ORIGINAL ARTICLE

Favorable outcomes after *in utero* transfusion in fetuses with alpha thalassemia major: a case series and review of the literature

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ABSTRACT

Objective Alpha thalassemia major (ATM) is often fatal *in utero* due to severe hydrops fetalis. Although *in utero* transfusions (IUTs) are increasingly used to allow fetal survival in ATM, prenatal and postnatal outcomes are not well described.

Methods We retrospectively reviewed cases of ATM at our institution treated with consecutive IUT. Clinical records were reviewed for transfusion history, neurodevelopmental outcomes, anatomic abnormalities, survival to hematopoietic cell transplantation, and transfusion independence. A systematic review was performed, and additional reported cases are discussed.

Results Three patients who underwent IUT for ATM were identified, and review of the literature revealed 17 reported cases. Of patients who received IUT, reported neurodevelopmental deficits occurred in 29% (4/14) and anatomic abnormalities in 55% (11/20). Four patients eventually underwent successful hematopoietic cell transplantation. Transfusion volumes were less than suggested guidelines for other causes of fetal anemia in 91.7% of the transfusions.

Conclusion This series demonstrates the potential for achieving full fetal development with normal neurologic outcomes in those affected by ATM. It provides support for continued patient and provider education about current benefits and risks of active prenatal therapy for fetuses with ATM, as well as continued research to optimize therapeutic strategies such as *in utero* transplantation. © 2016 John Wiley & Sons, Ltd.

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INTRODUCTION

Alpha thalassemia is a recessively inherited hemoglobinopathy caused by mutations in the alpha globin gene. It is one of the most common single-gene disorders worldwide, affecting approximately 5% of the population[1]; prevalence is highest in China, South East Asia, the Middle East, and India.[2] At least 40 different mutations are known to cause alpha thalassemia major (ATM),[2] the most common of which is the Southeast Asian deletion (−SEA).[3,4] Alpha thalassemia has varying degrees of severity depending on the number of deleted or mutated genes and remaining functional alpha globin genes. Normally, there are four copies of the alpha globin gene. The homozygous (−/−) form, often referred to as hemoglobin (Hb) Bart's, or ATM, results in the absence of all alpha globin production and is almost uniformly fatal *in utero*.

Fetal oxygen exchange is accomplished by embryonic Hb (ε) until 2 months of gestation.[2,5] Thereafter, fetal Hb (Hb F) forms from a combination of two alpha (α) and two gamma (γ) chains. In patients with ATM, there are no α chains available to form a functional tetramer with γ chains; the four γ chains combine into a nonfunctional tetramer with such a high oxygen affinity that the molecule cannot deliver oxygen to developing tissues.[5,6] Fetuses affected with ATM develop severe functional anemia, which results in nonimmune hydrops fetalis, cardiac failure, and *in utero* fetal demise. As with other conditions that result in nonimmune hydrops fetalis, there can be additional associated maternal complications such as anemia, polyhydramnios, preterm labor, and pre-eclampsia.[7] Alpha thalassemia mutations are common in many regions of the world, and fetal cases of ATM are numerous; however, survivors are rare.

The incidence of alpha thalassemia has increased in North America due to immigration patterns from higher risk populations to North America.[8] Since 1999, with initiation of

universal newborn screening for alpha thalassemia, almost 1000 cases of clinically significant alpha thalassemia disorders have been born in California.[9] The birth prevalence of alpha thalassemia syndromes is 9.6 per 100 000, with an ATM birth rate of 0.2 per 100 000 state births.[10] Because ATM is almost universally fatal, there must be a very large number of undetected fetal deaths from ATM. Recent programs to increase identification of alpha thalassemia carriers and the availability of prenatal diagnosis will result in more families seeking therapy for ATM.

Given the severity of the disease and underutilized interventional options, parents most often have elected to undergo termination of pregnancy in the face of a prenatal diagnosis of ATM.[11,12] More recently, *in utero* transfusions (IUTs) of red blood cells have been shown to reverse anemia, fetal growth restriction, and oligohydramnios, suggesting that fetal therapy can be a viable option to discuss with affected families.[13] Postnatal treatment options then include chronic transfusion therapy or hematopoietic stem cell transplantation (HSCT). Although several case reports indicate that serial blood transfusions can result in fetal survival,[1,13–27] a detailed analysis of prenatal management and postnatal outcomes with fetal intervention has not been reported.

As more patients seek fetal therapy for ATM, it is important to examine the risks and benefits of fetal intervention. In addition, the anticipated postnatal course and the success of HSCT or chronic transfusions (the two current postnatal options for survivors) need to be evaluated so that patients can be counseled accurately about the expected long-term prognosis. Here, we describe three patients who received IUT followed by postnatal HSCT or chronic transfusions and compare the management and postnatal outcomes to those of 17 previously reported cases. These cases illustrate the potential for successful outcomes with careful fetal and postnatal management of patients with ATM.

METHODS

Clinical and transfusion records of three ATM fetuses who received regular transfusions were reviewed. Transfusion records were analyzed for details of the transfusion volume, Hb F, hematocrit, and percent Hb Bart's. Outcomes were reviewed, including neurodevelopmental outcomes, anatomic abnormalities, survival to hematopoietic cell transplantation, and transfusion independence. The outcomes of six additional patients with ATM from California who did not undergo IUT were included for comparison. The study was evaluated and approved by the University of California, San Francisco Benioff Children's Hospital Oakland Institutional Review Board.

A review of the existing English literature on outcomes in fetuses with ATM who received IUT was performed. To identify studies of interest, search terms 'homozygous alpha thalassemia', 'ATM', 'Hb Bart's', 'Bart hemoglobinopathy', 'fetal therapy', and 'IUT' were used in PUBMED. The texts of studies were reviewed and determined if they were appropriate based on the presence of an ATM diagnosis and transfusion treatment. Furthermore, the reference lists of articles found during the initial search were examined for any additional appropriate publications. Inclusion criteria for this study were published cases in which prenatal therapy included IUT and survival to birth.

Statistical analysis to compare pre-IUT and post-IUT levels of Hb, hematocrit, and percent Hb Bart's was performed by using a Student's *t*-test. All statistical analyses were performed in PRISM GRAPHPAD (GraphPad Software, Inc, La Jolla, CA), and the results were reported as mean ± standard deviation. A *p*-value of less than 0.05 was deemed as statistically significant.

RESULTS

From 2000 to 2015, three affected fetuses were treated at our institution. All three patients were found to have fetal hydrops between 16 to 25 weeks' gestation and elevated middle cerebral artery peak systolic velocity by Doppler ultrasound examination. Further workup was then pursued, and the diagnosis of ATM was made. Two of the fetuses were of Filipino ancestry and carried the −SEA/−FIL deletion, and one was of Vietnamese ancestry and carried the −SEA/−SEA deletion. Details about prenatal IUT and outcomes for our patients and 17 previously reported cases[13–28] are presented in the succeeding texts (Table 1).

Fetal IUT, stem cell transplant, and pregnancy course

A total of 20 patients, including our three cases, received IUT. Seventeen out of twenty (85%) received more than one transfusion, and 11 transfusion episodes out of 66 IUTs (16.7%) received exchange transfusions; the remainder were direct transfusions.

Table 2 shows the details of transfusion volumes and changes in Hb in patients for whom these details were available. The volume of RBCs needed for transfusion in the setting of ATM is important to consider: Infusion of a high volume of blood in the setting of fetal hydrops can worsen the underlying high output cardiac failure. Conversely, an adequate transfusion volume may eventually require more blood than anticipated because the measured hematocrit value may underestimate the degree of functional anemia in the presence of Hb Bart's tetramers because the hematocrit calculation does not take into account the lack of functionality in these abnormal red blood cells. The direct measurement of the level of Hb Bart's provides greater insight into the true oxygen-carrying capacity when compared with the total Hb level. When the transfused volume for these patients is compared with the volume suggested by guidelines developed for other diseases, such as rhesus disease,[29,30] the transfusion volumes were less than the suggested in 11 of 12 (91.7%) transfusions. In fact, four patients (33.3%) received less than half of the suggested dose.

Despite the low volumes transfused, the Hb F responses were robust, as detailed by the mean pre-transfusion and post-transfusion Hb, hematocrit, and Hb Bart's for a subset of these cases (Table 3). These data indicate that the first IUT

