

Pregnancy in Upshaw-Schulman syndrome

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Keywords

Upshaw Schulman syndrome, pregnancy, TTP, plasma therapy, VWF, ADAMTS13

Summary

The Upshaw Schulman syndrome (MIM #274150) is a hereditary deficiency of the von Willebrand factor cleaving protease (ADAMTS13) due to homozygous or compound heterozygous mutations in the *ADAMTS13* gene. Patients are prone to bouts of thrombotic thrombocytopenic purpura. However, disease manifestation needs a second trigger event. Pregnancy is a known risk factor for TTP. Patients with USS may manifest during pregnancy and the postpartum period or relapse with a TTP bout. Before plasma therapy mortality for both the mother and the fetus was high, but even nowadays when plasma is delivered, therapy is challenging, still bearing a high risk for miscarriage or long term sequelae for the mother. In this report on pregnancies in three mothers with USS, plasma therapy was increased in frequency and amount given with regard to platelet count or ADAMTS13 activity, thus leading to a successful outcome.

Schlüsselwörter

Upshaw-Schulman-Syndrom, Schwangerschaft, TTP, Plasmatherapie, ADAMTS13

Zusammenfassung

Beim Upshaw Schulman Syndrom (#274150) besteht ein angeborener Mangel der von Willebrand-Faktor-spaltenden Protease (ADAMTS13) durch homozygote oder kombiniert heterozygote Mutationen im *ADAMTS13*-Gen. Dadurch kommt es bei den Patienten zu Schüben mit dem Bild der thrombotisch-thrombozytopenischen Purpura. Allerdings braucht es für diese Manifestation einen Auslöser. Schwangerschaft stellt einen bekannten Risikofaktor für die TTP dar. Bei Patientinnen mit USS kommt es entweder zur Erstmanifestation während der Schwangerschaft oder im Wochenbett oder zum Rückfall der TTP. Vor der Einführung der Plasmatherapie lag die Mortalität für Mutter und Kind hoch, doch auch heute mit Plasmasubstitution, stellt die Behandlung eine Herausforderung dar, mit einem hohen Risiko für vorzeitigen Abort oder Langzeitschäden bei der Mutter.

In diesem Bericht über Schwangerschaften dreier Mütter mit USS, führte die an die Blutplättchenzahl oder ADAMTS13-Aktivität angepasste Plasmagabe zu erfolgreichem Schwangerschaftsverlauf.

Pregnancy is a risk factor for the development of thrombotic microangiopathy. Sharing clinical features but having different etiologies they are named pregnancy associated TTP, HUS, or HELLP syndrome (5, 8, 20, 28). If left untreated mortality is high for the mother as well as for the fetus (7, 18, 30, 31, 33). Pregnancy associated thrombotic microangiopathies have an incidence of 1 in 25 000 to 100 000 deliveries and comprise up to 25% of TMA manifestations in adults (7, 10, 15, 26).

Upshaw Schulman syndrome (USS) is a hereditary deficiency of the von Willebrand factor cleaving protease (ADAMTS13) due to compound heterozygous or homozygous mutations in the gene encoding for ADAMTS13.

Patients are prone to bouts of thrombotic thrombocytopenic purpura. However, even in patients with severe ADAMTS13 deficiency TTP may not always manifest. Second triggering events may be important to start a TTP bout, as of which pregnancy appears to be one (22, 24, 25).

Plasma infusion is the mainstay of therapy in patients with USS.

Hereby, missing ADAMTS13 activity is delivered to regain von Willebrand factor proteolysis. Usually, administration of 10–20 ml/kg body weight every two to three weeks will keep ADAMTS13 activity at a level, which is considered to be sufficient to prevent the accumulation of ultra large VWF-multimers known to trigger platelet adhesion even at moderate shear rates. It is recommended to individualize

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Schwangerschaft bei Upshaw-Schulman-Syndrom

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dosage and frequency according to the patients' phenotype (24).

Three women with TTP

We report the courses of pregnancies in three women diagnosed with hereditary TTP with compound heterozygous and homozygous mutations in the *ADAMTS13* gene.

Patient 1

Two pregnancies in this patient have been reported before (9). In brief, the woman became pregnant at the age of 20 years. However, she lost the fetus in the fifth week of gestation.

