

Paroxysmal nocturnal hemoglobinuria in pregnancy

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia in which a defect of glycosylphosphatidylinositol (GPI)-anchored proteins in the cell membrane of bone marrow stem cells leads to increased sensitivity of the red cells to complement, causing intravascular hemolysis and hemoglobinuria. Other clinical features of this disease are cytopenia and an increased frequency of thrombotic events. We report a case of a pregnant woman with PNH on high-dosage anticoagulation therapy, the follow-up during the pregnancy, the delivery and the postpartum period. The obstetric literature on women with PNH is reviewed, the maternal and fetal risks are evaluated and the management of pregnancies and deliveries in such patients are discussed. During the pregnancy our patient was hypertransfused and used anticoagulation treatment. A healthy child was delivered in week 37 by cesarean section because of premature rupture of the membranes, unsuccessful induction and intrauterine infection. Because of bleeding problems a hysterectomy also had to be performed. In the postpartum period the patient developed her second episode of a liver vein thrombosis. She recovered gradually and 18 months after the delivery her disease is now in a stable phase. The literature shows a high maternal morbidity and mortality among pregnant PNH patients. Fetal wastage and prematurity rate are also high. Pregnancy in patients with PNH represents a high-risk situation for both the mother and the child and should not be recommended. A pregnant PNH woman should be followed closely by both obstetricians and hematologists.

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder affecting 1–10 individuals per 1000 000 in any given population. PNH is characterized by paroxysmal intravascular hemolytic attacks, hemoglobinuria, anemia, thrombocytopenia, diminished hematopoiesis and thrombosis tendency, especially of the

abdominal veins (1, 2), as well as increased susceptibility to infections.

PNH is mainly a disease of adults, including women of reproductive age (3, 4). The course of PNH is chronic, although spontaneous remissions are known to occur. The median survival time is 10–15 years from diagnosis. When death is related to PNH it is almost always caused by either thrombosis or thrombocytopenia-associated hemorrhage (5). Aplastic anemia often precedes the onset of PNH. However, in occasional unfortunate patients, the disorder may progress to aplastic anemia or very rarely to acute leukemia.

Abbreviations:

PNH: paroxysmal nocturnal hemoglobinuria; GPI: glycosylphosphatidylinositol; CRP: C-reactive protein; Hb: hemoglobin; LD: lactate dehydrogenase; HIT: heparin-induced thrombocytopenia.

Despite its rarity, PNH has aroused considerable interest among researchers because of its extraordinary clinical features, distinct laboratory findings and molecular defects. Most eukaryotic cell membrane proteins have stretches of hydrophobic amino acids that constitute a transmembrane polypeptide chain that embeds the proteins into the phospholipid double layer of the membrane (1). Some proteins, about 30 human membrane proteins, however, are attached to the outer leaflet of the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. This structure comprises a core containing a phosphatidylinositol (PI) moiety, one glucosamine and three mannose molecules and one ethanolaminephosphate unit (1). The C-terminus of the protein polypeptide is linked to this last moiety by an ordinary peptide bond. The anchor is synthesized in the endoplasmic reticulum and attached to the polypeptide post-translationally by a transamidase enzyme (6,7). The physiological purpose of this type of anchoring is unknown.

Most of the different symptoms in PNH can be tracked down to partial or total deficiency of GPI-anchored proteins in cell lines derived from a single hematopoietic stem cell (1,2). This deficiency is caused by somatic mutations in the PI glycan complementation class A (PIG-A) gene of the X chromosome (Xp22.1) that codes for a glycosyltransferase, which participates in the first step of the GPI-anchor biosynthesis (8).

Despite remarkable progress in our understanding of this disorder, treatment is still mainly supportive; erythrocyte and platelet transfusions and long-term anticoagulation therapy (5,9). The only potentially curative treatment currently available is bone marrow transplantation (10).

PNH may affect women of childbearing age (3,11,12). We report here a case of a pregnant patient with PNH; follow-up during pregnancy, delivery and postpartum period. Furthermore, the obstetric literature on women with PNH is reviewed; the maternal and fetal risks are evaluated and the management of pregnancy and delivery in such patients is discussed.

Case report

The patient is a female immigrant from Turkey. She was first seen at our clinic in 1998 when she was 35 years old. Just prior to her first appointment she was diagnosed with PNH in her home country. Since then she has been followed by the Section of Hematology, Department of Internal Medicine, Haukeland Hospital, Bergen, Norway. Until the pregnancy her disease had been fluctuating, but was progressive with many severe hemolytic episodes. In recent years she has also

shown signs of bone marrow failure with leukopenia, thrombocytopenia and severe anemia with inadequate reticulocyte response [hemoglobin (Hb) concentration between 6 and 8 g/dL] to such an extent that blood transfusions have been required. Lactate dehydrogenase (LD) was in the range 4000–8000 U/L. As part of her disease she had had one deep venous thrombosis in her left leg and a thrombosis in the hepatic vein (and consequently development of Budd–Chiari syndrome). She was therefore on lifelong anticoagulation therapy. She has blood type B rhesus-positive.

