Pregnancy with Paroxysmal Nocturnal Hemoglobinuria: A Case Series with Review of the Literature

Yara Mohammad Al‑Dosari1,2, Hazza Al‑Zahrani3, Fahad Al‑Mohareb4, Shahrukh Hashmi3,5

1Internal Medicine Department, Bahrain Defence Force Hospital and Royal Medical Services, 2King Faisal Specialist Hospital and Research Center, 3Adult Hematology/Bone Marrow Transplantation Section, Oncology Center, King Faisal Specialist Hospital and Research Center, 4Adult Hematology, HSCT Section, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, 5Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematopoietic stem cell disorder, and eculizumab and ravulizumab are its two approved therapies. Only few case series/reports have reported the outcomes of pregnancies in patients with PNH despite the increased risk of thrombosis. Similarly, there is limited knowledge regarding the effect of the approved treatments on conception and pregnancy outcomes. Here, we report the first series of pregnancies in PNH patients from the Middle Eastern region from our tertiary care hospital. Ten pregnancies in four females after diagnosis with PNH were identified. In terms of PNH management, only eculizumab was used, as the safety of ravulizumab use in pregnancies has not yet been established. In the antepartum period, the patients had variable symptoms that ranged from mild symptoms including epistaxis, tea-colored urine and vaginal bleeding to life-threatening vessel thrombosis. Further, red blood cell and platelet transfusions were required because of bleeding and hemolysis in four pregnancies. The pregnancy outcomes varied, but based on these, the safety of eculizumab use during pregnancy remained inconclusive. The postpartum period was complicated in one case by portal vein thrombosis and was managed accordingly. In conclusion, pregnant females with PNH are at an increased risk for complications due to PNH, and thus experienced hematologists and obstetricians should be involved jointly in their care.

Keywords: Complications, paroxysmal nocturnal hemoglobinuria, pregnancy
signs and symptoms of PNH include hemoglobinuria or hemosiderinuria, unexplained direct antiglobulin tests, negative hemolysis, aplastic anemia, thrombosis at unusual sites and dystonic symptoms (abdominal pain or dysphagia). For confirmatory diagnosis, flow cytometry is used, as it can demonstrate the absence or deficiency in the expression of GPI-anchored protein in a sizable portion of peripheral blood, mainly in red blood cells (RBC), neutrophils and monocytes, called as ‘PNH clones,’ which are fundamentals in diagnosing PNH.[5, 6-7]

Pregnancy is a challenging period due to the physiological changes, [8-11] and requires specific attention during interventions of chronic diseases, especially in hematological disorders. Further, pregnancy in patients with PNH increases maternal and fetal mortality and morbidity as a result of an exacerbation of intravascular hemolysis, thrombosis and bone marrow failure.[12, 13] In the management of PNH, eculizumab therapy has both been shown to be safe and effective as well as reported to potentially have teratogenic effects that may require dosage and frequency adjustments; the effect of ravulizumab on pregnancy outcomes has yet to be reported.[5, 14-17]

Currently, there is no report from Saudi Arabia or the Middle East regarding the prevalence and incidence of pregnancy in PNH, in addition to limited data in general regarding PNH in pregnancy and the management approaches in such a high-risk group [Table 1].[15-20] Therefore, this case series would add to existing literature.[11]

**DESCRIPTION OF CASES**

For this case series, the data of all patients with PNH who presented to our Hematology, Stem Cell Transplantation & Cellular Therapy center between 2013 and 2021 were retrospectively analyzed. The study was approved by the Research Advisory Council (RAC)/Ethics Committee at King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia.

During the period, a total of 20 patients with PNH had been treated at our center. Of these eight were females: two were not within the reproductive age, two died following hematopoietic stem cell transplant complications, and the remaining four had 10 pregnancies after the diagnoses of PNH.

The diagnosis was initially based on clinical presentations, and then following the minimal essential criteria for PNH diagnosis including: (1) flow cytometry analysis of peripheral blood erythrocytes, granulocytes or both (PNH clone), (2) complete blood count (CBC), reticulocytes count, serum concentration of lactic dehydrogenase (LDH), bilirubin and haptoglobin, and (3) bone marrow biopsy for those with concomitant underlying bone marrow disease.[5] The eculizumab therapy protocol was as stated in the literature:[17, 20, 21] initially a dose of 600 mg IV weekly for the first 4 weeks, followed by 900 mg IV for 1 week and then 900 mg every 2 weeks. Doses were modified or reduced based on the patient’s tolerance to the regular dosing, in the presence of side effects, and per the availability of the medication in the pharmacy, given its cost.

Below is the summary of each patient’s clinical course details regarding clinical features, relevant laboratory findings (e.g. hemograms, PNH clone, bilirubin and LDH), treatments, and the outcome are summarized in Tables 2 and 3.

