

# Pregnancy Associated Thrombotic Microangiopathy

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## ABSTRACT

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders characterized by thrombocytopenia, microangiopathic hemolysis and multiorgan dysfunction. The pathological features are vascular damage manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. Pregnancy associated TMA is a life threatening rare disease reported to occur in approximately 1 in 25000 pregnancies, can occur at any stage of pregnancy and can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). The pathogenesis of inherited (Upshaw-Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, a metalloprotease that cleaves vWF and ADAMTS13, respectively. The role of complement factor H (CFH) dysregulation has been reported in cases of pregnancy related HUS. Therapy is specific for each disease entity ranging from plasma exchange (PEX) in TTP/HUS and termination of pregnancy or delivery in HELLP syndrome. The likelihood of survival in patient cases is as high as 80–90% with early diagnosis and aggressive treatment using PEX. The chance of missing the cases is high because of the rarity of these disorders and diagnostic dilemmas. The patients need comprehensive care in close conjunction with physicians and obstetricians. The purpose of this review is to provide a prospective of pregnancy associated TMA and management options available to reduce maternal morbidity and mortality.

**KEY WORDS:** HELLP syndrome, plasma exchange, postpartum, pregnancy, thrombotic microangiopathy

## INTRODUCTION:

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders characterized by thrombocytopenia, microangiopathic hemolysis and multiorgan dysfunction. These include hemolytic uremic syndrome (HUS), thrombotic thrombocytopenia purpura (TTP), and a third rare event, confined to puerperium, termed as postpartum renal failure.<sup>[1]</sup> TTP was first described in 1924 by Moschcowitz. It presents as a pentad of thrombocytopenia, hemolytic anemia, fever, neurological abnormalities and renal dysfunction in a 16 year old girl.<sup>[2]</sup> HUS which is characterized by acute renal failure, microangiopathic

hemolytic anemia and thrombocytopenia, was first described in 1955 by Gasser et al.<sup>[3]</sup> Anemia is severe and microangiopathic in nature, with fragmented red blood cells (schistocytes) in the peripheral smear, high serum lactate dehydrogenase (LDH), circulating free hemoglobin, and reticulocytes.

TMA are diverse group of diseases which could be hereditary or acquired and occur in children and adults. Although diverse the TMA syndromes have defined uniting pathogenesis and clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.<sup>[4]</sup> The distinction between TTP and HUS is under debate. The pathogenesis in TTP is by von Willebrand factor (vWF) regulation by ADAMTS13 and in HUS is by alterations of complement activation and facilitates differential diagnosis.<sup>[5-8]</sup> A clinical distinction based on multi-organ involvement in TTP and renal involvement in HUS is not always apparent. Although many attempts have been made to differentiate TTP and HUS, none of the proposed criteria clearly separates the two syndromes. Even the most widely

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used criteria, the presence of neurological symptoms in TTP and of renal failure in HUS, fail to distinguish TTP from HUS since neurological involvement has been observed in HUS also. The fundamental pathological lesion, thrombotic microangiopathy, is identical in TTP and HUS, and identical aetiological agents and pathogenetic mechanisms have been proposed for both syndromes and thus the term TTP/HUS has been used to describe the patients of thrombotic microangiopathy representing a spectrum of single disease.<sup>[9, 10]</sup> The pathological features are vascular damage manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. Detachment of endothelial cells from the basement membrane due to vessel wall thickening and endothelial swelling with formation of platelet-fibrin hyaline microthrombi are histological features of TMA. The microthrombi occlude arterioles and capillaries.<sup>[11]</sup> In HUS/TTP the kidney shows characteristic vascular changes due to endothelial damage, that is, TMA, which should be clinically and morphologically differentiated from other diseases.<sup>[5]</sup> In a recent review the disorders have been classified as TMA syndromes based on available evidence describing a defined abnormality as hereditary or acquired with the cause and clinical features and initial management.<sup>[12]</sup> However, the disorders have also been described as in figure 1. Although rare pregnancy associated TMA is a serious disorder and has been reported in various stages of pregnancy and has led to significant maternal perinatal morbidity and mortality. Prompt diagnosis and treatment, distinction of this disease entity from other obstetric complications leading to diagnostic dilemmas are key issues laying emphasis in the need to understand the pregnancy associated TMA. This review is an attempt to describe the rare and important disease entity of pregnancy associated thrombotic microangiopathy and management options available to reduce maternal morbidity and mortality.

