blood advances

TO THE EDITOR:

Consensus statement for the perinatal management of patients with α thalassemia major

Tippi C. MacKenzie,[1–4] Ali Amid,[5] Michael Angastiniotis,[6] Craig Butler,[7] Sandra Gilbert,[7] Juan Gonzalez,[2,4] Roberta L. Keller,[3,4] Sandhya Kharbanda,[3] Melanie Kirby-Allen,[8] Barbara A. Koenig,[4,9] Wade Kyono,[10] Ashutosh Lal,[3] Billie R. Lianoglou,[1,4] Mary E. Norton,[2,4] Keith K. Ogasawara,[11] Tachjaree Panchalee,[12] Mara Rosner,[13] Marisa Schwab,[1,4] Alexis Thompson,[14] John S. Waye,[15] and Elliott Vichinsky[3,4]

[1]Department of Surgery, [2]Department of Obstetrics and Gynecology, [3]Department of Pediatrics and Benioff Children's Hospital, and [4]Center for Maternal-Fetal Precision Medicine, University of California San Francisco, San Francisco, CA; [5]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada; [6]Thalassemia International Federation, Strovolos, Cyprus; [7]Cooley's Anemia Foundation (CAF), New York, NY; [8]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [9]Program in Bioethics, University of California San Francisco, San Francisco, CA; [10]Department of Pediatrics, University of Hawaii John A. Burns School of Medicine, Honolulu, HI; [11]Department of Obstetrics and Gynecology, Kaiser Permanente Hawaii, Wailuku, HI; [12]Department of Obstetrics and Gynecology, Siriraj Hospital, Mahidol University, Nakhon Pathom, Thailand; [13]Department of Obstetrics and Gynecology, Johns Hopkins Center for Fetal Therapy, Baltimore, MD; [14] Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital, Feinberg School of Medicine, Northwestern University, Chicago, IL; and [15] Department of Pathology & Molecular Medicine, McMaster University, Hamilton, ON, Canada

α thalassemia is one of the most common single-gene disorders, with a 5% carrier rate globally[1] and nearly 40% carrier rate in endemic regions of South East Asia, India, and the Mediterranean.[2] This carrier rate results in a high incidence of newborns with severe α thalassemia: for example, a recent report estimates that there are thousands of affected pregnancies per year in Thailand.[3] Importantly, given the increased population of people of South East Asian ancestry in North America, severe α thalassemia represents an important and growing public health issue.[4] Newborn screening records in California, where there has been a 2000% increase in immigration from Asia in the past 30 years,[5] indicate that the prevalence of patients with a clinically significant α thalassemia diagnosis is 9.6 births in 100 000.[6]

α thalassemia disease severity depends on the number of affected α globin genes.[1] The 4-gene deletion results in α thalassemia major (ATM), which has the most severe presentation and typically manifests in utero. Affected fetuses are usually identified because of the clinical finding of hydrops fetalis (abnormal fluid accumulations identified by ultrasonography) that occurs secondary to severe hypoxia. If untreated, hydrops fetalis usually results in fetal demise and can lead to maternal complications such as preeclampsia or mirror syndrome.[7]

Historically, a family's options after a prenatal diagnosis of ATM have been limited to either termination of pregnancy or close surveillance with an expectation of fetal loss.[8] However, there are accumulating data from a patient registry,[9] case reports,[10] and case series[11-13] regarding outcomes of patients with ATM who survive to birth. Predictably, when in utero transfusions (IUTs) are performed, there is evidence that this therapy can improve oxygenation, reverse hydrops fetalis, and allow survival to birth, usually at or near term.[11-13] The prenatal cardiac findings secondary to anemia resolve with transfusions. Importantly, at follow-up, these series have reported that patients who have received IUTs can have normal or near-normal neurologic outcomes.[11-13] Survivors with ATM can have significant medical needs: after birth, the management of patients with ATM is similar to those with β thalassemia major, in that they require monthly transfusions to treat the underlying anemia. A hematopoietic stem cell transplantation, if available, can be curative. In addition, male fetuses with ATM often develop hypospadias,[14] which can be corrected with surgery.

