Sonographic Markers of Hemoglobin Bart Disease at Midpregnancy

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Objective. To evaluate the efficacy of various sonographic markers at midpregnancy in predicting fetal hemoglobin Bart disease. ***Methods.*** Four hundred eighty-eight pregnancies at risk of having fetuses with hemoglobin Bart disease were recruited for prenatal diagnosis with cordocentesis at 18 to 21 gestational weeks. Before cordocentesis, the sonographic markers, including cardiothoracic ratio, placental thickness, pericardial effusion, pleural effusion, ascites, subcutaneous edema, cord edema, dilated umbilical vein, and amniotic fluid index, were assessed and recorded. The definite fetal diagnosis was based on blood analysis. The efficacy of each sonographic marker in predicting hemoglobin Bart disease was evaluated by sensitivity and specificity. ***Results.*** Among 488 pregnancies undergoing prenatal diagnosis, 100 fetuses were proved to be affected by hemoglobin Bart disease. The cardiothoracic ratio gave the highest sensitivity, 95.0%, with specificity of 96.1%, followed by placental thickness. Signs of hydrops fetalis were observed in 33.0% of cases; they did not increase the sensitivity of the cardiothoracic ratio but strongly reinforced the diagnosis when they appeared. ***Conclusions.*** At midpregnancy, sonographic markers can effectively differentiate normal pregnancies from those with fetal hemoglobin Bart disease. Among couples at risk with no sonographic markers, the risk of having an affected child is nearly eliminated. The most sensitive marker was the cardiothoracic ratio, followed by placental thickness. ***Key words:*** cardiothoracic ratio; hemoglobin Bart disease; hydrops fetalis; sonography; thalassemia.

Abbreviations
C/T, cardiothoracic; Hb, hemoglobin; HPLC, high-performance liquid chromatography

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Hemoglobin (Hb) Bart disease (homozygous α-thalassemia) is inherited as an autosomal recessive disorder with a 25% recurrence rate for subsequent pregnancies. In southeast Asia, Hb Bart disease is the most common cause of hydrops fetalis, accounting for 60% to 90% of cases.[1–4] The prevalence of α-thalassemia (Southeast Asian type), a common α-thalassemia mutation in southeast Asia, is as high as 14% in northern Thailand.[2] With population migrations during the past decades, this syndrome is now seen in increasing numbers in other parts of the world. The affected fetuses inevitably either are stillborn or die soon after birth. Furthermore, serious obstetric complications are frequently seen in affected pregnancies, including preeclampsia, dystocia, postpartum hemorrhage due to

a large placenta, and the psychological burden of carrying a nonviable fetus to term. Therefore, the ability to make a prenatal diagnosis and to perform early termination of the pregnancy is essential.

At present, prenatal diagnosis is usually done by DNA analysis[5,6] or fetal blood analysis.[7] However, these techniques are invasive, and resources for analysis may be limited in areas where the condition is prevalent. In the past, before we had a program for control of severe thalassemia, we rarely encountered Hb Bart hydrops fetalis before midpregnancy, leading to the conclusion that hydropic changes due to Hb Bart disease were unlikely to occur before 20 weeks.[8] During the past 8 years, however, we have had a routine screening program for carrier detection of thalassemia and have had an opportunity to sonographically examine pregnancies at risk at midpregnancy. Our extensive experience suggests that early hydropic changes in affected fetuses may be detected by sonography earlier in gestation. Although some studies[9–11] reported that sonography could identify affected pregnancies with high sensitivity and specificity at 17 to 18 weeks, they included only small numbers of cases. Furthermore, our own preliminary data[12,13] suggested the criteria for prediction, but these remain to be tested in a wider population. This study, our new extended experience, was prospectively conducted to evaluate the effectiveness of all sonographic markers in predicting Hb Bart disease at midpregnancy.