**Case 1**

A 43-year-old female diagnosed with PNH in 2013 (aged 38 years) manifesting with mild cytopenia and PNH clone of 63% on WBC–monocytes, was treated with 900 mg of eculizumab every 2 weeks (standard dose) and remained in a stable condition. In 2015, she became pregnant with a singleton; eculizumab was continued throughout the antepartum period, and the dose was increased to 1200 mg because of worsening clinical situation, especially anemia. In addition to prophylactic low-molecular-weight heparin (LMWH) (dose of 20 mg subcutaneous daily), ferrous sulfate and folic acid were also prescribed. At 33 weeks of gestation, the pregnancy was complicated with

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**Table 1: List of case series/case reports on pregnancy with paroxysmal nocturnal hemoglobinuria in the literature**

| Study                  | Year | Region     | Number of cases |
|------------------------|------|------------|-----------------|
| de Guibert et al.      | 2011 | France     | 23              |
| Alashkar et al.        | 2020 | Germany    | 9               |
| Kelly et al.           | 2015 | Italy      | 6               |
| The current case series| 2021 | Riyadh, Saudi Arabia | 4 |
| Miyasaka et al. [2]    | 2016 | Japan      | 3               |
| Morita et al. [3]      | 2013 | Japan      | 2               |
| Rodríguez-Ferreras et al. [2] | 2019 | Spain | 1 |
| Bastos et al. [4]      | 2018 | Brazil     | 1               |
| Danilov et al.         | 2010 | Boston, USA| 1               |
| Marasca et al. [5]     | 2010 | Italy      | 1               |
| Ando et al. [24]       | 2014 | Japan      | 1               |
| Sharma et al. [6]      | 2015 | New York, USA| 1           |
| Patriquin et al. [7]   | 2015 | Canada     | 1               |
| Patel et al. [27]      | 2017 | Florida, USA| 1           |
| Vekemans et al. [8]    | 2015 | Belgium    | 1               |
| Gessoni et al. [29]    | 2015 | Italy      | 1               |
| Bjørge et al. [11]     | 2003 | Norway     | 1               |
| Lauritsch-Hernandez et al. [10] | 2018 | Switzerland | 1 |
| Singh et al. [12]      | 2014 | India      | 1               |
| Bais et al. [20]       | 1994 | Amsterdam  | 1               |
| Sasano et al. [21]     | 2016 | Japan      | 1               |
polyharmonies (amniotic fluid index, >24 cm) and large fetus for gestational age that required hospitalization for observation and monitoring.

At 38 weeks of gestation, after the failure of induction of labor, a caesarian section was performed. In addition, RBC and platelet transfusions were given intrapartum. The product was a full-term infant with a birth weight of 4000 grams (larger than the average childbirth weight in Saudi Arabia) with an Apgar score of 9, who was admitted in the neonatal intensive care unit (NICU) with a stable course. The infant had dysmorphic features, macrocephaly, hypotonia, right undescended testes and Hirschsprung disease, which is most likely because the family had a strong history of multiple congenital anomalies.

In the immediate postpartum period, the patient complained of acute abdominal pain, and ultrasound (US) doppler confirmed portal and superior mesenteric vein thrombosis, following which dose of LMWH was increased to 40 mg subcutaneous daily and dose was adjusted according to the platelet count, which ranged at that time between 17 to 33 × 10⁹/L.

The transient thrombocytopenia required platelet transfusion and the patient stabilized without any complications and was maintained on subhepatic LMWH. Six weeks post-delivery, she was shifted to rivaroxaban for long-term anticoagulation. On the last follow up in October 2020, she continued to have no acute events on maintenance eculizumab (900 mg) every 2 weeks and rivaroxaban.

**Case 2.1**
A 31-year-old lady was diagnosed with PNH in 2015 (aged 25 years). The patient had a history of bone marrow failure, received antithymocyte globulin therapy followed by cyclosporine and achieved complete remission. Five years later, patient presented with iron deficiency symptoms and hemolysis manifesting as tea-colored urine with rise of PNH clone size to WBC was 48.2%. She had not been on eculizumab therapy; the reason for the same was not clearly stated in our registry but could be because the patient had a stable disease course.

In 2017, she became pregnant, and was treated with 40 mg of enoxaparin for high risk of thrombosis. The antepartum period was stable with no complication, except for mild epistaxis. Fetal US was normal with no intrauterine growth restriction (IUGR). Spontaneous vaginal delivery occurred at 39 weeks of gestation after induction of labor with no complications. The product infant was stable, birth weight of 3020 g, Apgar score was 9, with no NICU admissions. Postpartum period was uncomplicated and LMWH prophylaxis (40 mg) was given for 6 weeks post-delivery.

The patient was followed-up every 3 months at the hematology clinic for assessment of disease control and iron replacement compliance, as needed (for any drop in hemoglobin). The assessment was based on clinical symptoms and laboratory parameters including hemoglobin, LDH, bilirubin, haptoglobin, reticulocytes and renal function to observe any signs of hemolysis.[16]

