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ADAMTS13, Thrombotic Thrombocytopenic Purpura and Pregnancy

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) which pathophysiology mainly relies on a severe deficiency (either acquired or inherited) of ADAMTS13, the specific von Willebrand factor (VWF) protease. TTP is characterized by a feminine predominance and pregnancy is a precipitating factor for TTP boots. Obstetrical TTP represents at least 20% of all TTP occurring in child-bearing age women.

In this review, an analyze of the English-language literature from 1955 to 2011 found about 350 cases of obstetrical TTP including about 40 case-reports/-series with well documented ADAMTS13 investigation (32 inherited and 17 acquired TTP with severe ADAMTS13 deficiency). In the 32 patients with inherited TTP, the first pregnancy was systematically associated with a TTP boot, mostly occurring during the third trimester; curative plasma therapy (PT) allowed a good maternal outcome although the fetal outcome was almost systematically bad. In the 17 patients with acquired TTP, TTP also occurred mostly *de novo* during the first pregnancy and after 20 weeks gestation; curative PT usually allowed a good maternal outcome and the birth of an alive baby in about 2 cases/3.

The diagnosis of obstetrical TTP is challenging because it mostly occurs in women with no antecedent of TTP and it has no specific clinical/biological symptoms except a severely deficient ADAMTS13. However, because of the severity of the prognosis in the absence of urgent treatment, any thrombocytopenia +/- hemolytic anemia in a pregnant woman with no alternative diagnosis to TMA should be considered as TTP.

The management of an obstetrical TTP boot consists in a blood collection for ADAMTS13 investigation followed by an emergency first-line treatment with PT yielding a maternal response rate of about 80% although the global stillbirth rate is likely to be close to 50%.

The follow-up of women who recovered from an obstetrical TTP boot should include a complete ADAMTS13 investigation to distinguish between the inherited and the acquired form of TTP, in order to both estimate the risk for relapse and optimize prophylaxis indication during subsequent pregnancies. The relapse rate appears to be 100% in inherited TTP and about 20% in acquired TTP. Early prophylactic PT is thus indicated systematically in inherited TTP as it is clearly beneficial for both the mother and the fetus outcomes. In contrast, the optimal management is still debated in subsequent pregnancies of women with acquired TTP whose clinical and biological monitoring should be very careful.

TTP is a very rare complication of pregnancy (about 1/100,000 pregnancies) but it is a life-threatening disease for both the mother and the fetus. Many advances have been performed in the last 10 years in terms of diagnosis and treatment. However, clear guidelines are still needed to optimize the management of subsequent pregnancies, which may be significantly different as a function of the pathophysiology for ADAMTS13 deficiency.

Introduction

Thrombotic Thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) defined by a microangiopathic hemolytic anemia and thrombocytopenia without an alternative cause [1,2]. Clinical manifestations of multivisceral ischemia (neurologic symptoms, renal and cardiac involvement…) are later events. In about half cases, TTP occurs in patients with previously or concomitantly diagnosed other clinical conditions (pregnancy, infections, autoimmune diseases, drugs, hematopoietic stem cell transplantation, cancer, malignant hypertension…) although in the other half of cases, TTP is apparently idiopathic [1,2]. TTP, especially idiopathic forms, is strongly associated with a severe functional deficiency (activity <10%) of ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 repeats, member 13), the specific metalloprotease that cleaves ultralarge (UL) multimers of von Willebrand factor (VWF), the most hemostatically active species of VWF [3]. Thus, the pathophysiology for about 75% of TTP is explained by the accumulation of platelet-hyperadhesive UL-VWF multimers leading to the spontaneous formation of microthrombi within the microcirculation [4,5]. ADAMTS13 severe deficiency may be due either to auto-antibodies to *ADAMTS13* (acquired autoimmune TTP) or to recessively inherited bi-allelic mutations of ADAMTS13 gene (hereditary TTP also named Upshaw-Schulman syndrome (USS) [6]. TTP is a rare disease as its prevalence is 4-10 cases/million people/year. In a large majority of cases, TTP is an adult-onset disease characterized by both a feminine predominance (2-3F/1M), a peak between 30 and

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40 years-old and more than 95% of acquired autoimmune forms. TTP usually occurs by recurrent boots separated by remission phases. The global mortality rate is estimated at 20% in spite of both plasma therapy (PT) which remains the reference treatment, and more recently, the addition of immunomodulating agents like Rituximab [1,2].

