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LDH/AST ratio: a future resource for thrombotic microangiopathies differential diagnosis in pregnancy

Abstract

Objective: To evaluate the clinical approach, the diagnostic method and the most appropriate therapeutic management of thrombotic microangiopathies (TMA) in pregnancy, still leading killers in the obstetric area today.

Materials and methods: A large review of the international literature and available clinical studies has been carried out in order to define the current state of the art regarding TMA in pregnancy. In the light of this, 9 clinical cases, among 152 TMA cases, of pregnant women hospitalized and who gave birth in the Pisa University Hospital O.O. U.U. Gynecology and Obstetrics 1 and 2 from 2010 to 2019, were identified, analyzed and re-discussed.

Results: Analyzing the diagnostic method and the medical records, we made a critical review of these 9 cases, accurately analyzing the diagnoses made. Among these cases, 6 Thrombotic Thrombocytopenic Purpura (TTP), 2 HELLP Syndrome and 1 Atypical Hemolytic Uremic Syndrome (aHUS) were diagnosed during pregnancy. By analyzing the medical records, the diagnostic method and the therapeutic management of these patients, we questioned the diagnoses made. These diagnoses, from our analytical point of view, are partially not corresponding, being 4 cases of TTP and 5 possible cases of aHUS.

Conclusion: From the review of our case history, in the Pisa Obstetric clinics, it is possible to find an under diagnosis of the aHUS cases compared to those of TTP and HELLP syndrome, due both to the unavailability of the ADAMTS13 functionality test and to the unused LDH/AST ratio, which in our opinion could represent a future resource in diagnostic approach to thrombotic microangiopathies in pregnancy.

Keywords: thrombotic microangiopathies, pregnancy, HELLP syndrome, thrombotic thrombocytopenic purpura

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Abbreviations: TMA, thrombotic microangiopathies; TTP, thrombotic thrombocytopenic purpura; aHEU, atypical hemolytic-uremic syndrome; CID, disseminated intravasal coagulation

Introduction

Thrombotic microangiopathies (TMA) comprise a heterogeneous group of syndromes that share common pathological characteristics, or rather endothelial cellular damage and microvascular thrombosis, and a clinical triad characterized by thrombocytopenia, hemolytic anemia and signs of ischemic suffering in various body areas, mainly, but not limited to kidney and central nervous system.[1]

TMA are: Pre-eclampsia/Eclampsia, HELLP syndrome, thrombotic thrombocytopenic purpura (TTP), atypical hemolytic-uremic syndrome (aHEU) and typical, disseminated intravasal coagulation (CID) and antiphospholipid antibody syndrome.

TMA are classified in primary and secondary forms. In their primary forms, the disease is defined by the presence of a thrombotic microangiopathies, such as TTP, due to the deficiency of ADAMTS13, a metalloprotease that cleaves the von Willebrand Factor (FvW), and as aHUS characterized by complement dysregulation.[2] In their secondary forms, on the other hand, they present themselves as events in which TMA arises as a complication of an underlying medical condition: pregnancy is the typical one, but also malignant hypertension, as a complication of a Preeclampsia or HELLP syndrome, drug use, kidney transplantation or bone marrow, systemic lupus erythematosus and tumors.[3]

TMA are problematic disorders, due to the imbalance between the coagulation systems, the immune system and the complement system.[4] Pregnancy is associated with physiological changes in the microcirculation and in the hemostatic balance, which can show a congenital TMA, hitherto silent, or it can be itself the trigger factor of a secondary TMA.[5]

In pregnancy there is a framework of hypercoagulation and hypofibrinolysis, with physiological state of "CID", mainly due to hormonal state, necessary to protect the mother from bleeding complications during pregnancy, but especially in the period of childbirth and postpartum.[6]

