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CASE REPORT

Anesthesia and Perioperative Medicine

# Glanzmann's Thrombasthenia in the Parturient Undergoing Cesarean Delivery- A Case Report and Discussion of Clinical Consideration

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## Abstract

*Glanzmann thrombasthenia (GT) is a rare hemorrhagic disorder characterized by the absence of IIb-IIIa platelet glycoprotein (GPIIb-IIIa) on the platelet surface. Many GT patients experience recurrent bleeding and require frequent platelet transfusion. Therefore, they are at risk for alloimmunization against platelet glycoprotein or Human leucocyte antigen (HLA) epitopes resulting in platelet refractoriness and therapeutic failure. We report a unique case of GT in pregnancy at risk for severe postpartum hemorrhage due to anti-GP IIb/IIIa and anti-HLA antibodies and the use of pro-hemostatic agents to optimize outcomes. A multidisciplinary approach is essential to achieving the best possible outcomes for these patients.*

**Keywords:** *alloimmunization, glanzmann thrombasthenia, maternal fetal medicine postpartum hemorrhage, thromboelastography*

**Abbreviations:** *ADP: Adenine Di-Phospate, GP IIb-IIIa: IIb-IIIa Glycoprotein, GT: Glanzmann Thrombasthenia, HCV: Hepatitis C Virus, HLA: Human Leucocyte Antigen, HPA: Human Platelet Antigen, PRBC: Packed Red Blood Cell, rFVIIa: Recombinant Factor VIIa Concentrate, RNA: Ribonucleic Acid, TEG: Preoperative Thromboelastography, WOMAN trial: World Maternal Antifibrinolytic Trial*

## Case Report

A written informed consent was taken from the patient to publish this case report.

A 34-year-old female, gravida 4 para 3, with past medical history significant for Glanzmann's thrombasthenia (GT) and Hepatitis C presented to our institution for scheduled Cesarean delivery due to oligohydramnios at 37 weeks of gestation. The patient had received a diagnosis of GT at 3 years of age following an aspirin-induced bleeding event, after which she continued to experience frequent episodes of gingival bleeding, hematochezia, epistaxis, melena, easy bruising and menorrhagia requiring packed red blood cell (PRBC) transfusions 3-4 times per year. At the time of presentation to our labor and delivery unit, the patient had an undetectable hepatitis C (HCV) RNA viral load and treatment had accordingly been deferred to the postpartum period. The patient's surgical history included a hernia repair, ankle surgery and wisdom teeth extraction, each of which was complicated by bleeding that necessitated administration of blood products. Most notably, the ankle surgery was complicated by intraoperative hemorrhage resulting in activation of a massive transfusion protocol where the patient received 2 units of PRBCs, 9 units of platelets and 1 gram of tranexamic acid. Preoperative screening in our department revealed the presence of 57 distinct HLA antibodies and a positive result for platelet GP IIb/IIIa antibodies. The patient's preoperative blood work demonstrated a hemoglobin of 10.5 mg/dL, thrombocyte count of 109 x $10^3$/ µL, white blood count of 10 x $10^3$/µL, and a fibrinogen level of 402mg/dL. Coagulation studies as well as basic hepatic and renal panels were unremarkable. Platelet aggregometry demonstrated an absent response to Adenine di-Phosphate (ADP), collagen, epinephrine and arachidonic acid followed by normal agglutination with ristocetin. Preoperative thromboelastography (TEG) revealed a decreased alpha angle (44.5) and a reduced maximum amplitude (38.7), indicating weak clot strength, as shown in (Figure 1).

