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Microangiopathic Hemolytic Anemia in Pregnancy

Lucy Neave [a], Marie Scully [b,*]

[a] Department of Haematology, UCLH, London, UK
[b] Department of Haematology, UCLH, Cardiometabolic Programme NIHR UCLH/UCL BRC, London, UK

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ABSTRACT

Thrombotic microangiopathies (TMAs) are associated with microangiopathic hemolytic anemia and thrombocytopenia, resulting in microvascular thrombosis and end-organ damage. In pregnancy, this may be the result of pregnancy-related TMAs such as preeclampsia; hemolysis, elevated liver enzymes, and low platelets; or pregnancy-associated TMAs, specifically thrombotic thrombocytopenic purpura (TTP) or complement-mediated hemolytic uremic syndrome (CM HUS). TTP and CM HUS are rare disorders, and their diagnosis may be missed, no less because features at presentation may be misdiagnosed as a pregnancy-related TMA, such as hypertension, proteinuria, fetal growth restriction, or in utero fetal death. The mainstay of treatment for pregnancy-associated TMAs is plasma exchange. Presentation is likely in the third trimester for TTP and postpartum for CM HUS. However, both conditions can present in any trimester, unlike pregnancy-related TMAs which rarely present before the second trimester, commonly in the third trimester. Delivery is the mainstay of treatment for pregnancy-related TMAs. More recently, it has become clear that pregnancy may be a trigger for late-onset congenital TTP, as well as immune-mediated TTP, diagnosed by ADAMTS13 analysis. Complement inhibitor therapy is the treatment of choice for CM HUS cases. However, their diagnosis is by exclusion, but complement inhibitor therapy reduces the risk of end-stage renal failure. Subsequent pregnancies can be supported for TTP and CM HUS.

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Microangiopathic hemolytic anemia [1] (MAHA) is a nonimmune intravascular hemolysis that is characterized by the presence of fragmented red cells (schistocytes) on the peripheral blood film. MAHA occurs in conjunction with microvascular thrombosis and consumptive thrombocytopenia in the clinically diverse thrombotic microangiopathies (TMAs). Single or multiple end-organ damage can result, leading to a variety of clinical signs and symptoms in addition to MAHA and thrombocytopenia [2].

There are a variety of causes of TMA in pregnancy. These can be classified, as shown in Table 1, into those which occur only in pregnancy (such as preeclampsia) and those which also occur in the nonpregnant

* Corresponding author at: Prof Marie Scully, Department of Haematology, UCLH, 250 Euston Rd, London, NW1 2PG, UK.
E-mail address: m.scully@ucl.ac.uk (M. Scully).

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Table 1
Causes of pregnancy-associated TMA

Pregnancy-associated TMA	TMA presenting in pregnancy
Hypertension of pregnancy	Lupus nephritis/SLE
Preeclampsia	Vasculitis
	APLS
HELLP syndrome	Sepsis
AFLP	Severe hemorrhage
Placental abruption	TTP
Undefined TMA	CM HUS

Review of TMAs inherent to pregnancy vs those precipitated by pregnancy and result in anemia and thrombocytopenia.
AFLP, acute fatty liver of pregnancy; APLS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

state but for which pregnancy can be a trigger [3]. Although there is overlap clinically, specific management varies significantly.

This review will focus on thrombotic thrombocytopenic purpura (TTP) and complement-mediated hemolytic uremic syndrome (CM HUS) in pregnancy. Pregnancy is a well-established trigger for both of these rare conditions. The incidence of TTP and CM HUS in pregnancy has previously been cited as 1 in 25,000 [4]. However, diagnoses have increased in recent years, presumably because of increased awareness and better diagnostics, and the true incidence is likely to be higher. Diagnosis in pregnancy is complicated by significant clinical overlap with the more common TMAs of pregnancy, specifically preeclampsia/hemolysis, elevated liver enzymes, and low platelets (HELLP). However, without timely diagnosis and appropriate management, there can be serious consequences for the patient and the pregnancy. It is important therefore to maximize awareness among clinicians and to maintain a high index of suspicion diagnostically.

