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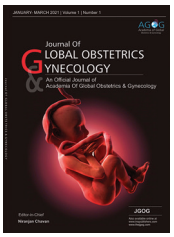
Case Report



# Thrombotic Thrombocytopenic Purpura in Pregnancy – Can't always go by the Book!

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## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy due to a severe deficiency of a disintegrin and metalloproteinase with thrombospondin motifs that can be either congenital or acquired. TTP could be precipitated in pregnancy and lead to fetal and maternal mortality in extreme forms. Hence, suspicion of TTP in pregnancy and simultaneously ruling out other causes of thrombocytopenia in pregnancy, such as HELLP, ITP, other hypertensive disorders of pregnancy, and infective etiology is extremely important for management. This case highlights an unusual presentation of TTP in pregnancy.

**Key words:** TTP, pregnancy, thrombocytopenia, plasmapharesis

## INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare type of thrombotic microangiopathy marked by microangiopathic hemolytic anemia, severe thrombocytopenia, and ischemic damage to organs caused by microvascular platelet-rich thrombi The condition is due to a severe deficiency of the von Willebrand factor (VWF)-cleaving enzyme, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS 13). This deficiency is most often acquired through the development of anti-ADAMTS 13 autoantibodies, but it can also be inherited through biallelic mutations in the ADAMTS 13 gene, resulting in congenital TTP (cTTP). In adults, TTP is usually immune mediated (iTTP), whereas congenital cases are often identified in childhood or during pregnancy. iTTP is more prevalent in women and can be fatal without timely diagnosis and treatment. The standard treatment includes daily plasma exchange with fresh frozen plasma (FFP) and immunosuppression using corticosteroids. Rituximab is a humanized anti-CD20 monoclonal antibody that targets ADAMTS13 autoantibodies is now added even as a first-line treatment in iTTP. In relapsed and refractory cases of TTP, additional treatment with anti-VWF therapy (caplacizumab), cyclosporine A, N-acetylcysteine, bortezomib, cyclophosphamide, vincristine, or splenectomy may be considered. A new treatment, recombinant ADAMTS 13 is currently being researched and holds promise for TTP management. Long-term follow-up is essential to monitor for relapses and to address any chronic complications of the disease.[2]

Women should be adequately counseled against conceiving for at least 12 months after exposure to rituximab[3] as unplanned pregnancies can be associated with neonatal infections, minor congenital anomalies such as club foot and conditions requiring neonatal intensive care unit (NICU) care.[4]

Pregnancy itself is a hypercoagulable state and von Willibrand factor levels increase especially in the 3rd trimester causing increased consumption of ADAMTS 13 which in turn will decrease its activity levels resulting in higher chances of precipitating TTP.[5]

Majority of the cases of pregnancy-associated TTP were due to late-onset cTTP. These women required plasma therapy, including plasma exchange during acute episodes and plasma infusions as a preventive measure in subsequent pregnancies. Presentation of TTP in early pregnancy (before 20 weeks) or late pregnancy (after 30 weeks) was linked to favorable outcomes, while those occurring between 20- and 29-weeks' of gestation were more often associated with severe fetal IUGR and fetal death. A significant number of patients carried the R1060W mutation, and 20% of those with cTTP needed regular ADAMTS 13 replacement therapy following pregnancy which is not yet available in our country determining ADAMTS 13 activity and inhibitor/antibody status is essential for identifying TTP subtypes, managing future pregnancies, and distinguishing TTP from other pregnancy-related TMAs. Studies

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have proven that women with a history of TTP can consider pregnancies with appropriate care.[6]

We should always be cautious, as without treatment, the prognosis for TTP is poor, with a survival rate under 10% with 80% of patients dying within 3 months.[7]

## COMING TO OUR CASE

Our Patient was diagnosed with cTTP in 2020 when incidentally her platelet count was found to be low on routine investigations, she was completely asymptomatic with normal creatinine, normal lactate dehydrogenase (LDH), her peripheral smear showed schistocytes and her ADAMTS 13 activity was below 10%, she underwent 17 cycles of plasma exchange (PLEX) and 4 doses RITUXIMAB therapy before her platelet counts started rising, she was discharged with normal platelet counts.

## PLANNING PREGNANCY

Our patient wanted to plan pregnancy in 2021, as we have mentioned earlier our advice was to wait for at least 1 year after exposure to rituximab as it may cause fetal anomalies and fetal demise, she was also explained the risk and outcomes of her pregnancy, and was advised to do ADAMTS 13 levels at regular intervals and complete blood counts (CBC) more frequently, especially in the third trimester.

