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Characteristics of Women Admitted to Obstetric ICU for Microangiopathic Hemolytic Anemia Variants (MAHA) A 5 year retrospective review

Thesis

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Heba Abd El Karim

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List of Abbreviations

Abb.	Full term
ACOG	American College of Obstetricians and Gynecologists
ADAMTS13	A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13
AFE	Amniotic fluid embolism
AFLP	Acute fatty liver of pregnancy
ALT	Alanine aminotransferase
APS	Antiphospholipid syndrome
AST	Aspartate aminotransferase
BP	Blood pressure
CFH	Complement factor H
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
C-TMA	Complement-mediated thrombotic microangiopathy
DGKE	Diacylglycerol kinase epsilon
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
GFR	Glomerular filtration rate
HELLP	Haemolysis, elevated liver enzymes and low platelets
HTN	Hypertension
HUS	Hemolytic uremic syndrome
ICU	Intensive care unit
IVIG	Intravenous immune globulin
LDH	Lactate dehydrogenase
MAHA	Microangiopathic Hemolytic Anemia
MELD	Model for End-stage Liver Disease

List of Abbreviations Cont...

Abb.	Full term
MRI	Magnetic resonance imaging
PET	Pre-eclamptic toxaemia
PEX	Plasma exchange
SPET	Severe preeclampsia
STEC	Shiga toxin-producing Escherichia coli
ST-HUS	Shiga toxin-mediated hemolytic uremic syndrome
TMA	Thrombotic microangiopathies
TTE	Transthoracic echocardiography
TTP	Thrombotic thrombocytopenic purpura

INTRODUCTION

Microangiopathic Hemolytic Anemia (MAHA) refers to anemia caused by destruction of erythrocytes due to physical shearing as a result of passage through small vessels occluded by systemic microthrombi. MAHAs are characteristically accompanied by thrombocytopenia in the absence of defects in coagulation ***(Moake et al., 2002).***

Thrombotic microangiopathies (TMA) are a group of related disorders that are characterized by thrombosis of the microvasculature and associated organ dysfunction, and encompass congenital, acquired, and infectious etiologies. A hallmark of these disorders is the fragmentation of erythrocytes by the microvascular thrombi, resulting in a nonimmune microangiopathic hemolytic anemia (MAHA) ***(Moake et al., 2002; George et al., 2014).***

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 HUS**,** 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, ***(Scully et al., 2012)*** but will not be dealt with in this review**.**

Conditions	Definition
Preeclampsia	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 ≥03 g protein in 24 h) ***(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).***
HELLP (haemolysis, elevated liver enzymes and low platelet count)	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).***
HUS	Hemolytic uremic syndrome (HUS) is a rare and severe form of thrombotic microangiopathy associated with a poor renal prognosis. It is characterized by the association of mechanical hemolytic anemia, thrombocytopenia, and kidney failure ***(Noris & Remuzzi, 2009).***
AFLP	This is a rare life-threatening illness (incidence approximately 5 per 100 000 deliveries) associated with significant maternal and perinatal mortality ***(Knight,***

Conditions	Definition
	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).***
TTP	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 (below150x 10^9/l, but more usually less than 50x10^9/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).***

Although these syndromes have similar pathologic features of TMA and similar clinical features, they are distinct entities with distinct etiologies and pathogenesis. The etiology of preeclampsia is not well understood. It may be related to abnormal placental function causing increased resistance to

placental blood flow, which may be related to the systemic hypertension ***(George et al., 2014).***

TTP is a systemic disorder of microvascular thrombosis related to severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), most commonly an acquired autoimmune disorder. TTP can also be hereditary, caused by homozygous or compound heterozygous *ADAMTS13* mutations ***(George et al., 2014).***

HUS is a disorder of dysregulation of the alternative complement pathway, most commonly hereditary with heterozygous mutations of genes encoding complement regulatory proteins. It may also be acquired with antibodies to complement factor H, the major regulatory protein of the alternative complement pathway ***(George et al., 2014).***

An important issue for the evaluation of a pregnant or postpartum woman with severe MAHA and thrombocytopenia is to appreciate the relative incidence of PE/HELLP syndrome, TTP, HUS, and AFLP. PE/HELLP syndrome is much more common than either TTP or HUS ***(George et al., 2014).***

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., 2012).***