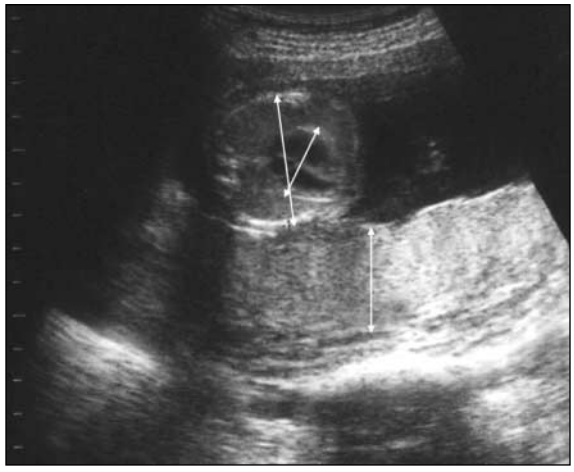
Materials and Methods

The study patients were recruited by our program to control severe thalassemia,[7] consisting of a screening program to identify carriers and pregnancies at risk, prenatal diagnosis, and pregnancy termination for those with affected fetuses. Prenatal diagnosis for couples at risk was made on the basis of cordocentesis and fetal blood analysis with high-performance liquid chromatography (HPLC). Actually, we screened for both α- and β-thalassemia at the same time; however, in this report, we focus only on α-thalassemia 1.

Before cordocentesis, we performed sonography for fetal biometric measurements and evaluation of sonographic signs of hydropic changes. Transabdominal real-time sonographic examinations with Aloka SSD-1700 and ProSound SSD-5000 scanners (Aloka Co, Ltd, Tokyo, Japan) having a transducer frequency of 3.5 MHz were performed by the authors. The sonographic data were prospectively recorded for subsequent analysis. The fetal age was determined by reliable last menstrual period or early fetal sonographic biometric measurements.

The sonographic markers (Figures 1–9) included the cardiothoracic (C/T) ratio, placental thickness, subcutaneous edema (scalp edema or nuchal thickening of 6 mm), pericardial effusion, pleural effusion, ascites, hepatomegaly, a dilated umbilical vein (>5 mm), cord edema, and amniotic fluid index. In the measurement of the C/T ratio, the transabdominal probe was oriented to obtain a cross-sectional view of the fetal thorax at the level of the 4-chamber view. The cardiac diameter was measured at the level of atrioventricular valves during end diastole; the transverse thoracic diameter was measured in the same image; and the ratio was calculated. A ratio of greater than 0.5 was considered abnormal.[12] In the measurement of placental thickness, the transabdominal probe was oriented perpendicularly to the placenta, and thickness was measured at the center in longitudinal and transverse sections. A thickness of greater than 3 cm was considered abnormal.[13] The sonographic diagnosis of hydrops fetalis was made if 1 or more of the following were seen: subcutaneous edema, pericardial effusion, pleural effusion, and ascites. A definite diagnosis of fetal Hb Bart disease was achieved by subsequent fetal blood analysis with HPLC. Pregnancies with other fetal anomalies or chromosome abnormalities were excluded from analysis.

Figure 1. Cardiothoracic ratio of greater than 0.5 and placental thickness of 3.1 cm. Upper short and long arrows indicate cardiac and thoracic diameters, respectively; and lower arrow, placental thickness.



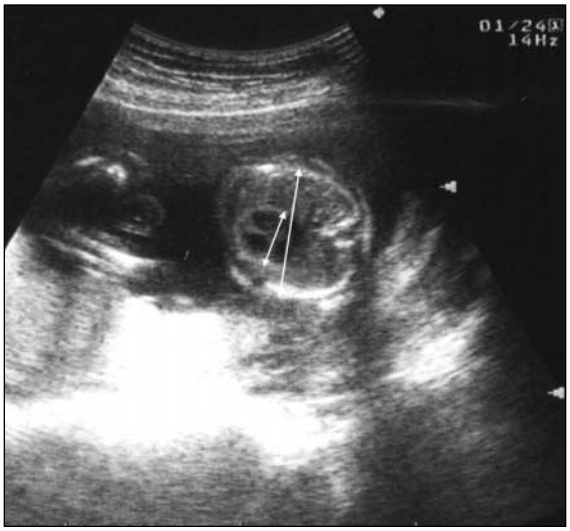


Figure 2. Cardiothoracic ratio of less than 0.5 (normal). Short and long arrows indicate cardiac and thoracic diameters, respectively.

Results

During the study period (June 1998–April 2003), 20,642 women were screened for severe thalassemia syndrome (both α- and β-thalassemia), and we identified 590 pregnancies at risk for having fetuses with Hb Bart disease. Four hundred eighty-eight pregnancies were sonographically evaluated and underwent cordocentesis for fetal blood analysis at 18 to 21 gestational weeks. Of the 488 fetuses, 100 were finally proved to be affected by Hb Bart disease, and the remainder had normal findings or an α-thalassemia 1 trait. The mean ± SD maternal ages were 26.9 ± 5.7 and 27.2 ± 5.4 years for women with normal and affected pregnancies, respectively. The mean gestational ages were 19.5 ± 1.2 and 19.6 ± 1.2 weeks for the normal and affected groups, respectively. No serious maternal complications, such as pregnancy-induced hypertension, were noted at midpregnancy.

