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Current insights into thrombotic microangiopathies: Thrombotic thrombocytopenic purpura and pregnancy

Charis von Auer [a,b], Anne-Sophie von Krogh [c], Johanna A. Kremer Hovinga [d], Bernhard Lämmle [b,d,*]

[a]Department of Medicine 3, University Medical Center, Mainz, Germany
[b]Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany
[c]Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology and Department of Haematology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[d]Department of Hematology and Central Hematology Laboratory, Inselspital Bern University Hospital and University of Bern, Bern, Switzerland

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ABSTRACT

The complex relation between thrombotic thrombocytopenic purpura (TTP) and pregnancy is concisely reviewed. Pregnancy is a very strong trigger for acute disease manifestation in patients with hereditary TTP caused by double heterozygous or homozygous mutations of ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 domains, no. 13). In several affected women disease onset during their first pregnancy leads to the diagnosis of hereditary TTP. Without plasma treatment mother and especially fetus are at high risk of dying. The relapse risk during a next pregnancy is almost 100% but regular plasma transfusion starting in early pregnancy will prevent acute TTP flare-up and may result in successful pregnancy outcome. Pregnancy may also constitute a mild risk factor for the onset of acute acquired TTP caused by autoantibody-mediated severe ADAMTS13 deficiency. Women having survived acute acquired TTP may not be at very high risk of TTP relapse during an ensuing next pregnancy but seem to have an elevated risk of preeclampsia. Monitoring of ADAMTS13 activity and inhibitor titre during pregnancy may help to guide management and to avoid disease recurrence. Finally, TTP needs to be distinguished from the much more frequent hypertensive pregnancy complications, preeclampsia and especially HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelet count) syndrome.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a severe, often fatal disease that needs urgent diagnosis and initiation of effective treatment [1–3]. Conceivably, TTP occurring in a pregnant woman may complicate the course of pregnancy posing mother and child at vital risk. Moreover, the possibility that pregnancy is a risk situation favouring the onset of acute TTP should be considered. In addition, the classic pregnancy complications such as preeclampsia/eclampsia and especially Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome have clinical signs and laboratory features that partially resemble those in TTP [4], making the differential diagnosis of HELLP syndrome versus TTP difficult.

Here, we present a brief overview on the thrombotic microangiopathies (TMAs), including TTP, hemolytic uremic syndrome (HUS) and HELLP syndrome. Then, we focus on the role of pregnancy as a trigger of acute disease manifestations in women with congenital severe ADAMTS13 (A Disintegrin And Metalloprotease whith ThromboSpondin type 1 domains, no.13) deficiency, on the outcome for mother and fetus and on possible prophylactic and therapeutic interventions. Finally, we examine whether pregnancy also constitutes a risk for the onset of acute acquired TTP caused by autoantibody-mediated severe ADAMTS13 deficiency and/or whether women having survived an acute acquired TTP are prone to suffer from disease recurrence during a subsequent pregnancy and whether there is any fetal or maternal risk besides an acute TTP flare-up.

Brief overview of thrombotic microangiopathies (TMAs)

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschcowitz in 1924 [5] and the diagnostic pentad of clinical findings, i.e. microangiopathic hemolysis with red cell fragmentation, thrombocytopenia, neurologic signs or symptoms, renal dysfunction and fever, was reported by Amorosi and Ultmann in 1966 [6] after reviewing some 250 published patients and adding 16 own cases. Patients nowadays clinically diagnosed with acute TTP have in most instances a severe functional deficiency of the von Willebrand factor (VWF)-cleaving protease, ADAMTS13 [1,7–10], in rare cases caused by homozygous or compound heterozygous mutations of the *ADAMTS13* gene leading to hereditary TTP (Upshaw-Schulman

* Corresponding author: Bernhard Lämmle, Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany. Tel.: +49 61 31 17 82 77 (82 15).
E-mail address: Bernhard.laemmle@uni-mainz.de (B. Lämmle).

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syndrome, USS) [11,12] and more often mediated by inactivating anti-ADAMTS13 autoantibodies leading to acquired TTP [1,3,7–10]. The resulting extremely adhesive unusually large VWF multimers [13] are responsible for the platelet clumping in the microvasculature and the resulting ischemic damage in various organs, including brain, kidney, heart and other organs [1–3].

A disease similar to TTP has been reported as the hemolytic uremic syndrome (HUS) in 1955 [14] and is conceptually distinguished from TTP by more pronounced renal failure [2,3]. Typical HUS is caused by shigatoxin-producing enteropathogenic E. coli or shigella and occurs mainly in children or elderly nursery home inhabitants whereas atypical HUS has in recent years been found to be often associated with an hyperactivatability of the alternative complement pathway, caused by hypofunctional mutations of the complement regulatory proteins CFH, CFI, MCP (CD46), THBD or hyperfunctional mutations of CFB or C3 [3,15,16]. In about 50% of patients diagnosed with atypical HUS heterozygous mutations in one of the above mentioned genes, enhancing alternative complement pathway activation, are found and in a small minority of atypical HUS patients autoantibodies inactivating CFH are present [3,15,16]. The clinical distinction between atypical HUS and TTP is difficult and often not possible at presentation [3] but may be important for optimal therapeutic intervention. Whereas plasma exchange (PEX) with replacement of fresh frozen plasma (FFP) and immunosuppression with corticosteroids remain the mainstay of treatment in acquired TTP [1–3,16], atypical HUS patients may benefit more from complement inhibitory treatment using eculizumab, a monoclonal antibody binding to and inhibiting the activation of C5 [3,16,17], even though PEX may be (partially) effective as well.

