Human Immunology 82 (2021) 371–378

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Research article

Pregnancy induced TMA in severe preeclampsia results from complement-mediated thromboinflammation

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ARTICLE INFO

Article history:
Received 23 November 2020
Revised 12 March 2021
Accepted 15 March 2021
Available online 2 April 2021

Keywords:
Preeclampsia
Thromboinflammation
Thrombotic microangiopathy
Complement system
Pregnancy

ABSTRACT

Preeclampsia is a multifactorial vascular disease unique to human pregnancy. While genetic and antiangiogenic factors are important contributors to preeclampsia susceptibility, recent studies have shown that dysregulation and/or over-activation of the complement system has an integral role in disease etiology. Furthermore, the role of the coagulation cascade may be underappreciated in the development of the disease. Traditionally, for research purposes, the pool of preeclampsia cases has been divided into non-severe and severe disease depending on the onset and severity of the symptoms. However, of particular interest are a small but important minority of cases that present with symptoms likening to those of hemolysis, elevated liver enzymes and low platelets syndrome, atypical hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura, all thrombotic microangiopathy (TMA) diseases, with the hallmark mechanisms of endothelial dysfunction and aberrant activation of complement and coagulation cascades. We therefore propose a third class, severe TMA-like preeclampsia to be included in the categorization of preeclampsia patients. Identifying these patients would target research, diagnostic differentiation, and novel treatment options to the subclass of patients with life-threatening disease that are most likely to benefit from next-generation drug development.

1. Introduction

Preeclampsia is characterized by newly onset hypertension and proteinuria during pregnancy, or in the absence of proteinuria, any of following features of severe preeclampsia: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, new-onset headache [1]. During pregnancy, maternal immune system is challenged especially locally in the decidua. Appropriate immune regulation has to take place to tolerate placental cells invading into the uterine tissue and maternal vascular walls. Development of the placenta is crucial in determining the fate of the pregnancy.

Preeclampsia is a multifactorial disease and accordingly, the clinical presentation of the disease is highly variable. Symptoms vary from mild maternal hypertension and proteinuria without obvious effects on the fetus to severe growth retardation of the fetus combined with systemic maternal disease. In severe cases, preeclampsia may lead to organ failure affecting vasculature, kidneys and liver and result in coagulopathy and eclampsia. HELLP syndrome is characterized by hemolysis, elevated liver enzymes and low platelets. It may occur independently, but is often considered preeclampsia-related. If HELLP syndrome is diagnosed during pregnancy, the delivery of the infant is usually imminent irrespective of the length of the pregnancy, often leading to prematurity and intensive care level treatment of the mother. HELLP syndrome, like preeclampsia, may be diagnosed after the delivery. Some preeclampsia patients show signs of hemolysis, elevated liver enzymes and low platelets in the laboratory parameters without fulfilling the strict diagnostic criteria of HELLP syndrome [2]. Previously, these patients were categorized as incomplete/partial HELLP

Abbreviations: ADAMTS13, A Disintegrin and Metalloproteinase with Thrombospondin Type 1 Motif 13; aHUS, Atypical Hemolytic Uremic Syndrome; FDA, U.S. Food and Drug Administration; HELLP, Hemolysis, Elevated Liver Enzymes and Low Platelets Syndrome; HUS, Hemolytic Uremic Syndrome; MAC, Membrane Attack Complex; NK, Natural Killer Cell; PlGF, Placental Growth Factor; sFlt1, Soluble Fms-like tyrosine kinase 1; TMA, Thrombotic Microangiopathy; TTP, Thrombotic Thrombocytopenic Purpura; VEGF, Vascular Endothelial Growth Factor; vWF, von Willebrand factor.

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https://doi.org/10.1016/j.humimm.2021.03.006
0198-8859/

patients, whereas the present diagnosis would be preeclampsia with severe features [1].

In the first part of this review, we describe the role of the complement system, endothelium, and angiogenesis in pregnancy and recapitulate TMA disease mechanisms. In the second part, we revisit these topics to highlight their interactions and role in preeclampsia pathogenesis. Finally, a novel diagnostic category, the TMA-like preeclampsia disease is proposed in the third part.

