How we manage thrombotic microangiopathies in pregnancy

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Summary

Differentiation between the thrombotic microangiopathies (TMAs) that present in pregnancy may be clinically challenging, but is critical to ensure correct management because of the impact on fetal and maternal outcomes. Thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS) are medical/obstetric emergencies that require specialist input, both at the time of acute diagnosis and follow-up in subsequent pregnancies. Features of preeclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) may precede or be present in evolving TTP or aHUS. Clinicians need to be mindful of how a presumed diagnosis of a specific TMA in pregnancy may evolve and be prepared to frequently reassess signs and symptoms and revise the diagnosis and management plan accordingly.

Keywords: thrombotic microangiopathies, pregnancy.

Thrombotic microangiopathies represent a spectrum of disorders characterized by thrombosis, primarily affecting small arterial vessels. Thrombocytopenia is usually present and review of the blood film confirms the microangiopathic process, with red cell fragmentation and, often, polychromasia. Considerable developments have been made in the field of TMAs in recent years and new genetic and autoimmune causes have been identified, particularly in haemolytic uraemic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) (Fujikawa et al, 2001; Levy et al, 2001; Taylor et al, 2010). These are acute conditions with significant morbidity and mortality.

However, in pregnancy, differentiation from other TMAs, some of which are specific to this period, may be very difficult. The primary diagnostic challenge is the differentiation from acute fatty liver of pregnancy (AFLP), preeclampsia (Pre-eclamptic toxaemia, PET) or eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets). Features of PET and HELLP may be the initial presentation prior to

the clinical picture evolving and subsequent diagnosis of TTP or aHUS (Scully et al, 2014), thus further complicating the diagnostic process. Antiphospholipid syndrome (APS), systemic lupus erythematosus and disseminated intravascular coagulation (DIC) may also present with a microangiopathic haemolytic anaemia (MAHA) picture in association with thrombocytopenia, but will not be dealt with in this review.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is an acute life-threatening disorder associated with thrombocytopenia, MAHA and symptoms related to microvascular thrombosis. Clinically, in addition to a low platelet count (below 150×10^9/l, but more usually less than 50×10^9/l), patients are anaemic secondary to fragmentation-haemolysis with an associated acute consumption of folate. Corresponding blood film changes include polychromasia, anaemia, thrombocytopenia and fragmented red blood cells. Bilirubin is often raised, but the direct antiglobulin test is negative and the coagulation screen is normal. Lactate dehydrogenase (LDH) is increased, often out of proportion to the degree of haemolysis, due to associated tissue ischemia (Scully et al, 2012).

TTP is the result of a deficiency of the enzyme ADAMTS13, 'a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13' (Fujikawa et al, 2001), required to cleave secreted von Willebrand factor (VWF). An inherited deficiency or acquired reduction of ADAMTS13 due to IgG autoantibodies to ADAMTS13, leads to persistence of ultralarge VWF multimers resulting in platelet aggregation and microvascular thrombosis. Thrombi in TTP are uniquely formed of platelets and VWF.

Pregnancy is an important precipitant of acute TTP, accounting for approximately 5–10% of all cases of TTP in women (Scully et al, 2008). TTP is more common in women and at least half of all cases of TTP occur in women of childbearing age.

Haemostatic changes of normal pregnancy – Factor VIII, von Willebrand Factor and ADAMTS13

Normal pregnancy is associated with marked haemostatic changes, which are hormonally mediated and provide a pro-

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tective effect against haemorrhage at delivery, and therefore lead to a hypercoagulable state. Factor VIII and von Willebrand Factor (VWF) increase in parallel in the first half of pregnancy; thereafter, the increase in VWF is greater throughout the remainder of pregnancy, returning to normal levels over the 6 weeks' postpartum. There is a reciprocal relationship between VWF and ADAMTS13. In normal women, there is a reduction in ADAMTS13 activity in the second and third trimesters of pregnancy (Mannucci et al, 2001). This reduction in ADAMTS13 activity after the first trimester continues until the end of the post-natal period, when the levels return to pre-pregnancy levels. There is a significant correlation between higher VWF antigen levels and lower ADAMTS13 activity (Sanchez-Luceros et al, 2004). The reason for the decrease in ADAMTS13 during pregnancy is thought to be two-fold. ADAMTS13 levels decrease, due to consumption, with excess substrate VWF but, in addition, a hormonal influence, probably oestrogen, lowers ADAMTS13 levels (Mannucci et al, 2001). Therefore, the persistent increase in VWF may 'consume' an already severely reduced ADAMTS13 level. This is particularly demonstrated in women with congenital TTP where requirements for plasma increase from the second trimester to maintain a normal platelet count, and it is from the second trimester that the greatest risk of complications are noted in untreated cases. The hormonal and hypercoagulable milieu of pregnancy extends into the postpartum period and the sustained effects of these triggers explain why pregnancy-associated TTP can develop throughout this period.