Despite the emerging evidence for favorable outcomes after fetal therapy for ATM, there is a reluctance in the medical community to offer serial IUTs as an option to expectant parents, often because of concerns that this will result in the birth of a child with a severe, debilitating disease. However, IUT has been

Submitted 10 August 2021; accepted 13 October 2021; prepublished online on *Blood Advances* First Edition 8 November 2021; final version published online 28 December 2021. DOI 10.1182/bloodadvances.2021005916.

routinely performed since 1963 to treat alloimmunization, with an excellent safety profile and has demonstrated minimal risks to the fetus and mother. Despite this experience, parents of fetuses with ATM are usually neither offered this treatment option nor counseled regarding the possibility of improved postnatal outcomes. In other words, families are not provided a full range of decision-making options. There is, in contrast, widespread acceptance of advanced fetal surgeries for several severe conditions that have a similar or more severe postnatal phenotype compared with ATM. For example, there are now numerous interventions for fetuses with spina bifida,[15] monochorionic twin complications, sacrococcygeal tumors, bladder outlet obstruction,[16] and congenital diaphragmatic hernia,[17] many of which result in the birth of a child with a severe disease requiring chronic medical care. ATM could be listed among the conditions for which there is now a life-saving therapy when a prenatal diagnosis is made.

On 8 and 9 January 2021, we convened an international conference (https://conference.globalcastmd.com/ucsf-alpha-thalassemia-major/archive) to review existing knowledge regarding the prenatal screening, perinatal care, and maternal and childhood outcomes of patients with ATM, and a group of stakeholders discussed the desirability of changing the current paradigm of prenatal counseling for this disease. Participants included several families whose children survived in utero transfusions and are now thriving, as well as physicians (perinatologists, neonatologists, pediatric hematologists), genetic counselors, bioethics scholars, patient advocates, and researchers. Here, we outline several points regarding the management of patients with ATM on which our team of prenatal and postnatal experts have reached a consensus. We believe that this outline provides important points to consider for creating best practice guidelines for in utero treatment of ATM.

Prenatal screening

- Couples who are at risk for offspring affected with ATM (those in which both parents are carriers for a 2-gene deletion in cis) should be counseled regarding the risks for this condition and the availability of prenatal screening to determine carrier status. Universal screening, including hemoglobin and red cell indices (mean corpuscular volume) in the preconception or early prenatal period is recommended by the American College of Obstetricians and Gynecologists. Women who are at risk of being carriers for ATM can be identified by a low mean corpuscular volume ($<$70 fL) on routine complete blood count analysis. Importantly, because red cell indices may fail to identify all carriers, molecular based screening should be pursued in high-risk populations to definitively identify α thalassemia carrier status.[18] Notably, hemoglobin electrophoresis and high-performance liquid chromatography tests are unable to identify α thalassemia carriers: although prospective parents should be offered these tests to rule out β thalassemia deletions, they should also be tested for α thalassemia mutations using molecular genetic testing.
- If both parents are carriers of ATM, they should be thoroughly counseled about the implications of this diagnosis. This counseling should include the etiology, clinical manifestations, prognosis, and the full range of long-term outcomes, depending on the expected severity of disease based on number of genes affected. Collaborative education (including consultation with pediatric hematologist who is familiar with the management of patients with thalassemia) may be valuable for these families for reproductive planning. Prospective parents should be informed of the option of preimplantation genetic testing for monogenetic conditions of embryos to prevent a pregnancy with ATM. Recognition of the limitations of preimplantation genetic testing[19] and need for confirmatory prenatal diagnostic testing[20] should be discussed. Patients who are already pregnant should be offered early prenatal diagnosis (via chorionic villus sampling or amniocentesis) to allow for informed decision making about the pregnancy.