1.1. Complement system

The complement system comprises of more than forty soluble and membrane-bound protein components that interact with each other resulting in a tightly regulated stepwise network of activation and regulation. Complement system is an integral part of the innate immune system responsible for inflammation, self/non-self discrimination, and clearance of damaged cells and foreign particles, including pathogens. Upon activation of the complement system by classical pathway via immunocomplexes, CRP and C1q binding, vasodilation occurs. Alternative pathway of the complement system may activate spontaneously by C3b deposition to a target structure lacking the sialic acid and glycosaminoglycan structures on host cells that allow for protection from complement activation by binding of factor H, a potent soluble complement inhibitor [3]. In the presence of factor H, complement C3 is cleaved and the C3b component attaches covalently to the target surface and is then inactivated by factor I to form iC3b. In the context of pregnancy, the third pathway of complement activation, lectin pathway, has received least attention. All pathways of complement activation lead to cleavage of C3 and formation of C5-convertases that have the capacity to activate the terminal pathway. Terminal pathway activation culminates in creation of the membrane attack complex (MAC), a pore structure that results in target cell lysis.

1.2. Clearance of placental debris is crucial for healthy pregnancy

Placenta is a transient rapidly growing organ responsible for maintaining the developing fetus during pregnancy. During the first trimester, the placental trophoblast cells invade into the decidua and further into the spiral arteries and other structures in the myometrium [4]. In the spiral arteries, the endothelialized trophoblast cells program the re-modulation of the spiral artery, thereby creating optimal high-flow, low-pressure conditions for the maternal blood flow into the placental intervillous space. The placenta sheds trophoblast debris into maternal circulation. The trophoblast components range from nanovesicles to multinucleated syncytial nuclear aggregates. In a healthy pregnancy, the trophoblast components result from normal turnover of the syncytium layer, which covers the placental villous trees and they are shed in moderation. Trophoblast particles in the maternal circulation are considered to induce peripheral tolerance.

1.3. Angiogenic balance during pregnancy

Increase of anti-angiogenic circulating factors soluble endoglin and soluble receptor fms-like tyrosine kinase 1 (sFlt1, soluble vascular endothelial growth factor receptor 1 sVEGFR1) are associated with increased risk of preeclampsia [5]. sFlt1 is predominantly expressed by trophoblast cells, endothelia, and inflammatory cells [6], and it is a soluble antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). In second and third trimesters of a healthy pregnancy, PlGF is more abundant than its ligand, sFlt1. When the levels of sFlt1 exceed levels of PlGF, placental development is compromised [7]. In the pregnant woman, sFlt1 limits vascular remodeling and neovasculogenesis while restricting growth of the placenta [8]. Furthermore, sFlt1 may act in an anti-inflammatory capacity [9].

1.4. Endothelium

The feto-maternal boundary consists of endothelia. Integrity of the endothelium is crucial to the successful pregnancy. The syncytiotrophoblast is a specialized endothelium that circumferentially encapsulates the placental villi. This proximal boundary is conventionally seen as the feto-maternal boundary. As placental extracellular material and apoptotic cells are peppered into the maternal circulation, it could be argued, that endothelia within the maternal vasculature and organs serve as a distal feto-maternal boundary and are therefore the target of potential endothelial damage due to the pregnancy. Dysfunction of the endothelium during pregnancy may thus result in maternal systemic symptoms and organ failure.

1.5. Coagulation disturbance is at the heart of the TMA

Thrombotic microangiopathy (TMA) is a group of diseases characterized by microangiophatic hemolysis, thrombocytopenia and microthrombi formation leading to ischemic tissue injury [10].

TMA is caused by endothelial injury in the microcirculation with activation of the complement system and/or coagulation cascade. This leads to ongoing thrombosis caused by platelet aggregation and mechanical breakdown of erythrocytes passing through the capillary vessels. Resulting thrombus formation causes ischemia and infarction in the end organ, and often affects the kidneys, brain, gastrointestinal tract, and heart. Symptoms are usually non-specific and in extreme cases, result in multi-organ dysfunction requiring intensive care [11].

Pregnancy is considered a hypercoagulable state, with the aim of protecting the laboring mother from excess blood loss. Physiological changes in pregnancy include decrease in the level of protein S and increased levels of fibrinogen, von Willebrand factor (vWF), factors II, VII, VIII, IX, and X by 20–1000%, reduction of antifibrinolytic activity, and progressive platelet activation. The levels of activated vWF-cleaving enzyme, a disintegrin and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) have been shown to decrease as pregnancy progresses [12]. The syncytiotrophoblast, like other endothelia, holds Weidel-Paladel bodies, intracellular structures where vWF is released from in the event of endothelial damage. In haemostasis, the vWF mediated coagulation with fibrin deposition repairs the damaged villous tissue and contains the damage.