**Case 2.2**
The patient had her second pregnancy in 2018, following which folic acid and prophylactic LMWH was started. During her follow up, she developed tea-colored urine and epistaxis at 27 weeks of gestation. Thus, signs of hemolysis...
| Case number | Maternal age at PNH diagnosis (years) | PNH clone size (%) | Diagnostic test | Clinical presentation | Maternal age at pregnancy (years) | Eculizumab | Anticoagulants in pregnancy (mg) | Transfusion Complications | Follow up |
|------------|--------------------------------------|-------------------|----------------|----------------------|----------------------------------|------------|-------------------------------|-------------------------|-----------|
| 1          | 36                                   | 67                | 63             | Fatigue, dizziness, heavy menstruation AA thrombocytopenia | 39                  | 900                          | 1200        | LMWH RBC, PLT Polyhydrarnnios, fetus LGA Thrombocytopenia PVT, PLT Trans | Stable |
| 2.1        | 25                                   | 56.7              | 48.2           | Fatigue AA           | 22                  | None                         | None        | LMWH RBC LMWH RBC LMWH None | None             |
|            |                                       |                   |                |                      | 23                  | None                         | None        | Epistaxis, dark urine Abdominal pain, PV bleeding PROM, PV, BMS exacerbation None Missed Ab None | None             |
| 3.1        | 32                                   | 76.8              | 80.6           | Fatigue, abdominal pain, dizziness, ski thrombophlebitis AA | 37                  | Refused                      | 600         | Fondsparinux, HIT positive RBC, PLT PROM, PV, BMS exacerbation None Missed Ab Unknown | Stable |
| 3.2        |                                       |                   |                |                      | 38                  | 600                          | 600         | Unknown RBC, PLT Unknown None Missed Ab Unknown | None             |
|            |                                       |                   |                |                      | 38                  | 600                          | 600         | Not yet started (1st trimester) None None Missed Ab Pregnant Unknown | Stable |
| 4.1        | 32                                   | 43.2              | 78.3           | Back pain AA         | 35                  | 900                          | 600         | LMWH RBC, PLT IUFD None | None             |
| 4.2        |                                       |                   |                |                      | 36                  | 900                          | 900         | LMWH None None None None | None             |
| 4.3        |                                       |                   |                | Pancytopenia HepB    | 37                  | 900                          | 900         | None None None Sp Ab None | None             |

PNH – Paroxysmal nocturnal hemoglobinuria; AA – Aplastic anemia; PROM – Preterm rupture of membranes; LGA – Large for gestational age; PVT – Portal vein thrombosis; PV – Per vaginal; BMS – Bone marrow suppression; HepB – Hepatitis B; IUFD – Intrauterine fetal death; Sp Ab – Spontaneous abortion. LMWH – Low-molecular-weight heparin; RBC – Red blood cells; PLT – Platelets; SP – Spontaneous; AB – Abortion; HIT – Heparin induced thrombocytopenia.
were confirmed with hemoglobin: 114 g/L, reticulocyte auto 86.8 \times 10^9/L, haptoglobin <0.1/L and LDH 596 U/L. The prophylactic dose of LMWH was maintained on 40 mg and she was advised for good hydration. Fetal US showed normal interval growth with no IUGR and normal blood flow.

Emergency C-section at 39 weeks of gestation was performed due to hyperstimulation and fetal distress with no complications. The product infant was stable with a birth weight of 3000-gram, Apgar score of 9 and with no NICU admission. The postpartum period was uneventful and LMWH prophylaxis was initiated post-delivery and continued for 6 weeks.

**Case 2.3**
The patient had her third pregnancy in November 2020 and was started on prophylactic LMWH of 40 mg. During the regular follow up, she complained of mild discomfort in the left leg (calf region), and accordingly deep vein thrombosis ruled out by US doppler. In her 8th week of gestation, the patient complained of lower abdominal pain and vaginal bleeding. A transvaginal US confirmed non-viable pregnancy and missed abortion, and thus she underwent emergency evacuation and curettage. Laboratory parameters was reassuring and did not show any signs of hemolysis. Postpartum period was uneventful, and she was discharged in a stable condition after 2 days and with advice to continue on prophylactic LMWH until her next follow up.

**CASE 3.1**
A 39-year-old female was diagnosed with PNH in 2013 (aged 32 years), manifesting with fatigability, skin thrombophlebitis and PNH on WBC clone size was 80.6%. The patient refused treatment with eculizumab at that time. However, she had a history of severe aplastic anemia for couple of years controlled on cyclosporine and aspirin (81 mg) because of worsening of her cytopenia. She had a history of four abortions, three intrauterine fetal deaths (IUFD) and one stillbirth due to brain atrophy.

In 2017, the patient became pregnant, and enoxaparin 40 mg and folic acid supplement were added to aspirin; however, cyclosporine was discontinued to avoid its teratogenicity. The antepartum period was complicated with bone marrow suppression, mild vaginal bleeding, frequent hemolysis and dropping of platelets level, and thus she required frequent RBC and platelet transfusion, glucocorticoid and intravenous immunoglobulin therapy. At 31-week of gestation, 600 mg eculizumab was started as she presented with low platelets and low hemoglobin. Enoxaparin was switched to prophylactic fondaparinux (2.5 mg) because the patient developed heparin-induced thrombocytopenia (HIT). However, fetal US showed normal interval growth and normal blood flow.

Preterm rupture of membranes occurred at 36 weeks of gestation, then induction of labor started and eventually progressed with spontaneous vaginal delivery. The infant was full term and stable, weighted 2320 grams, the Apgar score was 9, and had no complications that required NICU admissions. Postpartum period was completed with no complications and she was continued on eculizumab and fondaparinux for 6 weeks.

**Case 3.2**
During regular follow ups, the patient had a missed abortion in January 2019 despite being on eculizumab. The details are not known, as the diagnosis was in a local hospital; however, laboratory parameters were within normal range and no hemolysis or drop in hemoglobin was detected.

