Case Series

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

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Abstract

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

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal hematopoietic stem cell disorder caused by somatic mutation in phosphatidylinositol glycan class A gene (PIGA gene), resulting in deficiency or absence of glycosylphosphatidylinositol (GPI)-anchored proteins.[1]

Clinical manifestation of PNH is characterized by intravascular hemolysis, bone marrow failure (BMF) and thrombosis. It can also mimic other hematological disorders such as aplastic anemia (AA) and myelodysplastic diseases (MDS), although PNH can have a combination of both AA and MDS.[2,3] According to Brando *et al.*,[4] classical

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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.[1,5-7]

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].[18-20] Therefore, this case series would add to existing literature.[11]

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*.[19]	2011	France	23
Alashkar, *et al*.[21]	2020	Germany	9
Kelly *et al*.[9]	2015	Italy	6
The current case series	2021	Riyadh, Saudi Arabia	4
Miyasaka *et al*.[22]	2016	Japan	3
Morita *et al*.[13]	2013	Japan	2
Rodríguez-Ferreras, *et al*.[23]	2019	Spain	1
Bastos *et al*.[16]	2018	Brazil	1
Danilov *et al*.[24]	2010	Boston, USA	1
Marasca *et al*.[25]	2010	Italy	1
Ando *et al*.[26]	2014	Japan	1
Sharma *et al*.[12]	2015	New York, USA	1
Patriquin *et al*.[8]	2015	Canada	1
Patel *et al*.[27]	2017	Florida, USA	1
Vekemans *et al*.[28]	2015	Belgium	1
Gessoni *et al*.[29]	2015	Italy	1
Bjørge *et al*.[13]	2003	Norway	1
Lauritsch-Hernandez *et al*.[11]	2018	Switzerland	1
Singh *et al*.[10]	2014	India	1
Bais *et al*.[30]	1994	Amsterdam	1
Sasano *et al*.[31]	2016	Japan	1

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 underlining bone marrow disease.[5] The eculizumab therapy protocol was as stated in the literature:[17,20,32] 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

Table 2: Summary of cases and pregnancy outcomes with the use of eculizumab and anticoagulation therapy (the median values are stated for laboratory results)

Case number	Period	Laboratory tests					
		WBC (10^9/L)	RBC (10^{12}/L)	HGB (g/L)	PLT (10^9/L)	Total BILI (umol/L)	LDH (U/L)
1	Baseline	3.41	3.26	107	134	14	NA
	In pregnancy	3.25	2.33	83	33	24.1	545
	Postpartum	3.82	2.49	90	40	-	394
2	Baseline	4	2.90	99.5	29.5	9	281
	In pregnancy 2.1	8.37	3.47	105.5	183	6.55	650
	Postpartum 2.1	ND	ND	ND	ND	ND	ND
	In pregnancy 2.2	7.88	3.84	111	230	7.5	596
	Postpartum 2.2	8.2	3.77	111	212	7.5	596
	Postpartum 2.3	-	-	130	205	4	382
3	Baseline	3.89	3.33	114.5	131	69.5	921
	In pregnancy 3.1	5.06	2.80	87	45	15	508
	Postpartum 3.1	ND	ND	ND	ND	ND	ND
4	Baseline	NB	NB	NB	NB	NB	NB
	In pregnancy 4.1	2.44	2.52	96.5	52	22.6	1603.5
	Postpartum 4.1	2.00	2.46	88	61	22	ND
	In pregnancy 4.2	2.15	3.21	91	107	14	1133
	Postpartum 4.2	2.01	3.32	90	99	12	ND

WBC – White blood cells; RBC – Red blood cells; HGB – Hemoglobin; PLT – Platelets; BILI – Bilirubin; LDH – Lactic dehydrogenase; ND – Not done; NB – No baseline

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 increase to 40 mg subcutaneous daily and dose was adjusted according to the platelet count, which ranged at that time between 17 to 33 × 10^9/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

Table 3: Summary of cases and pregnancy outcomes with the use of eculizumab, anticoagulation therapy and documented complications (ante, intra, postpartum period)

Case number	Maternal age at PNH diagnosis (years)	Diagnostic test PNH clone size (%)		Clinical presentation	Maternal age at pregnancy (years)	Eculizumab		Anticoagulants in pregnancy (mg)	Transfusion	Complications			Follow up
		Granulocyte clone (%)	Monocyte, clone (%)			Before pregnancy (mg)	In pregnancy (mg)			Antepartum	Intrapartum	Postpartum	
1	36	67	63	Fatigue, dizziness, heavy mensuration AA thrombocytopenia	39	900	1200	LMWH	RBC, PLT	Polyhydramnios, fetus LGA	Thrombocytopenia	PVT, PLT Trans	Stable
2.1	25	56.7	48.2	Fatigue	22	None	None	LMWH	RBC	None	None	None	Stable
2.2				AA	23	None	None	LMWH	RBC	Epistaxis, dark urine	None	None	Stable
2.3					29	None	None	LMWH	None	Abdominal pain, PV bleeding	Missed Ab	None	
3.1	32	76.8	80.6	Fatigue, abdominal pain, dizziness, skin	37	Refused	600	Fondaparinux, HIT positive	RBC, PLT	PROM, PV, BMS exacerbation	None	None	Stable
3.2				thrombophlebitis	38	600	600	Unknown	Unknown	Unknown	Missed Ab	Unknown	
3.3				AA	38	600	600	Not yet started (1st trimester)	None	None	Pregnant	Pregnant	-
4.1	32	43.2	78.3	Back pain	35	900	600	LMWH	RBC, PLT	IUFD	None	None	Stable
4.2				AA	36	900	900	LMWH	None	IUFD followed by SCA	None	None	Stable
4.3				Pancytopenia HepB	37	900	900	None	None	None	Sp Ab	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; SCA – Spontaneous complete abortion. LMWH – Low-molecular-weight heparin; RBC – Red blood cells; PLT – Platelets; SP – Spontaneous; AB – Abortion; HIT – Heparin indiced thrombocytopenia

were confirmed with hemoglobin: 114 g/L, reticulocyte auto 86.8 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.[33] 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*.[20] 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%

Table 4: Review of literature for pregnancy with paroxysmal nocturnal hemoglobinuria

Case number	Reference	Number of cases	Maternal age at pregnancy	Anticoagulation therapy		Eculizumab therapy	
				Before pregnancy	During pregnancy	During pregnancy (duration of dose if stated)	Postpartum (mg)
1	Alashkar, *et al.*	9	NS	NS	NS	900 mg	900
2	Alashkar, *et al.*	9		NS	NS	900–1800 mg	900
3	Alashkar, *et al.*	9			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	900–1200 mg	900
8	Alashkar, *et al.*	9	NS	NS	NS	None	900
9	Alashkar, *et al.*	9		NS	NS	900 mg	900
10	Alashkar, *et al.*	9		NS	NS	900 mg	900
11	Alashkar, *et al.*	9		NS	NS	900–1200 mg	900
12	Alashkar, *et al.*	9	NS	NS	NS	None	None
13	Alashkar, *et al.*	9		NS	NS	900 mg	900
14	Alashkar, *et al.*	9		NS	NS	900 mg	900
15	Alashkar, *et al.*	9	NS	NS	NS	None	None
16	Alashkar, *et al.*	9	NS	NS	NS	900 mg	900 mg
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)	1200
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	From 27 weeks	Yes
32	Miyasaka *et al.*	3	29	No	Prophylactic heparin	From 18 weeks	Yes
33	Patel *et al.*	1	24	No	Prophylactic heparin	From 10 weeks	Yes
34	Vekemans *et al.*	1	41	No	Prophylactic LMWH	Entire pregnancy	Yes
35	Gessoni *et al.*	1	NS	No	Prophylactic LMWH	Entire pregnancy	Yes
36	Bjørge *et al.*	1	35	Warfarin	Therapeutic heparin	NS	NS
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	NS	NS

Contd...

Table 4: Contd...

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

Contd...

Table 4: Contd...

Case number	Complications		Mode of delivery (indication)	Newborn status
	Intrapartum	Postpartum		
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 RBC/PLT trans	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	Dead
13	Stillbirth	NS	Vaginal	Dead
14	Medical Ab	NS	-	Dead
15	Sp Ab	NS	Vaginal	Dead
16	RBC Trans, precplampsia	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 RBC/PLT trans	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 tans	SVD	Healthy
35	PE, BULT	PPE, PE, BULT, abdominal angina with TPI	CS (fetal distress)	Healthy
36	Chorioamnionitis secondry to IOL	PPH, LVT (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	Complications		Mode of delivery (indication)	Newborn status
	Intrapartum	Postpartum		
45	None	BCS	CS (failed IOL)	Healthy
46	None	None	CS (NS)	Healthy
47	Anemia, RBC trans	None	CS (failed IOL)	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	Hemorrhagic delivery	None	SVD	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
63	None	None	CS (NS)	Healthy
64	None	None	SVD	Fetal death
65	None	None	CS (failed IOL)	AFD
66	None	Cerebral VTE	NA	Healthy
67	RBC trans, mild preeclampsia	None	SVD	Healthy
68	RBC trans	None	SVD	Healthy
69	RBC, PLT trans	PSMVT, thrombocytopenia, PLT Trans	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	-
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 indiced thrombocytopenia; IUFD – Intrauterine fetal death; IUFD – 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*.[33] and Patel *et al*.[27] 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.[16] 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.[8,9,18,26,28,34,35]

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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