The sensitivity and specificity of each sonographic marker in identifying fetuses with Hb Bart disease are summarized in Table 1. Among these sonographic markers, the C/T ratio had the highest sensitivity, 95.0%, with specificity of 96.1%, followed by placental thickness, whereas hydrops fetalis had sensitivity of only 33%. Five affected fetuses had a normal placental thickness and C/T ratio but no signs of hydrops fetalis at gestational ages of 18 and 21 weeks. Full-blown hydrops fetalis, including generalized edema, apparent cardiomegaly, placentomegaly, pleural effusion, and ascites, was observed in 10 cases.

All fetuses with hydrops fetalis also had an increased C/T ratio and a thickened placenta. Most of them had only a mild degree of hydropic changes such as mild ascites and had a normal amniotic fluid index. However, 5 and 9 fetuses had oligohydramnios and polyhydramnios, respectively. All 5 fetuses with oligohydramnios had other signs of hydrops fetalis,

Figure 3. Pericardial effusion (arrows). Left, Real-time image of the fetal chest. Right, M-mode image of the fetal heart corresponding to the left image.

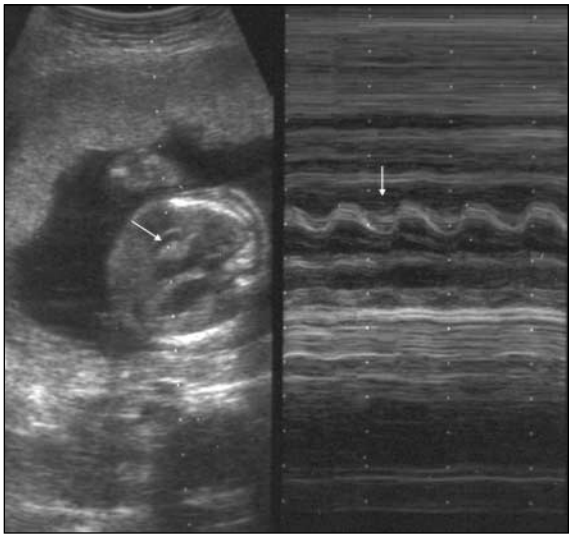
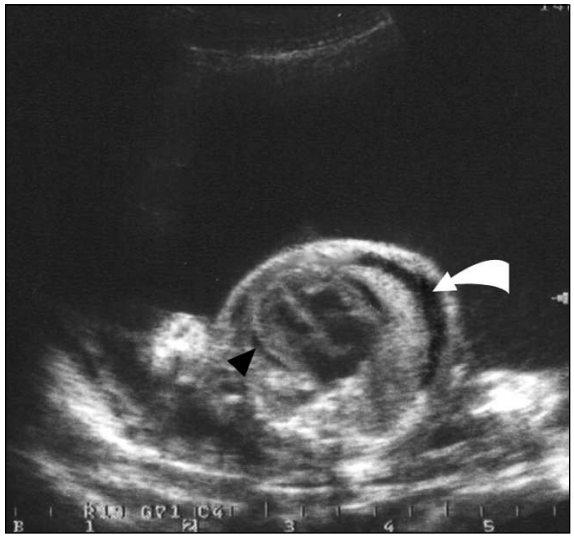


Figure 4. Pleural effusion (white arrow), minimal pericardial effusion (black arrowhead), and polyhydramnios.



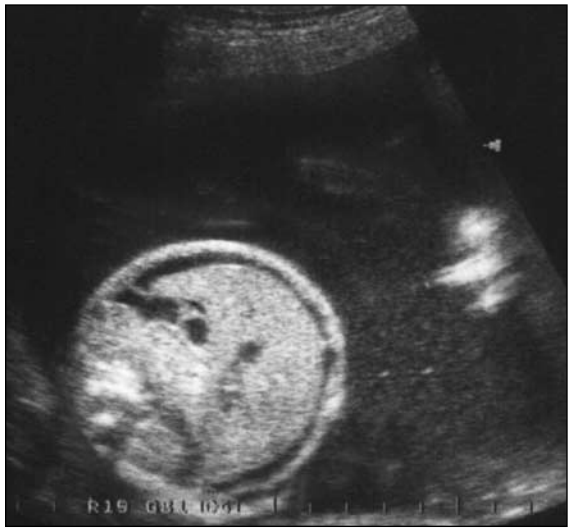


Figure 5. Mild ascites and polyhydramnios.

whereas 9 fetuses with polyhydramnios had only an increased C/T ratio or a thickened placenta without other hydropic changes. Nine of 12 fetuses with subcutaneous edema had a thickened nuchal fold, and 4 had only a thickened nuchal fold without edematous changes elsewhere.

