OPEN

Systematic Review

Pregnancy-Associated Atypical Hemolytic Uremic Syndrome

A Systematic Review

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OBJECTIVE: To evaluate disease presentation, diagnosis, treatment, and clinical outcomes in pregnancy-associated atypical hemolytic uremic syndrome (aHUS).

DATA SOURCES: We searched PubMed, MEDLINE, Cochrane Library, ClinicalTrials.gov, Web of Science, EMBASE and Google Scholar, from inception until March 2018.

METHODS OF STUDY SELECTION: We included English-language articles describing aHUS in pregnancy or postpartum. The diagnosis of aHUS was characterized by hemolysis, thrombocytopenia, and renal failure and was distinguished from typical diarrhea-associated hemolytic uremic syndrome. Patients were excluded if individual data could not be obtained, the diagnosis was unclear, or an alternative etiology was more likely, such as thrombotic thrombocytopenic purpura or Shiga toxin–producing *Escherichia coli*. Reports were appraised by two reviewers, with disagreements adjudicated by a third reviewer.

TABULATION, INTEGRATION, AND RESULTS: The search identified 796 articles. After review of titles, abstracts, and full text, we identified 48 reports describing 60 unique cases of pregnancy-associated aHUS, with 66 pregnancies. Twelve cases involved pregnancy in women with known aHUS, and 54 cases involved first-episode pregnancy-associated aHUS. Women with known aHUS, particularly those with baseline creatinine at or above 1.5 mg/dL, had a high rate of adverse pregnancy outcomes. For first-episode pregnancy-associated aHUS, diagnosis most often occurred postpartum (94%), after a cesarean delivery (70%), in nulliparous women (58%). Preceding obstetric complications were common and included fetal death, preeclampsia, and hemorrhage. Diagnosis was usually made clinically, based on the triad of microangiopathic hemolysis, thrombocytopenia, and renal failure. Additional testing included renal biopsy, complement genetic testing, and ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) testing. Treatment modalities included corticosteroids, plasma exchange, dialysis, and eculizumab. More women with first-episode pregnancy-associated aHUS achieved disease remission when treated with eculizumab, compared with those not treated with eculizumab (88% vs 57%, P=.02).

CONCLUSION: Pregnancy-associated aHUS usually presents in the postpartum period, often after a pregnancy complication, and eculizumab is effective for achieving disease remission.

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Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disorder, characterized by microangiopathic hemolysis, thrombocytopenia, and renal failure. It should be distinguished from typical diarrhea-associated hemolytic uremic syndrome, which is most commonly due to Shiga toxin–producing *Escherichia coli*. The incidence of aHUS is estimated at 0.23 per year per million people,[1] but

varies by population.[2–6] Approximately 10–20% of aHUS diagnoses occur in the setting of pregnancy,[7–9] where it has been termed *pregnancy-associated atypical hemolytic uremic syndrome.* Pregnancy is a complement amplifying condition,[10] and maternal exposure to semi-allogenic fetoplacental material increases over gestation, with peak exposure at delivery.[11–13] Excess complement activation is usually mitigated by soluble and membrane-bound regulators of the alternative complement pathway.[14–16] However, inherited mutations in complement regulators predisposed to increased complement activation, and such mutations are common in pregnancy-associated aHUS.[8,9]

In pregnancy and the postpartum period, recognition of pregnancy-associated aHUS is often delayed owing to misdiagnosis of similar thrombotic microangiopathy disorders, such as hemolysis, elevated liver enzymes, and low platelet count syndrome or thrombotic thrombocytopenic purpura (TTP).[17] Delayed diagnosis results in delayed treatment, which can be life-threatening. Corticosteroids and plasma exchange are sometimes effective, but pregnancy-associated aHUS often progresses to end-stage renal disease, dialysis, or kidney transplant.[9] Eculizumab, a monoclonal antibody against complement protein C5, is effective for treatment of aHUS[18,19] and received U.S. Food and Drug Administration (FDA) approval for this indication in 2011. However, pregnant women were excluded from clinical trials.[20] Thus, data on pregnancy-associated aHUS treated with eculizumab are limited, with only four cases reported from an international registry.[9] Therefore, we sought to perform a systematic review of pregnancy-associated aHUS case reports, to better characterize disease presentation, diagnosis, treatment, and clinical outcomes, before and after FDA approval of eculizumab for treatment of aHUS in 2011.

SOURCES

A systematic review of the literature was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and was registered with PROSPERO (registration number CRD42019129266). The primary objective of the search strategy was to identify cases of pregnancy-associated aHUS. English-language articles published until March 2018 were searched in the following databases: PubMed, MEDLINE, Cochrane Library, ClinicalTrials.gov, Web of Science, EMBASE and Google Scholar. The search criteria used the following MeSH terms: "thrombotic microangiopathy," "TMA," "hemolytic uremic syndrome," "HUS," "atypical hemolytic uremic syndrome," "aHUS," "pregnancy," "postpartum," and "peripartum." We did not exclude studies based on study design, location, or any other criteria. In addition, we reviewed reference lists of relevant articles to identify additional case studies.

STUDY SELECTION

All titles and abstracts of search results were independently screened and assessed for inclusion into the systematic review by two study authors (M.G. and S.G.). Cases of disagreement were reviewed and adjudicated by a third author (R.M.B.) to reach consensus. Articles were eligible for inclusion if full texts were available either through public or institutional access, or on request from the corresponding author. Articles were excluded for the following reasons: 1) not relevant to the study question or review article without original case data; 2) cases of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) and article failed to clarify a final diagnosis of either TTP or aHUS; 3) alternative etiology for HUS, such as Shiga toxin-producing *E coli* or scleroderma renal crisis; 4) case series or cohort studies without description of individual cases. For reports describing outcomes of subsequent pregnancies, the index pregnancy was evaluated as primary, first-episode pregnancy-associated aHUS and subsequent pregnancies were evaluated as known aHUS before conception.

