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ORIGINAL ARTICLE

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Fetal heart size measurements as new predictors of homozygous α-thalassemia-1 in mid-pregnancy

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Abstract

Objective: To evaluate the efficacy of using fetal heart size measurements derived from axial echocardiography to predict homozygous α-thalassemia-1.

Design: Prospective diagnostic study.

Setting: The carrier rate of α-thalassemia-1 (−/αα) in China's Guangxi Zhuang Autonomous Region is approximately 15%. If both parents are carriers, the risk of homozygous α-thalassemia-1 in one pregnancy is 25%.

Patients: Singleton mid-pregnancies at risk of homozygous α-thalassemia-1 were enrolled.

Outcome Measures: Fetal heart measurements, including heart diameter (HD), heart length (HL), heart circumference (HC), and heart area (HA), were measured. The *z*-scores for these heart parameters were then calculated separately based on previously constructed *z*-score models. Finally, the accuracy of these predictive variables was analyzed and compared to that achieved by cardiothoracic ratio (CTR) using a receiver operating characteristic (ROC) curves analysis.

Results: A total of 214 singleton pregnancies were recruited. The discriminatory power of HA and HD *z*-scores was better (*z*-test $P < .01$) while that of HC and HL *z*-scores was comparable to (*z*-test $P > .05$) that of CTR. HD combined with HA *z*-scores had the highest sensitivity (100%), and the specificity of HD and/or HA *z*-scores was 100%.

Conclusion: Fetal heart size measurements are novel, effective and noninvasive predictors of homozygosity for α-thalassemia-1 in mid-pregnancy. The discriminatory power of HD and HA *z*-scores was better than while that of HC and HL *z*-scores was comparable to that of CTR. Further investigation is needed to understand the effectiveness of these predictors.

KEYWORDS

fetal echocardiography, heart size, homozygous α-thalassemia-1, midpregnancy, prenatal diagnosis, *z*-scores

INTRODUCTION

China's Guangxi Zhuang Autonomous Region is one of the most endemic areas for α-thalassemia in the world. In this region, the carrier rate of α-thalassemia-1 (−/αα) is approximately 15%.[1] We estimate that the overall incidence rate of homozygous α-thalassemia-1 is approximately 5.6 per 1000 births as a result of autosomal inheritance. Homozygous α-thalassemia-1, also known as α-thalassemia major, Hb Bart's hydrops fetalis syndrome and HB Bart's disease, is the primary cause of nonimmune hydrops, which is a major fatal birth defect. This places a heavy burden on the public health system in endemic areas.[2] Although intrauterine blood transfusion followed by postnatal transfusions and bone marrow transplantation is a treatment protocol that has been successfully completed in several cases, there is currently no practical and effective treatment for affected patients.[3,4] Hence, the world-recognized approach to treating this condition has been to

selectively abort fetuses diagnosed based on prenatal genetic tests.[5] However, the invasive testing methods themselves result in an approximately 0.2%–6.8% fetal loss rate.[6]

Cardiomegaly brought on by fetal anemia may appear before the onset of fetal hydrops. Hence, this ultrasonographic marker could potentially be used as a noninvasively predictor of homozygous α-thalassemia-1 fetuses. The cardiothoracic ratio (CTR) is recognized as a highly sensitive indicator that can reduce fetal loss.[6,7] However, it is an indirect marker presented as the ratio of the size of the heart to that of the thorax. There is a variety of definitions and ways of measurement methods, resulting in causing confusion for the ultrasonographer and a reduction in the reproducibility and accuracy of the measurements.[8] We hypothesized that the accuracy rate might be increased by using direct heart size measurements to identify fetal cardiomegaly. No previous study has evaluated the efficacy of heart size measurement in predicting fetal homozygous α-thalassemia-1 with the exception of one article that used multiples of the median (MOM) of heart circumference (HC).[9]

The present investigation was based on our previously constructed heart size reference ranges, which can be used to calculate the *z*-scores for fetal heart sizes.[10] Our preliminary results also indicated that heart size was increased in nearly all fetuses with homozygous α-thalassemia-1.[10] The objective of this study was to evaluate the diagnostic performance of using *z*-scores of fetal heart size, including measurements of heart diameter (HD), heart length (HL), heart circumference (HC), and heart area (HA), in predicting homozygous α-thalassemia-1 during the second trimester. We compared the performance of this method with that of traditional CTR.