**Case 3.3**
In the last follow up at the time of reporting this case, patient was pregnant and advised to continue with eculizumab (600 mg every 4 weeks), but fondaparinux was not started, as the patient was in her first trimester. In addition, an expert obstetrician was consulted for following the patient.

**Case 4.1**
A 38-year-old female diagnosed with PNH in 2014 (aged 32 years) manifested with back pain, pancytopenia, hepatitis B infection (on Tenofovir therapy), PNH clone size on WBC of 78.3%, and bone marrow biopsy showing hypocellularity but no features of myelodysplasia. Initially, the patient remained on cyclosporine 100 mg and planned for stem cell transplantation, but patient refused treatment.

In 2016, the patient agreed for treatment and was started on eculizumab 900 mg. She had frequent RBC and platelet transfusions. In 2017, she became pregnant with a singleton; however, the gestation did not progress. The pregnancy was complicated by IUFD at 25 weeks of gestation, despite treatment with eculizumab, enoxaparin and folic acid. Platelet transfusion was given during the termination of pregnancy. The postpartum period was uncomplicated and LMWH was continued postpartum for 3 weeks.

**Case 4.2**
In 2018, while on treatment with 900 mg eculizumab, the patient again became pregnant. At 28 weeks of gestation, she presented to the emergency department (ED) with
vaginal bleeding and abdominal pain, and after a few hours, she delivered dead fetus and placenta spontaneously. The patient was admitted for 1 day for monitoring, and then discharged on 40 mg prophylactic enoxaparin for 6 weeks.

**Case 4.3**

On November 2020, during the telephonic follow up due to the COVID-19 pandemic, the patient reported that she became pregnant, but the pregnancy terminated spontaneously while on eculizumab therapy. In the last follow up in hematology clinic in January 2021, patient was in a stable condition clinically and laboratory, and advised to continue eculizumab regimen.

**DISCUSSION**

PNH often occurs in females during the reproductive age. Conception is discouraged in patients with PNH because of increased risk of thrombosis.[22] The high possibility of thrombosis is likely related to pregnancy physiological changes such as increase in complement activity and hypercoagulability state and also with the pathophysiology of PNH that might augment the risk of emergency delivery.[18,22,29,34] Thrombosis is associated with serious complications for the mother and the fetus, and thus obstetrician experts are involved in care of pregnant patients with PNH.[4,17]

In this case series, we present the course of 10 pregnancies in four patients after PNH diagnosis and add to the limited data available in the literature.[4,15,17] To the best of the authors knowledge, only 62 cases have been published in 20 articles discussing pregnancy with PNH, with the current paper being one of few series and the first from the Middle East region [Tables 1 and 4].

Clinical presentation of our patients varied from mild symptoms such as back pain and thrombophlebitis to severe potential symptoms such as bone marrow failure and life-threatening vessel thrombosis. However, three of the four patients had complete hypoplastic bone marrow features and hemolysis [Tables 2 and 3]. Antepartum maternal complications included thrombocytopenia and hemolysis manifesting as epistaxis and dark urine, in addition to poor significant outcome such as termination of pregnancy because of IUFD or spontaneous abortion.

During the antepartum period, platelet and RBC transfusions were on demand for all our patients when platelets counts were >20 or <50 or hemoglobin was <80 mg/L and at the time of delivery. During the delivery phase, three cases were planned for induction of labor for spontaneous vaginal delivery, and three cases had spontaneous abortion. In addition, two cases underwent cesarean section delivery due to failed induction of labor and fetal distress and one case had a missed abortion and underwent emergency evacuation and curettage. According to the existing literature and our case series, the mode of delivery (i.e., cesarean sections and spontaneous) were almost equal, suggesting that PNH might not have a significant impact on the mode of delivery.

The postpartum period was controlled clinically and with follow up parameters for hemolysis (CBC, LDH, haptoglobin, reticulocytes and bilirubin)[17] and thrombosis complications. All patients were maintained on prophylactic LMWH for 6 weeks after delivery. The postpartum period was uncomplicated in three cases except for Case 1, wherein portal vein thrombosis was reported and managed conservatively with no further complications.

Fetal outcomes for our patients were significant for two cases. In Case 1, the infant was large for the gestational age, with congenital anomaly, and was admitted to the NICU. In Case 4, the patient had IUFD and four abortions. Interestingly, Case 2, who was not on eculizumab, delivered a healthy fetus, whereas the other three patients who were on eculizumab had the above-mentioned fetal complications. From the literature, 86% of the newborns have been found to be healthy, 6% had fetal deaths, and in 8%, the outcomes were not stated with variable usage of eculizumab. Therefore, eculizumab might have a rule in the relatively safe conclusion discussed in the evidence.

We found that in the literature, the use of anticoagulants during pregnancy varied: 60% used prophylactic heparin, 18% had therapeutic doses of heparin, 16% did not receive any anticoagulants and in 4% its usage was not stated. Therefore, the preferable use of prophylactic or therapeutic strategy in pregnancy with PNH could not be determined.[9] It should be noted that unless contraindicated, prophylactic LMWH is prescribed to pregnant women during the third trimester and continued for 6–12 weeks postpartum, as the risk of thrombosis is high.[31,34] Many studies recommend it when the clone size is >50%. In our cases, all our patients received anticoagulants (enoxaparin/fondaparinux) during both antepartum and postpartum periods.

