesarean delivery at 39 weeks, and both mother and infant had uncomplicated outcomes. The second involved a 35-year-old woman with longstanding PNH (clone size, 98%) who conceived via in vitro fertilization.

She received LMWH, folate, and iron, but developed worsening anemia and thrombocytopenia; LMWH was reduced at 32 weeks when platelets fell. Eculizumab was started at 35 weeks. After her second dose, she developed preeclampsia and underwent cesarean delivery at 37 weeks following her third dose. She required perioperative transfusion, and her hemoglobin and platelet counts improved on maintenance therapy.

Ravulizumab

Ravulizumab was evaluated in 2 head-to-head phase 3 trials. Study 301 included patients with PNH naive to complement inhibitor therapy, whereas Study 302 included patients with PNH who were clinically stable during prior eculizumab therapy.[18,19] The multicenter, randomized, open-label, pivotal phase 3 Study 301 (CHAMPION-301) demonstrated ravulizumab's noninferiority to eculizumab in complement inhibitor–naive adults with PNH resulting in its FDA approval as a longer-acting C5 inhibitor in 2018 for the treatment of PNH.[18,20] In Study 301, ravulizumab effectively prevented transfusions and normalized lactate dehydrogenase (LDH) levels (73.6% vs 66.1% and 53.6% vs 49.4%, respectively) and had a safety profile similar to eculizumab.

Because ravulizumab has been on the market for the past 8 years, an increasing number of case reports are available for its use in pregnant patients with PNH. These point to reassuring maternal and fetal outcomes with ravulizumab. Most pregnancies reported to date occurred in women who conceived while already receiving ravulizumab, and many elected to continue therapy after counseling. In the limited instances when ravulizumab was discontinued early in pregnancy, eculizumab was typically substituted without loss of disease control.

The case of a 33-year-old patient with PNH who received ravulizumab in early pregnancy was reported by Fureder and colleagues.[21] This patient was diagnosed with PNH in 2016, began treatment with eculizumab in 2017, and then switched to ravulizumab in 2019. She was advised to switch back to eculizumab with an 8-month washout period for ravulizumab prior to becoming pregnant. However, she reported an unplanned pregnancy in May 2024 at gestational week 11, having received her last dose of ravulizumab at gestational week 3 while unknowingly pregnant. The next dose of ravulizumab was withheld; instead she received eculizumab starting with the induction dosing protocol, then followed with standard dosing. The patient's LDH and blood counts remained relatively stable after switching to eculizumab and the patient's dosage did not need to be further increased over the remainder of her pregnancy. A prophylactic dose of LMWH was given for anticoagulation, but because of retroplacental hematoma and vaginal bleeding at week 13, this dose was reduced. The LMWH dose was increased again at week 29, with no further bleeding complications and no breakthrough hemolysis. Sonograms suggested a large fetus for the gestational age, thus labor was induced at week 39. An unplanned caesarean section was performed when, after insertion of a vaginal prostaglandin insert, vaginal bleeding and pathologic fetal heart rate tracing occurred. The male infant was born with an Apgar score of 9/9/10 and no signs of perinatal morbidity. Three weeks after delivery, the patient was switched back to ravulizumab therapy; LMWH prophylaxis was continued until 6 weeks postpartum.

Morioka and colleagues reported on a 25-year-old patient with PNH who was found to be 8 weeks pregnant after receiving her third dose of ravulizumab.[22] She had previously received eculizumab. Ravulizumab was discontinued and eculizumab was restarted. Her hemoglobin declined, and she ultimately required several RBC transfusions and a platelet transfusion. She delivered a healthy baby at 39 weeks. Postpartum recovery was complicated by hemolysis triggered by mastitis, which was successfully treated with antibiotics.

In 2024, Hoechsmann and colleagues reported on a retrospective case series of 12 pregnancies in 5 women with PNH; 6 of these pregnancies occurred with eculizumab exposure and 6 with ravulizumab exposure.[23] In all 6 pregnancies with ravulizumab exposure, pregnancy occurred while the patient was receiving ravulizumab as standard treatment and all patients strongly preferred to continue treatment with ravulizumab. Prophylactic heparin was routinely administered once pregnancy was detected. Escalation of ravulizumab (dose increase or shortening of the interval or both) was required in 3 of the 6 pregnancies, but overall control of hemolysis was

In the Clinic: Prior to Initiating Therapy With a Complement Inhibitor

Patients should be vaccinated against meningococcal infection (serogroups A, C, W, Y, and B) according to current ACIP recommendations at least 2 weeks prior to initiation of a complement inhibitor. If urgent therapy with a complement inhibitor is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, the patient should be given antibacterial drug prophylaxis and these vaccines should be administered as soon as possible. Refer to the specific product prescribing information for more information.

maintained. The pregnancies were closely monitored. One child was delivered prematurely (35 weeks), whereas the other 5 were born between 38 and 42 weeks. All 6 pregnancies resulted in healthy, surviving children, and no developmental or constitutional abnormalities were noted over a median follow-up of 13 months.