Women presenting with acute TTP during pregnancy

Women presenting with TTP during pregnancy fall into two groups: those with acquired, antibody-mediated TTP and those with late onset congenital TTP presenting de novo in pregnancy. Diagnosis of congenital TTP is established by ADAMTS13 activity <5% with no evidence of an inhibitor or anti-ADAMTS13 IgG, and confirmed by mutational analysis of the ADAMTS13 gene, revealing a homozygous or compound heterozygous abnormality. In women with acquired TTP, there is evidence of an inhibitor/anti-ADAMTS13 IgG antibodies (Tsai & Lian, 1998). With the availability of ADAMTS13 activity measurement and detection of inhibitors to ADAMTS13 (or more specifically IgG antibodies), it is possible to distinguish TTP from other pregnancy-associated TMAs, specifically if ADAMTS13 activity is <10% and/or if IgG antibodies are present.

It is increasingly recognized that late-onset congenital TTP may be unmasked by pregnancy. From the UK TTP Registry, 66% of women (23/35 cases) presenting with acute TTP for the first time in pregnancy or the immediate postpartum period had late-onset, previously undiagnosed, congenital disease. In these cases, pregnancy was the initial and often the only precipitant of TTP (Scully et al, 2014). Similarly,

the French Reference Centre for Thrombotic Microangiopathies found 10/42 cases with pregnancy-onset TTP to have congenital disease – a much higher proportion than that in adult-onset TTP in general, and mostly related to a cluster of ADAMTS13 variants (Moatti-Cohen et al, 2012). The incidence of congenital TTP is probably underestimated and it has been suggested that congenital TTP cases may constitute up to 5% of cases of thrombocytopenia in pregnancy. In a cohort of women presenting with thrombocytopenia (platelet count <75 × 10^9/l) during pregnancy, even with normalization post-delivery, 5% women had ADAMTS13 activity <10%, with subsequent confirmed congenital TTP (Delmas et al, 2015).

An important feature of late onset congenital TTP is that anaemia may not be considered pathological and the thrombocytopenia may be at levels often seen in gestational or immune thrombocytopenia. Further questioning may reveal severe headaches or migraines, often specific to pregnancy, depression or previous pregnancies associated with fetal loss or severe growth retardation. The platelet count may drop precipitously and features consistent with PET may be present. As a rule, a platelet count <50 × 10^9/l warrants a repeat blood film, LDH and if suggestive, an ADAMTS13 activity level. It must be remembered, that the LDH reference range alters with pregnancy and is more than twice the non-pregnant level in the third trimester.

Clinical presentation of congenital and acquired TTP can be similar. The risk appears greatest in the second trimester associated with intrauterine fetal death (IUFD), but a greater proportion present in the third trimester or postpartum (Scully et al, 2014). More 'typical' TTP features, such as neurological symptoms, raised troponin levels and renal impairment, may occur in either TTP type.

Atypical haemolytic uremic syndrome

There are a number of causes of acute kidney injury in pregnancy and renal involvement may be seen with other pregnancy-mediated microangiopathies, such as PET. Atypical haemolytic uremic syndrome (aHUS) is rare and, in the majority of cases associated with pregnancy, occurs postpartum. There may be a family history of aHUS. However, the outcome is severe with two-thirds of cases in end-stage renal failure within 1 month. As with TTP, there is an increased risk of fetal loss and PET in patients with aHUS (Fakhouri et al, 2012).

Like all TMAs, it is a disease of microvascular endothelial activation, cell injury, and thrombosis, but aHUS is associated with complement deregulation, leading to an increase in activity in the alternative complement pathway (Taylor et al, 2010), with a predilection for the kidneys, for reasons that remain unclear. Typically, the presentation in aHUS is of MAHA, thrombocytopenia and renal impairment. The primary pathology is in the renal arterioles and interlobular arteries, with widespread endothelial cell swelling, leading to

exposure of the underlying basement membrane. The vessel lumens are occluded by red cells and platelet fibrin thrombi and the pre-glomerular pathology of aHUS may help distinguish it from Shiga toxin-producing Escherichia coli (STEC) HUS and TTP.

There is excess complement activation, particularly along glomeruli, arteriolar endothelium, and basement membranes. Mutations in complement genes controlling the alternative complement pathway, such as *CFH* (Factor H), *CFI* (Factor I) or *CD46* (also termed MCP) (Caprioli *et al*, 2006), or complement-activating genes, Factor B or C3 are found in 50–60% of cases (Taylor *et al*, 2010). Single nucleotide polymorphisms and autoantibodies, such as to Factor H, have also been found to play a role. *CFH* mutations are most common, accounting for 15–30% of all cases of aHUS (Taylor *et al*, 2010). *CD46* mutations account for 10–13% of aHUS patients, the majority being heterozygous and these patients have a milder clinical course (Richards *et al*, 2007). In aHUS, ADAMTS13 activity may be normal or moderately reduced but with no inhibitor/antibodies to ADAMTS13 (Hassan *et al*, 2015).