TTP occurring in an obstetrical context (pregnancy and post-partum) is an exciting entity as it presents several specificities and challenges. From 1955 to 2011, about 350 cases of obstetrical TTP or TTP/HUS have been counted in the English-language literature including 3 main general reviews [7-9]. These cases were very well clinically documented and most of them were in favor of an acquired form of TMA. However, the large majority of these cases were not investigated for ADAMTS13. In the last 10 years indeed, about 40 obstetrical TTP cases associated with a well documented severe ADAMTS13 deficiency (either acquired or hereditary) have been published in case-reports and case-series studies. This review will describe the miscellaneous aspects of pregnancy-associated TTP including epidemiology, pathophysiology, diagnosis, management, outcome and follow-up. A focus on TTP related to a severe ADAMTS13 deficiency including specificities related to the acquired or inherited feature of TTP will be performed.

Epidemiology and pathophysiology

On an obstetrical point of view, TTP is reported to complicate 1/25 000 to 1/100 000 pregnancies worldwide [7,8,9]. This very broad range may be explained by the heterogeneity of cases reported in the literature consisting either in "TTP/HUS" patients or miscellaneous "TTP" patients whose ADAMTS13 was not systematically investigated. Consequently, one can speculate that TTP associated with a well characterized severe ADAMTS 13 functional deficiency may not occur in more than (1/100 000) pregnancies and thus remains a very rare although life-threatening complication of pregnancy.

On a point of view focused on TMA, North American, European and Japanese registries report that pregnancy-associated TTP represents 10 to 30% of all adult TTP [8,10-15]. As expected, the rates higher than 20% are found in studies considering pregnancy-associated TTP only among child-bearing age women and they are certainly the most relevant. Interestingly, in a large majority of women with a pregnancy-associated TTP, the current TTP boot is the first manifestation of the disease [9].

The strong association between TTP and pregnancy may be explained by several mechanisms. First, it may be a consequence of the feminine predominance of TTP (being itself at least partially linked to the feminine predominance classically observed in any disease with an autoimmune background); furthermore, most women with TTP (between 60 and 70%) are child-bearing age women [1,2]. Second, pregnancy is associated with physiological coagulation changes predisposing to hypercoagulability and particularly to a dysbalance of the VWF/ADAMTS13 system: indeed, during the course of pregnancy, VWF levels in plasma increase progressively to reach levels 2.5-3 fold higher levels at term (with peak values occurring immediately following delivery) while ADAMTS13 decreases progressively (ADAMTS13 activity decreases of about 30% at term when compared to baseline levels before pregnancy) (Supplementary Table 1) [16-23]. The physiological decrease of ADAMTS13 during pregnancy may be due either to a consumption mechanism by its VWF substrate [16], or to a direct effect of hormonal substances on ADAMTS13 metabolism [24]. However, the physiological decrease of ADAMTS13 during normal pregnancy remains well above 10% (only ADAMTS13 values lower than the latter threshold are strongly associated with TTP [1,2,3]. In contrast, in case of severe ADAMTS13 functional deficiency, the physiological significant increase of VWF during the second trimester of gestation may act as a crucial triggering factor for a TTP boot. Indeed, TTP essentially occurs from the second third of pregnancy (second and third trimesters) and sometimes in post-partum [7], while it remains unusual during the first trimester of gestation [25,26].