Eleven months later she was pregnant again and developed TTP in the 20th week of gestation. She was treated with 17 plasma exchange (PEX) sessions. Laboratory examination revealed an *ADAMTS13* activity <5%.

In mixing studies an *ADAMTS13* inhibitor was detected and the diagnosis of acquired TTP due to an autoantibody directed against *ADAMTS13* was made. Indeed a trial with plasma infusion alone could not prevent a decline of *ADAMTS13* activity so that the patient received another 22 PEX sessions until Caesarean section was performed in the 32nd week of gestation.

The clinically healthy boy was premature though appropriate for gestational age. *ADAMTS13* activity in umbilical cord blood was reduced to 15% and a mild *ADAMTS13* inhibitor was documented in mixing studies, indicating transplacental transmission of *ADAMTS13* autoantibodies. The postpartum period was covered with 5 PEX sessions until platelet count returned to normal.

The next year the patient had an induced abortion in the 9th week of gestation when the blood count already revealed thrombocytopenia. Two years later the woman was admitted to hospital being 27 weeks pregnant, when platelet count dropped below $100 \times 10^9/l$, she revealed signs of ongoing haemolysis (no measurable haptoglobin) and proteinuria. She received two PEX sessions. Immune suppres-

sion was started with prednisone and cyclosporine A and prophylactic anticoagulation with low molecular weight heparin (LMWH) was initiated.

In the meantime methods of *ADAMTS13* activity and antibody detection had been changed to a commercially available assay (Technoclone®). With this new assay no antibody against *ADAMTS13* was detected in any of the patient's current plasma samples. Stored samples from the 2nd pregnancy were retested and showed also no anti-*ADAMTS13* IgG. Consequently, suspicion rose whether the diagnosis of Moschcowitz' disease (acquired autoantibody TTP) was correct and genetic testing was performed. The patient was found to be compound heterozygous for two mutations, 763–769dupl7bp in exon 7 and R1060W in exon 24 of the *ADAMTS13* gene. This later mutation is rather common and has been found in adult onset TTP and particularly often in women with a first TTP episode in pregnancy (3, 21).

The patient was further treated with plasma infusions only increasing in amount and frequency until it was decided to terminate pregnancy in the 32nd week of gestation because of medically uncontrollable hypertension and proteinuria. The day before the scheduled Caesarean section she had another plasma exchange. A healthy premature girl was delivered. Plasma was infused on day one and day two postpartum. Thereafter, no plasma was administered and *ADAMTS13* activity dropped to the baseline values without any indication of clinically overt TTP.

Patient 2

The initial presentation and diagnosis have been published elsewhere (14). The woman was diagnosed with USS at the age of 16 years. Her *ADAMTS13* activity was <1% due to compound heterozygous mutations in *ADAMTS13* exons 24 R1034X and 29 4143insA.

Since the diagnosis was established, she was treated with prophylactic plasma infusions 800 ml every two weeks. Throughout the following years the patient was asymptomatic but showed a decline in platelet count during periods of infection. At the age of 28 years she became pregnant and

was advised to have a very close monitoring of her platelet count and *ADAMTS13* activity.

The goal was to keep the *ADAMTS13* trough activity above 5% and to maintain a stable platelet count. During the course of pregnancy this was achieved by increasing the volume of plasma infused and shortening the interval of infusions. No anticoagulant or antiplatelet drug was used. Repetitive ultrasound examinations of the placental flow and the fetus showed normal fetal development. The pregnancy was maintained throughout the 40 weeks when she delivered a healthy boy.

Patient 3

This woman was diagnosed with USS at the age of 26 years in the context of a family investigation following a diagnosis of USS in her older brother. Their *ADAMTS13* activities were <5% in the absence of an *ADAMTS13* inhibitor and both siblings were found to be homozygous for the common *ADAMTS13* mutation 4143insA in exon 29.

The patient's first episode of thrombocytopenia and haemolytic anaemia was noted at the age of 11 months. Over the next 15 years the episodes recurred 2–3 times a year and were treated with corticosteroids and blood transfusions. Between the age of 16 and 28 she was asymptomatic, when at 13 weeks into her first pregnancy a drop in the platelet count to $29 \times 10^9/l$ was noted without signs of haemolysis.

