23. Lafrance J-P, Miller DR: Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 21: 345–352, 2010
24. Kellum JA, Bellomo R, Ronco C: Acute Dialysis Quality Initiative (ADQI): Methodology. *Int J Artif Organs* 31: 90–93, 2008
25. Vanbelleghem H, Vanholder R, Levin NW, Becker G, Craig JC, Ito S, Lau J, Locatelli F, Zoccali C, Solez K, Hales M, Lameire N, Eknoyan G: The Kidney Disease: Improving Global Outcomes website: Comparison of guidelines as a tool for harmonization. *Kidney Int* 71: 1054–1061, 2007
26. Eckardt KU, Kasiske BL: Kidney disease: Improving global outcomes. *Nat Rev Nephrol* 5: 650–657, 2009
27. Steinberg EP, Eknoyan G, Levin NW, Eschbach JW, Golper TA, Owen WF, Schwab S: Methods used to evaluate the quality of evidence underlying the National Kidney Foundation-Dialysis Outcomes Quality Initiative clinical practice guidelines: Description, findings, and implications. *Am J Kidney Dis* 36: 1–11, 2000
28. Sugarman JR, Frederick PR, Frankenfield DL, Owen WF Jr, McClellan WM: Developing clinical performance measures based on the Dialysis Outcomes Quality Initiative clinical practice guidelines: Process, outcomes, and implications. *Am J Kidney Dis* 42: 806–812, 2003
29. Goldman RS: Continuous quality improvement in ESRD: The role of networks, the United States Renal Data System, and facility-specific reports. *Am J Kidney Dis* 32[Suppl 4]: S182–S189, 1998

See related article, "Weekend Hospital Admission, Acute Kidney Injury, and Mortality," on pages 845–851.

Pulling the Trigger in Atypical Hemolytic Uremic Syndrome: The Role of Pregnancy

Timothy H.J. Goodship and David Kavanagh
Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, United Kingdom

J Am Soc Nephrol 21: 731–732, 2010.
doi: 10.1681/ASN.2010030308

In the past 15 years, our understanding of the molecular mechanisms that predispose to atypical hemolytic uremic syndrome (aHUS) has increased dramatically.[1] A series of studies established that dysregulation of the alternative complement pathway plays a significant role in the pathogenesis of disease in the majority of patients.[1,2] Mutations in both complement regulators (factor H, factor I, and membrane co-factor protein) and activators (C3 and factor B) have been described in both familial and sporadic forms. In addition, factor H autoantibodies, which impair the activity of factor H, and mutations in the gene encoding thrombomodulin are now known.[3,4]

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Timothy H.J. Goodship, Institute of Human Genetics, Newcastle University, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK. Phone: 44 191 241 8632; Fax: 44 191 241 8666; E-mail: t.h.j.goodship@ncl.ac.uk

More than one family member is affected in approximately 10% of patients with aHUS. The study of such families reveals a higher prevalence of the aforementioned mutations and indicates that not every individual who carries a mutation manifests the disease.[5] The rate of nonpenetrance is approximately 50%, and it has been shown that naturally occurring variability in single-nucleotide polymorphisms and haplotype blocks of the *CFH* and *CD46* genes encoding factor H and membrane co-factor protein, respectively, increase susceptibility to disease. Moreover, multiple concurrent factors such as single-nucleotide polymorphisms, mutations, and autoantibodies may be necessary for disease to manifest in individual families.[6]

Some event almost always triggers the disease in the majority of patients. aHUS typically presents in childhood, and a history of a preceding nondiarrheal viral infection is common. This is also true of adults and in females of childbearing age the phenotype of aHUS can present late in pregnancy or soon after delivery;[7] pregnancy may be the trigger in 10% of all patients with aHUS.[8]

