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Pregnancy Outcome of Women with Paroxysmal Nocturnal Hemoglobinuria

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NARRATIVE REVIEW

Pregnancy Outcome of Women with Paroxysmal Nocturnal Hemoglobinuria

Short title: Maternal and perinatal outcome in pregnant women with PNH

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ABSTRACT

Objective: To evaluate maternal and perinatal outcomes in pregnant women affected by Paroxysmal Nocturnal Hemoglobinuria (PNH) treated with eculizumab with a case series and literature review.

Methods: This was a case series study with literature review. Clinical records of all consecutive pregnant women with PNH were included in the study. The systematic review was conducted using electronic databases from inception of each database through May 2021. No restrictions for language or geographic location were applied. All reports of women with PNH in pregnancy, treated with eculizumab, were included in the review. Reports of women not treated or treated with other drugs rather than eculizumab (e.g. low molecular weight heparin alone) were excluded from the study. Maternal and perinatal outcomes were evaluated.

Results: Fifteen studies, including 24 pregnancies with PNH, were included in the review. All included women received eculizumab during the pregnancy, of them 10 received the treatment for the entire length of their gestation. Gestational age at delivery was reported in 18 cases, with preterm birth at less than 37 weeks occurring in fifteen women (83%). 57.1% of the women delivered by cesarean delivery. The cases series added three new cases in the literature. Two cases were already on eculizumab before pregnancy, while in one case eculizumab therapy was initiated in the second trimester of pregnancy. In all the three cases, there were no thrombotic complications, maternal or neonatal deaths, or fetal structural abnormalities.

Conclusion: PNH in pregnant women may be associated with an increased risk of obstetric complications, such us cesarean delivery or preterm birth. Eculizumab appears to be safe and effective for managing PNH during pregnancy.

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired stem cell hematopoietic disorder complicated by recurrent hemolysis, bone marrow failure and both arterial and venous thrombosis (1). PNH is a unique disease, and its clinical manifestations are caused by the deficiency in glycosylphosphatidylinositol-anchored proteins (GPI-APs) (2).

The lack of the complement regulatory proteins CD55 and CD59, who are anchored to the cell surface by the GPI-APS, appears to be the main causative mechanism of complications occurring in PNH affected patients(3). CD55 orchestrate the pathways leading to the formation and stability of the C3 and C5 convertases (4) whereas CD59 interferes with the terminal effector complement, blocking the incorporation of C9 onto the C5b–C8 complex, forming the MAC (5).

PNH erythrocytes are highly vulnerable to complement-mediated lysis owing to a reduction, or absence, of 2 important GPI-anchored complement regulatory membrane proteins, CD55 and CD59 (3). The observed dysregulation of complement mediated cell lysis is the underlying mechanism of the chronic hemolytic anemia that are frequently observed in these patients.

Thrombosis is another typical manifestation and is the leading cause of death in PNH (6). However, the pathophysiology and mechanism underlying the thrombophilia in PNH is not well understood.

Physiologically, pregnancy is accompanied by changes in the coagulation and fibrinolytic systems. These include increases in several clotting factors, a decrease in protein S levels and inhibition of fibrinolysis.

As gestation progresses, there is also a significant fall in the activity of activated protein C. Pregnancy in itself causes approximately a five-fold increased risk of deep venous thrombosis (7). Also, intravascular breakthrough hemolysis is more severe during pregnancy with higher transfusion dependence (8).

Therapy of PNH include treatment of the acute attacks, including steroids, and transfusions, and long-term therapy with anticoagulant, such as warfarin.

On March 2007, the FDA approved the use of Eculizumab for treating PNH. Prior to eculizumab the median life expectancy of an individual with PNH was approximately 10 years and obstetric outcome in pregnant patients were poor. Since that time, short and midterm studies of patients on eculizumab demonstrate that the drug returns the patient to a normal life expectancy, improves quality of life, and decreases the need for blood transfusions

Eculizumab is a humanized monoclonal antibody, that inhibits and prevents the C5 factor cleavage into its final products: C5a and C5b, a potent proinflammatory molecule and a C5b-C9 complex particle respectively. Eculizumab inhibits the intravascular hemolysis that leads to anemia but most importantly, by arresting complement mediated RBC destruction it prevents the release of thrombogenic products stored inside the RBC, thus reducing thrombotic complications (9).