The distinction of hereditary from acquired TTP may be equally important because acute disease bouts in hereditary TTP may be easily treated with simple FFP infusion [1,18] as opposed to acquired TTP where often daily PEX therapy over many days or weeks may be needed to achieve a remission [2,7–10]. Recurrent disease flare-ups in USS can be prevented by regular FFP infusions every 2–3 weeks [18], whereas recurrent attacks of acquired ADAMTS13 deficient TTP will have to be treated by PEX and their incidence may be reduced by intensified immunosuppression, including rituximab, or by splenectomy [1,2,16,19].

Besides classic hereditary and acquired TTP as well as typical and atypical HUS several other conditions may be associated with a similar clinical picture of schistocytic hemolytic anemia, thrombocytopenia +/− organ dysfunctions. These heterogeneous conditions have been variably referred to as TTP, HUS, TTP-HUS, TTP-like disease or secondary TTP [1] and include mainly hematopoietic stem cell transplantation-, disseminated neoplasia-, anticancer agent-, other drug-, human immunodeficiency virus-, systemic lupus erythematosus-, severe arterial hypertension- and pregnancy-associated thrombotic microangiopathies (TMAs) [2,3,16].

The pregnancy-associated HELLP syndrome is a severe form of preeclampsia [4] and may mimic acute ADAMTS13 deficient TTP. Preeclampsia and HELLP are much more common than acute TTP. Patients with HELLP syndrome have normal or moderately decreased ADAMTS13 activity but show increased VWF levels, a high VWF propeptide/VWF antigen ratio (suggestive of endothelial stimulation/damage) and an increased binding affinity of the VWF A1 domain to platelet glycoprotein Ib resembling the situation with the unusually large VWF multimers in severely ADAMTS13 deficient TTP [20]. In (severe) preeclampsia the antiangiogenic factors, fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) and endoglin, an inhibitor of transforming growth factor β (TGF-β) are released from the hypoperfused, hypoxic placenta and elevated in plasma [4]. In a recent longitudinal study on pregnant women with systemic lupus erythematosus and/or antiphospholipid syndrome, several women developing preeclampsia/HELLP syndrome showed dysfunctional mutations of MCP, CFI or CFH, presumably leading to enhanced complement activation, similar to the constellation in atypical HUS [21]. In addition, separate cohorts of 59 [21] or 11 [22] women suffering from severe preeclampsia/HELLP syndrome without underlying autoimmune disease similarly showed an increased prevalence of hypofunctional mutations in MCP, CFI or CFH suggesting that impaired complement regulation may be a relevant pathogenetic factor in severe preeclampsia/HELLP syndrome [21,22] as well as in atypical HUS [3,15,16].

Pregnancy and hereditary TTP

Among the 23 patients of 19 unrelated families with severe constitutional VWF-cleaving protease deficiency published in 2001, 4 of 10 females belonging to two different families had a first acute TTP bout during their first pregnancies whereas their two brothers having the same severe VWF-cleaving protease deficiency were still asymptomatic at ages of 44 and 37 years, respectively [18]. Several case reports of acute and sometimes fatal acute TTP occurring during a (first) pregnancy and leading to the later identification of a severe constitutional ADAMTS13 deficiency caused by compound heterozygous or homozygous *ADAMTS13* mutations [23,24] also suggest that pregnancy may be an important trigger for acute disease in USS. Fujimura et al. reported 9 women from 6 Japanese families with a pregnancy-onset of hereditary TTP [25]. All 9 women became thrombocytopenic during the second or third trimester of all 15 pregnancies and thrombocytopenia was often followed by full-blown acute TTP. Eight babies were stillborn or died soon after birth, the remaining 7 were premature except one whose mother received regular plasma infusions starting in early pregnancy [25]. Of 17 congenital TTP patients diagnosed and treated in the United Kingdom, there were 6 women with a pregnancy-onset (at ages 18–33 years), whereas 5 cases had a neonatal and 6 a childhood (18 months–10 years) disease onset [26]. All patients were reported as severely ADAMTS13 deficient and showed homozygous or compound heterozygous *ADAMTS13* mutations. Of note, 2 pregnancy-onset cases had a homozygous and heterozygous *ADAMTS13* p.R1060W mutation, respectively [26]. Carriers of the ADAMTS13 p.R1060W mutant were shown to display small residual ADAMTS13 activity [27]. Studying 29 hereditary TTP patients from 4 European centers (Milan, United Kingdom, Bergamo, France), Lotta et al. found 4 unrelated USS patients with homozygous p.R1060W mutations, all displaying some residual ADAMTS13 activity (about 5–7% as compared to normal plasma) and all having a disease onset in adulthood, pregnancy being a common trigger of a first TTP attack [27]. A cross-sectional overview of the national registry of the French Reference Center for Thrombotic Microangiopathies from 2000 to 2010 including 592 adulthood-onset severely ADAMTS13 deficient TTP patients (417 of them women, 280 women aged less than 45 years) revealed 42 women with a pregnancy-onset TTP (corresponding to 15% of women of childbearing age) [28]. Ten of these 42 women (24%) had USS syndrome (diagnosed retrospectively in most instances), a proportion much higher than that in adulthood-onset TTP in general (less than 5%). This clearly demonstrates that pregnancy is a common disease-trigger in USS. Eight of the 10 women carried a p.R1060W mutation besides a series of other mutations. Whereas all 10 pregnancy-onset USS patients survived, the outcome for the babies was severely compromised, with 2 miscarriages in the first trimester, 2 intrauterine fetal deaths at 26 and 27 gestational weeks, 2 deaths shortly after birth after premature deliveries at 25 and 30 gestational weeks, and only 4 surviving healthy babies, all born after 33 gestational weeks [28]. Moreover, follow-up of these women with USS with a total of 7 subsequent pregnancies showed successful outcome for mothers and babies with regular FFP infusions during pregnancy but TTP re-