According to Parker et al.[5] thrombophilia is the leading cause of mortality in PNH, with thromboembolic events being directly related to the PNH clone size. The study by Hall et al.[29] supports this hypothesis, as they found that in patients with PNH clone >50% GPI-AP–deficient granulocytes, the 10-year risk of thrombosis in PNH patient was 44% and it was 5.8% in patients with <50%...
| Case number | Reference                  | Number of cases | Maternal age at pregnancy | Anticoagulation therapy Before pregnancy | Anticoagulation therapy During pregnancy | Eculizumab therapy | Postpartum (mg) |
|-------------|----------------------------|-----------------|---------------------------|------------------------------------------|----------------------------------------|-------------------|-----------------|
| 1           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900 mg            | 900             |
| 2           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900–1800 mg       | 900             |
| 3           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 1200–1800 mg      | 1200            |
| 4           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900–1200 mg       | 900             |
| 5           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900–1200 mg       | 900             |
| 6           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900–1200 mg       | 900             |
| 7           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | 900             |
| 8           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900 mg            | 900             |
| 9           | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | 900–1200 mg       | 900             |
| 10          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 11          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 12          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 13          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 14          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 15          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 16          | Alashkar, et al.           | 9               | NS                        | NS                                       | NS                                     | None              | None            |
| 17          | Rodríguez-Ferreras, et al. | 1               | 39                        | None                                     | None                                   | 600 mg for 4 weeks then 900 mg every 2 weeks | Yes              |
| 18          | Bastos et al.              | 1               | 38                        | None                                     | Prophylactic LMWH                       | 900–1200 mg (forced reduction due unavailability) | Yes              |
| 19          | Danilov et al.             | 1               | 34                        | Therapeutic heparin                      | Therapeutic heparin                     | From 30 weeks     | Yes             |
| 20          | Kelly et al.               | 6               | 25                        | Warfarin                                 | Therapeutic heparin                     | Up to 5 weeks     | No              |
| 21          | Kelly et al.               | 6               | 22                        | Not known                                | Not known                               | Up to 14 weeks    | No              |
| 22          | Kelly et al.               | 6               | 26                        | Not known                                | Therapeutic heparin                     | Up to 4 weeks     | No              |
| 23          | Kelly et al.               | 6               | 27                        | No                                       | Prophylactic heparin                    | Entire pregnancy (increased from 28 weeks) | Yes              |
| 24          | Kelly et al.               | 6               | 35                        | No                                       | Therapeutic heparin                     | From 27 weeks (weekly) | Yes          |
| 25          | Kelly et al.               | 6               | 28                        | Warfarin                                 | Therapeutic heparin                     | Entire pregnancy  | Yes              |
| 26          | Marasca et al.             | 1               | 34                        | No                                       | Prophylactic heparin                    | Entire pregnancy  | Yes              |
| 27          | Ando et al.                | 1               | 37                        | No                                       | No                                     | Entire pregnancy  | Yes              |
| 28          | Sharma et al.              | 1               | 32                        | No                                       | Prophylactic heparin                    | Entire pregnancy (increased from 30 weeks) | Yes              |
| 29          | Patriquin et al.           | 1               | 30                        | No                                       | Prophylactic heparin                    | Entire pregnancy (increased from 2nd trimester) | Yes              |
| 30          | Miyasaka et al.            | 3               | 34                        | No                                       | Prophylactic heparin                    | Entire pregnancy  | Yes              |
| 31          | Miyasaka et al.            | 3               | 30                        | No                                       | Prophylactic heparin                    | Entire pregnancy  | Yes              |
| 32          | Miyasaka et al.            | 3               | 29                        | No                                       | Prophylactic heparin                    | From 27 weeks     | Yes              |
| 33          | Patel et al.               | 1               | 24                        | No                                       | Prophylactic heparin                    | From 18 weeks     | Yes              |
| 34          | Vekemans et al.            | 1               | 41                        | No                                       | Prophylactic LMWH                       | From 10 weeks     | Yes              |
| 35          | Gesson et al.              | 1               | NS                        | No                                       | Prophylactic LMWH                       | Entire pregnancy  | Yes              |
| 36          | Bjørge et al.              | 1               | 35                        | Warfarin                                 | Therapeutic heparin                     | NS                | Yes              |
| 37          | Lauritsch-Hernandez et al. | 1               | 27                        | Oral anticoagulation, Vitamin K antagonist | Therapeutic heparin                    | Entire pregnancy  | Yes              |
| 38          | Singh et al.               | 1               | 23                        | No                                       | No                                     | No                | No               |
| 39          | Morita et al.              | 2               | 30                        | No                                       | Prophylactic heparin                    | NS                | NS               |
| 40          | Morita et al.              | 2               | 41                        | NS                                       | Therapeutic heparin                     | NS                | NS               |
| 41          | Bais et al.                | 1               | 30                        | No                                       | No                                     | No                | No               |
| 42          | Guibert et al.             | 23              | 27                        | No                                       | No                                     | No                | No               |
Table 4: Contd...

