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Atypical haemolytic uraemic syndrome during pregnancy/postpartum

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This review is intended as an educational resource for healthcare professionals. The review will define and outline the various thrombotic microangiopathies (TMAs) that might arise during pregnancy. The differential diagnosis of these events and the management of the TMAs are then reviewed, with a focus on atypical haemolytic uraemic syndrome (aHUS) and its treatment with eculizumab.

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Abbreviations used in this review:

ADAMTS13 = a disintegrin and metalloprotease thrombospondin, number 13
aHUS = atypical haemolytic uraemic syndrome
AFLP = acute fatty liver of pregnancy
ALT = alanine transaminase
AST = aspartate transaminase
HELLP = haemolysis, elevated liver enzymes, low platelet count syndrome
HUS = haemolytic uraemic syndrome
LDH = lactate dehydrogenase
MAHA = microangiopathic haemolytic anaemia
MHT = malignant hypertension
PE = plasma exchange
PI = plasma infusion
STEC-HUS = Shiga toxin–producing Escherichia coli HUS
TMA = thrombotic microangiopathy
TTP = thrombotic thrombocytopenic purpura
vWF = von Willebrand factor

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) describes a pathological process in which the central event is severe damage to the vascular endothelium, associated with the activation of the complement and/or coagulation systems.[1,2] TMAs represent a spectrum of disorders characterised by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), and the clinical and laboratory abnormalities attributable to organ-specific dysfunction. The organs commonly affected included the kidneys, brain, heart and gastrointestinal tract.

TMA occurs in a wide variety of clinical settings including pregnancy and postpartum[2] when it is most commonly encountered with HELLP (haemolysis, elevated liver enzymes, low platelet count syndrome) or pre-eclampsia with severe features.[3] Pre-eclampsia and HELLP account for about 20% of all cases of thrombocytopenia in pregnancy.[4]

In rare instances, TMA may be due to thrombotic thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS).[4] In pregnancy or postpartum, aHUS and TTP are often misdiagnosed as HELLP or pre-eclampsia. Acute fatty liver of pregnancy (AFLP) is another rare event with overlapping symptoms.[4]

The differentiation of TMAs during pregnancy or postpartum can be clinically challenging.[3] However, a rapid differential diagnosis of TMA to determine the underlying condition is essential to ensure successful outcomes for both the mother and foetus. Delays in the appropriate diagnosis and treatment of the TMA may be life-threatening.[3]

Haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome

HELLP syndrome is a TMA characterised by haemolysis, elevated liver enzyme levels and a low platelet count.[5] There are usually additional signs and symptoms such as malaise, nausea/vomiting, or abdominal pain in the right upper quadrant or epigastric area (**Table 1**). HELLP generally occurs from >20 weeks of pregnancy through to the immediate postpartum period. However, HELLP syndrome can occur postpartum in up to 30% of the cases, making differential diagnosis difficult.[6]

Table 1. Differential features, symptoms and diagnosis of various pregnancy-related thrombotic microangiopathies[3,7-9]

	HELLP syndrome	Severe pre-eclampsia	AFL	TTP	aHUS
Usual time of onset	Third trimester, postpartum	Third trimester	Third trimester	Second and third trimester	Postpartum
Features					
RBC	MAHA, Coombs negative	± MAHA	Usually normal	MAHA, Coombs negative	MAHA, Coombs negative
Platelets	<100,000/uL	<100,000/uL	<150,000/uL	Often <30,000/uL	<150,000/uL
AST/ALT	>2x ULN	>2x ULN	Increased levels	Normal	Limited data
Creatinine	± >1.1 mg/dL	>1.1 mg/dL	± >1.1 mg/dL	>1.1 mg/dL	Often >2.0 mg/dL
Hypoglycaemia	-	-	+++	-	-
Elevated ammonia	±	±	+++	-	-
Clinical symptoms					
Hypertension	+++	+++	±	+	++
Proteinuria	+++	±	-	±	+
Abdominal pain	+++	±	++	+	+
Fever	-	±	±	+	±
Nausea and vomiting	±	±	±	+	±
Neurological defects	+	±	±	++	±
Renal dysfunction	+	±	+	+	+++
Purpura	-	-	-	+	-
Jaundice	±	±	++	±	±
Diagnosis	Resolves within 48-72 hours of delivery	Resolves within 48-72 hours of delivery	Suspect with hypoglycaemia, elevated ammonia coagulopathy	ADAMTS13 activity <10%	Exclude other conditions
Treatment recommendations	Delivery	Delivery	Supportive care	Plasma exchange	Eculizumab

