Case Report

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Pregnancy and Neonatal Outcomes in Patients with Paroxysmal Nocturnal Hemoglobinuria: A Case Series with Review of the Literature

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1. Abstract

1.1. Background:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder marked by intravascular hemolysis resulting from somatic cell mutations. The condition poses elevated risks of maternal and neonatal morbidity and mortality, with common complications including anemia, thrombocytopenia, bleeding, and an increased likelihood of fetal miscarriage and preterm birth. This study aims to analyze cases of PNH during pregnancy within our medical center and discuss key aspects of managing pregnant women with PNH.

1.2. Methods:

This study employed a retrospective case series approach, focusing on eight patients with PNH during pregnancy who received treatment at a tertiary medical center in China from 2000 to 2023. Detailed records were compiled encompassing patients' clinical manifestations, pregnancy complications, laboratory tests, treatment courses, delivery outcomes, and neonatal outcomes.

1.3. Results:

All pregnant women with PNH underwent blood transfusions. Following delivery, 71.4% of patients received prophylactic low-molecular-weight heparin anticoagulant therapy, with no observed thrombotic events. Cesarean section delivery was chosen by 85.7% of patients, resulting in 42.9% of newborns being premature, with an average birth weight of 1736g. One newborn experienced long-term neurodevelopmental delay. Notably, there were no cases of neonatal or maternal death.

1.4. Conclusions:

Pregnancy is discouraged for women with PNH, and caution is advised, requiring supervision by a multidisciplinary team. Postpartum anticoagulant therapy is imperative. Eculizumab, a complement inhibitor, emerges as a promising treatment for PNH.

Plain language summary

What is the context?

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare somatic mutation-induced hemolytic disease.
- The primary clinical manifestations of PNH involve hemolytic anemia, hemoglobinuria, and thrombocytopenia, with pregnancy potentially exacerbating these symptoms.
- Pregnant women with PNH face heightened morbidity and mortality, with venous thrombosis or embolism identified as the most common cause of death.
- Anticoagulant therapy, blood transfusion therapy and symptomatic therapy are the most important therapeutic measures. The safety and effectiveness of targeted therapy of Eculizumab still need to be further confirmed.

What is new?

- This study involved a retrospective analysis of eight cases of pregnancy with PNH from the years 2000 to 2023.
- We thoroughly examined essential personal characteristics, clinical manifestations, laboratory results, obstetric complications, treatment

strategies, delivery modes, and pregnancy outcomes.
- No adverse thrombotic events occurred.
- The importance of reasonable anticoagulant therapy for PNH pregnant women was confirmed.
- Women with PNH are usually complicated with thrombocytopenia. The pros and cons of anticoagulant therapy should be comprehensively evaluated to weigh the risk of postpartum hemorrhage and thrombosis.

What is the impact?
- enous thrombosis stands out as a leading cause of high mortality in women with PNH, emphasizing the critical need for postpartum anticoagulant therapy to avert thrombotic events.

2. Keywords:
Paroxysmal nocturnal hemoglobinuria (PNH), venous thromboembolism, anticoagulation, high risk pregnancy, eculizumab, pregnancy outcomes.

3. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon somatic mutation-induced hemolytic disease characterized by intravascular hemolysis, venous thrombosis, and smooth muscle dystonia [1]. The disease's progression can lead to bone marrow failure and, in severe cases, multiple organ damage. Timely diagnosis and standardized treatment are crucial, as pregnant women with PNH face elevated morbidity and mortality rates, along with a higher incidence of adverse pregnancy outcomes. The perinatal mortality rate among women with PNH ranges from 8% to 21%, with venous thrombosis emerging as the primary cause of death [2,3]. Neonatal mortality stands at 4-9%, with preterm birth constituting a significant risk factor [4,5]. Given the rarity of PNH and the limited availability of guidelines and clinical studies, managing the condition during pregnancy presents unique challenges. PNH is an uncommon hemolytic disorder characterized by abnormal complement activation, with the root cause attributed to somatic mutation. The primary pathophysiological mechanism involves the mutation of phosphatidylinositol glycan class A (PIGA) encoded by XP22., resulting in the reduction or deficiency of glycosylphosphatidylinositol-I-anchored proteins (GPI-APs) on blood cell surfaces. This deficiency, particularly of complement regulatory proteins CD55 and CD59, leads to abnormal complement pathway activation, triggering continuous blood cell destruction and hemolysis [1, 6]. Peripheral blood cells lacking GPI-APs, including red blood cells, neutrophils, and monocytes, form PNH clones, and the clone size significantly correlates with the risk of thrombosis [3,4,6]. Furthermore, the destruction of red blood cells prompts the release of significant amounts of free hemoglobin, directly or indirectly causing excessive nitric oxide (NO) consumption. NO depletion contributes to vascular endothelial damage, platelet activation, vasomotor dysfunction, and platelet consumption, resulting in a prothrombotic state [3,7]. The increased thrombus formation tendency and hypercoagulability in pregnant women with PNH elevate the risk of venous thrombosis, embolism, embryo termination, inevitable abortion, threatened abortion in early pregnancy [3], and hypertensive disorders such as preeclampsia and HELLP syndrome in the mid to late trimesters.