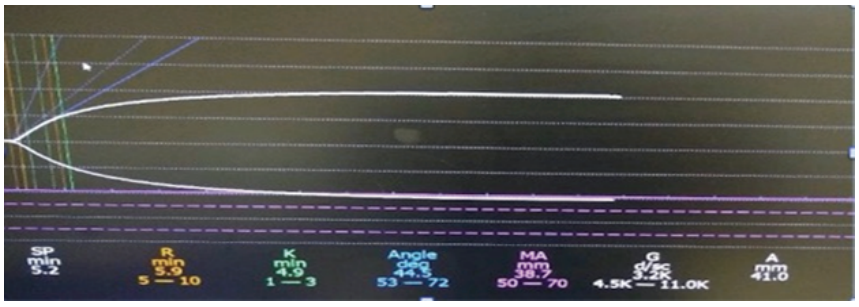


***Figure 1**. Thromboelastogram revealing a decreased alpha angle and reduced maximum amplitude.*

For our patient, Hematology department recommended to transfuse 2 units of HLA matched platelets 30 minutes prior to skin incision, 90 mcg/kg of rFVIIa and 1g of tranexamic acid immediately prior to skin incision and 90mcg/kg rFVIIa every 2 hours if adequate hemostasis cannot be readily achieved. Also, blood bank notification and readiness for additional platelet availability in the event of continued bleeding and to use of TEG intraoperatively to guide ongoing therapy in the event of severe hemorrhage. In preparation for a planned delivery by Cesarean-section, a large bore intravenous access was established, an arterial line was placed under ultrasound guidance and a rapid infuser system was readied in the operating room to facilitate adequate fluid administration and maintenance of normothermia in the event of hemorrhage. One hour prior to skin incision, the patient received 2 units of HLA matched platelets followed by 90 mcg/kg of recombinant factor VIIa concentrate (rFVIIa) and 1 gram of tranexamic acid, both given thirty minutes prior to incision. In the operating room, standard monitors were applied, the patient was induced with propofol and chemically paralyzed with succinylcholine. Her airway was secured with a 6.5mm cuffed endotracheal tube using C-Mac video laryngoscopy. No complications were encountered during intubation.

Fetal delivery was achieved through a low-transverse incision with placental delivery shortly after via manual massage. The uterus was subsequently exteriorized and cleared of clots and debris without evidence of excessive bleeding, at which time an oxytocin infusion (40 units in 1 Liter of Normal Saline) was initiated followed by administration of 0.2mg of intramuscular methylergonovine and 1000mcg of intravaginal misoprostol. The procedure concluded with no indication of ongoing hemorrhage and total blood loss was estimated at 800ml. The patient remained stable through the early postoperative period. She received 90mcg/kg of rFVIIa every 4 hours for the first 24 hours postpartum (8 doses total) and 1 gram of tranexamic acid every 8 hours until discharg. Hematological workup 24 hours postpartum revealed a hemoglobin level of 9.1 mg/dL, thrombocyte count of 134 x 103 and coagulation profile within normal limits. TEG parameters remained unchanged at 4 hours postoperatively, indicating persistence of the primary platelet receptor dysfunction as shown in (Table 1).

## Discussion and Literature Review

Glanzmann's thrombasthenia is an autosomal recessive coagulation disorder first described in 1918 by Eduard Glanzmann, a Swiss pediatrician. The cause is a deficiency or dysfunction of the platelet glycoprotein IIb/IIIa receptor, an essential mediator of appropriate platelet aggregation. GT typically presents with purpura, petechiae and/or abnormal bruising, often during childhood. Gingival bleeding and epistaxis are also common [1], and adolescent females may present with life threatening bleeding during menarche. Other prominent symptoms include prolonged surgical bleeding or excessive bleeding following tooth extractions. Many patients require frequent treatment with antifibrinolytic agents and platelet transfusion or rFVIIa due to bleeding tendencies. Alloimmunization against human platelet antigen (HPA) or human leucocyte antigen (HLA) epitopes is common and may be associated with refractory platelet dysfunction resulting in therapeutic failure of subsequent platelet transfusions. Maternal antibodies can cross the placenta, resulting in fetal thrombocytopenia and increased risk of fetal intracranial hemorrhage [2].

***Table 1***. *Pre- and post-treatment thromboelastogram with HLA matched platelets, factor VIIa concentrate and tranexamic acid.*

| Units and reference range | Preoperative | Immediate Postoperative | 4-hours Postoperative |
|---|---|---|---|
| Reaction Time (R) 5-10 min | 5.9 min | 6.8 min | 5.9 min |
| Kinectics (K) 1-3 min | 4.9 min | 5.2 min | 4.9 min |
| Alpha angle (A) 53-72 deg. | 44.5 deg. | 39.4 deg. | 44.5 deg. |
| Maximum amplitude (MA) 50-70 min | 38.7 min | 35.7 min | 38.7 min |

Pregnant patients with GT are at increased risk for major antepartum and postpartum hemorrhage. Postpartum hemorrhage is frequently severe and may occur up to 6 weeks after delivery [3]. The complex nature of these clinical cases mandates a multidisciplinary approach to patient care in order to optimize maternal and fetal outcomes. A collaboration between clinicians from maternal fetal medicine, anesthesia, hematology and neonatology is most likely to yield sound plans for appropriate therapy before, during and after delivery.

