Pregnancy-Related Thrombotic Microangiopathy (TMA): Case series

B. Al-Atia, T. Devos, G. Verhoef, D. Dierickx

Thrombotic microangiopathy (TMA) can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). TMA is a life threatening condition in pregnancy. It encompasses a spectrum of different disorders with a similar pathogenesis, but in most of the cases completely different therapy. It can take several days to obtain the diagnosis, and in case of doubt therapeutic plasma exchange (TPE) (plasmapheresis with plasma substitution) should be started immediately to ensure better outcome. By measuring the activity of the von Willebrand-factor-cleaving protease (ADAMTS13), it may be possible to distinguish between the different causes of thrombotic microangiopathy. Pregnancy-related TMA can occur before or after birth. A Pregnancy-related TMA that develops during the puerperium, typically develops about the fourth day postpartum. No other significant differences are seen between antepartum and postpartum pregnancy related TMA. In critically ill patients it may be difficult to distinguish TMA from sepsis with disseminated intravascular coagulation (DIC). DIC is generally associated with prolongation of global clotting times, prothrombin time and activated partial thromboplastin time (PTT, aPTT) due to consumption of clotting factors. TMA occurs by primary activation of platelets (congenital or acquired abnormalities of ADAMTS13), and by primary endothelial injury (as with HELLP syndrome). Antepartum pregnancy-related TMA usually occurs at 28 ± 8 weeks of pregnancy.

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Introduction

In this paper we describe a case series of five women presenting with pregnancy-related TMA. We emphasise that correct diagnosis is essential for correct management, and for optimal maternal and fetal outcomes. The patients described here developed thrombotic microangiopathy with a different etiology, despite every similar symptoms.

Clinical description of the cases, with theoretical aspects

Case 1: Idiopathic TTP

A 30 year-old woman was admitted to the gynecological department for urgent labor because she developed clinical manifestations of preeclampsia/HELLP at the gestational age of 28 weeks. Two days after delivery, she developed acute neurological features,

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Key words: Thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS), congenital TTP (CTTP), HELLP syndrome: H (haemolysis, which is the breaking down of red blood cells), EL (elevated liver enzymes), LP (low platelet count), ADAMTS 13 (A disintegrin and metalloprotease with Thrombo-Spondin 1 repeats, 13th member), disseminated intravascular coagulation (DIC), acute fatty liver (AFL), therapeutic plasma exchange (TPE).

with urgent need for intubation, and ventilation. TPE was initiated daily and after one week there was discontinuation of TPE because of a good response. However, she got recurrence of the symptoms after ten days and TPE was restarted together with administration of corticosteroids. As she did not respond rapidly, rituximab was added to the therapy, leading to a complete response. It was difficult to distinguish preeclampsia, HELLP syndrome and TTP in this patient, but actually the fulminant neurological and biochemical pictures two days after childbirth argued against preeclampsia/HELLP and was strongly suggestive for the diagnosis of TTP.

TTP (Moschcowitz disease) is an idiopathic, acquired, and severe disease. It is characterised by the combination of thrombocytopenia, microangiopathic haemolytic anemia, neurological abnormalities, fever and sometimes renal insufficiency although this pentade is not required for diagnosis.[1] ADAMTS13 activity is reduced, and mostly associated with autoantibodies(IgG). Moreover, there is sometimes clearance of ADAMTS13 from the circulation through IgG and IgM antibodies without inhibition of the activity of ADAMTS13.[2] Acquired ADAMTS13 deficiency is characterised by a high and unpredictable recurrence rate. Different stress factors (pregnancy, surgery, infection) play a major role in disease by increasing unusually large vWF multimers and generation of microvascular platelet thrombosis. Since the introduction of TPE, the mortality of patients with TTP has decreased from 90% to 10-25%.

