Paroxysmal nocturnal hemoglobinuria and pregnancy before the eculizumab era: the French experience

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ABSTRACT

Background
Pregnancy in women with paroxysmal nocturnal hemoglobinuria is rare, with few reports on maternal and fetal mortality rates.

Design and Methods
A specific questionnaire designed to solicit data on pregnancies in women with paroxysmal nocturnal hemoglobinuria was sent to all members of the French Society of Hematology in January 2008.

Results
We identified 27 pregnancies in 22 women at 10 French Society of Hematology centers between 1978 and 2008. The median age was 21.5 years at diagnosis of paroxysmal nocturnal hemoglobinuria and 27 years at pregnancy. None of these women had received eculizumab during their pregnancy. Maternal complications, consisting mostly of cytopenias requiring transfusions, occurred in 95% of cases. Two cases of severe aplastic anemia (*de novo* in one case and relapse in the other) were recorded. No thrombotic events occurred during pregnancy, whereas 4 postpartum thromboses (16%) were recorded, 2 of which were fatal (maternal mortality rate 8%). Most patients received antithrombotic prophylaxis during pregnancy and postpartum (n=16; 64%). Delivery was preterm in 29% of cases, and birth weight was less than 3 kg in 53% of cases. Fetal mortality rate was 4%.

Conclusions
Pregnancy during paroxysmal nocturnal hemoglobinuria is associated with increased maternal and fetal mortality rates (8% and 4%, respectively, in this series). Maternal mortality is related to postpartum thromboses. Prophylactic anticoagulation is recommended during pregnancy and for six weeks postpartum.

Key words: paroxysmal nocturnal hemoglobinuria, pregnancy, thrombosis.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, stem cell disorder characterized by hemolytic anemia, bone marrow failure, and venous thromboembolism. Manifestations of the disease are primarily related to complement-mediated intravascular hemolysis due to the lack of glycosylphosphatidylinositol-anchored complement regulatory proteins (GPI-AP) CD55 and CD59 on erythrocyte cells. Patients with PNH may present with a wide range of clinical manifestations such as weakness, pallor, and asthenia due to hemolysis, but also abdominal pain, dysphagia, or pulmonary hypertension.[1] Patients are at risk for thromboses, major life-threatening risks of PNH,[2] which often occur at unusual sites. A frequent association between PNH and aplastic anemia (AA) has been described, with 2 potential patterns of evolution: progressive marrow failure in PNH patients or AA in which a PNH clone is detected.[3]

Pregnancy in women with PNH is associated with an increased risk of complications for both mother and fetus, leading to high maternal and fetal mortality rates. Worsening cytopenias may complicate the management of pregnancy but the main concern is the occurrence of thrombosis, which is responsible for the high mortality rates in pregnant PNH patients. Although there is little information about PNH and pregnancy in the literature, a recent review identified 23 clinical reports published between 1965 and 2005 describing pregnancy outcomes in 43 women with PNH.[4] Maternal and fetal mortality rates were 11.6% and 7.2%, respectively. Venous thrombotic events (VTEs) were the major cause of maternal death.

Here, we retrospectively reviewed 27 cases of pregnancy in 22 French women with PNH between 1978 and 2008. We analyzed maternal and fetal complications during pregnancy, delivery, and the postpartum period.

Design and Methods

Study design

We designed a questionnaire to solicit data on pregnancies in women with PNH (*Online Supplementary Figure S1*). The questionnaire was sent to all members of the French Society of Hematology (SFH) in January 2008. Among the 10 responding centers, 22 patients who had 27 pregnancies were monitored from diagnosis to last follow up.

The study protocol was approved by the review board of the SFH and the study was carried out in accordance with the Declaration of Helsinki.

Data collection and definition

The following parameters were collected and analyzed for each patient and pregnancy.

PNH diagnosis

A diagnosis of PNH was defined as an unequivocally positive Ham test before 1996 or by flow cytometry demonstrating the presence of more than 5% GPI-AP deficient polymorphonuclear cells after this time point. Dates of diagnosis and circumstances leading to diagnosis (presence of cytopenias, hemolysis, or thrombosis) were recorded. Cytopenias were defined by 2 or 3 of the following criteria: anemia, defined as hemoglobin (Hb) levels less than 12g/dL; thrombocytopenia, defined as platelet counts less than 150×10^9/L; and neutropenia, defined as neutrophil counts less than 1.5×10^9/L. Pancytopenia was considered when the 3 hematopoietic lineages were altered. Delay between PNH diagnosis and pregnancy was also recorded, as well as specific PNH treatment during pregnancy. In cases of a PNH clone complicating a pre-existing AA, time of PNH diagnosis was considered as the time of initial identification of the GPI-AP deficient clone. None of these women had been previously treated with eculizumab.