Eculizumab therapy is started at moment of diagnosis by following an induction-maintenance protocol. Patients usually start with 600mg IV eculizumab every 7 days for 4 weeks followed by 900mg 7 days later and a lifelong maintenance dose of 900mg every 14 days (10).

No studies have shown security of eculizumab in pregnancy and placental passage may occur (11), but ELISA based essay for complement activity in the newborn showed that eculizumab at therapeutic dose in the pregnant women did not affect the complement system of the newborn (12).

Therefore, before eculizumab, a humanized anti-C5 monoclonal antibody (13) came into clinical use, pregnancy was relatively discouraged in PNH women. Nowadays, in the eculizumab era, although there are no RCT proving the effectiveness and security in pregnancy, maternal and neonatal morbidity is significantly decreased (14).

Objective

The aim of this study was to evaluate maternal and perinatal outcomes in pregnant women affected by PNH with a literature review and a case series.

METHODS

Literature review

The search for the systematic review was conducted using MEDLINE, EMBASE, Scopus, ClinicalTrials.gov, OVID and Cochrane Library as electronic databases. Articles were identified with the use of a combination of the following text words: “Paroxysmal Nocturnal Hemoglobinuria” “Marchiafava-Micheli syndrome” and “pregnancy,” from inception of each database through May 2021. Review of articles also included the abstracts of all references retrieved from the search. No restrictions for language or geographic location were applied. All reports of women with PNH in pregnancy, treated with eculizumab, were included in the review. Reports of women not treated or treated with other drugs rather than eculizumab (e.g. low molecular weight heparin alone) were excluded from the study because these treatments did not reflect current clinical practice. For each study, maternal and perinatal outcomes were extracted. The electronic search, the eligibility of the studies, and data extraction were independently assessed by two authors (FZ, GS). Definition of the evaluated outcomes were according to the definition of the original included study.

Case series

This was a single center case-series study. Clinical records of all consecutive pregnant women with PNH who were referred to University of Naples Federico II (Naples, Italy) from January 1, 2015 to December 1, 2019 were included in a dedicated database. Maternal and perinatal outcomes were evaluated.

RESULTS

Literature review

Fifteen studies (8,11-24), including 24 pregnancies with PNH, were included in the review (Figure 1). 13 studies were in English (8,11-17,19-21,23,24), one in Hungarian (15), and one in Japanese (16).

The 24 included pregnancies resulted in 23 healthy babies (21 singletons, 2 twins), one early miscarriage and one elective termination of pregnancy (Table 1). The granulocyte clone size in percentage reported a mean of 77.6%. LDH levels at baseline were available in 18 cases, ranged from 585 UI/ml to 10,300 UI/ml with a mean value of 2271 UI/ml. Anticoagulation with low molecular weight heparin (LMWH) was prescribed in 18 cases (Table 2).

All included women received therapy with eculizumab during the pregnancy. Fourteen women were treated with eculizumab for the entire length of their gestation. Ten women received eculizumab at different times during the pregnancy. One woman received Eculizumab up to the 4th week of gestation, and three women received eculizumab up to the 5th week of gestation. One woman received eculizumab from the 10th week of gestation, one from the 11th, one from the 18th, two from the 27th, one from the 30th. Seven patients experienced breakthrough maternal hemolysis, and nine women received at least one RBC transfusion during pregnancy. Two patients experienced a thrombotic event (Table 2).

Gestational age at delivery was reported in 18 cases, with 28 weeks being the lowest and 40 weeks being the highest gestational age at delivery with a mean value of 36 weeks. Preterm birth at less than 37 weeks occurred in fifteen women (15/18, 83%). Mode of delivery was reported in 21 pregnancy. Twelve women underwent a Cesarean section (12/21-57%) for cardiotocographic indication or failure of labour and seven women delivered vaginally (7-21-33%) (Table 3). Mean birth weight was 2,481 grams ranging from 853 to 4,000 grams. No congenital abnormalities were reported (Table 4).

Case-series

During the study period, three women affected by PNH and treated with eculizumab were referred to our Institution (Table 5, Table 6). Case 1 started eculizumab therapy at the time of PNH diagnosis in the second trimester of pregnancy. The woman was admitted for inpatient monitoring for early severe intrauterine growth restriction and delivered an 1,850-gr baby at 33 0/5 weeks of gestation. Case 2 and case 3 did not experience adverse outcome and delivered at term by planned cesarean delivery for breech presentation, and by vaginal delivery, respectively.