Moreover, NO depletion induces smooth muscle dysfunction, leading to clinical symptoms like dysphagia, fatigue, and muscle soreness. During labor, the contraction of uterine smooth muscle may be affected, resulting in weakened, prolonged, or stalled labor (in vaginal delivery). This can further lead to postpartum complications such as hemorrhage, abdominal distension, and postpartum abdominal pain [8, 9]. This paper presents a summary of eight cases involving PNH during pregnancy, offering insights into our experience in managing these complex situations. By sharing our experiences, we aim to enhance awareness of this disease and contribute valuable information to the medical community.

4. Methods

This study, conducted at Shandong University Qilu Hospital, involved a retrospective analysis of eight cases of pregnancy with PNH from the years 2000 to 2023. We thoroughly examined essential personal characteristics, clinical manifestations, laboratory results, obstetric complications, treatment strategies, delivery modes, and pregnancy outcomes

4.1. PNH diagnosis

The primary diagnostic method employs flow cytometry for peripheral blood cells, with more than 10% of CD55 or CD59 negative red blood cells or neutrophils serving as the main diagnostic criteria. Additional diagnostic tests encompass the acidified serum (Ham) test, sugar water test, urine occult blood test, and snake venom factor hemolysis test. A diagnosis of PNH can be established if there are more than 2 positive Coombs' tests, hemoglobin is less than 110 g/L, and other possible hemolytic diseases are excluded. Flow cytometry is conducted for all admitted patients. The diagnosis of chronic aplastic anemia relies on bone marrow aspiration. Pancytopenia is defined as anemia with hemoglobin less than 110 g/L, thrombocytopenia as a platelet counts less than 100×10^9/L, and neutropenia as a neutrophil count less than 1.5×10^9/L. The severity of anemia is categorized by hemoglobin levels: mild anemia, hemoglobin greater than 90 g/L; moderate anemia, hemoglobin between 60 g/L and 90 g/L; severe anemia, hemoglobin less than 60 g/L. Upon admission, essential auxiliary tests, including blood routine, urine routine, blood coagulation series, liver function, kidney function, and venous thrombosis risk assessment, are conducted. These tests are instrumental in evaluating the severity of PNH or obstetric complications and identifying potential complications in different organs.

Differential diagnostic tests include the rheumatic immune antibody test, anemia series (folic acid, ferritin, vitamin B12 assay), and others. For patients experiencing chest tightness or dyspnea, appropriate additional tests, such as chest computed tomography (CT), echocardiography, lower extremity arteriovenous ultrasound, B-type natriuretic peptide (BNP), and myocardial injury markers, are administered as needed. Hematology specialists actively participate in the consultation process, offering

treatment recommendations and closely monitoring patient conditions. The consultation and treatment of diverse cases involve multidisciplinary departments such as anesthesiology, neonatology, internal medicine, and critical care medicine.

5. Results

5.1. Maternal Characteristics

This study summarizes the characteristics of eight pregnant women diagnosed with PNH during mid to late pregnancy, as detailed in Table 1. The median age of these patients was 30 years, ranging from 22 to 35 years. Among the eight patients, only two had previously delivered healthy children, one was a primipara, while the majority (5 out of 8 cases, 62.5%) had a history of adverse pregnancies.

Table 1: Summary of patients' characteristics and treatment during pregnancy.