Obstetric data

Obstetric data included the number of pregnancies, miscarriages, and deliveries, as well as the term and mode of delivery. Preterm was defined as delivery prior to 37 amenorrhea weeks (AW). Newborn status and birth weight were also recorded. Postpartum is usually regarded as the period immediately following delivery until resumption of menses and cessation of breast-feeding. Its length is variable. As we cannot retrospectively obtain this information for our patients, we considered the postpartum period to be the six months following delivery, as usually accepted by obstetricians.

Maternal and fetal complications

Maternal and fetal complications during pregnancy (early miscarriages and therapeutic abortions excluded), at delivery, and postpartum were recorded. To be consistent with previous reviews of the scientific literature, maternal complications during pregnancy and postpartum were classified as major complications when hospitalization or intensive care was required, and as minor complications when no hospitalization was necessary. The use of prophylactic or curative antithrombotic therapy during pregnancy and postpartum, and the occurrence of VTEs, were carefully recorded. Maternal and fetal outcomes were documented at the last follow-up visit.

Results

Patients' characteristics

We identified 27 pregnancies in 22 women with PNH, followed up by 10 French centers, between 1978 and 2008. Five patients experienced 2 pregnancies each. Patients' characteristics are summarized in Table 1. Patient median age was 21.5 years (range 13-41 years) at PNH diagnosis and 27 years (range 21-38 years) at pregnancy. At diagnosis, PNH was associated with cytopenias in 15 cases, hemolysis in 5 cases, and both cytopenias and hemolysis in one case. In the vast majority (20 of 27 cases; 74%), pregnancy occurred in patients with a known PNH diagnosis. Median time from PNH diagnosis to pregnancy was 70.4 months (range 1-192 months). In 4 cases (18%), PNH diagnosis was made during pregnancy: 2 cases had cytopenia, and 2 others had hemolytic anemia. We recorded 3 pregnancies for which a PNH diagnosis was made between one month and nine years after delivery, but with substantial *a posteriori* evidence of PNH disease during pregnancy. One patient with chronic anemia associated with hemolysis had 2 pregnancies (cases n.10.1 and n.10.2): diagnosis of PNH was accurately made six years after the second pregnancy, but chronic regenerative anemia was reminiscent of undiagnosed PNH during pregnancy. In the other case (n.4.1), PNH diagnosis was made one month postpartum after the first pregnancy in a patient with cerebral sinus VTE associated with hemolysis. The patient had a second pregnancy five years later.

Maternal complications during pregnancy and postpartum (excluding thrombotic events)

During pregnancy and delivery

Among the 27 pregnancies, 2 resulted in abortions, and 23 of the remaining 25 pregnancies were evaluable for maternal complications (Table 2). Patient n.19 was receiving PNH treatment (eculizumab) when a gemellary pregnancy was discovered. Because of severe AA and fetal abnormalities, she underwent a therapeutic abortion at 14 AW and was scheduled for allogenic stem cell transplantation. Patient n.17 had previously experienced 2 normal pregnancies, and PNH diagnosis was made during the third pregnancy, which also resulted in a therapeutic abortion at six AW. Eculizumab therapy was initiated after the abortion had been performed. In these 2 cases, therapeutic abortion was decided in agreement with the parents after medical information about the risks associated with pregnancy in the context of PNH was provided. These 2 cases of early-term abortion were thus not assessable for complication analysis during pregnancy.

Table 1. Patients' characteristics.