COMMENT

Main findings

This study aimed to evaluate maternal and perinatal outcomes in pregnant women affected by PNH and treated with eculizumab. We presented three cases of PNH in which pregnancies were successfully managed with eculizumab therapy. In all cases PNH had been diagnosed before the women became pregnant. Two cases were already on eculizumab, while in one case eculizumab therapy was initiated in the second trimester of pregnancy. In our cases, there were no thrombotic complications, maternal or neonatal deaths, or fetal structural abnormalities.

The literature review showed only 15 studies (8,17-29), including 24 pregnancies. Pooled data showed a high rate of cesarean delivery (57.1%), admission to neonatal intensive care unit (NICU) (8.7%), and preterm birth (83%). Despite the therapy, 7 women experienced hemolysis, 9 women received RBC transfusions, and 2 women experienced a thrombotic event during the pregnancy.

All women were treated with eculizumab during pregnancy. 42.9% (9/21) of the women were exposed to the drug in the first trimester, and the 95.2% (20/21) in the third trimester of pregnancy. The review reported no drug related side effects. However, one woman experienced an early pregnancy loss at 6 weeks of gestation.[23] As shown in Table 2, 9 women had a granulocyte clone size ≥ 90%, among these women only 2 women experienced breakthrough hemolysis.

Conclusions

In summary, PNH in pregnant women may be associated with an increased risk of obstetric complications, such us cesarean delivery or preterm birth. Eculizumab appears to be safe and effective for managing PNH during pregnancy.

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TABLES

Table 1. Characteristics of the studies included in the review

	Study location	**N of included women with PNH**	**Study language**
Danilov 2009[13]	Boston, MA USA	1 singleton pregnancy	English
Marasca 2010[12]	Modena, Italy	1 singleton pregnancy	English
Kelly 2010[8]	Leeds, UK	6 singleton pregnancies and one twin pregnancy	English
Ando 2014[24]	Tokyo, Japam	1 singleton pregnancy	Japanese
Gessoni 2015[21]	Chioggia, Italy	1 singleton pregnancy	English
Patriquin 2015[11]	Hamilton, Canada	1 singleton pregnancy	English
Vekemans 2015[20]	Brussels, Belgium	1 singleton pregnancy	English
Sharma 2015[14]	Lake Success, NY USA	1 singleton pregnancy	English
Miyasaka 2016[22]	Tokyo, Japan	3 1 singleton pregnancies	English
Horànyi 2016[18]	Budapest, Hungary	1 singleton pregnancy	Hungarian
Patel 2017[19]	Gainesville, FL USA	1 singleton pregnancy	English
Bastos 2018[16]	Vitoria, Brazil	1 singleton pregnancy	English
Li 2018[15]	Saitama, Japan	2 singleton pregnancies	English
Lauritsch-Hernandez 2018[17]	Zurich, Switzerland	1 singleton pregnancy	English
Rodríguez-Ferreras 2019[23]	Oviedo, Spain	1 singleton pregnancy	English
TOTAL	-	24 pregnancies, 25 fetuses	-

PNH, Paroxysmal Nocturnal Hemoglobinuria

Table 2. Characteristics and outcome of the women included in the review

	PNH Clone size (%)	LDH at baseline (U/L)	Anti-coagulation Therapy	Eculizumab use in Pregnancy	Eculizumab augmentation needed	Maternal Hemolysis	Maternal Thrombosis	Maternal RBC transfusion	Other maternal complications
Danilov 2009[13]	30	1500	LMWH	Starting from 30 weeks and in post-partum	Yes 600-900 mg	NR	NR	Yes, 2 units	Thrombocytopenia
Marasca 2010[12]	69	NR	LMWH	Entire Pregnancy	None needed	NR	NR	NR	NR
Kelly 2010[8]	70	1,336	NR	Up to 5 weeks	ITOP	NR	NR	NR	NR
Kelly 2010[8]	93	2,376	LMWH	Up to 5 weeks	None needed	NR	NR	NR	NR
Kelly 2010[8]	96	2,014	NR	Up to 5 weeks	None needed	NR	NR	NR	Fever of unknown origin
Kelly 2010[8]	87	1,263	LMWH	Up to 4 weeks	None needed	NR	NR	NR	NR
Kelly 2010[8]	100	10,300	LMWH	Entire pregnancy	Yes, shortened infusion interval	Yes, at 26 weeks.	NR	Yes	NR
Kelly 2010[8]	97	1,616	LMWH	Starting from 27 weeks	Shortened Interval	NR	Postpartum portal vein thrombosis	NR	Postpartum hemorrhage
Kelly 2010[8]	98	2,642	LMWH	Entire Pregnancy	None needed	NR	NR	NR	NR
Ando 2014[24]	56	2,300	None	Entire pregnancy	None Needed	Yes, mild.	NR	NR	NR
Gessoni 2015[21]	78	3,380	LMWH	Entire pregnancy	Yes, shortened interval.	Yes, severe and recurrent	NR	Yes, 26 units	Postpartum pleuroperitoneal effusion, pulmonary embolism, upper limbs thrombophlebitis.
Patriquin 2015[11]	23	2,000	LMWH	Entire pregnancy	Yes, increased dose and	Yes, recurrent	NR	Yes, 25 units	NR