TTP in the General Adult Population

TTP results from a severe deficiency of ADAMTS13, a metalloprotease enzyme required for the cleavage of von Willebrand factor (VWF) [5,6]. Reduced ADAMTS13 activity leads to incomplete cleavage of ultra large multimers of VWF released from the endothelium. Spontaneous platelet aggregation then occurs in high shear conditions, such as within the microvasculature of certain organs (Fig 1). Microthrombus formation, MAHA with thrombocytopenia (usually severe), and multisystem end-organ damage then ensue. The most commonly affected organs are the brain, heart, and kidneys.

In the population at large, ADAMTS13 deficiency most commonly results from inactivation or clearance by an autoantibody. This is described as acquired or immune-mediated TTP. The diagnosis of immune TTP is confirmed by demonstrating an ADAMTS13 activity less than 10%, in the presence of IgG antibodies to ADAMTS13 [2]. An ADAMTS13 activity <10% but with a negative antibody assay points instead to the rarer diagnosis of congenital TTP. Here the deficiency of ADAMTS13 is inherited, and the diagnosis is confirmed by identification of pathogenic mutations in the ADAMTS13 gene.

The incidence of immune TTP is approximately 6 per million in the United Kingdom [7], which includes de novo and relapsed acute episodes. Congenital TTP is significantly rarer, with an estimated prevalence of less than 1 per million of the population. Despite the rarity, awareness among clinicians and timely appropriate management are vital, as untreated TTP is associated with a high early mortality.

The mainstay of treatment for TTP currently is plasma therapy. For confirmed congenital TTP, plasma infusions are sufficient to replete ADAMTS13 levels. For immune TTP, plasma exchange combined with immunosuppression (usually in the form of corticosteroids and anti-CD20 therapy) removes the causative autoantibody and also repletes ADAMTS13.

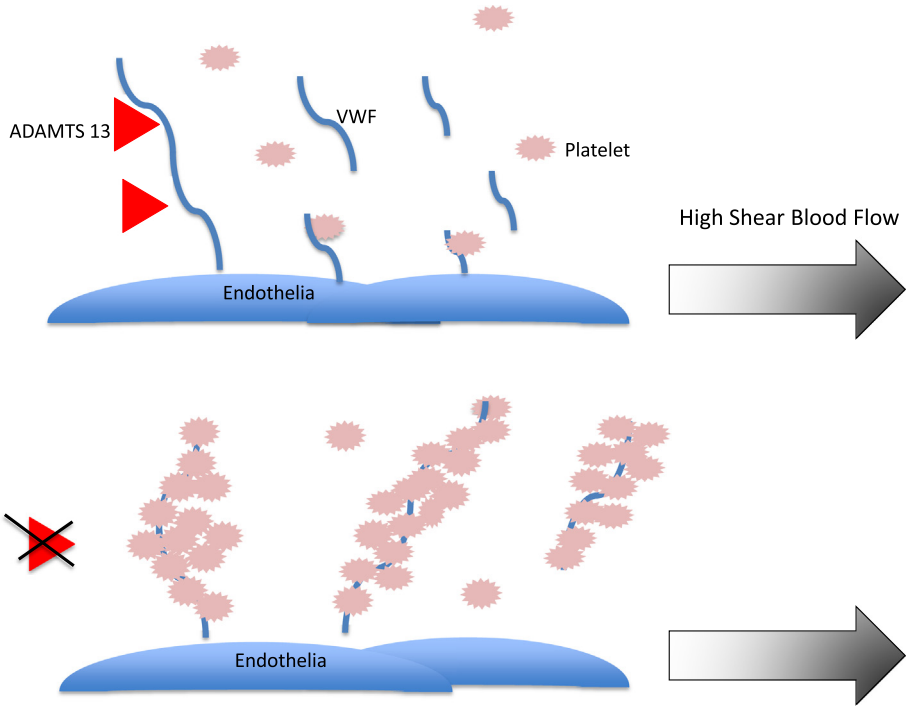

Fig 1. Pathophysiology of TTP. Under high sheer blood flow, VWF unravels and is cleaved into smaller multimers via the action of metalloprotease. The resulting smaller multimers bind platelets, important in normal hemostasis. In TTP, either because of an inherited deficiency or the result of antibodies to ADAMTS13, VWF multimers are not cleaved. This results in increased platelet binding and release of microthrombi, resulting in organ damage.

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