Lesion or injury of the endothelium is a central feature of TMA [13]. Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are hallmark TMA disorders, but other conditions are also associated with TMA. The underlying etiology differs between these disorders, and it is thought that in addition to underlying susceptibility, a second hit may be required to trigger the events leading to TMA. TMA may be induced secondary to an infection, transplantation, medication, malignancy, malignant hypertension, pregnancy/postpartum, or disseminated intravascular coagulation (DIC).

In TTP, the plasma levels of ADAMTS13, are diminished due to, for example, mutations in the *ADAMTS13* gene. However, in majority of cases, TTP is acquired and caused by induction of autoantibodies against ADAMTS13. Decreased levels of ADAMTS13 lead to unusually large activated vWF multimers on endothelial cells, and cause platelet aggregation and microvascular thrombosis. Typical HUS is caused by shiga toxin-producing *Escherichia coli* (STEC-HUS). AHUS is a complement-mediated disease, caused by deficiencies in the alternative pathway of complement activation. In aHUS, overt complement activation and endothelial cell activation

leads to a procoagulant and prothrombotic pathology [14]. In 60% of aHUS cases, there is a genetic defect in the complement system.

2. Discussion

2.1. Genetics of preeclampsia

Preeclampsia carries a familial predisposition; the largest influence is derived from the maternal genotype [15,16]. Preeclampsia is a complex disease with many loci contributing to the risk of disease, including variants associated with obesity and hypertension [17]. Genetic associations from angiogenic and immunological pathways have been described in association with preeclampsia [18–27].

Interestingly, genetics regulating the signaling of the natural killer (NK) cells have provided evidence supporting the role of the NK population in implantation and early placental development [28]. Recently genetic exploration into the KIR-receptors on NK cells and their ligands, HLA-C expressed on trophoblast cells, have revealed an important direction for future studies in preeclampsia [29–31].

In 2017, *FLT1* coding for sFlt1 was established as the first candidate gene in preeclampsia studies. While low-frequency protective coding variants were found in Finnish mothers, predisposing likely regulatory alleles were identified in infants born from preeclamptic pregnancies [18,19].

2.2. Complement dysregulation predisposes to preeclampsia

Early studies in animal models have shown that complement system is fundamentally important for the successful pregnancy. Inhibition of C3 is crucial, as shown in Xu *et al.*, who demonstrated that without C3 inhibitor Crry all concepti were lost [32]. Certain amount of C3 activation is needed for the normal placental development [33]. In addition to its conventional role in complement activation, C1q has been shown to be important in trophoblast invasion [34]. Systemic complement activation is present during normal pregnancy and further activation is observed in preeclampsia, preeclampsia with IUGR, and HELLP [35]. However, a delicate balance of activation and inhibition is a necessity [36–38]. The role of the complement system is pronounced in early onset preeclampsia. Furthermore, placental dysfunction is associated with the early-onset and severe preeclampsia, often leading to IUGR.

Among the immunological pathways, the complement system has been the target of important investigative efforts in recent years in preeclampsia and HELLP syndrome [35,39–42]. Inapt activation or insufficient regulation of the complement system may have implications in early pregnancy by rejection of the invading trophoblast cells, if complement activation results in an immune response targeted against the trophoblasts. Complement may also cause inflammation and systemic symptoms in late pregnancy, if complement mediated phagocytosis of opsonized components is inadequate [43]. While there is some indication of classical pathway's involvement in preeclampsia, most of the recent studies in the field have highlighted the role of the alternative pathway of complement activation [23,42,44–46].

Ma *et al.* showed elevated C5a deposition in the preeclamptic placenta. The potent anaphylatoxin C5a was observed in the placental macrophages and C5a receptor (C5aR) expression colocalized mainly with syncytiotrophoblast and trophoblasts in preeclamptic placentas [41]. The expression of IL-1β, TNF-α, IL-6, MCP-1 and sFlt1 measured by mRNA, was significantly higher in preeclamptic placenta, compared to normal pregnancy. The expression of these factors was shown to be upregulated in trophoblast cells after C5a stimulation. Simultaneously PlGF and IL-10 were shown to be decreased in preeclamptic placentas. Furthermore, after C5a stimulation, their expression was reduced. The serum level of C5a was shown to be significantly increased in preeclampsia patients when compared to normal pregnancy. These findings shed light on not only the role of the complement system in preeclampsia, but also the mechanisms underlying observed increased levels of sFlt1 levels seen in preeclampsia.