Fakhouri *et al.*[9] in their article in this issue of *JASN* provide us with substantial additional information that will be enlightening to all those who are interested in this condition. They confirm in female adults that aHUS associates with pregnancy in 20% of patients, and, in the majority, this occurs postpartum. Complement abnormalities were found in 86% of these patients; this is the highest prevalence reported in any subgroup of aHUS to date. The prognosis for such patients in the 1970s was extremely poor, with a mortality rate of approximately 55%, and of those who survived, approximately 50% required long-term dialysis.[10] Mortality has improved since then, but Fakhouri *et al.* indicate that 76% of patients develop ESRD despite receiving plasma exchange. The prognosis for renal transplantation in these patients is equally gloomy, especially in those who are known to have a factor H mutation, 80% of whom will lose an allograft to recurrent disease within 2 years of transplantation,[11] although liver-kidney transplants may do better.[12]

With the poor prognosis for these patients and their seeming resistance to plasma exchange, are there any other therapeutic maneuvers that might benefit management? Anecdotal reports suggest that the C5 mAb eculizumab may be an effective form of treatment for aHUS,[13] and the results of clinical trials currently being undertaken with this agent are awaited eagerly. If eculizumab proves to be effective, then could it be used in pregnancy or postpartum? Recent reports of patients with paroxysmal nocturnal hemoglobinuria showed no adverse effects when used in pregnancy,[14] and, in particular, there is no evidence the drug crosses the placenta or is present in breast milk.

What is it about pregnancy, particularly the postpartum period, that increases susceptibility to aHUS? That complement plays a pivotal role in the pathophysiology of pregnancy is well established.[15] In particular, complement-mediated placental damage is prevented by trophoblast expression of the complement regulators known as decay-accelerating factor,

membrane co-factor protein, and CD59. In the antiphospholipid antibody syndrome, it is excessive activation of the classical pathway with amplification through the alternative pathway that eventually leads to fetal loss.[15] Pregnancy is an immunologically privileged condition,[16] and levels of most complement proteins increase during pregnancy, subsequently falling after delivery.[17] Reversal of these two phenomena early in the postpartum period could decrease the threshold for aHUS.

In both the familial and sporadic forms of aHUS, family members who are at risk for carrying the same complement gene mutation often undergo genetic screening. Women who are found to be carriers and are of potential childbearing age often ask what the risk of pregnancy might be? The study by Fakhouri *et al.*[9] provides additional information to use in counseling such individuals. Twelve of the 21 patients with pregnancy-associated aHUS had at least one previous uncomplicated pregnancy. In the female patients of the Paris aHUS cohort, 44 with a complement gene mutation in total had 103 pregnancies; of these, only 18 (17.4%) were associated with aHUS. This is a level of risk for which many individuals might countenance, especially if in the future there is also an effective treatment.

It a fascinating observation, albeit uncontrolled, that the prevalence of preeclampsia and fetal loss looks to be higher than normal in women in the Paris aHUS cohort who were known to have a complement mutation. This observation supports other studies suggesting that complement may play a role in the pathogenesis of preeclampsia. For instance, elevated maternal levels of the complement activation product Bb in early pregnancy associates with increased risk for preeclampsia.[18]

There is much still to be learned about the interplay between complement and pregnancy in health and disease. Studies such as those of Fakhouri *et al.* help us to identify the next set of questions needing answers.

DISCLOSURES

T.H.J.G. is the UK chief investigator of trials of aHUS sponsored by Alexion and acts as a scientific advisor for Taligen Therapeutics and Laboratoire francais due fractionnement et des biotechnologies.