TTP and aHUS are not specific pathologies of pregnancy, but occur more frequently during or in relation to it. The incidence of these in pregnancy is respectively 1/20 pregnancies for Preeclampsia, 1/1000 pregnancies for HELLP syndrome, 1/25000 pregnancies for HUS and 1/200000 pregnancies for TTP.[7]

All TMA are characterized by a modest degree of thrombocytopenia (PLT<100,000 in pregnancy), the presence of schistocytes in the peripheral smear (>1%) and microangiopathic hemolytic anemia (elevated LDH levels, decreased hemoglobin and haptoglobin). Each

pathology has peculiar aspects: high blood pressure is a characteristic of Preeclampsia, gastrointestinal disorders (diarrhea, nausea and vomiting, abdominal pain in the upper right quadrant) of HELLP syndrome, renal commitment (increase of creatinine and decrease of glomerular filtration rate) of aHUS and neurological disorders (confusion mental, headache and visual disturbances) of TTP.[8]

TTP and aHUS differ mainly during their onset period; in fact TTP occurs in 83% of cases in the second and third trimesters, given the physiological reduction of ADAMTS13 activity during pregnancy which can induce an underlying pathology. Instead aHUS occurs in 78% of cases in the post-partum period, and this is believed to be due to the activation and dysregulation of the alternative pathway of the complement system; this is due to inflammation secondary to delivery, to release in the circulation of fetal cells, endothelial cellular damage and postpartum infections or hemorrhages.[9]

The differential diagnosis between these disorders is very complex, both because they have overlapping clinical features, and also because they affect various disciplines (gynecology, hematology, nephrology, etc.). They are often diagnosed as HELLP syndrome or severe eclampsia (PE-SF) during or after delivery. The confusion stems from the fact that HELLP and PE-SF are more common complications in pregnancy, compared to TTP and HUS which are very rare complications.[10] In addition, the clinical and laboratory presentation changes progressively and rapidly over time, so women must be followed constantly and it is essential to make an early diagnosis for the patient's outcome. Each syndrome has a specific and particular treatment which, if administered promptly, can save the life of the woman and/or the unborn child. Therefore, it is clear how important the differential and early diagnosis of these syndromes is, given their high mortality and morbidity.

The differential diagnosis between TMA calls for, where severe thrombocytopenia is found especially if less than 50,000/mm^3, the evaluation of blood pressure and proteinuria to make a DD with preeclampsia, the search for the presence of schistocytes in the peripheral smear, of the indices hemolysis, haptoglobin and Hb values, assessment of liver function and GI symptoms for DD with HELLP syndrome. In cases where worsening thrombocytopenia occurs, with LDH values greater than 1000IU and Creatinine values greater than 2mg/dl, the dosage of ADAMTS13 functionality is indicated. Values above 10% are strongly indicative for a possible diagnosis of aHUS, values below 10% are diagnostic for TTP.[10]

One of the main problems in the Pisa Obstetrics and Gynecology clinics is the lack of the ADAMTS13 functionality test, that is currently carried out in the Milan laboratories and therefore waiting times are extremely long and unacceptable for a timely diagnosis. It is desirable to start the ADAMTS13 dosage also in Pisa in our local laboratories to make increasingly precise and rapid diagnoses.

Furthermore, TMA occur mainly in the peri-partum period, and obviously carrying out an exhaustive diagnosis during such a delicate moment is very difficult, above all because maternal and fetal health worsens rapidly and therefore more than trying to put the diagnosis first, we try to intervene promptly to safeguard maternal and fetal life.

Since the differential diagnosis and the moment in which the syndromes occur are very difficult, a scientific study carried out by the Gynecology and Obstetrics departments of Los Angeles and New York, conducted by Dr. Gupta and Dr. Feinberg,[10] based on a systematic review of the scientific literature of recent years, the authors have formulated a diagnostic algorithm, to help address a differential diagnosis between TMA. The authors highlighted a substantial difference between the HELLP syndrome and the aHUS that could help clinicians orient themselves between the two often nuanced and confusing syndromes; in HELLP syndrome there is a higher increase in the liver damage indices compared to the hemolysis indices, while in the aHUS the opposite is evident. This difference can be summarized in the LDH/AST ratio, which is always less than 10 in the HELLP syndrome and greater than 10 in the aHUS. This report could be very useful to our clinicians to guide the diagnosis and exclude one of the two syndromes, together with the laboratory results (ADAMTS13) and the resolution or the continuous deterioration of the patient's clinical picture after the delivery, respectively in the HELLP syndrome and in the aHUS.

Purpose of the study

The study aims to evaluate the diagnostic and therapeutic management of TMA during pregnancy in the hospital setting, to offer the clinician an in-depth and updated knowledge of TMA, in the light of an updated literature, thanks to the attention of the scientific community relatively recent for this group of serious pathologies which are potentially fatal for the life of women and the unborn child and whose knowledge is still limited today.

The attention should be focused on the alarm bells of the TMA, useful in the timely and accurate diagnosis of these syndromes. The clinical signs of ALERT are: rapidly worsening thrombocytopenia (<50,000/mm^3), sudden worsening of renal function (Creatinine>2mg/dl), elevation of hemolysis indices and rapid peri-partum but especially post-partum onset. In these cases, we must always suspect a aHUS, evaluate the response to plasma therapy, follow the evolution of the clinical and laboratory framework frequently, and be prepared to promptly review the diagnosis.

The aim of the study is to make people understand the importance of these pathologies, which, although rare, are being diagnosed more and more in our departments in recent years, as knowledge is essential to being able to recognize and operate on time, in order to offer adequate and timely treatment and, where possible, to prevent it.

Materials and methods

A review of the international literature and available clinical studies has been carried out in order to define the current state of the art regarding TMA in pregnancy. In the light of this, 9 clinical cases, among 152 TMA cases, of pregnant women hospitalized and who gave birth in the Pisa University Hospital O.O. U.U. Gynecology and Obstetrics 1 and 2 from 2010 to 2019 were identified, analyzed and re-discussed. The clinical cases were researched, through the administrative management of health operations, the diagnosis of each patient through the clinical DRGs, the visualization of each medical record for exclude false positives to possible diagnosis of TMA, and patients with other comorbidities or other pathologies of pregnancy. The cases were selected based on the characteristics of each medical record, evaluating laboratory tests (platelets, LDH, transaminases, schistocytes present, the coagulation structure, bilirubin and especially creatinine), in response to childbirth or plasmapheresis. In addition, were investigated cases in which there was an unexplained thrombocytopenia in the peri-partum, and clinical cases in which there was an acute post-partum renal failure with creatinine values>2mg/dl, which make suspect an aHUS.

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In the diagnosed in our ward since 2010, there are 9 suspect cases whose critical diagnosis we analyzed and reviewed.

Results

Analyzing the diagnostic process and the medical records, we made a critical review of these 9 cases, questioning precisely the diagnoses made. Among these 9 cases, 6 cases of Thrombotic Thrombocytopenic Purpura, 2 cases of HELLP Syndrome and 1 case of Atypical Hemolytic Uremic Syndrome were diagnosed in pregnancy (Table 1).

Table 1 Critical review of 9 cases

Patients	Diagnosis made	Probable differential diagnosis
P.M.C.	TTP	aHUS
V.M.	TTP (correct)	
M.D.	TTP	aHUS post-partum
S.L.	TTP	aHUS post-partum
D.M.	HELLP	TTP
F.R.	TTP	aHUS post-partum
Z.N.	TTP (correct)	
E.M.H.	HELLP	TTP
M.G.	aHUS (correct)	

However, when analyzing these patients, we deduced that some of these diagnoses could be questioned and therefore from our critical review the 6 cases of TTP could be 4 possible cases of aHUS and 2 cases of TTP. In addition, the 2 cases diagnosed as HELLP syndrome in our opinion could be put in differential diagnosis with a TTP. Instead the diagnosis of aHUS was found to be correct.