| Case number | Reference | Number of cases | Maternal age at pregnancy | Anticoagulation therapy | Eculizumab therapy |
|-------------|-----------|----------------|---------------------------|-------------------------|-------------------|
| 43          | Guibert et al. | 23          | 26                       | No                      | NS                |
| 44          | Guibert et al. | 23          | 27                       | No                      | NS                |
| 45          | Guibert et al. | 23          | 27                       | Therapeutic LMWH        | NS                |
| 46          | Guibert et al. | 23          | 21                       | LMWH                    | NS                |
| 47          | Guibert et al. | 23          | 38                       | Danaparoid              | NS                |
| 48          | Guibert et al. | 23          | 21                       | Danaparoid              | NS                |
| 49          | Guibert et al. | 23          | 32                       | No                      | NS                |
| 50          | Guibert et al. | 23          | 29                       | Danaparoid              | NS                |
| 51          | Guibert et al. | 23          | 32                       | Danaparoid              | NS                |
| 52          | Guibert et al. | 23          | 31                       | LMWH                    | NS                |
| 53          | Guibert et al. | 23          | 24                       | LMWH                    | NS                |
| 54          | Guibert et al. | 23          | 30                       | No                      | NS                |
| 55          | Guibert et al. | 23          | 24                       | Danaparoid              | NS                |
| 56          | Guibert et al. | 23          | 22                       | LMWH                    | NS                |
| 57          | Guibert et al. | 23          | 36                       | LMWH                    | NS                |
| 58          | Guibert et al. | 23          | 28                       | No                      | NS                |
| 59          | Guibert et al. | 23          | 27                       | Danaparoid              | NS                |
| 60          | Guibert et al. | 23          | 27                       | NS                      | NS                |
| 61          | Guibert et al. | 23          | 26                       | LMWH                    | NS                |
| 62          | Guibert et al. | 23          | 27                       | No                      | NS                |
| 63          | Guibert et al. | 23          | 31                       | LMWH                    | NS                |
| 64          | Guibert et al. | 23          | 30                       | No                      | NS                |
| 65          | Guibert et al. | 23          | 24                       | Danaparoid              | NS                |
| 66          | Guibert et al. | 23          | 22                       | LMWH                    | NS                |
| 67          | Sasano et al. | 1 (1.2)      | 29                       | No                      | Prophylactic heparin | No |
| 68          | Sasano et al. | 1 (2.2)      | 33                       | No                      | Therapeutic UFH    | No |
| 69          | Our case 1    | 4            | 42                       | No                      | Prophylactic LMWH  | 1200 |
| 70          | Our case 2.1  | 4            | 29                       | No                      | Prophylactic enoxaparin | No |
| 71          | Our case 2.2  | 4            | 29                       | No                      | Prophylactic enoxaparin | No |
| 72          | Our case 2.3  | 4            | 38                       | No                      | Prophylactic enoxaparin | No |
| 73          | Our case 3.1  | 4            | 38                       | No                      | Fondaparinux (due to HIT) | 600 (started 31 weeks) |
| 74          | Our case 3.2  | 4            | 38                       | No                      | 600                | 600 |
| 75          | Our case 3.3  | 4            | 38                       | No                      | Not yet started (patient in 1st trimester) | 600 |
| 76          | Our case 4.1  | 4            | 37                       | No                      | Enoxaparin         | 900 |
| 77          | Our case 4.2  | 4            | 37                       | No                      | Prophylactic enoxaparin | 900 |
| 78          | Our case 4.3  | 4            | 37                       | No                      | No                 | 900 |
Table 4: Contd...