Perinatal management

- The finding of hydrops fetalis in the setting of a pregnancy at risk for ATM because of the parents' known carrier status is indicative of fetal ATM in most cases. In this situation, the diagnosis should be confirmed as quickly as possible so that parents can be counseled and intervention, if desired by the family, can be implemented. We recommend offering a percutaneous umbilical cord blood sampling with hemoglobin electrophoresis to measure the levels of γ-globin tetramers (ie, Hb Bart's) to confirm the diagnosis. If the family wishes to pursue intervention, an initial IUT can be performed while awaiting the diagnosis. This strategy avoids the longer turnaround time for amniocentesis results before initiating fetal therapy.
- In a pregnancy with a confirmed diagnosis of ATM, nondirective counseling should include the option of expectant management, pregnancy termination, or fetal therapy with IUTs. Parents should also be educated regarding options for a future pregnancy, including preimplantation genetic testing. They should be offered the opportunity to consult with a pediatric hematologist (particularly with one who cares for patients with α thalassemia) to understand the long-term outcomes, prognosis, and the requirements of postnatal and childhood management. If the family elects to pursue IUTs, they should be referred to a center with expertise in this technique if it is not available locally. Given risks for severe maternal complications in the setting of untreated hydrops fetalis,[21] expectant management should be discouraged and, if pursued, patients should be monitored closely.
- For patients electing to proceed with fetal therapy, IUTs should begin as soon as technically possible (currently 18 weeks at most fetal treatment centers) to minimize long-term impact from fetal hypoxia. The protocol for IUTs is similar to standard protocols for alloimmunization.[22]

Postnatal care

- Delivery should be planned at a tertiary care center with availability of perinatology, pediatric hematology, and neonatology teams.
- After birth, patients can be treated using guidelines similar to those followed for patients with transfusion-dependent thalassemia,[23] including chronic transfusions and iron chelation. Hematopoietic stem cell transplantation, when available and desired by parents, presents the possibility of a definitive cure.
- Although health care resources are different in each country and even unique to each patient, it is important to discuss the need for resources to enable chronic medical care with affected families.
- Patient advocacy organizations such as Cooley's Anemia Foundation (in the United States) and Thalassemia International Federation (for patients worldwide) can be valuable resources for linking families to each other and to expert physicians locally and for providing educational materials.
- Sharing patient data with an international registry (www.clinicaltrials.gov NCT04872179) will improve understanding of the disease, enable the creation of guidelines for best practices for pre- and postnatal care, and provide valuable information to families regarding long-term outcomes.

Conclusions

A strong consensus emerged among the multidisciplinary attendees at this international conference: ATM should no longer be considered universally fatal. Although decision making during pregnancy is complex and personal, and the availability of medical care varies globally, parents should be offered nondirective counseling regarding all options, including that of fetal therapy with IUTs. Perinatologists with expertise in performing IUTs for other conditions can offer this therapy in close collaboration with pediatric hematologists. After birth, patients can be treated with chronic transfusions or stem cell transplant. Given immigration patterns from regions with a high carrier frequency, there is a growing population of families at risk for ATM in North America and beyond. Recognition of the specific needs for these patients is critical in delivering optimal care. In addition to clinical resources, connecting families within the α thalassemia community via patient advocacy groups will be valuable in helping with informed decision-making.

Acknowledgments: The conference at which this consensus was discussed was funded by a grant from the California Institute for Regeneration Medicine to T.C.M. and funds from the University of California San Francisco Center for Maternal-Fetal Precision Medicine.

Contribution: T.C.M. conceived the project and wrote the paper with input from all authors; and A.A., M.A., C.B., S.G., J.G., R.L.K., S.K., M.K-A., B.A.K., W.K., A.L., B.R.L., M.E.N., K.K.O., T.P., M.R., M.S., A.T., J.S.W., and E.V. participated in consensus discussions and contributed to writing of the manuscript.

Conflict-of-interest disclosure: T.C.M. is on the Scientific Advisory Board of Acrigen.

ORCID profiles: S.K., 0000-0002-6014-7659; M.K., 0000-0002-9889-8538; B.L., 0000-0002-2661-6642; M.R., 0000-0001-5239-699X; A.T., 0000-0003-4961-8103.

Correspondence: Tippi C. MacKenzie, Department of Surgery, UCSF, 550 16th St, Box 0570, San Francisco, CA 94143-0570; e-mail: Tippi.mackenzie@ucsf.edu.

