Challenges and Considerations in Managing Thrombotic Microangiopathy and Disseminated Intravascular Coagulation in Postpartum Hemorrhage

The Author Replies: We highly appreciate the thoughtful comments by Orsi *et al*. and Rafat *et al*. on our recent report on the impact of short-term complement inhibition in patients with thrombotic microangiopathy (TMA)-associated with postpartum hemorrhage.

We emphasize the point that the precipitating causes of TMA and disseminated intravascular coagulation (DIC) in the complex context of pregnancy-associated physiological changes and acute obstetric complications, particularly bleeding and mass transfusions, cannot safely be discriminated and often leave the treating physician at a loss. A pragmatic therapeutic approach, which incorporates early and temporary complement inhibition in selected cases, is needed.

How can we recognize the interplay between hypercoagulation and hyperfibrinolysis, particularly in the event of major bleeding, and how should we distinguish from TMA as rightfully pointed out by Orsi *et al*.? Patients with bleeding after major surgery or those with obstetric complications are particularly susceptible to "the massive bleeding or consumptive type of DIC.[1] Here, the balance between coagulation and fibrinolysis is disrupted, resulting in the consumption of clotting factors and bleeding. However, standard procedures for quantifying C3 or C5 activation in relation to coagulation factors, particularly in the context of substitution of fresh frozen plasma and red blood cells, are currently lacking. Moreover, complement regulation occurs on cell surfaces as well as in the fluid phase, making measurements in blood samples less informative and pathophysiologic considerations more complex.

For pregnancy, the need for adapted scoring systems for DIC has long been suggested.[2] In a recent study, the nonpregnant International Society on Thrombosis and Hemostasis nonovert DIC score, was unable to identify any of the patients with nonovert DIC in a pregnancy cohort because of the chosen cut-off values for fibrinogen and d-dimers.[3] In contrast, a newly developed pregnancy-specific nonovert DIC scoring system demonstrated improved sensitivity and specificity in identifying patients at risk for obstetrical hemorrhage requiring blood product transfusion compared to existing scoring systems.[3] Although the patients in our study could have been sorted into a high-risk or low-risk group prior to delivery, neither test would discriminate between DIC and TMA.

Rafat *et al*. raise doubts about the need for complement inhibition in clinical TMA in the absence of a confirmed genetic predisposition. The authors suggest that expedited genetic testing may help to identify patients who could benefit from complement inhibition and contend that postpartum TMA generally has a favorable prognosis with supportive care only. "Fast track genetic testing" with turn-around times of less than 3 to 4 weeks is not available to us and within the German health care system (and will not be in the near future). This time frame has also been reported in the cited case-studies in the commentary.[4]

Currently, there is not enough evidence to prove the concept that the presence of atypical hemolytic uremic syndrome risk-haplotypes in the absence of proven atypical hemolytic uremic syndrome susceptibility variants (pathogenic variants) can be interpreted as a genetic modifier exacerbating the triggering event of postpartum hemorrhage.

In real-world scenarios, the discrimination between postpartum acute kidney injury (e.g., after HELLP-hemolysis, elevated liver enzymes, low platelet syndrome) versus postpartum TMA causing acute kidney injury (as in atypical hemolytic uremic syndrome) is often done in retrospect, when the clinical course and diagnostics have unfolded. Data from well-characterized atypical hemolytic uremic syndrome cohorts in pregnant patients suggest that an identifiable genetic abnormality may be present in as much as 40% to 55% of all cases with about 30% to 70% of all patients reaching end-stage kidney failure at 8 years after delivery.[5-7] The decision to treat with complement inhibition should therefore not be postponed, because neither genetic testing nor biopsy confirmation is needed for treatment initiation as opposed to treatment duration. We advocate for only short-term complement inhibition, which we deem advantageous when initiated promptly, ideally within the initial 72 hours.

With the currently available tools and knowledge, it remains impossible to discern all contributing factors in patients with pregnancy-related TMA. This gap in knowledge underscores the importance of continued research to develop robust diagnostic tools and

therapeutic strategies tailored to the unique pathophysiological mechanisms underlying TMA and/or DIC in different clinical scenarios; thus, improving outcomes in this critical area of maternal health.

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Received 18 May 2024; accepted 20 May 2024; published online 24 May 2024

Kidney Int Rep (2024) **9,** 2307–2308; https://doi.org/10.1016/j.ekir.2024.05.021