Case 2: Congenital TTP

A 34 year old woman got the diagnosis of CTTP (Upshaw-Schulman syndrome) since the age of 21 years during her first pregnancy. ADAMTS13 was <5% at that time. She was treated with TPE, vincristine, and regular plasma infusion. She received also low dose acetylsalicylic acid. It was decided to start TPE and also to continue administration of low dose acetylsalicylic acid because she developed ischemia of the corona radiata in the motor cortex (due to TTP). Careful monitoring and prompt initiation of adequate treatment is very important in patients with CTTP. CTTP is an autosomal recessive, rare and life-threatening illness. It is characterised by deficiency of ADAMTS13 caused by mutations in the corresponding gene on chromosome 9.[2,3] The spectrum of clinical phenotypes is broad in CTTP as it includes neonatal and adult diseases with a single episode of the disease but also chronic forms with repeated exacerbations.

Until now, 76 mutations of ADAMTS13 are reported in the literature.[4] The thirteenth member of the ADAMTS (A Disintegrin And Metalloprotease with ThromboSpondin 1 repeats) family is ADAMTS13. This is a plasma metalloprotease, responsible for cleaving ultralarge von willebrand factor multimers, preventing thrombus formation in case of increased stress.

If there is suspicion about TMA the following tests may help in establishing the (differential) diagnosis of idiopathic and congenital TTP:[5]

1. ADAMTS-13 activity.
2. ADAMTS13 antigen:neutralizing and non-neutralizing anti-ADAMTS-13 autoantibodies.
3. Genetic characterization of ADAMTS-13.

Case 3: HELLP syndrome

A 33-year-old woman developed at day one post partum three consequent epileptic insults and hematuria. The partum vaginal bleeding was normal and not excessive. EEG showed no signs of epilepsy. The laboratory results showed very low platelets count (48 10*9/L) and high total bilirubin (2.17 mg/dL). Abdominal ultrasound showed limited perihepatic, and perisplenic ascites fluid, with signs of acute renal disease. CT scan of the brain revealed no signs of intracranial hemorrhage. Following delivery she resolved spontaneously, without any persisting complications. HELLP syndrome is characterized by haemolysis, elevated liver enzymes, thrombocytopenia, and it is a severe form of preeclampsia. Fifteen to twenty percent of the patients have no history of hypertension or proteinuria, which brings the belief that HELLP syndrome is a distinct disorder from pre-eclampsia.[6] In general, HELLP syndrome can occur in about 1-2/1000 pregnancies, and in 10-20% of pregnant women there is a severe form of preeclampsia / eclampsia. 70% of the cases occur before delivery between 28-36 weeks gestation, and 30% after delivery, usually within 48 hours after delivery. In preeclampsia there is abnormal placentation. The maternal spiral arteries undergo extensive remodeling in healthy pregnancy secondary to trophoblast invasion. This remodeling is not complete in preeclamptic pregnancies, and the failure of the spiral arteries to transform to dilated flaccid tubes with a

4-fold increase in diameter. The frequent findings of atherosis lead to reduction in placental perfusion. It is proposed that the poor placental perfusion is the initiating cause of preeclampsia.[7]

Case 4: Overlap HELLPsyndrome/TTP/HUS

A 24-year-old primigravida developed hypertension, proteinuria and disturbed liver function tests at 28 weeks of pregnancy. The diagnosis of preeclampsia with HELLP syndrome was made and she underwent urgent caesarian section. Postpartum there was progressive microangiopathic hemolytic anemia, thrombocytopenia and disturbed renal function. Because of this evolution diagnosis of postpartum TTP/HUS was considered. The therapeutic option of plasma substitution, without plasma exchange, to maintain a good diuresis was chosen. The patient developed increasing drowsiness, paresthesias over the whole body, and visual disturbances. MRI of the brain showed multiple small areas of infarction. Because of this evolution we decided to extend the therapy and to start with TPE. Unfortunately, the patient died.

Case 5: Acute fatty liver (AFL).

At 34 weeks of pregnancy, a 25-year-old woman had episodes of abdominal pain, urine frequency with feature of urinary tract infection and proteinuria. There was also significant hepatic dysfunction, with deterioration of the renal function, and development of severe coagulopathy. Diagnosis of AFL of pregnancy was suspected. Liver biopsy was not feasible because of poor clotting, whereas abdominal ultrasound showed no steatosis. Initially she got only supportive therapy, but because of deterioration of her condition she was treated with plasma, platelets and erythrocyte transfusions, leading to correction of the clotting problems.