Case	Maternal age	Gravida	Maternal history	Diagnosis time	Clinical manifestation	Supportive therapy	Anticoagulant therapy	Transfusion therapy
1	35	G2P1	1 PNH cesare an delivery	5 years	Fatigue; hematuria; muscle soreness	Folic acid, iron, sodium bicarbonate, mecobalamin, prednisone, glutathione	Postpartum	4 RBC unit in 34 weeks 6 RBC unit in 38 weeks 2 RBC unit postpartum
2	30	G2P0	1 intrauterine fetal death	AA at 18 years; PNH at 30 years	Hematuria; hemorrhagicleucorrhea	Prednisone, iron, sodium bicarbonate	Postpartum	4 RBC unit in 32 weeks 4 RBC unit postpartum
3	29	G3P0	2 embryo damage	HA at 25 years; PNH at 27 weeks of pregnancy	Fatigue; hematuria	None	None	4 RBC unit in 27 weeks
4	30	G2P1	1 vaginal delivery	12 weeks of pregnancy	Fatigue; hematuria	Folic acid, iron, sodium bicarbonate, mecobalamin, Vitamin E	Postpartum	RBC transfusion in 12 weeks, no details
5	22	G2P0	1 embryo damage	8 weeks of pregnancy	Fatigue; hematuria	Sodium bicarbonate	Postpartum	6 RBC unit in 24, 35 weeks, postpartum
6	28	G3P0	2 spontaneous miscarriages	PNH with AA at 18 years	Fatigue; vaginal bleeding; muscle soreness	Sodium bicarbonate, prednisone, Vitamin E	None	4 RBC unit in 8,12,16,20 24weeks 10 RBC unit in operation 2 RBC and 16 platelet unit postpartum
7	30	G3P0	2 spontaneous miscarriages	HA at 20 years PNH at 36 weeks of pregnancy	Fatigue; hematuria	Sodium bicarbonate, prednisone, Vitamin E	12 weeks until 37 weeks; postpartum	3 times of RBC transfusions, no details
8	31	G1P0	None	27 years	Fatigue; dizzy; gingival bleeding; limb hemorrhagic spot; chest tightness; difficulty breathing	Sodium bicarbonate, prednisone, Vitamin E	None	16 platelet unit in 19 weeks, 2 RBC unit and 1 platelet unit in 19,25,29,33 weeks 8 RBC unit and 3 platelet unit in operation 2 RBC unit and 1 platelet unit postpartum

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PNH: Paroxysmal nocturnal hemoglobinuria; AA: Aplastic anemia; HA: Hemolytic anemia; RBC: Red blood cell

Two patients had experienced spontaneous abortions, two had undergone embryo terminations, and one had a history of stillbirth induction in the second trimester. More than half of the cases were diagnosed with PNH-related diseases before pregnancy. Four patients were diagnosed with PNH before their current pregnancies, including two cases with aplastic anemia. Two patients were initially suspected of having hemolytic anemia and were officially diagnosed with PNH through flow cytometry after hospitalization, with confirmed timings at 27 weeks and 36 weeks of gestation, respectively. The remaining two patients were diagnosed at 8 and 12 weeks of gestation. The clinical manifestations varied among the patients, with common symptoms including fatigue (7 of 8 cases, 87.5%), hematuria (6 of 8 cases, 75%), and bleeding in various body parts (3 of 8 cases, 37.5%) such as vaginal bleeding, bloody leukorrhea, skin hemorrhages, and ecchymosis. Other manifestations included muscle soreness (2 out of 8 cases, 25%), dizziness, chest tightness, dyspnea, etc. These severe manifestations may be linked to elevated pulmonary artery pressure or venous thrombosis caused by PNH and may also be closely associated with complicated obstetric complications such as preeclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. Blood routine results before transfusion treatment revealed severe anemia in six cases (75%), pancytopenia in one case, thrombocytopenia in four cases, and moderate anemia in two cases. Detailed laboratory results are shown in Table 2 All patients received at least one red blood cell transfusion during pregnancy, with one patient undergoing long-term blood transfusion treatment every month for a total of seven times throughout the entire perinatal period. Only two patients received platelet transfusion therapy, with one of them receiving platelet and red cell transfusions every 4 to 6 months since PNH was diagnosed at 19 weeks of gestation, totaling six red blood cell transfusions and seven platelet transfusions.

Table 2: Summary of laboratory results during pregnancy and postpartum, (the medianvalues are stated for laboratory results)

Case	Pregnancy							Postpartum	
	HB (g/L)	PLT(10^9/L)	LDH (U/L)	AKP (U/L)	TBIL (u mol/L)	DBIL (u mol/L)	IBIL (u mol/L)	HB (g/L)	PLT (10^9/L)
1	48	82	2311	171	32.4	9.7	22.7	58	60
2	53	62	1534	89	16.9	5.4	11.5	63	62
3	68	98	1906	120	12.1	2.9	9.2	72	119
4	33	138	1105	175	24	0	17	94	189
5	49	104	847	104	8.3	3	5.5	64	95
6	56	31	7913	107	33.7	6.7	27	63	17
7	83	120	427	150	11	0	6	63	101
8	43	6	623	133	10.9	3.8	7.1	76	13

HB: Hemoglobin; PLT: Platelet; LDH: Lactate dehydrogenase; AKP: Alkaline phosphatase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin.