Table 1 **Survivors of IUT for fetal alpha thalassemia major**

Ref.	Patient	Hydropic during pregnancy	Gestational age at 1st IUT (weeks)	Gestational age of subsequent IUT (weeks)	Gestational age at birth (weeks)	HSCT
Current	1	Yes	24	NR	29	Yes[a]
Current	2	Yes	25	NR	38	Yes[a]
Current	3	Yes	23	26, 29, 32, 35	$37^{4/7}$	No
15	4	Yes	25	$25^{5/7}$[b], 32[b]	34	No
21	5	Yes	29	32, 35	37	*In utero*[c]
17	6	No	13	19, 24, 27, 30	36	*In utero*[c]
22	7	Yes	23	25, 28	29	No
19	8	Yes	23[b]	25[b], 29[b]	$29^{4/7}$	No
18	9	No	30	None	34	No
33	10	Yes	29	$29^{4/7}$[b], $30^{3/7}$	$36^{6/7}$	No
26	11	Yes	21	25, 31, 35	38	No
23	12	Yes	31	NR	37	NR
23	13	Yes	31	Not applicable	33	NR
20	14	No	26	NR	34	Yes[a]
24	15	Yes	30	30–33[b]	34	NR
27	16	Yes	27	2 × NR; 31	34	Yes[c]
14	17	Yes[d]	NR	NR	34	No
16	18	No	25	28, 32	35 6/7	Yes[e]
13	19	No	26 4/7	NR	35	No
25	20	No	28 1/7	$30^{0/7}$, $33^{0/7}$, $36^{0/7}$	$39^{1/7}$	No
		Mean ± SD	25.7 ± 4.3		34.7 ± 3.0	

HSCT, hematopoietic cell transplant; IUT, *in utero* transfusion; NR, not reported.
[a]Successful HSCT.
[b]Exchange transfusion.
[c]HSCT failed.
[d]Hydropic at birth.
[e]First HSCT failed; cured with 2nd HSCT.

Table 2 **Details of transfusion volume and fetal hemoglobin levels in seven cases with reported details**

Ref.	Patient no.	IUT no.	Gestational age (weeks)	Pre-transfusion Hb (g/dL)	Transfusion volume given (mL)	Standard transfusion volume (mL)	% of standard transfusion volume
Current	1[a]	1	24	6.6	21	50	42.0
Current	3[a]	1	25	6.4	8	45	17.8
15	4[a]	1	25	7.3	45	46	97.8
15	4[a]	2	25	12.1	30	29	103.4
33	10[a]	1	29	7.0	20	93	21.5
26	11[a]	1	21	5.8	15	32	46.9
26	11[a]	2	25	9.7	20	40	50.0
13	19	1	26	5.7	60	72	83.3
25	20	1	28	6.6	48	84	57.1
25	20	2	30	9.6	45	77	58.4
25	20	3	33	9.6	85	111	76.6
25	20	4	36	11.2	70	94	74.5

Standard volume based on guidelines developed for fetal anemia from other diseases, such as rhesus disease; from current study cohort of patients.[29,30]
[a]Hydropic during pregnancy.

can elevate the fetus out of a critically low anemia, and that subsequent IUTs serve to maintain an appropriate Hb level. Likewise, when the Hb Bart's before the first transfusion was compared with that measured before subsequent transfusions, the values are significantly improved with *in utero* therapy ($p = 0.004$).

Table 3 **Hematologic characteristics before and after the first and subsequent IUT**

	Hemoglobin (g/dL)		Hematocrit (%)		Hb Bart's (%)	
IUT	Pre-transfusion	Post-transfusion	Pre-transfusion	Post-transfusion	Pre-transfusion	Post-transfusion
First	6.4 ± 1.8 (n = 10)	11.3 ± 0.5 (n = 4)	25.9 (n = 1)	37.2 ± 4.0 (n = 2)	87.0 ± 18.4 (n = 2)	91.0 (n = 1)
Subsequent	10.7 ± 1.3 (n = 10)	14.6 ± 2.5 (n = 10)	40.5 ± 3.8 (n = 3)	52.9 ± 1.9 (n = 3)	47.6 ± 13.6 (n = 5)	29.6 ± 24.3 (n = 5)

Values are reported as mean ± SD; n varies because of the variability in reported values among case reports; Hb Bart's (%) $p = 0.004$ (pre-1st IUT vs pre-subsequent IUT), $p = 0.34$ (pre-subsequent IUT vs post-subsequent IUT); Student's t-test was used to compare the two groups.

Two of the patients who underwent IUT also received *in utero* stem cell transplantation during their prenatal course. One patient received stem cell transfusions at 13, 19, and 24 weeks of gestation by using paternal haploidentical stem cells,[17] and the other received transplantations at 15 and 31 weeks of gestation from fetal liver cells were obtained from legal abortions in gestational weeks 6 to 12.[21] In both cases of stem cell transplantations, the engraftment levels were too low to be clinically significant.