Acute fatty liver of pregnancy

This is a rare life-threatening illness (incidence approximately 5 per 100 000 deliveries) associated with significant maternal and perinatal mortality (Knight, 2008). It typically presents in the third trimester, although it has been rarely described in the first and second trimesters. Acute fatty liver of pregnancy (AFLP) usually affects primigravid women, although there are reports of recurrence in subsequent pregnancies. Presentation is non-specific with headache, fatigue, nausea, vomiting (70%), and right upper quadrant or epigastric pain (50%). Progression of the illness is often rapid and, early in the presentation, there may be gastrointestinal haemorrhage, coagulation abnormalities, acute kidney injury, infection, pancreatitis, and hypoglycaemia. Later in the disease process, liver failure and encephalopathy may occur (Hay, 2008). Diagnosis may be aided by using the Swansea criteria (Kingham, 2011) (Table I). However, it is recognized that many women may also fulfil the criteria for HELLP and therefore the diagnosis may be challenging, but HELLP is more likely to occur in association with hypertension, whereas AFLP is not (Minakami *et al*, 2014). Including antithrombin deficiency (<65%) in the diagnostic criteria can help to differentiate HELLP from AFLP (Minakami *et al*, 2014). The risk of both HELLP and AFLP are increased with twin or triplet pregnancies (Malone *et al*, 1998).

Diagnosis is suggested by the clinical features and may be confirmed by liver biopsy, which reveals characteristic microvesicular steatosis. However, because of the acute presentation and coagulopathy, it is usually not possible to undertake liver biopsy, and the diagnosis is made by a combination of clinical and biochemical features. There may be a raised white cell count and thrombocytopenia with nor-

Table I. Swansea criteria for the diagnosis of AFLP.

Six or more of the following features in the absence of another explanation:
- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin (>14 μmol)
- Hypoglycaemia (<4 mmol)
- Elevated urate (>340 μmol)
- Leucocytosis (>11 × 10^9/l)
- Ascites or bright liver on ultrasound scan
- Elevated transaminases (AST or ALT >42 iu/l)
- Elevated ammonia (>47 μmol)
- Renal impairment (creatinine>150 μmol)
- Coagulopathy (PT > 14 s or APTT > 34 s)
- Microvesicular steatosis on liver biopsy

AST, aspartate transaminase; ALT, alanine transaminase; PT, prothrombin time, APTT, activated partial thromboplastin time.

moblasts on the blood film. DIC [with prolonged prothrombin time (PT), activated partial thromboplastin time (APTT) and reduced fibrinogen] is evident. Urea, creatinine and uric acid levels are raised; there are elevated ammonia levels and hypoglycaemia. Serum aminotransferases are markedly raised and alkaline phosphatase is three to four times the normal level (although this is raised in normal pregnancy because of placental production). The primary differential diagnoses are acute fulminant hepatitis and severe HELLP, although these are less likely to be associated with hypoglycaemia and coagulopathy (Hay, 2008), which are specific to AFLP.

With advances in molecular biology, it has become evident that AFLP may result from mitochondrial dysfunction. There is a strong association between AFLP and a deficiency of the enzyme long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in the fetus, a disorder of mitochondrial fatty acid beta-oxidation (Isaacs *et al*, 1996). LCHAD is part of an enzyme complex, the mitochondrial trifunctional protein (MTP). Approximately one in five women who develop AFLP may carry an LCHAD-deficient fetus (Ibdah *et al*, 2000). Screening of newborn infants at birth for this disorder of fatty acid oxidation can be lifesaving and allows for genetic counselling in subsequent pregnancies (Hay, 2008).

Pre-eclampsia

Pre-eclamptic toxaemia (PET) and HELLP account for about 20% of all cases of thrombocytopenia in pregnancy; the platelet count (and other pathological features) usually returns to normal within 3–5 d after delivery. PET is a multisystem disorder resulting from endothelial damage (Mol *et al*, 2016), defined as new-onset hypertension [blood pressure (BP) ≥140 mmHg systolic and/or ≥90 mmHg diastolic, based on at least two measurements taken at least 4 h apart] occurring in a pregnant woman after 20 weeks gestation, with

proteinuria (defined as urinary excretion of ≥0·3 g protein in 24 h) [National Institute for Health and Care Excellence (NICE) 2010]. PET is classified as mild (BP 140–149 mmHg systolic and/or 90–99 mmHg diastolic), moderate (BP 150–159 mmHg systolic and/or 100–109 mmHg diastolic) or severe (BP ≥160 mmHg systolic and/or ≥110 mmHg diastolic) (NICE 2010).