MATERIALS AND METHODS

Subjects

This prospective diagnostic study was performed at the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region from April 1, 2011, to July 31, 2016. The research ethics committee approved this study. Couples who were α-thalassemia-1 carriers were included, and all participants provided informed consent before joining the study. The following inclusion criteria were used: (1) singleton pregnancies at risk of fetal homozygous α-thalassemia-1 (the parents were all identified as α-thalassemia-1 carriers based initially on mean corpuscular volume (MCV) and erythrocyte fragility screening tests; and the Southeast Asian genotype of α-thalassemia-1 was then confirmed using PCR); (2) a gestational age (GA) between 15 and 22 weeks based on regular menstruation and corroborated by a first trimester ultrasound measurement of crown-rump length (CRL) or a second trimester measurement of the biparietal diameter (BPD); and (3) patients underwent amniocentesis for a genetic diagnosis. The following exclusion criteria were used: (1) fetal cardiac and extra-cardiac structural abnormalities; (2) fetal chromosomal abnormalities; (3) multiple pregnancies; (4) fetal anemia resulting from other causes; (5) fetal intrauterine growth abnormality; (6) maternal diseases, such as hypertension and diabetes mellitus, which can affect fetal development; and (7) failed amniocentesis.

All patients underwent a routine transabdominal ultrasound examination for fetal anatomical survey and biometry before amniocentesis. Two trained operators, Xinyan Li and Huan Huang, performed the scans. The ultrasound systems were equipped with a 3.5–5.0 MHz curved-array probe and included a Voluson E8 (GE Healthcare, Milwaukee, WI) and an Aloka 10 (Aloka, Tokyo, Japan). All measurements of the cardiac size were taken at end diastole in a standard four-chamber view that was obtained using fetal axial echocardiography.[9] The HD was defined as the transverse cardiac diameter at the level of the annuli of the mitral and tricuspid valves. The length from the apex to the bottom of the heart was defined as the HL (Figure 1A). The trackball was used to directly trace the edge along the outer contour of the heart, and the resulting measurements were expressed as the HC and HA (Figure 1B). The CTR was defined as the ratio of HD and transverse thoracic diameter (TD), which was the maximum outer-to-outer distance between thoracic ribs. In each case, three separate measurements were obtained, and the average value was digitally recorded. Taking the measurements usually took < 3 min.

A diagnosis of homozygous α-thalassemia-1 was confirmed using PCR testing from tissues obtained during amniocentesis. Karyotyping was also performed. The patients were then divided into the following two groups according to the final α-genotype: an affected group (pregnancies with homozygous α-thalassemia-1 fetuses) and an unaffected group (pregnancies with normal or α-thalassemia-1 carrier fetuses).

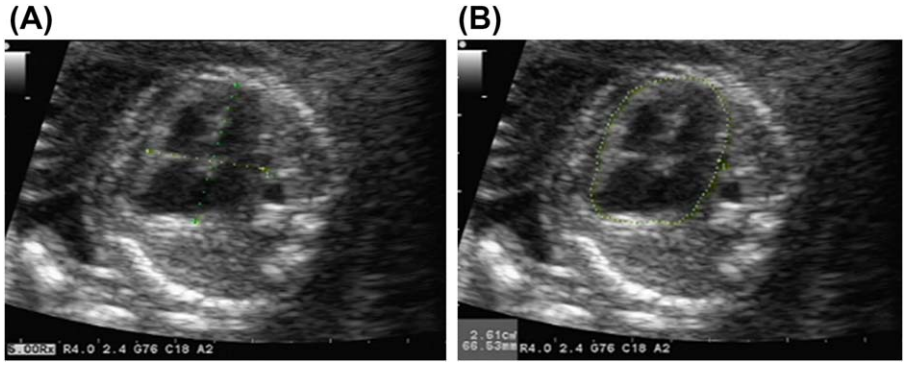

FIGURE 1 Measurements of the heart size of a fetus with homozygous α-thalassemia-1 at 18 weeks of gestation. (A) displays the measurements of HD and HL, and (B) displays the measurements of HC and HA

