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Vaginal Delivery in a Primipara with Glanzmann Thrombasthenia

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To editor:

Glanzmann thrombasthenia (GT) is a rare autosomal recessive bleeding disorder that is characterized by a quantitative and/or qualitative defect in the platelet integrin αIIbβ3 (previously known as glycoprotein (GP)IIb/IIIa), the major platelet receptor of fibrinogen. Defective αIIbβ3 can result in the absence of platelet aggregation. Pregnancy and delivery in women with GT can present specific challenges as there is a significant risk of both maternal and fetal bleeding. Cases of pregnant women with GT have rarely been reported in China; furthermore, existing reports originating from China only refer to cases involving cesarean section. In this article, we describe the case of a Chinese primipara with GT who delivered vaginally under a multidisciplinary team approach. We reviewed the patient's pregnancy, delivery, and postpartum details and then searched the existing literature to create new insight into the clinical management of future cases during and after pregnancy when facing this challenging situation in clinical practice. The study was approved by the ethics committee of First Affiliated Hospital of Soochow University (2022-211), and informed consent was obtained from the patient.

A 29-year-old gravida 1 para 0 Chinese primigravida (spontaneous pregnancy) with GT was booked into our obstetric service in the second trimester of pregnancy. The patient was diagnosed with GT because of mucocutaneous bleeding and menorrhagia at the age of 15 years. Molecular analysis showed that she had a homozygous missense mutation of the *ITGA2B* gene (c.2929C>T), which is known to exert serious adverse effects on the structure or function of GP IIb. Flow cytometry showed that CD61 was 4.25%. She had a negative familial history for this condition, and no consanguineous marriages were known in her family. Her partner was non-consanguineous; as such, paternal genotyping was not performed. From puberty, she experienced repeated episodes of purpura, petechiae, or abnormally easy bruising; these conditions were controllable by irregular medication treatment.

During pregnancy, the patient was regularly reviewed by a multidisciplinary team. The first multidisciplinary meeting between hematology, obstetrics, and nutrition teams was arranged for 20 weeks. The team initially discussed her diagnosis, treatment, and delivery mode, and then established follow-up projects. She subsequently developed gestational diabetes but remained stable with a controlled diet. Recurrent gingival bleeding during pregnancy was managed by topical measures and tranexamic acid. She was hospitalized for hematuria during the second and third trimester and discharged after treatment with antifibrinolytics, platelet transfusion, and recombinant activated factor VII (rFVIIa).

At the gestational age of 40 weeks, she was admitted to the obstetrics department to prepare for delivery. On admission, her blood pressure was 116/69 mm Hg, heart rate was 85 beats per minute, respiratory rate was 20 breaths per minute, temperature was 36.2 °C, height was 172 cm, weight was 83 kg, fundal height was appropriate for gestational age, and clinically estimated fetal weight was 3100 g. On admission, hematological workup demonstrated a normal platelet count of 119×10^9/L, a hemoglobin level of 118 g/L, a PT of 11 seconds, and an aPTT of 24 seconds; but absent platelet aggregation responses to ADP, epinephrine, and collagen, as well as a prolonged bleeding time (>15 minutes). Thrombelastography showed hypocoagulability. In addition, she was negative for platelet-specific antibodies. The entire multidisciplinary team discussed with her the plans for delivery mode, delivery risks, and postpartum risks. Following discussion, she expressed a strong will to give birth spontaneously. The team considered that there were no contraindications for vaginal and instrumental delivery. Therefore, a clear monitoring plan was established to manage delivery, including options for various potential emergencies, blood products, hemostatic therapies, and a maternal intensive care unit.

