In conclusion, Cushing disease is rare in pregnancy. Surgical treatment remains the gold standard and should not be delayed in favor of medical therapy. However, in patients who have undergone unsuccessful surgery, who are not candidates for surgery, or even in the interim awaiting surgery, medical therapy must be used to control accelerating symptoms of Cushing disease owing to significant maternal and fetal morbidity. This case demonstrates that cabergoline can be used to manage Cushing disease successfully during pregnancy, with an opportunity for a favorable outcome.

REFERENCES

1. Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK. Cushing's syndrome during pregnancy: personal experience and review of the literature. J Clin Endocrinol Metab 2005;90:3077–83.
2. Buescher MA, McClamrock HD, Adashi EY. Cushing's syndrome in pregnancy. Obstet Gynecol 1992;79:130–7.
3. Salenave S, Gatta B, Pecheur S, San-Galli F, VIsot A, Lasjuanias P, et al. Pituitary magnetic resonance imaging findings do not influence surgical outcome in adrenocorticotropin-secreting microadenomas. J Clin Endocrinol Metab 2004;89:3371.
4. Vilar L, Naves LA, Azevedo MF, Arruda MJ, Arhata CM, Silva LM, et al. Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. Pituitary 2010;13:123–9.
5. Robert E, Musatti L, Piscitelli G, Ferrari CI. Pregnancy outcome after treatment with the ergot derivative, cabergoline. Reprod Toxicol 1996;10:333–7.
6. Pivonello R, De Martino MC, Cappabianca P, De Leo M, Faggiano A, Lompardi G, et al. The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. J Clin Endocrinol Metab 2009;94:223–30.
7. Berwaerts J, Verhelst J, Mahler C, Abs R. Cushing's syndrome in pregnancy treated by ketoconazole: case report and review of the literature. Gynecol Endocrinol 1999;13:175–82.
8. Polli N, Giraldi FP, Cavagnini F. Cushing's disease and pregnancy. Pituitary 2004;7:237–41.

Eculizumab for Atypical Hemolytic Uremic Syndrome in Pregnancy

Gianluigi Ardissino, PhD, Manuela Wally Ossola, MD, Giulia Maria Baffero, MD, Angelo Rigotti, MD, and Massimo Cugno, MD

BACKGROUND: Atypical hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy often caused by mutations in complement genes. During pregnancy, disease outcome is poor both for mother and fetus. Since 2009, the humanized monoclonal antibody eculizumab has been successfully used in the treatment of atypical HUS in nonpregnant patients.

CASE: A 26-year-old woman with a homozygous mutation in complement factor H developed a relapse of atypical HUS at 17 weeks of gestation in her first pregnancy. Because the disease remained active despite multiple plasma exchanges, eculizumab was started at 26 weeks of gestation. It was well tolerated and has led to remission and to the delivery of a healthy neonate.

CONCLUSION: Eculizumab may be useful for the treatment of atypical HUS during pregnancy.

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Atypical hemolytic uremic syndrome (HUS) is a rare thrombotic microangiopathy whose incidence in the general population is not known. It is characterized by mechanical, nonimmune-mediated hemolytic anemia, platelet consumption, and renal impairment. Data from the French and Italian cohort have shown it has a poor prognosis with more than 50% of patients reaching end-stage renal disease 3–5 years after disease onset.[1]

As many as 70% of patients with atypical HUS have mutations in genes encoding complement regulatory proteins that cause the amplified and uncontrolled activation of the alternative complement pathway, leading to endothelial damage and thrombotic microangiopathy. The most common and severe abnormalities in patients with complement dysregulation-associated atypical HUS are those involving complement factor H.[2]

From the Center for HUS Control, Prevention and Management, the Obstetrics and Gynecology Department and the Internal Medicine, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan and Ospedale Infermi, Rimini, Italy.

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Corresponding author: Gianluigi Ardissino, PhD, Center for HUS Control, Prevention and Management, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy; e-mail: ardissino@italkid.org.

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Disease penetrance is highly incomplete, and the clinical expression of the mutation is commonly triggered by infections and pregnancy. The outcome of pregnancy in patients with atypical HUS is poor for both mother and fetus. Fakouri et al analyzed 100 patients with atypical HUS: the disease occurred during pregnancy in 21 women; in these patients, they reported severe renal involvement. Eighty-one percent of patients required hemodialysis at the acute phase of disease and 61% of patients reached end-stage renal disease less than 1 month after the onset of the disease; there was also an increased incidence of complications such as preeclampsia and fetal death, especially if the patient had a complement gene mutation.[3]

Until 2009, the only available treatment for atypical HUS was plasma exchange or infusion,[4] but it had little or transient effect. However, since then, eculizumab (a humanized recombinant monoclonal antibody targeting C5 and thus preventing the generation of the C5b-9 membrane-attack complex),[5] which was originally used for the treatment of paroxysmal nocturnal hemoglobinuria, has also been successfully used in patients with atypical HUS[1,6] and it has become the frontline treatment for this disease, receiving approval for the treatment of atypical HUS in the United States and Europe in late 2011.

Eculizumab has been safely and effectively used in pregnant women with paroxysmal nocturnal hemoglobinuria (U.S. Food and Drug Administration Category C)[7,8] but a specific search in PubMed and Google Scholar using a combination of keywords and text words related to atypical HUS, pregnancy, and eculizumab, without language restrictions, did not identify any report concerning its use during pregnancy in patients with atypical HUS during the past decade. We describe the case of a pregnant woman with persistent atypical HUS caused by a homozygous complement factor H mutation who was treated with eculizumab.

CASE

A 26-year-old white woman from Morocco was diagnosed as having atypical HUS in 2010 and, at that time, was treated successfully with 11 sessions of plasma exchange and achieved complete disease remission. She had a positive history of familial atypical HUS, with two of four siblings being affected; one younger brother died with end-stage renal disease at the age of 6 years, and one sister was undergoing chronic dialysis after the development of atypical HUS during her first pregnancy. Moreover, the parents of our patient were first-degree cousins.

Two uneventful years after the first episode, atypical HUS recurred at 17 weeks of gestation in the patient's first pregnancy. She presented with severe hypertension, and laboratory findings clearly indicated active thrombotic microangiopathy (platelets 89,000/mm^3, schistocytes 6%, lactate dehydrogenase level 1.8 times higher than the upper normal limit, undetectable serum haptoglobin, serum creatinine 1.0 mg/dL, and urinary proteins 2.4 g/d).

Plasma exchange with fresh-frozen plasma was immediately started, and the patient underwent a total of 29 sessions during the subsequent 6 weeks, leading to the apparent remission of thrombotic microangiopathy and normalization of creatinine (0.63 mg/dL). However, at 26 weeks of gestation, her platelet count decreased from a peak of 180,000/mm^3 to 131,000/mm^3 and, although plasma exchange was resumed, continued to decline (to a nadir of 102,000/mm^3) accompanied by persistently low haptoglobin levels, detectable schistocytes, and nephrotic-range proteinuria (greater than 3 g/d), albeit with normal renal function.

In the meantime, molecular biology for the complement regulatory gene identified a homozygous mutation on complement factor H (p.Arg53Cys; c.157C>T). Complement tests revealed alternative pathway dysregulation with low plasma levels of C3 (75 mg/dL [normal range 90–180 mg/dL]), normal levels of C4 (13 mg/dL [normal range 10–40 mg/dL]), little alternative complement pathway activity (21%), normal classical pathway activity (70%), normal levels of complement factor H antigen (114%), and the absence of anticomplement factor H antibodies.