Data abstracted from case reports included corresponding author information, journal reference, year of publication, patient characteristics (age, parity, pertinent family or medical histories), pregnancy and delivery characteristics (timing and mode of delivery and pregnancy or delivery complications), timing of disease presentation, diagnostic evaluation (laboratory testing, renal biopsy, and complement genetic testing), therapeutic approach (blood product transfusions, corticosteroids, dialysis, plasma exchange, and eculizumab), and maternal and neonatal outcomes. For patients treated with eculizumab, data were collected on dosing regimen and duration of treatment. Laboratory measures were abstracted as nadir values for hemoglobin, platelet count, or peak values for lactate dehydrogenase, alanine transaminase (ALT), aspartate transaminase (AST), and creatinine. We also abstracted data for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which is used to diagnose TTP (activity level below 10%). Neonatal outcomes were reported as liveborn or stillborn, or in early pregnancy cases whether pregnancy-associated aHUS followed abortion (spontaneous or therapeutic) or

ectopic pregnancy. For maternal outcomes, remission was determined by the final condition reported by the authors. Case studies were included if there were enough data to confirm the diagnosis of pregnancy-associated aHUS and treatment approach. Data on all variables were not required for inclusion, and unavailable data were listed as not available.

Data were described using means with SD, medians with interquartile range, and percentages, as was appropriate to the data characteristics (dichotomous or continuous) or distribution (normal or nonnormal). Statistical testing was performed using χ^2 or Fisher exact test, *t*-test, or Wilcoxon rank-sum test, with significance at $P<.05$. Data were analyzed with Stata 15.0.

RESULTS

Our initial search yielded 796 unique citations. After exclusions, 48 articles were included, with 60 unique cases of pregnancy-associated aHUS (Fig. 1) (Zschiedrich S, Prager EP, Kuehn EW. Successful treatment of the postpartum atypical hemolytic uremic syndrome with eculizumab [letter]. Ann Intern Med 2013;159:76.).[21–40,41–67] In four cases, outcomes of subsequent pregnancies were reported,[41,55,60] for a total of 66 pregnancies. Fifty-four cases described first-episode (new diagnosis) aHUS in pregnancy (n=3) or postpartum (n=51) (Table 1). Twelve cases described pregnancy in women with a known diagnosis of aHUS (Table 2).

For our initial assessment, we evaluated women with first-episode pregnancy-associated aHUS. In four cases, the timing of diagnosis was not specified. Diagnosis was predominantly in the postpartum period (47/50, 94%), at median (interquartile range) postpartum day 2 (1–4). When stated, first-episode pregnancy-associated aHUS occurred more often after cesarean delivery (33/47, 70%), in nulliparous

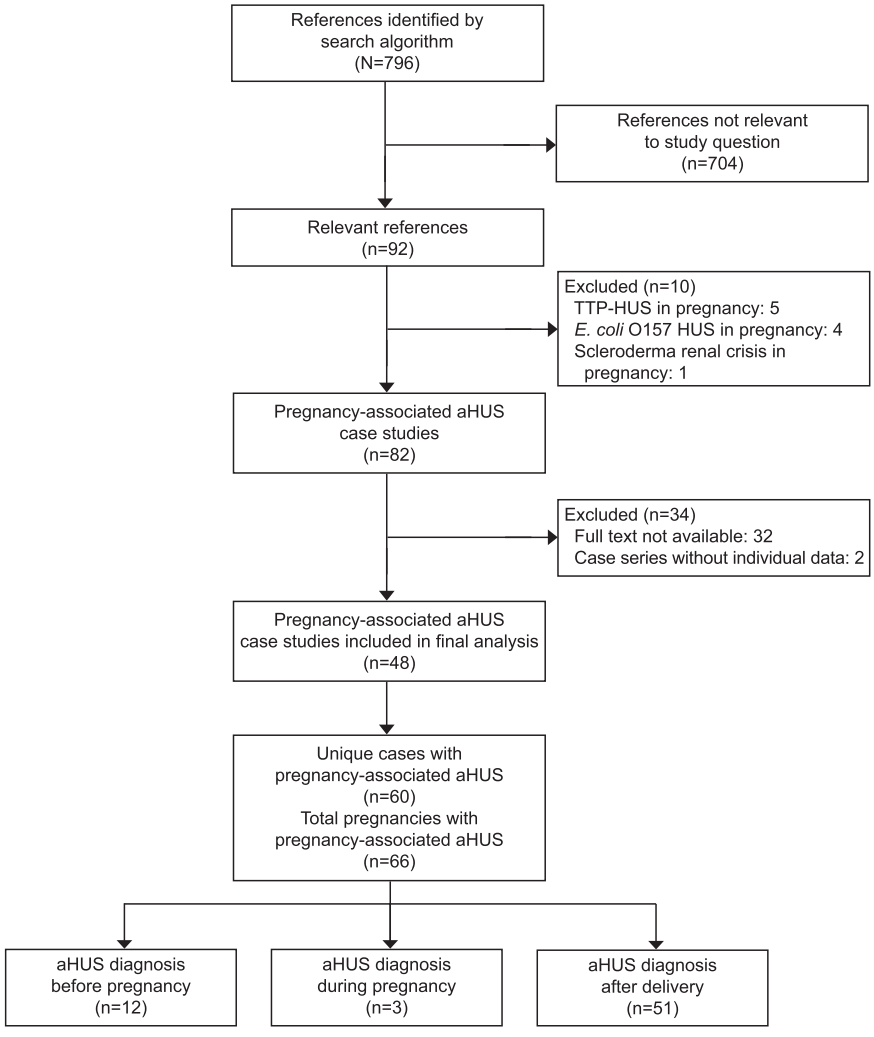

Fig. 1. Flow diagram of case report selection. TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome; HUS, hemolytic uremic syndrome; aHUS, atypical hemolytic uremic syndrome.