					shortened interval				
Vekemans 2015[20]	98	NR	LMWH	Entire pregnancy	Additional dose before delivery	NR	NR	Yes, 2 units every 2 week	NR
Sharma 2015[14]	90	NR	LMWH	Entire pregnancy	Significant increase in dose	NR	NR	Yes	NR
Miyasaka 2016[22]	96	2,200	LMWH	Entire pregnancy	None needed	Yes	NR	NR	NR
Miyasaka 2016[22]	71	2,300	LMWH	From 27 weeks	None Needed	NR	NR	Yes, 10 units	Heparin induced thrombocytopenia
Miyasaka 2016[22]	81	2,300	LMWH	From 18 weeks	None needed	NR	NR	NR	Postpartum hemorrhage
Horànyi 2016[18]	90	1,000	LMWH	From 11 week	Yes, increased dose	NR	Sinus thrombosis	NR	NR
Patel 2017[19]	50	NR	LMWH	From 10 week	None needed	NR	NR	NR	NR
Bastos 2018[16]	NR	1,111	LMWH	Entire pregnancy	Yes, increased dose	Yes, severe and recurrent	NR	Yes, 10 units	Acute kidney injury
Li 2018[15]	NR	NR	None	Entire pregnancy	None needed	NR	NR	NR	Failed induction of labor
Li 2018[15]	NR	NR	None	Entire pregnancy	Yes, preoperative	NR	NR	NR	NR
Lauritsch-Hernandez 2018[17]	80	585	LMWH	Entire pregnancy	Yes, shortened interval.	Yes	NR	Yes, 2 units	GDM, gestational HTN, thrombocytopenia
Rodríguez-Ferreras 2019[23]	80	658	None	Entire pregnancy	NR	NR	NR	NR	NR

PNH, Paroxysmal Nocturnal Hemoglobinuria; LDH, lactate dehydrogenase; RBC, red blood cells; NR, not reported; LMWH, low molecular weight heparin; ITOP, induced termination of pregnancy

Table 3. Obstetrics outcome of the women included in the review

	Gestational age delivery	**Mode of delivery**	**Preeclampsia**
Danilov 2009[13]	36	Cesarean Section	No
Marasca 2010[12]	38	Vaginal Birth	No
Kelly 2010[8]	5	Induced termination of pregnancy	No
Kelly 2010[8]	NR	NR	No
Kelly 2010[8]	NR	NR	No
Kelly 2010[8]	NR	NR	No
Kelly 2010[8]	Term	Vaginal Birth	No
Kelly 2010[8]	35	Cesarean Section	No
Kelly 2010[8]	28	Cesarean Section	Yes
Ando 2014[24]	37	Cesarean Section	No
Gessoni 2015[21]	37	Cesarean Section	No
Patriquin 2015[11]	36	Cesarean section	No
Vekemans 2015[20]	38	Vaginal Birth	No
Sharma 2015[14]	36	Cesarean Section	No
Miyasaka 2016[22]	37	Vaginal Birth	No
Miyasaka 2016[22]	28	Cesarean Section	Yes
Miyasaka 2016[22]	40	Vaginal Birth	No
Horànyi 2016[18]	39	Vaginal Birth	No
Patel 2017[19]	37	Vaginal Birth	No
Bastos 2018[16]	35	Cesarean Section	No
Li 2018[15]	40	Cesarean Section	No
Li 2018[15]	37	Cesarean Section	No
Lauritsch-Hernandez 2018[17]	37	Cesarean Section	No
Rodríguez-Ferreras 2019[23]	6	Early miscarriage	-
TOTAL	Mean 36 weeks [28 to 40]	Cesarean delivery 12/21 (57.1%) Vaginal delivery 7/21 (33.3%)	2/23 (8.7%)