On the basis of the evidence of persistently active disease, the documented complement factor H mutation (often responsible for severe disease), the positive (albeit anecdotal) results obtained with eculizumab in pregnant women with paroxysmal nocturnal hemoglobinuria,[8] and the awareness that daily plasma exchange with high exchange volumes might not be innocuous for the fetus (first for the risk of placental hemorrhage as a result of the high doses of heparin used during the procedure, second for the possible hemodynamic problems related to an extracorporeal procedure with high exchange volumes), we decided to administer 900 mg intravenous eculizumab. The drug was well tolerated and there were no side effects (most commonly reported are: headache, leucopenia, and allergic reactions to any of the ingredients as reported on the manufacturer's web site). One day later, global complement activity was completely inhibited (alternative and classical pathway activity, respectively, 2% and 0%), and laboratory findings indicated the remission of active thrombotic microangiopathy. Within 5 days, the patient's platelet count reached 163,000/mm^3, there was no evidence of serum

schistocytes, lactate dehydrogenase and haptoglobin values normalized, and proteinuria started to decline.

One week after the first dose of eculizumab, global complement activity tended to be slightly less inhibited (alternative and classical pathway activity, respectively, 8% and 12%), and so a second dose of 900 mg was administered and the patient then began continuous treatment (every 14 days until delivery) according to the standard schedule.[1]

The pregnancy proceeded uneventfully. Blood pressure was well controlled by 250 mg alpha-methyldopa three times daily; blood examinations documented a stable remission of the disease with normal platelet count and hemoglobin level, normal renal function tests, and a persistent but not worsening proteinuria. Regarding the fetus, ultrasonographic monitoring and daily heart rate tracing were consistent with fetal well-being. Growth was appropriate for gestational age, anatomy was unremarkable, and amniotic fluid index, Doppler velocimetry, and fetal heart rate patterns were normal.

Labor was induced at 38 weeks of gestation, 24 hours after the last dose of eculizumab, using intravaginal dinoprostone; a cesarean delivery was performed because of lack of fetal head engagement. An appropriate-for-gestational age live female neonate weighing 3,650 g was delivered (Apgar scores 9 at 1 minute 10 at 5 minutes). Histologic examination of the placenta revealed a slight chorioamnionitis without other abnormalities. Neonatal adaptation was normal, laboratory evaluation did not reveal any abnormality, and the neonate was discharged after 1 week.

Because patients on eculizumab are susceptible to infections by capsulated bacteria, the patient received prophylactic antibiotic treatment with amoxicillin until the vaccination against *Neisseria meningitides* was believed to be effective, as required by the U.S. Food and Drug Administration and the European Medicines Agency.

COMMENT

In this case, treatment with eculizumab was well tolerated by both mother and fetus and resulted in disease remission. Thrombotic microangiopathies are very rare during pregnancy (approximately one in 25,000 pregnancies); of these, probably only a small proportion of patients have a complement dysregulation.[3] This case suggests that eculizumab may be helpful during pregnancy in atypical HUS.

REFERENCES

1. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 2011;6:60.
2. Kavanagh D, Goodship T. Genetics and complement in atypical HUS. Pediatr Nephrol 2010;25:2431–42.
3. Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, Couzi L, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol 2010;21:859–67.
4. Clark WF. Thrombotic microangiopathy: current knowledge and outcomes with plasma exchange. Semin Dial 2012;25:214–9.
5. Thomas TC, Rollins SA, Rother RP, Giannoni MA, Hartman SL, Elliott EA, et al. Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv. Mol Immunol 1996;33:1389–401.
6. Nürnberger J, Philipp T, Witzke O, Opazo Saez A, Vester U, Baba HA, et al. Eculizumab for atypical hemolytic uremic syndrome. N Engl J Med 2009;360:542–4.
7. Kelly R, Arnold L, Richards S, Hill A, Bomken C, Hanley J, et al. The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. Br J Haematol 2010;149:446–50.
8. Marasca R, Coluccio V, Santachiara R, Leonardi G, Torelli G, Notaro R, et al. Pregnancy in PNH: another eculizumab baby. Br J Haematol 2010;150:707–8.