Acute fatty liver of pregnancy is a rare[8], but also very severe disease. It usually occurs in the third trimester of pregnancy. The incidence is estimated at 1:1,000,000/year. Until the early eighties there

Table 1. Initial clinical and biochemical parameters

	First patient (TTP)	Second patient (CTTP)	Third patient (HELLP)	Fourth patient (HELLP+TTP/HUS)	Fifth patient (AFL)
SYSTOLIC BP MMHG	130	181 ⇑	170 ⇑	180 ⇑	140
DIASTOLIC BP MMHG	74	100 ⇑	110 ⇑	110 ⇑	70
PLATELETS 10**9/L	65 ⇓	36 ⇓	29 ⇓	13 ⇓	88 ⇓
HEMATOCRIT %	0.243 ⇓	0.330 ⇓	0.198 ⇓	0.222⇓	0.378
Reticulocyte 10*9/L	149 ⇑	50	64	136 ⇑	28
Total LDH U/L	406	391	15280 ⇑	5515 ⇑	1029 ⇑
AST U/L	18	15	4401 ⇑	121 ⇑	156 ⇑
ALT U/L	21	10	3736 ⇑	30	159 ⇑
Uric acid mg/dL	4.4	4.3	16.9 ⇑	12.4 ⇑	11.1 ⇑
Urea mg/dL	48	43	122 ⇑	182 ⇑	26
Creatinine mg/dL	1.26 ⇑	0.92	4.12 ⇑	3.86 ⇑	0.94
Total bilirubin mg/dL	0.78	0.79	3.42 ⇑	2.92 ⇑	5.25 ⇑
ADAMTS13 activity %	<5	<5 ⇓	46	not determined	not determined

**TTP : Thrombotic thrombocytopenic purpura.*
**CTTP: Congenital TTP.*
**HELLP syndrome: H(haemolysis), EL(elevated liver enzymes), LP(low platelet count)*
**HUS: Haemolytic uremic syndrome.*
**ADAMTS 13 (A disintegrin And metalloprotease with Thrombo-Spondin 1 repeats, 13th member)*
**AFL: Acute fatty liver*

were fewer than 100 pregnant women with this condition reported in the literatures with a fetal and maternal mortality of 75 and 85% respectively.

For pregnant women with symptoms of nausea, vomiting and pain in the upper abdomen in the third trimester, liver function should be determined. If this is disturbed, the diagnosis of AFL should be considered, until proved otherwise. The pathogenesis of this complication is not completely understood, in some cases an enzymatic defect in the processing of fatty acids can be identified.

Treatment

A. TTP-CTTP:

(1) TPE

Microangiopathic haemolysis and platelet consumption, which are responsible for thrombus formation and symptoms, are reversed by TPE. The rationale for the use of TPE in idiopathic TTP is:[9]

- Removal of IgG inhibitor of ADAMTS13, and the circulating high molecular weight von Willebrand factor (VWF) multimers.
- Replacement of plasma from the patient through infusion of normal plasma, which provides the missing ADAMTS13. Plasma exchange with either fresh frozen plasma (FFP) or cryosupernatant is generally initiated with the goal of exchanging 1-1.5 plasma volumes (40 to 60 mL/kg) daily. It should be continued for a minimum of two days after complete normal platelet count is obtained. Although no randomised trials have been performed, many centres advocate to add corticosteroid therapy.[9] Following a first exacerbation during pregnancy, the probability remains very high to develop TTP during subsequent pregnancies.