The underlying pathogenesis of PET was originally described as a 2-stage process, whereby placental hypoperfusion results in systemic endothelial dysfunction. We now know that it is more complex than this and several factors, such as maternal genetics and environmental factors, also play an important role (Roberts & Hubel, 2009). PET is a leading cause of maternal and neonatal morbidity and mortality [Waterstone et al, 2001, Centre for Maternal and Child Enquiries (CMACE) 2011], affecting 3·4% of all pregnancies (Ananth et al, 2013). It is more common in primigravid women and rarely occurs before 24 weeks of gestation. The incidence rises as pregnancy advances, being most common in the third trimester. Symptoms include headache, visual disturbances (such as flashing lights before the eyes), epigastric pain or right upper quadrant pain, nausea or vomiting, sudden swelling of the face, hands or feet and decreased fetal movements. Signs include raised blood pressure and proteinuria, oedema, clonus, palpable liver edge or epigastric tenderness and papilloedema. Blood abnormalities may include thrombocytopenia and MAHA, and increased creatinine and urate. Liver involvement is common, but rarely severe; PET is the most common cause of hepatic tenderness and liver dysfunction in pregnancy.

Pre-eclamptic toxaemia is an indicator for delivery because of the increased risk of severe eclampsia, hepatic rupture, DIC and necrosis. The high perinatal morbidity and mortality are partly due to the association with placental insufficiency and intrauterine growth restriction, but also due to premature delivery for maternal indications. Severe PET is complicated in 2–12% of cases by HELLP syndrome (Sibai, 2007), consistent with the idea that they represent a spectrum of a single disorder. Renal impairment, eclampsia (convulsions) and abnormalities of the coagulation system are further complications.

Haemolysis, elevated liver enzymes and low platelets

Haemolysis, elevated liver enzymes and low platelets (HELLP) is a thrombotic microangiopathy, histologically associated with endothelial cell injury, fibrin deposition, platelet activation and consumption, and areas of hepatic haemorrhage and necrosis (Barton et al, 1992). The underlying cause is unknown, but it occurs only in pregnancy with an incidence of between 0·17% and 0·85% of all live births. Maternal mortality is 3–4%, with fetal mortality reaching approximately 25%, mainly due to prematurity (Barton & Sibai, 2004). Diagnostically, there is considerable overlap

with other TMAs, especially PET, and they may represent a single pathological spectrum. There are no obvious precipitating factors associated with the development of HELLP and it typically presents between the second and third trimesters, although can occur postpartum (Hay, 2008).

Presenting symptoms include upper abdominal pain and tenderness, nausea, vomiting, malaise, headache and, rarely, jaundice. There are no clinical or laboratory factors that are diagnostic, but bilirubin is not usually raised (Hay, 2008). Aminotransferases can be marginally elevated or up to 20-fold increased. HELLP syndrome may be classified according to the degree of thrombocytopenia: HELLP 1 (platelets ≤50 × 10^9/l), HELLP 2 (50–100 × 10^9/l) and HELLP 3 (100–150 × 10^9/l) (Martin et al, 1999). Serious maternal complications include DIC, placental abruption, acute kidney injury, pulmonary oedema and hepatic failure, occasionally requiring liver transplantation. Hepatic rupture is a rare, acute, life-threatening complication (Kia & Rinella, 2013). In HELLP syndrome, ADAMTS13 activity may be moderately reduced (median 31%, range 12–43%), but with no inhibitor/antibodies to ADAMTS13 and higher VWF levels (Lattuada et al, 2003).

Clinical assessment and investigations of a pregnancy-associated TMA

The clinical picture may give clues to the underlying diagnosis. Abdominal pain is common in PET/HELLP and AFLP, but may also be seen in TTP due to intestinal ischaemia (Scully et al, 2008). Hypertension is a prominent feature of PET and also HUS, but may be a feature of all the TMAs presenting in pregnancy. Acute kidney injury requiring haemodialysis is rare in TTP and more indicative of aHUS (Taylor et al, 2010). The gestation at presentation may also aid in differential diagnosis. Although pregnancy-associated TTP most commonly presents in the third trimester or postpartum period, TTP remains the most likely diagnosis of a TMA presenting in the first trimester.

In general, failure of PET or HELLP to respond within 48 h following delivery should prompt consideration of TTP as an alternative diagnosis. Similarly, in cases of PET or HELLP in which the platelet count is decreasing, especially below 50 × 10^9/l, a blood film and haemolysis screen, particularly LDH level, should be requested. A list of investigations (and expected results) in the pregnancy-associated TMAs is shown in Table II. The differential diagnosis is shown in Table III.

Treatment of acute TMA in pregnancy

This discussion is based on maternal factors, although fetal wellbeing and viability will dictate the timing of delivery.

Presentation of a TMA requires careful review of clinical features and laboratory parameters to aid in differential diagnosis. The primary decision is whether delivery will be

associated with remission of the TMA (as in PET or HELLP), or whether plasma exchange (PEX) should be urgently instigated as recovery following delivery is unlikely and there is a risk of multi-organ dysfunction/death.

Table II. Investigations and expected results in pregnancy-associated TMAs.