Specific features of pregnancy-associated TTP at presentation as a function of ADAMTS13 deficiency etiology

Pregnancy-associated TTP in women with hereditary TTP (USS): Data collected from publications between 1976 and 2011 found 32 patients with pregnancy-associated hereditary TTP (USS). In 8 patients, ADAMTS13 was not investigated but both clinical features and familial occurrence supported the diagnosis [7]. In 24 patients [27-36], ADAMTS13 was documented (ADAMTS13 activity lower than 10% in the absence of auto-antibodies) including 15 cases in whom ADAMTS13 genotype could also be characterized (Supplementary Table 2) [30,32,34,36]. Interestingly, all 6 cases reported from the Western World [30,32,36] carried the R1060W mutation (either heterozygous or homozygous), reported to be a marker for adult TTP [32], and they were indeed associated with an adult-onset USS initially recognized with the first pregnancy (Supplementary Table 2). In contrast, the largest series of 9 pregnancy-associated USS reported in Japan by Fujimura et al [34], showed miscellaneous mutations not including the R1060W ADAMTS13 variant: interestingly, 6 of these 9 women had episodes of severe to mild thrombocytopenia during childhood that had been incorrectly diagnosed as ITP while 3 patients had an adult-onset TTP initially recognized with pregnancy. Whatever may be the age of TTP onset, the first pregnancy was complicated by a TTP boot in all Japanese patients (Supplementary Table 2).

About 50 pregnancies could be documented from these 32 patients and showed that in almost 75% of cases, TTP occurred during the 3rd trimester of pregnancy (Supplementary Table 2). Considering the first pregnancy, thanks to curative PT performed in all cases from the 1990's, the maternal outcome consisted in remission without major sequellae; in contrast, the fetal outcome was dramatic consisting in intra-utero fetal death (IUFD) (miscarriage, stillbirth) or infant early death. In very rare cases however, the TTP boot occurring during the first pregnancy led to a curative PT maintained until delivery and allowing the birth of an alive baby (Supplementary Table 2) [27,31,34,35].

Pregnancy-associated TTP in women with acquired autoimmune TTP

Analysis of papers published from 2002 to 2011 shows 17 detailed case-reports [8,31,37-46], of acquired TTP where ADAMTS13 was documented (Supplementary Table 3).

In 12/17 cases (70%), TTP occurred during the second half of pregnancy (after 20 WG) including 7 cases during the 3rd trimester and 2 cases during the post-partum. In 14/17 patients (82%), the TTP boot occurred during the first pregnancy including 11 patients with no antecedent of TTP and 3 patients with either previous TTP boots or autoimmunity [29,31,40,44]. In 3/17 patients (18%), the TTP boot occurred during the second or the third pregnancy including either patients with antecedent of TTP [8,41] or not [42]. At presentation, in all patients, ADAMTS13 activity was lower than 10% and associated with detectable auto-antibodies in a large majority of cases (n=12); the acquired feature of TTP was however attested by later normalization of ADAMTS13 activity in most cases.

In most documented cases, PT was systematically performed as

a curative treatment, sometimes with additional immunomodulators (steroids, cyclosporine, rituximab) allowing a maternal survival. Three patients received platelet infusion and one of them died [42]. The fetal outcome showed 11 alive babies out of 15 documented cases. The good fetal outcome looks correlated to the term of pregnancy where TTP occurs because it is usually associated with late 3rd trimester boots (Supplementary Table 3).

Diagnosis of TTP during pregnancy

As previously described, either in hereditary or acquired ADAMTS13 severe deficiency, pregnancy-associated TTP occurs mostly in women with no antecedent of TMA. Consequently, at presentation, to reach the diagnosis of TTP is challenging and it should proceed in two main steps: first, the recognition of a TMA among the numerous causes of pregnancy-associated thrombocytopenia [46], and second the differential diagnosis with other pregnancy-associated TMA like preeclampsia (PE), the HELLP (Hemolysis Elevated Liver Enzyme Low Platelet count) syndrome or the hemolytic uremic syndrome (HUS) [47].

The most constant sign of TTP is thrombocytopenia [1,2]. During pregnancy, thrombocytopenia occurs commonly (6 to 10% of all pregnant women) and may be due to miscellaneous etiologies, some of which being unique to pregnancy (mainly gestational thrombocytopenia, PE, HELLP syndrome) while others may also occur in a non obstetrical context (mainly primary or secondary immune thrombocytopenia, TTP, HUS, disseminated intravascular coagulation (DIC) [46].