The patient had earlier experienced two uncomplicated pregnancies at term in Turkey, in 1988 and 1993. Both children were delivered by forceps due to prolonged second stage of labor. She had also experienced one spontaneous abortion in the 12th gestational week in 2000. She became pregnant once more in January 2001. The predicted dates of delivery were September 25, 2001 and October 4, 2001 using Naegele's rule and ultrasound estimation, respectively. During the first trimester her anticoagulation medication was changed from warfarin to low-molecular-weight heparin in therapeutic doses (12 500 IU \times 1). She was followed regularly and frequently throughout the pregnancy both by hematologists and obstetricians. We chose to hypertransfuse her, so that she kept an Hb level of around 10 g/dL during the whole pregnancy. Her blood platelet count was around 50×10^9 /L throughout this time.

She was hospitalized for some days at 15 weeks' gestation week due to vaginal bleeding. No specific bleeding focus was localized and the bleeding ceased spontaneously. Thereafter the pregnancy processed with very few complications until 34 weeks' gestation, when she was hospitalized again. She had experienced slight vaginal bleeding the preceding weeks, felt tired, and was suffering from pain in the upper right quadrant of the abdomen. Her blood pressure was 140/90 mmHg, but no proteinuria was detected. s-aspartate amino transferase (s-ASAT), s-alanine amino transferase (s-ALAT), s-gamma-glutamyl transferase (s- γ GT) and s-bilirubin were all in the normal range. The serum concentration of albumin was low, at 18 g/L. The fetus was in cephalic presentation. The placenta was located on the anterior wall. The cervix was closed and the amount of amniotic fluid was judged to be normal. During the 36th week of gestation a trial of induction was performed because her clinical condition worsened, with increasing blood pressure and edema. Before this attempt the low-molecular-weight heparin was replaced with heparin and she was given platelet

transfusions as her platelet number decreased to around $30 \times 10^9/L$. The heparin medication was monitored with the use of a CephotesTM. Initially she was somewhat resistant to this treatment. In addition, she developed a heparin-induced vasculitis in her left arm. Danaparoid sodium treatment was therefore tried, and monitored with the use of anti-factor Xa (anti-FXa). Unfortunately, she was also rather resistant to this form of treatment and therefore the medication was changed back to heparin infusions. Induction was first attempted by local applications of a prostaglandin analog into the fornix posterior of the vagina, followed by oxytocin infusion. The CephotesTM was at this point in the therapeutic range. On the second attempt the membranes ruptured, but she had no effective contractions despite oxytocin stimulation. That evening she developed fever, abdominal pain and other signs of intrauterine infection. At this point the concentration of Hb was 10 g/100 mL, the platelet count $39 \times 10^9/L$, C-reactive protein (CRP) 110 mg/L, LD 2228 U/L, fibrinogen 6.5 g/L, D-dimer 11.70 mg/L and s-albumin was 31 g/L. Antibiotic treatment was initiated for a presumed intrauterine infection, and as there were no signs of progression of labor, a cesarean section was performed under general anesthesia. A healthy boy with a birthweight of 3260 g was delivered. The Apgar scores were 4 at 1 min and 8 at 5 min. Despite close surveillance she was bleeding heavily during the operation. The obstetrician had problems with hemostasis due to uterine atony and a supra-cervical hysterectomy was performed. She had at this point been bleeding almost 2 L. She was operated on again the next day because of abdominal distension and large quantities of clotted blood were removed from the abdominal cavity. At this time there was good hemostasis. During the postoperative period her CRP was high and she was treated with antibiotics for a presumed chorioamnionitis. The heparin medication was continued for 1 week, before her anticoagulation medication was changed again to warfarin and low-molecular-weight heparin. At this time she was noted to have edema and ascites. Her condition was stable until the third week after the delivery, when she developed increasing abdominal pain due to distension. Image diagnostics showed that she had developed a new thrombosis of the hepatic vein. At this time she had severe liver failure with ascites as part of a new Budd–Chiari syndrome and bone marrow failure. She was transferred to The National Hospital in Oslo for further evaluation and follow-up. There she was judged to be neither a candidate for bone-marrow transplantation nor liver transplantation. Treatment of the ascites

was intensified and the condition stabilized with subsequent improvement and after about 1 month she was sent home in relatively good condition. She is now being treated as an outpatient and doing relatively well. She still requires her regular erythrocyte transfusions, but the symptoms due to her Budd–Chiari syndrome are improving with reasonable liver function tests and minimal ascites. Her anticoagulation therapy is continued with warfarin without complications. Except for a moderate form of atopic dermatitis the child is healthy and his development has been normal.