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **AFL**, acute fatty liver; **aHUS** = atypical haemolytic uraemic syndrome; **AST/ALT** = aspartate transaminase/alanine transaminase; **BP** = blood pressure; **HELLP** = haemolysis, elevated liver enzymes, and low platelet count; **MAHA** = microangiopathic haemolytic anaemia; **TTP** = thrombotic thrombocytopenic purpura; **ULN** = upper limit of normal.

Diagnostically, there is overlap of HELLP with other TMAs, especially pre-eclampsia. HELLP and pre-eclampsia are often thought to represent a single pathological spectrum.[4] A test for haemolysis is necessary and critical to diagnose, or rule-out, HELLP. If haemolysis is not present, then the woman is less likely to have TMA, and may have an alternative diagnosis.[3]

Pre-eclampsia with severe features

Pre-eclampsia is a pregnancy-specific hypertensive disorder with multi-system involvement.[8] Pre-eclampsia affects 2–7% of pregnant women and is defined by the association of hypertension and proteinuria after 20 weeks of gestation.[10] Pre-eclampsia with severe features has been defined as new-onset hypertension (≥160 mmHg systolic or ≥110 mmHg diastolic) occurring ≥20 weeks of pregnancy, in conjunction with at least one severe feature (including renal insufficiency as indicated by elevated creatinine, cerebral of visual disturbances, pulmonary oedema, impaired liver function with elevated liver enzymes, severe or persistent abdominal pain, and thrombocytopenia; see **Table 1**).[8] Proteinuria is the most commonly recognised additional feature after hypertension but should not be considered mandatory to make the clinical diagnosis.[11]

Acute fatty liver of pregnancy

ALFP is a rare life-threatening illness (incidence approximately 5 per 100 000 deliveries) that typically presents in the third trimester.[12] Patients may present with non-specific features such as headache, fatigue, nausea, vomiting and right upper quadrant or epigastric pain. Progression of the illness is often rapid. It is characterised by severe liver failure, high ammonia, encephalopathy, gastrointestinal haemorrhage, coagulation abnormalities, acute kidney injury, infection and hypoglycaemia.[4]

AFLP and HELLP syndrome share common features, and differential diagnosis between them can be difficult. Hypertension is more likely in HELLP syndrome, while hypoglycaemia, coagulopathy, liver failure, high ammonia, high triglycerides and cholesterol are usually present in AFLP.[13] Other differentiating features are given in Table 1. A liver biopsy, which reveals characteristic microvesicular steatosis, is the definitive diagnosis in AFLP; however, this is usually not possible in an acute presentation where prompt action is required.[14]

TTP in pregnancy

TTP is a rare event occurring in approximately 2-6 patients per million each year.[15, 16] However, pregnancy can be the precipitating factor for approximately 5– 25% of TTP cases.[4, 9, 17, 18] TTP is defined by the severely reduced (<5–10%) activity of ADAMTS13 (disintegrin and metalloprotease thrombospondin, number 13), and a von Willebrand factor (vWF)-cleaving protease.[3, 19] In TTP, there is an accumulation of large vWF multimers resulting in platelet aggregation and microvascular thrombosis. This acute life-threatening condition tends to develop during the second and third trimesters of pregnancy.[17] Neurological symptoms (e.g. delirium, seizures) are more common in this category of TMA, but renal impairment may occur and present similarly as in aHUS.[2, 17]

TTP during pregnancy/postpartum may be acquired TTP (with evidence of inhibitor/anti-ADAMTS13 IgG antibodies) or late-onset congenital TTP (whose diagnosis is established by the presence of mutations of the ADAMTS13 gene).[2, 4] In pregnant women who present with marked thrombocytopenia in the first half of pregnancy, it is important to consider a diagnosis of TTP. A family history of TTP is another potential indicator of TTP.[3]

Haemolytic uraemic anaemia

Haemolytic uraemic syndrome (HUS) is characterised by MAHA, thrombocytopenia, and acute organ injury, and it includes the subtypes Shiga toxin–producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS) and atypical HUS (aHUS).[2]

STEC-HUS is generally rare in adults (incidence of about 0.12 cases per 100,000 per year in Australia).[2, 20] Patients typically present with diarrhoea and renal failure, and sometimes neurologic impairment.[2] Although bloody diarrhoea is common, this does not distinguish STEC-HUS from aHUS or TTP. A stool sample or rectal swab should be obtained to detect Shiga toxins 1 and 2. Outbreaks of STEC-HUS have occurred in Australia and it is a notifiable disease.[20]

Atypical haemolytic uraemic syndrome

Atypical aHUS is characterised by MAHA, thrombocytopenia and end-organ injury (commonly the kidney).[3] This is a rare disorder occurring with an annual incidence of one to two cases per million in the general population.[21, 22] aHUS can be unmasked by complement-amplifying conditions such as pregnancy,[3] with an estimated incidence of one case per 25,000 pregnancies.[23] In a retrospective study of 100 French women with aHUS, 21% of the women presented with aHUS associated with pregnancy.[24]

aHUS is characterised by the dysregulation of the complement system.[25] The uncontrolled activity following complement activation results in endothelial damage, inflammation, secondary thrombosis and target organ injury (e.g. renal impairment, cardiovascular symptoms or retinopathy).

Risk factors for aHUS include genetic mutations and polymorphisms, and the presence of auto-antibodies (e.g. Factor H).[25] Studies have found that 56%[18] and 86%[23] of women with aHUS unmasked by pregnancy carried a complement gene mutation.[23] Genetic information may be a helpful guide for the long-term management strategy of the aHUS patient, including length of treatment, frequency of follow up, prognosis, and future pregnancy.[3, 26] However, 30–40% of individuals will not have an identifiable mutation.[25]

In general, aHUS associated with pregnancy occurs during the postpartum period (**Figure 1**).[23, 24, 27] Without prompt diagnosis and initiation of appropriate treatment, this condition can lead to disastrous consequences, with progression to end-stage renal failure commonly occurring.[28, 29]

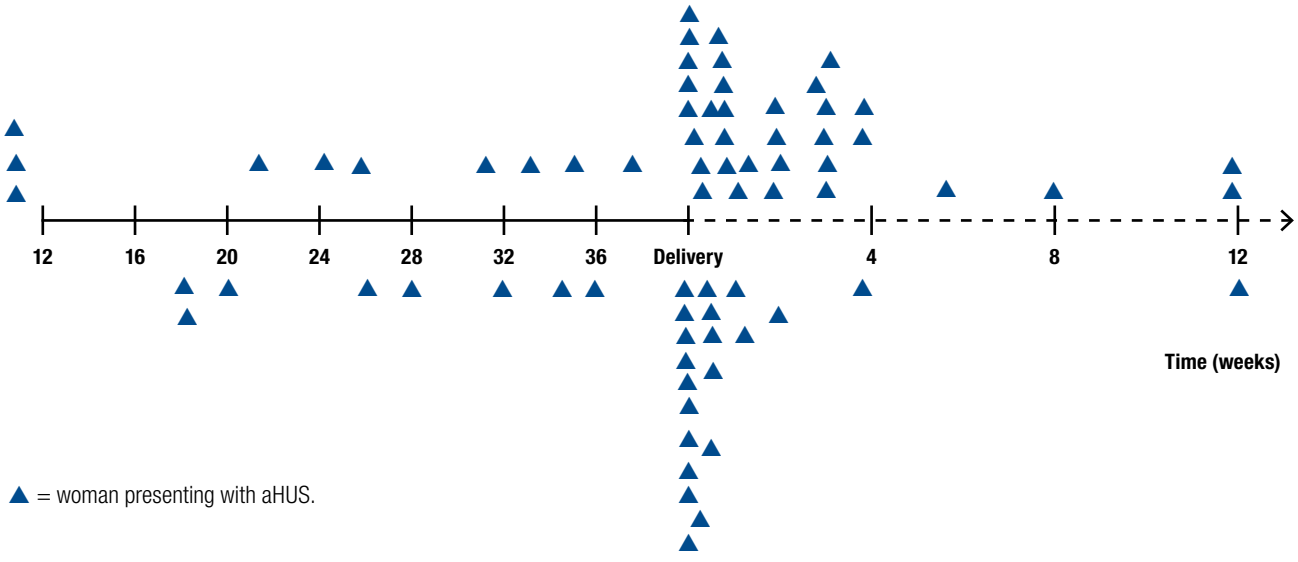

Figure 1. Time point of pregnancy-associated aHUS presentation in 87 women[24]

Adapted from Bruel A et al. Clin J Am Soc Nephrol. 2017;12(8):1237-1247.