Pregnancy course and birth

The pregnancy and perinatal courses for our three cases illustrate expected complications in fetuses with hydrops fetalis. Fetus 1 delivered preterm (secondary to chorioamnionitis) at 29 weeks. The neonatal course was complicated by respiratory distress, necrotizing enterocolitis (medically managed with antibiotics), and suspected hypoxic ischemic encephalopathy (by magnetic resonance imaging). She was discharged to home at 2.5 months. Fetuses 2 and 3 were born at term. Fetus 2 suffered from severe pulmonary hypertension, required extracorporeal membrane oxygenation starting on day of life 4, and was discharged to home following treatment in the neonatal intensive care unit. Fetus 3 was born at term and required neonatal intensive care unit care for 1 week.

As for the 20 cases as a whole, 14/20 (70%) were preterm births (less than 37 weeks), with an average gestational age of 34.7 ± 3.0 weeks. Only three were severe preterm births (28–31 weeks), and all three had chorioamnionitis.[19,22] Eight patients (40.0%) delivered late preterm (34–$36^{6/7}$ weeks), and six patients (30%) delivered at term (37–40 weeks). Of the 20 reported cases, 14 fetuses were hydropic prior to the initiation of IUT (70%). Of the 14 hydropic cases, only one case remained hydropic after therapy.

Although pregnant women who have fetuses with untreated ATM can suffer from pre-eclampsia and mirror syndrome,[2,31] only one patient had this complication, likely because in this series, fetal hydrops (which is secondary to anemia) was actively treated. Another patient developed uterine atony, severe postpartum hemorrhage, and disseminated intravascular coagulopathy requiring hysterectomy and blood transfusion[13] but ultimately recovered.

Postnatal treatment for ATM

All fetuses with ATM received serial transfusions postnatally to treat the underlying anemia. Postnatal HSCT remains the only proven treatment to achieve transfusion independence and cure ATM. As depicted in Table 1, two of our patients received HSCT: Patient 1 had a matched sibling-donor transplantation at age 1 year and became transfusion-independent by 18 months. Patient 2 had an HSCT at age 2 and was transfusion-independent by age 3. The third patient awaits a suitable donor. Of the other 17 cases, one was cured by one postnatal HSCT,[20] one was cured by two HSCTs,[16] and a third was not cured after HSCT.[27]

Neurodevelopmental outcomes

Neurodevelopmental outcomes were reported for 14 patients, including our three cases. Formal neurological testing was performed in four of the patients (Table 4); the remainder did not undergo formal testing. Ten patients (71%) were found to be normal, and four (29%) had some cognitive and/or motor delay at their last recorded evaluation.[13–15] While severe prematurity was not a contributing factor to the neurodevelopmental outcome, as these patients were born late preterm, at 34 to 36 weeks, prematurity could have been a significant contributing factor in the instances of neurodevelopmental delay in our cases born prior to term. It is highly likely that prematurity played a significant role in the neurological outcome of patient one.

Anatomic anomalies

Eleven of the total 20 cases had reported anatomical anomalies (Table 5). Hypospadias, commonly associated with ATM,[15,18,32] was found in one patient in our series and in seven of the previously reported patients,[14,15,18–20,24,32] giving a prevalence of 40.0% in this series. Additional anatomic anomalies in the patients treated with IUT included other genitourinary anomalies (undescended testes, bifid scrotum, and scrotal hypoplasia),[15,24] limb or digit hypoplasia (hand, fingers, foot, and/or toes, $n = 5$),[13–15,26] structural cardiac defects,[32] pulmonary hypoplasia,[24] and central nervous system anomalies (enlarged ventricles, subcortical cystic changes, and wide fontanelles).[14,24]

Outcomes of fetal ATM without IUT

We have reviewed the outcomes of six other patients with ATM from our region who did not have IUT. Neurological and anatomical outcomes were not available for this group. Two of these fetuses had not been diagnosed with ATM *in utero* but were treated with serial transfusions after birth, one of whom underwent HSCT at 3 years of age and was

