Molecular Advances in Preeclampsia and HELLP Syndrome

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Preeclampsia (PE) constitutes one of the principal reasons for maternal and perinatal morbidity and mortality worldwide. The circumstance typically implicates formerly healthful normotensive women, after 20 weeks of gestation, typically withinside the third trimester, without regarded threat elements or past deliveries. PE can be further complicated with hemolysis and thrombocytopenia, leading to the emergence of HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low platelets). Both conditions are classified as hypertensive diseases of pregnancy (HDP), and their pathogenesis has been linked to an excessive maternal inflammatory response, accompanied by enhanced endothelial activation.

ADAMTS-13 preeclampsia complement system

1. Introduction

Preeclampsia (PE) constitutes one of the major causes of maternal and perinatal morbidity and mortality worldwide. With its global incidence at 4.6%, which varies greatly among different countries and regions, it represents one of the four major reasons for maternal mortality, even in developed countries [1]. The condition usually implicates previously healthy normotensive women, after 20 weeks of gestation, most commonly in the third trimester, without known risk factors or past deliveries [2]. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), it manifests itself with hypertension and proteinuria and can progress to severe multisystem end-organ damage, resulting in liver or renal failure, convulsive activity (eclampsia), acute respiratory distress syndrome (ARDS) due to pulmonary edema or intrauterine growth restriction (IGR). PE can be further complicated with hemolysis and thrombocytopenia, leading to the emergence of HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), with distinctive right upper quadrant abdominal pain [3]. Both entities are included in the scope of hypertensive disorders of pregnancy (HDP), but their exact etiology remains elusive, although multiple studies suggest their multifactorial (maternal and fetal, genetic, and environmental) background [4]. Chronic hypertension, gestational hypertension, and finally, chronic hypertension with superimposed preeclampsia are the other three clinical entities, constituting the general category of hypertensive disorders of pregnancy [5].

The pathophysiology of PE is complex, with the precise underlying cause not fully elucidated, although probably heterogeneous. During PE, the syncytiotrophoblast is damaged, which has been suggested to lead to a compensatory increase in cytotrophoblast proliferation, resulting in poor differentiation of cytotrophoblast cells [6].

PE is also associated with maternal and placental vascular dysfunction, from placentation to beyond delivery. These defects have been attributed to various factors, including endothelial dysfunction, insufficient trophoblast invasion, oxidative stress, and poor placental oxygen extraction. It is uncertain whether the development of vascular impairments in PE is a result of underlying vascular pathology or exclusively a result of elevated trophoblast stress signals to the mother [7]. The PE and/or HELLP syndrome is correlated with, or attributed to, an exaggerated maternal inflammatory process, with increased endothelial activation. Numerous studies report that von Willebrand factor (vWF) antigen levels (vWF:Ag) are significantly increased, while its cleaving protease (ADAMTS-13, A Disintegrin-like and Metalloprotease with Thrombospondin type 1 motif, member 13) activity is normal to decreased in pregnancies affected by PE/HELLP [8][9]. Von Willebrand factor (vWF) is a cardinal mediator for the adhesion and aggregation of platelets' surface to the subendothelial matrix under shear stress. The vWF is synthesized from megakaryocytes and endothelial cells, in a primal form of large multimers that undergo proteolysis into smaller derivatives, under the cleaving assistance of ADAMTS-13. As it is known from the pathogenesis of thrombotic thrombocytopenic purpura (TTP), the inhibited expression of ADAMTS-13 leads to the impairment of vWF cleavage, which, in turn, results in the development of disseminated platelet-rich thrombi in the circulation and the consequent activation of the inflammatory course [10]. Because thrombotic microangiopathies (TMAs) and PE/HELLP syndrome present with similar clinical manifestations in pregnancy, such as end-organ failure due to ischemia, the irregularities in the proteolysis of vWF and the reduced or false expression of ADAMTS-13 are examined thoroughly, regarding their involvement in the development of PE and HELLP syndrome [8][11].

