TREATMENT OF THROMBOTIC MICROANGIOPATHY IN PREGNANCY WITH PLASMA EXCHANGE: A REPORT OF TWO CASES

Mé-jou Chen,¹ Hwei-Fang Tien,² and Hong-Nerng Ho¹,³

Abstract: Thrombotic microangiopathy is a rare disease that can be induced and precipitated by pregnancy, and is associated with high maternal and fetal morbidity and mortality. It results from abnormal intravascular platelet aggregation that leads to transient ischemia in various organs, including the central nervous system, kidneys and placenta. Plasma exchange is the most widely accepted method of treatment for this condition. Delayed diagnosis is the main reason for morbidity and mortality, and results from difficulty in differentiating thrombotic microangiopathy from other obstetric emergencies. We report two cases of thrombotic microangiopathy that occurred antepartum and postpartum, respectively. The first patient was a 33-year-old woman who had two previous episodes of intrauterine fetal death in the 13th and 28th weeks of gestation, respectively. She received early plasma exchange at the 23rd week of gestation during this pregnancy and the fetus was delivered uneventfully. The second patient was a 28-year-old woman with progressive thrombocytopenia, anemia and deterioration of renal and liver function postpartum. She received early plasma exchange and it markedly improved her thrombocytopenia without sequelae. In conclusion, early diagnosis and early initiation of plasmapheresis may improve both maternal and fetal prognosis in thrombotic microangiopathy.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are microangiopathic disorders that, before the introduction of plasmapheresis, were associated with high 3-month mortality rates of approximately 75% [1]. Predisposing factors to these conditions include antecedent viral or bacterial infection, pregnancy, chemotherapy, autoimmune disease, and drug therapy [2]. About 10 to 25% of TTP and HUS cases occur during pregnancy or the immediate postpartum period. The main manifestations of these conditions are: anemia; thrombocytopenia; impaired renal and liver function, which can mimic the clinical presentation of severe preeclampsia; hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome; Evans’ syndrome; and disseminated intravascular coagulation (DIC) caused by postpartum hemorrhage and sepsis. Uncertainty and delayed diagnosis can cause chaos in the treatment of these diseases and can increase morbidity and mortality for both mother and fetus/infant [3].

We report here the case histories of two patients with TTP (n = 1) or HUS (n = 1). Both patients were successfully treated with plasma exchange, resulting in good maternal and fetal outcomes. The differential diagnosis and therapeutic options of pregnancy-induced thrombotic microangiopathy are also discussed. For the patient with thrombotic microangiopathy, the fetal prognosis was good, despite delivery after the 33rd week of gestation, which has rarely been reported previously.

Case Reports

Case 1
A 33-year-old woman (gravida 3, para 1, and one spontaneous-
ous abortion) with TTP and a history of repeated fetal death during the second trimester of pregnancy was admitted due to progressive thrombocytopenia and oligohydramnios. TTP was first diagnosed in 1996, at 13 weeks' gestation in a twin pregnancy. The patient's initial signs and symptoms were impaired consciousness, fever, petechiae over the legs, icteric sclera, vaginal bleeding, and hematuria with normal blood pressure. Both fetuses were dead at that time. Laboratory data demonstrated severe anemia (hemoglobin, 4.3 g/dL), thrombocytopenia (platelet count, 15,000/µL), high reticulocyte index (17.8%), leukocytosis (17,300/µL), proteinuria (protein loss of 2.9 g/day), low haptoglobin level (5 mg/dL), elevated lactate dehydrogenase (LDH; 7,440 U/L), and fragmented red blood cells on blood smears. Direct and indirect Coombs' tests, and tests for antinuclear antibody were negative. After exclusion of sepsis with DIC, TTP was diagnosed and the patient received 10 plasma-exchange treatments (once daily in the first week, then once every other day in the second week; volume 2,500–2,700 mL), resulting in marked improvement of anemia, thrombocytopenia and renal function.

The patient's history was uneventful until she became pregnant in 1997 and was again treated with plasma exchange (a total of nine times through the whole course of pregnancy: initially once daily for 4 successive days, then once every other day for two occasions, then once every 2 weeks for three occasions; volume, 1,800–2,100 mL). Unfortunately, intrauterine fetal death (IUFD) occurred at 28 weeks' gestation. After termination of pregnancy, the patient's platelet count recovered gradually.

Case 2
A 28-year-old woman (gravida 1, para 1) whose blood pressure fluctuated with the onset of the third trimester underwent emergent cesarean section in 1996 at a local hospital due to a twin pregnancy with fetal distress at 39 weeks' gestation. Unfortunately, one of the twins died shortly after delivery. The patient was referred to our hospital because of severe postpartum hemorrhage. Physical examination revealed clear consciousness but icteric sclera and multiple purpura over both lower legs. Blood chemistry revealed elevated liver enzymes, hyperbilirubinemia (glutamate-oxaloacetate transaminase 102 IU/L, glutamate-pyruvate transaminase 42 IU/L, bilirubin 3.25 mg/dL), impaired renal function (serum creatinine 2.4 mg/dL), high LDH (1,440 U/L), and high reticulocyte index (2.51%). Hemogram showed thrombocytopenia (77,000/µL), anemia (4.2 g/dL), and leukocytosis. Meanwhile, both prothrombin time and partial thromboplastin time were prolonged. Under suspicion of postpartum hemorrhage secondary to HELLP syndrome or DIC, the patient was admitted to our ward. In spite of component therapy, both her hemoglobin and platelet counts remained low. Gynecologic examination revealed no evidence of retained placenta or uterine atony. Blood pressure was within the normal range.

Fig. 1. Case 1. Clinical course of the patient with two previous episodes of pregnancy-induced thrombotic thrombocytopenic purpura and intrauterine fetal death who was admitted at the 23rd week of gestation due to oligohydramnios and progressive thrombocytopenia found during antenatal examination (Fig. 1). Heparin, prednisolone and aspirin (100 mg daily) were administered after admission, but the patient's platelet count remained low. Therefore, she received 10 plasma exchange treatments (once every week; volume 1,800–2,100 mL). After each plasma exchange, the patient's platelet level rose to a normal level. The patient had an uncomplicated cesarean section at 33 weeks' gestation, because of preterm uterine contractions with fetal distress, and delivered a normal fetus. She was discharged 5 days later without further complications.
The patient’s condition deteriorated day by day after delivery. Peripheral blood smear showed many fragmented red blood cells. Due to suspicion of HUS, plasma exchange was started on the third day after admission. The patient received three treatments on successive days (volume, 2,500–3,000 mL). Her condition improved gradually, and her platelet count gradually returned to normal (594,000/µL) after the last plasma exchange (Fig. 2). The patient was discharged without further complications.

**Discussion**

While the pathogenesis of thrombotic microangiopathies is still unknown, some authors have postulated that decreased activity of the protease that cleaves plasma von Willebrand factor could result in unusually large von Willebrand factor multimers that later initiate the cascade of TTP [4–6]. Wright et al found that platelets in patients with TTP had significantly reduced levels of glycoprotein (GP) IIb/IIIa and GP IV [7]. Increased levels of platelet-associated immunoglobulins and or complement were also observed in more than half of TTP patients. These results indicate that antiplatelet and anti-endothelial cell antibodies may play an important role in the thrombocytopenia and vasculitis noted in thrombotic microangiopathy [7].

TTP and HUS have many clinical manifestations in common: impaired renal function, thrombocytopenia, and hemolytic anemia. However, arteriolar lesions are usually confined to the kidney and neurologic manifestations are uncommon in HUS. Peripheral blood findings and coagulation tests in HUS are usually indistinguishable from those of TTP. Because secondary DIC caused by tissue ischemia and concomitant tissue necrosis may complicate late-stage TTP or HUS, differentiating TTP or HUS from DIC becomes more difficult. While HELLP syndrome also manifests with thrombocytopenia, elevated liver enzymes and mildly elevated bilirubin, it rarely manifests with severe hemolytic anemia, which is associated with TTP and HUS. Severe preeclampsia or eclampsia usually occurs after the 20th week of gestation and resolution of disease is common after delivery. On the contrary, TTP and HUS may occur at any stage of pregnancy and rarely resolve after delivery [8]. Therefore, if thrombocytopenia, refractory hemolytic anemia, and end-organ dysfunction due to ischemia persist or even deteriorate after delivery, clinicians should consider TTP and HUS in the differential diagnosis.