Case number	Maternal age at PNH diagnosis (years)	Hematologic status at PNH diagnosis	PNH diagnosis/pregnancy (duration)	Year of pregnancy	Maternal age at pregnancy (years)	Obstetrical history	Pregnancy outcome
1	30	Cytopenias	During pregnancy	2005	27	-	Healthy newborn
2	13	Cytopenias	Before (13 y)	1991	26	1 miscarriage	Healthy newborn
3	23	Cytopenias	Before (4.5 y)	1992	27	-	Healthy newborn
4.1	22	Hemolysis*	After pregnancy (1 mo PP)	1989	21	-	Healthy newborn
4.2	-	-	Before (5 y)	1995	27	1 previous PNH pregnancy	Healthy newborn
5	14	Cytopenias	Before (7 y)	2005	21	-	Healthy newborn
6	22	Hemolysis	Before (16 y)	2002	38	1 VTOG, 1 miscarriage	Healthy newborn
7	20	Cytopenias	Before (8 mo)	2005	21	-	Healthy newborn
8	21	Cytopenias	Before (11 y)	2007	32	-	Healthy newborn
9.1	28	Cytopenias	Before (10 mo) (13 y after AA)	2001	29	-	Healthy newborn
9.2	-	-	Before (4 y) (16.5 y after AA)	2004	32	1 previous PNH pregnancy	Healthy newborn
10.1	41	Cytopenias	After pregnancy (9 y)	1998	32	-	Healthy newborn
10.2	-	-	After pregnancy (6 y)	2001	35	1 previous PNH pregnancy	Healthy newborn
11	20	Cytopenias	Before (2 mo)	2004	31	-	Healthy newborn
12	21	Cytopenias	Before (3 y)	2007	24	-	Healthy newborn
13	31	Hemolysis	During pregnancy	1978	30	1 previous pregnancy (before PNH diagnosis)	Healthy newborn
14	20	Cytopenias	Before (4 y)	1998	24	-	Healthy newborn
15.1	23	Cytopenias	During pregnancy	1992	22	1 previous pregnancy (before PNH diagnosis)	Healthy newborn
15.2	-	-	Before (2 y)	1996	26	2 previous pregnancies (before and after PNH diagnosis)	Healthy newborn
16	25	Cytopenias	Before (3 y)	2006	28	-	Healthy newborn
17	37	Hemolysis	During pregnancy	2007	37	2 previous pregnancies (before PNH diagnosis)	Therapeutic abortion†
18	27	Hemolysis	Before (1 mo)	2003	27	1 previous pregnancy (before PNH diagnosis)	Healthy newborn
19	21	Cytopenias and hemolysis	Before (6.5 y)	2008	27	1 miscarriage	Therapeutic abortion
20	18	Cytopenias	Before (8 y)	1996	26	-	Healthy newborn
21.1	16	Cytopenias	Before (11 y)	1998	27	-	Fetal death
21.2	-	-	Before (12.5 y)	2000	28	1 previous PNH pregnancy	Newborn with acute respiratory distress
22	NA	NA	Before (NA)	NA	NA	-	Healthy newborn

*AA: aplastic anemia; PP: postpartum; PNH: paroxysmal nocturnal hemoglobinuria; NA: not available; y: years; mo: months; VTOG: voluntary termination of gestation. *In this case, PNH was diagnosed one month PP of the woman's first pregnancy, following a cerebral venous thrombosis. †The indication of abortion in patient #17 was PNH-related risk and because of fetal abnormalities and aplastic anemia complication in patient #19.*

Table 2. Maternal complications during pregnancy, at delivery, and during postpartum.