REFERENCES

1. Noris M, Remuzzi G: Atypical hemolytic-uremic syndrome. *N Engl J Med* 361: 1676–1787, 2009
2. Sellier-Leclerc A-L, Fremeaux-Bacchi V, Dragon-Durey M-A, Macher M-A, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C, French Society of Pediatric Nephrology: Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 18: 2392–2400, 2007
3. Delvaeye M, Noris M, De Vriese A, Esmon CT, Esmon NL, Ferrell G, Del-Favero J, Plaisance S, Claes B, Lambrechts D, Zoja C, Remuzzi G, Conway EM: Thrombomodulin mutations in atypical hemolytic-uremic syndrome. *N Engl J Med* 361: 345–357, 2009
4. Skerka C, Jozsi M, Zipfel PF, Dragon-Durey MA, Fremeaux-Bacchi V: Autoantibodies in haemolytic uraemic syndrome (HUS). *Thromb Haemost* 101: 227–232, 2009
5. Martinez-Barricarte R, Pianetti G, Gautard R, Misselwitz J, Strain L, Fremeaux-Bacchi V, Skerka C, Zipfel PF, Goodship T, Noris M, Remuzzi G, de Cordoba SR, European Working Party on the Genetics of HUS: The complement factor H R1210C mutation is associated with atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 19: 639–646, 2008
6. Rodriguez de Cordoba S: aHUS: A disorder with many risk factors. *Blood* 115: 158–160, 2010
7. Saltiel C, Legendre C, Grunfeld JP, Descamps JM, Hecht M: Hemolytic uremic syndrome in association with pregnancy. In: *Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura*, edited by Kaplan BS, Trompeter RS, Moake JL, New York, Marcel Dekker, 1992, pp 241–254
8. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P, Mele C, Bresin E, Cassis L, Gamba S, Porrati F, Bucchioni S, Monteferrante G, Fang CJ, Liszewski MK, Kavanagh D, Atkinson JP, Remuzzi G: Genetics of HUS: The impact of MCP, CFH and IF mutations on clinical presentation, response to treatment, and outcome. *Blood* 108: 1267–1279, 2006
9. Fakhouri F, Roumenina L, Provot F, Sallee M, Caillard S, Couzi L, Essig M, Ribes D, Dragon-Durey MA, Bridoux F, Rondeau E, Fremeaux-Bacchi V: Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol* 21: 859–867, 2010
10. Weiner CP: Thrombotic microangiopathy in pregnancy and the postpartum period. *Semin Hematol* 24: 119–129, 1987
11. Bresin E, Daina E, Noris M, Castelletti F, Stefanov R, Hill P, Goodship THJ, Remuzzi G: Outcome of renal transplantation in patients with non-shiga toxin-associated hemolytic uremic syndrome: Prognostic significance of genetic background. *Clin J Am Soc Nephrol* 1: 88–99, 2006
12. Saland JM, Ruggenenti P, Remuzzi G, Consensus Study Group: Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 20: 940–949, 2009
13. Nurnberger J, Witzke O, Opazo Saez A, Vester U, Baba HA, Kribben A, Zimmerhackl LB, Janecke AR, Nagel M, Kirschfink M: Eculizumab for atypical hemolytic-uremic syndrome. *N Engl J Med* 360: 542–544, 2009
14. Kelly R, Arnold L, Richards S, Hill A, Bomken C, Hanley J, Loughney A, Beauchamp J, Khursigara G, Rother RP, Chalmers E, Fyfe A, Fitzsimons E, Nakamura R, Gaya A, Risitano AM, Schubert J, Norfolk D, Simpson N, Hillmen P: The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. *Br J Haematol* February 11, 2010 [epub ahead of print]
15. Girardi G, Bulla R, Salmon JE, Tedesco F: The complement system in the pathophysiology of pregnancy. *Mol Immunol* 43: 68–77, 2006
16. Aagaard-Tillery KM, Silver R, Dalton J: Immunology of normal pregnancy. *Semin Fetal Neonatal Med* 11: 279–295, 2006
17. Johnson U, Gustavii B: Complement components in normal pregnancy. *Acta Pathol Microbiol Immunol Scand* 95: 97–99, 1987
18. Lynch AM, Murphy JR, Byers T, Gibbs RS, Neville MC, Giclas PC, Salmon JE, Holers VM: Alternative complement pathway activation fragment Bb in early pregnancy as a predictor of preeclampsia. *Am J Obstet Gynecol* 198: 385 e1–e9, 2008

See related article, "Pregnancy-Associated Hemolytic Uremic Syndrome Revisited in the Era of Complement Gene Mutations," on pages 859–867.