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ملاحظات:

ملاحظات:



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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

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List of Contents

Title	Page No.
List of Tables	i
List of Figures	iii
List of Abbreviations.....	v
Introduction	1
Aim of the Work.....	6
Review of Literature	
Obstetric ICU Admissions	7
Microangiopathic Hemolytic Anemia.....	18
Patients and Methods.....	82
Results	85
Discussion	123
Summary	132
Conclusion	135
References	136
Arabic Summary	—

List of Tables

Table No.	Title	Page No.
Table (1):	Differential diagnosis of thrombocytopenia and microangiopathic haemolytic anaemia.	21
Table (2):	Comparison of frequency of signs, symptoms, and laboratory findings in TTP, HUS, HELLP, and AFLP.....	51
Table (3):	Demographic data.....	86
Table (4):	Obstetric history.	86
Table (5):	Prevalence of relevant medical diseases in the whole study population	87
Table (6):	Obstetric complications.	88
Table (7):	Mode of delivery:	89
Table (8):	ICU data.	90
Table (9):	Lab investigations	91
Table (10):	Final diagnosis and maternal outcome:.....	93
Table (11):	Neonatal outcome.	95
Table (12):	IUFD cases.	96
Table (13):	Demographic data.....	97
Table (14):	Obstetric history	99
Table (15):	Medical history	101
Table (16):	Obstetric complications.	103
Table (17):	Mode of delivery.	104
Table (18):	Neonatal outcome.	106
Table (19):	ICU data.....	109
Table (20):	Haemoglobin and INR	112
Table (21):	Platelet.	114
Table (22):	Shows comparison between study cases as regard kidney function tests.	116

List of Tables Cont...

Table No.	Title	Page No.
Table (24):	Comparison between study cases as regard liver function tests.....	117
Table (25):	Comparison between SPET and AFLP regarding liver enzymes:.....	118
Table (26):	Shows comparison between study cases regarding duration of ICU stay and maternal outcome:.....	119
Table (27):	Shows correlation between clinical data and poor outcome:.....	121
Table (28):	Showing correlation between laboratory finding and poor outcome.....	122

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Pregnant/postartum women with MAHA, Thrombocytopenia.....	21
Figure (2):	Data collection Flow chart.....	85
Figure (3):	Prevalence of relevant medical diseases in the study population.	88
Figure (4):	Mode of delivery.....	89
Figure (5):	Albumin in urine at the time of admission.....	92
Figure (6):	Final diagnosis	94
Figure (7):	Comparison between study cases regarding age.....	98
Figure (8):	Comparison between study cases regarding parity.....	100
Figure (9):	Comparison between study cases regarding different medical conditions found among study population	102
Figure (10):	Comparison between study cases regarding gestational age.....	102
Figure (11):	Comparison between study cases regarding mode of delivery.....	105
Figure (12):	Comparison between study cases regarding neonatal weight.	108
Figure (13):	Comparison between study cases regarding gestational age.....	108
Figure (14):	Comparison between study cases regarding ICU pulse and blood pressure.	110
Figure (15):	Comparison between study cases regarding urine output.....	110

List of Figures Cont...

Fig. No.	Title	Page No.
Figure (16):	Comparison between study cases regarding Galascow coma scale.....	111
Figure (17):	Comparison between study cases regarding Hb level.....	113
Figure (18):	Comparison between study cases regarding INR.	113
Figure (19):	Comparison between HELLP, HUS and TTP regarding PLT level lowest and at discharge.....	115
Figure (20):	Analysis of maternal mortality.	120
Figure (21):	Comparison between study cases regarding maternal outcome.....	120

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 <i>Escherichia coli</i>
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 toxemia, 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 (<i>Mol et al., 2016</i>), 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) (<i>NICE, 2010</i>). 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) (<i>NICE, 2010</i>).
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 (<i>Barton et al., 1992</i>).
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 (<i>Noris & Remuzzi, 2009</i>).
AFLP	This is a rare life-threatening illness (incidence approximately 5 per 100 000 deliveries) associated with significant maternal and perinatal mortality (<i>Knight,</i>

Conditions	Definition
	<i>2008</i>). 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 (<i>Hay, 2008</i>).
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 (below $150 \times 10^9/l$, but more usually less than $50 \times 10^9/l$), 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 (<i>Scully et al., 2012</i>).

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*).