Standardized treatment, guided collaboratively by obstetricians and hematologists, was administered to almost all patients (7 out of 8 cases, 87.5%). This primarily involved symptomatic treatment, including folic acid, sodium bicarbonate, prednisone, mecobalamin, and vitamin E. Notably, one patient opted not to undergo drug treatment during pregnancy, resulting in intrauterine fetal death at 27 weeks of gestation. Anticoagulant therapy with low molecular weight heparin (LMWH) was exclusively employed by one patient from early pregnancy until 37 weeks of gestation. Anticoagulation therapy recommenced 24 hours after surgery and was maintained throughout the postpartum period. No other patients utilized aspirin or heparin anticoagulant therapy during pregnancy. Of the remaining cases, three patients received prophylactic doses of LMWH within 6 weeks postpartum. However, two patients abstained from anticoagulant therapy due to low platelet counts and a heightened risk of bleeding. In summary, 71.4% of patients received prophylactic anticoagulant therapy post-delivery, and no thromboembolic events were reported in any of the eight cases.

5.2 Obstetric complications

Detailed descriptions of maternal complications during the prenatal and postnatal periods are provided in Table 3. Among the eight cases, obstetric complications manifested in five patients, encompassing premature rupture of membranes, oligohydramnios, gestational diabetes mellitus (GDM), placental abruption, HELLP syndrome, and two cases of preeclampsia. Postnatally, complications primarily included infection, elevated body temperature, and suspected thrombosis-related manifestations such as chest tightness and dyspnea. Cough occurred in three cases, dyspnea and chest tightness in two cases, postpartum fever in two cases, and one case exhibited thrombocytopenia and neutropenia that had not occurred during pregnancy. Other concurrent symptoms included expectoration, hoarseness, abdominal distension, hemoptysis, etc. Only two cases did not develop new complications. Patients 6 and 8 underwent comprehensive postpartum examinations, including blood gas analysis, bedside chest X-ray, chest CT, pulmonary artery computer tomography angiography (CTA), and lower extremity arteriovenous ultrasound. Continuous monitoring of blood routine, coagulation, bacteriological culture, and markers of myocardial injury was carried out to exclude serious complications such as venous thrombosis. Patient 6, experiencing mild chest tightness with no abnormal findings, may have had transient

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Table 3: Summary of complications of pregnancy and postpartum and outcomes of pregnancy and newborn.

Case	Hematologic complications	Obstetric complic-ations	Postpartum complications	Mode and time of delivery	Anesthesia methods	newborn weight(g)	Apgar score(s)	Fetal complic-ations	Trans-fer to NICU	Newborn status
1	Severe anemia;	None	Fever (max 39 ℃);	Caesarean section: 38+6 weeks	Combined spinal epidural	3000	10, 10, 10	None	NO	Healthy
	thrombocytopenia		abdominal distention							
2	Pancytopenia	PPROM	Fever (max 38 ℃);	Caesarean section: 32+4 weeks	Combined spinal epidural	1850	7, 9, 10	Neonatal asphyxia;	Yes	Healthy
			cough; hoarse					subcutaneous hematoma;		
								acute fetal distress		
3	Moderate anemia;	Stillbirth	None	Water sac induced labor: 27+1 weeks	None	None	None	None	None	None
	thrombocytopenia									
4	Severe anemia	None	No new symptoms	Vaginal delivery (Lateral perineal incision): 37+2 weeks	None	2500	10, 10, 10	None	NO	Healthy
5	Severe anemia	GDM; PE	Emerging thrombocy-topenia;	Caesarean section: 40+1 weeks	General anesthesia	3850	10, 10, 10	None	NO	Healthy
			granulocytopenia							
6	Severe anemia; thrombocy topenia	Severe PE;	Cough; expectoration;	Caesarean section: 28+3 weeks	General anesthesia	860	2, 5, 7	Neonatal asphyxia; NRDS; neonatal sepsis;	Yes	Intellectual behavior lags behind peers
		HELLP;	chest tightness;					hyperbilirubinemia; anemia; dysplasia;		
		placental abruption	difficulty breathing					bronchopulmonary;		
								premature encephalopathy		
7	Moderate anemia	Oligohyd-ramnios	NA	Caesarean section: 38+1 weeks	General anesthesia	2800	10,10,10	Neonatal hyperbiliru-binemia	Yes	healthy
8	Severe anemia;	None	Cough; hemoptysis;	Caesarean section: 35+6 weeks	General anesthesia	2500	9, 9, 10	Cardiac damage	Yes	healthy
	thrombocytopenia		chest tightness;							
			difficulty breathing							