Therapeutic abortion with misoprostol was successfully done in all affected pregnancies.

Discussion

The prenatal diagnosis of Hb Bart disease is currently made invasively, on the basis of chorionic villi sampling or amniocentesis for DNA analysis or cordocentesis for fetal blood analysis. All these invasive procedures are expensive, require well-trained operators, and carry considerable risks of fetal loss. Because of the unavailability of DNA analysis in our country, we usually perform cordocentesis for fetal diagnosis with HPLC at 16 to 24 weeks.[7]

Our results indicated that the C/T ratio was the most sensitive marker in predicting Hb Bart disease before the classic features of hydrops fetalis appear and were consistent with those reported by Lam et al,[9,14] who found that the sonographic markers may appear as early as 12 to 14 weeks' gestation, and the appearance becomes more obvious and more consistent at 17 to 18 weeks' gestation. However, the numbers of affected fetuses at 17 to 18 weeks were only 16 and 21 in their 2 reports.[9,14] Although our results showed that the C/T ratio is a very good predictor, the efficacy may not seem as excellent as that reported by our preliminary report[12] and by Lam et al,[15] who studied pregnancies at risk at 12 to 13 weeks and found sensitivity of 100%. Sonographic signs of hydropic fetalis other than the C/T ratio and placental thickness (eg, pericardial effusion, pleural effusion, ascites, subcutaneous edema, hepatomegaly, a dilated umbilical vein, cord edema, oligohydramnios, and polyhydramnios) were seen in only 33%, but these various findings strongly reinforced the diagnosis of Hb Bart disease, especially in cases of an increased C/T ratio or thickened placenta, because they are very specific and are never seen in fetuses with no abnormalities.

Figure 6. Hepatomegaly with ascites. H indicates heart; and arrow, liver span.

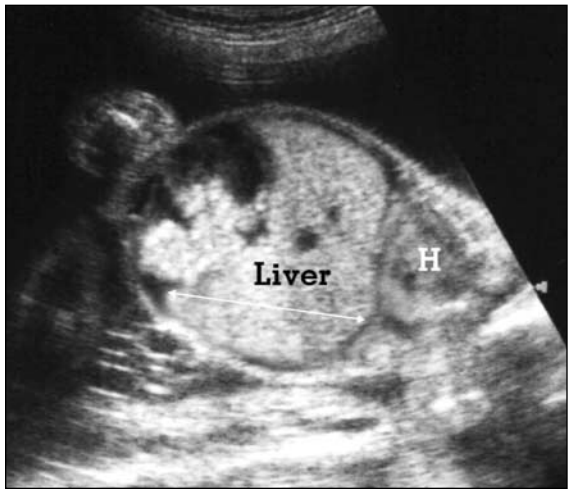
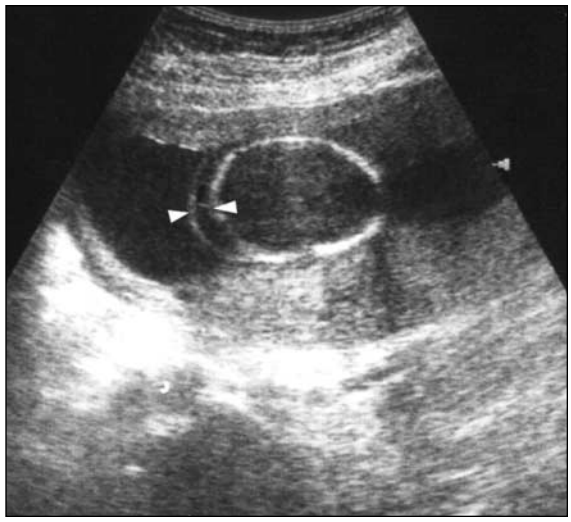


Figure 7. Nuchal edema (arrowheads).