In preeclampsia, the maternal symptoms are systemic and not limited to placental deficiency.

The amount of placental debris is increased in the preeclamptic pregnancy. To maintain healthy circulation, the placental debris must be cleared by phagocytosis by maternal macrophages. Excess burden of placental debris may cause the complement-mediated clearance of placental particles to be overwhelmed, which may result in exacerbated inflammation and activation of the immune response [47].

Macrophages are known to limit the depth of trophoblast invasion [48]. Phagocytosis by macrophages is dependent on several receptors that signal downstream to induce a polarizing response to favor either pro-inflammatory M1 or tolerogenic M2 population. Complement receptors CR3 and CR4 on macrophages bind to the opsonin iC3b. We have recently shown that altered iC3b binding of complement receptors CR3 and CR4 on macrophages is associated with preeclampsia, suggesting possibly impaired clearing function in preeclampsia [24]. Whether the CR3 and CR4 receptors have a direct impact on trophoblast invasion remains to be explored. 20% of early-onset cases are associated with hypoxia and inadequate trophoblast invasion [49]. In preeclampsia, the re-modulation of spiral arteries is inadequate, or occasionally in severe cases, absent [50,51]. The constricted spiral arteries result in a turbulent high-pressure blood flow that increases mechanical shear stress to the placental villi. The turbulent blood flow into the intervillous space may promote activation of the coagulation cascade within the intervillous space [52].

2.3. vWF in preeclampsia

Disturbance in coagulation pathway is a central symptom of TMA. Similarly, coagulation dysregulation is a feature of preeclampsia [53,54]. Shared evolutionary history between coagulation and complement cascades is reflected in the many interactions between these two pathways.

In the preeclamptic placenta, vWF expression in the syncytiotrophoblast is diminished, while intervillous vWF and maternal plasma levels are increased [55]. The excess multimeric vWF release due to syncytiotrophoblast damage bears potential for formation of intervillous clots and could contribute to the increased vWF that has been observed in the maternal circulation. In preeclampsia, the plasma levels of free-floating ADAMTS13 is further decreased likely due to depletion by excess vWF [56].

VWF has complex interactions with the complement system. Recombinant factor H and partially purified factor H cleave soluble vWF multimers, and full-length factor H have been shown to enhance ADAMTS13 function [57,58]. Conversely, factor H interacts with the vWF pathway of coagulation by inhibiting enzymatic activity of ADAMTS13 [59]. It has been shown, that vWF protects the endothelium from complement-mediated injury [60]. On the other hand, evidence exists that activation of the vWF pathway of coagulation may activate the alternative pathway of complement system [61].

While co-localization of vWF and factor H in endothelial cells has been shown, this remains to be verified in the syncytium of healthy and preeclamptic placenta [59]. However, we have seen factor H intracellularly within the placental syncytiotrophoblast and intracellular vWF in the syncytiotrophoblast has been reported elsewhere (Fig. 1) [21,55].