PPROM: Preterm premature rupture of membrane; GDM: Gestational diabetes mellitus; PE: Preeclampsia; HELLP: hemolysis elevated liver enzymes and low platelets count syndrome; NICU: Neonatal Intensive Care Unit.

Patient 7 was induced labor in the second trimester, with no pregnancy outcome or neonatal outcome. myocardial damage induced by the combination of severe preeclampsia and PNH. In contrast, Patient 8 developed symptoms of infection and acute heart failure post-delivery, including cough, sputum, significant breath-holding, and reduced oxygen saturation (73%-80%). Examination results revealed elevated B-type natriuretic peptide (BNP) levels (5635 pg/ml), lactate dehydrogenase (LDH) at 788 IU/L, echocardiography indicating left heart enlargement, a small amount of pericardial effusion, mild mitral and tricuspid valve and

pulmonary valve regurgitation, a left ventricular ejection fraction (LVEF) value of 0.67, and a mean pulmonary artery pressure of 23mmHg. Fortunately, no thrombotic events were detected. Treatment with cidilan, imipenem, and methylprednisolone significantly improved the patient's symptoms, and repeated examinations showed a gradual downward trend in improved the patient's symptoms, and repeated examinations showed a gradual downward trend in BNP levels. It was considered that the complications might have arisen due to acute cardiac dysfunction induced by infection or underlying peripartum cardiomyopathy.

5.3 Pregnancy and perinatal outcomes

Detailed pregnancy and neonatal outcomes are documented in Table 3. Among the final delivery methods, only one case involved vaginal delivery with lateral episiotomy, one case was induced by rupturing the water sac, and the majority (85.7%, 6 out of 7 cases) underwent cesarean section. Anesthesia methods varied, with two cases utilizing combined epidural anesthesia, and the majority (66.7%, 4 cases) opting for general anesthesia. Notably, none of the cases experienced postpartum hemorrhage. In terms of perinatal outcomes, 42.9% (3 out of 7 cases) were preterm infants, with an average birth weight of 1736g. The smallest case was delivered at 28+3 weeks due to emergency termination related to severe maternal HELLP complications. This preterm infant, with a postnatal Apgar score of 2/5/7, faced multiple challenges such as severe asphyxia, extremely low birth weight (860g), respiratory distress syndrome, neonatal sepsis, hyperbilirubinemia, bronchopulmonary dysplasia, and encephalopathy of prematurity. Long-term follow-up revealed developmental delays in intellectual capacities, characterized by slow responses and unclear language expression.

Another preterm case at 32+4 weeks, born after the mother experienced premature rupture of membranes, exhibited an Apgar score of 7/9/10 and a birth weight of 1850g. Despite fair overall condition, the newborn developed acute dyspnea an hour after birth, leading to transfer to the Neonatal Intensive Care Unit (NICU). Complications such as neonatal asphyxia, pneumonia, hypoproteinemia, and subcutaneous hematoma ensued. Fortunately, no significant sequelae were observed post-discharge. The last preterm case, born at 35+6 weeks, involved a mother with severe anemia and thrombocytopenia. The pregnancy was terminated after platelet transfusion therapy, resulting in an Apgar score of 9/9/10 and a weight equivalent to that of full-term infants (2500g). The newborn was briefly admitted to the NICU due to preterm birth and maternal risk factors but showed no abnormalities after one week of monitoring and treatment, eventually being discharged in good health. The remaining four cases resulted in full-term infants, with one being transferred to the NICU for pneumonia and hyperbilirubinemia treatment. All 4 children are currently in good physical health, and fortunately, there were no maternal or neonatal deaths.