Blood pressure	Elevated in PET but also TTP, aHUS
Urinalysis	Proteinuria +/− haematuria
FBC and blood film	Anaemia, thrombocytopenia, red cell fragmentation
Reticulocytes	Elevated
Haptoglobin	Reduced
Clotting screen	Normal in TTP
Urea and electrolytes	Renal impairment
Liver function tests	Abnormal in HELLP, AFLP
Calcium	May be reduced with PEX
Lactate dehydrogenase	Raised due to haemolysis and ischaemia
Direct antiglobulin test	Negative
Group and save	For provision of blood products
Hepatitis A/B/C/HIV serology	To exclude viral precipitant and before blood products
ADAMTS13 activity & antibody	To distinguish TTP from other TMAs
Autoantibody screen	Exclude autoimmune disease
Antiphospholipid antibodies	
Stool culture/STEC testing	If diarrhoea – for pathogenic E.coli and other STEC-producing organisms
To document organ damage Troponin level ECG/ECHO	
Fetal ultrasound/uterine artery Doppler scans	To assess fetal growth and well being

TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; aHUS, atypical haemolytic uraemic syndrome; HELLP, haemolysis, elevated liver enzymes, low platelets; AFLP, acute fatty liver of pregnancy; PET, pre-eclampsia (pre-eclamptic toxaemia); FBC, full blood count; PEX, plasma exchange; HIV, human immunodeficiency virus; STEC, Shiga toxin-producing Escherichia coli; ECG, Electrocardiogram; ECHO, Echocardiogram.

If platelet counts are $<75 \times 10^9$/l, and especially $<50 \times 10^9$/l, TTP should be considered. A raised LDH may be a further useful parameter. Women presenting with thrombocytopenia with a platelet count$<50 \times 10^9$/l, MAHA, neurological features (such as confusion, headaches, seizures, stroke/TIAs) and renal impairment, should be treated with PEX until the diagnosis of TTP is excluded. ADAMTS13 activity <10% is definitive, but PEX should be started urgently if there is a suggestion of TTP with transfer of the patient to a specialist centre if necessary (Fig 1).

Specific treatment – TTP

The mainstay of treatment of acute TTP in pregnancy is PEX. Plasma infusion should be considered if there is any delay in transfer for apheresis. Steroids may be used until an anti-ADAMTS13 antibody is excluded. Rituximab is reserved for the emergency situation where immune-mediated disease is particularly severe or refractory, and the mother's life is in danger. Rituximab has been used in pregnancy for a variety of other autoimmune conditions (Hyrich & Verstappen, 2014). On-going therapy will depend on the gestation of presentation, but plasma therapy is likely to be needed at regular intervals until delivery. Once platelet counts have normalized, plasma infusion for congenital TTP cases and PEX for immune-mediated TTP will be required during the remainder of pregnancy and into the postpartum period. Once normalization of the platelet count is achieved, the frequency of plasma therapy will be guided by subsequent platelet counts and ADAMTS13 activity levels in those with acquired disease. Weekly infusions of plasma would be recommended in congenital disease, but these should be guided by the platelet count.

If delivery is required more urgently during an acute presentation, for example because of progressive clinical symptoms or fetal distress, caesarean section is usually undertaken. Intensive PEX pre-caesarean should be considered if time permits. Pulsed methylprednisolone in those with immune-mediated TTP should be given post-PEX. Platelet transfusions should be avoided, but may be considered in cases with severe thrombocytopenia, ensuring PEX is undertaken following delivery.

Table III. Typical features in different pregnancy-associated microangiopathies (from Scully et al, 2012).

	MAHA	Thrombocytopenia	Coagulopathy	HBP	Abdominal symptoms	Renal Impairment	Neurological symptoms
PET	+	+	+/−	+++	+/−	+/−	++
HELLP	+	+	+/−	+	+++	+/−	+/−
TTP	++	+++	−	+/−	+	++	+++
HUS	+	++	+/−	++	+	+++	+/−
AFLP	+/−	+	++	+	++	+	+/−