Discussion

At the time our patient became pregnant she was already severely affected by her disease, and was followed closely at the Medical Department. She was on lifelong anticoagulation therapy with warfarin to prevent thrombosis. The controls were intensified during pregnancy by both the internist and obstetricians with focus on her hematological status (Hb, number of platelets) and anticoagulation therapy as well as the development of the fetus.

In the first trimester of pregnancy the medication was changed to low-molecular-weight heparin (13) as warfarin anticoagulation is associated with embryopathy, stillbirths, neonatal deaths, spontaneous abortions and premature delivery (14). Because she previously had developed a liver vein thrombosis under warfarin prophylaxis the dosage of heparin given was in the therapeutic range. It was decided to change from low-molecular-weight heparin to unfractionated heparin before attempting induction of labor as we considered a predictable reversibility by protamine to be important (15). At this point the patient's number of platelets were decreasing. We believed that this was due to aggravation of the PNH and not the development of heparin-induced thrombocytopenia (HIT). This was later supported by the fact that the number of platelets was stable under continuous heparin treatment.

Despite close surveillance of her anticoagulation therapy our patient developed another thrombosis of her hepatic vein. We surmise that this was triggered by the hemolytic crisis she developed secondary to the major surgical procedures and the chorioamnionitis. The process once begun tends to persist with periodic exacerbations and remissions and it is sometimes fatal (16). However, in our patient the process has gradually resolved under anticoagulation medication and intensified ascites therapy.

One of the main risks in cases of PNH is thrombocytopenic bleeding, and the platelet

number should therefore be followed closely. Ideally, maternal platelet counts should be maintained above $30 \times 10^9/L$ throughout the pregnancy and above $50 \times 10^9/L$ near term to minimize the risk of bleeding and need for platelet transfusions (17). The platelet count of our patient was $(40-50) \times 10^9/L$ until the 36th gestational week. At this time her platelet count reached the critical level of $30 \times 10^9/L$. Before the induction attempt she received 4 units of washed platelets from matched donors, thereafter the platelet count rose to $50 \times 10^9/L$.

Our patient had severe anemia (Hb between 6 and 8 g/dL), and throughout her pregnancy we chose to hypertransfuse her so that she kept an Hb level above 10 g/dL. Low hemoglobin concentration in pregnancy is associated with low birthweight (18–20). In the review by Ray et al. (21) almost half of all infants were delivered preterm and they were also growth retarded.

An induced vaginal delivery was the plan. Because she was on therapeutic-dosage anticoagulation medication she was judged by the anesthesiologist not to be a candidate for regional anesthesia (epidural). Therefore, to minimize labor stress and consequently to minimize the risk of a hematologic crisis, a regime with regular pethidine injections was selected (11). However, as she developed chorioamnionitis and there was no progress in the delivery process, a cesarean section had to be performed under general anesthesia.

The infection rate is disproportionately high in cases with PNH (22). Abnormalities of the granulocytes and monocyte (due to lack of GPI-anchored effector molecules) may predispose for this (23). Whether this predisposing factor played a part in the development of the chorioamnionitis remains a matter of speculation.

Pregnancies in women with PNH are seldom and less than 100 cases have been described; most of the descriptions and studies are casuistic (11,12,24,25) or include few patients (3,4). The paper by Ray et al. (21) is the largest reported series of PNH pregnancies and summarizes the results from 20 published clinical reports describing the outcome of the pregnancies of 33 women with PNH. Their data suggest that the complication rate is high, and that such pregnancies represent a high risk both for the mother and the child. Both anemia and thrombocytopenia were common, often necessitating red blood cell or platelet transfusions (21). Venous thromboembolisms during both the pregnancies and the postpartum periods were described, some of them fatal. The maternal mortality rate was around 20%. Almost half of all the infants were

delivered preterm. The perinatal mortality rate was almost 10%. This review seems to be representative of the published cases in general (11,12,24,25), although successful cases have also been reported (4).

In reproductive counseling we suggest that pregnancy in patients suffering from PNH should not be recommended, even though successful cases have been reported (4). However, if the woman insists on pregnancy, the pregnant woman should be followed closely by both obstetricians and hematologists throughout the pregnancy (3,21,24,25). We suggest that the patient's Hb concentration and platelet numbers should be monitored closely. The patients should be treated with low-molecular-weight heparin throughout the pregnancy with a change to unfractionated heparin before delivery. This latter medication should be continued in the first few days after the delivery, before changing back to low-molecular-weight heparin for the rest of the postpartum period. Planned delivery at a hospital with expertise in obstetric high-risk patients and hematology is mandatory.

Our report illustrates the challenges of modern medicine, and it is of particular interest because our patient was seriously affected by her illness when she became pregnant. Coordinated multidisciplinary treatment of mother and fetus by members of the internal medicine, neonatology and obstetrics services facilitated a good outcome of our case.

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