6. Discussion

Pregnancy is not recommended for women with PNH in the absence of proper treatment or during the active phase of the disease. The inherent physiological changes during pregnancy can exacerbate pre-existing PNH, leading to increased destruction of peripheral blood cells, intensified hemolytic anemia, higher susceptibility to infection, and a significantly elevated risk of venous thrombosis [2, 6, 9-14]. Consequently, pregnant women with PNH face heightened morbidity and mortality. A retrospective analysis by Fieni S et al. spanning the literature from 1965 to 2005 summarized the pregnancy outcomes of 43 PNH patients. The study revealed a maternal mortality rate as high as 11.6%, with venous thrombosis or embolism identified as the most common cause of death. Complications during the postpartum period were notably higher (30.2%) than those during prenatal (16.3%) or delivery phases [12].

6.1. Clinical Manifestation

In our case report, the predominant clinical manifestations were recurrent episodes of hemoglobinuria during pregnancy, often accompanied by vaginal bleeding, gingival bleeding, dermatorrhagia, and various bleeding manifestations. Persistent reductions in hemoglobin and platelet levels, unresponsive to drug therapy, constituted the primary reasons for pregnant women seeking medical attention. Furthermore, clinical presentations among pregnant women with PNH can vary. Existing literature suggests a spectrum of symptoms, including dizziness, fatigue, chest tightness, abdominal pain, dysphagia, difficulty breathing, pulmonary hypertension, and renal insufficiency [2, 7]. These variations may stem from prolonged complement activation and NO depletion, leading to impaired function in different organs [1, 7, 15].

6.2. Diagnosis and differentiation

Women of childbearing age exhibit a heightened incidence of PNH. While a majority of PNH patients receive their diagnosis before pregnancy, the rarity of the disease (with an annual incidence of 1-2 cases/million people) and limited clinician awareness contribute to the ongoing diagnostic challenges [3, 7, 13]. In a multicenter prospective study involving 93,824 individuals, Morado et al. identified effective medical indications for PNH screening, including hemolytic anemia (19%), hematuria (48%), and unexplained cytopenia (9%) [16]. Consequently, clinicians should consider diagnosing or screening for PNH when encountering clinically unexplained moderate to severe anemia, hemoglobinuria, or unexplained hemolysis [9, 11, 15]. The primary diagnostic method for PNH is flow cytometry, with detection criteria being the absence or severe deficiency of at least two GPI-anchored proteins (mainly CD55 and CD59) [1]. Notably, detecting GPI-APs-deficient neutrophils is often preferred over red blood cells, as it remains unaffected by transfusion therapy [9]. Secondary diagnostic tests, including the acidified hemolysis test (Ham's test), sugar water test, urine occult blood test, and anti-human globulin test (Coombs test), have largely been supplanted by flow cytometry due to their poor sensitivity and inability to quantitatively detect GPI-Aps [6]. When PNH is suspected, Anita Hill et al. recommend comprehensive laboratory tests encompassing complete blood count, reticulocyte count, peripheral blood smear, and lactate dehydrogenase assay [7]. LDH serves as a crucial indicator, commonly elevated up to 10 times the normal value,

providing insight into intravascular hemolytic activity [1]. According to the Korean PNH Registry, PNH patients with LDH levels ≥1.5 times the upper limit of normal face a mortality rate 4.8 times higher than the general population [17].

The diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) during pregnancy poses a formidable challenge for obstetricians due to its non-specific manifestations. These symptoms closely resemble the physiological effects of pregnancy anemia, HELLP syndrome, preeclampsia, idiopathic thrombocytopenic purpura, rheumatic immune diseases, and anticoagulant-induced thrombocytopenia [3, 13, 18]. Notably, distinguishing PNH crisis from HELLP syndrome can be intricate, as both conditions exhibit hemolytic anemia, thrombocytopenia, and abnormal elevation of lactate dehydrogenase and indirect bilirubin. This complexity underscores the significance of a meticulous differential diagnosis, crucial for implementing distinct therapeutic approaches [18]. Unlike PNH, where complement activation is fundamental, HELLP syndrome is often secondary to hypertensive disorders during pregnancy, with vascular endothelial injury resulting from small vessel spasm [18]. Preeclampsia, with its accompanying symptoms such as hypertension (> 140/90 mmHg), blurred vision, proteinuria, headache, and right upper abdominal pain, can complicate the clinical picture further. HELLP syndrome may present with nausea, vomiting, abnormal transaminase levels, and subcapsular hematoma [9]. Preeclampsia can exacerbate terminal complement activation, further complicating PNH development [14]. In our presented cases, Patient 5 was complicated with preeclampsia, and Patient 6 with severe preeclampsia, HELLP syndrome, and suspected placental abruption. The coexistence of PNH heightened the treatment complexity. Patient 5 underwent a cesarean section for a full-term pregnancy, while Patient 6, with a more intricate condition, underwent early termination following hypotensive therapy, blood transfusion, and the promotion of fetal lung maturation. The overall outcome was favorable, with no maternal or infant mortality or thrombotic events.