Statistical analyses

All statistical analyses were performed using the IBM SPSS package version 21.0 (SPSS, Inc., Chicago, IL) and MedCalc version 11.3.1.0 (MedCalc Software, Mariakerke, Belgium). Heart size measurements were converted into *z*-scores (*z*-scores = [observed value − fitted M]/fitted standard deviation [SD]) based on our previously published fetal heart size models. The fitted M and SD were median values at corresponding exact gestational weeks, respectively.[10]

The baseline characteristics of the affected and unaffected groups' demographic characteristics in addition to characteristics related to heart size, including the means and *z*-scores for HD, HL, HC, and HA, were compared. Mean (for normally distributed data) measurements, including CTR and *z*-scores for HD, HL, HC, and HA, were compared between normal and affected pregnancies using two-tailed Student *t* tests. Median (for non-normally distributed data) values, including HD, HL, HC, and HA, were compared using the Mann-Whitney *U* test. The correlation between heart size parameters and GA was assessed using Spearman's correlation coefficients. The discriminatory power of the heart size parameters was analyzed using a receiver operating characteristic (ROC) curves analysis. The *z*-test (analyzed using MedCalc Software) was used to compare the area under the curves (AUCs). $P < .05$ was considered statistically significant. The performance of the heart size parameters was assessed by calculating sensitivity, specificity, and positive and negative predictive values using the best cutoff point, which was determined using the ROC curve (Youden index (*J*) = uses, J = maximum [sensitivity + specificity−1]). The diagnostic index used for CTR was 0.5 for pregnancies between 15 and 18 weeks and 0.52 for those between 19 and 22 weeks. A cutoff value was also calculated, as was the efficacy of using the *z*-score of HD or HA alone or in combination.

The reproducibility of the heart size measurement was assessed using intraclass correlation coefficients for repeated measurements in a random sample of 30 patients. Li Xinyan's measurements were compared pairwise to those of the other rater (Huang Huan) to obtain a score for interobserver variability, and two random measurements obtained in a single patient by Li Xinyan were compared to evaluate the intraclass correlation coefficients.

RESULTS

A total of 221 pregnancies at risk of α-thalassemia-1homozygosity met the inclusion criteria during the study period. Applying the exclusion criteria resulted in the exclusion of 7 fetuses, including 4 with an extracardiac or cardiac abnormality, 1 with fetal chromosomal abnormalities, and 2 with anemia resulting from other causes. Finally, 214 cases were included. Among these, 115 presented at 15–18 weeks, and 99 presented at 19–22 weeks. The final results of genetic testing showed that 57 fetuses (29 at 15–18 weeks and 28 at 19–22 weeks) were homozygous for α-thalassemia-1.In all, 10 of these 57 cases (17.5%, 3 at 15–18 weeks and7 at 19–22 weeks) had hydrops. A total of 157 fetuses were unaffected, including 101 α-thalassemia-1 carriers and 56 normal fetuses. The incidence of homozygous α-thalassemia-1 in this investigation was 26.6% (57/214).

TABLE 1 Baseline characteristics of the affected and unaffected groups

Characteristic	Affected (n = 57)	Unaffected (n = 157)	*P* value
Maternal age, *y*	27.5 ± 3.2[a]	27.6 ± 3.6[a]	.848
Biparietal diameter, mm	42.2 ± 6.2[a]	43.5 ± 7.2[a]	.223
Gestational age, wk	18.7 ± 1.8[a]	19.1 ± 2.0[a]	.233

[a]Data were presented as the mean ± SD, Student *t* test was used to get P value.

The baseline characteristics of the affected and unaffected groups were not significantly different, as shown in Table 1.

Ultrasound measurements of heart size were compared between the affected and unaffected groups, as shown in Table 2. The means and *z*-scores for fetal heart HD, HL, HC, and HA measurements and CTR were significantly higher in the homozygous α-thalassemia-1 fetuses than in those in the unaffected group.

The relationships between GA and heart size parameters in the affected and unaffected groups are described in Table 3. As shown, the means for HD, HL, HC, HA, and CTR were significantly higher in both groups with GA, whereas the heart size *z*-scores were normally distributed in both groups.