### Pregnancy Associated Tma:

Pregnancy associated TMA is a life threatening rare disease entity reported to occur in approximately 1 in 25000 pregnancies.<sup>[13]</sup> Pregnancy is known to precipitate the disease both for the first time and also exacerbate the existing disease. During pregnancy, TTP usually presents in the second trimester<sup>[14]</sup>, whereas HUS usually occurs as a single episode, immediately after or some weeks after the delivery.<sup>[15]</sup> A study reported complication by thrombotic microangiopathy in 11 women with 13

pregnancies Between 1972 and 1997. Occurrence of disease before midpregnancy in 23%, in 62% peripartum and in 15% disease several weeks postpartum has been described<sup>[13]</sup>. In a review of the Oklahoma TTP-HUS registry of 335 patients no gender or race predilection has been found associated with pregnancy-associated TMA.<sup>[16]</sup> Another review has been published where 92 English-language publications from 1955 to 2006 of pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in 166 pregnancies were analyzed. The review reported that initial and recurrent TTP presents most often in the second trimester (55.5%) after 1-2 days of signs/symptoms.<sup>[17]</sup>

### Presenting Features of TMAs Associated with Pregnancy:

Thrombotic microangiopathy (TMA) can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). Most of the entities have overlapping presenting features . Typical differentiating features of common pregnancy-related TMAs, such as TTP , HUS pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) are described in Table 1. British guidelines have been formulated in order to provide evidence based guidance for management of TTP and MAHA and clinical features have also been described.<sup>[18]</sup>

Acute renal failure is a serious medical complication during pregnancy and in postpartum period. HELLP syndrome is characterized by haemolysis, elevated liver enzymes, thrombocytopenia, and it is a severe form of preeclampsia. 10-20% of pregnant women with HELLP syndrome have severe form of preeclampsia/ eclampsia and the syndrome can occur in about 1-2/1000 pregnancies. Most cases (70%) occur before delivery between 28-36 weeks gestation. Rest of the 30% cases usually occur within 48 hours post delivery. A case of a 25-year-old woman, at 34 weeks of pregnancy with significant hepatic dysfunction, with deterioration of the renal function, and development of severe coagulopathy has been reported . She had episodes of abdominal pain, urine frequency with feature of urinary tract infection and proteinuria. Diagnosis of AFL of pregnancy was suspected. Liver biopsy was not feasible because of poor clotting, whereas abdominal ultrasound showed no steatosis. Initially she got only supportive therapy, but because of

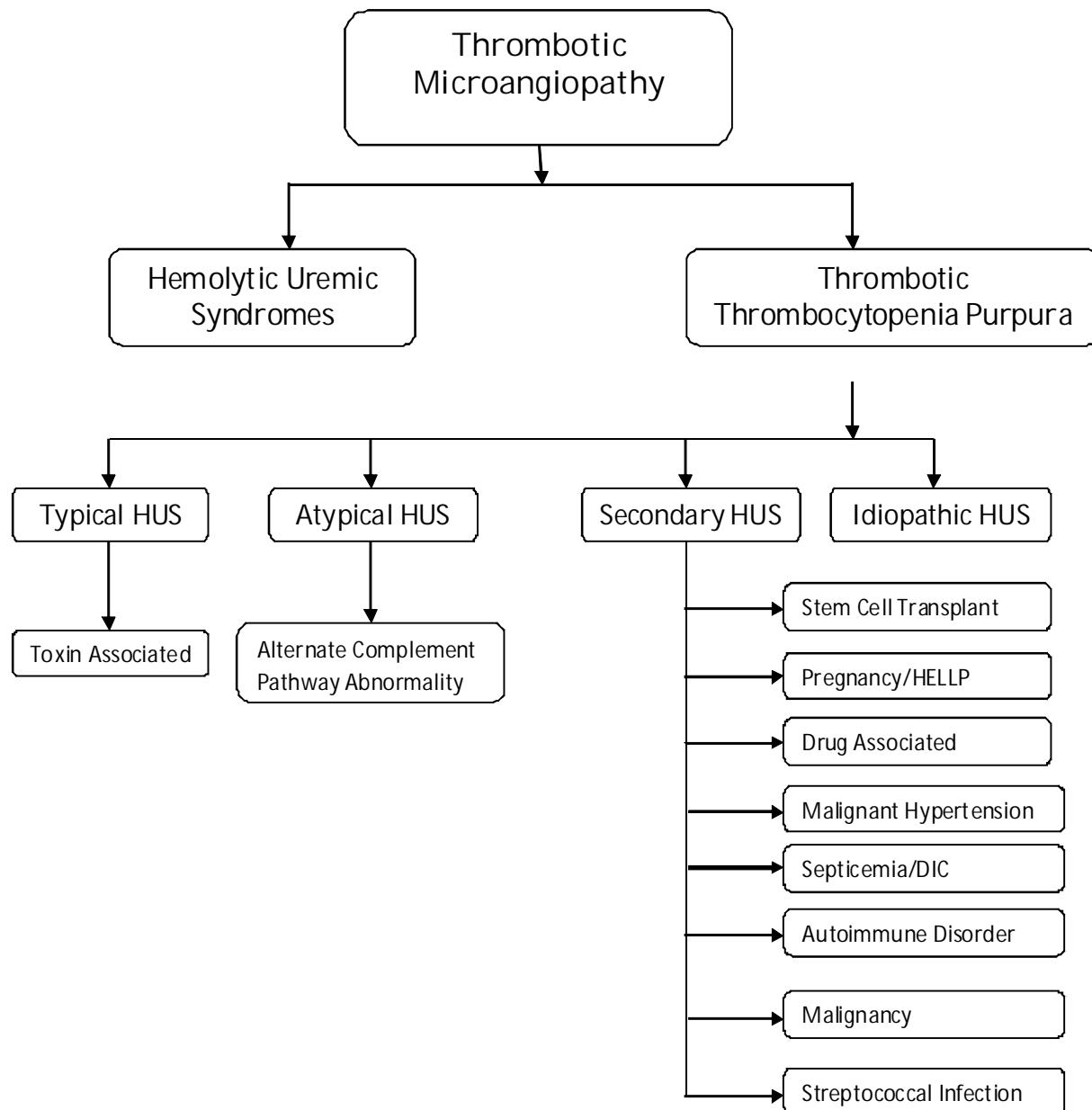
deterioration of her condition she was treated with plasma, platelets and erythrocyte transfusions, leading to correction of the clotting problems.<sup>[19]</sup> Postpartum HUS following abruption placenta has been also reported in a 32 year old woman. Persistent renal failure, microangiopathic hemolytic anemia characterized by fragmented red cells, thrombocytopenia and histopathologic findings of the renal biopsy, supported the diagnosis of HUS.<sup>[20]</sup> Another case has been reported, eight days post delivery, where patient had severe vomiting followed by hematuria, spontaneous bruising, marked pallor, icteric sclera, and lethargy. The 23-year-old parturient had laboratory findings of hemolytic anemia, thrombocytopenia, and acute renal failure. The patient died after a day of onset of symptoms and the diagnosis was confirmed only post-mortem examination.<sup>[21]</sup> Post partum TTP/HUS has been reported in three patients, referred to a tertiary care center, presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure.<sup>[22]</sup>

### **Pathogenesis and Diagnosis of Pregnancy Associated TMA:**

Pregnancy is associated with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity of von Willebrand factor cleaving metalloproteinase.<sup>[23]</sup> Prompt diagnosis on basis of clinical examination, laboratory investigations and clinical cause of the illness and early treatment intervention has led to better prognosis in management of life threatening pregnancy associated TMAs. Evidence has been generated in involvement of ADAMTS13, the regulator of von Willebrand factor in pathogenesis of pregnancy-associated microangiopathy. A series of 15 pregnancies with congenital deficiency of ADAMTS13 activity known as Upshaw-Schulman Syndrome has been reported.<sup>[24]</sup> The pathogenesis of inherited (Upshaw–Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, a metalloprotease that cleaves vWF and ADAMTS13, respectively. This defect alone, however, is not sufficient to result in TTP as individuals with a congenital absence of ADAMTS13 develop TTP only episodically. Additional provocative factors have not been defined. An antibody to ADAMTS 13 is found in many but not all sporadic cases of adult TTP/ HUS. Recent genetic and molecular studies have shed more light on the pathogenesis of thrombotic microangiopathy in atypical HUS, that is, disturbances of various aspects of the complement system.<sup>[5]</sup> Preeclampsia, HELLP

syndrome, HUS/TTP, AFL are multiple displays of pregnancy associated TMA and it is important to correctly identify each in early stages so as to manage the disease.<sup>[25]</sup> Preeclampsia results in TMA as it is hypertension-related disease during pregnancy as a result of systemic small artery spasm , damage and activation of endothelial cells, platelet activation and microthrombi formation.<sup>[26]</sup> HELLP syndrome is also clinically difficult to differentiate from TTP/HUS as it is characterized by hemolysis, elevated liver enzymes and thrombocytopenia. During late pregnancy AFL is a severe complication associated with coagulation dysfunction with acute presentation with gastrointestinal symptoms.<sup>[27]</sup> Postpartum haemorrhage is one of the presenting features complicating pregnancy. Low haemoglobin, hematocrit , high lactic dehydrogenase levels and poor urine output with vaginal bleeding may confuse the clinician to diagnose wrongly. The peripheral smears of patients developing thrombocytopenia post delivery could help in early diagnosis and recognition.<sup>[20]</sup>

Pentology of fever, TTP, microangiopathic hemolytic anemia, central nervous system damage, and kidney damage is hall mark of TTP. Under the shear stress of blood flow , adhesion of platelets and thrombosis occurs due to reduced enzymatic activity of ADAMTS13 which promotes excessive synthesis of the super-large polymer of vWF.<sup>[28,29]</sup> The discovery that the major regulatory protein complement factor H (CFH) has role to play in the pathogenesis of postpartum HUS has been a landmark development [30] . The damage to blood vessel has been implicated due to deficiency of CFH level resulting in continuous activation of complement bypass. In a retrospective analysis assessment of incidence of complement dysregulation in patients presenting with pregnancy associated HUS in a French cohort of adult patients with TMA was done. Complement abnormalities were detected in 18 of the 21 patients and the need for better understanding of complement deregulation in pregnancy with identification of high risk cases for close monitoring and also for developing anti complement targeted agents in the treatment of these disorders. Suspicion of the disease in absence of other identifiable causes , full blood count, peripheral blood smear, lactate dehydrogenase, reticulocytes, clotting, fibrinogen, urea and electrolyte, Troponin I/Troponin T, calcium , pregnancy test, blood group with antibody screen, ADAMTS13, Hepatitis A/B/C, HIV serology , autoantibody screen , amylase, Direct Coombs test , Liver function tests are the investigations to be performed before initiating treatment. Pre-treatment

**Figure1:** Thrombotic Microangiopathies: TTP and HUS.

ADAMTS13 assays are useful to distinguish congenital from acquired TTP and other pregnancy associated TMAs. Early diagnosis and prompt treatment are important for better prognosis. Urine analysis, stool tests and CT scan brain, chest /abdomen / Other investigations can be delayed after treatment has been started.<sup>[18]</sup> A summary of various studies and review articles suggesting pathogenesis, diagnosis and management of TMA are shown in Table 2a and Table 2 b.

#### Treatment Options and Prognosis:

The definitive treatment of pregnancy associated TMA is delivery but is not related to remission. Guidelines have been developed by American Society for apheresis, on the use of therapeutic apheresis in clinical practice on basis of evidence generated and the treatment of TMA is based on the categories I to IV and grading recommendations from 1 A to C and 2A to 2 C.<sup>[31]</sup> If a thrombotic

**Table.1** Differentiating features in pregnancy associated microangiopathies .

	TTP	HUS	HELLP	AFLP	PET
Peripheral Smear (MAHA)	++	+	+	±	+
Coagulopathy	-	-	+	++++	±
Thrombocytopenia	+++	++	++	+	+
Renal Involvement	++	+++	±	++	±
Neurological involvement	+++	±	±	+	++
Liver involvement	±	±	+++	+++	±
Hypertension	±	++	+	+	+++

PET, pre-eclampsia; HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, thrombotic thrombocytopenia purpura; HUS, haemolytic uraemic syndrome; AFLP: acute fatty liver of pregnancy; MAHA, microangiopathic haemolytic anaemia.

microangiopathy (TMA) cannot be fully explained by a non-TTP pregnancy-related TMA, then the diagnosis of TTP must be considered and Plasma exchange (PEX) has been recommended to be started (2B). Evidence has been generated that PEX therapy can help continuation of pregnancy and successful delivery when TTP has been diagnosed in first trimester. Regular ADAMTS13 supplementation has been recommended for mothers with congenital TTP throughout pregnancy and the post-partum period (1A). Close liaison with an obstetrician with a special interest in feto-maternal medicine is required in mothers with TTP(1A). In mothers with acquired TTP, ADAMTS13 activity should be monitored throughout pregnancy to help predict the need for adjuvant therapy and outcome (1B). A comprehensive approach including hemodialysis, antihypertensive treatment, anticoagulation medications, antibiotics, water electrolyte correction, and immune inhibition along with PEX is key to success in the management of TTP/HUS. Earlier the administration of comprehensive treatment better is the prognosis . Plasma exchange helps to remove harmful materials in the plasma. In certain conditions transfusion of fresh frozen plasma can complement the deficiency of platelet aggregation inhibitory factors and relieve the disease.<sup>[25]</sup> Pre-conceptual counseling is advised for subsequent pregnancies and women of child bearing age should be counseled about potential risks of pregnancy and combined oral contraceptive pill (COCOP)<sup>[18]</sup> With aggressive treatment using PEX likelihood of survival in cases of postpartum

hemolytic uraemic syndrome (HUS) is as high as 80-90% as compared to only 10 % in patients not treated with PEX. Patients of postpartum HUS presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure have been reported to have been managed aggressively with PEX in conjunction with hemodialysis with normal renal function tests, increased platelet counts and decreased lactic dehydrogenase levels. Awareness amongst treating physicians, early diagnosis and treatment with PEX have been recommended as the key factors in reducing maternal mortality due to postpartum HUS especially in developing countries.<sup>[22]</sup> Postpartum HUS following abruptio placenta treated with PEX therapy led to recovery of a patient from thrombocytopenia and renal failure. High degree of suspicion to recognize thrombotic microangiopathy in pregnancy with aggressive therapy is recommended.<sup>[20]</sup> PEX is a successful treatment modality in early pregnancy and continuation of pregnancy can be done . However in late pregnancy the effort is for successful delivery in conjunction with PEX. Plasma infusions should be done if the facility for PEX is not instantly available and then patient be referred for PEX especially in resource constraint countries.<sup>[32,33,34]</sup> PEX therapy thus should be initiated on suspicion of TMA in pregnancy and continued till the end of delivery and even postpartum.<sup>[35]</sup> A case of postpartum HUS has been reported where early diagnosis and prompt treatment was done. The option of PEX is still underutilized and such cases under reported due to lack of awareness of diagnosis amongst obstetricians

**Table 2(a):** List of various studies showing pathogenesis, diagnosis and treatment of thrombotic microangiopathies.

SN	Author/ Year	Objective	Results	Conclusion
1	Mokrzycki MH, et al, 1995 <sup>[33]</sup> .	The case report describes rare syndrome of Thrombotic thrombocytopenic purpura (TTP) which presenting with thrombocytopenia, microangiopathic hemolytic anemia, central nervous system symptoms, fever, and renal abnormalities.	This case report describes the earliest presentation of TTP in pregnancy (6 weeks of gestation) we could identify in the literature treated successfully with a prolonged course of plasma exchange.	The diagnosis of TTP in pregnancy bore a poor prognosis and high fetal mortality in early gestation. This study reviewed the differential diagnosis and pathogenesis of TTP and therapeutic options for better prognosis by plasma exchange with description of the case.
2	Dasche, et al, 1998 <sup>[13]</sup> .	To characterize perinatal outcomes and long-term maternal complications from thrombotic microangiopathy manifested during pregnancy, and to review the clinical course and long-term follow-up of pregnant women with this condition over past 25 years.	The study revealed an incidence of one per 25,000 births amongst pregnancies complicated by thrombotic microangiopathy. In ten other pregnancies, disease developed either peripartum (62%) or several weeks postpartum (15%). In three pregnancies (23%), severe and refractory disease developed before mid-pregnancy. The response to treatment was generally prompt. However, disease recurred at least once in 50% of these, two during a subsequent pregnancy and long term sequela occurred.	Thrombotic microangiopathy complicating pregnancy is rare, and with careful evaluation, it should not be confused with atypical preeclampsia. With prompt and aggressive treatment including plasma exchange, the likelihood of immediate survival is high; however, long-term morbidity and mortality are common.
3	Mannucci PM, et al, 2001 <sup>[23]</sup>	In patients with thrombotic thrombocytopenic purpura (TTP) formation of intravascular platelet thrombi has been linked to congenital or immunomediated deficiencies of the metalloprotease that cleaves physiologically von Willebrand factor (vWF) reduce or abolish the degradation of ultralarge vWF multimers. The study evaluated the specificity of low protease plasma levels in the diagnosis of TTP.	The protease was measured in 177 control subjects of different ages, in 26 full-term newborns, and in 69 women during normal pregnancy, using an enzyme immunoassay. The spectrum of acute phase reactions and multiorgan involvement was also studied. Pathologic conditions were also investigated included decompensated liver cirrhosis ( $n=42$ ), chronic uremia ( $n=63$ ), acute inflammatory states ( $n=15$ ), and the preoperative and postoperative states ( $n=24$ ). In healthy individuals protease levels were lower in persons older than 65 than in younger persons and in new borns, and in the last 2 trimesters of pregnancy than in the first. Protease levels were also low in patients with cirrhosis, uremia, and acute inflammation, and they fell in the postoperative period. There was an inverse relation between low protease and high plasma levels of vWF antigen and collagen-binding activity.	The fact that the protease is also low in several physiological and pathologic conditions indicates that low plasma levels of the vWF cleaving protease are not a specific beacon of TTP.
4	Wu VC, et al, 2002 <sup>[22]</sup> .	To describe a case of postpartum hemolytic uremic syndrome (HUS), an unusual complication that presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure after delivery.	A 32-year-old patient (gravida 3, para 1, artificial abortion 1) developed postpartum HUS following abruptio placenta. After cesarean delivery due to abruptio placenta, the patient developed acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia followed by hypertension. The patient recovered and showed recovery from thrombocytopenia. Plasma exchange led to improvement in renal function.	It is important to observe peripheral blood smears in patients with abruptio placenta with thrombocytopenia post delivery and initiate management.
5	Zheng XL, et al, 2004 <sup>[38]</sup>	The study aimed to prospectively analyze ADAMTS13 activity and inhibitor levels in 37 adults with TTP. Therapeutic plasma exchange is an effective empiric treatment for thrombotic thrombocytopenic purpura (TTP), but how therapy affects the level of a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) or inhibitor has not been reported in many patients.	In 16 of 20 patients with idiopathic TTP ADAMTS13 level at presentation was lower than 5% and none of 17 patients with TTP associated with hematopoietic stem cell transplantation, cancer, drugs, or pregnancy the level was lower ( $p<0.0001$ ). Out of the 16 patients with lower ADAMTS13 activity Seven (approximately 44%) had inhibitors. Plasma exchange led to complete clinical remission and a rise in ADAMTS13 level in 8 patients followed serially with ADAMTS13	Though a rare disease with poor outcomes with prompt diagnosis and treatment, lives could be saved with good outcomes clinically in patients diagnosed of Post-partum HUS as shown by the described case.

			activity lower than 5% but no inhibitor at presentation. Neither a rise in ADAMTS13 activity nor a reduction in the inhibitor titer was seen in 4 patients with low ADAMTS13 activity but high-titer inhibitor (> 5 units/mL), 3 had recurrent disease and 1 died. 10 out of 17 patients with AD-AMTS13 activity higher than 25%, died. Mortality rate for idiopathic TTP was 15%, whereas mortality for nonidiopathic TTP was 59% ( $p < .02$ ).	
6	Iannuzzi M, et al , 2006 <sup>[26]</sup> .	To describe a case of a 37-year-old woman admitted after twin delivery by caesarean section and severe renal failure.	Diagnosis of hemolytic-uremic syndrome, on basis of anuria, anemia, and moderate thrombocytopenia was made. Consecutive sessions of plasma exchange, substitution with fresh frozen plasma, hydrocortisone and ACE inhibitors were the treatment modalities. Recovery was evident with disappearance of active haemolysis and improvement of renal function within fifteen days. A genetic study demonstrated the absence of HF1 and MCP mutations.	Though a rare disease with poor outcomes with prompt diagnosis and treatment, lives could be saved with good outcomes clinically in patients diagnosed of Post-partum HUS as shown by the described case.
7	Martin JN, et al, 2008. <sup>[17]</sup>	A study / review of 92 publications of pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in 166 pregnancies from 1955 to 2006.	2-4 times higher aspartate aminotransferase (AST) values and lower total lactate dehydrogenase (LDH) to AST ratios (LDH to AST ratio = 13:1) are exhibited in TTP with preeclampsia (n= 28) compared with TTP without preeclampsia (LDH to AST ratio = 29:1). Initial and recurrent TTP presents most often in the second trimester (55.5%) after 1-2 days of signs/symptoms. Maternal mortality is higher with initial TTP (26% vs 10.7%), especially with concurrent preeclampsia (44.4% vs 21.8%, $p < .02$ ).	For improved care and diagnosis of TTP and HELLP syndrome/ preeclampsia rapid and readily available laboratory testing is needed. Even when plasma therapy has improved maternal mortality initial TTP confounded by preeclampsia/hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome remains a significant maternal-perinatal threat.
8	Shrivastava M, et al , 2009 <sup>[22]</sup> .	The study evaluated response of treatment of patients, diagnosed as postpartum HUS presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure to our managed aggressively with PE in conjunction with hemodialysis.	All patients showed clinical improvement, along with laboratory indicators like normal renal function tests, increased platelet counts and decreased lactic dehydrogenase levels.	Awareness amongst treating physicians, early diagnosis and treatment with PE could be the key factors in reducing maternal mortality due to postpartum HUS in developing countries. The likelihood of survival in cases of postpartum hemolytic uraemic syndrome (HUS) is as high as 80-90% with early diagnosis and aggressive treatment using plasma exchange (PE)
9	Fujimura Y, et al, 2009 <sup>[24]</sup>	A study of Upshaw-Schulman syndrome (USS) a congenital thrombotic thrombocytopenic purpura (TTP) due to mutations in the gene that encodes for ADAMTS13 and clinical correlation.	Nine women from six families of 37 patients with USS (24 females, 13 males) belonging to 32 families were included. Out of the nine patients, six had thrombocytopenia misdiagnosed as idiopathic thrombocytopenic purpura during childhood. Thrombocytopenia occurred during the second-third trimesters in each of their 15 pregnancies, with 16 babies (one twin pregnancy), often followed by TTP. All nine patients included had severely deficient ADAMTS13 activity.	Measuring ADAMTS13 activity in the evaluation of thrombocytopenia during childhood and pregnancy is of importance.
10	Dekker R R, et al , 2011 <sup>[27]</sup> .	A retrospective study to assess maternal death (between 1983 to 2006) and severe maternal morbidity (between 2004 and 2006) from acute fatty liver of pregnancy (AFLP) in the Netherlands.	0.13 MMR per 100,000 live births (95% CI 0.05-0.29) and maternal morbidity 3.2 per 100,000 deliveries (95% CI 1.8-5.7) from AFLP were reported.	Severe maternal morbidity and in some cases mortality are outcomes of AFLP a rare condition and treatment be initiated once diagnosed or patients should be referred to a tertiary care hospital for treatment.

10	Dekker R R, et al , 2011 <sup>[27]</sup> .	A retrospective study to assess maternal death (between 1983 to 2006) and severe maternal morbidity (between 2004 and 2006) from acute fatty liver of pregnancy (AFLP) in the Netherlands.	0.13 MMR per 100,000 live births (95% CI 0.05-0.29) and maternal morbidity 3.2 per 100,000 deliveries (95% CI 1.8-5.7) from AFLP were reported.	Severe maternal morbidity and in some cases mortality are outcomes of AFLP a rare condition and treatment be initiated once diagnosed or patients should be referred to a tertiary care hospital for treatment.
11	Delmas Y, et al , 2013 <sup>[39]</sup> .	To report a case of atypical haemolytic-uraemic syndrome (aHUS) a disease of uncontrolled complement alternative pathway activation	A week after childbirth 26 year old woman was admitted for aHUS. A 26-year-old woman was admitted 1 week after her first childbirth for aHUS with creatinine 6.2 mg/dL (550 µmol/L), haemoglobin 3.6 g/dL (36 g/L), lactate dehydrogenase 2155 U/L (upper normal limit 248), 9% schizocytes and platelet count $49 \times 10^3/\mu\text{L}$ ( $49 \times 10^9/\text{L}$ ). Daily PEX was started with 60 mL/kg fresh frozen plasma substitution. On Day 3 post-admission owing to family history and suspected genetic background the patient was switched to, 900 mg eculizumab.	Eculizumab is an effective therapeutic option in aHUS which induces terminal complement blockade (TCB), and has been approved by the US Food and Drug Administration and the European Commission.
12	Mu J, et al, 2015 <sup>[21]</sup> .	To report a rare case of unexpected death due Postpartum hemolytic uremic syndrome (PHUS), a severe thrombotic microangiopathy (TMA) that is clinically characterized by hemolytic anemia, renal dysfunction, and low platelet levels after childbirth.	After an uneventful pregnancy and delivery by cesarean section a 23-year-old developed severe nausea and vomiting followed by hematuria, spontaneous bruising, marked pallor, icteric sclera, and lethargy. After 29h of onset of symptoms the patient died. The patient had hemolytic anemia, thrombocytopenia, and acute renal failure. PHUS was confirmed on postmortem examination.	Early diagnosis and awareness about disease entity amongst obstetricians is of importance PHUS. Renal biopsy is suggested as histopathological finding of endothelial cell injury in renal micro vessels is characteristic feature of PHUS and speed and accuracy of diagnosis are crucial to optimize maternal outcomes.