6.3. Pregnancy Outcomes

In our study, 75% of patients reported a history of adverse pregnancy experiences, encompassing embryo termination, stillbirth, and spontaneous abortion. A parallel investigation by Morita, Y., et al., examining 69 PNH patients, disclosed adverse outcomes in 13.0% of pregnancies, including spontaneous abortion and neonatal death [19]. Examining collective case series reports, the preterm birth rate for newborns with PNH ranged between 29-53%, heightening infant morbidity and mortality [3, 12, 14, 20]. In a separate study involving 34 women with PNH, the average newborn weight was 2,800 grams, accompanied by a perinatal infant mortality rate of 8.8% [20]. Elective cesarean section emerges as the preferred delivery method for pregnant women with PNH, as demonstrated in a cesarean section rate of 30% across prior case reports [5, 12, 19]. This preference is attributed to the severity of anemia and thrombocytopenia, with cesarean section offering a timely resolution to prevent further deterioration. Additionally, smooth muscle dystonia in PNH patients may impede uterine contractions, potentially prolonging labor [4]. Among successful delivery cases in our study, two patients with platelet counts exceeding 60 received combined spinal epidural anesthesia, while four others underwent general anesthesia. One patient opted for vaginal delivery without labor analgesia. Notably, Patient 7, despite lacking thrombocytopenia, received general anesthesia due to an increased risk of epidural hematoma associated with prolonged prophylactic heparin treatment [21]. An illustrative case by Stocche, R.M., et al., showcased labor analgesia in a PNH patient with thrombocytopenia, incorporating anticoagulant prophylaxis post-epidural catheter removal, resulting in no observed thrombosis or epidural hematoma in the long term [22].

6.4. Anticoagulant Therapy

The incidence of venous thrombosis events in pregnant women with PNH ranges from 6.1% to 16%, influenced by the lack of prospective clinical studies and potential case selection bias [4, 11, 20]. Despite the undeniable prominence of venous thromboembolism as a leading cause of death during pregnancy in PNH women, our case series reported an all-cause mortality rate of 20.8% [20], and no maternal thrombotic complications were observed throughout the entire perinatal period. his aligns with findings from de Guibert et al., where a retrospective analysis of 22 pregnancies in 27 women revealed no thrombotic events during pregnancies, irrespective of anticoagulant therapy administration and the gestational age at which treatment commenced [4]. The disparity in results may be attributed to timely diagnosis before pregnancy and the initiation of standard hematological treatment, maintaining PNH in a controllable state. Our follow-up extended only to the end of the puerperium, differing from the observations by de Guibert, who reported severe postpartum thrombotic events occurring at 5, 7, and 9 months after delivery, leading to fatal outcomes [4]. Reviewing case reports globally, VTE occurred postpartum in 7 of 78 pregnancies among 62 PNH women [11]. This emphasizes the heightened risk for venous thrombosis in the postpartum period, warranting strengthened anticoagulation therapy. The prophylactic dose of LMWH might not suffice, necessitating consideration of therapeutic doses based on coagulation results or alternative anticoagulant drugs like warfarin, extending the treatment to at least 6 weeks postpartum [4, 6]. The necessity of anticoagulation during pregnancy remains unclear, with recommendations leaning towards patients with a history of multiple spontaneous abortions or a thrombotic predisposition [19]. Yet, the benefits and risks should be thoroughly evaluated in patients concurrently experiencing thrombocytopenia. Notably, in our cases, patients 6 and 8 did not receive anticoagulation due to low platelet counts, which could have heightened bleeding risks and further reduced platelet counts. However, both exhibited alarming symptoms of dyspnea, suggesting the possibility of an underlying prethrombotic state or venous thrombosis in uncommon locations. Ray et al.'s retrospective study underlines the predilection of venous thrombosis in intra-abdominal veins, primarily hepatic and mesenteric veins Ray et al.'s retrospective study underlines the predilection of venous thrombosis in intra-abdominal veins, primarily hepatic and mesenteric veins [20]. This underscores the critical role of postpartum anticoagulation in averting thrombotic events, necessitating vigilant monitoring of platelet counts alongside coagulation indicators to

ensure treatment safety. In cases where necessary, anticoagulation therapy can proceed with platelet transfusion support [6].

