Pregnancy-associated atypical haemolytic uraemic syndrome in the postpartum period: a case report and review of the literature

M Egbor PhD MRCOG*, **A Johnson** MBChB MRCOG*, **F Harris** PhD FRCP†, **D Makanjola** MD FRCP† and **H Shehata** MD FRCOG*

*Department of Obstetrics and Gynaecology, Epsom & St Helier University Hospital; †Renal Unit, Epsom & St Helier University Hospital, Carshalton, UK

Summary: Pregnancy has been reported to be a trigger in about 10% of all patients with atypical haemolytic uraemic syndrome (aHUS). However, in contrast to pregnancy-associated thrombotic thrombocytopenic purpura, the presentation of pregnancy-associated aHUS remains ill defined and can therefore be difficult to diagnose and manage appropriately. Here we report a case of pregnancy-associated relapse of aHUS in a patient with a previous medical history of aHUS prior to pregnancy.

Keywords: atypical haemolytic uraemic syndrome, complications, pregnancy, hypertension, nephrology

INTRODUCTION

Pregnancy has been reported to be a trigger in about 10% of all patients with atypical haemolytic uraemic syndrome (aHUS).¹ The presentation of pregnancy-associated atypical haemolytic uraemic syndrome (P-aHUS) remains ill defined however, and therefore can be difficult to diagnose and manage appropriately.

Here, we report a case of pregnancy-associated relapse of aHUS in a patient with a previous medical history of aHUS.

CASE REPORT

A 35-year-old lady presented to the obstetric medicine clinic at St Helier Hospital, at five weeks gestation, in December 2008. Relevant family history included the death of her sister in childhood due to haemolytic uraemic syndrome (HUS). She had a past history of coeliac disease and was known to the renal services with chronic kidney disease stage 3, secondary to a previous episode of aHUS. She initially presented in 2003 with a creatinine of 139, headaches, hypertension and an elevated lactate dehydrogenase (LDH). A renal biopsy was performed and showed changes consistent with a thrombotic microangiopathy. The picture was suggestive of HUS and subsequent investigations revealed a deficiency in complement Factor I, supporting a diagnosis of aHUS. She was anaemic, with low erythropoietin levels which, although her renal insufficiency was mild, were presumed to be due to her renal disease. Investigations, including a bone marrow biopsy, had shown

no other abnormalities. Thereafter, she was maintained on subcutaneous erythropoiesis stimulating agents.

She expressed a desire to conceive, and was referred to the obstetric physician for pre-pregnancy counselling. She was counselled about the increased risk of complications including severe preeclampsia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and relapse of aHUS. Metformin was commenced to treat her infertility, which was thought to be related to polycystic ovarian syndrome.

She became pregnant within a few months and was booked for joint management in the renal/obstetric medicine clinic. Methyl-dopa was used to control her blood pressure from nine weeks of gestation, and monthly urine protein:creatinine ratios were obtained, along with full blood count, liver function tests, urea, electrolytes and creatinine. C3 and C4 complement levels were also checked intermittently (Table 1). A blood sample was sent for ADAMTS 13 activity, which was found to be 87% (normal range 66–126%).

She remained well and regular growth scans at 24, 28, 32 and 36 weeks showed normal liquor volume and Doppler studies. Delivery was by an emergency caesarean section for failure to progress, following induction of labour for prolonged rupture of membranes at term.

Six weeks postpartum, she presented with persistent headaches and hypertension. There was no associated diarrhoea. Laboratory investigations showed evidence of haemolysis with anaemia (Hb nadir 9.6 g/dL), thrombocytopenia (platelet nadir 102) and rising LDH, which peaked at 862 mmol/L. There was associated renal impairment with a rise in creatinine (peaked at 311 µmol/L, estimated glomerular filtration rate (eGFR) 14 mL/minute). The serum C3 fell, but C4 was normal. The ADAMTS 13 activity was not measured again, but based on her past medical history, current clinical

Correspondence to: Michael Egbor
Email: megbor@nhs.net

Table 1 Summary of results through the pregnancy

	1st trimester	2nd trimester	3rd trimester
Haemoglobin (g/dL)	11.8–13.1	10.8–12.0	10.4–12.1
Platelets (150–400)	374–391	342–395	284–329
ALT (1–50)	58–67	25–37	21–23
Creatinine (μ mol/L)	65–75	61–67	58–60
UPCR* (mg/mmol) (0.0–15.0)	152–650	65–83	91–468
C3 (g/dL) (0.75–1.65)	0.8	1.04	1.00
C4 (g/dL) (0.14–0.54)	0.26	0.33	0.27

UPCR, urine protein: creatinine ratio; ALT, alanine transaminase
Normal ranges shown in parentheses

presentation, and laboratory findings, a diagnosis of relapse of aHUS was made. Urgent treatment with plasmapheresis was commenced. Fresh frozen plasma was used as the replacement fluid and 3 L exchanges were performed daily for 12 days. She developed worsening renal impairment, with hypertension and fluid overload, but this improved with judicious diuretic use, as well as an escalation of antihypertensive therapy. Laboratory indices and clinical parameters improved following 12 sessions of plasma exchange and she did not require haemodialysis. Her eGFR rose from 14 to between 30 and 35 mL/minute. Prior to pregnancy, her blood pressure was controlled with Irbesartan alone; however, 18 months following her relapse, she is on four agents to achieve reasonable blood pressure control. The urine protein-to-creatinine ratio peaked at 715 mg/mmol, but is now 25 mg/mmol. She remains on an erythropoiesis-stimulating agent for her anaemia.