At presentation, the exclusion of gestational thrombocytopenia, secondary immune thrombocytopenia (Evans syndrome) or DIC is usually performed easily thanks to the severity of thrombocytopenia (usually lower than 50 G/L), negative direct Coomb's test and normal coagulation profile, respectively. Primary immune thrombocytopenia may also be excluded because of the presence of mechanical hemolytic anemia (shistocytes on peripheral blood smear) specifically in TTP. In contrast, other TMA syndromes like PE, HELLP and HUS may be very challenging to distinguish from TTP because they may share many overlapping features like the microangiopathic anemia, the multivisceral ischemia leading to end stage organ failure (neurologic, renal, cardiac, digestive involvement) as well as hypertension [7,9,33]. Also, the term of gestation may not be informative as all these TMA syndromes may occur during the second half of pregnancy. Thus, using clinical symptoms and standard biology, a definitive diagnosis of TTP in a pregnant patient with such manifestation may be impossible to achieve prospectively at presentation.

In contrast, retrospective analysis of pregnancy-associated TMA syndromes shows that several features may distinguish TTP from other TMA. First, unlike PE and the HELLP syndrome, termination of pregnancy (fetal extraction) does not induce remission of TTP/HUS [46,47]. Second, HUS is the only TMA to be more frequent during post-partum [2]. Indeed, puerperium and post-partum TTP are more rare than ante-partum TTP and they usually occur following a late 3rd trimester delivery (about 38 WG) and a median 4th day post-partum (range 0-42 days) [9]. Third, several studies led in women with pregnancy-associated TMA showed that a severe ADAMTS13 deficiency (activity <10%) was specific for TTP: indeed, only normal or partially deficient ADAMTS13 levels (usually >20%) have been described in either PE, HELLP syndrome or HUS (Supplementary Table 4) [17,19,21-23]. ADAMTS13 activity measurement remains however unavailable in emergency as a routine assay and it may not be useful to argue for a TTP diagnosis at presentation in emergency. Consequently, as neither clinical features nor biological parameters are able to specifically identify TTP in emergency and because of the severity of the prognosis in the absence of urgent appropriate treatment (PT), any pregnant patient with thrombocytopenia and mechanical hemolytic anemia with no other alternative diagnosis than TMA should be considered to have TTP and treated accordingly [7,9,46,47].

In more rare cases, pregnancy-associated TTP occur in women with TTP antecedents [8,34,41,42]. In these women, the diagnosis of TTP at presentation is less challenging as pregnancy is established to be a precipitating factor for TTP [1,2].

Management and outcome of a TTP boot during pregnancy

Laboratory investigation: Before to initiate any treatment, especially in women whose TTP came *de novo* during pregnancy, venous blood should be collected to measure ADAMTS13-related parameters (ADAMTS13 activity and anti-ADAMTS13 IgG): indeed, even if not available in emergency in most hospitals, ADAMTS13 investigation is useful as it will allow to both confirm the diagnosis of ADAMTS13 severe deficiency and, in most cases, identify anti-ADAMTS13 autoantibodies supporting the diagnosis of acquired autoimmune TTP. In some cases however, anti-ADAMTS13 auto-antibodies may not be detectable during the TTP boot [2]. Thus, only further ADAMTS13 testing in remission including ADAMTS13 activity, anti-ADAMTS13 auto-antibodies and if necessary, ADAMTS13 gene sequencing, will allow the differential diagnosis between acquired and inherited TTP (see infra).