(2) Corticosteroids

Some reports indicate success in patients after the use of corticosteroids, as in many cases TTP is an autoimmune disease. Their potential benefit may be limited to patients with severe ADAMTS13 deficiency. Patients who are unlikely to have severe ADAMTS13 deficiency, such as patients with severe renal failure or patients with a history and clinical presentation suggesting for drug-associated TTP or E.coli O157:H7 infection, should not be treated with corticosteroids.[10]

(3) Rituximab

Monoclonal anti-CD20 antibody has emerged as a promising new therapeutic approach in patients with idiopathic TTP. It might be indicated in:

a) Severe course of illness, with worsening of the disease including neurological or cardiac complications, and inappropriate response to plasmapheresis and corticosteroids.
b) Recurrence, with re-occurrence of anti-ADAMTS13 autoantibodies leading to insufficient ADAMTS13 cleavage. The monitoring of ADAMTS13 level at regular intervals in recurrent TTP may help us to identify patients at high risk for further relapse. Such a relapse may be prevented, or at least delayed with timely rituximab therapy.

Recent literature reviews showed that rituximab can be administered because of refractory disease or at relapse, together with re-initiation of TPE, with remission rates of more than 85%.[11,12] In a detailed case series 25 patients received rituximab for relapsing or refractory acquired ADAMTS13-deficiency TTP. All patients showed a complete remission, which occurred within eleven days following rituximab administration. In this study there was confirmation of the inverse relationship between successful rituximab therapy and decreased antibody levels and increased ADAMTS13 activity.[13]

A report of the regional United Kingdom TTP Registry showed that the number of patients having received adjuvant rituximab therapy in the period 2004-2006 was significantly increased in comparison with other adjuvant therapies.[14] An American multicentric randomised phase III trial (STAR Study) was initiated in 2009 to see if there is benefit to use rituximab together with TPE as standard treatment for newly diagnosed or relapsed TTP. Two hundred twenty patients were foreseen to be included in this trial, randomised to receive TPE and corticosteroids with or without rituximab. However, this trial was prematurely terminated due to a low enrollment rate (http://clinicaltrials.gov/ct2/show/NCT00799773).

The French Thrombotic Microangiopathies Reference Centre reported on an open label prospective study with 22 adult TTP patients with no response or a disease exacerbation following treatment with TPE. These patients were given rituximab therapy. Rituximab 375 mg/m^2 was given on day 0, +3, +7 and +14, with day 0 being the day of diagnosis of suboptimal response to TPE. The patients were compared historically with another group of patients

who received TPE with or without vincristine. Rituximab therapy was associated with a shorter overall treatment duration and reduced relapse rate at one year. No serious side effects were recorded in this trial.[15] In another United Kingdom multicentric non-randomised phase II trial examining the use of rituximab in newly diagnosed or relapsed TTP patients, 40 patients were included. In contrast to the French trial, all patients were given rituximab 375 mg/m²/week during four consecutive weeks, starting within three days following diagnosis. The study group was also compared to a historical control group who had never received rituximab. Rituximab reduced significantly both plasma exchange and hospital duration and relapse rate. In 92,5% of the patients ADAMTS13 levels increased whereas ADAMTS13 antibodies decreased. No infections or serious adverse events were observed.[15]

(4) Antiplatelet agents (aspirin, dipyridamole)

This medication is only beneficial when added with plasmapheresis. Because of the high risk of bleeding in thrombocytopenic patients, aspirine is only recommended as adjuvant therapy if platelets >50,000 per microliter.

(5) Platelet transfusion

Platelet transfusion can lead to new or worsening neurological symptoms and acute renal failure, probably due to the new production/or the extension of microvascular thrombi by increased consumption of platelets.[16]

B. HELLP syndrome:

Anti-hypertension:

Trying to keep tension less than 160/105 mmHg, and to avoid seizure.[17]

Platelet transfusions:

Is indicated in severe maternal haemorrhage, or if platelet count is very low (less than 10,000-20,000 per microliter).

Termination of pregnancy:

a) In case of severe maternal morbidity (multiorgan dysfunction, DIC, liver infarction or haemorrhage, renal failure, placental abruption), and if there is no fetal status reassuring, delivery should be considered, regardless of gestational age.
b) For pregnant women ≥34 weeks, there is a great chance to have preterm delivery, which is the major cause of perinatal morbidity and mortality. Thus for this group of patients there is a recommendation to promote childbirth instead of treating hypertension.