DISCUSSION

HUS is characterized by a microangiopathic haemolytic anaemia, thrombocytopaenia and renal impairment.¹ The 'typical' form of HUS is preceded by a diarrhoeal illness usually caused by Shiga toxin-producing strains of *Escherichia coli* (mostly *E. coli* 0157:H7), and is seen mainly in children. In adults, HUS is predominantly of the atypical form (Table 2). Atypical HUS shares many clinical features with thrombotic thrombocytopaenic purpura (TTP). However, TTP

is associated with more marked thrombocytopaenia, transient focal neurological abnormalities and less severe renal involvement.² Conversely, significant renal impairment is more commonly associated with aHUS.^{2,3} Recent advances in the understanding of the pathophysiology of these conditions has improved our ability to differentiate between them. An acquired or constitutional deficiency in ADAMTS13, a von Willebrand factor-cleaving protease, has emerged as a specific cause of TTP, whereas in about 50% of cases, aHUS may be predisposed to by the presence of underlying genetic abnormalities, typically mutations in one or more genes coding for proteins involved in the regulation of the alternative pathway of complement activation.^{4,5}

Although the incidence of aHUS among all pregnancies is reported to be only one in 25,000,¹ a recent study has clearly shown that P-aHUS is a frequently encountered subtype of aHUS, accounting for up to 20% of all patients with this condition.^{6,7} Pregnancy, therefore, appears to be an important triggering factor for aHUS. In addition to *de novo* disease, aHUS that initially occurs in non-pregnant women may recur during, or soon after a subsequent pregnancy, and there are reports of recurrent aHUS in successive pregnancies.^{8–10}

The time of onset of aHUS in pregnancy is variable. In one report of 13 pregnancies complicated by the disease, three developed before mid-pregnancy, eight occurred peri-partum (when it can be difficult to distinguish from preeclampsia) and two occurred several weeks postpartum.⁶ However, in a recent retrospective review by Fakhouri *et al.*,⁴ involving 100 women with aHUS, 75% of the presentations were in the post-partum period, highlighting the need for close monitoring of these women during this time.

During pregnancy, levels of most complement proteins increase, subsequently falling after delivery.¹¹ The increased susceptibility during the postpartum period could be explained by the fact that patients with P-aHUS, like those with non-pregnancy-related aHUS, have a high incidence of mutations in complement genes (86% and 76%, respectively) with complement Factor H mutations being the most frequently encountered (48%).⁴

Important clinical features that may be helpful in early recognition of P-aHUS include a positive family history of aHUS (as in our patient whose younger sibling died aged 3 years from a non-diarrhoeal HUS), and severe renal involvement, with more than two-thirds of patients reaching dialysis dependence within a month after the onset.⁴ Renal biopsies, when performed, reveal typical features of a thrombotic microangiopathy. Neurological symptoms are uncommon.

In a pregnant woman who develops acute kidney injury in association with microangiopathic haemolytic anaemia and thrombocytopaenia, the differential diagnosis is broad.⁷ Relevant antibody tests as well as a detailed history will help to make the diagnosis of systemic lupus erythematosus, scleroderma, antiphospholipid antibody syndrome and drug-induced thrombotic microangiopathy. It can be more difficult to differentiate between TTP, P-aHUS, severe preeclampsia or the HELLP syndrome. A history of preceding proteinuria and hypertension might favour preeclampsia/HELLP. However, in our patient this would not have been discriminatory as she had hypertension and minor proteinuria prior to pregnancy. The presence of elevated liver enzymes is strongly suggestive of HELLP syndrome, rather than TTP or P-aHUS. The time of onset may also help to distinguish between these conditions, as preeclampsia typically develops in the late third trimester,

Table 2 Causes of atypical HUS

Auto-immune disease	Systemic lupus erythematosus Scleroderma renal crisis Antiphospholipid antibody syndrome Auto-antibodies to complement factors H and I
Genetic abnormalities	Factor H deficiency Factor I deficiency Membrane co-factor protein (CD46) deficiency Thrombomodulin C3 Factor B
Drugs	Cyclosporin, tacrolimus ticlopidine, clopidogrel mitomycin C, cisplatin, bleomycin, gemcitabine Quinine, oral contraceptives, cocaine
Infections	HIV <i>Streptococcus pneumoniae</i>
Other	Pancreatitis Stem-cell transplantation

HUS, haemolytic uraemic syndrome

including the intrapartum period, with very few cases developing in the postpartum period – usually in the first 24–48 hours, but P-aHUS presents more frequently in the postpartum period.⁴ While measurement of ADAMTS 13 activity is of paramount importance in confirming the diagnosis of TTP, the assay is not yet widely available and results may not be available for several days. Likewise, testing for abnormalities in the complement system is important when aHUS is suspected, but again this requires the services of specialist laboratories, and the results may take a while to become available. In practice, the diagnosis of TTP or aHUS in the acute setting remains clinical, and is confirmed once the results of further investigation become available.