The Table 2 above shows the probable cases of undiagnosed aHUS in yellow and the cases of TTP in white. As we can see, all have a more or less high degree of thrombocytopenia, the liver involvement occurs mainly in the cases of TTP instead the renal one is more specific than the aHUS, in all cases there are schistocytes and the elevation of the hemolysis indices but as we can see the LDH/AST ratio showed a substantial difference between the aHUS and the TTP. In fact, as announced by the scientific study carried out by the Gynecology and Obstetrics departments of Los Angeles and New York,[8] the LDH/AST ratio is greater than 10 in cases of aHUS and less than 10 in cases not only of HELLP syndrome (as the study showed di Gupta) but also in cases of TTP, as it appears in our patients.

Some of these patients had hypertension and proteinuria, therefore, had been diagnosed as cases of preeclampsia. Neurological symptoms were present only in cases of TTP, almost all of them were treated with plasmapheresis except for one case diagnosed as aHUS that was treated with the drug Eculizumab. It can be noted that the onset of clinical and laboratory symptoms occurred mainly in the post-partum period, but the maternal outcome is substantially different; as we can see the patients probably affected by aHUS after treatment with plasmapheresis, in two cases acute renal failure has arisen, in the others the stabilization of platelet values (PLT>100.000/mm^3) occurred after at least 1-2 weeks of continuous plasma therapy. However, in the patient treated with Eculizumab, the resolution occurred in just 3 days. In the probable cases of TTP, where plasmapheresis is the first line of treatment, the stability of the blood chemistry values, on the other hand, occurred at most in 5 days, except in a particular case where the woman was suffering from severe post-partum hemorrhage and therefore the resolution of the laboratory values took place after 10 days (Table 3).

Table 2 The probable cases of undiagnosed aHUS in bold and the remaining cases of TTP

Patients	Thrombocytopenia	Transaminase	Creatinine	Schistocytes	LDH	LDH/AST
P.M.G.	**++**	**+**	**+++**	**+**	**+++**	**73**
V.M.	+++	+++	-	+	+++	<10
M.D.	**++**	**-**	**++**	**+**	**++**	**31**
S.L.	**+++**	**+**	**++**	**+**	**++**	**>10**
D.M.	+++	++	-	+	+	<10
F.R.	**+++**	**-**	**+++**	**+**	**+++**	**27**
Z.N.	++	-	-	+	+	<10
E.M.H.	+++	+++	-	+	+++	<10
M.G.	**+++**	**++**	**+++**	**+**	**++**	**>10**

Trombocytopenia: + >70.000, ++50-70.000, +++ <50,000. Transaminase: + <100, ++100-500, +++ >500. Creatinine: + >1,2, ++ >2, +++ >3. LDH: + <1000, ++ >1000, +++ >1500

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Table 3 Some of these patients had hypertension and proteinuria, therefore, had been diagnosed as cases of preeclampsia

Hypertension	Protenuria	Neurological symptoms	Therapy	Delivery	Onset	Maternal outcome	Fetal outcome/ apgar
-	**-**	**-**	**Plasmapheresis**	**in another Hospital**	**22 weeks**	**Kidney Failure**	
++	-	+	Plasmapheresis	Emergency C-section at 32 weeks	post-partum	Stabel after 3 days	Alive
++	**+**	**-**	**Plasmapheresis**	**Induced at 34 weeks**	**post-partum**	**Kidney Failure**	**Alive/9**
++	**+**	**-**	**Plasmapheresis**	**Spontaneous at 39 weeks**	**post-partum**	**Stabel after 7 days**	**Alive/9**
+	+	+	Plasmapheresis	Urgency C-section at 31 weeks	pre-partum	Stabel after 5 days	Alive/7
-	**-**	**-**	**Plasmapheresis**	**Urgency C-section at 31 weeks**	**post-partum**	**Stabel after 14 days**	**Dead (traced alterations)**
-	-	+	Plasmapheresis	Spontaneous at 36 weeks	pre-partum	Stabel after 10 days	Alive
++	++	+	Plasmapheresis	Emergency C-section at 29 weeks	post-partum	Stabel after 4 days	Alive/7
-	**-**	**-**	**Eculizumab**	**Emergency C-section at 34 weeks**	**post-partum**	**Stabel after 3 days**	**Alive/7**