PET, Pre eclampsia (pre-eclamptic toxaemia); HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, Thrombotic thrombocytopenic purpura; HUS, Haemolytic uraemic syndrome; AFLP, Acute fatty liver of pregnancy; HBP, hypertension.
+/−: possibly occurs.
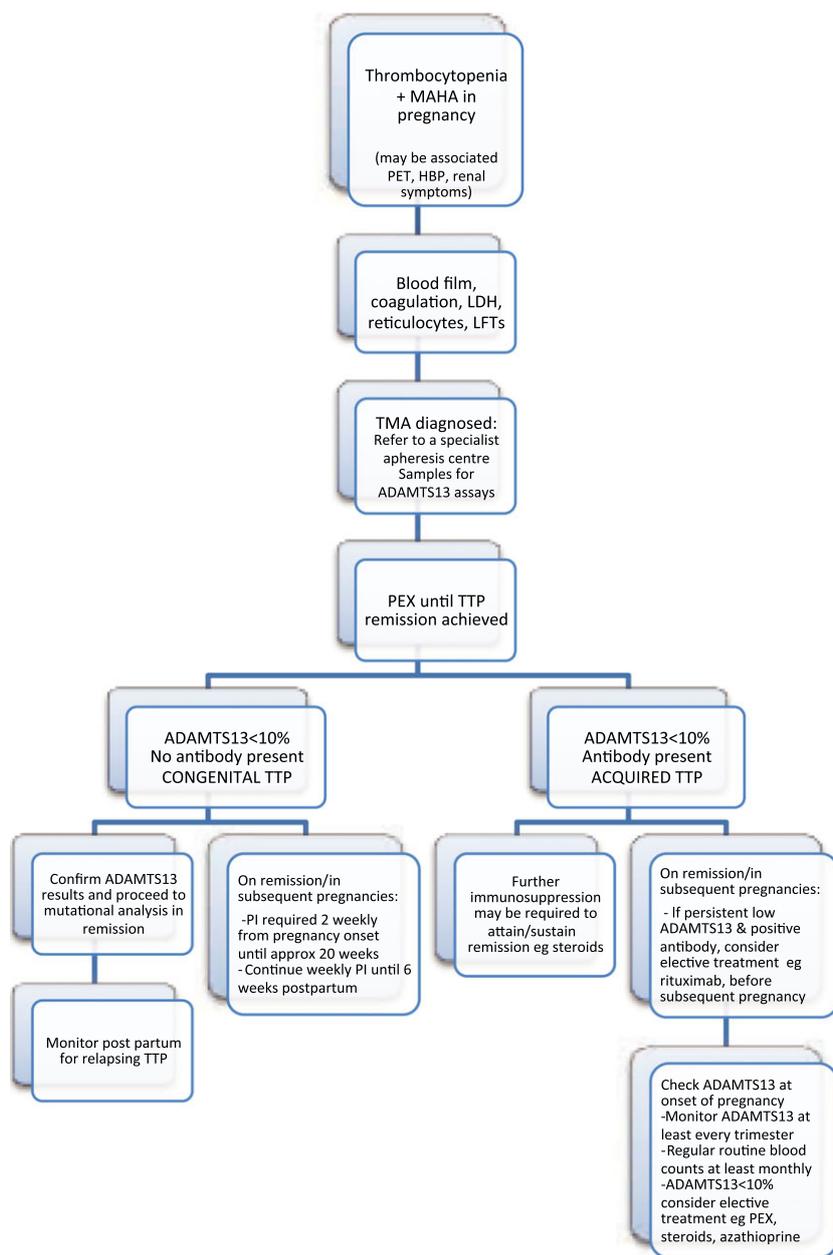+++: definite feature.

Fig 1. Summary of the management of a patient presenting with acute thrombotic thrombocytopenic purpura (TTP) in pregnancy. All women require specialist obstetric review, regular fetal growth scan, and uterine artery Doppler monitoring. On achieving a platelet count of $50 \times 10^9/l$, low-dose aspirin (LDA) should be started. Following an acute presentation, low molecular weight heparin (LMWH) thromboprophylaxis should be given. HBP, hypertension; LDH, lactate dehydrogenase; LFT, liver function test; MAHA, microangiopathic haemolytic anaemia; PET, preeclampsia; PEX, plasma exchange; PI, plasma infusion; TMA, thrombotic microangiopathy.

Specific treatment – aHUS

Treatment of aHUS includes supportive measures, such as red cell transfusion, blood pressure control and dialysis (Taylor *et al*, 2010). PEX should be started in the acute setting with identification of a TMA, but with confirmation of ADAMTS13 levels not in keeping with TTP, complement inhibition with eculizumab is the therapy of choice. Eculizumab is a humanized monoclonal antibody inhibitor of complement C5, which prevents formation of the terminal membrane attack complex (Kaplan, 2002). Eculizumab has been used in pregnancy in women with paroxysmal nocturnal haematuria (PNH) and there have been case reports of its use in pregnancy-associated aHUS (Mussoni *et al*, 2014).

Women receiving eculizumab require antibiotic prophylaxis and vaccination against encapsulated organisms.

Specific treatment of pre-eclampsia

If a diagnosis of pre-eclampsia (PET) is confirmed the woman should be admitted, in view of increased risk of placental abruption and eclampsia. The primary treatment is control of hypertension, intravenous magnesium sulphate, fetal monitoring and steroids in pregnancies <34–36 weeks gestation (Arulkumaran & Lightstone, 2013). Definitive treatment is delivery and stabilization of haematological parameters usually occurs approximately 48 h after delivery.

However, with continuing thrombocytopenia post-delivery, or deterioration in clinical symptoms, the diagnosis of TTP and therapy with PEX should be considered.

Specific treatment of HELLP

A Cochrane review compared corticosteroids with placebo or no treatment in HELLP (Woudstra et al, 2010). There was no difference in the risk of maternal death, severe maternal morbidity or perinatal/infant death. The only clear effect of treatment on individual outcomes was improved platelet count, which was greater for those receiving dexamethasone than those receiving betamethasone. These benefits appear to be greater in Class I HELLP syndrome. There is, to date, insufficient evidence of benefits in terms of substantive clinical outcomes to support the routine use of steroids for the management of HELLP. The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile (Woudstra et al, 2010). The collaborative randomized controlled trial on corticosteroids in HELLP syndrome (COHELLP) aims to determine the effectiveness of dexamethasone for accelerating postpartum recovery in patients with Class I HELLP (NCT00711841).