Infante and colleagues reported on an analysis of solicited and spontaneous cases in the postmarketing setting in patients who had received a minimum of 1 dose of ravulizumab during pregnancy.[24] A total of 72 cases had pregnancy outcomes; of these, 23.6% received ravulizumab treatment throughout pregnancy, 26.4% switched to eculizumab during pregnancy, and treatment exposure details were incomplete in 41.6%. A total of 47 live births were reported, in addition to 20 spontaneous abortions, 3 fetal deaths, and 2 elective terminations. Detailed ravulizumab exposure information was available for 32 cases (which included 25 live births and 7 spontaneous abortions). Medical history and maternal comorbidities reported in these 32 cases included aplastic anemia, Budd-Chiari, thrombosis, gestational hypertension, preeclampsia, renal failure, and gestational diabetes. Of those 25 cases resulting in live births, 14 received ravulizumab throughout the entire pregnancy, 3 received ravulizumab beyond week 12 but discontinued sometime prior to delivery, and 8 received up to 12 weeks of ravulizumab exposure.

An international multicenter retrospective analysis of 16 PNH patients with 19 pregnancies managed with ravulizumab was recently published.[1] The outcomes of these pregnancies were compared with those of 8 earlier pregnancies in the same patients treated with eculizumab. Eculizumab was associated with 3 miscarriages and 1 early preterm delivery for threatened fetal demise and massive fetal growth retardation. Ravulizumab, on the other hand, was associated with the birth of live infants in all cases and no developmental abnormalities or severe infectious complications in children after a median follow-up of 16.2 months. Moreover, 2 pregnancies with intensified ravulizumab dosing noted detectable ravulizumab levels in cord blood testing consistent with transplacental transfer. The analysis from this series provides evidence for the safety and effectiveness of ravulizumab in managing PNH during pregnancy and breastfeeding, with favorable maternal and fetal outcomes. It further suggests that ravulizumab may represent a reasonable alternative to eculizumab during pregnancy, with its pharmacokinetic profile advantageous in reducing the risk of breakthrough hemolysis.

Long-term data are still needed, but these reports provide growing reassurance that ravulizumab can be used safely with appropriate expertise and close monitoring. This is particularly relevant given the increasing number of patients maintained on ravulizumab; for those who become pregnant, these collective experiences offer a measure of confidence that successful outcomes are achievable.

In the Clinic: Monitoring Checklist

Hematologic surveillance

- Complete blood count
- Reticulocyte count
- Lactate dehydrogenase
- Bilirubin
- Haptoglobin
- Iron studies
- Transfusion needs
- Clinical monitoring for thrombotic symptoms, particularly with heightened vigilance during the third trimester and postpartum period
- Breakthrough hemolysis
- Basic metabolic panel
- Liver enzymes

Fetal monitoring

- Serial ultrasounds to evaluate growth and placental function

Pegcetacoplan

Pegcetacoplan, a C3 inhibitor that received FDA approval in 2021, was designed to target the proximal complement pathway to prevent both intravascular and extravascular hemolysis.[25] Two open-label phase 3 trials were used to evaluate pegcetacoplan: PRINCE (in patients with complement inhibitor-naive PNH) and PEGASUS (in patients with anemia despite eculizumab therapy).[26,27] In PEGASUS, pegcetacoplan showed significant improvement in the mean change in hemoglobin level from baseline to week 16 compared with eculizumab (mean difference, 3.84 g/dL).[26]

Given its more recent introduction to the market, just 1 case report has been published with pegcetacoplan in a pregnant patient with PNH, demonstrating its feasibility. The absence of broader experience precludes firm conclusions.