Case number	Hematologic status at pregnancy	VTE prophylaxis during pregnancy (type, start)	Maternal complications during pregnancy	Maternal complications at delivery	VTE prophylaxis during PP (type, duration)	Maternal complications during the PP period	Maternal outcome
1	Normal CsA initiation during pregnancy	-	Severe AA, PLT	-	-	-	Alive, persistent asymptomatic hemolysis
2	Normal	-	Thrombocytopenia, arterial hypertension PLT	HELLP, PLT	-	-	Alive, healthy
3	Normal	-	-	-	LMWH, NA	-	Alive, healthy
4.1	PNH diagnosis after pregnancy	-	Thrombocytopenia	-	-	Cerebral sinus VTE (1 mo PP)	-
4.2	NA	Curative LMWH, 1st trim	Anemia, RBC	-	LMWH, until death	Budd-Chiari syndrome (first days PP)	Dead (1 mo PP)
5	Normal, CsA	LMWH, 1st trim	Anemia, thrombocytopenia, RBC, PLT	-	LMWH, 4 weeks PP	-	Alive, eculizumab therapy
6	Anemia	Danaparoid, 3rd trim	Anemia, RBC	Anemia, RBC	Danaparoid, 4 weeks PP	-	Alive, healthy
7	Anemia, thrombocytopenia, CsA	Danaparoid, 3rd trim	Anemia, thrombocytopenia RBC, PLT	-	Danaparoid, 6 weeks PP	-	Alive, healthy, CsA therapy
8	Normal	-	Neutropenia	-	LMWH, 3 mo PP	Nose-ear-throat infections	Alive, healthy
9.1	Anemia, CsA	Aspirin 1st, danaparoid 3rd trim	Anemia, thrombocytopenia, PLT	-	Danaparoid, 6 weeks PP	Febrile neutropenia	-
9.2	Anemia, thrombocytopenia, CsA	Aspirin 1st, danaparoid 3rd trim	Anemia, thrombocytopenia, PLT	-	Danaparoid, 6 weeks PP	Cerebral infarction (9 mo after delivery)	Alive, eculizumab therapy
10.1	Normal	-	Anemia, thrombocytopenia	-	-	-	-
10.2	Normal	-	Anemia	-	-	Thrombocytopenia	Alive, healthy
11	Normal	LMWH, 3rd trim	Anemia, thrombocytopenia	-	LMWH, 8 weeks PP	-	Alive, healthy
12	Normal	LMWH, 2nd trim	Thrombocytopenia	-	LMWH, 3 mo PP	Hepatic and splenic VTE (5 mo PP)	Alive, eculizumab and anticoagulant therapy
13	NA	-	NA	-	-	-	Alive, healthy
14	Isolated thrombocytopenia	Danaparoid, 3rd trim	Thrombocytopenia	Hemorrhagic delivery	Danaparoid, 2 mo PP	-	Alive, eculizumab therapy
15.1	NA	LMWH, 3rd trim	Anemia, thrombocytopenia, RBC, PLT arterial hypertension, diabetes	-	LMWH, 4 weeks PP	-	-
15.2	NA	LMWH, 3rd trim	Anemia, thrombocytopenia, RBC, PLT arterial hypertension, diabetes	-	LMWH, na	-	Alive, eculizumab therapy
16	Normal	-	Severe AA (relapse at 6 mo), RBC, PLT, arterial hypertension	-	-	Thrombocytopenia, PLT Hemorrhage (5 days PP) Mesenteric VTE (7 mo after delivery)	Alive, eculizumab followed by allo SCT
18	Anemia	Danaparoid, 1st trim	Anemia	-	Danaparoid, 7 weeks PP	Uterine hematoma, RBC	Alive, eculizumab
20	Anemia, thrombocytopenia, CsA	LMWH, 3rd trim	Anemia, thrombocytopenia, RBC	-	LMWH, 4 weeks	-	Alive, healthy
21.1	Anemia	Aspirin 2rd trim	Anemia	-	-	-	
21.2	Anemia, CsA initiation at pregnancy	Aspirin, 1st trim	Pancytopenia, arterial hypertension, RBC	-	-	-	Alive, allo SCT, healthy
22	NA	LMWH, NA	NA	-	LMWH, until death	Cerebral VTE (1 mo PP)	Dead (1 mo PP)

AA: aplastic anemia; LMWH: low molecular weight heparin; trim: trimester; mo: months; HELLP: hemolysis elevated liver enzymes and low platelet count; Plt: platelet; RBC: red blood cells; NA: not available; VTE: venous thrombotic event; allo SCT: allogenic stem cell transplantation; PP: postpartum; PLT: platelet transfusion; RBC: red blood cell transfusion. Shaded boxes: patients with worsening cytopenias during pregnancy.

Table 3. Fetal outcomes.

Case number	Fetal complications during pregnancy	Term of delivery	Delivery method	Newborn status	Birth weight
1	-	NA	NA	Healthy	NA
2	-	Preterm (34 AW + 6d)	Induced, caesarian	Healthy	2,210 g
3	-	Term	Vaginal	Healthy	NA
4.1	-	Post term	Induced, caesarian	Healthy	NA
4.2	-	Term	Induced, caesarian	Healthy	3,100 g
5	-	Preterm (36 AW)	Caesarian	Healthy	2,500 g
6	-	Term	Induced, caesarian	Healthy	3,080 g
7	-	Preterm (35 AW + 2 d)	Induced, vaginal	Healthy	2,330 g
8	-	Term	NA	Healthy	NA
9.1	-	Term	Induced, vaginal	Healthy	3,490 g
9.2	-	Term	Induced, vaginal	Healthy	2,940 g
10.1	-	Term	Vaginal	Healthy	NA
10.2	-	Term	Vaginal	Healthy	NA
11	-	Preterm (34 AW)	Induced, caesarian	Healthy	2,890 g
12	-	Term	Induced, vaginal	Healthy	2,600 g
13	-	Term	Vaginal	Healthy	3,690 g
14	-	Term	Vaginal	Healthy	3,630 g
15.1	-	Preterm (35 AW)	Induced, caesarian	Healthy	2,840 g
15.2	-	Term	Induced, caesarian	Healthy	3,400 g
16	-	Term	Induced, vaginal	Healthy	NA
18	Acute fetal distress	Term	Induced, vaginal	Healthy	3,045 g
20	-	Term	Caesarian	Healthy	NA
21.1	Severe intrauterine growth restriction	Preterm (24 AW)	Vaginal	Dead	400 g
21.2	Severe intrauterine growth restriction	Preterm (27 AW + 6 d)	Induced, caesarian	Alive, acute respiratory failure	750 g
22	NA	Term	NA	Healthy	NA

AW: amenorrhea week; d:days; g: grams; NA: not available.