6.5. Symptomatic Treatment

The primary focus of our patients' pregnancy management centered on symptomatic treatment. Core interventions included folic acid and iron supplementation, urinary alkalization using baking soda, glutathione (GSH) for cell membrane stabilization, prednisone hormone therapy addressing acute or chronic hemolysis, and necessary transfusion therapy. While short-term glucocorticoid shock therapy effectively managed acute hemolysis, the prolonged use of hormone therapy in PNH remains contentious, potentially leading to heightened complications such as infection, Cushing's syndrome, and osteoporosis [6]. In our cases, all pregnant women underwent blood transfusion therapy. Those with hemoglobin levels below 60g/L and/or platelet counts under 20×10^9/L received component transfusion therapy. Treatment frequency and the volume of red blood cell or platelet units significantly increased compared to non-pregnant counterparts, attributable to elevated complement activation during pregnancy [2, 13]. A noteworthy example is Patient 8, presenting with anemia and thrombocytopenia, who received seven blood transfusions, amounting to 18 units of red blood cells and 24 units of platelets. To avert a hemolytic crisis, transfusion of complement-rich plasma was consciously avoided [13]. Given the heightened destruction of red blood cells in PNH, the iron requirement is elevated. However, cautious administration of intravenous iron is crucial, as rapid infusion can spur the production of new red cells susceptible to complement attack, exacerbating hemolysis [3]. Optimal management strategies involve oral iron supplementation and judicious blood transfusions to ameliorate anemia effectively.

6.6. Targeted Therapy

Eculizumab, a humanized monoclonal antibody, is the sole U.S. FDA-approved drug for PNH, acting by binding to complement protein C5 and inhibiting the complement terminal pathway [1, 5]. Clinical trials have demonstrated its efficacy in reducing intravascular hemolysis, elevating hemoglobin levels, decreasing transfusion requirements, and mitigating thrombosis risks [14, 15, 23, 24]. While prospective clinical studies on eculizumab's safety during pregnancy are lacking, previous case reports underscore substantial reductions in maternal complications and mortality [13, 14, 25]. Quantitative analysis of umbilical cord blood samples by Kelly et al. revealed eculizumab presence in seven samples, yet at levels insufficient to affect the newborn's complement pathway, indicating normal complement activity in newborns [14, 26]. A study following the long-term outcomes of newborns for up to 16 months reported no significant adverse effects [2]. Importantly, eculizumab does not excrete through breast milk and does not impact newborn breastfeeding [14]. However, despite these positive aspects, eculizumab remains categorized as a Class C drug during pregnancy [19]. Breakthrough hemolysis in the middle and late stages of pregnancy leading to PNH crisis has been reported as a potential drawback [25, 27, 28]. Moreover, an elevated risk of meningococcal infection, which can be fatal to pregnant women, is associated with eculizumab use [1, 7, 19]. Another limiting factor is its cost and the need for indefinite dosing, making its widespread use a subject of controversy [1]. Eculizumab has not been approved for marketing in China, so we did not carry out targeted therapy. Based on the benefits and risks of complement inhibitors, it is necessary to use them with caution after fully evaluating the pros and cons.

7. Conclusion

Women diagnosed with PNH should receive comprehensive information about the elevated pregnancy-associated risks and adhere rigorously to supervision by hematologists, obstetricians, intensive care unit specialists, anesthesiologists, and neonatologists. The primary clinical manifestations of PNH involve hemolytic anemia, hemoglobinuria, and thrombocytopenia, with pregnancy potentially exacerbating these symptoms. Venous thrombosis stands out as a leading cause of high mortality in women with PNH, emphasizing the critical need for postpartum anticoagulant therapy to avert thrombotic events. The poor neonatal prognosis is intimately linked with preterm birth, highlighting the importance of managing pregnancy and delivery with precision. Eculizumab emerges as a promising treatment for pregnant women grappling with PNH. However, the efficacy and safety of this drug during pregnancy require further substantiation through ongoing research. As women navigate the complex intersection of PNH and pregnancy, a multidisciplinary approach, clear communication, and adherence to medical guidance are imperative for optimizing maternal and neonatal outcomes.

8. Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. This study was reviewed and approved by the Ethical Committee of Qilu Hospital of Shandong University (protocol number 2020093), and with a waiver for informed consent.

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