She conceived in 2024 by ovulation induction and was on regular follow-up, with ADAMTS 13 activity at more than 40% in the first and second trimesters. She was on hematinics, folic acid, calcium supplements, and micronized progesterone to maintain pregnancy with monthly monitoring of her CBC (which was within normal limits). She had a normal fetal anomaly scan at 20 weeks. However, at 29 weeks of gestation her platelet count started dropping and was 152,000/cumm, as mentioned earlier 29–30 weeks of gestation is the time we have to be most careful about precipitation of TTP hence she was admitted and given FFP transfusions. Her platelet counts increased to 190,000/cumm. Fetal activity was normal, and she was discharged with the advice of more frequent follow-ups and CBCs.

We faced a clinical challenge in assessing ADAMTS 13 activity, as the test for ADAMTS 13 activity is not available at all places and the reporting takes 2 weeks as the samples are usually batched before they are tested! We emphasize that checking ADAMTS 13 levels guides not only the diagnosis but also the decision of timing of therapeutic interventions such as FFP transfusions or PLEX and monitoring to see the response of the treatment and timely discontinuation of plasma exchange.

Our patient was advised to do ADAMTS 13 activity at regular intervals, hence, on a follow-up, when she came at 33 weeks of gestation with ADAMTS 13 activity being zero and platelet count of 100,000/cubic mm we admitted her for FFP transfusions and decided to keep her under observation with a daily CBC.

## DURATION OF HOSPITAL STAY

At 33 weeks of gestation, the patient had no symptoms, her BP was normal, renal function tests and liver function tests were all within normal limits, she had no fever, was conscious, oriented, and cooperative, and her peripheral smear showed no schistocytes, there was a mild drop in hemoglobin from 11.8 g/dL to 10.8 g/dL but her LDH was normal. The only laboratory abnormality, she had was a low platelet count of 100,000/cumm, and additional tests did not fit into the criteria for HELLP or any other thrombocytopenic cause including other hypertensive disorders of pregnancy or any infective etiology.

Her platelet counts kept on decreasing and were 64,000/cumm on day 4 of admission, she was started on steroids after an obstetrician consult for fetal lung maturity and inadvertent benefit for TTP, Despite this her platelet count dropped to 60,000/cumm the next day but she did not exhibit any symptoms and none of the TTP pentad (fever, neurological abnormalities, renal abnormality, thrombocytopenia, MAHA) was present which is unusual. Since no other cause of thrombocytopenia was evident, we took the decision to go ahead with plasma exchange. She underwent 3 cycles of plasma exchange and after the third cycle, her platelet counts doubled, and her repeat ADAMTS 13 activity levels increased to 64%. She was discharged on enoxaparin and advised to continue doing alternate day CBC and ADAMTS 13 activity levels after 4 days

Plasma exchanges have significantly improved outcomes, with survival rates nearing 80% at 6 months. The absence of schistocytes should not delay the initiation of plasma exchanges if clinical and biological signs suggest TTP.[7] However, leaving alone schistocytes, in this case, there was no other sign except for thrombocytopenia.

Preemptively, we decided on an early delivery as she was now 34 weeks pregnant and fetal weight was adequate, uterine artery doppler showed a normal resistance pattern, and sonography showed normal fetal movements. CBCs had rising platelet counts, waiting more would increase the chances of placental infarct which would compromise maternal as well as fetal health.

The patient was stable after discharge, there was no drop in platelets, elective lower segment cesarian section was done at 34 weeks, and a female baby of 1.6 kg was delivered and shifted to NICU in view of prematurity. The baby was stable on RT feeds and nasal $O_2$. The patient was discharged on day 3 with HB of 11 g/dL and platelet count of 148,000/cumm.

Importantly, no transfusions were required in the pre-operative phase and there was no drop in platelet counts. The patient was on antibiotics for 5 days; the advice was to continue Enoxaparin 40 mg SC for 3 weeks postdelivery along with continuing monitoring of CBC and ADAMTS 13 activity.

TTP in pregnancy is a medical emergency for both the affected woman and fetus, with specific disease-related and treatment-related risks. TTP needs a multidisciplinary approach involving expert hematological and obstetric care and laboratory expertise with the availability of ADAMTS 13 activity measuring facilities.

## TO CONCLUDE

We have been studying TTP and TTP in pregnancy and how it manifests, the signs the symptoms the peripheral smear, and treatment options based on them, however in practice when no signs and symptoms are present, we have to trust our intuition and clinical judgment. To do PLEX/FFP transfusions in a 35-year-old primigravida in a hypervolemic state of advanced pregnancy just based on the clinical judgment can be learned only from cases like thus, WE CANNOT ALWAYS GO BY THE BOOK.

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