and initiation of prompt treatment.<sup>[36]</sup>

A study demonstrated importance of prenatal management , differential diagnosis of pregnancy associated TMAs , acquired and congenital TTP . Prophylactic plasma infusions, aspirin and low molecular weight heparin have been effective in congenital TTP and unlike pregnancy associated TTP/HUS, PEX is not necessary therapy.<sup>[37]</sup> Corticosteroids have to be administered carefully preferably only in cases with severe ADAMTS13 deficiency. Monoclonal anti-CD20 antibody, rituximab has emerged as a promising new therapeutic approach in patients with severe refractory idiopathic TTP. Contrary to TTP where pregnancy can be continued with patients on regular PEX therapy, termination of pregnancy is the only treatment option in HELLP syndrome. Platelet Transfusions are contraindicated in TTP /HUS while in HELLP , preeclampsia the platelet transfusions can be given to achieve the desirable preoperative counts . However a sudden rise in platelet counts warrants thrombosis exacerbating the disease and low dose aspirin is indicated in such cases.<sup>[19]</sup>

ADAMTS 13 activity and inhibitor levels can help monitor the disease in terms of outcome and

treatment tailoring in TTP patients. In a prospective study a mortality rate of 15% for idiopathic TTP and 59% for non idiopathic TTP was reported along with good predictive value of these assays. [38] Eculizumab treatment through induction of terminal complement blockade has been used along with daily PEX therapy with success in post partum atypical HUS.<sup>[39]</sup>

## CONCLUSION:

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders and pregnancy associated TMAs such TTP, HUS , HELLP syndrome, or AFL are life threatening serious conditions presenting with diagnostic difficulties and treatment dilemmas leading to high maternal mortality and morbidity . Though rare, the spectrum of disorders has different etiopathogenesis and requires immediate treatment on case to case basis and based on the diagnosis, the therapy is different for different disease entity. With awareness about the disease amongst treating midwives, physicians and obstetricians, high index of suspicion, early recognition and aggressive therapy with PEX, plasma infusion and termination of pregnancy or successful

**Table 2(b):** List of review articles showing pathogenesis, diagnosis and treatment of thrombotic microangiopathies.

S N	Author/year	Observation	Conclusion
1.	Ruggenenti et al, 2001 [6].	To review the disease pathogenesis clinical symptoms and outcomes of HUS and TTP.	Depending on whether renal or brain lesions prevail, both are pathologically indistinguishable however, clinically different entities. TMA is associated with injury to endothelial cell, loss of physiological thrombo resistance, leukocyte adhesion to damaged endothelium, complement consumption, abnormal von Willebrand factor release and fragmentation, and increased vascular shear stress. Shiga toxin-associated HUS reveals good outcomes in childhood, whereas, atypical and familial form HUS and TTP end up with renal and neurological complications.
2.	Fakhouri F, 2007 [8].	To review the advancement in identification of disease symptoms of HUS, TTP, TMA and to identify research gap.	The new advances in the identification of pathogenic features- deficiency of the metalloprotease ADAMTS13 in TTP and association of mutated complement proteins with atypical HUS has helped the clinicians to distinguish between the two diseases. The research gap was identified as questions needed to be answered: is it important to patient management that HUS be distinguished from TTP? By discussing what is known about the pathogenesis, clinical features and treatment of these two conditions we address this question, and propose a new nomenclature for TMA.
3	Desch K 2007 [11].	To review the recent progress and shared mechanisms of HUS and TTP.	Both the disorders were considered to be same disease shared pathophysiological processes possessing distinct clinical and pathologic entities.
4	Benz K et al, 2009 [5].	To review the epidemiological pathogenesis and typical morphological aspects of all the three types of membranoproliferative glomerulonephritis (MPGN), HUS and TTP is on light microscopical, immunohistological or immunofluorescence and electron microscopical level.	Dysregulation of the complement system, distinct molecular defects in C3 factor H, the major regulatory protein of the alternative pathway of complement activation and deficiency of von Willebrand factor (VWF)- cleaving protease i.e. ADAMTS13 were highlighted.
5	James George, 2014	To review the knowledge of disease pathogenesis, management, and outcomes of primary TMA syndromes that has accelerated in recent years.	The recent advancement in understanding of primary TMA has enhanced the diagnosis and management of the and have created opportunities for specific treatments thereby reducing the mortality and also answering previously unrecognized long term morbidities.

delivery, depending upon pregnancy associated TMA, can reduce mortality and morbidity in pregnant women to a great extent .

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