Differential diagnosis of TMA in pregnancy

Differentiating HELLP, pre-eclampsia and aHUS is essential to determine the first-line treatment for optimal outcomes of mother and baby. A treatment algorithm that may assist in the diagnosis is given in **Figure 2**. The involvement of a multidisciplinary team of clinicians with expertise in TMA (e.g. Critical Care, Haematology, Maternal Foetal Medicine, or Nephrology) may be essential and life-saving in complex cases.[3]

*Proteinuria: 24 h urine protein ≥300 mg/dL or urine protein/creatinine ratio ≥0.3 mg/mg.

**Evidence of MAHA: negative direct coombs, haptoglobin < lower limit of normal, or peripheral smear with schistocytes.

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **aHUS** = atypical haemolytic uraemic syndrome; **Cr**, creatinine; **Hgb**, haemoglobin; **HELLP** = haemolysis, elevated liver enzymes, low platelet count syndrome; **HTN**, hypertension; **LDH** = lactated dehydrogenase; **MAHA** = microangiopathic haemolytic anaemia; **Plt** = platelet; **PE** = Plasma exchange; **RUQ** = right upper quadrant; **TMA** = thrombotic microangiopathy; **TTP** = thrombotic thrombocytopenic purpura; **ULN** = upper limit of normal.

