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

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Abstract:

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Alpha 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 alpha 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 alpha 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 alpha thalassemia diagnosis is 9.6 births in 100,000.[6]

Alpha thalassemia disease severity depends on the number of affected alpha globin genes.[1] The four-gene deletion results in alpha thalassemia major (ATM), which has the most severe presentation and typically manifests *in utero.* Affected fetuses are usually identified due to 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 beta 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 routinely performed since 1963 to treat alloimmunization, with an excellent safety profile and 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 to 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 January 8 and 9, 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 two-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, MCV) 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 MCV (<70 fL) on routine complete blood count analysis. Importantly, since red cell indices may fail to identify all carriers, molecular based screening should be pursued in high-risk populations to definitively identify alpha thalassemia carrier status.[18] Notably, hemoglobin electrophoresis and high performance liquid chromatography tests are unable to identify alpha thalassemia carriers: while prospective parents should be offered these tests to rule out beta thalassemia deletions, they should also be tested for alpha 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 (PGT) for monogenetic conditions of embryos to prevent a pregnancy with ATM. Recognition of the limitations of PGT[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 due to 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 (PUBS) with hemoglobin electrophoresis to measure the levels of gamma-globin tetramers (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, non-directive 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

alpha 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 due to 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.

- While healthcare 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 (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 multi-disciplinary attendees at this international conference: ATM should no longer be considered universally fatal. While decision-making during pregnancy is complex and personal, and the availability of medical care varies globally, parents should be offered non-directive 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 alpha thalassemia community via patient advocacy groups will be valuable in helping with informed decision-making.

Author contributions:

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

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