Minor maternal complications occurred in all but one of the 23 evaluable pregnancies (95%), mainly consisting of cytopenias. Anemia (Hb < 12 g/dL) was documented in 17 of 23 cases (74%), 9 of whom required red blood cell transfusions. Thrombocytopenia (platelet counts < 150×10^9/L) occurred in 16 of 20 patients (80%), 9 of whom received platelet transfusion. Isolated neutropenia was observed in one patient (n.8) at 22 AW. In 7 cases patients received cyclosporine treatment for cytopenias during pregnancy. Cyclosporine was initiated during pregnancy in 2 of those 7 cases, whereas the other 5 patients were already being treated at the time of pregnancy. Arterial hypertension was noted in 5 pregnancies, and diabetes in 2 pregnancies.

Major maternal complications were recorded in 2 of 25 pregnancies (8%). In both cases, maternal complications were related to the onset of severe AA during pregnancy. In case n.1, AA was diagnosed at five months of gestation resulting in a diagnosis of PNH, whereas in case n.16, the patient presented with a relapse of a previously treated AA at six months of gestation.

At delivery, maternal complications were recorded in 3 of 25 evaluable cases (12%): hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome that required platelet transfusion (n=1); anemia that required red blood cell transfusion (n=1); and hemorrhagic delivery of mild intensity (n=1).

Postpartum

During postpartum, minor complications were documented in 3 of 25 evaluable cases (12%): thrombocytopenia (n=2) and ear-nose-throat infections (n=1). Major maternal complications other than thrombosis included one case of hemorrhagic delivery requiring arterial embolization at five days postpartum, one uterine hematoma, and one episode of febrile neutropenia (absolute neutrophil count < 500 cells/mm^3). Postpartum appears to be a more crucial period regarding thrombotic risk, with 4 cases of VTE, which are detailed below. Overall, major complications during postpartum occurred at a rate of 28%.

Aspirin, anticoagulation, and thrombosis

During pregnancy

Pregnancy occurred in 3 patients who had a previous history of VTE during PNH. Patient n.4, who developed cerebral sinus VTE at one month postpartum of her first pregnancy, received low molecular weight heparin (LMWH) at therapeutic dosage during her second pregnancy five years later. Patient n.21, who previously experienced superficial VTE, received aspirin prophylaxis during her 2 pregnancies, whereas aspirin was not continued postpartum. In the remaining 22 cases, pregnancy occurred in patients with no thrombotic history. In 13 of

these 22 pregnancies (59%), the patient was administered prophylactic anticoagulation therapy, consisting of LMWH in 7 of 13 cases (54%) and danaparoid in 6 of 13 cases (46%), preceded by aspirin in 2 cases.

Overall, antithrombotic therapy was delivered in 64% of cases. Treatment was initiated during the first trimester in 6 cases (40%), during the second trimester in 2 additional cases (13%), and during the third trimester in the 7 remaining cases (47%).

No maternal thrombotic events were recorded during pregnancy, even in patients who did not receive prophylactic anticoagulation.

Postpartum

Antithrombotic therapy was maintained during the postpartum period in 14 of 16 cases (Table 2). In 2 cases (n.3 and n.8), the patients did not receive anticoagulation therapy during pregnancy, but prophylaxis was initiated postpartum and continued for three months in one case (data were not available for the other case). Patient n.21 received aspirin only during her 2 pregnancies but not during the postpartum period.

Severe thrombotic events occurred in 4 cases during the postpartum period. During her first pregnancy, patient n.4, who had not received prophylactic anticoagulation therapy, experienced cerebral sinus VTE at one month postpartum. She fully recovered after receiving curative anticoagulant therapy. During her second pregnancy five years later, thromboprophylaxis with LMWH was initiated during the first trimester and continued after delivery. However, the patient developed Budd-Chiari syndrome leading to her death at one month postpartum while she was still receiving anticoagulation therapy. During her pregnancy, patient n.12 received thromboprophylaxis with LMWH that was continued until the third month postpartum. At five months postpartum, she developed hepatic and splenic VTE, and recovered after receiving anticoagulation therapy. Eculizumab treatment was initiated. Patient n.22 developed a fatal cerebral sinus VTE at one month postpartum while she was receiving LMWH.

We recorded 2 additional cases of severe VTE (mesenteric VTE in patient n.16, and cerebral infarction in patient n.9.2) occurring after the classical six months postpartum (seven and nine months after delivery, respectively).

The maternal mortality rate was 8% for the entire series, all deaths being related to postpartum thrombotic complications.