Fresh frozen plasma (FFP), 11 ml/kg, was administered for five consecutive days followed by prophylactic infusions of 6 ml/kg every two weeks to maintain a target platelet count $>100 \times 10^9/l$. From 25 weeks gestation the FFP dose had to be gradually increased and a treatment with LMWH in a prophylactic dose was started (at this point plasma levels of factor VIII, von Willebrand factor antigen and von Willebrand factor activity were 250%, 381% and 566%, respectively). Despite these measures, the patient developed severe thrombocytopenia ($25 \times 10^9/l$) and haemolytic anaemia in the 37th week of gestation, requiring daily FFP infusions to maintain a platelet count between 60 and $70 \times 10^9/l$.

During the whole pregnancy no signs of kidney, brain or other organ ischaemia were observed. A healthy boy with normal birth weight was delivered by Cesarean section at 39 weeks gestation.

The total FFP volume transfused during the whole pregnancy was 15 600 ml. The peak ADAMTS13 plasma levels following FFP infusions ranged from 20 to 45% while the minimum level immediately before scheduled FFP infusion was frequently below the detection limit. Four weeks after delivery thrombocytopenia ($21 \times 10^9/l$) and haemolytic anaemia recurred and monthly FFP infusions had to be reintroduced. The patient recovered six months later. No further bouts with thrombocytopenia and/or anemia have been observed and she did not require any treatment for USS ever since (► Fig. 1c).