After a diagnosis of PNH in 2018, a 33-year-old patient began treatment with eculizumab, achieving suboptimal outcomes with maintenance therapy requiring RBC transfusions every 2 to 4 weeks owing to breakthrough hemolysis.[28] She experienced 2 miscarriages while receiving eculizumab; the first at 12 weeks' gestation and the second at 24 weeks' gestation (despite an increase in

eculizumab dosage during the second trimester to prevent further hemolysis). Owing to her suboptimal PNH control, the patient opted to switch to pegcetacoplan and showed improvement as soon as 2 weeks after initiating treatment. In 2022, she became pregnant and chose to continue pegcetacoplan during pregnancy. Enoxaparin was added during the second trimester. The patient's hemoglobin was well maintained. At week 30, she developed breakthrough hemolysis and a placental abruption, requiring an emergency cesarean section and delivering a healthy-appearing male infant. She was treated for breakthrough hemolysis (2 doses of eculizumab), recovered within 1 week, and was discharged from the hospital on a maintenance dosage of pegcetacoplan as well as 6 weeks of prophylactic enoxaparin.

Multidisciplinary Coordination and Monitoring During Pregnancy

Management of patients with PNH who become pregnant requires close multidisciplinary coordination among many specialties, with individualized strategies for anticoagulation, transfusion support, and complement inhibition throughout pregnancy and the postpartum period, when thrombotic risk remains especially high.

Intensive, longitudinal monitoring is needed to detect worsening hemolysis, thrombotic complications, and obstetric morbidity throughout gestation and the postpartum period.[32] Hematologic surveillance typically includes frequent CBCs, reticulocyte count, LDH, bilirubin, and haptoglobin to assess hemolysis and bone marrow reserve, along with periodic assessment of iron status and transfusion needs.

Close clinical monitoring for thrombotic symptoms is essential, particularly with heightened vigilance during the third trimester and postpartum period when risk is greatest. Complement inhibitor dosing may require adjustment during pregnancy owing to increased plasma volume and complement activation, necessitating careful assessment of breakthrough hemolysis. Fetal monitoring with serial ultrasounds to evaluate growth and placental function is also important, and care should be coordinated through a multidisciplinary team—including hematology, maternal-fetal medicine, and anesthesia—to optimize maternal and neonatal outcomes.

Conclusion

Effective care for pregnant patients with PNH begins with recognizing the complexity of its management and initiating early counseling for women who desire pregnancy. Complement inhibitors have transformed pregnancy outcomes in PNH, reducing maternal mortality, improving fetal survival, and enabling successful pregnancies even in medically complex cases like that of AK. Nonetheless, both maternal and fetal risks cannot be ignored necessitating vigilant surveillance for hemolysis and thrombosis particularly in the postpartum period and coordinated multidisciplinary care that addresses both PNH and coexisting conditions.

Across published cohorts, management strategies are consistent involving nearly universal LMWH prophylaxis, close hematologic monitoring, and rapid adjustment of complement inhibitor dosing when hemolysis emerges. Although eculizumab remains the most extensively studied therapy in pregnancy with some clinicians electing to switch patients to eculizumab early

In the Clinic: Expert Collaboration and Multidisciplinary Management

This was by far among the most challenging of cases of my career.

A key lesson from this case is the critical role of expert collaboration in managing complex PNH pregnancies. When I learned that AK had conceived while receiving ravulizumab, I immediately sought input from colleagues with extensive experience in PNH. Despite the absence of robust pregnancy-specific data for ravulizumab, there was consensus that maintaining therapy and prioritizing disease stability offered the safest course. Their guidance was invaluable and underscored the importance of collegial support in high-risk scenarios.

Multidisciplinary management was equally essential to AK's successful outcome. Our team communicated frequently and directly, ensuring seamless management across specialties. I worked closely with her liver transplant physician to monitor immunosuppression, particularly as her splenomegaly worsened early in pregnancy. Collaboration with her obstetrician was continuous; we alternated visits every 2 weeks to maintain close surveillance and respond promptly to any changes in her condition. AK was transferred to an academic center at 20 weeks owing to the increasing complexity of her case and history of liver transplant, with ongoing collaboration between the 2 centers to ensure safety of the mother and fetus.

in pregnancy because of it, emerging experience with ravulizumab is increasingly reassuring. Case reports, small series, postmarketing analyses, and a recently published international multicenter retrospective analysis describe stable maternal disease control, favorable neonatal outcomes, and no consistent safety signals, with dose escalation needs similar to eculizumab.

Ravulizumab's extended half-life offers practical advantages: reduced infusion frequency (8 weeks), possibility of weight-based dosing (which is helpful in pregnancy), and potentially lower risk of breakthrough hemolysis. AK's case underscores that even in the setting of profound comorbidity, sustained complement inhibition with ravulizumab and coordinated interdisciplinary management can support a successful maternal and neonatal outcome.

Disclosures

Dr Patel has received consulting honoraria from Alexion, Novartis, and Geron.

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