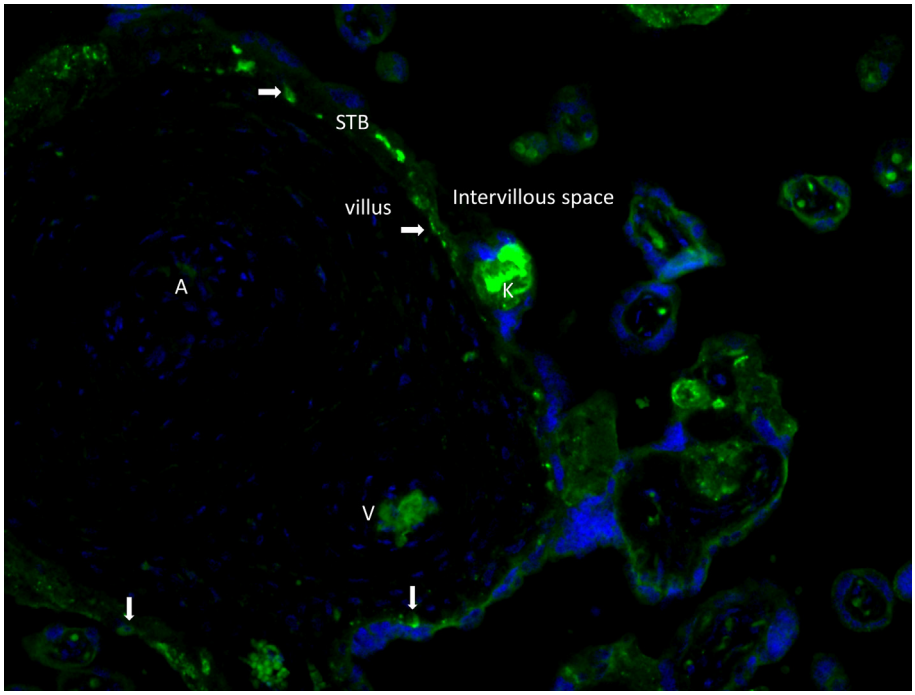

Fig. 1. Factor H envelopes the placental villi circumferentially to protect the placenta from complement-mediated damage. An immunofluorescence staining from paraffin section of week 34 placenta from a preeclamptic pregnancy after delivery by cesarean section. Blue staining shows nuclei (DAPI) and green factor H (dilution 1:1000, fitc). STB indicates syncytiotrophoblast, the fetal-maternal interface with factor H staining. K indicates apoptotic syncytial knot. Arrowheads point to intracellular staining of factor H on the syncytiotrophoblast. A – placental artery, V – placental vein, 200x magnification.

In the preeclamptic pregnancy, factor H may therefore have the capacity to aggravate the development of the TMA independently of complement activation. Based on the contradictory results presented above, it seems that a certain balance is required between the complement and vWF pathways to ensure adequate protection and damage control, when protection against pathogens and tissue injury repair is required, in order to prevent over-activation of either complement or coagulation pathways. Therefore, slight changes in the delicate balance might trigger a dangerous cascade of events leading to, for example, TMA.

2.4. Complement and angiogenetic factors in complicated pregnancy

Complement mediated endothelial disturbance and inflammation underlie many of the key symptoms of preeclampsia depending on the targeted organ. If complement system fails to opsonize the placental particles in the maternal circulation, they will promote inflammation and clotting in the small vessels, likely contributing to hypertension. When vascular endothelium is compromised, leakage exacerbated by complement-mediated vasodilation may lead to edema. When the basal membrane of the kidney glomeruli lose protection by factor H, proteinuria follows [62]. Similarly to preeclampsia, the symptoms seen in HELLP syndrome are related to complement mediated endothelial damage [63].

Angiogenic imbalance is well-documented in preeclampsia [64]. A consensus now exists of the role of excess sFlt1 in preeclampsia and it is among the best biomarkers for the disease. The role of sFlt1 in preeclampsia has been shown in biomarker studies [65,66], animal models [67,68], and most recently genetic association studies [18,19]. During the second trimester of a pregnancy that will later develop preeclampsia, an excess placental production of sFlt1 is detectable from the maternal serum. Levels of sFlt1 typically correlate with the severity of preeclampsia [69]. Persisting high levels of sFlt1 after preeclampsia have been associated with cardiovascular morbidity during pregnancy and in later life [70]. Women with preeclampsia are at an increased risk to develop cardiovascular disease and chronic kidney disease in later life, especially within 5 years after the preeclamptic pregnancy [71-73].

Murine studies have added to the mechanistic understanding of the complex relationships between the antiangiogenic sFlt1, the complement system, and the vWF/ADAMTS13 arm of coagulation cascade. An antibody-independent mouse model exploring spontaneous miscarriage and intrauterine growth restriction (IUGR) showed that increased complement activation results in increased levels of circulating sFlt1 [67]. Elegantly, Erpenbeck et al (2016) showed using ADAMTS13-/- mouse model, that introducing overexpression of sFlt1 results in TMA (thrombocytopenia, schistosytosis, anemia, and VWF-positive microthrombi in multiple organs), and recombinant human ADAMTS13 (rhADAMTS13) abolished the classical features of TMA in these mice [68]. Furthermore, monocytes can be stimulated to express an excess of sFlt1 in vitro, when exposed to C3a, an anaphylatoxin released by early complement pathway activation and C5a, which is analogously cleaved by activation of the terminal pathway of the complement system. Release of the early complement anaphylatoxin C3a correlates with upregulation of Flt1 expression by the syncytiotrophoblast in a terminal pathway-dependent way [50,51].

