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Letter to the Editor

LETTER TO THE EDITOR

Complement-activating conditions as potential triggers of pregnancy-related atypical haemolytic uraemic syndrome

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Pregnancy-related atypical haemolytic uraemic syndrome (p-aHUS) is a rare but life-threatening disorder associated with unfavourable patient outcomes. p-aHUS is a form of thrombotic microangiopathy (TMA), which can be induced by inherited or acquired dysregulation of the alternative complement pathway. Historically, pregnancy was considered as one of the important p-aHUS triggers [1]. However, recent studies suggest that pregnancy complications such as preeclampsia, eclampsia and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, as well as pregnancy-related surgical interventions (i.e. Caesarean section), rather than pregnancy *per se* may be complement-activating conditions (CACs) predisposing to the development of p-aHUS [2–4]. We studied associations of CACs with the number of pregnancies and the complement genetic profile in a large cohort of patients with newly diagnosed p-aHUS.

This retrospective analysis included 75 patients with p-aHUS who were admitted to Russian perinatal centres between 2011 and 2021. The pregnancy associated with aHUS was considered as the index pregnancy. Diagnosis of p-aHUS was made clinically, based on the TMA and acute kidney injury developed during pregnancy or within 42 days postpartum after excluding all other TMA causes. Most of our patients (72/75) developed p-aHUS within several hours to 8 days post-delivery. The mean age (mean ± standard deviation) at p-aHUS diagnosis was 29.4 ± 6.4 years. In 50/75 patients with p-aHUS the index pregnancy was their second or more pregnancy. All previous pregnancies were uncomplicated. The frequencies of CACs were similar in patients divided by the index pregnancy number (Figure 1A). Caesarean section, preeclampsia and bleeding were the most common CACs. Fifty-seven of 75 patients (76%) had at least three CACs. Interestingly, in patients with p-aHUS developing in their third or more pregnancy the number of CACs was larger than in those with first or second pregnancy, but the differences were not statistically significant (Figure 1B).

The complement system genes (Complement 3, complement factors H and I) were tested in 17 patients with p-aHUS. Pathogenic variant(s) were revealed in 7 patients and the other 10 patients had variant(s) of uncertain clinical significance. Numerous CACs were reported for patients with both pathogenic variant(s) and variants of uncertain clinical significance. The most frequent CAC was preeclampsia, which was observed in 100% patients with pathogenic variant(s) and 50% patients with variant(s) of uncertain clinical significance (Figure 2).

Our findings are consistent with previous data suggesting that p-aHUS usually occurs during repeat pregnancy associated with various CACs [2–4]. We did not find an association between

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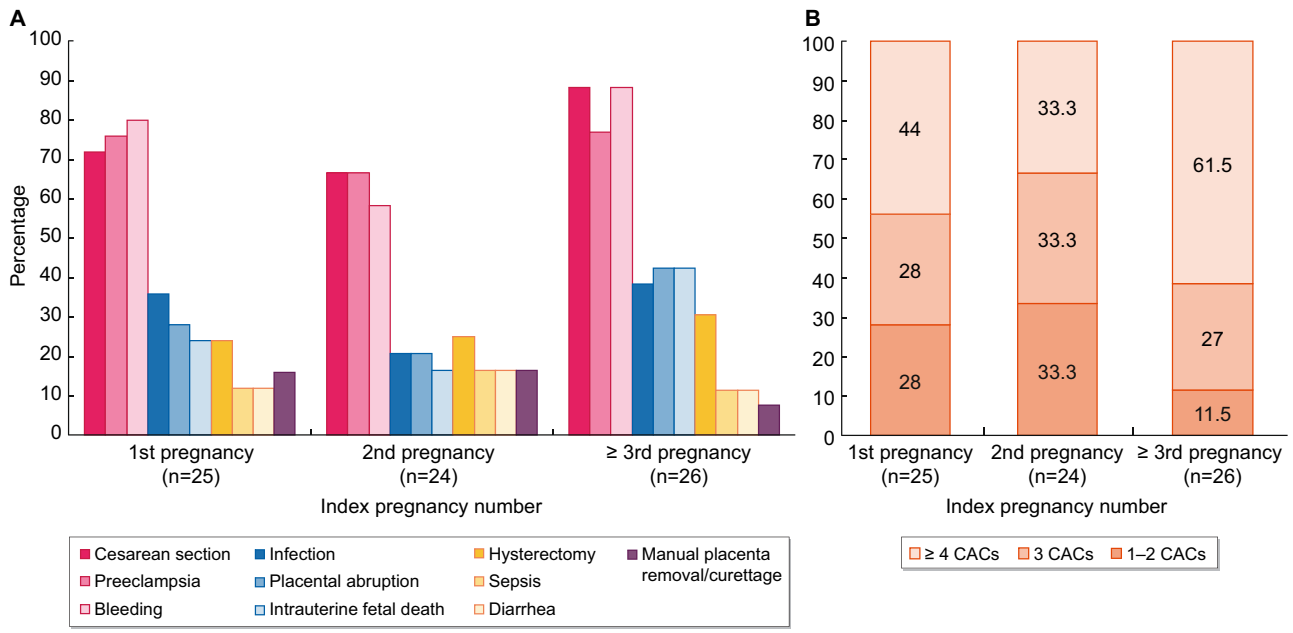

FIGURE 1: Distribution of CACs by type (**A**) and number (**B**) in p-aHUS patients depending on index pregnancy number.