Gupta. Pregnancy-Associated Hemolytic Uremic Syndrome. Obstet Gynecol 2019.

Table 1. Data for Patients With First-Episode Pregnancy-Associated Atypical Hemolytic Uremic Syndrome

1st Author* (Publication Year)	Age (y)	Nullip	p-aHUS Dx	Delivery (wk)	Treatment	Neonatal Outcome	Pregnancy or Delivery Complication	Diagnostic Testing	Maternal Outcome
Strauss[59] (1976)	35	No	PPD 14	38	T	Live neonate	Preeclampsia	Renal biopsy	Death at 5 mo postpartum; renal, heart failure
Nissenson[49] (1979)	28	Yes	PPD 8	34	HD	Live neonate	Preeclampsia	Clinical diagnosis	Remission at 13 mo
Brandt[25] (1980)	34	Yes	PPD 1	N/A	None	N/A	Preeclampsia	Clinical diagnosis	Remission
Webster[61] (1980)	31	Yes	PPD 4	31	T, HD	N/A	Severe HTN	Clinical diagnosis	Renal insufficiency, Cr 1.4 mg/dL
Spencer[58] (1982)	23	No	PPD 0	34	T, PE, HD	Stillbirth	Preeclampsia, IUFD, placental abruption	Clinical diagnosis	Renal insufficiency, Cr 1.4 mg/dL
Sagawa[53] (1985)	31	Yes	PPD 0	36	T, S	Live twin neonates	Preterm labor, HTN	Clinical diagnosis	Remission
Schwartz[54] (1986)	28	No	PPD 3	36	T, PE	Live twin neonates	PPROM, HTN	Clinical diagnosis	Renal insufficiency, Cr 1.4 mg/dL
Creasy[31] (1987)	32	No	PPD 8	7	None	Ruptured ectopic	Hemorrhage	Renal biopsy	Remission
Li[45] (1988)	28	Yes	PPD 2	38	HD	Live twin neonates	Fetal distress at 38 wk	Renal biopsy	Remission
Olah[50] (1990)	21	No	PPD 9	39	T, HD	Live neonate	Uncomplicated	Renal biopsy	Remission
Crone[32] (1995)	29	N/A	PPD 44	39	T	Live neonate	Uncomplicated	Clinical diagnosis	Remission
Martinez-Roman[47] (1996)	34	Yes	18 wk	36	T, S, PE, HD	Live neonate	PPROM	Clinical diagnosis	Remission
Kahra[43] (1998)	30	Yes	PPD 0	37	S, HD	Live neonate	Preeclampsia	Renal biopsy	Remission
Gherman[39] (1989)	30	No	PPD 4	36	S, HD	Live neonate	Preeclampsia	Renal biopsy	Remission
Mahalati[46] (1999)	36	Yes	PPD 0	33	PE	N/A	Preeclampsia	Clinical diagnosis	Remission
Hebisch-1a[41] (2001)	29	Yes	PPD 0	36	T, S, PE	Stillbirth	Placental abruption	Clinical diagnosis	Remission
Plante[51] (2002)	18	Yes	PPD 0	38	T, S, PE, HD	Live neonate	Cystic fibrosis; preeclampsia, HELLP	Renal biopsy	Renal failure on dialysis
Anacleto[21] (2003)	17	Yes	PPD 0	33	T, S, HD	Stillbirth	Preeclampsia, placental abruption, PPH	Renal biopsy	Renal insufficiency, Cr 2.0 mg/dL
Yamanaka-1[65] (2005)	28	Yes	PPD 1	35	T, PE, HD	Live neonate	Preeclampsia, IUGR	Clinical diagnosis	Renal failure on dialysis
Yamanaka-2[65] (2005)	34	No	POD 1	14	T, PE, HD	Stillbirth	IUFD, PPH and hysterectomy after D&C	Clinical diagnosis	Remission
Iannuzzi[42] (2006)	37	No	PPD 0	37	T, S, PE	N/A	Preeclampsia	Heterozygous CFH risk variant	Renal insufficiency, GFR 48 mL/min
Habek[40] (2007)	37	No	PPD 8	N/A	S, PE	Live neonate	Placenta percreta, PPH, hysterectomy	Clinical diagnosis	Remission
Shrivastava-1[56] (2011)	27	Yes	PPD 3	Term	T, S, PE, HD	Live neonate	Uncomplicated	Clinical diagnosis	Remission

(*continued*)

Table 1. Data for Patients With First-Episode Pregnancy-Associated Atypical Hemolytic Uremic Syndrome (*continued*)