Other measures include control of blood pressure as for PET and the use of magnesium sulphate (Martin, 2013). In women with class I HELLP (platelet count less than 50×10^9/l) or with evidence of deteriorating clinical disease, PEX should be considered. The benefit of PEX in this scenario was demonstrated some 20 years ago (Martin et al, 1994, 1995) and is especially relevant now we understand that some cases presenting with features of HELLP may be TTP. Measuring the aspartate transaminase/LDH ratio has been advocated as a means to differentiate between HELLP and TTP (Keiser et al, 2012), but the authors would not suggest this to be helpful. Rather, clinical decision-making should be guided by progression of symptoms, worsening thrombocytopenia and confirmation by an ADAMTS13 assay.

Specific treatment of AFLP

Early delivery is imperative and recovery occurs over 1–4 weeks postpartum, although an improvement in liver function is usually seen within a few days of delivery. There is a significant requirement for supportive care before and after delivery, which may be required for days or weeks. This may include dialysis, support of hypoglycaemia and correction of coagulopathy. However, there appears to be a role for PEX, with outcomes in cohorts suggesting improved survival, particularly when started early after diagnosis (Jin et al, 2012; Ding et al, 2015). Benefits of using PEX included reversing multiorgan dysfunction, improving renal perfusion and aiding correction of coagulation defects; it has also been suggested to reduce liver cell damage and improve liver

dysfunction. Indeed, remission rates of up to 95% have been quoted (Jin et al, 2012). More recently, in a comparison to supportive therapy, mortality in those receiving PEX was approximately 17%, compared to over 81% for supportive care only. Patients who were treated with PEX also had a significant improvement in liver and renal function (Ding et al, 2015).

In summary, in women with pregnancy-associated TMAs who do not improve with delivery, particularly those with PET/HELLP who have severe presenting disease, e.g. class I HELLP, or evolving clinical symptoms, signs or laboratory features of organ involvement, e.g. increased troponin T, consideration should be given to the possibility of a diagnosis of TTP or complement defects. The limited evidence suggests a role for PEX in the management of HELLP and AFLP, but PEX is critical if TTP is contemplated. Follow-up in the post-partum period is recommended to ensure TTP and complement abnormalities are excluded.

Management of subsequent pregnancies in patients diagnosed with TTP

A particular concern in women who have had previous acute TTP unrelated to pregnancy is the risk of relapse from TTP during a subsequent pregnancy. A previous TTP episode is not a contra-indication to pregnancy, but close specialist monitoring is an absolute requirement. There should be a multidisciplinary approach with haematologists working in conjunction with obstetricians that specialize in high-risk pregnancies. Patients should have regular fetal growth scans and uterine artery Doppler studies.

Congenital TTP in subsequent pregnancies

The risk of relapse in subsequent pregnancies in women with confirmed congenital TTP is such that elective plasma therapy during pregnancy is warranted (Fig 1). Plasma therapy is guided by the platelet count, aiming to maintain a normal count throughout pregnancy with no rise in LDH. Plasma infusions may be satisfactory; however, to deliver sufficient volumes, PEX may be required, particularly later in pregnancy. The optimal frequency of plasma replacement is unknown: although the half-life of ADAMTS13 is 2–3 d (Furlan et al, 1999), plasma therapy every 1–2 weeks appears satisfactory (Scully et al, 2014). It is advisable to consider delivery at a maximum of 37 weeks gestation. Induction of labour and vaginal delivery is encouraged. We suggest low dose aspirin (LDA) throughout pregnancy, given the effect of microthrombi formation on placenta with multiple ischaemic lesions seen histologically (Scully et al, 2014). Prophylactic low molecular weight heparin (LMWH) should be considered in women with a higher thrombotic risk.

Data from our group and the UK TTP registry shows the success of this approach – historic untreated pregnancies had a live birth rate of only 39%, but those treated throughout

pregnancy had 100% live birth rate and maternal survival (Scully *et al*, 2014).

Acquired TTP in subsequent pregnancies

In women with acquired TTP, it is not as easy to predict who may relapse. ADAMTS13 activity at the onset of pregnancy is a useful prognostic marker, as a normal ADAMTS13 activity at the onset of pregnancy appears to predict women at reduced risk of subsequent relapse (Scully *et al*, 2014). If ADAMTS13 activity is low (<10%) at the onset of pregnancy, consideration should be given to elective therapy to prevent relapse, such as regular PEX throughout pregnancy (Fig 1). We use a schedule of weekly PEX in the elective setting. Immunosuppression with azathioprine can be considered as steroid-sparing therapy that can be used throughout pregnancy, particularly if the ADAMTS13 levels are not normal or drop during pregnancy (Scully *et al*, 2014).