The mechanistic link between complement activation and sFlt1 further implicates the role of over-activation of complement in preeclampsia pathogenesis. Interestingly, TMA can be induced by certain drugs, including VEGF inhibitors, used in chemotherapy [14,74]. Interesting aspect for future studies would be to analyze the role of sFlt1 in severe preeclampsia from the perspective of drug-induced TMA.

3. TMA-like preeclampsia

Pregnancy combines different predisposing factors for TMA; the physiological increase in coagulation factors and an increase of vWF combined with decreasing levels of ADAMTS13. Furthermore,

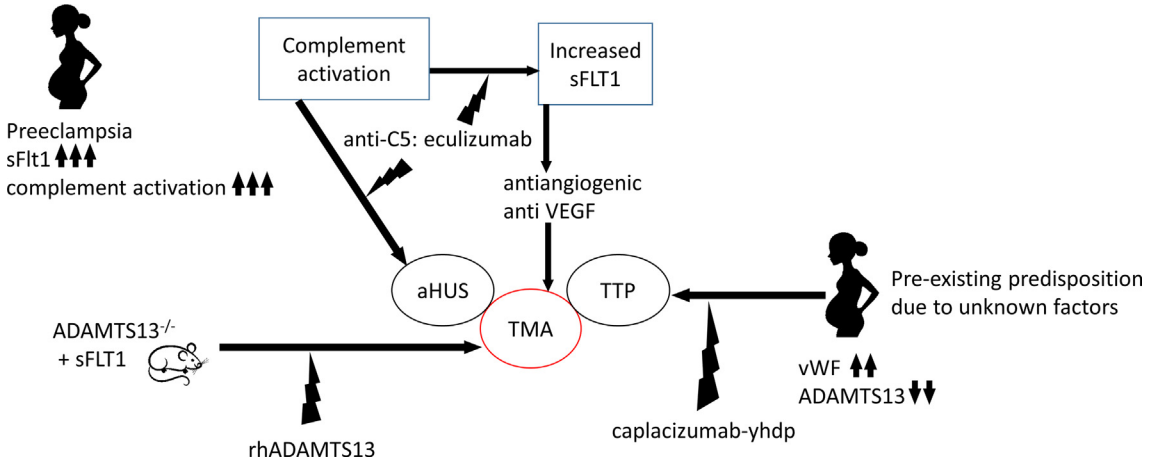

Fig. 2. Pregnancy induced TMA. Hypothesis of pregnancy induced TMA. Pregnancy itself is an inflammatory and procoagulative state. In preeclampsia, inflammation is exacerbated through placental dysfunction and released of shedding particles causing endothelial disturbance. Resulting changes are the over-activation of complement system, and an anti-angiogenic and prothrombotic shift. Slight disturbances in the underlying control mechanisms might trigger TMA especially in women with pre-existing genetic predisposition. Lightning arrows represents available and future targets for treatment.

subtle inflammation is associated with the normal pregnancy, as observed in increased levels of leukocytes and complement activation.

Severe preeclampsia is akin to TMA diseases. Dysregulation of complement system is indicated in both and coagulation disturbance is not uncommon in severe preeclampsia as evidenced by HELLP, making diagnostic differences vague. In preeclampsia, the defective placental development results in turbulent blood flow into the placental bed and villous trees causing increased mechanical stress to the villi and increased shedding of placental debris into the maternal circulation. This increased placental debris in the systemic circulation may cause endothelial injury, and in the presence of pregnancy related changes in coagulation and complement system, may trigger TMA, including TTP or aHUS. In other words, many preeclampsia patients might suffer from an underdiagnosed TMA.