The ROC curves for heart size *z*-scores and CTR for predicting which fetuses were homozygous for α-thalassemia-1 are shown in Figure 2.

The characteristics of the ROC curve of heart size that was used to predict which fetuses had homozygous α-thalassemia-1 are summarized in Table 4.

TABLE 2 Fetal heart sizes were compared between affected and unaffected groups

Parameters	Affected (n =57) (median-IQR) or mean (±SD)	Unaffected (n = 157) (median-IQR) or Mean (±SD)	*P* value
HD, mm	20.15 (17.05, 23.73)[a]	16.00 (14.20, 18.80)[a]	<.001
HL, mm	23.80 (21.35, 28.49)[a]	20.40 (18.10, 24.48)[a]	<.001
HC, mm	80.52 (66.57, 91.49)[a]	65.72 (58.65, 75.23)[a]	<.001
HA, mm	393 (285.50, 540.50)[a]	263 (212, 352)[a]	<.001
Z-score of HD	4.91(±2.17)	0.55 (±0.99)	<.001
Z-score of HL	3.11 (±1.62)	0.53 (±1.04)	<.001
Z-score of HC	3.60 (±1.58)	0.48 (±0.94)	<.001
Z-score of HA	5.10 (±2.50)	0.68 (±1.69)	<.001
CTR	0.59 (±0.05)	0.47 (±0.04)	<.001

[a]Not normally distributed data were presented as median-IQR and the Mann–Whitney U test was used; otherwise, the normally distributed data were presented as mean ± SD and the Student *t* test were used to get *P* value.
Abbreviations: CTR, cardiothoracic ratio; HA, heart area; HC, heart circumference; HD, heart diameter; HL, heart length; IQR, interquartile range; SD, standard deviation.

TABLE 3 The relationships between heart size parameters and GA in affected and unaffected groups

Parameter	Affected (n = 57)		Unaffected (n = 157)	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
HD, mm	0.844	<.001	0.925	<.001
HL, mm	0.820	<.001	0.908	<.001
HC, mm	0.847	<.001	0.906	<.001
HA, mm	0.809	<.001	0.822	<.001
Z-score of HD	0.182	.175	0.063	.435
Z-score of HL	0.143	.287	0.107	.230
Z-score of HC	0.176	.190	0.074	.382
Z-score of HA	0.126	.350	−0.018	.827
CTR	0.512	<.001	0.263	<.001

Abbreviations: CTR, cardiothoracic ratio; HA, heart area; HC, heart circumference; HD, heart diameter; HL, heart length.

The diagnostic indices of the heart size parameters that were used to differentiate the affected and unaffected fetuses based on the best cutoff value are summarized in Table 5. We observed that the highest sensitivity (100%) was achieved using the HD and HA *z*-scores, while the highest specificity (100%) was achieved for HD and/or HA *z*-scores.

For HD, HL, HC, and HA, the intraclass correlation coefficients were 0.88, 0.86, 0.90, and 0.89, respectively, for interobserver variability and 0.92, 0.93, 0.94, and 0.96, respectively, for intraobserver variability.

Clinical outcome: among 57 affected cases (fetal homozygous a-thalassemia-1 confirmed by genetic testing), 55 patients had induced labor after confirmation, 2 patients refused induced labor of which 1 fetus died in utero at 33 weeks and the other died at 36 weeks. Among 157 unaffected pregnancies, 153 continued to full-term while the other 4 delivered preterm. No apparent abnormality or severe anemia was noticed in any of these unaffected fetuses.

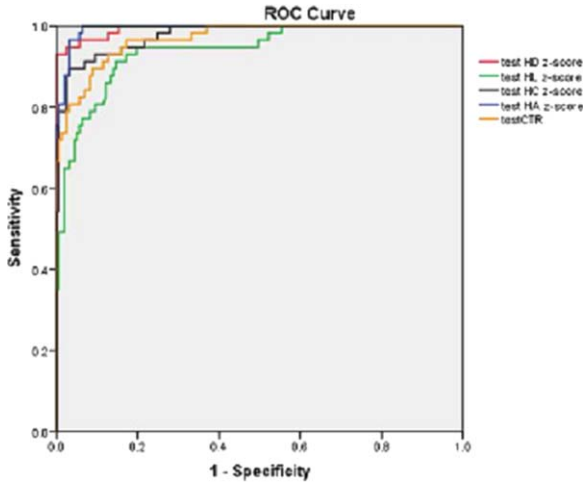

FIGURE 2 ROC curve of heart size *z*-scores and CTR in predicting fetuses with homozygous α-thalassemia-1.
Abbreviations: ROC, receiver–operator characteristic HD, heart diameter; HL, heart length; HC, heart circumference; HA, heart area; CTR, cardiothoracic ratio