References

1. Piel FB, Weatherall DJ. The α-thalassemias. *N Engl J Med.* 2014;371(20):1908–1916.
2. Goh LPW, Chong ETJ, Lee PC. Prevalence of alpha(α)-thalassemia in Southeast Asia (2010-2020): a meta-analysis involving 83,674 subjects. *Int J Environ Res Public Health.* 2020;17(20):17.
3. Hockham C, Ekwattanakit S, Bhatt S, et al. Estimating the burden of α-thalassaemia in Thailand using a comprehensive prevalence database for Southeast Asia. *eLife.* 2019;8:e40580.
4. Vichinsky EP, MacKlin EA, Waye JS, Lorey F, Olivieri NF. Changes in the epidemiology of thalassemia in North America: a new minority disease. *Pediatrics.* 2005;116(6):e818–e825.
5. Hoppe CC. Newborn screening for hemoglobin disorders. *Hemoglobin.* 2011;35(5-6):556–564.
6. Feuchtbaum L, Carter J, Dowray S, Currier RJ, Lorey F. Birth prevalence of disorders detectable through newborn screening by race/ethnicity. *Genet Med.* 2012;14(11):937–945.
7. Derderian SC, Jeanty C, Fleck SR, et al. The many faces of hydrops. *J Pediatr Surg.* 2015;50(1):50–54, discussion 54.
8. Tongsong T, Charoenkwan P, Sirivatanapa P, et al. Effectiveness of the model for prenatal control of severe thalassemia. *Prenat Diagn.* 2013;33(5):477–483.
9. Songdej D, Babbs C, Higgs DR; BHFS International Consortium. An international registry of survivors with Hb Bart's hydrops fetalis syndrome. *Blood.* 2017;129(10):1251–1259.
10. Pang D, Shang X, Cai D, et al. Unusual survival of a twin with homozygous α^{o}-thalassemia due to chimerism. *Haematologica.* 2020;106(5):1507–1510.
11. Chan WY, Leung AW, Luk CW, Li RC, Ling AS, Ha SY. Outcomes and morbidities of patients who survive haemoglobin Bart's hydrops fetalis syndrome: 20-year retrospective review. *Hong Kong Med J.* 2018;24(2):107–118.
12. Kreger EM, Singer ST, Witt RG, et al. Favorable outcomes after in utero transfusion in fetuses with alpha thalassemia major: a case series and review of the literature. *Prenat Diagn.* 2016;36(13):1242–1249.
13. Zhang HJ, Amid A, Janzen LA, et al. Outcomes of haemoglobin Bart's hydrops fetalis following intrauterine transfusion in Ontario, Canada. *Arch Dis Child Fetal Neonatal Ed.* 2021;106(1):51–56.
14. Fung TY, Kin LT, Kong LC, Keung LC. Homozygous alpha-thalassemia associated with hypospadias in three survivors. *Am J Med Genet.* 1999;82(3):225–227.
15. Adzick NS, Thom EA, Spong CY, et al; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *N Engl J Med.* 2011;364(11):993–1004.
16. Morris RK, Malin GL, Quinlan-Jones E, et al; Percutaneous vesicoamniotic shunting in Lower Urinary Tract Obstruction (PLUTO) Collaborative Group. Percutaneous vesicoamniotic

shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet.* 2013; 382(9903):1496–1506.

17. Jani JC, Nicolaides KH, Gratacós E, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol.* 2009;34(3):304–310.
18. Shang X, Peng Z, Ye Y, et al. Rapid targeted next-generation sequencing platform for molecular screening and clinical genotyping in subjects with hemoglobinopathies. *EBioMedicine.* 2017;23: 150–159.
19. Wilton L, Thornhill A, Traeger-Synodinos J, Sermon KD, Harper JC. The causes of misdiagnosis and adverse outcomes in PGD. *Hum Reprod.* 2009;24(5):1221–1228.
20. Hardy T. The role of prenatal diagnosis following preimplantation genetic testing for single-gene conditions: A historical overview of evolving technologies and clinical practice. *Prenat Diagn.* 2020; 40(6):647–651.
21. Norton ME, Chauhan SP, Dashe JS; Society for Maternal-Fetal Medicine (SMFM). Society for Maternal-Fetal Medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. *Am J Obstet Gynecol.* 2015;212(2):127–139.
22. Mari G, Norton ME, Stone J, et al; Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org. Society for Maternal-Fetal Medicine (SMFM) clinical guideline #8: the fetus at risk for anemia–diagnosis and management. *Am J Obstet Gynecol.* 2015;212(6):697–710.
23. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, eds. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). Nicosia, CY: Thalassaemia International Federation; 2014.