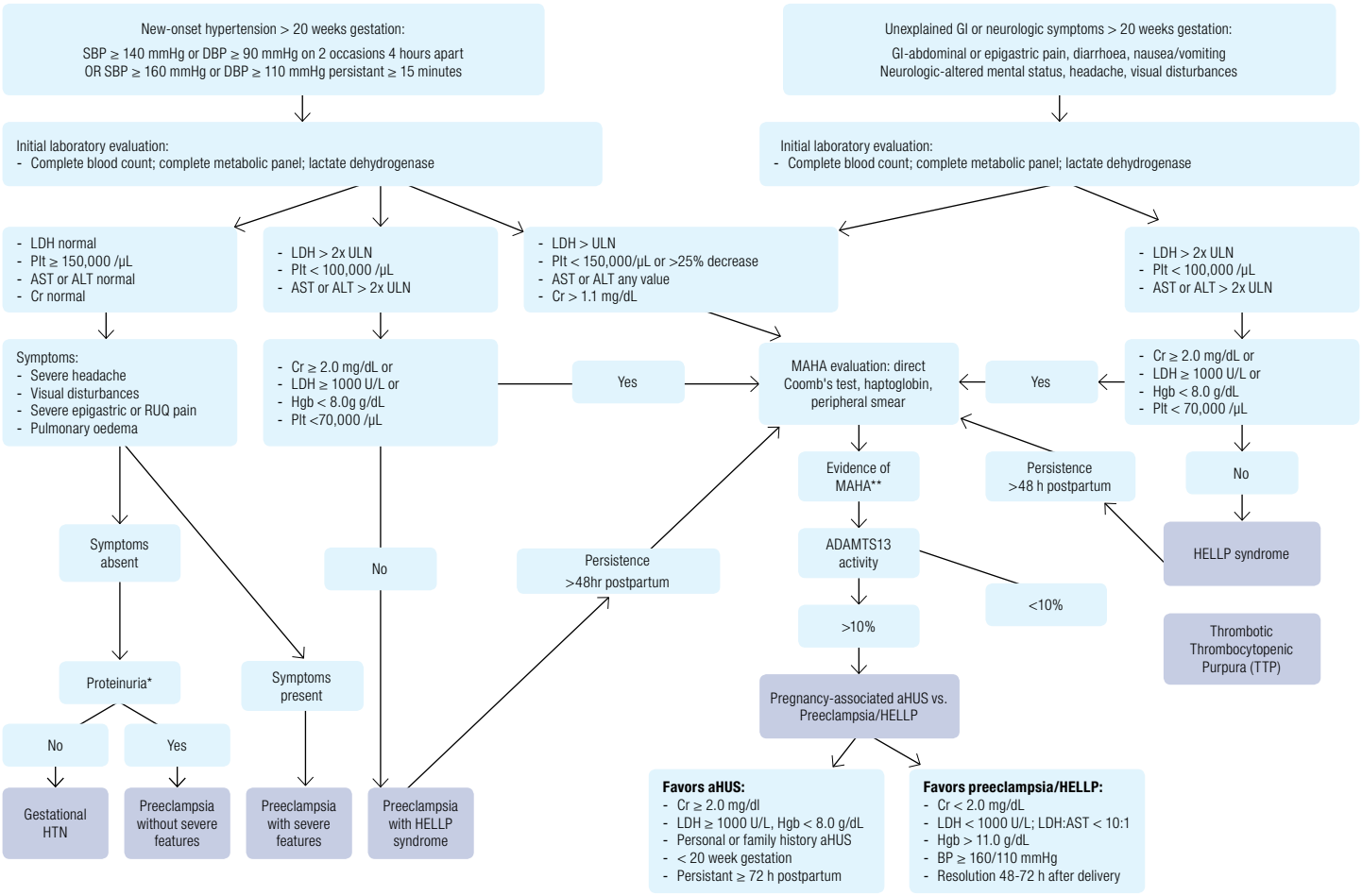

Figure 2. TMA diagnostic algorithm[3]

In most cases of severe pre-eclampsia and HELLP, clinical improvement occurs within 48–72 hours of delivery (**Table 1**).[3] If unexplained haemolysis and kidney injury continue or worsen postpartum, then aHUS should be suspected.[3]

The initial diagnosis of aHUS is currently based on exclusion of STEC-HUS and TTP (**Figure 3**).[2] ADAMTS13 testing is critical for distinguishing between TTP and aHUS.[30,31] TTP is diagnosed if there is reduced ADAMTS13 activity (<10%) in the setting of otherwise unexplained MAHA and thrombocytopenia.[3] A blood sample should be collected for ADAMTS13 testing prior to any plasma therapy. If STEC-HUS is suspected (e.g. TMA and bloody diarrhoea), a stool sample or rectal swab should be obtained for PCR-based detection of Shiga toxins 1 and 2. TTP can be excluded if ADAMTS13 activity is ≥10%.[2, 32] Several Australian laboratories measure ADAMTS13 activity and results can be available within 24 hours.[2]

Exclusion of STEC-HUS and TTP may be sufficient for a diagnosis of aHUS. However pregnancy-related aHUS shares many overlapping features with pre-eclampsia and HELLP (see **Table 1** and **Figure 2**).[3, 33]

Haemolysis

Lactate dehydrogenase (LDH) level may be a useful measure of haemolysis in HELLP, aHUS and TTP, with other options including total or indirect bilirubin, haptoglobin or peripheral smear.[3] LDH values >1000 U/L may occur in aHUS but less frequently in HELLP syndrome (see **Figure 2**). aHUS should be considered if LDH is >1000 U/L, combined with a serum creatinine >1.1 mg/dL. A personal or family history of aHUS, high LDH: aspartate transaminase (AST) ratio (>10:1) or low haemoglobin (<8.0 g/dL) may also indicate aHUS.[3] Haemoglobin level is typically very low in aHUS, but can be normal with severe pre-eclampsia or HELLP.

Liver enzymes

AST or alanine transaminase (ALT) levels are elevated in HELLP syndrome and severe pre-eclampsia, and have also been reported in some cases of aHUS.[3] Increased levels of AST or ALT should not exclude a diagnostic work-up for aHUS or TTP.

Platelet count

A low platelet count commonly occurs with severe forms of pre-eclampsia, HELLP, TTP and aHUS.[3, 34] A platelet count <30,000/µL may be indicative of TTP, but the platelet count cannot be used to distinguish between the remaining TMAs.[3]

Serum creatinine

During pregnancy or post-partum, an elevation of serum creatinine (>2× upper limit of normal) is not common in severe forms of pre-eclampsia or HELLP, but should trigger evaluation for aHUS, regardless of platelet count or liver enzyme values.[3] Dramatic and rapid increases in serum creatinine, often >3–4 mg/dL, are characteristic of aHUS. aHUS should also be suspected if an elevation of serum creatinine >1.1 mg/dL persists for more than 72 hours postpartum.