1st Author* (Publication Year)	Age (y)	Nullip	p-aHUS Dx	Delivery (wk)	Treatment	Neonatal Outcome	Pregnancy or Delivery Complication	Diagnostic Testing	Maternal Outcome
Shrivastava-2[56] (2011)	25	No	PPD 3	Term	T, S, PE, HD	Live neonate	Uncomplicated	Clinical diagnosis	Renal insufficiency, Cr 2.4 mg/dL
Shrivastava-3[56] (2011)	30	No	PPD 0	Term	T, S, PE, HD	Stillbirth	IUFD	Clinical diagnosis	Renal insufficiency, Cr 1.8 mg/dL
Brown[26] (2012)	26	Yes	N/A	36	PE, HD	Live neonate	HTN; prior liver transplant	Homozygous CD46 risk haplotype; heterozygous CFH donor mutation	Renal failure on dialysis
Dixit[36] (2012)	21	Yes	PPD 2	N/A	T, PE, HD	N/A	Uncomplicated	Clinical diagnosis	Remission
Zhou[66] (2012)	20	Yes	PPD 9	35	T, S, PE, HD	N/A	Preeclampsia	Renal biopsy	Vision loss; renal failure on dialysis
Wu-1[63] (2014)	38	No	POD 9	8	T, S, HD	Abortion	Uncomplicated	Renal biopsy	Remission
Wu-2[63] (2014)	41	No	POD 1	12	T, S, HD	Abortion	Uncomplicated	Renal biopsy	Remission
Mu[48] (2015)	23	Yes	PPD 8	40	None	N/A	Uncomplicated	Autopsy findings	Death on day of presentation
Song-1[57] (2015)	36	N/A	PPD 3	39	T, S, PE, HD	N/A	Preeclampsia	2 CFH risk variants; renal biopsy	End-stage renal disease
Song-2[57] (2015)	33	N/A	PPD 2	39	T, S, PE, HD	N/A	Preeclampsia	2 CFH risk variants; renal biopsy	Remission
Song-3[57] (2015)	26	N/A	PPD 3	40	T, S, PE, HD	N/A	Uncomplicated	2 CFH risk variants, THBD risk variant; renal biopsy	End-stage renal disease
Song-4[57] (2015)	27	N/A	PPD 2	39	PE, HD	N/A	Uncomplicated	CFH risk variant, 2 THBD risk variants; renal biopsy	End-stage renal disease
Song-5[57] (2015)	35	N/A	PPD 1	36	T, PE	Stillbirth	Abruption, IUFD	CFH risk variant, THBD risk variant; renal biopsy	Remission
Tsai-1a[60] (2016)	20	No	PPD3	N/A	PE	N/A	Hypertension	Clinical diagnosis	Recurrence in next pregnancy
Carr[28] (2013)	20	N/A	PPD 7	N/A	S, PE, HD, Ecu	N/A	Not specified	CFH mutant allele	Relapse after drug cessation at 9 mo; remission on Ecu
Zschiedrich (2013)[†]	31	N/A	PPD 3	41	S, PE, HD, Ecu	Live neonate	PPH	Heterozygous CFI frame shift mutation	Remission
Canigral[27] (2014)	32	N/A	N/A	N/A	S, PE, Ecu	N/A	PPH, cesarean hysterectomy	Clinical diagnosis; negative genetic panel	Remission
Kourouklaris[44] (2014)	23	N/A	PPD 5	31	PE, HD, Ecu	N/A	Preeclampsia	Renal biopsy	Disease progression 4 mo postpartum on PE/HD; remission on Ecu
De Sousa Amorim[33] (2015)	41	Yes	PPD 4	N/A	T, PE, HD, Ecu	N/A	Uncomplicated	Homozygous CFH, MCP risk haplotype; renal biopsy	Remission

(*continued*)

Table 1. Data for Patients With First-Episode Pregnancy-Associated Atypical Hemolytic Uremic Syndrome (*continued*)

1st Author* (Publication Year)	Age (y)	Nullip	p-aHUS Dx	Delivery (wk)	Treatment	Neonatal Outcome	Pregnancy or Delivery Complication	Diagnostic Testing	Maternal Outcome
Demir[35] (2016)	17	N/A	17 wk	31	PE, Ecu	Live neonate	Fetal distress at 31 wk	2 homozygous SNPs in CFH; renal biopsy	Remission
Saad[52] (2016)	19	Yes	PPD 1	39	T, S, PE, Ecu	N/A	Preeclampsia	Heterozygous CD46 variant	Remission
Williams[62] (2016)	21	No	PPD 1	Term	PE, Ecu	N/A	Uncomplicated	CFH mutation	Remission
Andries[22] (2017)	30	No	10 wk	36	T, S, PE, HD, Ecu	Live neonate	No adverse pregnancy outcomes	Clinical diagnosis; negative genetic panel	Remission
Asif[24] (2017)	33	N/A	PPD 1	33	T, PE, HD, Ecu	Stillbirth	Abruption, IUFD, PPH; cesarean hysterectomy	Clinical diagnosis	Remission
Cavero-1[29] (2017)	27	N/A	N/A	N/A	PE, Ecu	N/A	Not specified	Renal biopsy; negative genetic panel	Renal insufficiency, Cr 1.5 mg/dL
Cavero-2[29] (2017)	35	N/A	N/A	N/A	PE, HD, Ecu	N/A	Not specified	Clinical diagnosis; negative genetic panel	Remission
Chua-1[30] (2017)	34	N/A	PPD 0	33	T, PE, HD, Ecu	Stillbirth	IUFD, severe HTN	Homozygous CFHR1-CFHR3 deletion (author reply)	Remission
Chua-2[30] (2017)	29	N/A	PPD 1	37	PE, Ecu	Stillbirth	IUFD, PPH	Variant of unknown significance in C3 gene (author reply)	Remission
Gately[38] (2017)	32	Yes	PPD 1	40	T, PE, HD, Ecu	N/A	Massive PPH, DIC	Clinical diagnosis; No genetic tests (author reply)	Renal insufficiency, Cr 1.7 mg/dL
Yamaguchi[64] (2017)	25	Yes	PPD 2	37	T, PE, HD, Ecu	Live neonate	Preeclampsia	Homozygous CFH mutation	Remission
Misal[67] (2018)	37	Yes	PPD 1	38	S, HD, Ecu	Live neonate	Uncomplicated	Clinical diagnosis; negative genetic panel	Remission

Nullip, nulliparous (predelivery, index pregnancy); p-aHUS, pregnancy-associated hemolytic uremic syndrome; Dx, diagnosis; PPD, postpartum day; T, transfusion; HD, hemodialysis; N/A, not available; HTN, hypertension; Cr, creatinine; IUFD, intrauterine fetal death; PE, plasma exchange; S, steroids; PPROM, preterm prelabor rupture of membranes; HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome; PPH, postpartum hemorrhage; IUGR, intrauterine growth restriction; POD, postop day; D&C, dilation and curettage; CFH, complement factor H; GFR, glomerular filtration rate; THBD, thrombomodulin; Ecu, eculizumab; CFI, complement factor I; MCP, membrane cofactor protein; SNP, single nucleotide polymorphism; CFHR, complement factor H-related; DIC, disseminated intravascular coagulopathy.

* Cases were sorted by use of eculizumab and then publication year. For reports describing more than one case, each case was given a unique number (eg, 1, 2, 3) after the author name, and subsequent pregnancies from the same case were given a unique letter (eg, 1a, 1b, 1c).

† Zschiedrich S, Prager EP, Kuehn EW. Successful treatment of the postpartum atypical hemolytic uremic syndrome with eculizumab [letter]. Ann Intern Med 2013;159:76.

women (22/38, 58%), with mean (SD) maternal age 29.0 (6.2) years and delivery gestational age 36.4 (2.7) weeks. Four cases occurred after an early pregnancy loss or termination. Of these, two occurred after uncomplicated dilation and curettage,[63] one after a complicated dilation and curettage procedure necessitating exploratory laparotomy and hysterectomy,[65] and one after a ruptured tubal ectopic pregnancy necessitating exploratory laparotomy and massive transfusion.[31]

The diagnosis of pregnancy-associated aHUS was usually suspected based on markedly abnormal laboratory findings, including: median (interquartile range) concentration of serum lactate dehydrogenase 2,438 (1,235–3,885) units/L; hemoglobin 6.8 (6.1–7.8) g/dL; platelet count 43 (30–61) k/microliter; and

Table 2. Data for Patients With a Known Diagnosis of Atypical Hemolytic Uremic Syndrome Before Pregnancy

1st Author (Publication Year)	Age (y)	Nullip	Baseline Kidney Function	aHUS Recurrence	Delivery (wk)	Treatment*	Neonatal Outcome	Pregnancy or Delivery Complication	Prior Diagnostic Testing	Maternal Outcome
Hebisch-1b[41] (2001)	33	No	N/A	None	Term	None	Live neonate	No adverse pregnancy outcomes	Clinical diagnosis	Recurrent aHUS in next pregnancy
Hebisch-1c[41] (2001)	36	No	N/A	28 wk	30	T, PE	Live neonate	Recurrent aHUS	Clinical diagnosis	Persistent renal failure, on transplant list
Egbor[37] (2011)	35	N/A	Cr 0.8 mg/dL	PPD 42	Term	T, PE	N/A	Uncomplicated	CFI deficiency; renal biopsy with TMA	Persistent hypertension requiring 4 blood pressure agents
Ardissino[23] (2013)	26	Yes	N/A	17 wk	38	T, PE, Ecu	Live neonate	Recurrent aHUS; no adverse pregnancy outcomes	Homozygous CFH mutation	Remission after starting eculizumab at 29 wk
Delmas[34] (2013)	26	N/A	N/A	PPD 7	N/A	T, HD, PE, Ecu	N/A	Not specified	Heterozygous CFH, CFI mutations	Remission
Tsai-1b[60] (2016)	22	No	N/A	22 wk	22	Ecu	Stillbirth	Recurrent aHUS; Labor induction	CFH mutation; renal biopsy with TMA	Remission
Servais-1a[55] (2016)	31	Yes	Cr 1.9 mg/dL	29 wk	29	T, Ecu	Live neonate	HELLP vs recurrent aHUS with placental abruption	Heterozygous CFH mutation	Persistent renal insufficiency at 1 y, Cr 1.6 mg/dL
Servais-1b[55] (2016)	33	No	Cr 1.6 mg/dL	None	34	Ecu	Live neonate	Vaginal bleeding at 34 wk	Heterozygous CFH mutation	Persistent renal insufficiency at 2 y, Cr 1.5 mg/dL
Servais-2[55] (2016)	29	Yes	Cr 1.5 mg/dL	30 wk	30	Ecu	Live neonate	Preeclampsia and worsening kidney injury	Heterozygous C3 mutation; renal biopsy with TMA	Persistent renal insufficiency at 6 mo, Cr 1.6 mg/dL
Servais-3a[55] (2016)	25	Yes	Cr 3.4 mg/dL	12 wk	12	HD, PE, Ecu	Abortion	Recurrent aHUS	Heterozygous CFI mutation; rare C3 variant	Persistent renal insufficiency at 12 mo, Cr 2.3 mg/dL
Servais-3b[55] (2016)	26	No	Cr 2.3 mg/dL	None	24	Ecu	Stillbirth	IUFD at 24 wk	Heterozygous CFI mutation; rare C3 variant	Persistent renal insufficiency at 5 mo, Cr 2.2 mg/dL
Servais-3c[55] (2016)	27	No	Cr 2.2 mg/dL	None	30	Ecu	Live neonate	Preeclampsia, IUGR	Heterozygous CFI mutation; rare C3 variant	Persistent renal insufficiency at 8 mo, Cr 1.9 mg/dL

Nullip, nulliparous; aHUS, atypical hemolytic uremic syndrome; T, transfusion; PE, plasma exchange; N/A, not available; Cr, creatinine; PPD, postpartum day; CFI, complement factor I; TMA, thrombotic microangiopathy; Ecu, eculizumab; CFH, complement factor H; HD, hemodialysis; HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction.