Table 4 **Neurodevelopmental outcomes for children treated with IUT for ATM**

Ref.	Patient no.	EGA at birth (weeks)	Age at assessment	Neurodevelopmental outcome
Current	1	29	4 years	At age 3: fine and gross motor delay requiring physical and occupational therapy; educational assistance required; deficits attributed to premature birth; developmentally normal at age 4
Current	2	38	3 years	Normal
Current	3	$37^{4/7}$	8 months	Normal[a]
15	4	34	21 months	Motor and neurodevelopmental delay; cognitive functioning[b] = 16 months, gross motor[c] = 7 months; fine motor[c] = 16 months
19	8	$29^{4/7}$	3 months	Normal
18	9	34	12 years	Normal
31	10	34	2 years	Normal
26	11	38	17 months	Normal
20	14	34	5 years	Normal
27	16	34	5.5 years	Normal; bilingual (English and Hmong)
14	17	34	6.5 years	Early psychomotor delay, persisted through age 5 when cognition,[d] vocabulary,[e] and IQ[f] were at 4-year-old level; normal sensory and coordination skills at 6.5 years old
16	18	$35^{6/7}$	7 years	Mildly impaired neuropsychological development; special-education class in age-appropriate school
13	19	35	15 months	Mild motor delay
25	20	$39^{1/7}$	18 months	Normal[g]

[a]Denver Development Scale.
[b]Bayley II Scales of Infant Development.
[c]Peabody Developmental Gross and Fine Motor Scales.
[d]Columbia Mental maturity Scale.
[e]Peabody Picture Vocabulary Test.
[f]Kaufman Assessment Battery for Children.
[g]Battelle Developmental Inventory, 2nd ed.

Table 5 **Anatomic abnormalities for children treated with IUT for ATM**

Ref.	Patient no.	Gender	No. of IUTs performed	Anatomic abnormalities
Current	3	Male	6	Hypospadias, right incompletely descended testicle, syndactyly, foot deformity
15	4	Male	3	Hypospadias, right scrotal hypoplasia, undescended right testicle, foreshortened left foot with only one distal phalanx and two metacarpal bones, valgus deformity of the left ankle
19	8	Male	3	Hypospadias
18	9	Male	3	Hypospadias
31	10	Male	3	Hypospadias, patent ductus arteriosus
26	11	Female	4	Bilateral transverse palmar creases, lobster claw deformity of right foot
20	14	Male	4	Hypospadias
24	15	Male	6	Hypospadias, pulmonary hypoplasia, bilateral cryptorchidism, wide anterior fontanelle, small paraventricular cyst
27	16	Male	4	Cardiomegaly
14	17	Male	5	Hypospadias, hypoplasia of left hand phalanges II–IV, asymmetrically enlarged cerebral ventricles, right ventricular dilation
13	19	Female	2	Minor anatomic anomalies of the left hand and foot

cured. Four patients were diagnosed *in utero* and elected not to undergo IUT; these patients had pregnancy termination ($n=1$), *in utero* demise ($n=2$), or neonatal demise ($n=1$).

DISCUSSION

Our analysis of three new cases and 17 previously reported ones indicates that IUT is an achievable treatment option

for fetuses with ATM, and when used in combination with postnatal HSCT, can result in a definitive cure and normal neurologic outcome, as demonstrated in two of our cases. This case series demonstrates feasible alternative options to termination of pregnancy or expectant management in the setting of a prenatal diagnosis of ATM and should be incorporated in the counseling of families faced with dilemmas on how to approach this diagnosis.

Because IUT is a relatively uncommon course of treatment for this diagnosis, the applied treatment protocol for this intervention should be carefully defined. It appears that even when relatively low volumes are transfused (compared with standards established for more common indications such as rhesus disease), the outcomes remain favorable. Our review found no report of *in utero* fetal demise after IUT but may be affected by reporting bias. The most common complication of IUT was preterm labor, likely a result of the underlying pathology of fetal hydrops and known risks associated with this fetal intervention. Although we previously reported that fetal intervention in the setting of hydrops can lead to increased incidence of preterm labor,[7] two of the patients reported here (and 30% of the total series of 20) were born at term, suggesting that active treatment with transfusions of the hydropic state may prevent preterm labor. Three of the 20 patients had chorioamnionitis leading to early preterm delivery, which highlights a possible complication of repeated fetal intervention.

