# Management of Thrombotic Microangiopathy overlap syndrome: A clinical trial

#### Thesis

Submitted for Partial Fulfillment of M.D.

Degree
in Obstetrics & Gynecology

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## Acknowledgement

First of all, all gratitude is due to Allah almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to Mohamed Adel El-Nazer, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.

I would like also to express my sincere appreciation and gratitude to Dr. Abdelatif Galal El Kholy, Assistant professor of obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his continuous directions and support throughout the whole work.

I cannot forget the great help of Dr. Moustafa Fouad Gomaa, Assistant professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his invaluable efforts, tireless guidance and for his patience and support to get this work into light.

Words fail to express my love, respect and appreciation to my Wife for her unlimited help and support.

Jast but not least, I dedicate this work to My family, specially My mother, whom without their sincere emotional support, pushing me forward this work would not have ever been completed, of course My Father & his Soul Who has been my mentor & enlightened the path for me.



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#### List of Abbreviations

ADAMTS13 A disintegrin and metalloproteinase with a

thrombospondin type1 motif, member 13

**AFLP** Acute fatty liver of pregnancy

**aHUS** Atypical hemolytic uremic syndrome

**APHge** Antepartum hemorrhage

**APLS** Antiphospholipid syndrome (catastrophic)

(CAPS)

**APS** Antiphospholipid syndrome

**ARDS** Adult respiratory distress syndrome

**AST/ALT** Aspartate aminotransferase/Alanine

aminotransferase

**ATIII** Antithrombin III

**BMI** Body mass index

**BP** Blood pressure

**BUN** Blood urea nitrogen

**CBC** Complete blood cell

**CMP** Complete metabolic panel

**COCP** Combined oral contraceptive pill

**CSA** Cyclosporine A

**CT** Computerized tomography

**DAT** Direct antiglobulin test

**DIC** Disseminated intravascular coagulation

**ESRD** End-stage renal disease

**FBC** Full blood count

**FDA** Food and drug administration

**GVHD** Graft-versus-host disease

#### Tist of Aberrations &

**HAART** Highly active antiretroviral therapy

**HBP** High blood pressure

**HCT** Hematocrit

**HEENT** Head, ears, eyes, nose and throat

**HELLP** Hemolysis, elevated liver enzymes and low

platelets

**HGB** Hemoglobin

**HIV** Human immunodeficiency virus

**HRP** Horseradish peroxidase

**HUS** Hemolytic uremic syndrome

**ICHge** Intracranial hemorrhage

**IgG** Immunoglobulin G

**IQR** Interquartile range

**IV** Intravenously

**LCHAD** Long-chain 3-hydroxyacyl-CoA dehydrogenase

deficiency

**LDH** Lactate dehydrogenase

**LFTs** Liver function tests

**LMWH** Low molecular weight heparin

**LSCS** Lower segment cesarean section

MAHA Microangiopathic hemolytic anemia

**MRI** Magnetic resonance imaging

**OD** Once daily

**PET** Pre-eclampsia

**PEX** Plasma exchange

**PG** Primigravida

**PGF** Placental growth factor

#### Flist of Aberrations &

**PI** Plasma infusion

**PPHge** Postpartum hemorrhage

**PT** Prothrombin time

**PV** Plasma volume

**S/D FFP** Solvent/detergent-treated fresh frozen plasma

**SIRS** Systemic Inflammatory Response Syndrome

**SLE** Systemic lupus erythematosus

Stx-HUS Shiga toxin–associated hemolytic-uremia

syndrome

**SVD** Spontaneous vaginal delivery.

**sVEGFR-1** Soluble vascular endothelial growth factor

receptor-1

**TAM** Transplant-associated microangiopathy

**TBV** Total blood volume

TLC Total leucocytic count

**TMAs** Thrombotic microangiopathies

**TMB** Tetramethylbenzidine

**TTP** Thrombotic thrombocytopenic purpura

 $\mathbf{U} + \mathbf{E}$  Urea and Electrolytes test

**ULVWF** Ultra large multimers of VWF

**VEGF** Vascular endothelial growth factor

**VWF** Von Willebrand factor

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#### Introduction

The thrombotic microangiopathies are microvascular occlusive disorders characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia and mechanical erythrocytes. injuries to the The thrombotic microangiopathies include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The incidence of thrombotic microangiopathies is one in every 25000 births. These microangiopathies are often mistaken for preeclampsia and the HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome leading to a delay in the diagnosis and treatment thus contributing to the significant mortality and morbidity (Patnaik et al., 2003).