Fetal outcome

Among the 25 evaluable pregnancies, abnormal fetal development was observed in 3 cases. One case (patient n.18) of acute fetal distress at 37 AW led to therapeutically induced vaginal delivery of a healthy newborn (Table 3). One woman with PNH (patient n.21) experienced two pregnancies which were both associated with severe intrauterine growth restriction observed at 24 and 27 AW, respectively: fetal death due to severe placental ischemic lesions in case n.21.1 and birth of a very premature baby (27 AW + 6 days) presenting with acute respiratory distress in case n.21.2. This child's development was otherwise favorable. Fetal mortality for the entire series was 4%.

In 29% of documented cases, pregnancy ended in preterm delivery (ranging from 27 AW + 6 days to 36 AW). Delivery was therapeutically induced in 64% of cases, and a caesarian section was performed in 45% of cases.

Median birth weight (documented in 16 cases) was 2.9 kg (range 0.4-3.6kg). Live newborns weighed under 3 kg in 53% of cases. No child died following delivery.

Discussion

This report describes a series of 27 pregnancies in 22 women with PNH at 10 French centers between 1978 and 2008. Pregnancy in women with PNH was associated with an increased risk of maternal and fetal complications, as well as higher maternal (8%) and fetal (4%) mortality rates. Maternal mortality was related to postpartum thromboses, whereas no thrombotic events occurred during pregnancy. The majority of patients developed maternal complications, primarily in the form of cytopenias that required transfusions. Two cases of severe aplastic anemia were also recorded. Nearly two-thirds of PNH patients received antithrombotic prophylaxis during pregnancy and postpartum. Preterm delivery occurred in approximately one-third of cases, and although more than half of the babies were of low birth weight, outcomes were generally favorable.

The maternal and fetal mortality rates reported in this series compare favorably to historic rates reported in the literature. To date, fewer than 30 reports[4-22] have been published, comprising case reports or small series of no more than 7 patients. Fieni et al.[4] reviewed obstetric literature about pregnancy and PNH published between 1965 and 2005. They assessed 43 cumulative cases which revealed maternal and fetal mortality rates of 11.6% and 7.2%, respectively. In our series, we observed a lower rate of maternal complications. This difference may be explained by a reduced bias in our series, which reports every pregnancy regardless of outcome, whereas isolated reports in the literature generally focus on dramatic cases. This difference may also be explained by the fact that, in our series, 64% of patients had received antithrombotic prophylaxis during pregnancy or after delivery. In the literature review of Fieni et al., only 16% of patients had received antithrombotic therapy. However, in our series, only 6 out of the 22 patients had hemolysis at the time of PNH diagnosis. Therefore, thrombotic events might be higher in a group of PNH patients the majority of whom have predominant hemolytic features.

The occurrence of thrombotic events is the major cause of PNH-related mortality.[23-24] Pregnancy occurring in women with PNH is particularly high-risk because pregnancy itself is considered a prothrombotic state.[25-26] Among 43 pregnancies reported in the medical literature between 1965 and 2006, 8 were associated with thrombosis. Two incidents of thrombosis occurred during pregnancy[5,19] and the remaining 6 occurred during the postpartum period,[4,7,19,21-22,27] leading to maternal death in 3 cases.[19,21,27] In our series, we recorded no thrombotic events during pregnancy, possibly because most (64%) of our patients received antithrombotic prophylaxis.

In our series, 95% of patients displayed at least minor complications during pregnancy, mainly cytopenias, which required transfusions in more than half of all cases. Major maternal complications during pregnancy were limited to the onset of AA in 2 cases. In 7 cases, patients received cyclosporine therapy either for a previous instance of AA or for active disease during pregnancy. The effect of pregnancy on AA outcome remains unclear, but

it has been suggested that pregnancy can trigger AA in some cases with spontaneous remission after delivery.[21] In one case (patient n.1), we observed spontaneous improvement of hematologic parameters after delivery with only persistent asymptomatic hemolysis. In the other case (patient n.16), the severity of AA necessitated cord blood transplantation. Because of the potential for complications, pregnancy in PNH patients must be carefully and continuously monitored by both obstetricians and hematologists.[23]

The issue of prophylactic anticoagulation in PNH patients remains a matter of debate. In pregnancy, however, prophylactic anticoagulation is recommended as soon as pregnancy is confirmed.[23-24] In our series, the type of antithrombotic therapy used varied, consisting of either LMWH or danaparoid; 2 patients also received aspirin. During pregnancy, coumadin is contraindicated because of its teratogenic potential during the first trimester and hemorrhagic risk later in gestation. Low molecular weight heparin appears to be the most appropriate drug during pregnancy and can be briefly discontinued as the delivery date nears. As there are no studies of antiplatelet agents such as aspirin and clopidogrel in PNH, these drugs are not recommended. In this series, there were no thrombotic events observed during pregnancy, even in patients who did not receive prophylactic anticoagulation, raising doubts as to the benefits of anticoagulation treatments during this time period.

The situation is dramatically different during the postpartum period. Four cases of severe thromboses, 2 of which were fatal, were reported during the postpartum period, resulting in a maternal mortality rate of 8%. Postpartum anticoagulation is thus strongly recommended. The main concern is the appropriate date after delivery to terminate this treatment. Continuation of anticoagulation treatment is usually recommended until six weeks postpartum.[23] We observed one mesenteric thrombosis at five months postpartum and 2 later VTE complications at seven and nine months after delivery, which questions the wisdom of continuing antithrombotic therapy. However, these 2 latter cases of late thrombosis may be associated with PNH-related thrombotic risk rather than pregnancy itself. Thromboses occurred in patients who received anticoagulation as well as in patients who did not, confirming that prophylactic antithrombotic therapy is not always sufficient to prevent thromboembolism in PNH patients.[24]

In comparison with previous reports,[4,28] we recorded a high incidence of premature delivery and caesarian section. A planned and therapeutically induced delivery was preferred in the vast majority of cases to improve management of the patient during this particularly risky period. Another possible explanation for the high rate of caesarian deliveries is the PNH-related smooth muscle dystonia that may compromise the progress of labor in PNH patients. Fetal mortality was 4%, which is lower than the 7.2% reported by Fieni *et al.*[4] In our study, newborn birth weight was generally low, though overall outcome was favorable for these children.

Limitations of our study include its retrospective design and possible areas of study which were not taken into consideration. Nevertheless, this is the largest series assessing the outcome of PNH pregnancies over one entire national network, reported on the basis of coexisting PNH and pregnancy, regardless of the outcome for both mother and fetus.

In conclusion, we describe the largest series of pregnancies occurring in PNH women in France over a 30-year time period. We confirm that pregnancy in these patients is associated with a higher risk for both maternal and fetal complications, with maternal and fetal mortality rates of 8% and 4%, respectively. Thromboses mainly occurred during the postpartum period, being by far the major cause of maternal death. Prophylactic anticoagulation should be initiated by the 6th month of gestation, and continued during the postpartum period. Currently, there is no consensus regarding the optimal duration of prophylactic anticoagulation treatment following delivery, but late complications may occur. Moreover, we also confirmed that anticoagulation treatment is not sufficient to prevent thrombotic complications. Several recent reports suggest that eculizumab, a humanized monoclonal antibody that binds to the terminal complement protein C5 has the potential to prevent PNH-associated complications in pregnant women receiving anticoagulation therapy and is well tolerated.[29-31] However, further, larger studies are required in this setting to confirm these findings.

Authorship and Disclosures

References

1. Brodsky RA. Narrative review: paroxysmal nocturnal hemoglobinuria: the physiology of complement-related hemolytic anemia. Ann Intern Med. 2008;148(8):587-95.
2. Ziakas PD, Poulou LS, Pomoni A. Thrombosis in paroxysmal nocturnal hemoglobinuria at a glance: a clinical review. Curr Vasc Pharmacol. 2008;6(4):347-53.
3. Noguera ME, Leymarie V, Bittencourt E, Gluckman E, Sigaux F, Socie G. Aplastic anemia and paroxysmal nocturnal hemoglobinuria: a follow-up study of the glyco- sylphosphatidylinositol-anchored proteins defect. Hematol J. 2000;1(4):250-3.
4. Fieni S, Bonfanti L, Gramellini D, Benassi L, Delsignore R. Clinical management of paroxysmal nocturnal hemoglobinuria in pregnancy: a case report and updated review. Obstet Gynecol Surv. 2006;61(9):593-601.
5. Bais J, Pel M, von dem Borne A, van der Lelie H. Pregnancy and paroxysmal nocturnal hemoglobinuria. Eur J Obstet Gynecol Reprod Biol. 1994;53(3):211-4.
6. Beresford CH, Gudex DJ, Symmans WA. Paroxysmal nocturnal haemoglobinuria and pregnancy. Lancet. 1986;2(8520):1396-7.
7. Bjorge L, Ernst P, Haram KO. Paroxysmal nocturnal hemoglobinuria in pregnancy. Acta Obstet Gynecol Scand. 2003;82(12):1067-71.
8. Buisson MP, Quereux C, Palot M, Pignon B, Wahl P. [Nocturnal paroxysmal hemoglobinuria disclosed during pregnancy. Apropos of a case]. J Gynecol Obstet Biol Reprod (Paris). 1991;20(1):83-6.
9. Forman K, Sokol RJ, Hewitt S, Stamps BK. Paroxysmal nocturnal haemoglobinuria. A clinicopathological study of 26 cases. Acta Haematol. 1984;71(4):217-26.
10. Frakes JT, Burmeister RE, Giliberti JJ. Pregnancy in a patient with paroxysmal nocturnal hemoglobinuria. Obstet Gynecol.