In contrast, women with normal ADAMTS13 activity at the onset of pregnancy, who maintain normal routine laboratory parameters, ADAMTS13 activity and anti-ADAMTS13 antibody levels throughout pregnancy, do not usually require intervention for TTP. Full blood counts should be monitored at least monthly. ADAMTS13 activity should be monitored carefully throughout pregnancy – at least in each trimester, but our practice is to measure it monthly. A fall in ADAMTS13 activity to <10% prompts elective PEX therapy to prevent relapse.

Low dose aspirin (LDA) and prophylactic LMWH should be considered in women with a higher thrombotic risk. Women with a previous pregnancy loss due to TTP or with low ADAMTS13 activity at the onset of pregnancy can be assumed to be at increased risk of further placental disorder in subsequent pregnancies (Ridolfi & Bell, 1981; Ezra *et al*, 1996; Ducloy-Bouthors *et al*, 2003; Shamseddine *et al*, 2004). The aim of anti-thrombotic therapy is to optimize implantation and preserve placental function given that abnormalities of the utero-placental circulation, resulting in insufficiency, are established in the first trimester. However, this therapy has not been formally evaluated in pregnancy-associated TTP.

Where low ADAMTS13 activity precedes pregnancy, rituximab may be used electively to normalize ADAMTS13 activity before conception, with subsequent successful pregnancy outcomes (Scully *et al*, 2014). Patients are advised to wait 12 months following rituximab before conceiving. However, some women became pregnant before this with no ill effects to mother or fetus (Scully *et al*, 2014). Indeed, waiting until normalization of CD19 lymphocyte levels, at approximately 6 months, with no detectable serum rituximab may be satisfactory (McDonald *et al*, 2010).

aHUS in subsequent pregnancies

Patients with a known history of aHUS require counselling pre-pregnancy and multi-disciplinary management through-out pregnancy. Careful monitoring of blood pressure, renal function and haematological parameters is required, as well as specialist obstetric monitoring, including regular growth scans and uterine artery Doppler scans. Women with a history of aHUS are at similar risk to TTP patients with regards both disease relapse and obstetric complications, such as fetal loss or intrauterine growth restriction.

As soon as pregnancy is confirmed, antihypertensive therapy should be switched from angiotensin-converting-enzyme (ACE) inhibitors to other treatments acceptable during pregnancy. In women not on anti-hypertensive therapy, strict monitoring of the blood pressure should be undertaken and therapy started if required. It is usual for renal protein leak to increase during pregnancy in aHUS cases. Monitoring of protein-creatinine ratios, in conjunction with creatinine levels, will dictate if therapy is required.

Eculizumab has been successfully used in pregnancy and in lactating mothers (Mussoni *et al*, 2014). In women on therapy pre-pregnancy, this should continue through to the postpartum period, which is the greatest period of relapse. More difficult are the cases where women are not already on therapy, and determining when treatment should be started. This decision should be individualized for each patient, in conjunction with the current process for eculizumab authorization in the UK. However from the authors' experience, it can be difficult to pre-empt relapse using routine laboratory parameters, by which time it is too late to effectively give therapy to avert fetal and maternal complications. Similar to congenital TTP, it is probably appropriate to start complement inhibition therapy at least by the second trimester and continue until the end of the postpartum period.

Subsequent pregnancies in PET/HELLP

The risk of PET in subsequent pregnancies may be predicted by a number of factors, specifically previous preterm delivery at or before 37 weeks, but especially before 34 weeks. Placental abruption in the index pregnancy, age >35 years and chronic hypertension are also risk factors associated with recurrence (Melamed *et al*, 2012). Pooled studies reveal a risk of approximately 14% but recurrence rates in individual studies are up to 50%. Recurrent PET is associated with an increased maternal and fetal morbidity. The risk of recurrent HELLP is only 0·2% (van Oostwaard *et al*, 2015). Women with hypertensive disease during a previous pregnancy should be advised to take 75 mg aspirin daily from 12 weeks until the birth of the baby (NICE 2010).

Subsequent pregnancies in AFLP

The risk of recurrence is up to 70% in subsequent pregnancies, depending on whether there is a demonstrable defect in fatty acid oxidation. In pregnancies in which the fetus had an LCHAD deficiency, the mother was likely to develop AFLP or HELLP syndrome. Subsequent pregnancies without

a LCHAD deficient fetus progressed normally, with no liver dysfunction (Usta *et al*, 1994; Castro *et al*, 1999). Women who opt for another pregnancy will require regular monitoring by a high-risk pregnancy team.

Conclusion

Differentiation between the thrombotic microangiopathies (TMAs) that present in pregnancy may be clinically challenging, but it is critical to determine the correct diagnosis, as this will dictate management. The primary decision is whether delivery will be associated with remission of the TMA (as in PET or HELLP), or whether PEX should be urgently instigated because TTP or aHUS cannot be excluded. Data from our group and elsewhere has demonstrated that a previous episode of TTP is not a contraindication to future pregnancy. Management of subsequent pregnancies in women with a history of TTP requires a multidisciplinary approach, with close specialist monitoring and treatment resulting in excellent pregnancy outcomes.

Author Contributions

All authors contributed to writing and reviewing the paper.

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