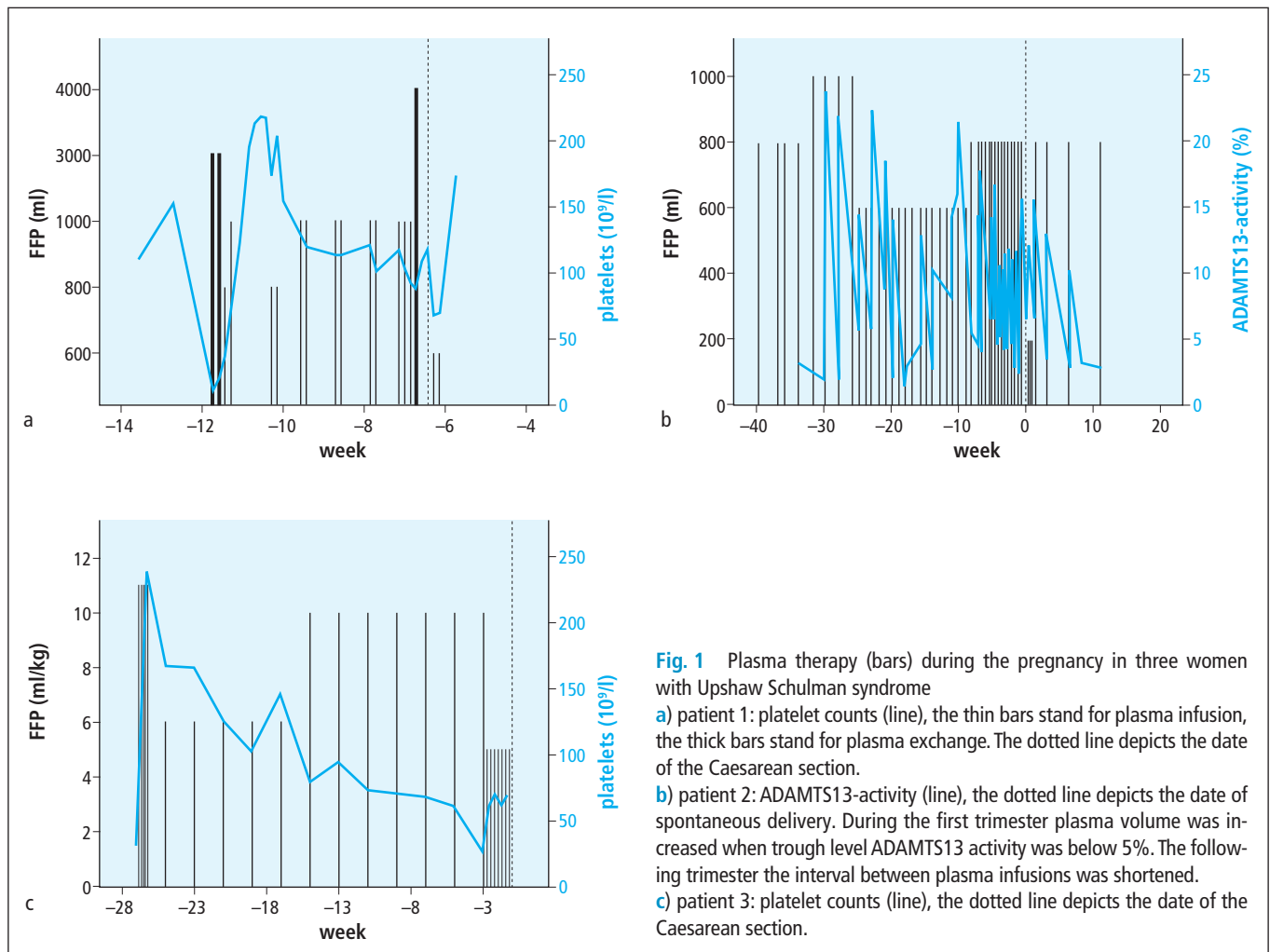
Plasma therapy

Plasma is the only source of ADAMTS13 yet available. In patients with acquired TTP due to auto antibody induced severe ADAMTS13 deficiency plasma exchange is the mainstay of treatment to remove the antibodies and to replenish ADAMTS13 activity (23). USS patients may be treated with plasma infusions alone to deliver ADAMTS13 (11).

- The amount of plasma to achieve sufficient VWF-multimer proteolysis depends on the patient's plasma volume and the amount of VWF in circulation.
- The frequency of plasma infusion depends on the half life of ADAMTS13 activity. (24).

Initially, patient 1 had been misdiagnosed as acquired TTP with severe antibody-me-

diated ADAMTS13 deficiency. When her platelet count dropped without any other signs of TTP during pregnancy she received two plasma exchanges whereby ADAMTS13 activity was increased from 5.4 % to 38.6 % and platelet count raised to values above $100 \times 10^9/l$ (10). She was put on regular plasma infusions, of which volume administered and frequency were increased whenever the platelet count dropped. When uncontrollable proteinuria and hypertension developed it was decided to terminate the pregnancy in the 32nd week by Caesarean section for which she was prepared by one PEX session in order to further increase ADAMTS13 activity without the downside of volume overload of plasma infusions. After delivery she received 400 ml of plasma for two days each. Thereafter, platelet count remained stable above $100 \times 10^9/l$ (► Fig. 1).



Patient 2 was on regular prophylaxis with 800 ml FFP (16 ml/kg body weight) every fortnight before she became pregnant. As she had no residual ADAMTS13 activity it was aimed to keep ADAMTS13 trough level above 5%. During the course of pregnancy this could only be achieved by increasing the volume and frequency of plasma administration (► Fig. 1b) Hereby, platelet count remained stable at $200 \times 10^9/l$. The postpartum period was covered with 200 ml plasma infusion per day until after one week the patient returned to the prophylactic regimen she had had before the pregnancy.

VWF:AG and activity (VWF:RCo) increased during pregnancy to

- 576% and 500% in patient 1,
- 575% and 492% in patient 2 and
- 381% and 566% in patient 3.

The multimeric pattern of VWF was analysed in patient 1 and 2. Patient 1 exhibited ultralarge VWF-multimers when ADAMTS13 activity was low before the first PEX and during the course when a drop in platelet count was noted (► Fig. 2). Patient 2 exhibited ultralarge multimers throughout her pregnancy (not shown).

Discussion

Pregnancy constitutes a trigger for severe acute TTP episodes in patients with USS (12, 32). Pregnancy or the post-partum period is an associated or underlying condition in 10–30% of adult-onset TTP (7, 15, 26, 31), with an unexpected high frequency of USS cases among such cases (10/42; 24%) in a recent publication of the French TMA registry (21). In this study, eight of the ten USS cases with pregnancy associated TTP were heterozygous carriers of the R1060W mutation as was our case 1 and as are several cases in the British cohort on adult-onset TTP (3).

In this French study on 42 women with pregnancy-onset of TTP (32 acquired TTP, 10 USS) two died (4.7%) and three (7.1%) survived with persistent organ damage (all five had acquired TTP). This maternal outcome is more favourable than in previous studies and may be attributable to earlier recognition and initiation of plasma ther-

apy. A recent British survey found that over a 5 year period 1% of all maternal deaths were due to TTP (10). Organs involved in microangiopathic damage are the kidneys, the brain, the heart and the placenta. Pathological examination documented placental infarction in USS patients with fetal loss (4, 13, 19, 27, 33).