Treatment of aHUS mainly includes plasma infusions and plasma exchange. Plasma exchange with fresh frozen plasma has been shown to be the most beneficial form of treatment.¹² Because of the severity of renal disease in P-aHUS, aggressive treatment with plasma exchange needs to be commenced rapidly.⁴ Plasma exchange is not a technique that is available at all hospitals, and there is evidence to show that high-dose plasma infusion (25–30 mL/kg/day) can, if tolerated, serve as emergency initial treatment.^{13,14} Temporary dialysis is often employed to treat the accompanying renal failure. Complement activation modulators (Eculizumab and human Factor H) have been used for severe forms of aHUS, but their efficacy is yet to be established in cases of P-aHUS.¹⁵

In antenatal presentations, if the disease is severe and the fetus is viable, delivery should be induced. Although delivery does not generally lead to resolution of P-aHUS,¹⁶ there is anecdotal evidence that it may do so in some patients.¹⁷ Furthermore, as discussed earlier, it can be difficult to be certain of the diagnosis initially, and delivery will be the appropriate treatment for preeclampsia. In less severe cases, however, termination of pregnancy is usually not required.^{18–20}

In both familial and sporadic forms of aHUS, family members who are at risk for carrying the same complement gene mutation should undergo genetic screening. It is important to state that the identification of these mutations does not allow an accurate prediction of the risk of P-aHUS, but on the basis of the results by Fakhouri *et al.*,⁴ patients with complement dysregulation should be informed of the relatively high risk (20%) of P-aHUS and any pregnancy must be very closely monitored.

Awareness of P-aHUS, a severe form of aHUS with a potentially debilitating outcome (rapid progression to end-stage renal disease, 62% in less than 1 month in a recent study)⁴ should permit earlier recognition, aggressive treatment and counselling regarding prognosis.

DECLARATIONS

Disclosure of interest: None.

Funding: No funding required.

Acknowledgement: None.

REFERENCES

- Norris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;**361**:1676–87
- Furlan M, Robles R, Galbusera M. von Willebrand factor –cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. *N Engl J Med* 1998;**339**:1578–84
- Levy GG, Nichols WC, Lian EC. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 2001;**413**:488–94
- Fakhouri F, Roumenia L, Provot F, *et al.* Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol* 2010;**21**:895–67
- Noris M, Remuzzi G. Genetic abnormalities of complement regulators in hemolytic uremic syndrome: how do they affect patient management? *Nat Clin Pract Nephrol* 2005;**1**:2–3
- Dashe JS, Ramin SM, Cunningham FG. The long term consequences of thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) in pregnancy. *Obstet Gynecol* 1998;**91**:662
- George JN. The association of pregnancy with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. *Curr Opin Hematol* 2003;**10**:339
- Ezra Y, Rose M, Elder A. Therapy and prevention of thrombotic thrombocytopenic purpura during pregnancy: a clinical study of 16 pregnancies. *Am J Hematol* 1996;**51**:1
- Vesely SK, Li X, McMinn JR, *et al.* Pregnancy outcomes after recovery from thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Transfusion* 2004;**44**:1149
- Mokrzycki MH, Rickles FR, Kaplan AA, Kohn OF. Thrombotic thrombocytopenic purpura in pregnancy: successful treatment with plasma exchange. Case report and review of the literature. *Blood Purif* 1995;**13**:271
- Johnson U, Gustavii B. Complement components in normal pregnancy. *Acta Pathol Microbiol Immunol Scand* 1987;**95**:97–9
- Rock GA, Shumak KH, Buskard NA, *et al.* Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med* 1991;**325**:393–7
- Coppo P, Bussel A, Charrier S, *et al.* High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. *Medicine (Baltimore)* 2003;**82**:27–38
- Novitzky N, Thomson J, Abrahams L, du Toit C, McDonald A. Thrombotic thrombocytopenic purpura in patients with retroviral infection is highly responsive to plasma infusion therapy. *Br J Haematol* 2005;**128**:373–9
- Numberger J, Witzke O, Opazo Saez A. Eculizumab for atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;**360**:542–4
- McCrae KR, Cines DB. Thrombotic microangiopathy during pregnancy. *Semin Hematol* 1997;**34**:148
- Natelson EA, White D. Recurrent thrombotic thrombocytopenic purpura in early pregnancy: effect of uterine evacuation. *Obstet Gynecol* 1985;**66**:54S
- Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine (Baltimore)* 1966;**45**:139
- Bell WR, Braine HG, Ness PM, *et al.* Improved survival in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. *N Engl J Med* 1991;**325**:398
- Egerman RS, Witlin AG, Friedman SA, Sibai BM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy. Review of 11 cases. *Am J Obstet Gynecol* 1996;**175**:950

(Accepted 31 March 2011)