Pregnancy associated aHUS represented 16% of HUS cases occurring in women aged between 18 and 45 years reported in three national registries. Intriguing hints arise from the susceptibility for TTP onset by pregnancy. TTP is a rare disease, with pregnancy induced TTP accounting for 10–30% of all adult cases of TTP [75]. Considering the pregnancy-related decrease of ADAMTS13 levels, could preeclampsia, in discordant cases, present as a TTP-like disease? In TTP treatment, a specific drug, caplacizumab-yhdp, a nano-antibody, which inhibits the interaction between vWF and platelets has been approved by the U.S. Food and Drug Administration (FDA) in 2019.

HELLP syndrome is a TMA disorder that affects 0.5–0.9% of pregnancies. In HELLP syndrome, up to 46% of cases have been found to have complement mutations [76]. In a recent review, Burwick and Feinberg comprehensively summed up the literature concerning complement in preeclampsia and HELLP syndrome. They observed that complement mutations have been reported in altogether in 14% of severe preeclampsia and/or HELLP syndrome patients [63]. Recently, Youssef *et al.* described blood proteomics of early-onset severe preeclampsia [77]. The most different expression patterns between preeclamptic patients and controls were discovered in complement and coagulation pathways. Platelet function and vWF were also indicated. These and other accumulating data supporting complement disturbance in preeclampsia further corroborates that certain preeclampsia patients suffer from a TMA-like disease even in the absence of some of the conventional criteria. Based on the overactivation of complement system, they might regardless benefit from anti-complement therapy, which is successful in the treatment of TMA.

We therefore suggest a subtype of preeclampsia; TMA-preeclampsia, and we propose laboratory investigations to detect TMA in potential cases. The diagnostic criteria could be modified from TMA diagnostics as follows: for TMA-preeclampsia, we propose the diagnostic criteria of thrombocytopenia (thrombocytes < 100 E9/L) to indicated disruption of the coagulation pathway, hemoglobin level < 100 g/L with erythrocyte fragmentation to indicate microangiopathic hemolytic anemia, and alanine aminotransferase (ALT) > 100 U/L or serum creatinine level > 100 μmol/L to indicate organ dysfunction in the pregnant mother.

4. Conclusions and perspectives

With many contributing phenomena, preeclampsia remains the disease of theories. However, the accepted view is that preeclampsia causes disturbance in the endothelium resulting in hypertension and proteinuria. Complement and coagulation are key elements in the protection of the integrity of endothelium. Basic research has proven the involvement of complement over-activation in preeclampsia. HELLP syndrome is recognized as part of the TMA disorders due to the well-documented complement disturbance occurring in HELLP syndrome [63]. The full implications of the complex interactions between alternative pathway of complement activation and vWF/ADAMTS13 activity for the TMA pregnancy and preeclampsia remain to be explored.

We propose that a subtype of preeclampsia patients present with a complement dysregulation-mediated TMA-like disease (complement mediated TMA in preeclampsia). It is time to step forward in the preeclampsia field. We now begin to unravel a mechanistic view of the pathophysiology in a subphenotype of preeclampsia (Fig. 2). As a significant subgroup of preeclampsia patients show altered laboratory measurements indicative of TMA type of disease, we urgently need to bring diagnostic tools into the clinic, so that these different subtypes could be differentiated. Combining pregnancy specific expertise and TMA diagnostics, we could pinpoint a subgroup of patients who could benefit from the advances of medicine, including next generation drugs with specific target, such as eculizumab, which has been shown to abolish aberrations in laboratory values indicating TMA in a case report describing the treatment of a HELLP patient [78]. Other novel drugs

targeting complement system are being developed with haste [79]. Preeclampsia causes, in severe cases, very early prematurity and need for intensive care treatment for the infant. Using eculizumab could reduce the morbidity caused by prematurity and financial cost from intensive care level treatment, not to mention the emotional strain caused for the families.

To further support the proposition that a subtype of preeclampsia could share the pathogenetic mechanisms behind other TMA, interesting findings have been made through the COVID-19 outbreak. Some pregnant women with severe COVID-19 infection replicate preeclampsia symptoms, and a recent study proposed tools for differentiation of true preeclampsia from COVID-19 induced form [80]. In conclusion, COVID-19 has proven what we postulated based on the accumulating data on complement and preeclampsia i.e. preeclampsia, similarly to HELLP syndrome is, in discordant cases, a TMA disorder.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Professor Berthold Huppertz and Ms. Monika Siwetz for collaboration in producing the immunohistochemistry image in Fig. 1. This study was financially supported by Helsinki University Hospital (J.H.-E., research grant TYH2019213).

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