TABLE 4 Characteristics of the ROC curve of heart parameters for predicting fetuses with homozygous α-thalassemia-1

Parameter	AUC	SD	*Z* value[a]	*P* value	95% CI
Z-score of HD	0.9936	0.0039	2.286	.0223	0.987–1.000
Z-score of HL	0.9393	0.0180	1.396	.1628	0.904–0.975
Z-score of HC	0.9769	0.0091	0.5432	.6080	0.959–0.995
Z-score of HA	0.9934	0.0033	2.247	.0247	0.987–1.000
CTR	0.9680	0.0110	–	–	0.935–0.988

Z values [a]are z-test values of AUC of heart size parameters compared with those of CTR in predicting fetuses with homozygous α-thalassemia-1.
Abbreviations: AUC, area under the curve; CI, confidence interval; CTR, cardiothoracic ratio; HA, heart area; HC, heart circumference; HD, heart diameter; HL, heart length; SD, standard deviation.

DISCUSSION

Based on the results of our previously study, we assessed the discriminatory power of heart size *z*-scores for detecting fetuses with homozygous α-thalassemia-1 in this study and found that heart size measurements are effective predictors of homozygosity during mid-pregnancy. Among these parameters, the HD and HA *z*-scores were better predictors of homozygosity than was found for traditional CTR.

The fetal *z*-score model is a quantitative standardized method in which a *z*-score is expressed as multiples of the SD to assess fetal biometry.[11] Our previously constructed heart reference range models conveniently allowed us to calculate heart size *z*-scores.[10] Our results demonstrate that the means and *z*-scores of fetal heart size parameters are significantly higher in fetuses with homozygous α-thalassemia-1 than in those in the unaffected group. The CTR is relatively stable but increased slightly from 15 to 22 weeks of GA in both groups. Unlike CTR, the fetal heart size *z*-scores remained stable from 15 to 22 weeks' GA in both study groups. Therefore, it was convenient for us to define a best cutoff value for heart size *z*-scores that could be used as a predictor during the second trimester. We searched the literature and identified only one published work (by Siwawong et al.[9]), that used heart size as a predictor of fetal homozygous α-thalassemia-1. The authors found that although HC effectively detected affected fetuses at 18–22 weeks' GA with a sensitivity and specificity of 86.4% and 78.1%, respectively, when a cutoff level of greater than 1.17 MOM was applied, the efficacy of traditional CTR was superior to that of HC. There are discrepancies between their results and ours. In our study, we used a HC *z*-score instead of a HC MOM to predict this disease, and the results showed that the effectiveness of HC *z*-scores was higher than that of HC MOM, as reported by Siwawong W et al. In addition, our data show that efficacy is comparable between HC *z*-scores and CTR.

TABLE 5 Diagnostic indices of heart size parameters in detecting fetuses with homozygous α-thalassemia-1 based on the best cutoff value

Parameter	Best cutoff value[a]	SENS (%)	SPEC (%)	PPV (%)	NPV (%)
Z-score of HD	2.76	92.98	100	100	97.5
Z-score of HL	1.50	91.23	85.35	69.3	96.4
Z-score of HC	1.88	89.47	96.82	91.1	96.2
Z-score of HA	2.08	100	93.63	85.1	100
CTR	0.52	87.72	91.72	79.4	95.4
CTR	15–18 > 0.5;19–22 W > 0.52	94.3	87.2	72.4	97.6
z-score of HD and HA	–	100	93.10	84.5	100
z-score of HD and/or HA	–	92.45	100	100	97.1

[a]The best cutoff value was determined by Youden index (j), J = maximum (sensitivity + specificity − 1).
Abbreviations: CTR, cardiothoracic ratio; HA, heart area; HC, heart circumference; HD, heart diameter; HL, heart length; NPV, negative predictive value; PPV, positive predictive value; SENS, sensitivity; SPEC, specificity.