Families whose fetus is affected by ATM should be counseled about the options for HSCT, as this treatment offers a cure and an alternative to chronic transfusions that can entail complications associated with transfusion-related iron overload and iron chelation.[33] Iron chelation therapy has decreased mortality and morbidity in patients with thalassemia major; however, adverse effects include growth retardation, agranulocytosis, ophthalmologic toxicity, auditory toxicity, arthralgias, rash, and gastrointestinal upset depending on the chelation regimen.[34] Additionally, iron chelation therapy is costly, and adherence to chelation regimens is poor[34] due to adverse reactions. Human leukocyte antigen-matched sibling transplantation is usually the preferred option for most patients because of its very high event free survival rates. HSCT from alternative donors for β thalassemia major is currently undergoing clinical trials, and recent outcomes are promising. However, the nature of that conversation will continue to evolve as additional therapies such as *in utero* HSCT are developed. In this series, two patients who received *in utero* transplantation had engraftment that was too low to be clinically relevant.[17,21] Since the publication of these reports in 1996[21] and 1998,[17] it has been suggested that high dose infusion of maternal cells may improve engraftment levels[35] because the maternal immune response is critical in mediating rejection of third-party cells transplanted into the fetus.[36,37] Importantly, successful *in utero* HSCT would preclude or decrease the need for myeloablative conditioning with cytotoxic agents, which are required to achieve engraftment in postnatal HSCT.[7,35,38]

One possible outcome of fetal therapy is saving the life of a child who may have an unfavorable neurologic outcome. The neurological outcomes of the 14 patients for whom these data are available were generally favorable, with mild delays noted in just four patients. In contrast, among fetuses with ATM who do not undergo blood transfusions but survive to birth, 25 to 50% are affected by neurological or developmental shortcomings,[14,39] presumably from prolonged *in utero* hypoxemia. In one series, 5 of 11 fetuses with ATM who survived to birth without IUT were found to have neurodevelopmental delay, including speech and hearing difficulties ($n=1$), motor delay ($n=1$), spastic quadriplegia ($n=1$), and global developmental delay ($n=2$).[39] A possible reason for these findings is that serial IUTs can correct hypoxia and prevent ongoing hypoxic ischemic brain injury. This hypothesis is supported by findings in other settings of IUT: In a prospective study of 40 patients treated with IUT for isoimmunization, formal neurodevelopmental evaluation for patients up to 5 years of age demonstrated normal outcomes.[40] Thus, active management of fetal anemia and avoidance of prolonged hypoxia can improve neurologic outcomes with hydrops, providing a compelling rationale to pursue *in utero* therapy for ATM.

In our series and case review, 55% of patients had anatomical abnormalities that ranged from hypospadias to multisystem defects (central nervous system, genitourinary, and cardiopulmonary). The underlying pathogenesis from these anomalies remains unclear. Hypospadias was the most common abnormality followed by limb defects. The most serious non-neurological anatomic defect reported was pulmonary hypoplasia found in one patient. That patient survived and has met age-appropriate milestones at 6 months of age.[24] Despite the relatively high rate of congenital anomalies, the bulk was not life threatening. It appears more likely that the degree of fetal anemia contributes more to developmental malformations than the number of interventions, and that aggressive and early management to limit fetal hypoxia would decrease not only poor neurological outcomes but also anatomic anomalies.

Families counseled for a diagnosis of fetal ATM have sometimes had multiple affected pregnancies, often with *in utero* demise, and are motivated to seek alternative therapies. During prenatal consultation, nondirective counseling that includes the options of IUT, pregnancy termination, or the choice of no fetal therapy is critical. This will facilitate families reaching an informed decision about the most appropriate medical course for them. The education for these families should include the possibility of congenital malformations, in particular, genitourinary malformations despite the use of IUT. It should also include discussions on the probability of complications from fetal intervention, including preterm birth and its attendant morbidities, as well as the risks, benefits, and limitations of postnatal management including both chronic transfusions and hematopoietic cell transplantation.

In summary, this series indicates that for fetuses with ATM, there is a potential for survival to term with normal neurologic outcomes. These findings provide support for continued patient and provider education about the possibility of active prenatal therapy for fetuses with ATM, as well as the need for continued research to optimize therapeutic strategies such as

in utero stem cell transplantation. The establishment of an international registry of prenatally diagnosed cases with ATM and analyzing their outcomes with and without fetal intervention will be critical for improving our knowledge regarding this diagnosis. Our series further highlights the need to keep an international registry of and prospectively analyze interventions and outcomes.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Alpha thalassemia major is caused by a homozygous mutation in the alpha globin gene that leads to an inability to form properly functioning hemoglobin. The disease results in fetal demise if not treated with *in utero* transfusions.

WHAT DOES THIS STUDY ADD?

- Fetuses with alpha thalassemia major often die *in utero*, and rare infants who survive to birth have severe neurological impairments due to *in utero* anemia or prematurity. Our study demonstrates that fetal therapy with serial *in utero* transfusions can result in survival with normal neurological outcomes.

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