NR, not reported

Table 4. Perinatal outcome of the cases included in the review

	Miscarriage	Fetal death	Neonatal death	Birth weight (gr)	Admission to NICU	Congenital abnormalities
Danilov 2009[13]	No	No	No	NR	No	No
Marasca 2010[12]	No	No	No	3430	No	No
Kelly 2010[8]	No	No	No	NR	No	No
Kelly 2010[8]	No	No	No	NR	No	No
Kelly 2010[8]	No	No	No	NR	No	No
Kelly 2010[8]	No	No	No	NR	No	No
Kelly 2010[8]	No	No	No	4000	No	No
Kelly 2010[8]	No	No	No	2400-2000	No	No
Kelly 2010[8]	No	No	No	900	Yes	No
Ando 2014[24]	No	No	No	2428	No	No
Gessoni 2015[21]	No	No	No	NR	No	No
Patriquin 2015[11]	No	No	No	NR	No	No
Vekemans 2015[20]	No	No	No	NR	No	No
Sharma 2015[14]	No	No	No	NR	No	No

Miyasaka 2016[22]	No	No	No	NR	No	No
Miyasaka 2016[22]	No	No	No	2662	No	No
Miyasaka 2016[22]	No	No	No	853	Yes	No
Horànyi 2016[18]	No	No	No	3110	No	No
Patel 2017[19]	No	No	No	NR	No	No
Bastos 2018[16]	No	No	No	2140	No	No
Li 2018[15]	No	No	No	2775	No	No
Li 2018[15]	No	No	No	NR	No	No
Lauritsch-Hernandez 2018[17]	No	No	No	2730	No	No
Rodríguez-Ferreras 2019[23]	Yes at 6 weeks	-	-	-	-	-
TOTAL	1/24 (4.2%)	0/23	0/23	Mean 2,481 grams [853 to 4,000]	2/23 (8.7%)	0/23

NICU, neonatal intensive care unit; NR, not reported

Table 5. Cases included in the case series: maternal outcomes

	Case 1	**Case 2**	**Case 3**	**TOTAL**
Diagnosis of PNH	At 16 weeks of	Before pregnancy	Before pregnancy	-
First prenatal visit	At 9 weeks	At 11 weeks	At 7 weeks	-
PNH clone size (%)	85	60	75	Mean 73
LDH at baseline (U/L)	1,650	850	540	Mean 1,013
Anti-coagulation therapy	LMWH	LMWH	LMWH	-
Eculizumab use in pregnancy	Starting from 18 weeks	Entire pregnancy	Entire pregnancy	-
Eculizumab augmentation needed	No	No	No	0/3
Maternal hemolysis	Yes	No	No	1/3 (33.3%)
Maternal thrombosis	No	No	No	0/3
Maternal RBC transfusion	No	No	No	0/3
Preeclampsia	No	No	No	0/3
Gestational age at delivery	33 0/5 weeks	38 2/7 weeks	40 6/7 weeks	-
Preterm birth	Yes	No	No	1/3 (33.3%)
Mode of delivery	Cesarean delivery	Cesarean delivery	Vaginal delivery	Cesarean delivery 2/3 (66.7%) Vaginal delivery 1/3 (33.3%)

PNH, Paroxysmal Nocturnal Hemoglobinuria; LDH, lactate dehydrogenase; RBC, red blood cells

Table 6. Cases included in the case series: perinatal outcomes

	Case 1	**Case 2**	**Case 3**	**TOTAL**
Miscarriage	No	No	No	0/3
Fetal death	No	No	No	0/3
Neonatal death	No	No	No	0/3
Birth weight (gr)	1,850	3,350	3,180	Mean 2793
Intrauterine growth restriction	Yes	No	No	1/3 (33.3%)
Admission to NICU	Yes	No	No	1/3 (33.3%)
Congenital abnormalities	No	No	No	0/3

NICU, admission to neonatal intensive care unit

FIGURES

Figure 1. Study flow chart

Figure