As described in this case report, invasive blood pressure monitoring, large bore peripheral venous access and rapid transfusion capabilities are vital safety measures warranted for any patient with elevated risk for perioperative or postpartum hemorrhage. Point-of-care TEG can be used in these cases and also for guided-transfusion strategy in adult trauma, surgical or critical ill patients to provide timely evaluation of coagulation status [10] and reduce blood products transfusions, when available. In this case, a baseline TEG was obtained on the day of surgery to assess coagulation status and help guide blood product administration. The results were consistent with a qualitative platelet deficiency characteristic of Glanzmann's thrombasthenia. Following a relatively uncomplicated Cesarean delivery, 4-hour postoperative TEG results were appropriately reassuring to discharge patient from the recovery unit to postpartum inpatient care. Mother and baby were ultimately discharged home in stable condition on postpartum day 3 with scheduled outpatient follow up.

Current literature suggests first line of management for severe hemorrhage is platelet transfusion. However, a significant proportion develop antibodies against the GP IIb/IIIa receptor or HLA and become refractory to platelet transfusion [6]. The patient described in this case demonstrated antibodies against both HLA and the GP IIb/IIIa receptor following years of repeated blood product transfusions. The blood bank at our institution was able to provide 2 units of HLA matched platelets from a single donor for our patient.

In addition, antifibrinolytic therapy has shown to decrease mortality due to postpartum hemorrhage as demonstrated by the WOMAN trial, however the efficacy of tranexamic acid in patients with GT has not been well established. GT patients are likely to require aggressive treatment with combination therapy comprising rFVIIa, platelet concentrates and antifibrinolytics as per expert opinion. Recombinant factor VIIa concentrate is used for patient's refractory to platelet transfusion or those who demonstrate the presence of antibodies. Current guidelines for pregnant patients with GT recommend anti-fibrinolytic agents or rFVIIa as prophylaxis for both vaginal and operative deliveries [11]. At higher concentrations, rFVIIa can directly activate factor X to factor Xa, resulting in thrombin generation – a phenomenon

often referred to as “thrombin burst”. The augmented thrombin results in increased platelet activation and deposits at the wound site, which continues further propagation of platelet activation. The augmented thrombin also influences the conversion of fibrinogen to fibrin, resulting in formation of a primary hemostatic plug formation [7]. Thromboembolism is a known complication of rFVIIa administration, with an incidence of about 4% in the general population, however the risk in patients with GT is still unknown [8]. Siddiq et al [4] published a systemic review of the literature for pregnancy outcomes in parturient with GT and found that prophylaxis with rFVIIa alone reduces maternal exposure to donor platelets, thus minimizing the risk of maternal alloimmunization. He further reported that in all cases of neonatal or fetal death, the mother possessed platelet alloantibodies.

We treated this patient with rFVIIa as a platelet sparing agent for bleeding prophylaxis in the first 24 hours following Cesarean delivery. To date, severe postpartum hemorrhage in these patients has been treated effectively with large doses of uterotonics followed by platelet transfusion and rFVIIa [9]. Infants born to GT mothers with antiplatelet antibodies are at risk for neonatal thrombocytopenia, which can lead to intracranial hemorrhage if severe [7]. Newborns should initially be monitored in a neonatal intensive care setting for thrombocytopenia and related complications. In addition, HLA matched platelets must be available for management of any postpartum hemorrhage. Two units of HLA matched platelets were ordered and held for the newborn in this case, who luckily progressed well and did not develop thrombocytopenia. Mother and baby were discharged home on postpartum day 3 with no apparent complications.

## Conclusion

Patients with GT are at high risk for severe, uncontrolled hemorrhage both during and after any surgical procedure. A multidisciplinary approach to care and interdepartmental cooperation among obstetricians, hematologists, anesthesiologists and neonatologists are essential to achieving the best possible outcomes for these patients. Aggressive prophylactic treatment for potential postpartum hemorrhage should be well-informed and carefully planned..

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