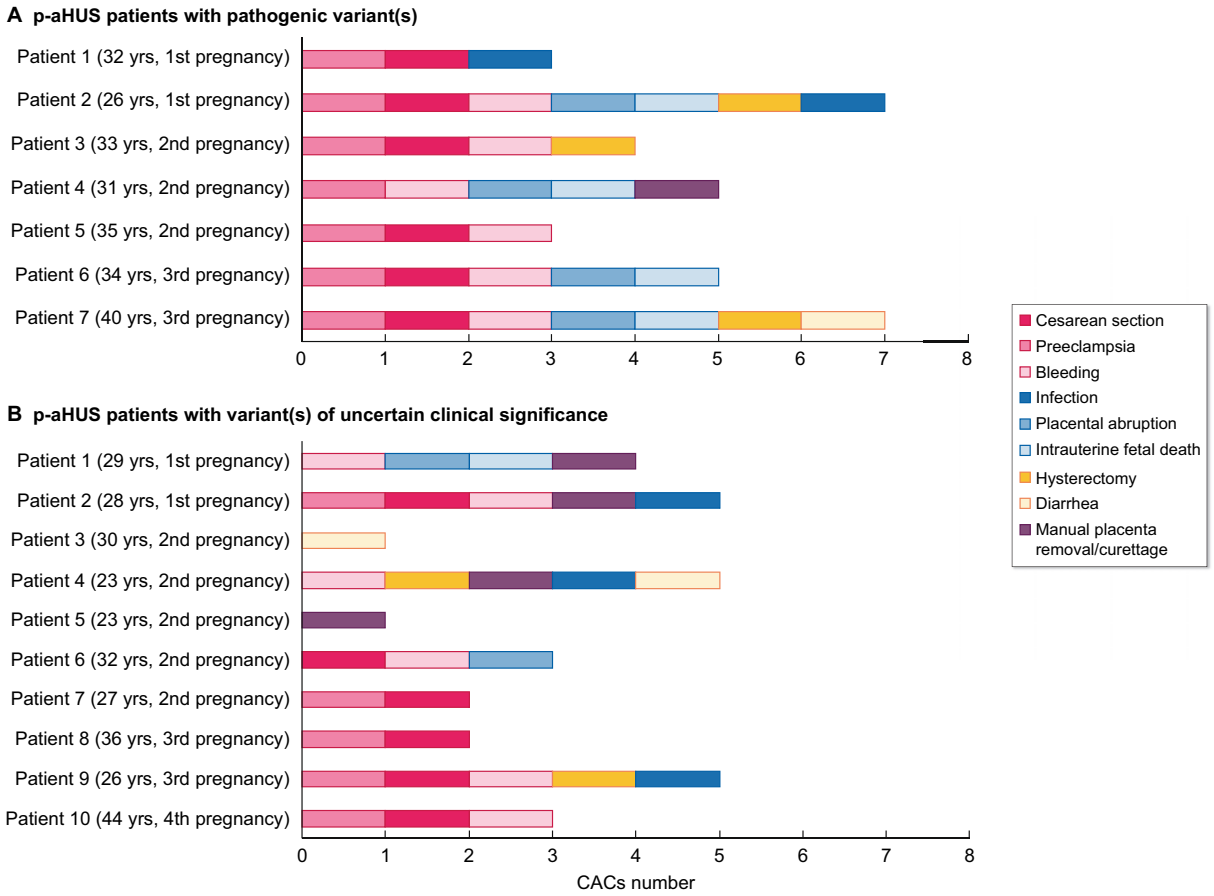

FIGURE 2: (**A**) p-aHUS patients with pathogenic variant(s). (**B**) p-aHUS patients with variant(s) of uncertain clinical significance.

CACs and either the number of pregnancies or the complement genetic profile. However, it seems that uncontrolled alternative complement pathway, the main mechanism of endothelial damage in aHUS, may be induced by various combinations of CACs in patient both with and without pathogenic variant(s) in the complement system gene. However, it is still unknown how many CACs are needed for the development of p-aHUS in an individual patient. The risk of p-aHUS seems to be higher in patients with preeclampsia, which causes many other obstetric complications, such as placental abruption, intrauterine foetal death and bleeding, and often necessitates Caesarean section, all of which represent additional CACs. Future studies are needed to better understand mechanisms of p-aHUS and its triggers.

DATA AVAILABILITY STATEMENT

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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