In view of her unfavorable cervical status, Prostaglandin E2 (Dinoprostone Suppositories) was used for the induction of labor. A prophylactic transfusion of one unit of single donor platelets was performed after labor induction. On the day of induction, labor was initiated. At the beginning of labor, she experienced intermittent vaginal bleeding and hematuria. A vaginal

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examination revealed slight bleeding on the surface of her cervix. She received transfusions of blood products transfusions and other treatments. At 3-cm cervical dilation, artificial rupture of the membranes was performed yielding clear amniotic fluid. During the first stage of labor, with an estimated blood loss of 400 mL, she received three units of single donor platelets and 12 mg of rFVIIa. During the second stage of labor, however, the fetus showed severely abnormal fetal heart rate tracings. Forceps were chosen to expedite delivery to avoid fetal hypoxia and neonatal hypoxic-ischemic encephalopathy. The baby weighed 3250 g at birth and was an apparently healthy child (Apgar scores: 7–9–10). Intramuscular injections of oxytocin (20 U) and carboprost tromethamine (0.25 mg) were given to enhance contraction of the uterus and protect her from postpartum hemorrhage. At delivery and 2 hours after delivery, the total estimated blood loss, assessed by weight, was 970 mL. The administration of four units of platelets, three units of leukocyte reduced red blood cells, and 12 mg of rFVIIa led to complete hemorrhage control throughout labor. The hemoglobin monitored at this time was 98 g/L and the platelet count was 181×10^9/L. However, 3 hours after delivery, she experienced hematuria and produced temporary shapeless bloody stools. On the first day postpartum, her hemoglobin level was 69 g/L and the platelet count was 90×10^9/L. The symptoms of bleeding improved with the transfusion of red blood cells, plasma, and rFVIIa, as well as oral iron and tranexamic acid. She was discharged 9 days after delivery with a hemoglobin level of 94 g/L and a platelet count in the normal range (171×10^9/L); there was no secondary postpartum hemorrhage.

GT, an inherited disorder of platelet aggregation, is rare except in populations where consanguineous marriages are common. This disease presents significant challenges to women during pregnancy, delivery, and postpartum. A systematic review of the literature (in Chinese and English) was carried out using PubMed and Web of Science without time restrictions; this identified 12 cases of women with GT who delivered a viable baby vaginally[1–10]; the characteristics of these women are presented in SDC Table 1, http://links.lww.com/MFM/A33. All of the reported cases delivered vaginally. Our patient was induced by Prostaglandin E2 and delivered by forceps; this is unusual and has not been reported in China. Moreover, our patient was diagnosed and treated by a multidisciplinary team during pregnancy, delivery, and postpartum, thus resulting in good pregnancy outcomes. In particular, our patient received a multidisciplinary approach with regard to the choice of delivery mode. Combined with her strong desire to have a vaginal delivery, the team discussed possible situations and countermeasures, such as whether the trial of labor and/or instrumental delivery were potential contraindications for her condition. The team also discussed emergency measures for cesarean section during the vaginal trial. After discussion, the team concluded that GT itself was not a contraindication for spontaneous vaginal delivery and instrumental delivery.

Women with GT are often diagnosed at a young age with epistaxis and menorrhagia being common symptoms. These women often need to take anti-fibrinolytics and/or contraceptives, and sometimes need blood transfusions or treatment with rFVIIa to stop bleeding.[11] Pregnancy is a particular challenge in women with GT. The risks of peripartum and postpartum hemorrhage are high.[12] Thus, the primary goal of treatment is to control bleeding episodes. Platelet transfusion is the standard first-line therapy. However, antibodies to integrin αIIbβ3 and/or HLA antigens can be observed in pregnant women who have received platelet transfusions, thus resulting in refractoriness to such transfusions. Moreover, antibodies are capable of crossing the placenta and may cause intrauterine fetal bleeding and/or neonatal thrombocytopenia and hemorrhage.[13] In a previous article, Léticée *et al.*[14] reported a case of intrauterine death due to intracranial hemorrhage in a mother with GT and positive antibodies at 31 weeks of gestation. In another study, Barg *et al.*[15] reported that three out of nine newborns had severe thrombocytopenia, and all three babies were delivered by mothers with positive antibodies. Studies show that large doses of uterine contractions prevent PPH. Plasmapheresis is also used for the prevention and treatment of intrapartum and postpartum bleeding as this reduces the number of antiplatelet antibodies, thus making transfusions effective.[8] rFVIIa is increasingly being used to correct PPH, especially in women whose platelet transfusions have failed to arrest the hemorrhage; this is because of antiplatelet antibodies and/or patients who are refractory to platelet transfusions.[16] Published data suggest that rFVIIa represents a safe and effective agent for the management of bleeding and for surgical prophylaxis. Generally, the normal dose of rFVIIa is ≥80 μg/kg every ≤2.5 hours for non-surgical bleeds and 90 to 140 μg/kg every ≤2.5 hours for more than two doses for minor surgery with additional doses for major surgery until hemostasis is secured.[17] The prophylactic administration of a uterotonic agent immediately after delivery is recommended for all women with GT to prevent blood loss. Oral antifibrinolytic drugs, hormones, and prednisolone have also been used to treat secondary PPH in some centers. Sometimes, some form of hemostatic agent is also given for prophylaxis at delivery. However, a previous study by Civaschi *et al.*[18] showed that this prophylactic therapy appears to be limited, as more than half of women with GT who had received prophylactic platelet transfusions experienced excessive bleeding requiring blood transfusion, thus suggesting that better preventive treatments are required.

The optimal mode of delivery (vaginal *vs.* cesarean) for pregnant women with GT remains controversial. The mode of delivery does not appear to be associated with PPH. Symptomatic and asymptomatic intracranial hemorrhage of newborns have been reported in all delivery modes; higher rates have been reported after prolonged labor and instrumental delivery.[19] However, during the second stage of labor, when a fetus has an abnormal fetal heart rate, it is necessary to deliver rapidly to avoid fetal hypoxia and neonatal hypoxic-ischemic encephalopathy. In such a difficult situation, instrumental delivery should be performed as this may be more beneficial to both the mother and the neonate than cesarean delivery. Vacuum extraction carries the highest risk and should be avoided. Compared with forceps, vacuum extraction increases the risk of cephalhematomas, diffuse subcutaneous hematomas of the scalp, and intracranial hemorrhage. For this reason, forceps are the better choice for instrumental delivery.[10] Epidural analgesia is contraindicated because of the potential risk of epidural or spinal hematoma during insertion and removal of the catheter. Therefore, current best practice is to decide the most appropriate mode of delivery based on the specific situation of the mother and the fetus. Maternal and fetal risks and benefits must be considered in a multidisciplinary team approach and the pregnant woman and her family should be enrolled in the discussion. A prospective and individualized

management plan should be established for delivery and postpartum monitoring, and should involve obstetric, hematology, neonatology, and anesthetic input.

In the current case, our patient with GT received multidisciplinary management during pregnancy. She had two episodes of hematuria with no apparent cause during the second and third trimester. In her first episode of hematuria, there were no urinary tract infections, urinary tract tumors, or kidney stones. Therefore, the team considered that the hematuria was caused by GT and the bleeding was controlled by platelet transfusions. In the second episode of hematuria, the combination of platelet transfusion and antifibrinolytic drugs was not effective. First, we checked for infection. The same form of bacteriuria was found in two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of $\geq 10^5$ colony-forming units/mL. Therefore, the patient underwent asymptomatic management for bacteriuria. This included antibiotic therapy tailored to culture results and follow-up cultures to confirm sterilization of the urine. Furthermore, following consultation with a hematologist, rFVIIa was administered and this symptom was relieved. This suggests that asymptomatic bacteriuria should be excluded in the presence of hematuria. This experience also suggests that rFVIIa may be an effective treatment for bleeding, especially when platelet transfusions are refractory. During the peripartum period, the patient also received a multidisciplinary approach. An individualized delivery plan was established to ensure optimal maternal and fetal outcomes. Finally, because of abnormal fetal heart rate tracings, we performed forceps-assisted delivery. The patient received multiple hemostatic therapies, such as platelet transfusions, red-cell transfusions, rFVIIa, uterine tonics, antifibrinolytic drugs, and uterine urination; bleeding was well controlled throughout labor and postpartum. These data emphasize the need for multidisciplinary management and antenatal delivery planning for pregnant females with GT.

In conclusion, GT is a rare autosomal recessive bleeding disorder. Pregnancy and delivery represent a particular challenge for women with GT. It is important to stress the need for a multidisciplinary approach for managing these patients, and the newborn infants, including pre-pregnancy counseling, and an individualized plan for pregnancy, delivery, and postpartum monitoring.

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Conflicts of Interest

None.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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