Another key aspect of the pathogenetic mechanisms entailed in the development of PE and HELLP syndrome is the role of the complement system [12]. The complement system is activated and strictly regulated through the classic, lectin, or alternative pathway, as an integral part of the innate immune response to a number of pathogens or damaged cells. Normally, there is some degree of complement activation in pregnancy, which, however, is kept under control, as the placenta expresses complement-inhibiting proteins to sustain the maternal immunological tolerance [4]. Research has suggested that the characteristic of insufficient placental perfusion and the consequent impairments in the utero-placental unit are inextricably linked to disproportionate complement activation, as proven by the elevated urine excretion of the terminal complement complex C5b-9, as well as its increased deposition in the placental surface in preeclamptic women [3]. A great scientific effort is currently ongoing and contributes to the clarification of what triggers the imbalanced complement cascade, whether it is a genetic deficiency in the regulation of the complement system or a maternal immune reaction to the placental cells, or most likely, a combination of both [4].

2. Differential Diagnosis of TMAs

Thrombotic microangiopathies (TMAs) constitute a group of clinical entities with a similar pattern of clinical manifestations and, more specifically, the combination of different organ dysfunction, low platelet counts, and microangiopathic hemolytic anemia. HELLP syndrome and TTP have been correlated with different pathogenetic mechanisms, belonging, however, to the general category of TMAs [13].

Apart from those clinical entities, there are other primary and secondary pathological conditions falling under the general category of TMAs, such as drug-induced and transplantation or malignancy-related TMAs, Uremic Hemolytic Syndrome, conditions related to autoimmune diseases (scleroderma, Systemic Lupus Erythematosus), malignant hypertension and, finally, Disseminated Intravascular Coagulation [13].

The initial step of the diagnostic process is the exclusion of clinical entities, according to the medical record of the investigated patient, for example, the absence of drug intake, transplantation history, or autoimmune diseases [14]. However, the differential diagnosis among different conditions, belonging to the broad spectrum of TMAs, constitutes a challenge in everyday clinical practice and cannot always be based exclusively on clinical manifestations. Therefore, during the past decades, there has been much interest in understanding the pathogenetic mechanisms of TMAs and detecting biomarkers that can lead to a safe and definite diagnosis and prognosis of the clinical course [13].

More specifically, the initial steps of the diagnostic process should be orientated in clinical conditions commonly seen in pregnancy, such as acute fatty liver of pregnancy, preeclampsia, preeclamptic toxemia, eclampsia, and HELLP syndrome. Other clinical entities, which should also be excluded, are antiphospholipid syndrome, systemic lupus erythematosus, disseminated intravascular coagulation, and sepsis [14].

First, the acute fatty liver of pregnancy is characterized by an elevation in conjugated bilirubin, along with intense pain, situated on the upper right abdominal side and is usually a diagnosis based on clinical criteria [14][15]. Weight loss, increased urination, polydipsia, decreased glycose serum levels, along with prolongation in prothrombin time, low factor V and antithrombin levels, and signs of kidney dysfunction, coexist in most of the cases [14]. Echo-Doppler is useful to exclude the possibility of Budd–Chiari syndrome [15].

Moreover, specific laboratory and clinical criteria exist for the diagnosis of antiphospholipid syndrome and systemic lupus erythematosus (International consensus Sydney classification criteria, 2019 EULAR/ACR classification criteria). Sepsis with multiple organ dysfunction should be suspected in the presence of relevant conditions (chorioamnionitis, endometritis, urinary tract infection, severe inflammatory syndrome) and is diagnosed with the conduction of blood cultures, even if high fever is absent [15].

Uremic hemolytic syndrome is frequent in the pediatric population and shares some basic laboratory and clinical characteristics with TTP (jaundice with free bilirubin elevation, liver enzymes and LDH elevation, presence of schistocytes in peripheral blood, extreme thrombocytopenia). The main difference between those two clinical conditions is the predominance of neurological symptoms (blurry vision, convulsions, paresis) in TTP, in contrast with the profound kidney dysfunction in patients with TTP [14]

Furthermore, HELLP syndrome is characterized by an increase in body weight, edema, hypertension, profound urine protein, liver enzymes, and LDH elevation.

