EXTENDED ABSTRACT

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LDH/AST Ratio: A Future Chance for Differential Diagnosis in Pregnancy Thrombotic Microangiopathies and Beyond

Battini Lorella2*, Mei Federica1, Falchi Nadia1, Taramaschi Denise2, Nigro Serena1, Bertolotto Alessandra3, Bianchi Cristina3, Trojano Giuseppe2, Simoncini Tommaso1, Egidi Maria Francesca4, Bottone Pietro2

1. Fetal Maternal Department, Pisa University, Healthcare System, First Unit, AOUP, Pisa, Italy
2. Fetal Maternal Department, Pisa University Healthcare System, Second Unit, AOUP, Pisa, Italy
3. Endocrinology and Metabolism Department, Pisa University, Healthcare System, AOUP, Pisa, Italy
4 Nephrology, Transplants and Dialysis Unity, Pisa University Hospital, Pisa, Italy

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Abstract

Thrombotic microangiopathies (TMA) include 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, haemolytic anaemia 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 haemolytic-uremic syndrome (a-HUS) and typical, disseminated intravascular 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 (Fv-W), and as a-HUS 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 haemostatic 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 hypo-fibrinolysis, 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 a-HUS 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 haemolytic anaemia (elevated LDH levels, decreased haemoglobin 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 a-HUS and neurological disorders (confusion mental, headache and visual disturbances) of TTP.8

TTP and a-HUS 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 a-HUS 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 foetal 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 (gynaecology, haematology, 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/mm3, 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 haemolysis, 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 Gynaecology 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 foetal health worsens rapidly and therefore more than trying to put the diagnosis first, we try to intervene promptly to safeguard maternal and foetal life.

Since the differential diagnosis and the moment in which the syndromes occur are very difficult, a scientific study carried out by the Gynaecology and Obstetrics departments of Los Angeles and New York, conducted by Gupta and 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 a-HUS 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 haemolysis indices, while in the a-HUS 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 a-HUS. 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 a-HUS.

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. Gynaecology and Obstetrics 1 and 2 from 2010 to 2019, were identified, analysed and re-discussed.

Results: Analysing the diagnostic method and the medical records, we made a critical review of these 9 cases, accurately analysing the diagnoses made. Among these cases, 6 Thrombotic Thrombocytopenic Purpura (TTP), 2 HELLP Syndrome and 1 Atypical Haemolytic Uremic Syndrome (a-HUS) were diagnosed during pregnancy. By analysing 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 a-HUS.

Conclusion: From the review of our case history, in the Pisa Obstetric clinics, it is possible to find an under diagnosis of the a-HUS 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 and beyond.

Our next commitment would be to verify if the generalised vasculitis observed in COVID 19 could stand its clinic findings and pathophysiology on a microangiopathy model, both TTP and a-HUS – like, opening the possibility not only to be prevented by low molecular weight heparin and corticosteroids but also treated by plasmapheresis and/or anticomplement drugs in more severe hospitalized patients. From this prospective, obstetric sciences could be a lighthouse to show the escape route from this killer pandemic for human beings, worldwide.