1976;47(1):22S-4S.

11. Greene MF, Frigoletto FD Jr, Claster S, Rosenthal D. Pregnancy and paroxysmal nocturnal hemoglobinuria: report of a case and review of the literature. Obstet Gynecol Surv. 1983;38(10):591-6.

12. Heilmann L, Siekmann U, Ludwig H. [Paroxysmal nocturnal haemoglobinuria (PNH) and pregnancy (author's transl)]. Geburtshilfe Frauenheilkd. 1980;40(8):682-7.

13. Hurd WW, Miodovnik M, Stys SJ. Pregnancy associated with paroxysmal nocturnal hemoglobinuria. Obstet Gynecol. 1982;60(6):742-6.

14. Imai A, Takagi H, Kawabata I, Sumi H, Shiraki S, Tamaya T. Successful pregnancy in a patient with paroxysmal nocturnal hemoglobinuria: case report. Arch Gynecol Obstet. 1989;246(2):121-4.

15. Jacobs P, Wood L. Paroxysmal nocturnal haemoglobinuria and pregnancy. Lancet. 1986;2(8515):1099.

16. Lange JG, Griever GE, Brand A, van Roosmalen J. [Paroxysmal nocturnal hemoglobinuria in pregnancy]. Ned Tijdschr Geneeskd. 1998;142(42):2308-11.

17. Mori H, Okada S, Takizawa Y, Hagiwara S, Niikura H, Terada H. [Pregnancy in paroxysmal nocturnal hemoglobinuria--report of two cases]. Rinsho Ketsueki. 1987;28(9): 1645-50.

18. Solal-Celigny P, Tertian G, Fernandez H, Pons JC, Lambert T, Najean Y, et al. Pregnancy and paroxysmal nocturnal hemoglobinuria. Arch Intern Med. 1988; 148(3):593-5.

19. Spencer JA. Paroxysmal nocturnal haemoglobinuria in pregnancy: case report. Br J Obstet Gynaecol. 1980;87(3):246-8.

20. Svigos JM, Norman J. Paroxysmal nocturnal haemoglobinuria and pregnancy. Aust N Z J Obstet Gynaecol. 1994;34(1):104-6.

21. Tichelli A, Socie G, Marsh J, Barge R, Frickhofen N, McCann S, et al. Outcome of pregnancy and disease course among women with aplastic anemia treated with immunosuppression. Ann Intern Med. 2002;137(3):164-72.

22. Wozniak AJ, Kitchens CS. Prospective hemostatic studies in a patient having paroxysmal nocturnal hemoglobinuria, pregnancy, and cerebral venous thrombosis. Am J Obstet Gynecol. 1982;142(5):591-3.

23. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(12):3699-709.

24. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2009;113 (26):6522-7.

25. Danilov AV, Brodsky RA, Craigo S, Smith H, Miller KB. Managing a pregnant patient with paroxysmal nocturnal hemoglobinuria in the era of eculizumab. Leuk Res. 2010;34(5):566-71.

26. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143(10):697-706.

27. Colvin BT. Thrombocytopenia. Clin Haematol. 1985;14(3):661-81.

28. Ray JG, Burows RF, Ginsberg JS, Burrows EA. Paroxysmal nocturnal hemoglobinuria and the risk of venous thrombosis: review and recommendations for management of the pregnant and nonpregnant patient. Haemostasis. 2000;30(3):103-17.

29. Danilov AV, Smith H, Craigo S, Feeney DM, Relias V, Miller KB. Paroxysmal nocturnal hemoglobinuria (PNH) and pregnancy in the era of eculizumab. Leuk Res. 2009;33(6):e4-5.

30. Kelly R, Arnold L, Richards S, Hill A, Bomken C, Hanley J, et al. The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. Br J Haematol. 2010;149(3): 446-50.

31. Marasca R, Coluccio V, Santachiara R, Leonardi G, Torelli G, Notaro R, et al. Pregnancy in PNH: another eculizumab baby. Br J Haematol. 2010;150(6):707-8.