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Thrombotic thrombocytopenic purpura and pregnancy

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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, nr. 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 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 in pregnancy 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, nr.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 \textit{ADAMTS13} gene leading to hereditary TTP (Upshaw-Schulman 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 \textit{Escherichia coli} or shigella and occurs mainly in children 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 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 – 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 recurrence without prophylaxis (28). Von Krogh et al. reported on 15 pregnancies in 8 Norwegian patients with diagnosed USS (29). Two of the 8 women had received a diagnosis of recurrent TTP before their first pregnancies, in 2 others there were probable undiagnosed earlier TTP attacks and 4 had true pregnancy-onset TTP. All women experienced complications during pregnancy and there were only 6 living infants, of which only one was born near full-term with normal birth weight. Prophylactic plasma infusions given in two pregnancies after a diagnosis of USS resulted in living even though severely premature neonates. Four of the 8 unrelated Norwegian USS patients had a homozygous ADAMTS13 c.4143_4144dupA mutation without any residual ADAMTS13 activity, and 2 others were compound heterozygotes with one c.4143_4144dupA allele. Two women carried one p.R1060W allele (29).

Because several of these 8 Norwegian USS women had shown signs and symptoms suggestive of severe preeclampsia/HELLP syndrome during their 15 pregnancies before USS was finally diagnosed and given the high prevalence of hereditary TTP in Central Norway (AS von Krogh, JA Kremer Hovinga
et al. unpublished), the question was raised whether there were any so far undetected USS cases among patients diagnosed with preeclampsia or HELLP syndrome. A systematic case finding study in more than 1400 women discharged from St Olavs Hospital Trondheim University Hospital over a ten year period (2001-2010) with the diagnosis of preeclampsia, eclampsia and an additional diagnosis compatible with TTP was conducted (29). Twenty-nine patients fulfilled the inclusion criteria for ADAMTS13 screening and 17 underwent ADAMTS13 testing. None had severe ADAMTS13 deficiency. This clearly demonstrates that USS is not a frequent cause of the much more common hypertensive pregnancy complications, preeclampsia and HELLP syndrome. However, the rare women having severe hereditary ADAMTS13 deficiency are at a very high risk of severe pregnancy complications often masquerading as severe preeclampsia or HELLP syndrome (29). To make a correct diagnosis of USS is of utmost importance, as regular FFP infusions started in early pregnancy may not only prevent acute TTP attacks but also permit a normal pregnancy outcome (24,25,28,29).

Pregnancy and acquired TTP

Pregnancy may also constitute a risk factor for the onset of acute acquired TTP caused by autoantibody-mediated severe ADAMTS13 deficiency. Analysis of the Oklahoma TTP-HUS registry, a population-based inception cohort of all consecutive patients with suspected TTP for whom PEX was requested, shows that 27 of 376 patients enrolled between 1989 and 2008 were categorized as “pregnant/postpartum” (9). Of the 261 patients included from 1995 – 2008 who had undergone ADAMTS13 activity testing upon admission before starting PEX, 15 were pregnant/postpartum and only 3/15 had a severe (acquired) ADAMTS13 deficiency (9). The cross-sectional analysis of the national registry of the French Reference Center for Thrombotic Microangiopathies covering the time period from 2000 – 2010 overviewed 592 adult-onset TTP patients with a severe ADAMTS13 deficiency and 42 of them had a pregnancy-onset TTP (28). As mentioned above (Pregnancy and hereditary TTP), 10 were USS cases and 32 had severe acquired ADAMTS13 deficiency. Thus, out of 280 women of childbearing age (less than 45 years) with acute TTP, 10 had pregnancy-onset TTP and severe congenital ADAMTS13 deficiency (s. above) and 32 (11.5%) had pregnancy-onset TTP with severe acquired ADAMTS13 deficiency (28). Even though the risk of acute disease manifestation triggered by pregnancy may be especially high for women with USS, pregnancy may also be a (possibly milder) risk factor for acquired TTP. Jiang et al. investigated all ten women from the Oklahoma TTP-HUS registry who became pregnant after having survived a first acute TTP episode with severe acquired ADAMTS13 deficiency (30). During 16 subsequent pregnancies in these 10 women, acute TTP recurred in 2 women, 9 and 29 days post delivery, respectively. Five of the 16 pregnancies (31%) in 3 women were complicated by (severe) preeclampsia, a much higher occurrence than expected. Thirteen of the 16 pregnancies resulted in normal children (30). Jiang and colleagues did an extensive and systematic literature search finding only 6 reports on 10 pregnancies in 8 women having survived a previous acute TTP with severe acquired ADAMTS13 deficiency: There were 6 TTP recurrences in 10 pregnancies and 2 instances of (severe) preeclampsia. This much higher incidence of recurrent acquired TTP in subsequent pregnancies as compared to the Oklahoma Registry data may possibly be ascribed to a publication bias of individual case reports.

Additional data were recently published by Scully and coworkers from the United Kingdom TTP Registry (31) including the pregnancy-onset USS cases previously published (26). Twelve women with acquired TTP occurring in pregnancy are presented. There were 7 live births, 4 intrauterine fetal
deaths and one pregnancy termination. All twelve women survived, 6 women had 8 subsequent pregnancies with one TTP relapse at 6 gestational weeks and one relapse postpartum as well as one IUFD (31). Furthermore Scully et al. report on 18 pregnancies in 12 women having recovered from an acute acquired TTP not related to pregnancy. These women were subjected to regular monitoring of the ADAMTS13 activity, at least once per trimester, if the values remained normal and more frequently, if they decreased. There were no relapses of TTP, in one woman with ADAMTS13 falling below 10%, targeted intervention with short-term PEX seemed to prevent a clinical relapse, and one woman developed acute lupus, needed immunosuppressive therapy but retained normal ADAMTS13 values. Finally, a nested case-control study on 15 pregnant women out of 254 having survived an earlier acquired TTP was performed (Drs. Barbara Ferrari, Flora Peyvandi et al., unpublished). Four cases of gravidic TTP, 5 miscarriages and 6 controls with uncomplicated pregnancies were selected. It was shown that ADAMTS13 levels in the first trimester were severely decreased in cases with recurrent (gravidic) TTP, moderately reduced in those with miscarriage and normal in the controls.

In sum, acquired TTP may probably occur slightly more often in pregnancy as compared to non-pregnant women (28). Acute acquired TTP occurring in pregnancy may pose a high vital risk, especially for the fetus. Having recovered from acute acquired TTP, associated or not with pregnancy, the risk of recurrent TTP during a subsequent pregnancy may not be substantially elevated (30,31), if the generally high recurrence rate of acquired severely ADAMTS13 deficient TTP is taken into account (9). It is very likely, however, that the risk of preeclampsia in subsequent pregnancies is increased and the outcome for the babies may be compromised (30,31). Uncontrolled data suggest that pregnancy monitoring by regular ADAMTS13 measurement may improve the pregnancy outcome (31).

Summary

This short (and necessarily incomplete) review of the complex relation between pregnancy and thrombotic thrombocytopenic purpura shows that for a better understanding of such clinically important questions further prospective studies on unselected consecutive patients are essential. It would be desirable to not only include all consecutive patients upon admission but also to plan a structured and systematic follow-up. To this end, a registry has been set up for the hereditary TTP patients (www.ttpregistry.net; www.clinicaltrials.gov registration number NCT01257269) (32), and similar prospective cohorts for acquired TTP patients will increase our knowledge and improve patient management in the future.

References