Maternal therapeutic management and outcome: The UK guidelines for the management of TTP in pregnancy (curative treatment) recommend to treat with plasma exchange as non pregnant patients (Grade C, level IV) [48], this treatment yielding a response rate of about 80% similar to that observed globally in TTP [46]. The maternal prognosis of patients with post-partum-onset TTP is similar to that of patients with ante-partum-onset TTP (average mortality rate of 20%) [9]. In contrast, the combination of TTP and PE/HELLP syndrome significantly increases maternal mortality (44%) [9]. The immune background of most TTP also provides a rationale for the use of corticosteroids: however, their benefit in TTP has not been determined through randomized studies and they are associated with an increased risk of complication in pregnant individuals [46]. In contrast to PE or the HELLP syndrome, delivery is recommended only for those women who do not respond to plasma exchange (Grade C, level IV) [48]. Also, in those women who do not correctly respond to this first line treatment, the indication of rituximab, a chimeric monoclonal antibody directed against B-cell surface antigen CD20, may be debated. Rituximab is indicated for some hematologic malignancies and rheumatoid arthritis but it has also been successfully used in other autoimmune diseases like lupus erythematosous, idiopathic thrombocytopenic purpura or TTP [49]. However, a review of the literature focused on the use of rituximab in 231 pregnancies shows that it is able to cross the placenta and may induce hematologic abnormalities or malformation in the neonates [50]. The use of rituximab in a pregnancy-associated TTP has been reported in only one patient [31], the indication was a refractory TTP of the 3rd trimester of pregnancy. No maternal or fetal toxicity were observed.

Fetal outcome: Globally, the stillbirth rate in pregnancy-associated TTP is reported to be about 40% mainly due to IUFD and/or spontaneous abortions and prematurity [9]. In pregnant women with initial TTP, the result of the fetus ultrasonographic evaluation appears dependent on the pregnancy term where the TTP boot occurs: at presentation, most early-term TTP (1st and 2nd trimesters)

are associated with an IUFD [7,9] (Supplementary Tables 2 and 3) although the 3rd trimester perinatal loss is reported to be 17% since the initiation of PT in 1996 [9]. This 17% rate remains global and may be underestimated because calculated from patients with TMA diagnosed as TTP on clinical features but not investigated for ADAMTS13. In rare cases however, 1st and 2nd trimester-TTP were not associated with IUFD but led to delivery of alive babies from 32 WG thanks to continuous PT until post-partum [31,34,35,43]. This observation makes likely the benefit of maternal PT also for the fetus. Indeed, by replacement of ADAMTS13 in both the maternal and fetal circulation, PT may reduce the placental micro-occlusion arterial process observed in rare TTP cases where a placental anatomopathology investigation was performed [33-35,51]. This placental ischemia may indeed be a major pathophysiological mechanism for intrauterine fetal growth retardation and death observed in obstetrical TTP [35]. Interestingly, no case of fetal thrombocytopenia or haemolytic anemia has been described in maternal TTP although the molecular weight of anti-ADAMTS13 IgG allow them to cross the placental barrier. In only one case of maternal autoimmune acquired TTP, blood analysis from the neonate showed a reduced ADAMTS13 activity of 15% together with a detectable anti-ADAMTS13 IgG [43]. However, the neonate's platelet count and hemoglobin level were normal.

Follow up of Women who Recovered from a Pregnancy-Associated TTP

ADAMTS13 investigation to distinguish between acquired and inherited TTP

After recovery from a pregnancy-induced TTP with severe ADAMTS13 deficiency, a first crucial step of the follow-up should focus on making a differential diagnosis between an acquired and an inherited form of the disease. Indeed, to elucidate the cause of ADAMTS13 deficiency (either genetic or autoimmune) is essential for the patient as it conditions the outcome of the disease in terms of risk of relapse (especially during the subsequent pregnancies, see infra) and further both curative and prophylactic treatments (resort to immunomodulators only in case of acquired TTP for example). In addition, in case of USS, a familial inquiry should also be performed (especially in asymptomatic never-child bearing sisters of pregnancy-onset USS patients).

In that regard, combined analysis of ADAMTS13-related parameters during the TTP boot and in remission is necessary to identify the cause of ADAMTS13 severe deficiency. In some cases, the diagnosis of acquired autoimmune TTP may be highly suspected as soon as the TTP boot if ADAMTS13 severe deficiency is associated with anti-ADAMTS13 IgG. In contrast, if anti-ADAMTS13 IgG are not detectable during the TTP boot, the differential diagnosis between acquired and inherited TTP cannot be performed. Thus, ADAMTS13 investigation in remission may be helpful: 1/ if ADAMTS13 activity has become detectable, the diagnosis of acquired TTP may be established; 2/ if ADAMTS13 activity is still undetectable, ADAMTS13 gene sequencing should be performed to confirm the suspicion of USS.