The risk of miscarriage or fetal death is elevated.

The French cohort states a stillbirth rate of 40% for mothers with USS. The majority of patients become symptomatic in the late second to early third trimester of pregnancy. An earlier manifestation was associated with worse pregnancy outcome (7, 32).

Most patients with USS, who have a history of frequent relapses, are on prophylactic plasma therapy.

The risk for a recurrence of a TTP bout in women with USS in a subsequent pregnancy without plasma therapy is 100% (6, 7, 32). Pregnancy seems to change the metabolic rate of VWF proteolysis. There is an increase in VWF synthesis while ADAMTS13 activity decreases during pregnancy (6, 16, 17, 29). The patients reported here, revealed an increase in VWF antigen and activity during the course of their pregnancies:

- Patient 1 shows a residual ADAMTS13 activity of 5% and has had overt TTP only during pregnancies.
- Patient 3 was asymptomatic for 12 years and consequently not on prophylactic plasma regimen, became thrombocytopenic as the first sign of the haemostatic imbalance.
- In patient 2, who received prophylactic fortnightly plasma infusion already before the pregnancy, an increased consumption of ADAMTS13 can be assumed based on lower ADAMTS13 activity levels at the end of the interval. Interestingly, the pregnancy in this patient, who has no residual ADAMTS13 activity, went uneventful throughout 40 weeks. The main difference compared to patients 1 and 3 is that she was never thrombocytopenic, which means that there was no platelet consumption.

Apparently, it is more difficult to stop an ongoing TTP bout than to prevent it (1).

Multimeric analysis of VWF, available in patients 1 (► Fig. 2) and 2, showed non proteolysed ultralarge VWF in patient 2 throughout the whole pregnancy although no signs of microangiopathy were seen. Patient 1 had ultralarge VWF multimers only during periods when a drop in platelet count, suggestive of ongoing platelet consumption and discrete signs of haemolysis were recorded. Therefore, VWF multi-

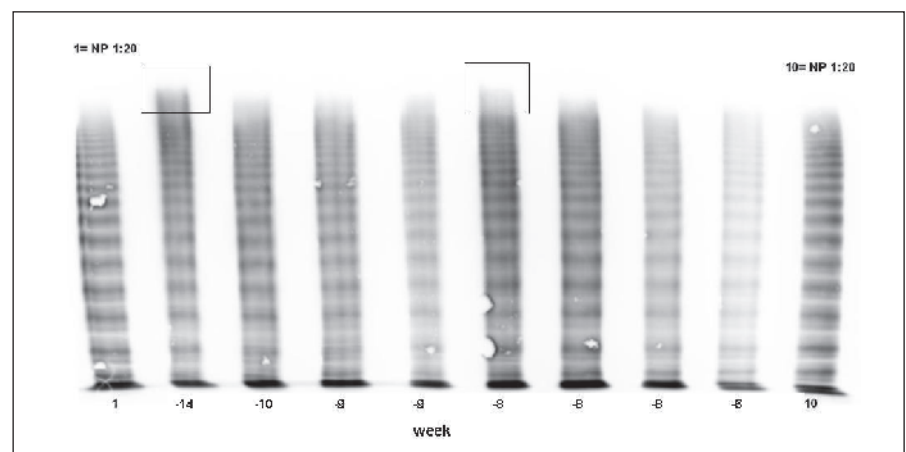


Fig. 2 Multimeric analysis of plasmatic VWF in a low affinity SDS-agarose-gel of patient 1 (no. 1 and no. 10 are normal human pool plasma): The patient's plasma shows ultralarge VWF multimers before the initiation of plasma therapy in week -14 and before plasma administration in week -8 (squares).

meric analyses may be of limited value in risk estimation for an upcoming TTP bout.

Conclusion

The decision on starting plasma therapy should be based on the

- platelet count,
- VWF antigen and activity and
- ADAMTS13 activity.

Dosage and interval should be estimated on repetitive measurements, which reflect consumption of ADAMTS13 and its substrate (1). In our experience the threshold to start or increase plasma therapy should be low in pregnancy.

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Conflict of interest

The authors declare no conflict of interests.

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