3. Role of ADAMTS13, vWF, and the complement system in the Differential Diagnosis

Differential diagnosis between TTP and HELLP syndrome/preeclampsia is crucial because of the different management options. More specifically, delivery is considered the treatment of choice for managing HELLP syndrome and preeclampsia, and a disease resolution is expected 1–2 days postpartum. Complement inhibition may also be beneficial in the broad spectrum of complement-mediated TMAs, including HELLP syndrome. Nevertheless, delivery is not thought to be an acceptable treatment for TTP, as symptoms keep deteriorating postpartum, unless plasmapheresis is performed [15].

In the literature, there are many published case reports, in which TTP was diagnosed postpartum due to the persistence of the disease. Moreover, HELLP syndrome or preeclampsia should also be considered in pregnant women with a personal history of hereditary or acquired TTP. It should also be noted that the coexistence of TTP and PE/HELLP syndrome should not be excluded from the beginning [16][17][18][19][20]. Otherwise, PE/HELLP are thought to be more frequent in patients who have already recovered from TTP, or even induce the development of TTP in predisposed pregnant women [16][19][20]. Although delivery is not mandatory in TTP, it is required when TTP is combined with preeclampsia, even at a gestational age before 34 weeks [21].

The first steps of the diagnostic process should be immediate, based on the co-estimation of personal history, clinical manifestations, and basic laboratory results, since primary intervention plays a critical role in patients' survival. Early gestational age (<20 weeks) can arouse suspicion that the issue is TTP. Nevertheless, it is sometimes difficult to discriminate TTP from HELLP during the third trimester of pregnancy, as there is an overlap in clinical manifestations and laboratory parameters [16]. Hemolysis, low platelets count, hypertension, renal dysfunction, increased liver enzymes and LDH can be found in both clinical entities. On the other hand, the coexistence of seizures, mobility issues, reddish urine, prominent anemia with the presence of schistocytes, and decreased haptoglobins with mild liver enzymes elevation (LDH/AST > 22.12), severely low level of platelets, and fever is more indicative of TTP [15].

ADAMTS13 activity is a key diagnostic tool, since ADAMTS13 deficiency (<20%) confirms TTP diagnosis. In the literature, the cut-off value, below which the diagnosis of TTP can be considered definitive, varies in range, between 5–20% (10% is the most frequently reported) [14][15][16]. In the review of Pourrat et al., it is stated that the measurement of ADAMTS13 activity is considered a reliable practice for the differential diagnosis between TTP and HELLP syndrome. ADAMTS13 is undetectable in TTP, whereas lower levels are found in patients with HELLP syndrome. ADAMTS13 activity has been found to be 31% (12–43%), whereas the expected average value of ADAMTS13 in late pregnancy is higher (71%) [15].

The question is whether ADAMTS13 could be considered a reliable biomarker for the diagnosis of TTP, since there are several studies supporting a statistically significant decrease in ADAMTS13 in other TMAs, such as HELLP syndrome/preeclampsia [2][22][23][24][25][26][27][28]. ADAMTS13 activity values can vary from 12% to 43% in HELLP syndrome. Consequently, even if a deficient level of ADAMTS13 activity is highly diagnostic of TTP, a more

average one cannot exclude the possibility of HELLP syndrome/preeclampsia. Nevertheless, it is believed that a complete absence of ADAMTS13 activity is not compatible with the diagnosis of HELLP syndrome/preeclampsia [20]. The differential diagnosis in patients with average levels of ADAMTS13 activity is usually based on clinical parameters, and further research is needed to establish the use of new and more reliable biomarkers.

On the other hand, whilst the complement system is a crucial part of the inflammatory process of PE and increased amounts of complement components and their activation products, such as C5a, and C5b-9 complex, have been documented in the circulation of PE patients when compared to normal pregnancy, results remain diverse and larger samples are required [29]. Complement activation products have also been discovered in the urine of severe PE, and they are thought to be a sign of complement-mediated kidney injury [30][31]. Moreover, increased levels of the alternate route activation fragment Bb have been proposed to predict PE development [30]. These suggestions, along with the genetic findings that indicate the existence of mutations that facilitate the excessive or unregulated activation of the complement's alternative pathway [32], might constitute, in the future, solid predictive and prognostic factors for an earlier diagnosis of PE and HELLP syndrome.