Discussion

Discussing on our analytical review, four cases diagnosed as TTP probably concealed an aHUS, both in relation to the worsening increase in creatinemia in the peri-partum period and the onset of an acute renal failure with values of thrombocytopenia not responsive to plasmapheresis.

The correct diagnosis of aHUS is genetic but in the peri-partum period the onset of the syndrome is acute and it is impossible to carry out a genetic screening, therefore our goal is to warn clinicians in some rare and particular cases that can make suspect an aHUS . The alarm bells are: rapid and worsening thrombocytopenia, sudden worsening of renal function (creatinine>2mg/dl) and elevation of the hemolysis indices, pre or especially postpartum, which do not improve with plasmapheresis.

In fact, there are criteria in favor of aHUS: creatinine>2mg/dl, LDH>1000IU and hemoglobin <8mg/dl, positive family history for the syndrome, postpartum onset and persistence of signs and symptoms even after 72 hours from childbirth.[10]

ADAMTS13 dosage is essential to implement a timely and accurate differential diagnosis between TTP and aHUS. In the case of delayed reporting of ADAMTS 13, if after 5 days of plasma therapy, the platelet count and the LDH level are not normalized or the serum creatinine level has not decreased by at least 25%, we must put the diagnostic suspicion of aHUS and promptly switch to Eculizumab.[11]

In patients with aHUS, Eculizumab treatment blocks the uncontrolled activation of the terminal portion of the complement cascade and the consequent mediated complement thrombotic microangiopathy. Data relating to pregnancies exposed to Eculizumab indicate that there is no increased risk of fetal malformations or fetal/neonatal toxicity. Eculizumab has proven to be a safe drug in pregnancy and has been the first treatment line for HUS since 2011. Numerous studies have confirmed that its use can change maternal outcome very quickly and determine a prompt resolution of TMA with recovery of kidney function.[12] When the availability of a diagnostic test does not exist, to orientate differential diagnosis among these syndromes it is desirable to use the LDH / AST ratio, which is higher than 10 in the aHUS and lower in the HELLP and/or TTP syndrome.[10]

Conclusion

From the review of our case history in the obstetric clinic we can see an under diagnosis of the aHUS cases compared to those of TTP, mainly due to the lack of the functionality test of the ADAMTS13 (not available in Pisa) which is essential to make a quick and precise differential diagnosis between TMA.

What we can deduct from this work is that the road to a correct differential diagnosis is very tortuous and demanding, especially without the availability of the ADAMTS13 functionality test, but we can propose the alternative use of the LDH/AST ratio to suspect an aHUS in pregnancy and differentiate it from HELLP syndrome, a practical and simple turning point to guide the diagnosis even without the use of ADAMTS13. The multi- and inter-disciplinary approach to tackle these rare diseases characterized by high diagnostic-therapeutic and caring complexity and burdened by high lethality and morbidity also appears fundamental. In addition to the gynecologist, the multidisciplinary team must also include the hematologist, nephrologist, immunologist, apheresis transfusionist and neonatologist. To all these specialist figures, also the geneticist must be added, due to the fundamental role in the pre-conceptional phase of re-planning of possible and further pregnancies.[13]

In loving memory of C.C., TTP in 1988, united in commitment and in hope that the memory of her sacrifice will help save many more lives!

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Conflicts of interest

The authors declare there are no conflicts of interest.

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