Delivery

Delivery is the definitive treatment for severe pre-eclampsia and HELLP, with symptoms improving within 48–72 hours of deliver in most instances.[3] However, aHUS should be suspected if symptoms persist beyond 72 hours.

Expert commentary

A differential diagnosis of TMA in pregnancy is difficult as there is no one diagnostic tool to differentiate the TMA disorders. Some useful tools include:

- Clinical history
  - A family history of aHUS, early cerebrovascular accident or development renal failure after pregnancy may assist in diagnosis
- Timing of TMA
  - If a TMA occurs before 20 weeks gestation, then TTP or sepsis are more likely. However, if a TMA occurs postpartum, then aHUS or HELLP are more likely.
- ADAMSTS-13
  - This is a useful tool, with a rapid turnaround in Australian laboratories. ADAMSTS-13 decreases in pregnancy, but does not fall below threshold levels <10%.
- Timing of recovery
  - The platelet count is normally expected to recover over 72 hours. If the clinical situation is deteriorating despite appropriate management and intervention, then consider an alternative diagnoses.
- Clinical constellation
  - If platelets <30,000/µL and neurological disease is present then TTP is more likely. If creatinine is >200 µmol/L, then consider aHUS.
  - Utility of soluble fms-like tyrosine kinase 1 (sFLT)/placental growth factor (PIGF) ratio. This ratio is normally increased in hypertensive disorders such as pre-eclampsia and HELLP and is often used to rule in or rule out these disorders. It has not been accepted as a diagnostic test by the International Society of Hypertension in Pregnancy. There is no information of the utility of this test in other causes of MAHA in pregnancy.
- Renal biopsy
  - A renal biopsy may be useful but it is often not practical in the setting of thrombocytopenia. In pre-eclampsia or HELLP, a renal biopsy more commonly shows endotheliosis and acute tubular necrosis.[35] Thrombotic angiopathy is normally seen in other cases such as aHUS, TTP and other secondary microangiopathies.

Management of TMAs

TMA is a medical emergency, and it has the potential for rapid and fatal decline.[2] Consultation with, or transfer to, centres with TMA management expertise should be considered.

The initial treatment decision should be whether delivery will be associated with remission of the TMA (as in pre-eclampsia or HELLP), or whether plasma exchange should be urgently instigated until a differential diagnosis of TTP or aHUS has been made.[4] Plasma exchange/plasma infusion may be initiated while waiting for the results of ADAMTS13 testing (or STEC-HUS testing if suspected).[2]

Treatment of STEC-HUS is with supportive care.[2] Patients with TTP are likely to respond to treatment with plasma exchange or immunosuppression, but this is usually not the case for patients with ADAMTS13 activity >10% and alternative management will be needed.[36, 37]

Once TTP or STEC-HUS has been excluded and aHUS is diagnosed, then eculizumab treatment should be started as soon as possible.[2] Continued treatment of aHUS with plasma exchange generally results in an incomplete or limited response, with poor long-term outcomes.[23, 24, 37, 38]

Eculizumab

The management of aHUS has changed since the approval of Soliris® (eculizumab *rmc*) for this indication.[39] The eculizumab product information and local vaccination guidelines should be referred to before starting eculizumab in patients with aHUS.[39]

Eculizumab is a humanised, monoclonal antibody that binds with high affinity to the α-chain of the C5 complement protein.[39, 40] Consequently, it inhibits the cleavage of C5 into C5a and C5b, and prevents the generation of the terminal complement complex C5b-9. By blocking complement hyperactivation and dysregulation, eculizumab reduces the haemolysis, prothombotic activity, and inflammation associated with aHUS.[41]

Clinical trials that led to the approval of eculizumab demonstrated that the early initiation of treatment with eculizumab resulted in rapid normalisation of haematological parameters and time-dependent improvement in renal function in patients with aHUS.[42]

Eculizumab is well tolerated, but its use is associated with an increased susceptibility to *Neisseria meningitidis,* with risk of meningococcal sepsis or meningitis. The eculizumab label carries a black box warning to this effect.[39] Patients should receive a meningococcal vaccine at least two weeks prior to receiving Soliris, unless the risk of delaying Soliris therapy outweighs the risk of meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. The eculizumab product information and vaccination guidelines should be referred to before starting eculizumab.[39]