In the last 15 years there has been a marked increase in the understanding of the pathogenesis of TTP. It is now recognized that congenital and acute acquired TTP are due to a deficiency of von Willebrand factor (VWF) cleaving protein (*Fujikawa et al.*, 2001; Levy et al., 2001).

Ultra large multimers of VWF (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart and kidneys. Diagnosis can be difficult, as there is clinical overlap with haemolytic uraemic syndrome (HUS),

autoimmune disease and a spectrum of pregnancy-related problems (*Furlan et al.*, 1998).

Thrombotic thrombocytopenic purpura was originally characterized by a pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurological signs, renal impairment and fever, often with insidious onset. However, TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation and renal abnormalities and fever are not prominent features. The revised diagnostic criteria state TTP must be considered in the presence of thrombocytopenia and MAHA alone (Galbusera et al., 2006). This can result in an increased referral of other TMAs. TTP remains a diagnosis based on clinical history, examination of the patient and the blood film.

The Subgroups of TTP are congenital TTP, Acute idiopathic TTP, HIV-associated TTP, Drug-associated TTP, Transplant-associated microangiopathy, Malignancy-associated thrombotic microangiopathy, Pancreatitis-associated TTP and Pregnancy-associated TTP.

Pregnancy can be the initiating event for approximately 5–25% of TTP cases (*Vesely et al.*, 2004; *Scully et al.*, 2008), which are late onset adult congenital TTP or acute idiopathic TTP. Differentiating TTP from the

more common pregnancy-related TMAs, such as preeclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and HUS is difficult, especially if TTP presents post-partum (Table 1). Thrombosis occurs in the placenta in untreated TTP pregnancies and results in fetal growth restriction, intrauterine fetal death and pre eclampsia. There is a continued risk of relapse during subsequent pregnancies (*Ducloy-Bouthors et al.*, 2003; Scully et al., 2006).

Table (1): Selective intensity of the main parameters in HELLP syndrome and its main imitators (*Pourrat et al.*, 2015).

	HELLP	AFLP	TTP	HUS
Hemolysis	+ to +++	0 to +	+++	++ to +++
Schistocytosis	+ to ++	0 to +	+++	++ to +++
Elevated LDH	++ to +++	+ to ++	+++	++ to +++
Elevated liver enzymes	++ to +++	++ to +++	0 to +	0 to +
Low platelet count	++ to +++	+ to ++	+++	++ to +++
Factor V	N or ↓	11	N	N
Total bilirubin	+	++ to +++	+ to ++	+ to ++
Proteinuria	+++	+	+ to ++	+ to +++
Renal failure	0 to ++	+	0 to ++	++ to +++
DIC	+ to ++	+ to +++	0	0
Hypoglycemia	0 to +	+ to +++	0	0
ADAMTS 13 activity	Detectable	NA	Undetectable	Detectable
Fever	0	+	++	0

HELLP, hemolysis, elevated liver enzymes and low platelet count; AFLP, acute fatty liver of pregnancy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic and uremic syndrome; LDH, lactate dehydrogenase; DIC, disseminated intravascular coagulation; ADAMTS 13, a disintegrin and metalloproteinase domain with thrombospondin type-1 motif A disintegrin and metalloproteinase with a thrombospondin type1 motif, member 1; NA, not assessed.

The Haemolytic uraemic syndrome is divided into diarrhea positive (D+) HUS, associated typically with verotoxin-induced bloody diarrhea, is treated with supportive care, which in some cases includes renal dialysis. Diarrhea negative (D-) HUS, not typically associated with bloody diarrhea, but may sometimes be associated with multisystem symptoms, similar to TTP, should be urgently treated with Plasma exchange (PEX) (*Kim et al.*, 2011).

The primary differentiating factor between HUS and TTP is the presence of oliguric/anuric renal impairment/failure in HUS. Increasingly, the role of complement defects in D-, atypical HUS is being defined (*Kavanagh & Goodship*, 2010) and use of the complement inhibitor, eculizumab, appears successful in these cases (*Al- Akash et al.*, 2011; *Riedl et al.*, 2011), but may also have a role in severe D+HUS (*Lapeyraque et al.*, 2011).

During the treatment of acute TTP we should start PEX with 1.5 PV exchanges, using plasma in all age groups and reassessed daily, the volume of exchange can be reduced to 1.0 PV when the clinical condition and laboratory test results are stabilizing but intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases.