The natural course of pregnancies in women with primary atypical haemolytic uraemic syndrome and asymptomatic relatives

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Summary

Pregnancy has been linked to various microangiopathies, including primary atypical haemolytic uraemic syndrome (aHUS). Complement dysregulation, often linked to rare variants in complement genes, is key for primary aHUS to manifest and may play a role in pregnancy complications of the mother and fetus. The burden of such complications is unknown, making counselling of women with primary aHUS and asymptomatic relatives difficult. We analyzed the maternal and fetal outcomes of 39 pregnancies from 17 women with primary aHUS and two asymptomatic relatives. Seven out of 39 pregnancies were complicated by pregnancy-associated aHUS. Five out of 32 pregnancies not linked to pregnancy-associated aHUS were complicated by pre-eclampsia or HELLP. Rare genetic variants were identified in 10 women (asymptomatic relatives, n = 2) who had a total of 14 pregnancies, including 10 uncomplicated pregnancies. Thirty-five out of 39 pregnancies resulted in live birth. Eight out of 19 women had progressed to end-stage kidney disease, with an incidence of 2.95 (95% confidence interval, 1.37–5.61) per 100 person-years after the first pregnancy. Thus, we emphasized the frequency of successful pregnancies in women with primary aHUS and asymptomatic relatives. Pregnancies should be monitored closely. Rare genetic variants cannot predict the risk of a given pregnancy.

Keywords: primary atypical haemolytic uraemic syndrome, thrombotic microangiopathy, pregnancy, complement, genetics.

Healthy pregnancy has been linked to significant haemodynamic and immunologic shifts for maternal adaptation, placentation and fetal tolerance. Defects in these processes can lead to a spectrum of microangiopathies, having great impact on maternal and fetal morbidity and mortality. Microangiopathic disorders of pregnancy range from pre-eclampsia to HELLP (i.e. haemolysis, elevated liver enzymes, low platelets) and, although rare, the syndromes of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and primary atypical haemolytic uraemic syndrome (aHUS). Most of these microangiopathies occur late in pregnancy, suggesting a common denominator. In the last decade, complement has been linked to the mechanism of primary aHUS, either related to pregnancy1 or not.2,3 and, to a lesser extent, pre-eclampsia4 and HELLP.5,6 The complement cascade is part of innate immunity and an effector system involved in host homeostasis and the defence against pathogens, which can be activated via the classic, lectin and alternative pathway (AP).7 The latter is a continuously active surveillance system operating in the circulation and on cell surfaces. Host cells, including those from the placenta, are protected from the harmful effects of complement by regulatory proteins. Of note, tight complement regulation at the fetomaternal surface is crucial for
pregnancy to succeed. Rare variants in genes encoding proteins that either regulate or activate complement and/or autoantibodies that affect AP regulation can cause complement dysregulation and are prevalent in primary aHUS. These abnormalities per se are not sufficient for TMA to occur. Pregnancy, however, may precipitate the onset or subsequent relapses of life-threatening episodes of primary aHUS. Furthermore, the incidence of pre-eclampsia and HELLP may be higher in pregnant women with primary aHUS.

The risk for complications in pregnant women prone for complement dysregulation, that is, patients with primary aHUS and asymptomatic relatives carrying rare variants in complement genes, is therefore considered high. In clinical practice, however, it is difficult to counsel such women as robust clinical data are lacking. Moreover, the impact of pregnancies on fetuses and the role of prophylactic measures remain to be established. The current study focussed on maternal and fetal outcomes of 39 pregnancies in a well-defined cohort of women with primary aHUS and asymptomatic relatives. Furthermore, we report the long-term follow-up.

Patients and methods

Patient population

Female patients with TMA and at least one reported pregnancy were recruited from the Limburg Renal Registry, Maastricht, The Netherlands, and the Cliniques universitaires Saint-Luc, Brussels, Belgium. TMA was defined as typical morphologic features of TMA on kidney biopsy or microangiopathic haemolytic anaemia (haematocrit <30%, haemoglobin <10 g/l, lactate dehydrogenase >500 U/l and schistocytes on peripheral blood smear), platelets <150 G/l and acute kidney injury in patients with no pathologic proof of TMA. Patients with primary aHUS, defined as TMA, were included. Pregnancy, however, may precipitate the onset or subsequent relapses of life-threatening episodes of primary aHUS. The risk for complications in pregnant women prone for complement dysregulation, that is, patients with primary aHUS and asymptomatic relatives carrying rare variants in complement genes, is therefore considered high. In clinical practice, however, it is difficult to counsel such women as robust clinical data are lacking. Moreover, the impact of pregnancies on fetuses and the role of prophylactic measures remain to be established.

The current study focussed on maternal and fetal outcomes of 39 pregnancies in a well-defined cohort of women with primary aHUS and asymptomatic relatives. Furthermore, we report the long-term follow-up.

The clinical data were obtained from the Limburg Renal Registry and/or the patients’ medical records. The study was approved by the appropriate ethics committees and is in accordance with the Declaration of Helsinki.

Complement analysis

DNA was tested for rare variants, that is, variants with a minor allele frequency <1%, and single nucleotide polymorphisms in coding regions of CFH, CFI, CD46, CFB, C3, CFHR1-5, THBD and DGKE using sequencing. Rare variants were classified according to international standards. Pathogenic variants were defined as those with functional studies supporting a defect in complement regulation, including null variants in genes linked to complement regulation and variants that cluster in patients with primary aHUS as demonstrated by Osborne et al. Likely pathogenic variants were defined as those with functional studies supporting a defect in complement regulation that were located in a mutational hotspot and critical functional domain. The CFH-CFHR1-5 genomic region was analyzed for rearrangements by multiplex ligation probe amplification. Factor H autoantibodies were assessed by enzyme-linked immunosorbent assay in selected cases.

Patients with no variants identified were screened for unrestrained ex vivo C5b9 formation on microvascular endothelial cells of dermal origin (HMEC-1; ATCC, Manassas, VA, USA) as described. Briefly, HMEC-1 were used when >80% confluent, incubated with serum diluted in test medium for 3 h at 37°C, fixed in 3% formaldehyde and blocked with 2% bovine serum albumin for 1 h. Rabbit anti-human C5b9 (Calbiochem, San Diego, CA, USA) and Alexa488-labelled anti-rabbit (Life Technologies, Carlsbad, CA, USA) were used. The results were compared with pooled normal human serum (NHS) run in parallel.

Statistical analysis

Continuous variables were presented as mean (±SD) or median (interquartile range [IQR]) as appropriate. Descriptive statistics were used to analyze the cohort. Ex vivo C5b9 formation on HMEC-1 was compared with NHS by the paired sample t test or the Wilcoxon signed rank test as appropriate.

Results

Patient population

Twenty-five women with primary aHUS and five asymptomatic relatives were recruited from the Limburg Renal Registry (n = 18) and Cliniques Universitaires Saint-Luc (n = 12). Eleven nulliparous women (three asymptomatic relatives) were excluded; one of them with three episodes of primary aHUS with a background of a pathogenic variant in...
C3 remained intentionally childless to lower the risk of relapse.

Thus, 19 women at risk for complement dysregulation and a total of 39 pregnancies were analyzed (Table 1). Rare variants in complement genes were found in eight (47%) out of 17 patients with primary aHUS; combined variants were identified in one case. Five variants in six carriers were considered pathogenic (Table 2). A pathogenic variant in CD46 was identified in two asymptomatic relatives (patient no. M12, B7). The at-risk haplotypes CFH-H3 and MCP_{GGAAC} were found in three and two patients with primary aHUS, respectively, but not in asymptomatic carriers. The homozygous genomic deletion of CFHR1 and CFHR3 but no factor H autoantibodies were identified in one patient with primary aHUS. Massive ex vivo C5b9 formation on HMEC-1 confirmed unrestrained complement activation in nine patients with no variants identified at the time of acute primary aHUS. The patients’ disease courses can be found in Table SI.

### Maternal complications of pregnancy

We analyzed 39 pregnancies, all of whom were managed with no prophylactic measures.

P-aHUS developed in seven (18%) out of 39 pregnancies at the time of delivery (n = 4) or postpartum (n = 3); four episodes were linked to the first pregnancy. Patients invariably presented with severe kidney failure (median serum creatinine 492 μmol/l; IQR, 194–557), including six patients who needed dialysis. Low platelets and Coombs negative microangiopathic haemolytic anaemia were observed in five patients. Major bleeding, requiring blood and platelet transfusion, precipitated P-aHUS in one patient. Pre-eclampsia and HELLP were clinically inferred prior to the recognition of P-aHUS in four and one patient respectively. Plasma exchange with fresh frozen plasma was started in six patients and associated with a complete clinical response in two cases, that is, normalization of kidney function. Eculizumab, a potent C5 inhibitor, was started in three refractory patients; two patients who initially required dialysis recovered kidney function and improved to CKD stage G2, while the other patient progressed to ESKD. The patient not treated with plasma exchange was diagnosed with pre-eclampsia, but proved to have acute TMA on kidney biopsy, and progressed to CKD G4; ESKD developed after a subsequent pregnancy complicated by pre-eclampsia and major bleeding.

Five (16%) out of 32 pregnancies not linked to P-aHUS were complicated by pre-eclampsia (n = 4, 12.5%) and HELLP (n = 1, 3%).Furthermore, one patient had gestational hypertension. No maternal complications occurred in 26 (67%) out of 39 pregnancies, including 10 (71%) out of 14 pregnancies from carriers of rare variants in complement genes (five patients with primary aHUS and two relatives with 11 and three pregnancies respectively).

### Fetal outcomes

Fetal outcomes of all 39 pregnancies are depicted in Table 3. Thirty-five (90%) out of the 39 pregnancies resulted in live birth, three pregnancies resulted in a spontaneous abortion, and one pregnancy was terminated at week 14 for unknown reasons. Twenty-two (63%) out of the 35 live births occurred at full term, 10 (29%) at preterm and two (6%) at postterm. Eight of the preterm deliveries were induced because of pre-eclampsia, HELLP and/or P-aHUS, the extremely preterm infant (i.e. gestational week 26 + 2) died from infantile respiratory distress syndrome two days after delivery. Pregnancies complicated by P-aHUS resulted in eight newborns. Three (38%) were small for gestational age and one died from asphyxiation.

### Long-term kidney outcome after pregnancy

The women were followed for a median of 13 (IQR, 3–36) and 3-1 (IQR, 1-5–7.9) years after their first pregnancy and the onset of primary aHUS respectively. At last follow-up, six patients and one asymptomatic relative had normal kidney function, that is, an estimated glomerular filtration rate >60 ml/min/1.73 m². Two patients had progressed to CKD G3, one to CKD G4 and eight patients to ESKD; one asymptomatic relative had progressed to CKD G3 but primary aHUS never developed.25 The rate of ESKD in all 19 women after the first pregnancy was 2.95 (95% CI, 1.37–5.61) per 100 person-years; after excluding both asymptomatic relatives, the rate of ESKD was 3.72 (95% CI, 2.75–7.16) per 100 person-years. In total, seven donor kidneys were transplanted in five recipients, all of whom had a high estimated risk for primary aHUS to reoccur.13 None of the recipients became pregnant.

### Discussion

Pregnancy is a critical condition in women predisposed to complement dysregulation as it can precipitate primary aHUS with the attendant risk of sequela. The first episode of primary aHUS can be linked to pregnancy, that is, P-aHUS, in up to 20% of women.9 P-aHUS can occur as often in the first pregnancy as in subsequent pregnancies. Numerous women at risk therefore decided not to become pregnant. Here, we demonstrate that the risk of pregnancy in women predisposed to complement dysregulation may be too pessimistic. P-aHUS occurred in <20% of pregnancies in the setting of additional potential precipitants, while the burden of pre-eclampsia and HELLP appeared lower than appreciated. Rare variants in complement genes did not predict the course of a given pregnancy.

The clinical course of P-aHUS resembles primary aHUS and has been linked to the first pregnancy in ~50% patients, suggesting a high burden of complicated pregnancies in women with primary aHUS. Previous studies, however, did
### Table I. Maternal outcomes of the 39 pregnancies.

| No. | Variant(s) | CKD prior to P | Complicated/total P | Adverse event | Treatment of P-aHUS | Sequelae | Follow-up,* years | Age, years | CKD at last visit |
|-----|-------------|----------------|---------------------|---------------|---------------------|----------|------------------|------------|-------------------|
| **Primary aHUS prior to first pregnancy** | | | | | | | | | |
| B5  | C3 c.3125G>A² | – | 0/2 | – | N/a | – | 4 | 28 | – |
| P-aHUS | | | | | | | | | |
| M1  | C3 c.481C>T¹ | – | 3/3 | HT, P-aHUS (+60 days) | PEX | ESKD | 18 | 47 | G5+/T |
| M5  | – | – | 6/7 | PE, P-aHUS (+2 days) | – | CKD G4 | 16 | 35 | ESKD |
| M9  | – | – | 1/1 | P-aHUS (+0 day), bleeding | PEX, Ecu | – | 3 | 30 | – |
| M11 | – | – | 1/1 | PE, P-aHUS (+0 day) | PEX, Ecu | – | 1 | 30 | – |
| B1  | – | – | 1/2 | PE | N/a | HT | 13 | 39 | – |
| B2  | – | – | 1/1 | PE, P-aHUS (+0 day) | PEX | – | 1 | 30 | – |
| B6  | CHI c.772G>A² | – | 1/1 | PE, P-aHUS (+1 day) | PEX, Ecu | ESKD | 1 | 32 | ESKD |
| **Primary aHUS after last pregnancy** | | | | | | | | | |
| M2  | CHI c.1420C>T³ | C3 c.463A>C² | – | 0/1 | – | N/a | – | 36 | 62 | G5+/T |
| M3  | C3 c.481C>T¹ | – | 1/1 | PE | N/a | Unknown | 14 | 49 | G3/T |
| M4  | CHI c.2558G>A¹ | – | 0/1 | – | N/a | Unknown | 10 | 40 | G3/T |
| M6  | C3 c.481C>T¹ | – | 1/1 | HELLP | N/a | Unknown | 7 | 32 | G2/T |
| M7  | – | – | 1/4 | PE | N/a | None | 45 | 74 | G4 |
| M8  | – | – | 0/4 | – | N/a | – | 21 | 46 | ESKD |
| M10 | – | – | 3/3 | HT | N/a | HT | 49 | 74 | G3 |
| B3  | CHI c.3486delA¹ | – | 0/1 | – | N/a | – | 2 | 32 | – |
| B4  | – | – | 0/2 | – | N/a | – | 46 | 73 | G3 |
| **Asymptomatic relative** | | | | | | | | | |
| M12 | CD46 c.811_816delGACAGT¹ | – | 0/1 | – | N/a | – | 50 | 82 | G3 |
| B7  | CD46 c.811_816delGACAGT¹ | – | 0/2 | – | N/a | – | 6 | 37 | – |

aHUS, atypical haemolytic uraemic syndrome; B1–7, Brussels cohort; CKD, chronic kidney disease (T, transplantation); Ecu, eculizumab; ESKD, end-stage kidney disease; HELLP, haemolysis, elevated liver enzymes, low platelets; HT, (gestational) hypertension; M1–12, Maastricht cohort; P, pregnancy; PE, pre-eclampsia; PEX, plasma exchange.

*Follow-up after the first pregnancy. Rare variants in complement genes were classified as 'pathogenic' or 'uncertain significance.'
not report on uncomplicated pregnancies in detail. In our study, the incidence of P-aHUS as well as pre-eclampsia and HELLP appeared lower than anticipated. Gaggl et al.11 corroborated our findings, indicating that uncomplicated pregnancies are common among women predisposed to complement dysregulation, including those with pathogenic variants in complement genes. Most of these variants have been linked to complement dysregulation on the endothelium and require a precipitating factor26 before primary aHUS can manifest. We confirm that rare variants per se cannot predict the risk of P-aHUS in a given pregnancy, underscoring the key role of additional precipitants, such as bleeding and hypertension.11

Rare variants in complement genes were found in half the patients with primary aHUS, identical to findings in two large registries.2,3 DNA testing of genes encoding complement proteins showed that variants can also be found in women with pre-eclampsia4 and HELLP,5,6 although conflicting results have been reported.27,28 Most of these studies, however, report on variants in complement genes of either uncertain or no significance, overestimating the prevalence of disease-causing variants.19 Moreover, pre-eclampsia or HELLP may develop in pregnant women on eculizumab treatment.29,30 Placental release of antiangiogenic factors, such as soluble Fms-like tyrosine kinase 1, appeared more relevant for both conditions to develop.31

It should be emphasized that women with pre-eclampsia or HELLP may in fact have P-aHUS. This is particularly the case in patients with severe kidney disease not improving after delivery. In one-third of patients with P-aHUS, ESKD can develop within three months after presentation,9 contrasting the low risk of ESKD linked to pre-eclampsia.32 Kidney tissue specimens can aid the differential diagnosis as acute TMA and in particular glomerular thrombosis, and favour a diagnosis of P-aHUS.35 The correct recognition of patients with P-aHUS is of utmost importance given the potential benefit of therapeutic complement inhibition.34–36

The outcome of pregnancies appeared favourable, although the long-term kidney outcome resembled primary aHUS with high rates of ESKD.2,3 Management of pregnant women with primary aHUS or asymptomatic relatives has not been delineated in current guidelines.1 Prophylactic plasma infusions during pregnancy have been proposed,11 identical to treatment for thrombotic thrombocytopenic purpura.32 Prophylactic treatment, however, is debatable as pregnancy is a predictable event, the penetrance of primary aHUS in normal pregnancy is low, and the typical occurrence is in the postpartum period. Eculizumab, however, has been proven safe, both for mother and child,30 and effective9,38 for the treatment of P-aHUS. Pregnancy is therefore not contraindicated in women predisposed to complement dysregulation, although close and careful monitoring in centres of expertise is warranted for at least three months after delivery. In patients with active disease, eculizumab should be immediately available. These data, however, cannot be extrapolated to patients diagnosed with primary aHUS and sequelae, such as hypertension and CKD. Future prospective studies are therefore needed to optimize the management of women predisposed to complement dysregulation.

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Table III. Fetal outcome of the 39 pregnancies.

| No. | P | P-aHUS | Year | Outcome | Sex | Delivery | Weight, g | Gestational week |
|-----|---|--------|------|---------|-----|----------|------------|------------------|
| M1  | 1 | –      | 2000 | Live birth | F   | Vaginal  | 2480†      | 38               |
| 2   | – | –      | 2001 | Live birth/died from IRDS (+3 days) | M   | Vaginal  | 890        | 26 + 2           |
| 3   | + | 2002   | Live birth | M   | Vaginal  | 2975      | 37               |
| M2  | 1 | –      | 1982 | Live birth | F   | Vaginal  | 2450†      | 40               |
| M3  | 1 | –      | 2004 | Live birth | M/M | Vaginal* | 2655/2580  | 36 + 5           |
| M4  | 1 | –      | 2009 | Live birth | M   | Vaginal  | 3640       | 40               |
| M5  | 1 | –      | 2002 | Live birth | M   | Vaginal* | 3435       | 39               |
| 2   | – | 2005   | Live birth | M   | Vaginal  | 3600       | Full term       |
| 3   | – | ND     | Proven abortion (14th wk) | M   | Vaginal  | 3290       | Full term       |
| 4   | – | 2007   | Live birth | M   | Vaginal  |            |                 |
| 5   | – | ND     | Spontaneous abortion (unknown) | M   | Vaginal  |            |                 |
| 6   | + | 2013   | Live birth, IUGR | M/M | Vaginal* | 1120†/1300† | 33 + 0           |
| 7   | – | 2014   | Live birth, IUGR | F   | CS*     | 1001†      | 31 + 2           |
| M6  | 1 | –      | 2011 | Live birth | M   | CS*      | 1460†      | 31 + 5           |
| M7  | 1 | –      | 1973 | Live birth | M   | Vaginal  |            | Full term       |
| 2   | – | 1974   | Live birth | M   | Vaginal  |            | Full term       |
| 3   | – | ND     | Spontaneous abortion (6th wk) | M   | Vaginal  |            |                 |
| M8  | 1 | –      | 1978 | Live birth | M   | Vaginal  |            | Full term       |
| 2   | – | 1999   | Live birth | M   | Vaginal  |            | 39               |
| 3   | – | 2004   | Spontaneous abortion (13th wk) | M   | Vaginal  |            | 38               |
| M9  | 1 | +      | 2016 | Live birth | F   | Vaginal  | 3255       | 39 + 5           |
| M10 | 1 | –      | 1969 | Live birth | M   | Vaginal  |            | Full term       |
| 2   | – | 1970   | Live birth | M   | Vaginal  |            | Full term       |
| 3   | – | 1975   | Live birth | F   | Vaginal  |            | Full term       |
| M11 | 1 | +      | 2019 | Live birth/died from asphyxia (+4 days) | M   | CS      |            | Full term       |
| M12 | 1 | –      | 1966 | Live birth | M   | ND      |            | ND               |
| B1  | 1 | –      | 2005 | Live birth | M   | CS*     | 1500†      | 32 + 0           |
| 2   | + | 2016   | Live birth | F   | CS*     | 1250†      | 31 + 3           |
| B2  | 1 | +      | 2017 | Live birth | F   | CS*     | 2350       | 35 + 6           |
| B3  | 1 | –      | 2016 | Live birth | M   | Vaginal  | 2675       | 35 + 5           |
| B4  | 1 | –      | 1971 | Live birth | M   | Vaginal  | 3500       | Full term       |
| 2   | – | 1978   | Live birth | F   | Vaginal  | 3200       | Full term       |
| B5  | 1 | –      | 2014 | Live birth | M   | Vaginal  | 3885       | 42 + 0           |
| 2   | – | 2017   | Live birth | F   | Vaginal  | 3370       | 38 + 0           |
| B6  | 1 | +      | 2018 | Live birth | F   | CS*     | 1380       | 31 + 0           |
| B7  | 1 | –      | 2012 | Live birth | F   | Vaginal  | 2850       | 39 + 2           |
| 2   | – | 2013   | Live birth | F   | Vaginal  | 3060       | 40 + 2           |

B1–7, Brussels cohort; CS, Caesarean section; F, female; IRDS, infantile respiratory distress syndrome; IUGR, intrauterine growth restriction; M, male; M1–12, Maastricht cohort; ND, not documented; P, pregnancy.

*Induced labour or CS.
†Small for gestational age, defined as a birth weight below the 10th percentile for gestational age.

Conflicts of interest
The authors declare to have no potential conflicts of interest regarding the present work.

Author contributions
ST, MS, and PVP designed the study. ST performed the research, analyzed the data, and wrote the first version of the paper. AW, CR, JD, and JM revised the manuscript critically.
All authors approved the submitted and final version of the paper.

**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table SI. Patients’ disease course.**

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