Risk for Relapse and Prophylaxis during Subsequent Pregnancies

Thus, a second crucial concern for the patient is the risk for relapse, especially during subsequent pregnancies and consequently, the methods for an appropriate prophylaxis. Data from the literature suggest that the risk for relapse and the therapeutic management during subsequent pregnancies are quite different as a function of the cause of ADAMTS13 deficiency.

In case of inherited TTP (USS), the risk for relapse is 100% in the subsequent pregnancy in the absence of prophylaxis [8,34]. Analysis of the literature (Supplementary Table 2) clearly shows the benefit of prophylactic PT (either plasma exchange or, rather, plasma infusion) which should now be performed systematically in pregnant women with known USS [31,33-35,36]. In those patients, prophylactic PT should be initiated as soon as the end of the 1st trimester (about 10 WG or maybe before) until early post-partum to prevent TTP boots as well as severe fetal complications due to placental microinfarctions. In some cases, PT was empirically associated with steroids, aspirin [31,33-35],or LMWH [31,36]. Additional studies would be however useful to better clarify the efficacy of such medications in this context. In exceptional cases however, uneventful pregnancies and deliveries were possible with no prophylactic PT but with aspirin [33,34]. Interestingly, no case of allo-antibodies to ADAMTS13 has ever been described in patients with USS in spite of regular prophylactic PT. In addition, pregnant women with USS should have folic acid supplementation because of latent continuous hemolysis. They should also be immunized against hepatitis B [9].

In case of acquired TTP, the accurate risk of recurrence in subsequent pregnancies remains unknown because of limited reports [1,7]. Globally, this risk was reported to be about 20% when considering the Oklahoma registry confronted to a review of the literature [8]. However, this risk is probably dependent on both ADAMTS13 activity just before pregnancy initiation and the time course of ADAMTS13 activity until delivery. In women who clinically recovered from a TTP but who are diagnosed with a severely deficient ADAMTS13 activity at the onset of pregnancy, regular plasma exchange (at least fortnightly) and serial monitoring of ADAMTS13 activity were reported to have a benefit for both the maternal and the baby outcome in a few patients [31]. However, the experience of systematic use of prophylactic PT during the whole pregnancy in women with a previously diagnosed acquired TTP (either pregnancy-induced or not) remains extremely limited. Forthcoming studies should establish whether therapeutic schedules including immunomodulatory drugs similar to the treatment for lupus could be safely used in this context. In contrast, during the puerperium and a few days during the post-partum, prophylactic PT is usually performed to prevent a TTP boot because delivery is highly suspected to be a trigger for TTP relapse [1,2,7]. Also, there is only anecdotal evidence to suggest that the use of anti-platelets agents or steroids may prevent TTP relapse during subsequent pregnancies in women with an antecedent of acquired TTP [48].

Conclusion

This review of the literature clearly shows a better awareness of the "TTP option" among the miscellaneous TMA associated with pregnancy for the last 10 years. The curative management of a *de novo* obstetrical TTP is well established and allows a good maternal outcome in a large majority of cases although the stillbirth rate remains high. Concerning the risk for relapse in subsequent pregnancies, the analysis of the literature emphasizes that inherited and acquired TTP may constitute two distinct entities. Inherited TTP (USS) is associated with a very high risk for relapse and severe fetal complications, and evidence-base medicine clearly supports the benefit of an early prophylactic PT for both the mother and the fetus. In contrast, there is still no clear guideline for prophylaxis during pregnancy in women with an antecedent of acquired TTP probably because: 1/ the risk for relapse is not predictable and not clearly evaluated yet (in that regard, the interest

of *ADAMTS13* time course as a prognosis marker has to be studied); 2/ the benefit of PT may be balanced to the iatrogenic risk of re-boost of the anti-*ADAMTS13* autoantibody; 3/ the alternative therapeutic approaches i.e. steroids, aspirin, LMWH have been only poorly and empirically used. Further studies supported by TTP registries are strongly needed to answer these crucial questions about obstetrical TTP, in order to better define appropriate recommendations validated by multidisciplinary teams involving intensive care unit physicians, hematologists, obstetricians and pediatricians.

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