In addition to HC, this study is the first to assess the effectiveness of HD, HL, and HA for detecting homozygous α-thalassemia-1 in fetuses. Among these parameters, the highest AUC was found for HD and HA, followed by HL. Discriminatory power was higher for *z*-scores for HD and HA than for CTR. Although the efficacy of HL appeared to be slightly inferior to that of CTR, a comparison *z*-test of the AUCs of HL and CTR showed that there was no significant difference between them($P > .05$). In addition, we found that the *z*-score for combining HD and HA showed that predictive accuracy was improved. The highest sensitivity (100%) was achieved by a HD *z*-score > 2.76 and a HA *z*-score > 2.08, while the highest specificity (100%) was achieved by a HD *z*-score > 2.76 and/or a HA *z*-score > 2.08. Our final results partially support our previous hypothesis, which stated that more accurate results might be obtained when using direct measurements of heart size than when using CTR. Furthermore, our results underscore the notion that α-thalassemia-induced cardiomegaly maybe the most obvious in both area and the transverse dimension, whereas circumference and length are not as obviously affected. Although Leung KY et al.[7] found that combining CTR with MCA-PSV decreased the false-positive rate at 16–20 GA and increased sensitivity at 12–15 GA, our study is the first to identify any singleton sonographic marker with a predictive value superior to CTR. This phenomenon might also hold true earlier in a pregnancy or in other types of anemia-induced fetal cardiomegaly. However, this possibility requires further study.

The prognosis of homozygous a-thalassemia-1 is poor. Although 2 patients with affected fetus refused to terminate the mid-pregnancy, both fetuses died in the third trimester. In contrast, all unaffected pregnancies had very good outcome. The strengths of our study include the following: (1) a relatively large sample size (214 cases) of at-risk pregnancies; (2) calculations of *z*-scores for heart size were based on data obtained in our previous study, and the accuracy of the reference standard is, therefore, ensured; (3) fetal heart size, including HD, HL, HC, and HA, that reflect cardiomegaly along several dimensions were assessed in our study; (4) this study is the first to assess the predictive power of fetal heart HD, HL, and HA. Limitations of this study include the following: (1) the efficacy of using heart size to predict homozygous α-thalassemia-1 in first trimester fetuses requires further study, and (2) the predictive efficacy of other markers, such as PT and MCA-PSV, were not explored in this study.

In summary, our results show that *z*-scores of fetal heart size measurements are novel, effective and noninvasive predictors of fetal homozygous α-thalassemia-1 in the second trimester. The predictive efficacies of HA and HD were superior to that of CTR in mid-pregnancy in our study. Combining HA and HD further improved their predictive value. These data suggest that these accurate and noninvasive markers might be very useful in clinical practice. Obtaining a comprehensive understanding of the diagnostic value of these parameters will require further research.

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AUTHOR CONTRIBUTIONS

Study design: Qiu, Tian
Manuscript writing: Xinyan Li
Measurements: Xinyan Li, Huang, Xueqin Li
Manuscript revision: Qiu, Zhao
Data collection and analysis: Meng Li

CONFLICT OF INTEREST

There are not any commercial or other associations that might pose a conflict of interest in connection with this article.

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APPENDIX : AN EXAMPLE OF THE HEART SIZE *Z*-SCORE CALCULATION

BPD = 35 mm

HD =15.8 mm

Bases on our previous study (from Table 1),[10] the fitted mean value of HD = $1.152 + 0.2644 \times 35 + 0.00168 \times 35 \times 35$ =12.5 mm

From Table 2,[10] the fitted SD = $-0.130 + 0.0298 \times 35 = 0.91$ mmz = (observed value – fitted mean value)/fitted SD = (15.8 – 12.5)/0.91 = 3.6

The HD *Z*-score was +3.6 SD above the fitted mean value for BPD; therefore, the fetus was considered to have cardiomegaly. Because both parents are α-thalassemia-1 carriers, we predicted that the fetus might have homozygous-α-thalassemia-1; subsequent amniocentesis and DNA testing confirmed this finding.