* Cases were sorted by publication year. For reports describing more than one case, each case was given a unique number (eg, 1, 2, 3) after the author name, and subsequent pregnancies from the same case were given a unique letter (eg, 1a, 1b, 1c).

creatinine 5.4 (4.1–7.6) mg/dL. Laboratory testing was often triggered by symptoms such as nausea, vomiting, abdominal pain, headache, shortness of breath, or elevated blood pressure. Liver enzymes (ALT, AST) were reported in 17 cases, and levels were more than twice the upper limit of normal in 52% (9/17) of cases, with median (interquartile range): ALT 47 (28–333) units/L; AST 114 (20–373) units/L. In 19 cases, haptoglobin was assessed to confirm red cell hemolysis and levels were low or undetectable in all instances (19/19, 100%). Microangiopathic hemolysis was confirmed by detection of schistocytes on peripheral smear (46/47, 98%).

For our initial analysis of first-episode pregnancy-associated aHUS, we stratified cases into two groups: group 1 (n=37), in which eculizumab was not used for treatment, and group 2 (n=17), in which eculizumab was used for treatment. Before and after introduction of eculizumab in 2011, maternal age, parity, gestational age at delivery, and timing of diagnosis were

similar (Table 3). The median (interquartile range) postpartum day of diagnosis was 2.0 (0–8.0) before eculizumab and 1.0 (1.0–3.5) after eculizumab, and this difference was not significant. Among reports in which pregnancy outcomes were reported and the pregnancy was carried beyond 24 weeks of gestation, the diagnosis of pregnancy-associated aHUS was often preceded by a pregnancy complication: hypertension or preeclampsia (21/37, 57%); obstetric hemorrhage (8/37, 22%); or intrauterine fetal death (7/25, 28%). Obstetric complications were not significantly different in pregnancy-associated aHUS cases reported before or after introduction of eculizumab.

Although the diagnosis of pregnancy-associated aHUS was suspected based on clinical symptoms and laboratory findings, other studies were often used to confirm the diagnosis or rule out other etiologies, including renal biopsy, ADAMTS13 activity level, and complement genetic testing. Before introduction of eculizumab in 2011, 49% of pregnancy-associated aHUS diagnoses were made by clinical criteria alone and 44% incorporated renal biopsy findings, but these numbers have dipped since 2011, to 35% and 24%, respectively (Table 4). Renal biopsy was often used to confirm a diagnosis of thrombotic microangiopathy, and findings included fibrin thrombi within glomeruli, luminal stenosis in arterioles, subendothelial swelling, mesangiolysis, and fragmented erythrocytes. The decline in use of renal biopsy was countered by a marked increase in both ADAMTS13 activity testing and complement genetic testing after eculizumab was introduced into practice (19% vs 82%, $P<.001$). ADAMTS13 activity level was above 10% in all 21 cases of pregnancy-associated aHUS in which it was tested, ruling out TTP. This emphasizes the value of ADAMTS13 testing to rule out TTP and to help expedite the diagnosis of aHUS.

Complement factor H risk variants were the most common genetic abnormality reported before introduction of eculizumab in 2011. Five of seven cases were reported by the same author, who also reported concomitant thrombomodulin risk variants in three cases.[57] As complement genetic panels have expanded, case studies have described additional variants in pregnancy-associated aHUS. Some of these findings, summarized in Table 1, include heterozygous complement factor I frameshift mutation (Zschiedrich S et al. Ann Intern Med 2013;159:76.), heterozygous CD46 variant,[52] and homozygous deletion in complement factor H–related genes 1 and 3 (*CFHR1-CFHR3* deletion).[30]

Next, we sought to compare the treatment approach to pregnancy-associated aHUS before and after introduction of eculizumab in 2011 (Table 4). Use of corticosteroids and dialysis were similar between the two groups, and there was a slight, but nonsignificant decrease in use of blood transfusion with eculizumab (68% vs 41%, $P=.07$). There has been an increase in the reported use of plasma exchange after introduction of eculizumab (60% vs 100%, $P=.002$). However, in all 17 cases in which eculizumab was used for treatment of pregnancy-associated aHUS, it was given after plasma exchange had failed. Moreover, eculizumab was usually a second- or third-line treatment after intravenous (IV) corticosteroids, plasma exchange, or hemodialysis.