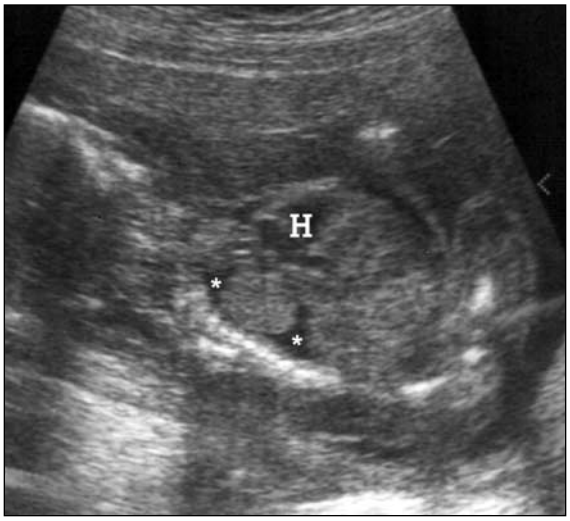


Figure 8. Pleural effusion (asterisks), minimal ascites, and oligohydramnios. H indicates heart.

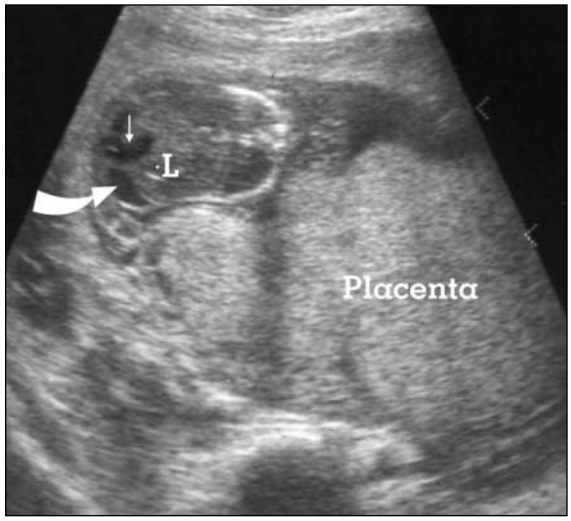


Figure 9. Ascites (large arrow), dilated umbilical vein (small arrow), oligohydramnios, and marked placentomegaly. L indicates liver.

At midpregnancy, approximately two thirds of fetuses with Hb Bart disease have no signs of hydrops fetalis, and they are likely to be missed for the diagnosis if careful measurement for cardiac size and placental thickness is not done. Furthermore, even in the cases with hydropic changes, the signs were not as obvious as seen in late pregnancies, such as only a mild degree of pericardial effusion or ascites, which could be missed if special attention is not paid.

Although hydropic changes are still subtle in the first half of pregnancy, with new high-resolution sonography, early hydropic signs could be detected in some fetuses, and subtle markers (placental thickness and C/T ratio) could predict the disease in nearly all cases. Both an increased C/T ratio and a thickened placenta at midpregnancy are highly suggestive, but not absolutely diagnostic, of an affected pregnancy, for which an invasive diagnostic procedure is strongly indicated. It is important to emphasize that the absence of sonographic markers after 18 to 21 weeks is reassuring and may obviate the need for further invasive procedures to confirm normality, although follow-up sonography may be required. With this approach, invasive proce-

Table 1. Sensitivity and Specificity of Various Sonographic Markers in Predicting Hb Bart Disease at Midpregnancy

Sonographic Markers	Affected, n (n = 100)	Unaffected, n (n = 388)	Sens, %	Spec, %	PPV, %	NPV, %
Cardiac enlargement	95	15	95.0	96.1	86.4	98.7
Thickened placenta (>3 cm)	74	15	74.0	96.1	83.1	93.5
Hydrops fetalis	33	0	33.0	100.0	100.0	85.3
Ascites	25	0	25.0	100.0	100.0	83.8
Pericardial effusion	12	0	12.0	100.0	100.0	81.6
Subcutaneous edema	12	0	12.0	100.0	100.0	81.6
Pleural effusion	10	0	10.0	100.0	100.0	81.2
Hepatomegaly	6	1	6.0	99.7	85.7	80.5
Cord edema	3	0	3.0	100.0	100.0	80.0
Enlarged umbilical vein	7	1	7.0	99.7	87.5	80.6
Oligohydramnios	5	0	5.0	100.0	100.0	80.3
Polyhydramnios	9	1	9.0	99.7	90.0	81.0

NPV indicates negative predictive value; PPV, positive predictive value; Sens, sensitivity; and Spec, specificity.

dures can be selectively performed, and fewer pregnancies will be lost unnecessarily. The reduction in medical expenses and procedure-related fetal loss is likely to be substantial. Therefore, cordocentesis or DNA analysis should be reserved only for cases with positive sonographic markers. Moreover, this diagnostic approach is extremely valuable in areas where the disease is prevalent and cordocentesis or DNA analysis is not readily available. Although a few affected fetuses may be missed by this approach, they can be suspected or detected by later serial sonography. Moreover, because the disease is uniformly lethal, and termination of pregnancy can be offered at any time when the diagnosis is reliably made, missing a very small number of cases will not affect overall outcome greatly. Despite the very high accuracy of sonographic markers, the diagnosis should be confirmed with definitive methods such as fetal blood analysis to exclude false-positive findings, although very infrequent, and hydrops fetalis secondary to other causes.