C. Acute fatty liver

Bleeding and/or severe coagulopathy should be treated with plasma transfusion and other blood products as indicated. If there is maternal hypotension further damage to the liver, kidneys and other organs should be prevented aggressively. In AFL it is better to avoid cesarean section because of high risk of bleeding and other complications of coagulopathy.[8] In the postpartum period frequent serial hematological, hepatic and renal function measurements should be performed. Typically an improvement is observed after two to three days after delivery. In some patients the liver function, renal function, mental status and coagulation tests are deregulated for more than one week. Martin et al reported on using postpartum plasma exchange to treat severe cases of AFL in the postpartum period. Patients with severe encephalopathy, on ventilator support, or with severe liver or renal insufficiency who failed to respond to conventional management, underwent plasma exchange. All patients showed improved signs and laboratory values.[18] There is no need for liver transplantation in surviving patients.[8,19]

Discussion

Although pregnancy alters the human body in many ways, it does not confer an immunity to death. Maternal mortality during pregnancy fits into one of two classifications: maternal mortality in which the disease process is interrelated with pregnancy, and maternal mortality occurring during pregnancy but not caused by pregnancy. TMA is present, either primarily or as a secondary manifestation of another disease. The management of TTP during pregnancy is similar to that in the non-pregnant patient, with TPE yielding a response rate of approximately 80-90%. Neurological improvement in TTP can be quick, usually within hours or days, while normal biochemical values occur within weeks. Renal failure is the last disorder that can be improved. Sometimes the liver function, renal function, and mental status, remain abnormal for more than one week. In this condition plasmapheresis will be the best choice. Rituximab is used for patients with persistent TTP,

Table 2. Differential diagnosis of the various clinical manifestations and laboratory profiles of thrombotic microangiopathies (TMAs)

	First patient (TTP)	Second patient (CTTP)	Third patient (HELLP)	Fourth patient (HELLP+TTP/ HUS)	Fifth patient (AFL)
Haemolysis	+++	+++	++	++	–
Reticulocytosis	+	+	–	+++	–
Thrombocytopena	++	++	–/+	+++	–/+
Coagulopathy	–	–	–	–/+	++
Proteinuria	With hematuria	–	++	++	–/+
Hypoglycemia	–	–	–	–	–/+++
ADAMTS 13 deficiency	–/+++	++++	–	–	–
⇑Ureum	–	–	+++	+++	–
⇑Creatinine	–	–	+++	+++	–
⇑ Ammonia	–/+	–/+	–	–	–/+
⇑ Bilirubin	–/+	–/+	–/+	+++	++
⇑	+	+	+	+++	+++
Histopathology	Pronounced platelet thrombi (VWF-rich)	Pronounced platelet thrombi (VWF-rich)	Thrombi only in the glomeruli (fibrin-rich)	Hepatocyte necrosis + fibrin in periportale sinusoid	Enlarged hypatocyte

and patients with severe recurrent TTP and persistent anti-ADAMTS13 anti-bodies.[15] In HELLP, if a cesarean delivery is planned, it is recommended to prescribe platelet transfusions, as necessary, to achieve a pre-operative platelet count higher than 40,000-50,000 cells per microliter. Severe preeclampsia and HELLP syndrome may be associated with other hepatic manifestations, such as infarction, haemorrhage, and rupture of the liver.[17] The only method of treatment in HELLP syndrome is termination of pregnancy. On the contrary, pregnancy can be continued without termination in TTP.

Rapid increase in platelet in TMA during therapy can also be associated with thromboembolic process, thus low dose aspirin might be indicated if platelets >50.000/ml. Complications of plasmapheresis are usually related to the insertion of a central venous catheter, like thrombosis (DVT), or infection.

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Key messages:

1. TMA is a rare but serious life-threatening condition in pregnancy, with different causes and with different treatment.
2. Stress (such as pregnancy, surgery, infections) might lead to exacerbation of TTP by increased secretion of unusually large vWFmultimers, and stimulation of microvascular platelet thrombus formation.
3. Rituximab can be added to TPE in patients with refractory or relapsing TTP, and this can result in a durable clinical remission.
4. The only method of treatment in HELLP syndrome is termination of pregnancy. Pregnancy can be continued without termination in TTP.

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