IUFD and preterm delivery are the most common complications of TTP and HUS during pregnancy. In 1955, when the first case of pregnancy-related TTP was reported, splenectomy was the only effective treatment, but only 20 to 30% of infants survived after splenectomy [9]. Since that time, many treatment

![Fig. 2. Case 2. Clinical course of the patient who experienced hemolytic uremic syndrome after delivery. After three sessions of plasma exchange, platelet count recovered gradually. Liver function and serum creatinine seem unrelated to the plasma exchange. GOT = glutamate-oxaloacetate transaminase; GPT = glutamate-pyruvate transaminase.](image-url)
strategies have been attempted to increase the survival of both the mother and the fetus/infant. After plasma exchange was introduced as a first-line therapy in 1988, the outcomes of pregnancy-related TTP and HUS improved, and rates of maternal mortality and fetal loss decreased to 18% and 30%, respectively [10]. When TTP or HUS occurs during the initial 20 weeks of gestation, therapy such as plasma exchange should be initiated immediately and aggressively. When these conditions develop after the 21st week of gestation, the differential diagnosis between TTP and severe pre-eclampsia should be made carefully to determine whether delivery is necessary. Among postpartum women with TTP or HUS, differential diagnosis with DIC is important because of the completely different treatments required for each condition. Close fetal monitoring is also very important because placental insufficiency in TTP and HUS may lead to spontaneous IUFD [11]. Although a severity-scoring system [12] has been used to predict the prognosis of thrombotic microangiopathy, the system was shown to be of limited use [10]. Some authors suggest that the in vitro bleeding-time test system (Platelet-Stat™) [13] is a better prognostic indicator than the conventional parameter of LDH, but this remains controversial.

Because of insufficient placental blood flow and early calcification, progressive thrombotic microangiopathy may lead to IUFD or preterm delivery. Premature babies, especially those delivered before the 32nd week of gestation, have a higher complication and mortality rate because of an immature respiratory system. Most reported cases of thrombotic microangiopathy occurring during pregnancy resulted in IUFD, or preterm delivery before the 33rd week of gestation with grave fetal outcome. This is the first report of a successful outcome of a fetus, delivered uneventfully beyond the 33rd week of gestation, from a patient with thrombotic microangiopathy.

Early plasma exchange and aggressive fetal monitoring strongly influence fetal survival rate. The importance of these treatment factors has been emphasized [3]. Plasma exchange is a relatively safe procedure during pregnancy that is unlikely to adversely affect the fetus. However, a large shift in plasma volume may be harmful to the fetus and should be avoided [14, 15]. In addition to plasma exchange, corticosteroids, non-steroidal anti-inflammatory drugs, and transfusion with fresh-frozen plasma or packed red blood cells are also used in the treatment of TTP and HUS. Conversely, heparin and intravenous immunoglobulin have proved ineffective [16]. Platelet transfusion should be avoided unless life-threatening bleeding, such as intracranial hemorrhage, occurs. Splenectomy and chemotherapeutic agents, such as vincristine sulfate and azathioprine, are reserved for refractory cases only. It is worth mentioning that, in cases refractory to plasma exchange or plasmapheresis, coexistent occult infection [17] or retained products of contraception [18] should be considered.

In conclusion, both maternal and fetal survival depend largely on early diagnosis, early initiation of plasmapheresis or plasma exchange, and close fetal monitoring. All obstetricians-gynecologists should be familiar with the diagnosis of thrombotic microangiopathy.

References