The prevalence of Hb Bart disease in pregnancies at risk was only 20% in our study, instead of the theoretical rate of 25%. This was due to the presence of some carriers with false-positive findings in the screening program.[7] However, the prevalence of the disease does not affect the sensitivity and specificity of the test.

According to our previous findings, during our first few years of experience with sonography, we never identified hydrops fetalis before 20 weeks because of the very subtle signs before midpregnancy, and we had no opportunity to perform ultrasonography early because we had no indication. In contrast, the data presented here show that nearly all fetuses with Hb Bart disease had subtle hydropic changes.

Because of the fact that termination of pregnancy was done whenever Hb Bart disease was diagnosed, we were unable to recognize the correct sequences of the appearance of various sonographic signs. However, on the basis of the prevalence of positive sonographic markers at midpregnancy and previous reports,[8,13–15] the earliest sign may be an increased C/T ratio, followed by placental thickness. The typical evidence of fluid collection in a body cavity appeared subsequently. Generalized subcutaneous edema and oligohydramnios may be late signs, whereas polyhydramnios is an early sign, but it occurs inconsistently. Notably, a thickened nuchal fold and isolated subcutaneous edema were found in 9 cases. Therefore, the differential diagnoses of a thickened nuchal fold must also include hydrops fetalis, especially in areas with high prevalence.

Of interest, oligohydramnios is very common in late Hb Bart hydrops fetalis, occurring in as many as 82% of cases,[8] whereas it is rarely seen in early cases such as those in this study. In contrast, polyhydramnios is more prevalent in early stages and is almost never seen in late cases. Moreover, in this study, polyhydramnios was found in cases of only mild hydropic changes, whereas oligohydramnios was found in cases of obvious hydrops fetalis. These findings indicate that polyhydramnios may be secondary to the same mechanism in other causes of hydrops fetalis with high-output heart failure, in which polyhydramnios may be found in as many as 75% of cases.[16] These findings provide evidence that polyhydramnios is an early marker, related to high-output heart failure, whereas oligohydramnios is a late marker, appearing as a sign of anemic hypoxia or fetal distress.

Combined with our own late series, the data suggest the progressive nature of the disease, from subtle changes, undetectable without careful measurement of the placenta and C/T ratio, in most cases before midpregnancy, to frank hydrops fetalis, in most cases after midpregnancy. The finding of a frequent early appearance of ascites suggests that portal hypertension due to hepatosplenomegaly may play an important role in the pathophysiologic process of Hb Bart hydrops fetalis.

Fetuses with Hb Bart disease have deficient α-globin synthesis. Because α-globin-dependent Hb F is the major Hb of the fetus from 8 weeks' gestation onward, anemia can develop in affected fetuses as early as the first trimester. The anemia can manifest early as placentomegaly, which is evident on sonography from 10 weeks onward.[10] However, the deficiency of the α-globin chain is usually compensated for by an increase of another embryonic Hb or a delay in switching from embryonic Hb to Hb F. Therefore, the severity and timing of the development of hydropic changes varied extensively. However, our data with an adequate number of cases suggest that nearly all affected fetuses already have some sonographic markers at midpregnancy.

In conclusion, among couples at risk with no sonographic markers, the risk of having an affect-

ed child is nearly eliminated. Pregnancies at risk have a 25% chance of having an affected child, and 75% of them carry fetuses without abnormalities and risk undergoing unnecessary invasive procedures. Sonographic markers can effectively, although not absolutely, differentiate normal pregnancies from those requiring an invasive workup. Therefore, our findings can contribute to a change in clinical decision making, especially for pregnancies at risk that are examined during the second trimester, and sonographic markers for Hb Bart disease should be taken into account as a part of routine screening for fetal anomalies as well, especially in areas with high prevalence of the disease. This study has established the sonographic signs of Hb Bart disease at midpregnancy; therefore, further studies should concentrate on first-trimester sonographic findings, especially the C/T ratio, as suggested by previous studies.[9,14]

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