In addition, in everyday clinical practice, there are some cases where the measurement of ADAMTS13 is not possible or immediate action is needed. Therefore, initial diagnosis and, by extension, the choice of the most appropriate treatment among the available options, is based exclusively on clinical and basic laboratory parameters.

4. Proposed Algorithm for the Differential Diagnosis and Management of Pregnant Women with TMA

4.1. Diagnosis

First, detailed medical history plays a crucial role in the differential diagnosis between different clinical entities. Personal history of preeclampsia, thrombophilia, or chronic hypertension, primiparity, very young age or age over 35 years old, obesity and multiple pregnancy is thought to predispose one to the development of preeclampsia. In fact, preeclampsia does not only occur in previously healthy pregnant women, but also in the presence of underlying pathological conditions (maternal PE).

On the other hand, the personal history of hereditary or acquired TTP can arouse the suspicion of TTP, measurement of ADAMTS13 should also be performed, and in case of levels < 20%, TTP is suspected, and anti-ADAMTS13 autoantibodies should also be measured [33].

Neurological manifestations are common in both TTP and PE. In the case of seizures, it is essential to immediately perform a CT angiography and basic laboratory tests to exclude any other possible emergency causes, which put a pregnant woman at risk and require a different clinical approach, such as brain hemorrhage, hypoglycemia, and electrolyte imbalance. It is also essential to estimate the fetus's condition and measure the fetal heart rate with the use of ultrasonography [16].

Further laboratory investigation is also required for the differential diagnosis (blood count, renal and liver function tests, LDH, total and indirect bilirubin). A microscopical blood smear investigation could indicate the presence of schistocytes, burr cells, or echinocytes and speaks for the diagnosis of microangiopathic hemolytic anemia (TTP, Diffuse Intravascular Coagulation or HELLP syndrome) [14][16].

4.2. Management

First, action is needed to prevent seizures and achieve lower levels of arterial blood pressure, using medication that can safely be administered during pregnancy, such as diazepam, MgSO4, labetalol, and methyldopa [16].

Delivery is the treatment of choice in patients with HELLP syndrome or preeclampsia, and amelioration is expected 1–2 days postpartum. In case there is no resolution or even worse, there is a deterioration of the clinical manifestations or the laboratory parameters (persistent anemia, neurological symptoms, further thrombocytopenia) in the first days postpartum, TTP is the most probable diagnosis and plasmapheresis should be performed without any further delay. In the literature, there are several case reports in which TTP was diagnosed postpartum because of deteriorating clinical and laboratory parameters after delivery [16][17][18][19][20][21][33].

Whenever TTP diagnosis is not conclusive, trial-plasmapheresis is a therapeutical option that would be applied a couple of days before delivery, while the effect of corticosteroids and MgSO4 is expected to result in an increase in platelets count. Moreover, in the case of improvement, TTP is the most probable diagnosis, over HELLP syndrome or preeclampsia [20]. In fact, TTP is more likely to cause the pregnant woman's death (10–20% of all cases) compared with HELLP syndrome [16].

It should be noted that an immediate initiation of treatment is necessary, even in case there are no results of ADAMTS13 activity, ADAMTS13 inhibitor, or autoantibody measurement. Those results can be evaluated at a second time and are likely to contribute to the confirmation of the diagnosis or the differential diagnosis between the hereditary and the acquired form of the disease [16]. Identifying the specific form of the disease can help to decide which is the optimal therapeutic option in each case—corticosteroids or rituximab in the acquired form and plasma administration or plasmapheresis in the hereditary [21]. Corticosteroids should also be combined with plasmapheresis in the beginning, until the acquired form of the disease is excluded with the negativity of anti-ADAMTS13 autoantibodies [19].

According to the protocol presented in the special report of Fakhouri et al., in the case of a pregnant woman or a woman who had given birth recently with signs of TMA, symptomatic treatment and delivery are the best options, if typical findings of preeclampsia or HELLP syndrome are present. If the diagnosis is not precise and there are no neurological manifestations or signs of cardiac involvement, the woman should be closely monitored for 24–72 h. If there is no resolution of the clinical manifestations or improvement of the laboratory tests, or in case of neurological or heart involvement from the beginning, plasmapheresis should be initiated immediately with the administration of fresh frozen plasma [34].

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