| Case number | Intrapartum | Complications                                      | Mode of delivery (indication) | Newborn status |
|-------------|-------------|---------------------------------------------------|-------------------------------|----------------|
| 1           | Hemolysis, RBC trans | NS                                                 | Vaginal                       | Healthy        |
| 2           | BH, RBC trans    | NS                                                 | Vaginal                       | Healthy        |
| 3           | BH, RBC trans    | NS                                                 | Vaginal                       | Healthy        |
| 4           | BH, BCS, RBC/PLT trans, cholecystitis | NS                                                 | CS                            | Healthy        |
| 5           | BCS, cholecystitis | NS                                                 | CS                            | Healthy        |
| 6           | BH              | NS                                                 | CS                            | Healthy        |
| 7           | BH              | NS                                                 | Vaginal                       | Healthy        |
| 8           | Sp Ab, RBC trans | NS                                                 | Vaginal                       | Dead           |
| 9           | Sp Ab           | NS                                                 | Vaginal                       | Dead           |
| 10          | Sp Ab           | NS                                                 | Vaginal                       | Dead           |
| 11          | BH              | NS                                                 | CS                            | Healthy        |
| 12          | Sp Ab, RBC trans | NS                                                 | Vaginal                       | Healthy        |
| 13          | Stillbirth      | NS                                                 | Vaginal                       | Healthy        |
| 14          | Medical Ab      | NS                                                 | -                             | Healthy        |
| 15          | Sp Ab           | NS                                                 | Vaginal                       | Healthy        |
| 16          | RBC trans, preclampsia | NS                                                 | CS                            | Stillbirth     |
| 17          | Heavy vaginal bleeding, abdominal pain | None                                              | Vaginal                       | Sp Ab (1st trimester) |
| 18          | AKF, hemolytic anemia, RBC trans | Hospitalized                                     | Emergency CS                  | Healthy        |
| 19          | Thrombocytopenia | None                                              | CS (twin-breech)              | Healthy        |
| 20          | None            | None                                               | NS                            | Healthy        |
| 21          | None            | FUO                                                | NS                            | Healthy        |
| 22          | None            | None                                               | NS                            | Healthy        |
| 23          | BH, RBC trans    | None                                               | SVD                           | Healthy        |
| 24          | None            | PPH                                                | CS (twin)                     | Healthy        |
| 25          | Preeclampsia    | None                                               | CS (preeclampsia)             | Healthy        |
| 26          | None            | None                                               | SVD                           | Healthy        |
| 27          | None            | None                                               | CS (breech)                   | Healthy        |
| 28          | BH, RBC trans    | None                                               | CS (elective)                 | Healthy        |
| 29          | BH, RBC trans    | None                                               | CS (placenta previa)          | Healthy        |
| 30          | BH, RBC trans    | None                                               | SVD                           | Healthy        |
| 31          | Preeclampsia    | None                                               | CS (preeclampsia)             | Healthy        |
| 32          | None            | PPH                                                | SVD                           | Healthy        |
| 33          | None            | None                                               | SVD                           | Healthy        |
| 34          | RBC trans       | RBC trans                                          | SVD                           | Healthy        |
| 35          | PE, BULT        | PPE, PE, BULT, abdominal angina with TPI           | CS (fetal distress)           | Healthy        |
| 36          | Chorioamnionitis secondary to IOL | PPH, IVT (liver failure, BCS, BMF) | CS (failed IOL)              | Healthy        |
| 37          | None            | None                                               | CS (transverse presentation)  | Healthy        |
| 38          | PROM            | Sepsis, ARF, PRES                                  | SVD                           | NS             |
| 39          | None            | None                                               | Emergency CS (reduction fetal heartbeat) | NS |
| 40          | None            | None                                               | CS (breech)                   | NS             |
| 41          | PLT trans       | Hemolytic crisis, PMVT, IC                         | SVD                           | Healthy        |
| 42          | None            | None                                               | NA                            | Healthy        |
| 43          | HELLP, PLT trans | None                                               | CS (failed IOL)               | Healthy        |
| 44          | None            | None                                               | SVD                           | Healthy        |

Contd...
Table 4: Contd...

| Case number | Intrapartum | Complications                  | Mode of delivery (indication) | Newborn status |
|-------------|-------------|--------------------------------|-------------------------------|----------------|
| 45          | None        | BCS                            | CS (failed IOL)               | Healthy        |
| 46          | None        | None                           | CS (NS)                       | Healthy        |
| 47          | None        | Anemia, RBC trans              | NA                            | Healthy        |
| 48          | None        | None                           | SVD                           | Healthy        |
| 49          | None        | NET infections                 | NA                            | Healthy        |
| 50          | None        | Febrile neutropenia            | SVD                           | Healthy        |
| 51          | None        | Cerebral infarction            | SVD                           | Healthy        |
| 52          | None        | None                           | CS (failed IOL)               | Healthy        |
| 53          | None        | Hepatic and splenic VTE        | SVD                           | Healthy        |
| 54          | None        | None                           | SVD                           | Healthy        |
| 55          | None        | Hemorrhagic delivery           | NA                            | Healthy        |
| 56          | None        | None                           | CS (failed IOL)               | Healthy        |
| 57          | None        | None                           | CS (failed IOL)               | Healthy        |
| 58          | None        | Thrombocytopenia, PLT trans, PPH, mesenteric VTE | SVD | Healthy |
| 59          | None        | Uterine hematoma, RBC trans    | SVD                           | Healthy        |
| 60          | NS          | NS                             | NS                            | Therapeutic abortion |
| 61          | None        | None                           | CS (NS)                       | Healthy        |
| 62          | None        | None                           | SVD                           | Fetal death    |
| 63          | None        | None                           | CS (failed IOL)               | Healthy        |
| 64          | None        | None                           | SVD                           | Healthy        |
| 65          | None        | RBC trans, mild preeclampsia   | SVD                           | Healthy        |
| 66          | None        | None                           | SVD                           | Healthy        |
| 67          | None        | RBC trans                       | SVD                           | Healthy        |
| 68          | None        | RBC, PLT trans                  | SVD                           | Healthy        |
| 69          | None        | Thrombocytopenia, PLT trans, PPH, mesenteric VTE | CS (IOL) | NICU, dysmorphic features |
| 70          | None        | None                           | SVD                           | Healthy        |
| 71          | None        | None                           | Emergency CS (fetal distress) | Healthy        |
| 72          | Lower abdominal pain, PV bleeding | None                            | Emergency evacuation/curettage | Missed Ab |
| 73          | PV bleeding, thrombocytopenia, hemolysis, RBC/PLT trans (before introducing eculizumab) | None | SVD | Healthy |
| 74          | Unknown     | Unknown                        | SVD                           | Missed Ab      |
| 75          | None        | Pregnant                       | Pregnant                      | IUFD           |
| 76          | IUFD, PLT trans | None                        | SVD                           | IUFD           |
| 77          | PV bleeding | None                           | SVD                           | Sp Ab          |
| 78          | None        | None                           | SVD                           | Sp Ab          |

Trans – Transfusion; NS – Not stated; PLT – Platelets; RBC – Red blood cells; BH – Breakthrough hemolysis; BCS – Budd-chiari syndrome; SP – Spontaneous; AB – Abortion; PVT – Portal vein thrombosis; CS – Caesarean section; FUO – Fever of unknown origin; SVD – Spontaneous vaginal delivery; PPH – Postpartum hemorrhage; PPE – Pleural peritoneal effusion; PE – Pulmonary embolism; BULT – Bilateral upper limb thrombophlebitis; TPI – Transient paralytic ileus; LVT – Liver vein thrombosis; IOL – Induction of labor; BMF – Bone marrow failure; ARF – Acute renal failure; PRES – Posterior reversible encephalopathy syndrome; PMVT – Portal mesenteric vein thrombosis; IC – Ischemic colitis; NA – Not available; NET – Nose-ear-throat; VTE – Venous thromboembolism; PSMVT – Portal and superior mesenteric vein thrombosis; ICU – Intensive care unit; HIT – Heparin induced thrombocytopenia; IUFD – Intrauterine fetal death; IUDF – Intrauterine fetal deaths; PV – Per vaginal; LMWH – Low-molecular-weight heparin; UFH – Unfractionated heparin; PROM – Preterm rupture of membranes; AKF – Acute kidney failure; HELLP – Hemolysis elevated liver enzymes and low platelets.
GPI-AP–deficient granulocyte. In another study, it was shown that compared with patients with PNH clone of 20% those with >70% GPI-AP–deficient granulocytes had an 11.8-fold increased risk of thrombosis. Therefore, observing clone size can assist in the management plan, in addition to the hypercoagulable state of pregnancy, which tremendously increases the risk of thrombosis.[24]

The efficacy of anticoagulants in pregnancy with PNH have been supported strongly by Morita et al.[13] and Patel et al.[23] whereas de Guibert et al.[19] reported some cases with thrombosis even after the use of anticoagulants. Therefore, there is need for further studies that provide stronger evidence for use of antithrombotic medications in pregnancy with PNH.

Eculizumab and ravulizumab are the approved medication for management of PNH. There is contrasting evidence regarding the safety of eculizumab use in pregnancy, as it has been reported to not cross the cord blood/placental barrier or be excreted in the breast milk, but it has also been reported that some proportion does cross cord blood/placental barrier.[11] In the study by Kelly et al.[9] eculizumab was detected in low levels in 7 of 20 cord blood samples. Eculizumab was also found in the placental blood of two patients with PNH after delivery, but with normal complement activity. Therefore, evidence suggests that in cases of suggests that if eculizumab does cross the placenta, the levels are very low to activate the complement system and cause any adverse effects to the fetus.[9] In PNH generally, a multinational longitudinal study found that eculizumab effectively stops intravascular hemolysis, thereby reducing risk of thrombosis and improving the quality of life.[10] However, specifically during pregnancy, its safety remains unclear as reported by Rodríguez-Ferreras and Velasco-Roces[23] that the Drug’s Technical Data Sheet and studies have warned regarding its potential teratogenic risk and discourage its use. This contrasts with the observations of other case series and recent reviews about its safety during pregnancy.[9,18,26,34,35]

In the cases reported by Guibert et al. (which account for 52% of all reported cases in the literature), eculizumab was not prescribed during either antepartum or postpartum periods. Overall, its use varied (Table 4), with 22% of all cases receiving it during the entire pregnancy, 18% in different trimesters and 8% did not receive it. During postpartum, 30% of the reported cases received eculizumab, and 14% did not. However, in our cases, three patients received eculizumab during antepartum and postpartum, but Case 2 did not and the reason for not initiating this therapy was not documented. In Case 3, the patient initially refused the therapy, but it was initiated at 31 weeks of gestation and postpartum; notably, both cases remained stable. The eculizumab dosage and frequency usually increased during pregnancy due to the physiological and pathophysiological factors of pregnancy and PNH, respectively, an approach supported by the existing literature.[16]

Overall, the findings in our cases and existing literature outcomes are similar. Management of pregnancy with PNH is based on observational data and preexisting published experience; therefore, there is need for an established protocol to standardize management plans for such a high-risk group.

CONCLUSION

Based on our experience from the reported cases, it can be stated that pregnancy is not recommended in patients with PNH due to the high risk of complications, and in cases of pregnancies, both hematological and obstetrician experts should be involved in patient care. All PNH pregnancies should be monitored clinically and through laboratory parameters for any symptoms/signs of hemolysis or thrombosis and to determine use prophylactic anticoagulants for thrombosis prevention and for use of eculizumab therapy. The safety of eculizumab use during pregnancy remain inconclusive, and thus there is need for prospectively studies with long-term follow-up to determine the effectiveness of eculizumab as well as determine the outcome of pregnancy with PNH.

Ethical considerations

This case series was approved by the Research Advisory Council /Ethics Committee at King Faisal Specialist Hospital, (Ref no: RAC#2131-049) and adhered to the guidelines of the Declaration of Helsinki, 2013.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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