Table 3. Characteristics and Pregnancy Complications in First-Episode Pregnancy-Associated Atypical Hemolytic Uremic Syndrome

	p-aHUS Cases		
Characteristic or Pregnancy Complication*	Treated Without Eculizumab (n=37)	Treated With Eculizumab (n=17)	*P*
Maternal age (y)	29.1±6.0	28.6±6.8	.77
Primiparous	55 (17/31)	71 (5/7)	.42
Gestational age at delivery (wk)	36 (34–38)	37 (33–39)	.41
Postpartum diagnosis	97 (35/36)	86 (12/14)	.12
Day of postpartum diagnosis	2.0 (0–8.0)	1.0 (1.0–3.5)	.36
Uncomplicated pregnancy and delivery	19 (5/26)	18 (2/11)	1.0
Hypertension or preeclampsia	65 (17/26)	36 (4/11)	.15
Obstetric hemorrhage	15 (4/26)	36 (4/11)	.20
Fetal death	12 (3/26)	27 (3/11)	.64

p-aHUS, pregnancy-associated atypical hemolytic uremic syndrome.
Data are mean±SD, % (n/N), or median (interquartile range) unless otherwise specified.
P-value was determined by χ^2 or Fisher exact test (cell counts below 5), *t*-test, or Wilcoxon rank sum test (medians).
* Pregnancy complications for those delivering at 24 weeks of gestation or beyond.

Table 4. Diagnosis, Treatment, and Long-Term Outcomes in First-Episode Pregnancy-Associated Atypical Hemolytic Uremic Syndrome

Diagnosis, Treatment and Long-Term Outcomes	p-aHUS Cases		
	Treated Without Eculizumab (n=37)	Treated With Eculizumab (n=17)	*P*
Clinical diagnosis only*	49 (18/37)	35 (6/17)	.36
Renal biopsy performed	44 (16/36)	24 (4/17)	.23
ADAMTS13 activity assessed	19 (7/37)	82 (14/17)	<.001
Above 10%	100 (7/7)	100 (14/14)	1.0
Complement genetic testing performed	19 (7/37)	82 (14/17)	<.001
Pathogenic complement gene mutation or high-risk variant	100 (7/7)	64 (9/14)	.07
Blood transfusion	68 (25/37)	41 (7/17)	.07
Corticosteroids	49 (18/37)	35 (6/17)	.36
Plasma exchange	60 (22/37)	100 (17/17)	.002
Dialysis	65 (24/37)	59 (10/17)	.67
Disease remission†	57 (21/37)	88 (15/17)	.02
Persistent renal insufficiency or severe hypertension	19 (7/37)	12 (2/17)	.70
Renal failure, dialysis, or death	24 (9/37)	0 (0/17)	.04

p-aHUS, pregnancy-associated atypical hemolytic uremic syndrome; GA, gestational age; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.
Data are % (n/N) unless otherwise specified.
P-value was determined by χ^2 test or Fisher exact test (cell counts below 5).
* Diagnosis made by clinical symptoms and laboratory findings alone, including peripheral smear.
† Disease remission at completion of case study, as reported by author.

In the majority (15/17, 88%) of cases of first-episode pregnancy-associated aHUS in which eculizumab was used, both diagnosis and treatment occurred in the postpartum period. Only two women were newly diagnosed with pregnancy-associated aHUS and treated with eculizumab in the antepartum period, at 10[22] and 17 weeks of gestation.[35] The eculizumab regimen was not stated for the latter, but Andries et al used the FDA-approved regimen for treatment of aHUS, which is eculizumab 900 mg IV weekly for 4 weeks (loading regimen), then 1,200 mg IV in week 5 followed by 1,200 mg IV every other week (maintenance regimen). Of the 15 women treated with eculizumab in the postpartum period, the standard loading regimen was used in 12 (80%) but was unspecified in three others. The standard maintenance regimen was used in 11 patients (73%); the maintenance regimen was unspecified in two patients, and was reported as 900 mg IV twice weekly in one[33] and 1,200 mg IV monthly in another.[62]

Table 4 also describes long-term outcomes in women after first-episode pregnancy-associated aHUS. More women achieved disease remission when treated with eculizumab compared with those not treated with eculizumab (88% vs 57%, *P*=.02). In addition, among 17 cases of pregnancy-associated aHUS treated with eculizumab, there were no reports of persistent renal failure, dialysis, or death, compared with 24% (9/37) of such cases not treated with eculizumab (two maternal deaths, seven end-stage renal disease or dialysis). In eight cases, postpartum treatment with eculizumab was stopped at a median (range) of 7 (1–22) months; in four cases, treatment was ongoing at 7, 7, 20, and 22 months. In other cases, treatment duration was not specified.

We separately assessed characteristics and outcomes of women with known aHUS entering pregnancy (Table 2). There were eight unique cases, with a total of 12 pregnancies. Seven cases, and 10 pregnancies, were in women with a known complement mutation or deficiency, most commonly complement factor H (n=4) or complement factor I (n=3). Nine women were treated with eculizumab during pregnancy. Mean (SD) age at pregnancy was 29.1 (4.4) years, with median (range) starting creatinine 1.9 (0.8–3.4) mg/dL. Only one case started pregnancy with a normal serum creatinine below 1.2 mg/dL,[37] but baseline creatinine was not reported in five pregnancies. Recurrence of aHUS occurred in 67% (8/12) of pregnancies, leading to pregnancy termination in two instances[55,60] and preterm birth in three others.[41,55] In two pregnancies, recurrence occurred postpartum.[34,37] There was only one pregnancy (1/12, 8%) with aHUS that resulted in a healthy term delivery, without pregnancy complication or disease recurrence.[41] However, in that case, the subsequent

pregnancy was complicated by recurrent aHUS at 28 weeks of gestation and premature delivery at 30 weeks. As expected, in three women (six pregnancies) with chronic kidney disease entering pregnancy (all creatinine at or above 1.5 mg/dL), pregnancy outcomes were particularly poor, with deliveries at 12, 24, 29, 30, 30, and 34 weeks of gestation.[55]

DISCUSSION

We have summarized data for 54 unique cases of first-episode aHUS occurring in pregnant or postpartum women (pregnancy-associated aHUS), of whom 17 patients were treated with eculizumab. In addition, we assessed 12 pregnancies in women with known aHUS before conception, of whom nine were treated with eculizumab. We find that, despite similar clinical characteristics to women not treated with eculizumab, those treated with eculizumab for first-episode pregnancy-associated aHUS had higher rates of disease remission with no cases of persistent renal failure, dialysis, or maternal death. Moreover, successful treatment of first-episode pregnancy-associated aHUS with eculizumab usually occurred despite failure of other modalities such as plasma exchange, corticosteroids, and hemodialysis.