Eculizumab in pregnancy-associated aHUS

Although pregnant women were excluded from the clinical trials that led to the approval of eculizumab, a number of case reports have indicated that eculizumab is associated with renal improvement and the normalisation of haematological parameters in women with pregnancy-related aHUS.[7, 29, 43-49]

A larger retrospective study reviewed 22 cases of pregnancy-associated aHUS from the Spanish aHUS Registry.[27] Pathogenic variants of complement genes were found in 9/22 (41%) of these women. Most of the instances of aHUS occurred postpartum, with most of the cases occurring after caesarean section.[27] Of the 10 women treated with eculizumab, renal survival was 100% at 24 months, irrespective of any inherited complement abnormalities the women may have had. In contrast, seventeen patients underwent plasma treatments, but renal response was positive in only three cases.[27]

Outcomes were poor with plasma exchange in a retrospective study of 87 patients with pregnancy-associated aHUS.[24] In this study, fifty-six (78%) patients underwent plasma exchange, 21 (41%) received plasma infusions, but only four (5%) received eculizumab. Of the four who received eculizumab, three (two with complement gene variants, one without) had a complete recovery of kidney function. However, plasma exchange did not improve the renal outcome of pregnancy-associated aHUS, with the risk of end-stage renal failure remaining high (around 50%).[24]

In Australia, eculizumab is a pregnancy category B2 drug, eculizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the mother, fetus and/or neonate. Unless pregnancy is specifically desired, women should use adequate contraception during eculizumab treatment, and for up to 5 months after discontinuing treatment.[39] Limited data indicate that eculizumab treatment during pregnancy does not impair the complement function in the newborn.[50] Although limited published data does not report detectable levels of eculizumab *rmc* in human milk, maternal IgG is known to be present in human milk. There are no data on the effects of eculizumab *rmc* on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Soliris and any potential adverse effects on the breastfed child from Soliris or from the underlying maternal condition.[39]

Expert Opinion

The management of TMAs in pregnancy should involve a multidisciplinary team and a tertiary referral centre, as the patients often need referral to an intensive care unit if they are unstable and requiring dialysis therapy. If the clinical situation warrants, then the initiation of plasma exchange and plasma infusion should be considered and this may be required prior to the ADAMTS13 results becoming available. If the ADAMTS13 levels are normal, and there is no evidence of improvement, then treatment with eculizumab should be considered.

There are only case reports of eculizumab use in pregnancy, with the majority of exposures being in the paroxysmal nocturnal haemoglobinuria population.[51] In 2017, the United Kingdom Teratology Information Service reported that there were 119 case reports of eculizumab use in pregnancy with only one congenital malformation out of 109 cases of use in the first trimester.[52] This malformation was thought to be secondary to warfarin exposure.[52] There was an observed higher rate of premature delivery and intra-uterine growth restriction but these were complex pregnancies. There are also no good data on the short- or long-term effects on the immune system of the offspring. The timing of administration also has to be considered as immunoglobulin transfer via the placenta to the foetus is not static: it is minimal in the first trimester and reaches maximal transfer by the third trimester. Supplemental dosing is recommended when eculizumab is administered to aHUS patients receiving plasma infusion or exchange.

The decision to use eculizumab is complex and is made on a case by case basis, as these women are often severely unwell and have life-threatening conditions. Eculizumab should not be withheld on account of pregnancy. Eculizumab is the only effective therapy available for prevention of end stage renal failure and chronic kidney disease in aHUS. Plasma exchange and infusion have no impact on renal outcomes. The rapid initiation of eculizumab therapy is also associated with better renal prognosis.

Take home messages

- TMAs are characterised by MAHA, thrombocytopenia and end-organ injury
- During pregnancy and post-partum, TMAs are usually encountered with HELLP or pre-eclampsia with severe features; however, the TMA may be the result of TTP or aHUS in rare instances
- The overlapping features of TMAs often complicate differential diagnosis in the pregnancy/postpartum setting
- However, delays in appropriate diagnosis and treatment may be life-threatening and health professionals should be aware of the range of TMA disorders so that an accurate diagnosis is made
- A multidisciplinary team approach may be necessary to ensure prompt and accurate diagnosis and treatment of the specific TMA

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