Clinical trials have shown that eculizumab effectively decreases complement-mediated hemolysis, thrombocytopenia, and kidney injury in nonpregnant adults with aHUS.[20,68] Thus, successful treatment of pregnancy-associated aHUS with eculizumab is in line with our understanding of the disease as a complement-mediated thrombotic microangiopathy disorder. International registry data have shown that pregnancy-associated aHUS is like adult aHUS in nearly all aspects and should be treated similarly.[8,9] Although a minority of pregnancy-associated aHUS cases occurred after an uncomplicated pregnancy, preceding obstetric complications were common and included preeclampsia, hemorrhage, and fetal death. Thus, a major limitation to expedited diagnosis and treatment of pregnancy-associated aHUS may be co-occurrence with other pregnancy complications. It is important to study these cases because preeclampsia and hemorrhage may trigger development of pregnancy-associated aHUS, particularly in those with complement gene mutations. However, pregnancy-associated aHUS is a clinical diagnosis based on the clinical phenotype, and genetic testing is not required. Although other etiologies should be evaluated and ruled out, we found a very characteristic pattern of laboratory values in first-episode pregnancy-associated aHUS, including microangiopathic hemolysis (elevated lactate dehydrogenase, low haptoglobin, schistocytes), thrombocytopenia, and severe renal failure. This triad should alert the health care provider to the diagnosis of pregnancy-associated aHUS, especially if laboratory parameters worsen, rather than improve, in the postpartum period. When obstetricians suspect pregnancy-associated aHUS, they should involve other health care providers with expertise in diagnosing and treating aHUS, and this may include maternal–fetal medicine, nephrology, hematology, or critical care physicians.

Atypical hemolytic uremic syndrome is a complement-mediated disorder that is best treated with complement blockade,[68] yet we found that plasma exchange was often used as a first-line option for pregnancy-associated aHUS, even after FDA approval of eculizumab. Although the American Society for Apheresis states that the role of therapeutic plasma exchange in treatment of aHUS is not established,[69] the decision to start plasma exchange may be driven by the desire to treat TTP presumptively until it can be ruled out. Like aHUS, TTP is a life-threatening thrombotic microangiopathy disorder, but unlike aHUS, TTP is best treated with plasma exchange because it is usually due to ADAMTS13 autoantibodies.[70–73] Thrombotic thrombocytopenic purpura can be easily ruled out with an ADAMTS13 activity level greater than 10% and the absence of autoantibodies. Likewise, complement genetic testing may be performed to support a diagnosis of aHUS, particularly when a pathogenic mutation is discovered. However, ADAMTS13 and complement genetic testing are send-out labs in most institutions, limiting turnaround time. To expedite diagnosis and treatment of aHUS, and to help rule out TTP more quickly, it may be beneficial for clinicians to work with their laboratory medicine department and hospital leadership to review options for ADAMTS13 and complement genetic testing. Until a diagnosis of pregnancy-associated aHUS can be made with reasonable certainty, the initial treatment approach should be made on a case-by-case basis. Once the diagnosis of pregnancy-associated aHUS is made, eculizumab should be considered for on-label treatment as it appears to improve long-term remission of disease when compared with women with pregnancy-associated aHUS not treated with eculizumab.

Our data are limited by the nature of case reports, which are rich in detail but biased by a lack of control data. There may be a publication bias toward cases with a positive outcome or an unusual feature, such as a newly described genetic variant. Thus, these cases may not be a fully representative sample. Some reports in our analysis were also hindered by missing data (eg, parity, gestational age) or lack of long-term follow-up. However, our data set has many strengths.

It is the largest compilation to-date of pregnancy-associated aHUS cases treated with eculizumab, and it is the largest study of first-episode pregnancy-associated aHUS cases that included all women regardless of obstetric history. Inclusion of women with obstetric complications such as preeclampsia, hemorrhage, and fetal death allowed us to demonstrate the variety of ways in which pregnancy-associated aHUS may present–an important aspect that has been missing from registry reports. Finally, it is important to note that eculizumab is a high-cost drug that may not be readily available at every institution and despite on-label use, insurance coverage may vary. Health care providers considering using eculizumab should work with the pharmacy department to discuss drug access, inpatient cost considerations, plan for outpatient infusions, and long-term follow-up.

In assessing our data, we wish to emphasize that, once someone is diagnosed with aHUS or pregnancy-associated aHUS, the prognosis for future pregnancies is guarded. Our data suggest that women with aHUS who develop chronic kidney disease, particularly with serum creatinine at or above 1.5 mg/dL, have particularly poor pregnancy outcomes and a high rate of recurrent disease. Although women with well-controlled aHUS may be able to achieve successful pregnancy outcomes in the era of eculizumab, such data are extremely limited. Pregnancy care, and decisions regarding future pregnancy, should be made in conjunction with obstetrician-gynecologists, maternal–fetal medicine specialists, hematologists, and nephrologists, among others. Both aHUS and pregnancy-associated aHUS are serious, life-threatening thrombotic microangiopathy disorders, and women stand to benefit greatly from care that is guided by an expert, multidisciplinary team.

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